



REVIEW ARTICLE

Adhesion G protein-coupled receptors



Tobias Langenhan^{1, 2, 3, *} , Garret R. Anderson⁴ , Demet Araç⁵, Gabriela Aust^{6, 7},
 Monserrat Avila-Zozaya⁸ , Sofie Morsing Bagger⁹, Patrick Barth¹⁰,
 Sandra Berndt^{11, 12} , Stephen C. Blacklow¹³ , Beatriz Blanco-Redondo¹ ,
 Antony A. Boucard¹⁴, James P. Bridges^{15, 16} , Lara-Sophie Brodmerkel¹,
 Kathleen M. Caron⁸ , Yin Kwan Chung (鍾炫坤)⁹ , Andrew N. Dates¹⁷,
 Virginea de Araujo Farias¹⁸ , Daniel Del Toro¹⁹ , Joseph G. Duman²⁰ ,
 Felix B. Engel^{21, 22}, David M. Favara^{23, 24, 25} , Caroline J. Formstone²⁶ , Chaoyu Fu²⁷,
 Alain Garcia De Las Bayonas^{28, 29} , Anastasia Georgiadi^{30, 31}, David E. Gloriam³² ,
 Randy A. Hall³³, Jörg Hamann^{34, 35} , Peter W. Hildebrand³⁶, Cheng-Chih Hsiao^{34, 35} ,
 Bill X. Huang³⁷, Jonathan A. Javitch^{38, 39} , Hee-Yong Kim (김희용)³⁷, Robert J. Kittel⁴⁰ ,
 Gunnar Kleinau⁴¹, Richard Leduc⁴², Ines Liebscher^{11, 12} , Hsi-Hsien Lin⁴³,
 Joshua Linnert⁴⁴, Marie-Gabrielle Ludwig⁴⁵ , David C. Martinelli⁴⁶,
 Signe Mathiasen⁹ , Daniel Matúš⁴⁷ , Mariam Melkumyan³⁷ ,
 Ana L. Moreno-Salinas⁴² , Jan Mulder^{48, 49} , Michael A. Nash^{50, 51} , Kasturi Pal⁵² ,
 Daniel T. Pederick⁵³ , Nicole A. Perry-Hauser⁵⁴ , Xianhua Piao⁵⁵,
 Yu-Qi Ping (平玉奇)⁵⁶, Dimitris G. Placantonakis⁵⁷, Fabian Pohl¹, Simone Prömel⁵⁸ ,
 Mette M. Rosenkilde⁹ , Laurent Sabbagh⁵⁹ , Richard C. Sando⁶⁰,
 Patrick Scheerer⁴¹ , Torsten Schöneberg^{61, 62} , Elena Seiradake^{63, 64},
 Mareike Selcho⁴⁰ , Florian Seufert³⁶ , Abhishek K. Singh²¹ , Georgios Skiniotis⁶⁵,
 Katja Spiess^{9, 66} , Norbert Sträter⁶⁷, David Strutt⁶⁸ , Thomas C. Südhof^{47, 69},
 Jinpeng Sun (孙金鹏)⁷⁰, Gregory G. Tall⁷¹, Doreen Thor⁶¹ , Douglas G. Tilley⁷²,
 Kimberley F. Tolia²⁰, Mario Vallon⁷³, Erwin G. Van Meir¹⁸, Benoit Vanhollebeke^{74, 75} ,
 Giselle R. Wiggin⁷⁶ , Uwe Wolfrum^{44, 77}, Jie Yan²⁷ , Nathan A. Zaidman⁷⁸,
 Yimin Zou (邹益民)⁷⁹, Nicole Scholz^{1, *} 

¹ Rudolf Schönheimer Institute of Biochemistry, General Biochemistry, Medical Faculty, Leipzig University, Leipzig, Germany² Comprehensive Cancer Center Central Germany (CCCG), Leipzig, Germany³ Faculty of Life Sciences, Institute of Biology, Leipzig University, Leipzig, Germany⁴ Department of Molecular, Cell, and Systems Biology, University of California Riverside, Riverside, California⁵ Department of Biochemistry and Molecular Biology, University of Chicago, Chicago, Illinois⁶ Research Laboratories, Department of Orthopedics, Trauma and Plastic Surgery, Medical Faculty, Leipzig University, Leipzig, Germany⁷ Research Laboratories, Department of Visceral, Transplantation, Vascular and Thoracic Surgery, Medical Faculty, Leipzig University, Leipzig, Germany⁸ Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina⁹ Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark¹⁰ Interfaculty Institute of Bioengineering and Ludwig Institute for Cancer Research Lausanne, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland¹¹ Rudolf Schönheimer Institute of Biochemistry, Signal Transduction, Medical Faculty, Leipzig University, Leipzig, Germany¹² Department of Translational Drug Research and Signal Transduction, Center for Biotechnology and Biomedicine, Leipzig University, Leipzig, Germany¹³ Department of Biological Chemistry and Molecular Pharmacology, Blavatnik Institute, Harvard Medical School, Boston, Massachusetts¹⁴ Department of Cell Biology, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (Cinvestav), Mexico City, Mexico¹⁵ Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, National Jewish Health, Denver, Colorado¹⁶ Department of Medicine, Division of Pulmonary Sciences and Critical Care, University of Colorado Anschutz Medical Campus, Aurora, Colorado

* Address correspondence to: Dr Tobias Langenhan, Rudolf Schönheimer Institute of Biochemistry, General Biochemistry, Medical Faculty, Leipzig University, Johannisallee 30, 04103 Leipzig, Germany. E-mail: tobias.langenhan@gmail.com; or Dr Nicole Scholz, Rudolf Schönheimer Institute of Biochemistry, General Biochemistry, Medical Faculty, Leipzig University, Johannisallee 30, 04103 Leipzig, Germany. E-mail: scholzlab@gmail.com

T.L. and N.S. contributed equally to this work.

- ¹⁷ Department of Psychiatry and Behavioral Sciences, University of California San Francisco, San Francisco, California
- ¹⁸ Laboratory of Molecular Neurooncology, Department of Neurosurgery, O'Neal Comprehensive Cancer Center, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama
- ¹⁹ Department of Biomedical Sciences, Institute of Neurosciences (IDIBAPS), University of Barcelona, Barcelona, Spain
- ²⁰ Department of Neuroscience, Baylor College of Medicine, One Baylor Plaza, Houston, Texas
- ²¹ Department of Nephropathology, Institute of Pathology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
- ²² Department of Cardiology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
- ²³ Division of Structural Studies, MRC Laboratory of Molecular Biology, Cambridge, UK
- ²⁴ Department of Oncology, University of Cambridge, Cambridge, UK
- ²⁵ Department of Oncology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
- ²⁶ Department of Clinical, Pharmaceutical and Biological Sciences, University of Hertfordshire, Hatfield, UK
- ²⁷ Department of Physics and Mechanobiology Institute, National University of Singapore, Singapore, Singapore
- ²⁸ Department of Molecular and Cell Biology, University of California, Berkeley, California
- ²⁹ Howard Hughes Medical Institute, Chevy Chase, Maryland
- ³⁰ Institute for Diabetes and Cancer, Helmholtz Centre Munich, Neuherberg, Germany
- ³¹ Deutsches Zentrum für Diabetesforschung, Neuherberg, Germany
- ³² Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark
- ³³ Department of Pharmacology and Chemical Biology, Emory University School of Medicine, Atlanta, Georgia
- ³⁴ Department of Experimental Immunology, Amsterdam Institute of Immunology and Infectious Diseases, Amsterdam University Medical Center, Amsterdam, the Netherlands
- ³⁵ Neuroimmunology Research Group, Netherlands Institute for Neuroscience, Amsterdam, the Netherlands
- ³⁶ Institute for Medical Physics and Biophysics, Medical Faculty, Leipzig University, Leipzig, Germany
- ³⁷ Laboratory of Molecular Signaling, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, Maryland
- ³⁸ Departments of Psychiatry and Molecular Pharmacology and Therapeutics, Columbia University Vagelos College of Physicians and Surgeons, New York, New York
- ³⁹ Division of Molecular Therapeutics, New York State Psychiatric Institute, New York, New York
- ⁴⁰ Department of Animal Physiology, Institute of Biology, Faculty of Life Sciences, Leipzig University, Leipzig, Germany
- ⁴¹ Charité - Universitätsmedizin Berlin, corporate member of the Freie Universität Berlin, Humboldt-Universität zu Berlin, Institute of Medical Physics and Biophysics, Group Structural Biology of Cellular Signaling, Berlin, Germany
- ⁴² Department of Pharmacology-Physiology, Université de Sherbrooke, Sherbrooke, Québec, Canada
- ⁴³ Department of Microbiology and Immunology, College of Medicine, Chang Gung University, Taoyuan City, Taiwan
- ⁴⁴ Institute of Molecular Physiology (imP), Johannes Gutenberg University Mainz, Mainz, Germany
- ⁴⁵ Biomedical Research, Novartis Pharma AG, Basel, Switzerland
- ⁴⁶ University of Connecticut Health, Farmington, Connecticut
- ⁴⁷ Department of Molecular and Cellular Physiology, Stanford University School of Medicine, Stanford, California
- ⁴⁸ Department of Neuroscience, Karolinska Institute, Stockholm, Sweden
- ⁴⁹ Department of Protein Science, Science for Life Laboratory, KTH Royal Institute of Technology, Stockholm, Sweden
- ⁵⁰ Department of Chemistry, Institute of Physical Chemistry, University of Basel, Basel, Switzerland
- ⁵¹ Department of Biosystems Sciences and Engineering, ETH Zurich, Basel, Switzerland
- ⁵² Department of Biology, Ashoka University, Sonapat, India
- ⁵³ Department of Neuroscience, School of Medicine, Johns Hopkins University, Baltimore, Maryland
- ⁵⁴ Centre for Translational Pharmacology, School of Molecular Biosciences, University of Glasgow, Glasgow, UK
- ⁵⁵ Weill Institute for Neuroscience, University of California San Francisco, San Francisco, California
- ⁵⁶ Medical Science and Technology Innovation Center, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, China
- ⁵⁷ Departments of Neurosurgery and Cell Biology, NYU Grossman School of Medicine, New York, New York
- ⁵⁸ Institute of Cell Biology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
- ⁵⁹ Domain Therapeutics, St-Laurent, Quebec, Canada
- ⁶⁰ Department of Pharmacology, Vanderbilt Brain Institute, Vanderbilt University, Nashville, Tennessee
- ⁶¹ Rudolf Schönheimer Institute of Biochemistry, Molecular Biochemistry, Medical Faculty, Leipzig University, Leipzig, Germany
- ⁶² University of Global Health Equity (UGHE), Kigali, Rwanda
- ⁶³ Department of Biochemistry, University of Oxford, Oxford
- ⁶⁴ Kavli Institute for Nanoscience Discovery, University of Oxford, Oxford
- ⁶⁵ Department of Structural Biology and Center of Excellence for Structural Cell Biology, St. Jude Children's Research Hospital, Memphis, Tennessee
- ⁶⁶ Department of Virology and Microbiological Preparedness, Statens Serum Institut, Copenhagen, Denmark
- ⁶⁷ Institute of Bioanalytical Chemistry, Center for Biotechnology and Biomedicine, Leipzig University, Leipzig, Germany
- ⁶⁸ School of Biosciences, University of Sheffield, Sheffield
- ⁶⁹ Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California
- ⁷⁰ Advanced Medical Research Institute, Cheeloo College of Medicine, Shandong University, Jinan, China
- ⁷¹ Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan
- ⁷² Department of Cardiovascular Sciences, Aging and Cardiovascular Discovery Center, Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania
- ⁷³ Institute of Anatomy and Cell Biology, University of Würzburg, Würzburg, Germany
- ⁷⁴ Laboratory of Neurovascular Signaling, Department of Molecular Biology, ULB Neuroscience Institute, Université libre de Bruxelles, Gosselies, Belgium
- ⁷⁵ WEL Research Institute, Wavre, Belgium
- ⁷⁶ Nxera Pharma UK Ltd., Cambridge, UK
- ⁷⁷ Institute for Quantitative and Computational Biosciences (IQCB), Johannes Gutenberg University Mainz, Mainz, Germany
- ⁷⁸ Department of Biochemistry and Molecular Biology, University of New Mexico School of Medicine, Albuquerque, New Mexico
- ⁷⁹ Neurobiology Section, Biological Sciences Division, University of California, San Diego, La Jolla, California

Abstract	4
Significance Statement	4
I. Introduction	4
II. Receptor terminology	4
III. Generic residue numbering	5
IV. Structures of adhesion G protein-coupled receptors	7
A. GPCR autoproteolysis-inducing domains	7
B. Extracellular domains and ligand-bound structures	7
C. 7TM domains	8
V. Autoproteolytic processing	15

VI. Alternative splicing and protein variants of adhesion G protein–coupled receptors	15
VII. Subcellular trafficking, localization, and cellular functions of adhesion G protein–coupled receptors	18
VIII. Anatomical and cellular distribution of human adhesion G protein–coupled receptor transcripts	18
IX. Interactions	19
A. Ligands (extracellular binding partners)	19
B. Intracellular binding partners (except G proteins, arrestins, and Rac/Ras/Rho GTPases)	20
X. Receptor activation modes	20
A. TIA/Stachel-dependent signaling: Dissociation model	20
B. TIA/Stachel-dependent signaling: Nondissociation model	21
C. TIA/Stachel-independent signaling	21
XI. Signaling routes	21
A. Cell-autonomous signaling	21
1. G proteins	21
2. Arrestins	22
3. Signaling pathways independent of G proteins and arrestins	22
4. Signaling with coreceptors	22
B. Non–cell autonomous signaling	23
XII. Physiology and pathophysiology	23
A. Organ systems	23
1. Nervous system: Glia and neurons	23
2. Sensory systems	24
3. Vasculature	24
4. Lymphatic vessels	25
5. Skin	26
6. Heart	26
7. Lung	26
8. Musculoskeletal system	26
9. Immune system and spleen	27
10. Kidney	27
11. Pancreas	28
12. Metabolism, fat, and liver	28
13. Gastrointestinal tract	28
14. Female reproductive system	28
15. Male reproductive system	29
B. Diseases	29
1. Cancer	29
a. Tumor progression and growth	29
b. Tumor cell migration/invasion and metastasis	29
c. Immune evasion	30
d. Angiogenesis	30
2. Type 2 diabetes	30
3. Viral infection	30
4. Bacterial infections	30
5. Neurodevelopmental, neurodegenerative, and neuropsychiatric disorders	30
XIII. Adhesion G protein–coupled receptors as drug targets	31
A. ADGRA	31
B. ADGRB	31
C. ADGRD	31
D. ADGRE	31
E. ADGRF	31
F. ADGRG	31
G. ADGRL	32
XIV. Phylogeny of adhesion G protein–coupled receptor(s) and model organisms	32
A. Phylogenetic relationships of adhesion G protein–coupled receptor(s) subfamilies and homologs	32
B. Model organisms for adhesion G protein–coupled receptor(s) research	32
1. Choanoflagellates	32
2. Fruit fly (<i>Drosophila melanogaster</i>)	32
3. Roundworm (<i>Caenorhabditis elegans</i>)	33
4. Zebrafish (<i>Danio rerio</i>)	33
5. Chick (<i>Gallus gallus</i>)	34
6. Mouse (<i>Mus musculus</i>) and rat (<i>Rattus norvegicus</i>)	34
XV. Experimental technologies for adhesion G protein–coupled receptor(s) interrogation	34
A. Molecular dynamics studies	34
B. Homology modeling	34
C. Acute receptor activation	36

D. Force assays	37
E. Receptor dissociation	37
XVI. Perspectives	38
References	39

ARTICLE INFO

Associate Editor: Gunnar Schulte

ABSTRACT

Adhesion G protein–coupled receptors (aGPCRs) constitute a structurally and functionally distinct group within the superfamily of GPCRs. In 2015, the International Union of Pharmacology invited the Adhesion GPCR Consortium to publish a comprehensive review about aGPCRs and establish a unified nomenclature. Since then, substantial progress has been made in delineating the biological roles, molecular architecture, biochemical properties, expression profiles, ligand repertoire, and activation and signaling strategies of aGPCRs. Commensurate with these advances, their relevance to human pathophysiology has become increasingly apparent. In a coordinated effort, the Adhesion GPCR Consortium has reviewed recent progress in this field and provides a comprehensive assessment of the current understanding of aGPCR biology, including a focus on human and mammalian aGPCRs, their evolutionary origins, methodological approaches, and model systems for their investigation, as well as emerging approaches for their therapeutic targeting.

Significance Statement: Adhesion G protein–coupled receptors are versatile cell-surface proteins that integrate structural, biochemical, and physiological functions, with major roles in health and disease. This review summarizes current knowledge of their molecular features, functions in diverse model systems, and emerging opportunities for therapeutic targeting, providing a comprehensive resource that connects basic biology with translational applications across multiple scientific disciplines.

© 2026 The Author(s). Published by Elsevier Inc. on behalf of American Society for Pharmacology and Experimental Therapeutics. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

I. Introduction

Adhesion G protein–coupled receptors (aGPCRs) form a remarkable set of molecules within the superfamily of GPCR.¹ Ever since aGPCRs were recognized as a receptor family² and alternatively classified as B2 GPCRs,³ researchers across many scientific research fields have focused on elucidating their molecular architecture, biochemical features, pharmacological properties, physiological functions, and involvement in disease. This review summarizes the current state of knowledge on aGPCRs, covering a broad range of aspects relevant to the various scientific communities interested in these receptors.

In the following sections, we present an introduction to the general molecular, cellular, and physiological characteristics of all aGPCRs, with an emphasis on human and other mammalian family members. Furthermore, this review offers an overview of current efforts to elucidate the role of aGPCR dysfunction in various diseases and explores strategies for their pharmacological targeting. Finally, we provide a survey of the principal model organisms and experimental approaches currently employed in aGPCR research.

II. Receptor terminology

Similar to other GPCRs, the structural organization of aGPCRs can be topologically subdivided into the following 3 main regions: an extracellular N-terminus (ENT), a 7-transmembrane helix domain (7TMD) including extra- (ECL) and intracellular loops (ICLs), and an intracellular C-terminus (ICT) (Figs. 1 and 2).^{1,4–16} The ENTs of aGPCRs frequently contain a variety of protein domains commonly associated with adhesive functions (Fig. 3).^{17–23} This structural complexity can contribute to the unusually large size of many aGPCRs and underlies the substantial structural and

functional diversity of this receptor class. Although the ICTs of aGPCRs can also be very large, no annotated domains have been identified to date. Nevertheless, ICTs can facilitate interactions through PDZ (PSD95/Dlg1/ZO-1)-binding motifs (PBMs) to PDZ domains of scaffold proteins.²⁴

The GPCR autoproteolysis-inducing (GAIN) domain is the only extracellular structural element consistently found across nearly all aGPCRs (Figs. 1A and 2A),²⁵ with the exception of Eutherian A1 orthologs.¹⁴ Located just outside the membrane, the GAIN domain of many, but not all, aGPCRs¹⁶ can mediate receptor autoproteolysis at its intradomain GPCR proteolysis site (GPS),^{25,26} resulting in the cleavage of many, albeit not all, aGPCRs into N-terminal (NTF) and C-terminal (CTF) fragments (Fig. 4).²⁷ These fragments remain noncovalently associated at the cell surface,^{28–30} where they can dissociate spontaneously and in response to ligand binding combined with mechanical stimuli. The structural entity of the GAIN domain–cleaved aGPCRs may be termed NTF-CTF complex rather than NTF-CTF dimers or heterodimers to avoid confusion with GPCRs that form functional oligomeric assemblies of more than 1 receptor molecule, for example, GABA_B or metabotropic glutamate receptors.³¹

The NTFs of GAIN domain–cleaved aGPCRs comprise various extracellular domains, including the larger part of the cleaved GAIN domain (Fig. 3), whereas the CTF includes the C-terminal β -strand of the GAIN domain, the linker connecting the GAIN domain and 7TMD, the full 7TMD (Fig. 4), and the complete ICT. The segment corresponding to the last β -strand of the GAIN domain, which forms the N-terminus of the CTF, can undergo structural changes to engage directly with its own 7TMD and activate the receptor. Accordingly, this segment is referred to as a tethered or intramolecular agonist, also known as the *Stachel* (German for “stinger”; Fig. 2A). The *Stachel* sequence of aGPCRs does not represent a separate “tethered” ligand but an integral segment of each receptor’s polypeptide chain. Peptide mapping established its hydrophobic core as sufficient for receptor activation; however, unlike

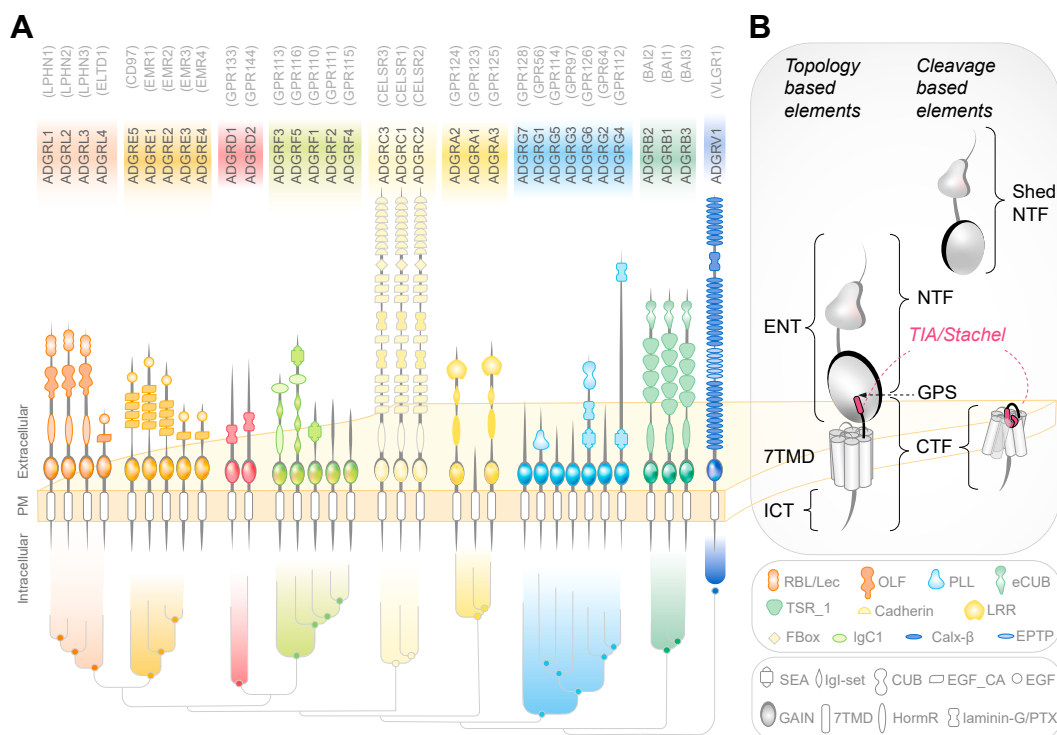


Fig. 1. (A) Overview of human orthologs of the aGPCR family, their domain architecture, and phylogenetic relationship.⁷ Receptor names conform to current IUPHAR nomenclature¹; previous names are given above in brackets. Domains are not drawn to scale, domain numbers per ortholog can vary depending on splice variant/isoform; the phylogenetic relationship is not shown for E4 due to its pseudogene status. NCBI's Conserved Domain Database⁸ and ExPASy PROSITE⁹ were used to annotate domains. Additionally, models were generated using AlphaFold2¹⁰ (except for V1) to corroborate the sequence-based with a structure-based approach. In case of a mismatch, FoldSeek¹¹ was used to identify similar, known domains, based on its predicted structure. Where available (see Sections IV.A and B), known structures of aGPCR ENTs were used to verify predicted domains. Different types of Ig domains were assigned according to their specific topology.¹² A laminin EGF-like domain was predicted N-terminal to the GAIN domain of all C receptors but was absent in the cryo-EM structure of ADGRC1¹³ and was thus omitted from the sketches. Legend: domain shapes only found in 1 subfamily are color-filled, and domains found in more than 1 subfamily are left blank. (B) Schematic depiction of receptor elements of aGPCR based either on their topology (left) applicable to noncleaved and self-cleaved receptors or on autoproteolysis (right) applicable to self-cleaved receptors only. Autoproteolyzed aGPCRs can exist as nondissociated or dissociated noncovalent NTF-CTF complexes. TIA/Stachel is indicated in pink. 7TMD, heptahelical transmembrane domain; CA, cadherin; Calx-β, Na-Ca exchanger β; CTF, C-terminal fragment; CUB, complement C1r/C1s, Uegf, Bmp1; eCUB, extended complement C1r/C1s, Uegf, Bmp1; EGF, epidermal growth factor; ENT, extracellular N-terminus; EPTP, epitempin; GAIN, GPCR autoproteolysis-inducing; GPS, GPCR proteolysis site; HormR, hormone receptor motif; IgI-set, immunoglobulin I-set; ICT, intracellular C-terminus; IgC1, immunoglobulin C1-set; LLR, leucine-rich repeat; NTF, N-terminal fragment; OLF, olfactomedin; PLL, Pentraxin/Laminin/neurexin/sex-hormone-binding-globulin-like; PM, plasma membrane; PTX, pentraxin; RBL/LEC, rhamnose-binding lectin/lectin; SEA, Sea urchin sperm protein, Enterokinase, Agrin; TIA, tethered/intramolecular agonist; TSR, thrombospondin repeat. See section II.

covalently bound chromophores (eg, retinal in opsins), the *Stachel* is encoded, synthesized, and retained within the same chain.^{32,33} Consequently, the *Stachel* functions as an intramolecular agonist and may also be termed as such.¹⁶ In the course of this review, the agonist is referred to by the compound abbreviation tethered/intramolecular agonist (TIA) or by the term *Stachel*.

The stretch of amino acid (AA) residues linking the extracellular domains N-terminal to the GPS motif was historically denominated as a “stalk.”^{34,35} It was later shown that the “stalk” and “GPS motif” are constituent sequences of the GAIN domain.²⁵ Thus, the term “stalk” has become superfluous, and its use should be discontinued.³⁶ Of note, the coordinates of the “stalk” region are distinct from the TIA, which immediately follows C-terminal to the GPS.¹⁶

Since the adoption of the revised nomenclature system for aGPCRs in 2015 by the Adhesion GPCR Consortium, Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), and Human Genome Organisation Gene Nomenclature Committee (HGNC), the updated gene/protein names using the adhesion G protein-coupled receptor (ADGR) prefix have been successfully integrated into scientific communication.¹ We suggest using these new names alongside their traditional synonyms, for example, “ADGRB1/BA1” or “ADGRL3/Latrophilin-3,” at least at the first mention in a publication. Once introduced, shorthand versions of the receptor names (eg, B1 or L3) may be used, as conducted throughout this review.

III. Generic residue numbering

Generic residue numbering (GRN) schemes enable the comparison of corresponding AA residue positions in homologous proteins within or between species. The common principles for generating GRNs are based on either (1) identifying the most highly conserved AA positions in aligned protein sequences, which allows for assigning reference residues or (2) identifying structural alignments (superimpositions) that consider secondary or even tertiary structures within conserved folds to define corresponding AA positions. Such comparisons can be critical to infer function, establish structure-function relationships across diverse datasets (eg, conserved sequence motifs, structural interactions, and pharmacologically and pathologically relevant mutations), or facilitate a more consistent understanding of evolution.

Most GPCRs, including aGPCRs, share an archetypal 7TMD (Fig. 4) with an ENT and an ICT. The complex, often multidomain structure of the aGPCR ENT varies across receptor subtypes, even within the same receptor group (Figs. 1 and 3). As a result, a common GRN scheme for the N-termini of different aGPCR groups is not feasible. Furthermore, multiple transcript variants of individual members³⁷ add further complexity to the numbering system. This also applies to the GAIN domain, found in 31 human aGPCRs (not considering E4 due to its pseudogene status). The

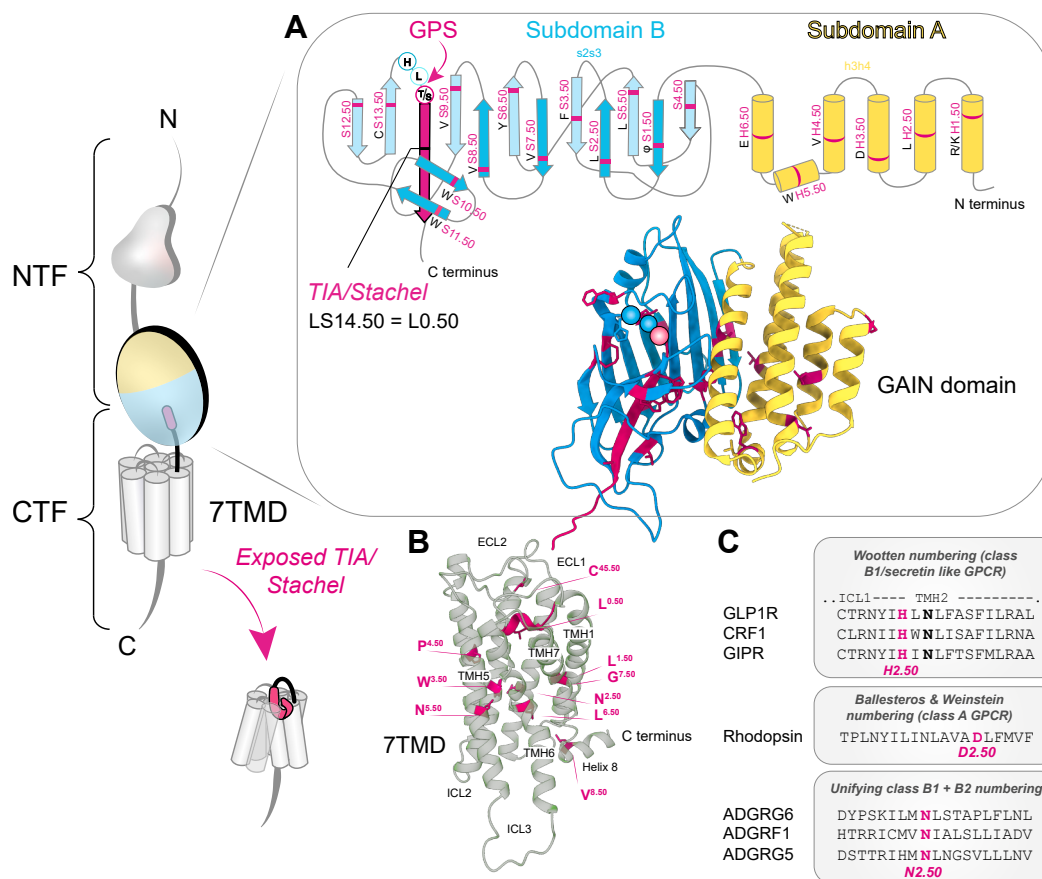


Fig. 2. Generic residue numbering schemes for the GAIN domain and 7TMD of aGPCRs. Generic residue numbers indicate the position of a specific AA within a secondary structural element relative to the most conserved residue of the respective segment, which is assigned the number “X.50.” (A) The GAIN domain, located N-terminal to the 7TMD, is subdivided into subdomain A (yellow), which contains several α -helices (TMH1–TMH6), and subdomain B (blue), which consists of β -strands (S1–S14) and the GPS (red circles). S14 corresponds to the β -strand formed by the *Stachel* core in its in GAIN-bound conformation.¹⁴ Disordered regions connecting structural elements are labeled using the abbreviations of the adjacent segments, such as h3h4 or s2s3. The schemes in (A) represent structural models of aGPCR fragments determined through analysis of GAIN subdomain A (UniprotKB: A0A2Y9F628) and GAIN subdomain B (UniprotKB: A0A2I4CCH8). (B) The 7TMD is composed of 8 α -helices (TMH1–7 and helix 8), each with highly conserved AA residues characteristic of class B GPCRs,¹⁵ visualized at the CTF structure of F1 (PDB ID 7wu5). The TIA/*Stachel* core with the highly conserved L0.50 as part of the CTF can be bound as a helical segment in the 7TMD. The conserved ECL2 residues C45.50 and V8.50 in the cytosolic helix 8 are included in supposed class B GRNs.¹⁶ (C) Example of a comparison between different GPCR numbering schemes for TMH2. See section IV.A, C.

protein sequences of the GAIN domain vary substantially among aGPCR members, making reliable sequence alignment for assigning reference residues extremely difficult.^{14,16}

The *Stachel* core sequence and the GPS motif comprise the first highly conserved extracellular AA sequences directly adjacent to transmembrane helix (TMH) 1. The *Stachel* core has been observed as a β -strand bound within GAIN domain or ENT structures (Fig. 2A) but adopts an α -helical structure within the 7TMD in active state-like CTF structures (Fig. 2B). A recent sequence-based numbering approach focused on this conserved extracellular *Stachel* core sequence^{32,33} and identified a leucine (L0.50) within the TxFxxLM core motif as the most highly conserved residue.¹⁶ Here, “0” indicates the CTF region, although highly conserved TMH residues are denoted by the respective helix number (1, 2, etc.) combined with the “.50” designation (eg, L1.50), allowing for up- or down-counting of adjacent residues. This scheme is an adaptation of the Ballasteros-Weinstein numbering system for class A GPCR.³⁸

Due to the high sequence variability of the GAIN domain, an alternative GRN scheme was developed based on the structural comparison of 14,435 vertebrate GAIN domain models.¹⁴ This analysis revealed a secondary structure consensus of 6 α -helices (H1–H6) in the more structurally variable subdomain A (Fig. 2A),

where some aGPCR subfamilies, for example, D and G, show heterogeneity ranging from 2 to 6 α -helices. In the more conserved subdomain B, 14 β -strands (S1–S14) were defined, with the GPS motif individually indexed (Fig. 2A). In this GRN scheme, the *Stachel* is designated as S14 (strand 14 of subdomain B), with its most highly conserved residue LS14.50 (equivalent to L0.50) located in the *Stachel* core.

For the 7TMD, the Wootten numbering scheme³⁹ was originally developed for the secretin receptor-like family (class B1 GPCRs) based on sequence conservation analyses and was later also applied to aGPCRs (class B2 GPCRs) (Fig. 2C). This scheme was subsequently extended to include ICL1, ECL2, and helix 8, and the TMH1–7 numbering was revised to incorporate structural data that account for helix bulges or constrictions.^{40,41} These GRNs were integrated into the GPCR database, alongside the GAIN GRN scheme.^{14,42,43}

Importantly, phylogenetic analyses revealed that secretin-like receptors evolved from aGPCRs.^{7,44,45} Consequently, a unified GRN scheme for most of the CTF region (*Stachel*–7TMD–intracellular helix 8), based on high sequence conservation across both aGPCR and secretin-like receptors, was recently proposed (Fig. 2C).¹⁵ This provides a standardized framework for residue comparison across diverse receptor groups and members.

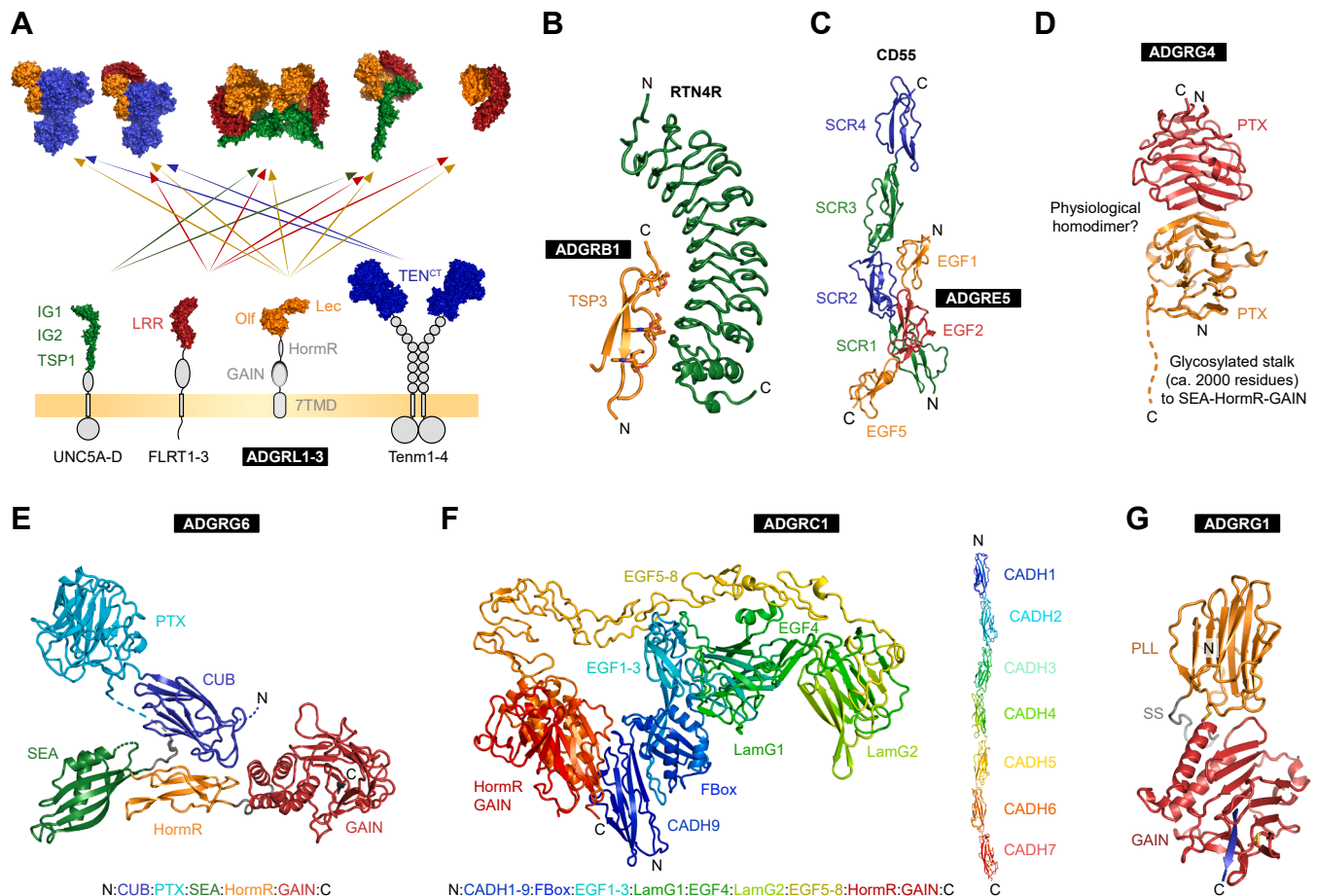


Fig. 3. Extracellular domains of aGPCRs and their interactions. (A) Experimentally shown and predicted extracellular complex formations of L1-3 LEC and OLF domains (orange).^{17–23} (B) Interaction of the TSR3 domain of B1 with RTN4R. Mannose and fucose residues at the binding interface are shown as sticks. (C) Crystal structure of the E5-CD55 complex. (D) The G4 pentraxin domain forms a homodimer. (E) The N-terminal CUB domain of the ENT of G6 interacts with the HormR-GAIN domains resulting in a compact ENT structure. (F) Cryo-EM structure of CADH9-GAIN part (left) and crystal structures of the N-terminal cadherin domains 1–7 (right) of the C1 ENT. (G) Crystal structure of the ENT of G1. A disulfide bridge (SS) links the PLL and GAIN domains. See section IV.B.

IV. Structures of adhesion G protein-coupled receptors

A. GPCR autoproteolysis-inducing domains

Crystal structure analyses of the GAIN domains of human B3 and rat L1⁸ showed that the previously identified GPS motif,²⁶ which comprises roughly 40–60 residues and includes several highly conserved residues,⁴⁶ is located at the C-terminus of a larger fold comprising approximately 320 residues and 2 subdomains (Figs. 3 and 4).

The N-terminal subdomain A consists of up to 6 α -helices, with 5 of them forming a roughly parallel bundle, whereas a shorter helix 5 typically sits perpendicular to the others like a lid on top. Subdomain A is sometimes short through the lack of several α -helices (section III; Fig. 4A), for example, in mouse G1,⁴⁷ human G3,⁴⁸ or human E5.²⁷

The core fold of the C-terminal subdomain B consists of a twisted β -sandwich, including 11 β -strands in 2 antiparallel β -sheets. Additionally, short α -helices or β -strands may be found within flexible loop regions. Two highly conserved disulfide bridges stabilize subdomain B, both anchoring with one end close to the expected cleavage site (CxCxHL[T]).

The cleavage site itself (referred to as GPS) is located within a sharply bent loop right before the last β -strand, which corresponds to the *Stachel*^{32,33} (Fig. 4A). The GPS is flanked by 2 flexible regions,

dubbed Flap 1 and Flap 2, which influence solvent accessibility and exposure of the GPS.³⁰ Structures of human F1,⁴⁹ G3,⁴⁸ L3,⁵⁰ mouse G1,⁴⁷ zebrafish G6,⁵¹ and rat L1⁸ in the cleaved state demonstrated that the *Stachel* remains tightly bound within the GAIN domain fold after self-cleavage. The GAIN domains of human B2,⁵² B3,²⁵ and a cleavage-deficient mutant of E5³⁵ were observed in an uncleaved state. To date, no receptor has been structurally characterized in both a precleavage and cleaved state.

B. Extracellular domains and ligand-bound structures

Adhesion GPCRs exhibit diverse architectures of the ENTs that are critical for their unique activation mechanisms and functional specificity. Although the membrane-proximal GAIN domain is present in most and the hormone receptor motif (HormR) domain in many aGPCRs, a diverse set of more N-terminal domains form a plethora of structures and interaction surfaces for binding partners of each individual aGPCR. Recent studies using mainly X-ray crystallography and single-particle cryogenic electron microscopy (cryo-EM) have begun to uncover the structural diversity of these domains and their complexes. Although each structure appears unique, there are commonalities in how aGPCRs use their ENTs to recognize ligands (Table 1).^{53–158}

A recurring feature is a multidomain architecture in which several individually folded domains are attached to 1 another via

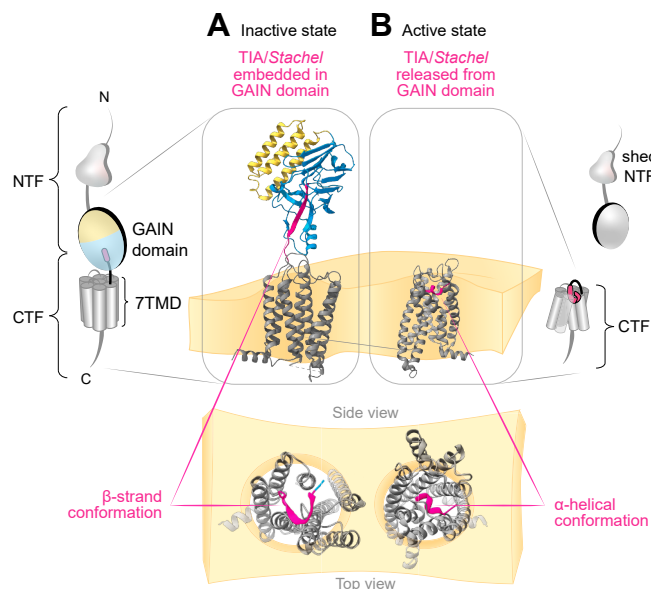


Fig. 4. Adhesion GPCR activation mediated by the TIA/Stachel. The illustration exemplifies the structural transition of an aGPCR from its inactive to active state using structures of E5.²⁷ (A) In the inactive conformation (PDB ID: 8IKJ), the TIA (in pink) is embedded in the GAIN domain as a buried β -strand. (B) Upon activation, the NTF dissociates from the CTF exposing the TIA. The TIA then inserts into the orthosteric binding pocket of the 7TMD through its N-terminal α -helical segment (PDB ID: 8IKL). See section IV.C.

linkers. Another emerging feature is their ability to form higher-order receptor complexes (Fig. 3A), or signaling hubs, that bring together multiple copies of the receptor and/or multiple ligands in a context-specific way.

ADGRL are exemplary with regard to these features. First described as receptors for the α -component of the black widow spider toxin “latrotoxin,”^{159–161} they are now known to bind different endogenous ligands such as fibronectin leucine-rich transmembrane protein¹⁴⁰ and teneurins,¹³⁹ using distinct binding domains (Fig. 3A). Structures suggest the formation of large signaling hubs that involve 3 or more proteins.^{17–22} B1 and B3 require glycans—C-mannosylated tryptophan and O-fucosylated threonine residues in their thrombospondin domains—to bind to its ligands, the reticulon-4 receptors (Fig. 3B).^{62,64} The extended complement C1r/C1s, Uegf, Bmp1 (CUB) domain^{75,162} (also referred to as atypical CUB domain¹⁶³) of B3 (Fig. 1A) interacts with its ligand, complement component 1q-like 3 (C1ql3),^{76,164,165} Ca^{2+} -dependently in a 3:3 stoichiometry.¹⁶³ This hexameric subunit displays an unusual atomic interface architecture that differs from a previously resolved C1q domain-receptor costructure¹⁶⁶ and may be further joined into higher order complexes, for example, a 36-meric supercomplex.¹⁶³ Crystal structures of E5 in complex with CD55¹⁶⁷ and of E2¹⁶⁸ showed that the 3 epidermal growth factor (EGF) domains of E5 have a stable conformation for a *trans*-interaction with 3 short consensus repeat domains of CD55 in an antiparallel orientation (Fig. 3C). However, in many cases, the individual domains of the ENT are connected by flexible linkers. An extreme example is G4, which contains a ~2000 AA long glycosylated, flexible region between the N-terminal pentraxin domain and the SEA-HormR-GAIN domains (Fig. 3D).¹⁶⁹

Important insights were gained with the full ENT structures of G6 (Fig. 3E), C1 (Fig. 3F), and G1 (Fig. 3G), which demonstrated that the extracellular domains display varying, isoform-dependent conformations that range from “compact/closed” to “extended/open-like” and dictate conformation-dependent downstream signaling. In some examples, the most distal, N-terminal domain is

positioned near the transmembrane region, where it has a regulatory role in signaling.^{13,47,51,170} Contrasting with larger aGPCRs is G3, which contains a minimal GAIN domain and just a short helical extension in the ENT.⁴⁸

Taken together, these results underscore the complexity of aGPCR signaling and the critical roles of their extracellular regions in receptor interaction, function, and regulation.

C. 7TM domains

The N-termini of self-cleaved aGPCR-CTFs are ~20–25 AA long segments that extend extracellularly from TMH1. In cleaved but nondissociated aGPCR NTF-CTF complexes, these CTF sequences are buried in a β -strand configuration within the NTF GAIN domain core (Fig. 4A). After NTF-CTF dissociation, the 7 AA long N-terminus of the CTF is liberated and becomes the TIA activating the CTF and driving G protein signaling, suggesting that the agonists bind intramolecularly to a 7TMD orthosteric site (Fig. 4B).^{32,33}

Cryo-EM structures of TIA-activated G1 and L3, in complex with $\text{G}\alpha_{13}$,¹⁷¹ and D1, F1, G2, G4, and G5, in complex with $\text{G}\alpha_s$,^{172–174} revealed a shared hook-like, partial α -helical TIA pose that occupied a common orthosteric binding site within the core of the 7TMD bundle (Fig. 4B). The TIA consensus sequence TxFxxLM contacts multiple TMH spans and residues from ECL2.^{36,175}

In TIA-activated aGPCR-G protein complexes, the conserved toggle switch residue W6.53 directly engages the TIA to mediate receptor activation. As demonstrated for E5, W6.53 exhibited a marked rotational shift upon receptor activation, transitioning between inactive and active states.²⁷ Unlike class A and canonical class B GPCRs, which depend on conserved activation motifs (eg, PIF, NPxxY, and DRY), aGPCRs lack these canonical sequences. Instead, activated aGPCRs show TMH6-TMH7 breaks or kinks like class B1 GPCR. Notably, the class B1 helix-unwinding residues G6.50/G7.50 are conserved in many aGPCRs, indicating that they are a common feature of TIA-mediated aGPCR activation.

In the glucocorticoid-bound G3 complex, the receptor adopts a 7TMD architecture distinct from that of TIA-activated aGPCRs.¹²⁹ The glucocorticoid interacts with W6.53 to support receptor activation. One unconventional feature of the G3/GPR97- $\text{G}\alpha_o$ complex structure is the palmitoylation of the mini- $\text{G}\alpha_o$ C-terminus, which is inserted deeply into the 7TMD core. This modification is crucial for cortisol-induced coupling of G3 to $\text{G}\alpha_o$. However, it remains unclear whether this modification is present in native $\text{G}\alpha_o$.

Apo structures of E5 and G2 exhibit inactive- and active-state conformations, respectively.^{27,128} The active-state G2 conformation is indistinguishable for the apo or dehydroepiandrosterone-bound forms, indicating that it is stabilized by the bound $\text{G}\alpha_s$ and nanobody 35, as G2 can be activated by its TIA.¹⁷⁶ E5 exhibits an inactive, compact 7TMD conformation with pronounced inward shifts of the extracellular ends of TMH6 and TMH7, creating a constrained orthosteric pocket shielded by ECL hydrophobic residues, W685 and F760. The GAIN domain stabilizes an auto-inhibited state through direct interactions with ECL1 and 2, whereas the TIA remains sequestered within the hydrophobic core of the GAIN domain, preventing its interaction with the 7TMD core. A conserved “triad tethering motif” (W545-Y683-F760) forms a tight hydrophobic interaction to lock the inactive E5 conformation. Understanding whether these features are common to other apo-aGPCRs requires more structural investigations.

Critical synopsis and outlook: Structural insights into aGPCRs have fundamentally strengthened earlier concepts of TIA-dependent receptor activation and have enabled the delineation of 7TMD features that distinguish aGPCRs from other GPCR families. Not least, recent structural biology studies revealed the unexpected finding that steroids can bind to and activate aGPCRs by occupying positions that

Table 1

Identity, level of evidence, effect, and interface of known interaction partners of aGPCRs

Receptor	Endogenous Ligands/ Interactors	Exogenous Ligand	Species/ Organism of Receptor	Identification/Isolation Method	Tissue of Identification or Tissue/Cell Expression	Signaling Pathways	Interaction Interface	References
Subfamily A								
A2	RECK/Wnt7a/Wnt7b/ Dishevelled-2		Mouse Zebrafish		Endothelium	β -catenin Cdc42		53–60
A2	$\alpha_v\beta_3$ Integrin, α_5 Integrins		Human	Adhesion assay, affinity chromatography	Human umbilical vein endothelial cells (HUVEC)		ENT, HormR domain RGD motif	61
A2	Heparin		Human	ELISA	HUVEC cells		Unknown, but depends on the ionic strength of the environment (1M NaCl)	61
A2	Glycosaminoglycans (chondroitin sulfate A, heparan sulfate, dermatan sulfate)		Human	ELISA	HUVEC cells			61
A2	SDC1/SDC 2 (Syndecan)		Human	Cell-based genome-wide approach with CRISPR activation	HEK293 cells	-	-	62
A2	Discs large		Human	-	-	-	ICT, PDZ-binding motif(PBM)	63
Subfamily B								
B1	RTN4s/NoGo receptors (RTN4R, RTN4RL1, RTN4RL2)		Mouse, Human	Cell-based genome-wide approach with CRISPR activation, cell surface labeling assay, quantitative cell adhesion assay, binding affinity measurements surface plasmon resonance, pulldown, mass spectrometry	Neuron/glia, HEK293 cells	-	ENT, TSR3 domain (B1-RTN4R K_d = 26.8 nM, B1- RTN4RL1 K_d = 9.6 nM, ENT, B1- RTN4RL2 K_d = 30 nM)	62,64,65
B1	Neuroligin 1		Mouse	Functional Assays, coimmunoprecipitation	Hippocampal neurons, HEK293 cells	-	ENT, Vasculostatin	66
B1	Phosphatidylserine		Mouse	Overlay binding assays phagocytosis assay (in vitro), engulfment assay (in vivo)	LR73 Chinese hamster ovary cells, J774 macrophages and NIH 3T3 cells) and primary cells (mouse astrocytes); apoptotic thymocytes injected into mouse peritoneum	ELMO1/Dock/Rac	ENT, TSR	67
B1	ATP11A			Coimmunoprecipitation assays	HEK293T cells	Reduces constitutive $G_{\alpha_{12/13}}$ signaling	NTF	68
B1	Lipopolysaccharide		Mammalian	Biotin-streptavidin- phycoerythrin based flow cytometry	Macrophages	Rac/ELMO/Dock	ENT, TSRs	69
B1	Integrin $\alpha_v\beta_5$		Mouse	Immunoprecipitation of mouse brain lysate	HUVEC cells	-	ENT	70
B1	BAI-associated protein 2/ IRSp53		Human	Y2H	-	-	Binding between AAs 1304 - 1584	71

(continued on next page)

Table 1 (continued)

Receptor	Endogenous Ligands/ Interactors	Exogenous Ligand	Species/ Organism of Receptor	Identification/Isolation Method	Tissue of Identification or Tissue/Cell Expression	Signaling Pathways	Interaction Interface	References
B1 B2	BAI-associated protein 3 GIP3 (glutaminase interacting protein)		Human Human	Coimmunoprecipitation Human fetal brain cDNA library screened using a yeast 2-hybrid assay, Circular Dichroism, Nuclear Magnetic Resonance spectroscopy	COS-7 cells Human brain	- $G\alpha_{16}$, NFAT pathway	ICT ICT, C-terminal sequence RDGDFQTEV	72 73,74
B3	C1q-like proteins		Mouse	Affinity chromatography, Mass spectrometry, pulldown, proteomics	Mouse brain samples, HEK293 cells, C2C12 cells (muscle cell line)	-	ENT, eCUB, (C1ql-4) ($K_d = 1-20$ nM)	75-78
B3	RTN4R and RTN4RL1		Mouse	Cell surface labeling assays, quantitative cell adhesion assay, pulldown	HEK293 cells	-	ENT, TSR2 (B3- RTN4R with binding affinity of $K_d = 1.9$ nM)	64,65
B3	Stabilin-2		Mouse, Chicken	Proteomics	Purified BAI3 HEK293T cells and to affinity purify proteins from the supernatant of differentiating C2C12	ELMO proteins, β - Arrestin2	ENT	78
B3	Neuronal pentraxins (NPTX1/ NPTXR)		Mouse	Time-controlled cross- linking, Aggregation assay, Coimmunoprecipitation, mass spectrometry	Mouse brain lysates, HEK293 cells		-	75
Subfamily C								
C1	ADGRC1 (homophilic <i>trans</i> -interaction)		Mouse	Cell binding assay	HEK293 cells	-	ENT, cadherin repeats	79
C1	ADGRC2 (heterotypic <i>trans</i> -interaction)		Mouse	Cell binding assay	HEK293 cells	-	ENT; cadherin repeats	79
C1	Vangl-2		Mouse	Fluorescence-based recruitment assay, coimmunoprecipitation	Cultured keratinocytes, HEK293T cells	-	-	80,81
C1	Frizzled-6		Mouse	Fluorescence-based recruitment assay	Cultured keratinocytes	-	-	80
C1	LRRK2		Mouse, Human	Coimmunoprecipitation, mass spectrometry	Substantia nigra cells (SN4741), HEK293T cells	WNT/ β -catenin pathway	-	82
C2	ADGRC2 (homophilic interaction)		Rat	Coculture and aggregation assays, Calcium imaging	Cortex and hippocampal neurons, HEK293 cells	CaMKII, calcineurin, Ca^{2+} signaling	ENT, cadherin repeats	79,83
C2	ADGRC1 (homophilic <i>trans</i> -interaction)			Cell binding assay	HEK293 cells	-	ENT, cadherin repeats	79
C3	ADGRC3 (homophilic <i>trans</i> -interaction)		Rat	Cell binding assay, Co-IP (exogenous and brain lysate), aggregation assays, Calcium imaging	Cortex and hippocampal neurons, HEK293 cells	Ca^{2+} signaling	ENT, cadherin repeats	83,84
C3	Dystroglycan		Mouse	Live-cell binding assay, coimmunoprecipitation	COS-7 cells, HEK293 cells		ENT, LG1 domain	84
C3	Frizzled-3		Mouse	Coimmunoprecipitation	Brain extracts	-	-	85
C3	PSD-95		Mouse	Coimmunoprecipitation	Brain extracts	-	-	85
C3	SV2		Mouse	Coimmunoprecipitation	Brain extracts	-	-	85
Subfamily D								
D1	Protein Tyrosine Kinase 7 (Ptk7)		Human-patient derived, Mouse	Affinity copurification, mass spectrometry	Patient-derived GBM cells, HEK293T cells	cAMP (specifically in <i>trans</i>), requires membrane anchoring	NTF	86,87

D1	5-hydrotestosterone		Mouse	cryo-EM structure	HEK293 cells	$G\alpha_s$, cAMP-PKA	7TMD	88
D1	Plexin Domain-Containing Protein 2		Human	Library of single-transmembrane-spanning human cell surface receptors followed by interaction screening based on AVExis method	Expi293F cells	Increase in cAMP	ENT, PTX domain	87
D1	Methenolone		Mouse	cAMP screen, cryo-EM structure	HEK293 cells	$G\alpha_s$, $G\alpha_o$ cAMP-PKA	7TMD	88
D1		AP503		cryo-EM structure	HEK293 cells	$G\alpha_s$, cAMP-PKA	7TMD	88
Subfamily E								
E2	Dermatan sulfate (chondroitin sulfate B)		Human	Cell-based ligand-binding assay	Most cell surface, ECM	Mast cell degranulation (histamine release)	ENT, EGF-like domain 4	89,90
E2	FHR1		Human	RNA sequencing/Gene associated disease analysis, direct protein-protein interaction assay	Complement system protein in blood	Inflammasome activation in monocytes	ENT	91
E3	Unknown surface ligand		Human	Cell-based ligand-binding assay	Macrophages and activated neutrophils	ND	ENT	92
E4	Unknown surface ligand		Mouse	Cell-based ligand-binding assay	A20 mouse B-cell lymphoma cell line	ND	ENT, EGF-like domain 2	93
E5	CD55		Human/Mouse	Ab blocking assay/biochemical analysis	Red blood cells, lymphocytes, etc.	Induces $G\alpha_{13}$ signaling in cDC2 and marginal zone B cells in the spleen	ENT, EGF-like domains 1, 2, 5	94–97
E5	Dermatan sulfate		Human	Cell-based ligand-binding assay	Most cell surface, ECM	ND	ENT, EGF-like domain 4	90,98
E5	$\alpha 5\beta 1$, $\alpha v\beta 3$ integrin		Human	Functional blocking Abs in cell attachment assay	HUVEC cells	Enhances HUVEC chemotactic migration and angiogenic response	ENT, RGD motif	99
E5	CD90		Human	Cell adhesion assay/protein-cell binding assay	Activated endothelial cells, Glioblastoma cells	ND	ENT, GAIN domain	100,101
E5	LPAR1		Human	Co-IP of tagged receptors, in situ proximity ligation assay	Prostate cancer and thyroid cancer cells	Increased Rho-ERK signaling	7TMD	102,103
E5	RIG-I		Mouse	Immunoprecipitation	HEK-293T or HeLa cells	Inhibition of IFN-I signaling	ICT	104
E5		Gingipain K protease	Human	Multiplexed bioactivity screening of GPCRs, microbiome-GPCRome interactions	<i>Porphyromonas gingivalis</i>	Increased Tango reporter activity	ENT, cleavage at K290 residue	105
E5		SteD surface effector	Mouse	Pulldown, mass spectrometry, coimmunoprecipitation	MutuDCs (immortalized dendritic cells)	Ubiquitination of a cytoplasmic lysine residue	CTF	106
E5	DLG1		Human	GST-Pulldown, proximity ligation assay	CD97-(over) expressing HT1080 cells; DLD1 cells		ICT, PBM	107
Subfamily F								
F1	N-docosahexaenylethanolamine (synaptamide)		Mouse	Pull down coupled to mass spectrometry	Mouse fetal brains or NSCs, HEK293	$G\alpha_s$	ENT, GAIN domain	108,109

(continued on next page)

Table 1 (continued)

Receptor	Endogenous Ligands/ Interactors	Exogenous Ligand	Species/ Organism of Receptor	Identification/Isolation Method	Tissue of Identification or Tissue/Cell Expression	Signaling Pathways	Interaction Interface	References
F1	Occludin		Mouse	Chemical cross-linking, affinity purification, and mass spectrometry	HEK293	ND	ND	110
F1	Laminin-211		Human/ Mouse	Cross-linking-aided IP coupled with mass spectrometry	BT474 and SKBR3 cells overexpressing Adgrf1	Inhibition of $G\alpha_s$	ND	111
F5 F5	Surfactant protein D FNDC4		Mouse Mouse	Coimmunoprecipitation Fluorescent flow cytometry binding assay in live cells	HEK293T Immortalized pre adipocytes (imm. SVF) from inguinal WAT	$G\alpha_s$, increase in cAMP		112 113
Subfamily G G1	Phosphatidylserine			Flow cytometry, membrane lipid strips	Ba/F3 cells	ND	ENT, GAIN domain	114
G1	Transglutaminase 2		Mouse, Human	Radioimmunoprecipitation assay	Lung, melanoma cells, keratinocytes	ROCK-dependent activation of ADAM17	ENT, STP region	115,116
G1	Collagen III		Mouse	In vitro biotinylation/ proteomics and MS	Meningeal Fibroblasts	RhoA activation	ENT, PLL domain	117
G1	Laminin				HEK293T	Together with TG2 increase in SRE luciferase		118
G1	L-phenylalanine		Human	High resolution mass spectrometry, NMR and coinjection analyses of the active fraction	Supernatant of human gut bacteria	$G\alpha_s$ -Gat and $G\alpha_s$ - $G\alpha_o$ chimera-mediated increase in CRE- SEAP assay		119
12 G1	Heparin		Mouse, Human	ELISA, pulldown	Purified protein	Induction of receptor shedding and increased cell adhesion but no identified increased signaling	ENT, AA 26-35	120
G1	Progastrin		Human	Immunofluorescence staining and FACS analysis	Colo320 cells	ND	ND	121
G1	CD9, CD81		Human	Mass spectrometry protein sequencing	NT2RA, HEK293 cells	Scaffolding of $G\alpha_{11}$ and $G\alpha_q$	ND	122
G1	Plectin		Mouse	Unbiased mass- spectrometry screen, co-IP	P5 sciatic nerves	ND	NTF and CTF	123
G1		Antibody	Mouse-human chimera	Cell-based fluorescence binding assay	HEK293T	SRF increase	ENT, GAIN domain	124
G1		Monobody	Mouse		HEK293T	SRE luciferase inhibition	ENT	47
G1		Small molecules incl. dihydromunduletone, 3- α - acetoxydihydrodeoxygedunin		In vitro substance screen	Compound library	SRE luciferase activation		125–127
G2	Dehydroepiandrosterone		Mouse, Human	In vitro substance screen	Compound library	Increase in cAMP	7TMD	128

G2	Deoxycorticosteron		Mouse, Human	In vitro substance screen	Compound library	Decrease in cAMP	7TMD	128
G3	Cortisol, 11-deoxycortisol			In vitro substance screen	Compound library	Binding to receptor	7TMD	129
G3	L-phenylalanine		Human	High resolution mass spectrometry, NMR and coinjection analyses of the active fraction	Supernatant of human gut bacteria	PRESTO Tango Assay activation		119
G3		Beclomethasone		In vitro substance screen	Compound library	Go activation	7TMD	129,130
G3		Ezetimibe, Flunarizine, Zeranol		In vitro substance screen	Compound library	β -arrestin recruitment		131
G3		Compound 36, compound 4		In vitro substance screen	Compound library	G α_{13} activation	7TMD (assumed)	127
G5		Dihydromunduletone, 3- α -acetoxydihydrodeoxygedunin	HEK293T cells	In vitro substance screen	Compound library	G α_{13} inhibition	7TMD (assumed)	125
G6	Collagen IV		Zebrafish	Coimmunoprecipitation	Sciatic nerve	Increase in cAMP	ENT, CUB/Pentraxin	132
G6	Collagen VI		Mouse	Pull down coupled to mass spectrometry	Sciatic nerve	G α_i , decrease in cAMP	ENT, GAIN domain	133
G6	Laminin-211		Zebrafish, mouse	Coimmunoprecipitation	Sciatic nerve	Increase in cAMP when combined with mechanical forces	ENT, GAIN domain	132,134
G6	Prion protein		Zebrafish	Coimmunoprecipitation	HEK293, SW10 cells	Increase in cAMP	ENT (assumed)	135
G6	Progesterone, 17-hydroxyprogesterone		HEK293 cells, breast cancer cells	In vitro substance screen	Compound library	G α_i , decrease in cAMP	7TMD (assumed)	136
G6		Apomorphine	Zebrafish, COS7 cells	In vivo substance screen and in vitro verification	Compound library	Increase in cAMP	7TMD (assumed)	137
G6		Multiple small molecules	Zebrafish	In vivo substance screen	Compound library	ND		138
Subfamily L								
L1	Teneurin-2 (Lasso)		Rat	Affinity purification	Brain lysates	cAMP decrease, Ca ²⁺ increase	ENT, RBL/LEC domain	139
L1	FLRT1, 3		Rat	Affinity purification	Brain lysates	cAMP increase/decrease	ENT, OLF domain	140
L1	Neurexin-1 α , -1 β , -2 β , -3 β		Rat	Cell binding assays	HEK293 cells	cAMP increase/decrease	ENT, OLF domain	141
L1	Contactin-6		Mouse	Affinity purification	Brain lysates and HEK293 cells	Apoptosis	ENT	142
L1	Shank		Human, rat	Y2H, Co-IP	cDNA libraries of human brain, brain lysates		ICT	143
L1	TRIP8b		ND	Y2H SOS recruitment assay	cDNA library of rat brain		ICT	144,145
L1	glucose		Mouse	Affinity purification-LC/MS, ligand-receptor binding assays	Hypothalamic neurons, CHO cells	G α_i /cAMP decrease	ND	146
L1		LK29, LK30, LK31 (engineered synthetic binders)	Human	Single-point protein ELISA, epitope mapping, Surface plasmon resonance			ENT, RBL/LEC domain	147
L1		α -Latrotoxin		Cell-based Ca ²⁺ -uptake and neurotransmitter-release assays	Neurons	Massive neurotransmitter-release	GAIN/TMH1 (residue 467–891)	148
L2	FLRT3		Rat	Affinity chromatography, mass spectrometry, coimmunoprecipitation	Brain lysates, transfected heterologous cell lysates	Not determined (ND)	ENT	140
L2	Teneurin-2		Mouse	Ligand-receptor binding via SPR	HEK293T		ENT, RBL/LEC domain	149
L2	Leucine-rich α -2-glycoprotein 1 (LRG1)		Mouse	Ligand-based receptor capture followed by LC–MS/M	HEK293T	Increase in Lyn-PI3K-AKT-NF- κ B p65 pathway		150,151
L3	FLRT1, 3		Rat	Affinity purification	Brain lysates	Not determined (ND)	ENT	140
L3	FLRT2		Mouse					20

(continued on next page)

Table 1 (continued)

Receptor	Endogenous Ligands/ Interactors	Exogenous Ligand	Species/ Organism of Receptor	Identification/Isolation Method	Tissue of Identification or Tissue/Cell Expression	Signaling Pathways	Interaction Interface	References
L3	UNC5D (only in ternary complex) with FLRT2		Mouse	Crystal structure, coimmunoprecipitation, surface plasmon resonance	HEK293 cells, HeLa cells, cultured neurons	Cell adhesion and repulsion	ENT, LEC/OLF domain	20
L3	FLRT3		Human	Crystal structure, pull-down, mass spectrometry	HEK293 cells	Cell adhesion	ENT, LEC/OLF domain	19
L3	Teneurin-3		Rat	Coimmunoprecipitation	HEK293 cells	ND	ENT	140
L3		LK29, LK30, LK31 (engineered synthetic binders)	Human	Single-point protein ELISA, epitope mapping, Surface plasmon resonance	-	SRE	ENT, RBL/LEC domain, breaks interaction between L3 with TEN2 but not FLRT3	147
L3		LK12 (engineered synthetic binders)	Human	Single-point protein ELISA, epitope mapping, Surface plasmon resonance		SRE	ENT, LEC/OLF domain	147
L4	ku80		Human		HUVEC cells	NFAT	ENT	152
L4	β -spectrin		Human		HUVEC cells	NFAT	ENT	152
Cir1	Toll-8/Tollo		<i>D. melanogaster</i>	Mass spectrometry, functional readouts	Lysates from <i>Drosophila</i> embryo and pupae	ND	ENT	153,154
HC110R	FMRamide-like neuropeptides AF1, AF10, PF2		<i>H. contortus</i>	Surface plasmon resonance	-	ND	ENT	155
LAT-1	LAG-2 (DSL protein/Notch ligand)		<i>C. elegans</i>	BRET (in vitro) and BiFC (in vivo) assays	Somatic gonad, germ cell	ND	GAIN, RBL domain	156
Subfamily V								
V1	Harmonin		Mouse	GST-Pulldown, coimmunoprecipitation, yeast 2-hybrid assays	COS-1 cells, bacterial lysates	ND	ICT, PBM	157
V1	Whirlin		Mouse	Glutathione S-transferase (GST) pulldown assays, yeast 2-hybrid assays, immunoprecipitation assays	COS-1 cells, bacterial lysates	-	ICT, PBM	158

overlap with the canonical TIA-binding site. In the near future, it will be of prime interest to determine whether TIA- and steroid-mediated agonism are mutually exclusive or cooperative modes of receptor activation, how these modes relate to the receptors' perception of mechanical stimuli, and under which physiological conditions they occur individually or in concert.

The GAIN domain will likewise continue to attract structural attention. To date, only a single GAIN–7TMD costructure has been solved, and many more are needed to understand the central role this domain plays in aGPCR signaling behavior. In particular, studies addressing the steric relationship and potential contacts between the GAIN domain and the 7TMD are still lacking. Similarly, the dynamic behavior of the GAIN domain under mechanical stimulation remains ill-defined, and approaches such as Förster resonance energy transfer imaging, nuclear magnetic resonance, and double electron–electron resonance spectroscopy are in high demand to resolve structural transitions of the domain during receptor activation, signaling, and rest.

Structural work has also made major strides in uncovering how individual aGPCRs can engage multiple ligands, which has been a central conundrum in the field for a long time. A complex picture is emerging, in which aGPCRs act as membrane-embedded hubs that integrate diverse extracellular cues—sometimes cooperative, sometimes mutually exclusive, into coherent cellular decisions. Frequently, however, this combinatorial logic remains unresolved. Subsequent work must therefore focus on how the structures of aGPCR–ligand complexes can illuminate cellular responses in the presence of more than 1 ligand for a given receptor. Cryo-electron tomography of intact aGPCR–ligand complexes at endogenous expression sites within their native tissue context remains elusive but will ultimately be required to complement—and in parts correct—our current understanding derived largely from studies of isolated domains or receptor fragments.

V. Autoproteolytic processing

Autoproteolytic cleavage at the GPS is a defining feature of many aGPCRs.^{177–179} Prior to the discovery of the GAIN domain,²⁵ a region of approximately 40–60 AAs, which is characterized by 4 conserved Cys, 2 invariant Tyr residues, and 1 consensus tripeptide cleavage sequence, had been dubbed the “GPS motif.”^{29,46,180,181} The GPS proteolytic reaction typically occurs at a 3 AA His(P-2)-Leu/Ile(P-1)-Ser/Thr(P+1) sequence within the GAIN domain (Fig. 2A).^{26,181} Deglycosylation and pulse-chase experiments suggest that this autoproteolytic process likely takes place in the endoplasmic reticulum (ER) during receptor biosynthesis.^{26,46,182–184} Subsequent studies have demonstrated that early N-glycosylation plays a crucial role in regulating the efficiency of GPS proteolysis, highlighting the stringently controlled nature of receptor cleavage.^{184–186} Recent advances have further uncovered key structural determinants and molecular interactions surrounding the GPS, which are essential for ensuring the completion of the autoproteolytic reaction.^{52,187} Furthermore, translational formation of the 7TMD and distance of the GAIN domain to the inner leaflet of the ER membrane enhances GAIN domain cleavage efficiency, probably by localizing the nascent GAIN domain in proximity to components of the N-glycosylation machinery required for correct domain folding and ER exit (see also Section VII).¹⁸⁴

GAIN domain autoproteolysis dissects the receptor into an NTF and a CTF, which remain tightly bound as a noncovalent complex at the cell surface (Fig. 2A).^{28–30} Notably, the NTF of some aGPCRs, such as L3, are, in part, spontaneously shed at the GPS,¹⁸⁸ whereas the NTFs of other aGPCRs, such as B1 and A2, are cleaved by proteinases at non-GPS locations, releasing different fragments that can mediate non-cell autonomous functions.^{189–192}

Further analysis of crystal, cryo-EM, and AlphaFold structures of various aGPCRs has highlighted the functional significance of the GAIN domain as an evolutionarily conserved protein fold, consisting of subdomains A and B (Fig. 2), necessary and sufficient for receptor autoproteolysis at the GPS.^{25,187,193} The first reported structures analyzed GAIN domains of L1 and B3,²⁵ which contain a long subdomain A built of 6 α -helices. Later studies showed that GAIN domains with a significantly shorter subdomain A, containing only 2–3 α -helices, are able to autoproteolyze as well (see sections III and IV.A), for example, G1,⁴⁷ G3,⁴⁸ and E5.²⁷ Hence, although the structure of subdomain B appears largely conserved across the aGPCR family, subdomain A exhibits much higher structural variability that is still compatible with GAIN domain autoproteolysis. These structural insights also enhanced the understanding of the molecular basis of Stachel-mediated aGPCR activation^{171–174} and the role of aGPCRs as metabotropic mechanosensitive receptors^{89,94,153,194,195} (see sections X and XV.D).

Interestingly, several non-aGPCR cell surface proteins, including the sea urchin sperm receptors for egg jelly and polycystic kidney disease 1–like proteins, also contain a GAIN domain and undergo autoproteolysis.^{193,196–198} These findings indicate a broader functional role for GPS cleavage in receptor biology.¹⁴ As a result, specific point mutations in the GAIN domain that impact receptor structural stability and proteolysis have been associated with a range of unique genetic pathological disorders.^{89,199–202} Overall, GAIN domain-mediated autoproteolytic processing is a vital post-translational modification that ensures the correct structural organization and functionalization of many aGPCRs.

Critical synopsis and outlook: Autoproteolytic processing of aGPCRs has been studied intensively. The remarkable evolutionary conservation of the GAIN domain and its autoproteolytic capacity underscores the substantial contribution this mechanism has made to the fitness of multicellular organisms. Nonetheless, many questions concerning the process itself, its cell biological role, and its physiological consequences remain unresolved. For example, is the steric flexibility of the GAIN domain a prerequisite for, or a consequence of, its self-cleavage? Are there extrinsic factors that cells can deploy to promote or inhibit receptor autoprocessing? Moreover, if the autoproteolytic step serves as a checkpoint for ER exit, what mechanisms does the ER use to assess whether cleavage of a given receptor molecule has taken place? Addressing these questions will be essential to extend our understanding of why many aGPCRs undergo autoproteolysis, whereas others do not.

VI. Alternative splicing and protein variants of adhesion G protein–coupled receptors

Adhesion GPCRs are encoded by large genes with extended exon-intron structures that facilitate extensive transcript variation through alternative promoter usage and splicing events.^{28,37,95,203–205} This genomic complexity enables the generation of multiple mRNA variants from a single gene, which can change the cell expression specificity and/or the open reading frame, potentially resulting in protein variants with distinct structural and functional properties.

Many aGPCRs and their transcript variants are expressed in a tissue-specific manner (Fig. 5).^{206–208} For instance, certain variants are predominantly found in neural tissues, whereas others are more common in immune cells.^{47,204} This selective expression suggests that different protein forms may be adapted to meet cell-type specific needs. Beyond tissue specificity, spliceosomal reprogramming of aGPCR transcripts was also shown to occur within the same tissue or cell in a stimulus-dependent manner.²⁰⁹ A striking example of this comes from the postsynaptic receptor L3, whose ability to promote synapse formation in the

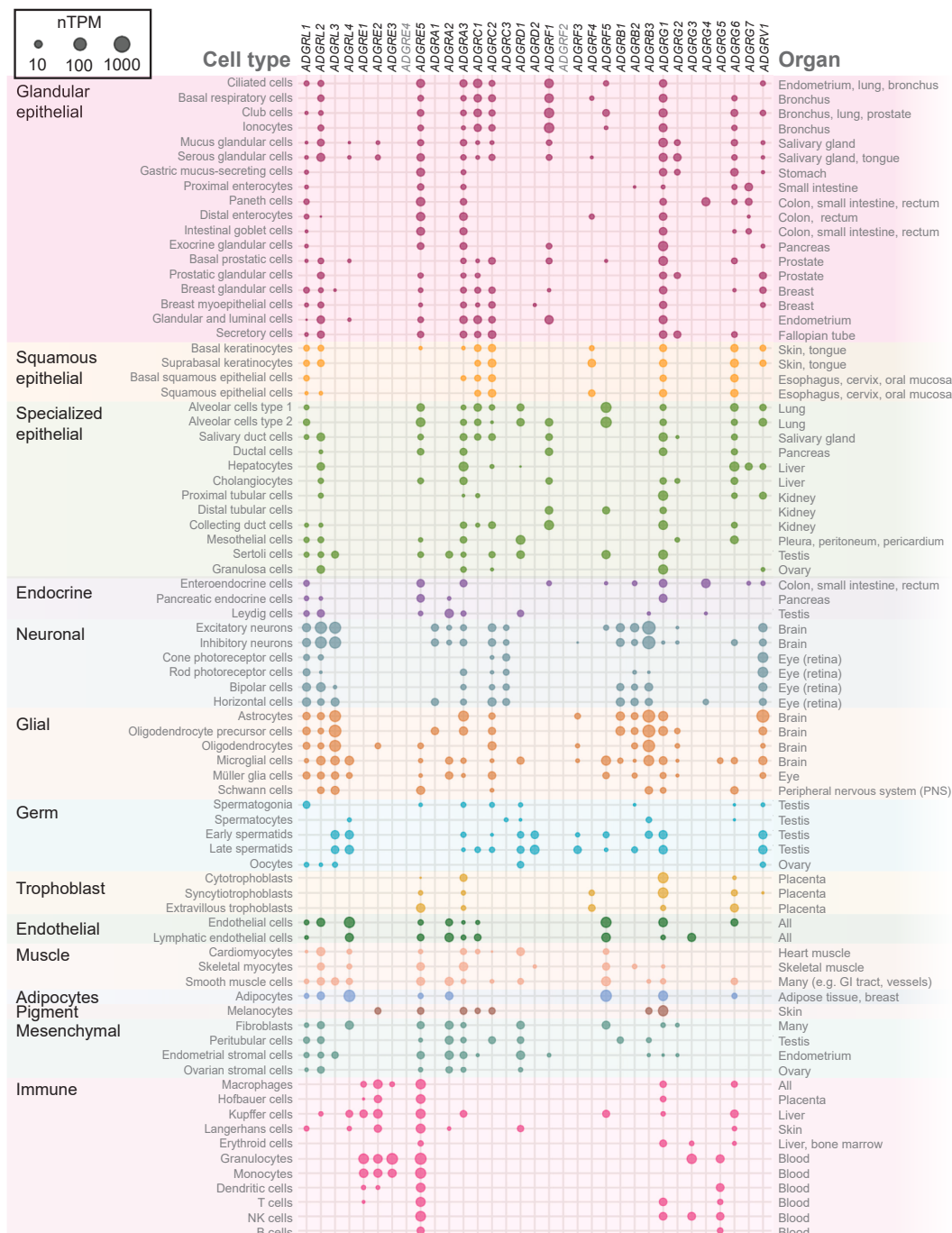


Fig. 5. Overview of gene expression of aGPCRs across human cell types obtained by single-cell RNA sequencing data from solid tissues and bulk RNA sequencing data from sorted blood collected by the Human Protein Atlas (HPA) consortium.²⁰⁶ Note that (1) cell types are grouped primarily by function, not by tissue, (2) ubiquitous cell types, such as endothelial cells lining vessels, appear only once, although present in many tissues, (3) organs contain various cell types and can appear in multiple categories (eg, liver: hepatocytes and cholangiocytes under “specialized epithelial cells” and Kupffer cells under “immune cells”), (4) hard-to-isolate cells, such as osteocytes and chondrocytes, are not covered in this list, (5) enucleated cells/cell fragments, like red blood cells and platelets, are not included, although they may express aGPCRs, and (6) data represent healthy adult tissues. Normalized transcripts per million (nTPM) values represent the number of transcripts detected for a given gene. The size of the dot depends on the nTPM value (cutoff value of ≥ 4). Each data point represents gene expression and does not distinguish between transcript variants. *ADGRE4*^{207,208} and *ADGRF2* are currently considered as pseudogenes in humans; however, transcripts originating from both loci have been reported.²¹ See sections VIII and XIA.

hippocampus²¹⁰ relies on 2 convergent pathways Gas-mediated signaling and the assembly of postsynaptic scaffold condensates, both of which are governed by activity-dependent alternative splicing of L3.²⁰⁹ Furthermore, alternative splicing of the L homolog Cirl in *Drosophila* generates both canonical 7TMD-containing and atypical 7TMD-lacking proteins, whose coexpression

enables G protein signaling and the discrimination between different mechanical stimulus intensities in sensory neurons.²¹¹

Although the identity of the specific factors guiding these processes remains unknown, these data unveil an intrinsic potential for cell autonomous modulation of aGPCR splicing events, which can sustain tissue/cell plasticity throughout development.

Comparative analyses across species have revealed that transcript variants are conserved, suggesting that their functional significance may be evolutionarily conserved.^{37,204}

Alternative splicing can lead to considerable modifications in receptor structure. Variations may include the differential inclusion or exclusion of extracellular domains, segments of the 7TMD or ICT.^{37,204,212} Such differences can influence key aspects of receptor function, including ligand binding affinity, receptor activation, and the modulation of downstream signaling pathways (Fig. 6).^{212–215} Experimental studies have verified the existence of multiple aGPCR protein isoforms, exhibiting unique signaling properties and protein interaction profiles.^{209,211–216} A well established example of the latter is E5 and its ligand CD55 in the immune system. The E5 ENT exists in 3 different layouts containing between 3 and 5 EGF-like repeats, each of which is characterized by a different binding affinity to CD55 (Fig. 3C).^{28,203,217} Furthermore, a prominent protein variant of L3 that excludes an element with inhibitory influence on transsynaptic interactions diminished Cav1.4 calcium channel activity, profoundly disrupted synaptic release by cone photoreceptor cells, and resulted in synaptic transmission deficits.²¹⁸ The L ortholog in *Drosophila*, Cirl, is alternatively spliced, giving rise to structurally disparate protein variants that act in concert to control mechanosensitive bandwidth in peripheral neurons.²¹¹ In *Caenorhabditis elegans*, variants comprising only the ENT of L/LAT-1 and therefore lacking a functional 7TMD are present and could mediate 7TMD-independent function of the protein in the reproductive system in a non-cell autonomous manner (Fig. 6C).²¹⁹ G1 has multiple variants, and

experiments with transgenic mice showed that the S4 variant is dispensable for cortical development and central nervous system (CNS) myelination but is essential for microglia-mediated synaptic pruning.²²⁰ Use of alternative promoters is another way to generate protein diversity and differential regulation. For example, the B1 gene has an alternative promoter in the distal portion of intron 17 that drives the synthesis of shorter B1 isoforms lacking the ENT and resembling the ICT obtained after autoproteolytic cleavage at the GPS but with variable N-termini that can include new AAs.²⁰⁵ These findings highlight the functional heterogeneity within the aGPCR class and illustrate how structural differences arising from alternative splicing can determine specific cellular outcomes.

The impact of natural, disease-causing mutations further emphasizes the importance of alternative splicing. Mutations located in exons common to all splice variants generally lead to a broad loss of receptor function, whereas mutations confined to alternatively spliced regions may selectively impair individual isoforms.³⁷ One such example is provided in the C-terminus of C1, which varies in length and sequence. Here, a P²⁹⁸³A mutation leads to faulty protein trafficking and is associated with neural tube defects.²²¹ However, P²⁹⁸³A is located in the variable C-terminus of C1 and warrants thorough investigation of its pathogenicity. Such a differential effect may account for tissue-specific disease manifestations and underscores the necessity of considering the splicing landscape when investigating the molecular basis of aGPCR-related disorders. The presence of multiple splice variants also carries significant experimental implications. When

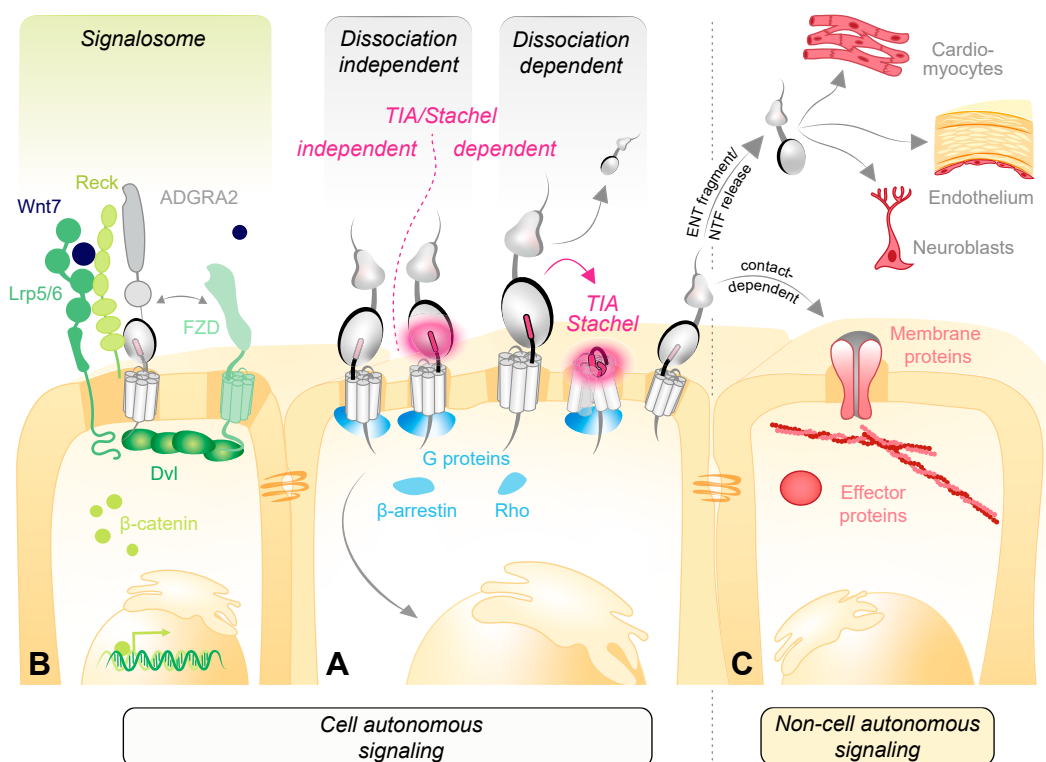


Fig. 6. Activation and signaling modes of aGPCRs. (A) Central to the activation of many aGPCRs is the TIA/Stachel (in pink), but it is not necessarily a prerequisite for triggering aGPCR activity. Both TIA-dependent and TIA-independent activation modes have been reported. Ligand binding and/or mechanical force application can induce TIA-dependent aGPCR signaling in the intact NTF-CTF receptor complex (dissociation-independent TIA-dependent activation). Alternatively, the bipartite NTF-CTF complex can dissociate and trigger TIA-dependent metabotropic activity (dissociation-dependent TIA-dependent activation). Both scenarios can induce cell autonomous signaling in the aGPCR-expressing cell. (B) Some receptors such as A2 function as part of a signalosome complex, where they not necessarily fulfil a metabotropic function but may be required for other aspects, for example, for ligand recognition. (C) aGPCRs can also relay non-cell autonomous signals via direct membrane-anchored aGPCR-ligand contact between neighboring cells or by shedding ENT fragments, including the NTF that affect the activity of distant cells. See sections X and XI.

generating transgenic animal models or developing antibodies, it is crucial to consider the full spectrum of aGPCR variants to avoid misinterpretation of experimental results. Furthermore, specifying the exact transcript variant used in functional or structural analyses is essential for ensuring reproducibility and for accurately correlating observed phenotypes with specific protein isoforms.

In summary, alternative promoter usage and alternative splicing are fundamental mechanisms that contribute to the structural and functional diversity of aGPCRs, thereby influencing receptor activity in both physiological regulation and pathology.

Critical synopsis and outlook: Motivated by the complex genomic architecture of many aGPCR loci, analyses of their splicing repertoires have begun to reveal a fascinating versatility in their gene products. This diversity ranges from subtle structural variations—some with critical consequences for receptor signaling—to major alterations that generate products no longer conforming to a canonical GPCR architecture. Thus far, only a few studies have traced individual splice forms through to their protein products and examined their occurrence and physiological functions in animal models; however, these have already uncovered intriguing roles in aGPCR activity. Many more such in-depth structure-function analyses will be required to understand how a cell chooses to express a particular splice form or a subset of splice forms of an aGPCR gene, and to what end.

VII. Subcellular trafficking, localization, and cellular functions of adhesion G protein-coupled receptors

Adhesion GPCRs mediate cell-cell or cell-matrix interactions, thus requiring proper trafficking to the plasma membrane.^{114,210,222,223} Anterograde trafficking guiding aGPCRs to the plasma membrane follows the ER-Golgi route, with the ENT acquiring N-glycosylation and mucin-type O-glycans.^{224–227} Experiments with L1, E2, and D1 have shown that the GAIN domain undergoes autoprolysis in the ER.^{26,28,29,46,184,224,226}

Our understanding of molecular cues directing aGPCR intracellular trafficking has largely been provided by mutational analyses. Mutagenesis of G1 with disease-relevant point mutations, including in the GAIN domain, unveiled disruption of its anterograde transport and accumulation in the ER.^{200,201,228,229} However, mutations affecting self-cleavage within or in the immediate vicinity of the GPS in E2, E5, and D1 did not alter the receptors' principal ability to be trafficked to the plasma membrane but rather the extent of protein exiting the ER.^{30,184,226,230} In addition, also uncleaved subpopulations of cleavage-competent receptors were observed to be trapped in the ER, potentially due to their incomplete or improper GAIN domain folding.^{184,226} These observations suggest that correct protein folding, but not GPS cleavage, is necessary for anterograde trafficking of aGPCR to the plasma membrane. GPS cleavage may act as a folding indicator before ER exit, but is not absolutely required for it. However, the importance of autolytic cleavage for these phenomena may vary among aGPCRs.^{25,46,184,231}

N-glycosylation is an important determinant of aGPCR self-cleavage, maturation, and trafficking.^{184–186} Mutating N-glycosylation sites in the E2 NTF produced variable effects on plasma membrane localization of the receptor,²²⁷ whereas pharmacologic inhibition of glycosylation or glycosylation-incompetent mutants impaired autoprolysis of E2¹⁸⁴ or E5.¹⁸⁵ Furthermore, N-glycosylation within the G6 NTF was shown to affect ER exit, whereas GPS cleavage was dispensable for membrane trafficking.¹⁸⁶

Retrograde trafficking of aGPCRs from the plasma membrane can occur spontaneously or upon ligand binding, as exemplified by L1, whose NTF and CTF undergo internalization into distinct endocytic organelles,^{141,224} some identified as early endosomes.²³² Studies with G2 suggest that arrestin-dependent endocytosis of its

CTF is prominent upon dissociation from the NTF.²³³ In contrast, A3 undergoes endocytosis via an arrestin-independent, clathrin-mediated mechanism.²³⁴

V1, the largest aGPCR, is an interesting example of the wide variety of cellular functions mediated by a single receptor. V1 is found in the microvilli-like stereocilia of the mechanosensory hair cells in the inner ear and at the cilium of the photoreceptor cells of the retina and forms adhesion complexes with other molecules associated with Usher syndrome.²³⁵ These depend on the formation of fibrous links between neighboring membranes by its exceptionally long ENT. V1 is targeted to the base of primary cilia by its interaction with a cytoplasmic chaperonin complex consisting of T-complex protein 1 ring complex/chaperonin-containing T-complex protein 1 chaperonins and the Bardet-Biedl syndrome chaperonin-like proteins.^{236,237} V1 was also described as a metabotropic mechanoreceptor in focal adhesions controlling cell shape and motility.^{238,239} Furthermore, V1 is a component of specialized mitochondria-associated ER membranes, where it is involved in Ca²⁺ release from the ER and its uptake into mitochondria, thus regulating cellular Ca²⁺ homeostasis.²⁴⁰ Finally, V1 can inhibit the autophagy process at different steps.²⁴¹

Critical synopsis and outlook: In recent years, several connections have emerged between the post-translational processing of aGPCRs and their intracellular localization, helping us to bridge gaps in our understanding of aGPCR self-cleavage, glycosylation, and subcellular trafficking. For a few receptors, a basic understanding of their distribution within specific cell types has begun to take shape. However, it remains striking that for many aGPCRs, their proposed roles in sensing adhesive or mechanical cues are not yet supported by direct evidence of their localization to the subcellular sites where such cues are encountered. This includes a broader lack of studies addressing the colocalization of aGPCRs with their cognate ligands. A coordinated effort will be needed to address this substantial deficit in our understanding of aGPCR biology. Emerging technologies—such as advanced super-resolution microscopy, next-generation protein-labeling approaches including genetic code expansion and click chemistry, and the continuous development of highly specific binders (antibodies, nanobodies, and monobodies)—promise to accelerate this progress. Together, these tools will be essential for determining the precise localization of aGPCRs at their native expression sites within cells.

VIII. Anatomical and cellular distribution of human adhesion G protein-coupled receptor transcripts

Mammalian genomes contain a collective of 33 aGPCR loci, but the count in individual species varies (Fig. 7).^{1,15,242,243} For example, as the mouse genome encodes 31 aGPCRs, as orthologs of E2 and E3 are lacking,^{244–246} and because D2 is considered a pseudogene,¹⁵ only 30 aGPCR genes are likely to produce functional receptor proteins in the mouse. Of the 33 human aGPCR loci, E4 and F2 are currently annotated as pseudogenes. Although some studies reported that these loci generate transcripts that encode truncated proteins²⁰⁷ or are transcriptionally inactive (Fig. 5), respectively, other studies detected the expression of E4 and F2 transcripts.³⁷ Until it is conclusively demonstrated that these transcripts fail to produce functional proteins and that the loss of E4 or F2 has no phenotypic consequences, their gene status remains unresolved.

Figure 5 summarizes single-cell RNA sequencing data across 31 human tissues and bulk RNA sequencing of blood samples for all aGPCRs. It is unlikely that any of the approximately 200 cell types in the human body completely lack aGPCR expression. In Fig. 5, the complex data are visually simplified by grouping cells with similar or overlapping functions, even if they originate from different

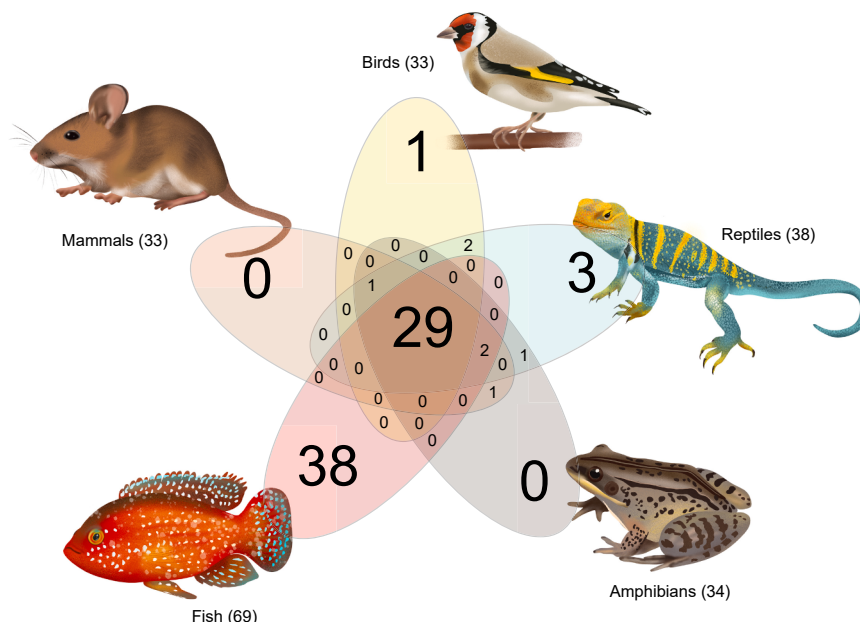


Fig. 7. The number of shared and private aGPCRs in vertebrate genomes. The dataset of human aGPCR genes (including the pseudogene *E4*) was used to extract the orthologous aGPCRs from all vertebrate classes using the webtool OrthoDB v11.²⁴³ In total, 87.9% of human aGPCRs are shared within vertebrates as shown in the Venn diagram. The high number of fish aGPCR is mainly due to genome duplication in some ray-finned fish (*Actinopterygii*). Of note, the number of private fish, amphibian, reptile, and bird aGPCRs is biased by the fact that only human aGPCRs were used to extract the orthologous sequences. Animal icons are examples. See section III.A.

organs. For example, serous secretory epithelial cells are found in the exocrine pancreas, as well as in salivary and mammary glands. These cells may not share the same embryonic origin. Interestingly, the presence of an aGPCR in a specific cell layer of 1 organ often corresponds to its presence in the same cell layer of another organ. For instance, *F4* is found in the epidermis, the squamous (cornified) epithelium of the skin,²⁴⁷ and is likely also present in organs or cavities lined by squamous (noncornified) epithelium.

Some aGPCR transcripts are omnipresent in various functionally distinct cell types. The most prevalent examples are *E5* and *G1*. *E5* is not only predominantly expressed in immune cells but also at moderate levels in smooth muscle,²⁴⁸ skeletal muscle,²⁴⁹ and lung epithelial cells. The presence of *G1*, first shown in circulating natural killer (NK)²⁵⁰ and cytotoxic T cells,²⁵¹ has been confirmed for many (secreting) epithelial cells, as well as microglia and astrocytes.²⁵²

On the other hand, there are more selective aGPCRs expressed in only a few cell types. This applies to *E1–E3*, *G3*, and *G5*, all expressed by immune cells.²⁵³ Furthermore, *D2* and *F3* are restricted to spermatids and spermatids/glia cells, respectively, whereas *G4* is a specific marker of intestinal enteroendocrine/enterochromaffin and Paneth cells. No transcripts encoding *F2*, which shares notable sequence homology with *F4*, were found in any tissue in the current analysis.

Although the cellular expression patterns of aGPCRs are becoming increasingly elucidated, there are cell types, such as osteocytes in bone and chondrocytes in cartilage, that are difficult to isolate for RNA sequencing, leaving knowledge lagging behind.²⁵⁴ Moreover, most of these transcriptomic data still require validation at the protein level. One reason for the gaps in our knowledge about protein expression is the lack of thoroughly evaluated antibodies for most aGPCRs. Exceptions are antibodies targeting members of the E, G, and L subfamilies. Generating a comprehensive set of tools for detecting aGPCRs at the protein level would benefit from a community effort, which includes rigorous quality controls such as cells expressing ectopically

tagged aGPCRs and CRISPR-generated aGPCR-deficient cell lines.^{252,255} Another reason is the structural complexity of aGPCRs due to extensive alternative transcription,³⁷ splicing,²⁰⁴ and posttranslational modification. These processes result in cell type- and context-specific expression of isoforms (eg, *E2* and *E5*),²⁵⁶ protein truncation (eg, by proteolytic cleavage within or outside the GPS),¹⁷⁸ and glycosylation (eg, *E5*).^{248,257}

Critical synopsis and outlook: Modern single-cell sequencing technologies have enormously widened the grasp of cellular expression patterns for aGPCRs. However, as with the demanding transition from splice- to isoform-level repertoires, single-cell protein expression studies that extend transcriptional information to the translational landscape are still lagging behind. Such analyses are urgently needed to establish where—and ideally at isoform-specific resolution—individual aGPCRs execute their functions.

IX. Interactions

A. Ligands (extracellular binding partners)

As bona fide adhesion molecules, aGPCRs participate in both heterophilic and homophilic protein-protein interactions (PPIs) that stabilize cell-cell or cell-matrix contacts while also allosterically regulating receptor signaling. Interactions with extracellular ligands are mediated by subfamily-specific aGPCR domains and the GAIN domain located in the ENT (Table 1, Fig. 3). Efforts to identify extracellular ligands have been carried out in the cellular and tissue context in which individual aGPCRs are expressed. These efforts aim to shed light on a plethora of physiological processes involving a wide range of receptor-ligand pairs. Early work on the immunological response led to *E5* being among the first orphanized aGPCR.⁹⁶ Meanwhile, the neurotropism of an exogenous toxin would lead to its pairing with *L1*.^{29,258} Subsequent studies on tissue development revealed that, thus far, only members of subfamilies C^{79,259} and V^{260,261} engage homophilically as adhesive aGPCR pairs.

These observations highlight the potential of aGPCRs to participate in diverse types of ligand interactions.^{98,139,262}

The molecular basis for this ligand diversity resides in the presence of distinct domains, many with adhesive functions, organized into separate modules in different aGPCR subfamilies (Figs. 1 and 3). For example, G subfamily members interact with cell surface antigens, phospholipids, extracellular matrix (ECM) molecules, steroid hormones, or small molecule ligands through structurally distinct N-terminal adhesion modules (Fig. 3D, E, G) or within their transmembrane domains.^{114,115,117–120,122,125,128,138,263} Interaction patterns are prone to further diversification as adhesion modules can accommodate many ligands at once,²¹⁰ be modified by alternative splicing to regulate ligand binding,^{114,214} or stabilize interactions occurring in *trans* (across cells) (Fig. 3A–D) as well as in *cis* (within the same cell) configurations (Fig. 3).^{141,142,264}

Transcending their mere adhesion role, a growing number of aGPCRs is shown to utilize their ligand interactions to initiate signaling through both G protein-coupled mechanisms^{86,94,108,213,265} and G protein-independent pathways.⁵³ These advances have facilitated the identification of ligands with both positive and negative allosteric effects on aGPCR signaling.^{108,111}

Emerging from these studies is a pattern of wide physiological relevance, wherein a given aGPCR can engage with distinct cellular contexts to regulate cell-specific functions (Fig. 5). For example, F5 binding with its ligand sFNDC4 in adipose tissue contributes to glucose uptake,¹¹³ whereas in the lung, its interaction with the Sp-D ligand regulates surfactant homeostasis.^{112,266,267} However, more than 30% of vertebrate aGPCRs still lack assigned ligands including members of the V subfamily, whose ligand-pairing remains elusive despite or because it harbors the largest ENT among all aGPCRs.²³⁸ Future efforts focusing on ligand discovery are likely to enhance our understanding of aGPCR functions.

B. Intracellular binding partners (except G proteins, arrestins, and Rac/Ras/Rho GTPases)

Many aGPCRs bind to postsynaptic density protein 95/disc large tumor suppressor/zona occludens 1 (PDZ) scaffold proteins via their cytoplasmic C-termini. Notably, nearly half of the 33 mammalian aGPCRs possess a PBM—typically the last C-terminal 4–5 AAs of the C-terminus—that can specifically dock into the binding pocket of target PDZ domains.²⁶⁸ These PPIs can influence receptor signaling, link receptors to the cytoskeleton, and/or influence the subcellular localization of both the receptors and their PDZ partners (Fig. 6A). For example, mechanical force-induced phosphorylation of E5 in its PBM alters the intracellular binding of E5 to the F-actin cytoskeleton.¹⁰⁷

Several aGPCR interactions with PDZ proteins have been reported. For example, L and B receptors are targeted to the postsynaptic membrane of neurons by binding to PDZ domains of the Shank (SH3 and multiple ankyrin repeat domains) and membrane-associated guanylate kinase proteins.^{143,269,270} In sensory cells, V1 is integrated into adhesion complexes by binding to the PDZ proteins harmonin, whirlin, and PDZD7, as well as to other proteins related to the Usher syndrome.^{157,158,236,268} In non-neuronal cells, the membrane-associated guanylate kinase protein DLG1 interacts with A2, A3, and E5.^{63,107,271} A2, A3, and C1 interact with the PDZ protein Dishevelled to modulate WNT signaling (Fig. 6B).^{54,272,273} A2 was also found to interact with MAGI3 and DLG4237.

Regarding non-PDZ-mediated PPIs, E5 binds to β -catenin independently of the WNT pathway.²⁷⁴ B1, B3, and A2 interact with the ELMO/DOCK180 complex regulating the F-actin cytoskeleton via RAC.^{67,275–278} Additionally, the tetraspanin CD81 binds to G1, inhibiting NK cell activation.²⁷⁹

Systematic affinity proteomic screens have validated known PPIs and have identified numerous novel putative interacting partners for A1–3, B1–3, D1, E5, L2, and V1.^{24,262,280} These PPIs were associated with synapses, focal adhesions,²³⁸ mitochondria, the ER, ER-plasma membrane bridges,²⁸⁰ mitochondria-associated ER membranes,²⁴⁰ autophagosomes,²⁴¹ the γ -secretase complex, nuclear-cytoplasmic shuttling, and primary cilia. At primary cilia, V1 was found to bind to CCT molecules of the TRiC-chaperonin complex and chaperonin-like Bardet-Biedl syndrome proteins.^{236,237} V1 also binds to the Sigma-1 receptor and ACSL4 in mitochondria-associated ER membranes and controls Ca^{2+} flux from the ER,²⁴⁰ whereas suppression of D1 signaling by ESYT1, a Ca^{2+} -dependent ER-plasma membrane molecular bridge, is abrogated by Ca^{2+} elevation.²⁸⁰

Critical synopsis and outlook: Recent work has uncovered a strikingly diverse interaction landscape for aGPCRs, spanning extracellular ligands and intracellular binding partners. Extracellularly, aGPCRs engage heterophilic and homophilic partners through subfamily-specific adhesion modules and the GAIN domain, enabling both adhesive functions and allosteric regulation of signaling. The breadth of identified ligands—from ECM proteins and cell-surface antigens to steroid hormones and small molecules—highlights the modularity and contextual adaptability of their ENT architecture. However, more than one-third of vertebrate aGPCRs remain orphan receptors, illustrating persistent gaps in ligand discovery and tissue-specific mapping. Intracellularly, many aGPCRs harbor PBMs that link them to synaptic scaffolds, cytoskeletal networks, and polarity complexes, whereas additional non-PDZ interactions connect them to pathways controlling actin remodeling, organellar crosstalk, autophagy, and Ca^{2+} flux. Proteomic screens have further expanded this repertoire, revealing associations with mitochondria, ER-plasma membrane bridges, focal adhesions, and primary cilia. Looking ahead, a central challenge will be to mechanistically integrate these diverse interactions into unified models of aGPCR function. Key priorities include systematic ligand discovery, structural elucidation of receptor-partner complexes, and resolving how context-dependent extracellular and intracellular interactions converge to shape signaling bias. Such efforts will be essential for unlocking the pharmacological potential of this receptor family.

X. Receptor activation modes

A. TIA/Stachel-dependent signaling: Dissociation model

Autoproteolytic cleavage of aGPCRs, first observed for E5²⁸ and L1,²⁹ results in the presentation of stable NTF-CTF receptor complexes at the cell surface and is essential for the subsequent dissociation capacity of receptor fragments (Fig. 6).^{26,30} Self-cleavage is essential for the function of many aGPCRs. This is exemplified, for example, by a mouse strain carrying a cleavage-deficient F5 point mutant knock-in as it displayed the same phenotype of pulmonary surfactant oversecretion as F5 knockout (KO) animals.²⁸¹ Engineered NTF deletions of G1 and B2 (ie, CTF-only) had elevated signaling.^{73,282,283} Numerous studies reporting enhanced constitutive activity of expressed CTF-only receptors support these findings.^{32,33,73,282–284} The observation of receptor NTF-CTF complex dissociation via NTF release sensors (NRSs) of endogenously expressed aGPCRs in *Drosophila* demonstrated NTF-CTF separation in vivo.¹⁵³ Recovery of isolated aGPCR NTF from tissues and cells further corroborated NTF-CTF complex dissociation models of aGPCRs.^{285,286} Additionally, chaotropic salt was used to dissociate NTFs from CTFs in overexpressed aGPCR membrane preparations, leading to robust receptor and G protein activation.^{33,287}

These observations, along with structural insights revealing the autoproteolytic mechanism of the GAIN domain,²⁵ have led multiple groups to propose a model for the enhanced activity of isolated

aGPCR-CTFs. In this model, the residual ENT of the CTF is masked by NTF structural elements in intact NTF-CTF complexes; upon fragment dissociation, the CTF N-terminus is decrypted and binds intramolecularly to an orthosteric site within the CTF, serving as a TIA (Figs. 4B and 6A). A series of complementary studies with G1, G2, G5, G6, D1, F1, and L3 support this TIA hypothesis.^{33,176,216,287–289} Furthermore, multiple structural analyses have demonstrated the commonality of TIA binding to aGPCR/G protein complexes^{36,175} and are described in detail in section IV.

Acute activation of aGPCRs by exogenous proteases at engineered cleavage sites positioned N-terminal to the TIA of L3²⁹⁰ and D1²²⁶ helped confirm the model. A follow-up study found that TIA-mediated signaling of L3 required NTF dissociation and that ~5% of the receptor population spontaneously sheds its NTF, potentially accounting for the majority of basal activity (Fig. 6A).¹⁸⁸ This parallels a study in which D1 was activated by an NTF-specific antibody in a cleavage-dependent manner; presumably, the antibody promoted partial NTF dissociation.²⁹¹ Modes of TIA-dependent and independent aGPCR activation mechanisms have been reviewed extensively (Fig. 6A).^{292,293} A recent profiling study of TIA-dependent signaling and trafficking of human aGPCRs supported the TIA activation model for most receptors, including those above.²⁸⁴ However, despite strong TIA sequence conservation across the entire receptor panel, not all aGPCRs exhibited TIA-dependent signaling (Fig. 6A), which correlated with AlphaFold predictions identifying receptors unlikely to exhibit TIA-binding to the CTF.²⁸⁴

B. TIA/Stachel-dependent signaling: Nondissociation model

In addition to the dissociation-dependent activation of aGPCRs, findings conflicting with this activation scenario have also been reported. Several *in vitro* and *in vivo* studies have indicated that receptor self-cleavage is not essential for signaling or cell autonomous functions of certain aGPCRs supporting a model in which NTF release is not required to induce aGPCR activation via the TIA (Fig. 6A). However, not all reports dissected basal receptor activities from TIA-mediated stimulation.

For example, a study in *C. elegans* indicated that a cleavage-deficient mutant of LAT-1/L can rescue phenotypic defects similar to the cleavable receptor.²⁹⁴ However, its metabotropic signaling activity was not examined at the time, and since the TIA sequence had not yet been described, its necessity for receptor function was not assessed. Its metabotropic signaling activity was discovered thereafter, and its TIA sequence identified.²⁹⁵ Similarly, basal activities of cleavage-deficient mutants of D1,²⁹⁶ G1,²⁹⁷ and G2²⁹⁸ were not significantly affected in all examined pathways. However, a contribution of the TIA to these signals was not directly tested. Of note, when dissecting the contribution of self-cleavage from agonism, it is important to consider that the most C-terminal AA of the HL/T cleavage triad overlaps with the N-terminus of the TIA. A study in *Drosophila melanogaster* actively addressed this by creating H>A (−2) and T>A (+1) alleles of the L homolog Cir1, showing that disruption of the internal agonist (T>A) failed to rescue the receptor function, whereas the lack of cleavage showed wildtype results.¹⁹⁵ Additional support for cleavage-independent and thus nondissociative aGPCR activation via the TIA sequence comes from uncleavable G5 and D1 receptors, which can be activated by mechanical forces in an TIA-dependent manner.^{172,216} However, conflicting reports exist for both examples,^{287,291} and studies frequently differ in their observations regarding self-cleavability of aGPCRs.^{216,291,299}

C. TIA/Stachel-independent signaling

Although the TIA is clearly important for the activation of signaling by several aGPCRs, it is not universally important (Fig. 6A). For example, deletion or mutation of the TIA has little impact on G protein-mediated signaling by B1,²⁹⁷ C1, or C3,³⁰⁰ whereas parallel studies revealed signaling by G1²⁹⁷ and C2³⁰⁰ to be heavily TIA-dependent. Similarly, mutation of the TIA was found to have no effect on stimulation of full-length G1 by an activating antibody,³⁰¹ although TIA exposure is essential for signaling by the isolated G1 CTF region.^{33,297} These observations demonstrate that the importance of the TIA for signaling varies by receptor as well as by the mode of activation.

Consistent with these findings, a recent comprehensive analysis of G protein-mediated signaling by the CTF regions of all human aGPCRs revealed TIA-dependent signaling in approximately half the receptors.²⁸⁴ In contrast, the signaling activities of the other aGPCRs examined in this study appeared to be TIA-independent. Intriguingly, AlphaFold models of the isolated CTF correlated strongly with the TIA dependence of signaling for each receptor, with intramolecularly bound TIA sequences predictive of TIA-dependent signaling.²⁸⁴

Two distinct views have emerged regarding TIA-independent aGPCR signaling. First, for some aGPCRs, there may be additional points of contact between the NTF and CTF beyond those by which the NTF sequesters the TIA. These interactions may enable the NTF to influence CTF conformation, consistent with recent cryo-EM studies on L3 showing that the GAIN domain exhibits conformational coupling with the 7TMD region.⁵⁰ Second, TIA-independent signaling could be indicative of tonic signaling capabilities by certain 7TMD, which could feasibly underlie long-lasting actions of particular aGPCRs, such as control of planar cell polarity (PCP) by C1-3^{302,303} or conventional dendritic cell type 2 positioning in the spleen by E5.⁹⁴ In this model, an important role of the NTF may be to guide the subcellular targeting of the CTF to ensure that TIA-independent signaling occurs in the right location.

Critical synopsis and outlook: How aGPCRs become activated has naturally been one of the most intensely studied questions in the field. The demonstration of tethered agonism more than a decade ago catalyzed research on individual aGPCR functions across pharmacological, structural, and physiological levels. Together with the discoveries of receptor dissociation through autoprolytic processing and the mechanosensitivity of many aGPCRs, the role of the TIA in receptor signaling has remained a central focus of investigation. Despite substantial progress—supported by structural studies elucidating the conformation of the TIA bound to the 7TMD—several observations remain incompatible with the most parsimonious model of TIA-dependent activation via receptor dissociation. Chief among these is the finding that non-autoprolyzed aGPCRs can nevertheless signal in a TIA-dependent manner. In addition, convincingly, TIA-independent signaling events have been documented, raising the question of whether these distinct signaling modes can be mediated by the same receptor protein and under which conditions aGPCRs may become biased toward one mode or another. A critical and systematic dissection of these phenomena is therefore warranted to reconcile these disparate mechanistic models and define the principles that govern aGPCR activation.

XI. Signaling routes

A. Cell-autonomous signaling

1. G proteins

G proteins are the primary transducers of most GPCR-driven cellular responses (Fig. 6A). Receptors bind G proteins and

catalyze nucleotide exchange, enabling interaction with various secondary effectors to propagate intracellular responses.^{304,305}

Evidence linking aGPCRs with G protein-mediated signaling was derived from affinity chromatography and immunoprecipitation studies, which revealed interactions between G proteins and L1¹⁶¹ and G1.¹²² Subsequently, regulation of Ca²⁺ mobilization and RhoA activation, indicative of G protein signaling, were observed downstream of L1⁴⁴ and G1,³⁰⁶ respectively. Mice lacking G1 or collagen III exhibit similar cerebral cortex defects as animals with neuronal α 12/13 KOs,^{117,307–309} suggesting a link between collagen binding to G1 and G12/13 signaling. A diversity of G protein-coupling partners has since been indicated for multiple aGPCRs.^{32,33,107,130,176,209,211,216,233,270,287,290,296,310–314}

Biochemical studies showed that the TIA of aGPCR mediates receptor activation and stimulation of G protein GTP γ S binding.^{32,33} This approach helped identify many other aGPCR-G protein coupling interactions.^{171,287,290}

A large-scale profiling study used G protein conformational biosensors and signaling assays downstream of G protein activation to define the TIA-dependent coupling patterns of the human aGPCR family in a single system.²⁸⁴ This identified a preference for signaling through the α 12/13 subfamily, which activates RhoGEF to control cytoskeletal dynamics, thereby influencing cell migration, contractility, shape, and adhesion.^{315–317} All these biological activities align well with the role of aGPCRs as mechanoreceptors.

The concordance of receptor and G protein KO phenotypes,^{94,295} the stimulation of aGPCR signaling by synthetic peptide agonists,^{286,318} and the disruption of secondary messenger pathways upon receptor deletion or mutation^{134,209,211,295,319} have collectively confirmed several aGPCR-G protein signaling axes in vivo. Specific G protein signaling pathways have also been linked to various aGPCR-driven human disease states.^{320–322} However, the physiological significance of other biochemically identified aGPCR-G PPIs remains to be investigated.

2. Arrestins

Arrestins are cytosolic proteins that facilitate the desensitization and internalization of activated and phosphorylated GPCRs. Receptor phosphorylation by GRKs (G protein receptor kinases) (Fig. 6A) creates a phosphorylation pattern of serine or threonine residues, which directs arrestin interactions and function. In addition to turning off G protein-mediated signaling, recruitment of arrestins to GPCRs can result in the initiation of signaling cascades by scaffolding and activating effector proteins like ERK1/2 or JNK3.^{323,324}

Regarding arrestin interactions with aGPCRs, the CTF of G1,^{283,297} B1,^{270,297} B2,³²⁰ and G2²³³ have been shown to robustly coimmunoprecipitate with arrestins. In the case of G2, arrestin binding can facilitate complex formation with cystic fibrosis transmembrane conductance regulator (CFTR).³¹⁴ In bioluminescence energy transfer (BRET)-based studies, both F5³¹⁸ and L3²⁹⁰ have shown to recruit arrestins in an activity-dependent manner.

Recently, comprehensive BRET assays were performed with all human aGPCR CTF constructs to determine potential arrestin interactions.²⁸⁴ In these studies, TIA/*Stachel*-dependent recruitment of arrestins was observed for E1, E3, F1, F4, and G7. Similarly, recent screening using a cumate-inducible Tango-Trio assay revealed arrestin binding to A1, A3, F1, G1, G2, and G5.³²⁵ Further work in this area is likely to reveal many more examples of aGPCR regulation and signaling mediated by arrestin recruitment.

3. Signaling pathways independent of G proteins and arrestins

Beyond their best-characterized G protein and arrestin pathways, aGPCRs signal through noncanonical mechanisms that

utilize intracellular scaffolds and ectodomain-assembled receptor complexes (Fig. 6A). For example, subfamily B members control Rho-GTPase signaling and cytoskeletal remodeling by interacting with Rho-GTPase regulatory proteins (GEFs/activators and GAPs/inhibitors) via their large ICTs. B1 and B3 are associated with the ELMO/Dock180 Rac1-GEF complex to drive Rac1-dependent phagocytosis, myoblast fusion, and neuronal morphogenesis,^{67,69,277,278,326} although the expression of B1 in macrophages remains debated.²⁵⁵ In neurons, B1 recruits the Par3/Tiam1 Rac1-GEF complex to synapses to promote Rac1-dependent dendritic spine and excitatory synapse development,^{66,222} and later engages the Rac1-GAP/RhoA-GEF Bcr to switch signaling toward RhoA-dependent dendrite growth arrest.³²⁷ Additionally, B1 ICL1 interacts with the E3 ubiquitin ligase MDM2, preventing MDM2-mediated PSD95 and p53 degradation and impacting synaptic plasticity and medulloblastoma tumorigenesis.^{328,329} These findings highlight ICT-dependent effectors as aGPCR signal transducers beyond G proteins and arrestins.

4. Signaling with coreceptors

Adhesion GPCRs interact with various coreceptors to regulate intrinsic G protein signaling or extrinsic signaling through associated receptors (Fig. 6B). These interactions are crucial for diverse physiological processes, including vascular development, neural functions, and immune responses.

E5 was the first aGPCR shown to heterodimerize with another receptor, the lysophosphatidic acid receptor 1, leading to amplified LPA-dependent Rho and extracellular signal-regulated kinase activation.^{102,103}

A2 forms complexes with the WNT coreceptors RECK, FZD, and LRP5/6, regulating WNT7A/B-specific β -catenin signaling in brain endothelial cells, crucial for angiogenesis in the developing CNS and for blood-brain barrier integrity (Fig. 6B).^{53–57,330,331}

B1 and B3 interact with RTN4/NoGo receptors regulating neuronal development.^{62,64}

The cadherin-like C subfamily regulates epithelial PCP and synaptogenesis by forming asymmetrical cell-cell contacts.^{85,332} The C-VANGL complex on 1 cell interacts with the C-FZD complex on the adjacent cell. Notably, A and C subfamily members may not always signal through G proteins,²⁸⁴ whereas C receptors can couple to G proteins.³⁰⁰

D1 interacts with protein tyrosine kinase 7 (PTK7) on neighboring cells, which positively regulates D1 signaling and requires both NTF interactions and cleavage at the GPS.⁸⁶ These findings shed light on the role of D1 in physiological processes and pathological conditions, such as glioblastoma and other malignancies.^{88,333,334}

G1 interacts with CD81 in resting NK cells, inhibiting NK effector functions.²⁷⁹ Cross-linking of the G1 NTF by anti-G1 mAbs leads to dissociation of the G1-CD81 complex, activating NK cells. G3/GPR97 is a critical component of the PR3-CD177-G3-PAR2-CD16b complex on neutrophils, promoting enzymatic activity of membrane PR3 to cleave PAR2 thus orchestrating PAR2-induced neutrophil activation.⁴⁸ Thus, ENT-mediated aGPCR-GPCR complexes represent another signaling mechanism by which aGPCRs regulate diverse cell-type-specific functions.

In *Drosophila*, the L homolog Cirl is expressed as both a conventional 7TM receptor and a single-pass transmembrane (1TM) variant. These Cirl isoforms appear to heterodimerize (7TM–1TM) via ENT-driven interactions, forming a complex that signals through α _o proteins to enable physiological mechanosensing in sensory neurons.²¹¹ Aside from other long-known extracellular interactions,³³⁵ mammalian L1 associates with CNTN6 in cultured neurons, inhibiting proapoptotic signaling.¹⁴²

B. Non-cell autonomous signaling

Non-cell autonomy refers to the ability of a gene to influence a phenotype, behavior, or response in cells other than those expressing its gene products (Fig. 6C). An illustrative example of non-cell autonomy is the action of a hormone that is secreted by a gland cell that acts on neighboring (paracrine) or distant target cells (endocrine). Non-cell autonomous signals can also be transmitted contact-dependently (juxtacrine), where the sending cell is in direct contact with the receiving cell, for example, via interacting membrane proteins (Fig. 6C). The structure of aGPCRs lends itself to non-cell autonomous signaling as NTF or other ENT fragment shedding through mechanical forces or proteases can liberate signals from receptor molecules that impact adjacent neighboring or distant cells. In addition, the formation of aGPCR-ligand complexes between cell neighbors can underlie the non-cell autonomy of aGPCR signals (Fig. 6C).^{5,6,193} Therefore, for this form of signaling, the terms “N terminus-only,” “TSM-independent,” or “trans-signaling” are sometimes used.¹⁹⁰

For example, shed ENT fragments of E5 and the vasculostatin released from B1 ENTs impact angiogenesis.⁹⁹ Released extracellular fragments of A2⁶¹ and B1⁷⁰ fragments may control endothelial cell survival by engaging with integrins and/or CD36.³³⁶

The ENT of L4 promotes epithelial-mesenchymal transition in myofibroblast-like cells and enhances angiogenesis. It is speculated that the NTF is released upon epithelial damage in endothelial extracellular vesicles and aids endothelial sprouting.³³⁷

L3 is expressed in postsynaptic horizontal cell dendrites in the mouse retina and controls synaptic release from presynaptic cone photoreceptor cells,²⁰⁹ although it is unclear whether the NTF of L3 needs to be released for that effect or remains in the mature NTF-CTF receptor complex.

Furthermore, it has been reported that the NTF of G6 can be secreted and bind to cardiomyocytes.³¹⁹ In addition, loss of G6-NTF results in defective compact-wall myocardium in zebrafish.³³⁸ Based on these data, G6 appears to be expressed exclusively in the endocardium in the heart and to regulate cardiomyocyte behavior in a non-cell autonomous manner and is required for proper heart development.

In *Drosophila*, the aGPCR Mayo is expressed in the midgut, where it regulates the generation of enterocytes by affecting cell lineage decisions. Genetic removal of *Mayo*, however, also causes a drastic increase in cardiac pacing, a site where no Mayo expression is observed, through the dysregulation of potassium levels in the hemolymph by an unknown mechanism.³³⁹

The Toll-like receptor (TLR) Toll-8/Tollo controls the number of neurons in the cortex of *D. melanogaster* by stimulation of asymmetric neuroblast divisions. This activity is suppressed by the L homolog Cirl, which is expressed in neighboring cortex glial cells, from where it releases its NTF that acts as an inhibiting modulator of the TLR Tollo/Toll-8.¹⁵³ A similar interaction between Cirl and Toll-8 in *trans* is employed to control asymmetric myosin-II polarization at cell-cell boundaries during embryogenesis and tissue morphogenesis in the fly.¹⁵⁴ Structural, functional, and expression studies in *C. elegans* further support the interaction between subfamily L aGPCRs and TLR.³⁴⁰

Also, in *C. elegans*, it was shown that the LAT-1 ENT directly interacts with a ligand of the DSL (Delta, Serrate, and LAG-2) family, thereby modulating the Notch pathway in a non-cell autonomous fashion.¹⁵⁶ This interaction occurs on the same cell; the signal, however, is relayed to the opposing cell via the Notch receptor. It remains unclear whether the LAT-1 NTF is released in this context, as non-cell autonomy can also emerge from direct interactions of the ENT of an aGPCR with surface-mounted partners without NTF release. For instance, a membrane-bound LAT-1

NTF is sufficient to modulate fertility by controlling sperm guidance, ovulation, and germ cell apoptosis in a non-cell autonomous manner.^{219,294} The receptor further controls neuronal morphogenesis solely by its NTF.³⁴¹ Another example is the expression of B1 or B3 on glial cells or neurons, which can mediate interaction with RTN4/NoGo receptors on adjacent neurons,⁵¹ controlling neural network activity.⁶⁴

The C ortholog Flamingo is required for correct photoreceptor axon targeting in the fly's retina in a non-cell autonomous fashion,³⁴² an effect that was also observed for the nematode homolog *fmi-1* in neuronal pathfinding.³⁴³

Critical synopsis and outlook: The complex and expanding repertoire of signaling routes in which aGPCRs are embedded is undoubtedly one of the most fascinating—and most consequential—considerations for their prospects as pharmacological targets, a goal that remains unmet to date. Their potential druggability has both benefited from and been complicated by this functional versatility. Insights into the involvement of aGPCRs in multiple signaling pathways and complexes, and even their ability to act as ligands rather than solely as receptors, have broadened the landscape of potential sites for pharmacological intervention through small molecules or biologicals. At the same time, identifying modulators that selectively interfere with only one of several receptor signaling routes may prove particularly challenging.

XII. Physiology and pathophysiology

A. Organ systems

In this section, we provide a dataset on the anatomical and cellular distribution of all human aGPCR transcripts (section VIII; Fig. 5).

1. Nervous system: Glia and neurons

In vertebrate nervous system development, neural tube closure—the fusion of neural folds at the midline that gives rise to the brain, spinal cord, and neural crest cells—occurs first, followed by neuronal birth and the migration of newborn neurons. Adhesion GPCRs play essential roles in each step, and consequently, their dysfunction is associated with neurological diseases. C1 is required for neural tube closure in mice.³⁴⁴ G1 regulates the birth and placement of cortical neurons. Loss-of-function mutations in G1 elicit bilateral frontoparietal polymicrogyria, a devastating human brain malformation,^{345,346} characterized by neuronal overmigration, ectopias on the brain surface, and myelination deficits.^{345,347} G1 binds collagen III presented in the pial basement membrane¹¹⁷ to initiate the proper stop signal. Similarly, subfamily L aGPCRs also direct neuronal migration using contact repulsion through binding to teneurins and fibronectin leucine-rich transmembrane protein (Fig. 3A).²¹ Following migration, neurons extend axons and dendrites (regulated by subfamily B^{64,327} and C⁸³ members) and identify their partners in neural circuits. L2 facilitates hippocampal partner finding through spatially restricted expression and interaction with Teneurin-3, mediating axonal repulsion from incorrect targets³⁴⁸ through G protein signaling.³⁴⁹

Synaptogenesis follows brain patterning. Adhesion GPCRs of the L, B, and C subfamilies regulate dendritic spine and synapse formation throughout the CNS, including the hippocampus, cerebellum, cortex, olfactory bulb, and neuromuscular junction.^{66,76,77,85,210,223,328,350–359} Intriguingly, these receptors may contribute to a molecular code that specifies distinct synapse types, for example, L1 is implicated in inhibitory synapses, L2/3 in excitatory inputs,^{210,223,350} and B3 in the formation of climbing fiber, but not parallel fibers.^{77,353} Recently described ADGRL-

containing transsynaptic adhesion complexes regulated by alternative splicing are required for synapse assembly.^{209,210,360,361} In some cases, lipid metabolites appear to regulate synaptogenesis through F1, which promotes neurite growth and synaptogenesis by binding to its ligand N-docosahexaenylethanolamine.^{108,109}

Myelination is largely postnatal, involving oligodendrocytes (in the CNS) and Schwann cells (in the peripheral nervous system [PNS]) wrapping hydrophobic membranes around axons, enabling saltatory transmission of action potentials and providing trophic support. G1 functions cell autonomously in oligodendrocyte development and CNS myelination. Its loss-of-function yields CNS myelin deficits in zebrafish,³⁶² mice,³⁶³ and humans.^{345,364} G1 interaction with microglia-derived transglutaminase acts in this process.³⁶⁵ V1 regulates myelination by means of MAG protein stability in myelin-forming cells of the auditory pathway.³⁶⁶ In the PNS, G1 regulates myelin formation and maintenance through RhoA and the scaffold plectin.¹²³ G6 is indispensable in Schwann cell development and PNS myelination.^{367–369} Its binding to collagen IV and laminin-211 initiates a $G\alpha_s$ /cAMP signal to instruct myelin wrapping.^{132,134}

Adhesion GPCR research in glial function is nascent and an area of expected growth. Microglia regulate interneuron development,³⁷⁰ synaptic pruning,¹¹⁴ and protective response to amyloid deposition³⁷¹ through G1. Astrocytes actively regulate synaptic function by forming tripartite synapses with pre- and postsynaptic terminals. Many aGPCRs are present in astrocytes^{372,373} and could serve as receptors enabling astrocytic sentinel functions at synapses. For example, astrocytic V1 controls glutamate homeostasis,³⁷⁴ and its dysfunction may be linked to epilepsy.³⁷⁵

Collectively, these findings establish aGPCRs as essential stage-specific regulators of nervous system development, from neural tube closure through neurogenesis, migration, synaptogenesis, and myelination, whose disruption drives human neurological disease.

2. Sensory systems

Members of the aGPCR family are involved in both the development and physiology of sensory systems. Pathogenic variants of V1 are causative of defects in the auditory and visual systems that are clinically recognized as Usher syndrome type 2 (USH2C), a subtype of human Usher syndrome, the most common form of hereditary deaf-blindness.^{376,377} USH2C is related to dysfunctions in the sensory cells of the inner ear and eye, where the extraordinarily long ENT of V1 forms fiber links. V1 establishes the ankle-links between neighboring stereocilia, which are essential for the correct hair bundle development of mechanosensory hair cells,³⁷⁸ and it forms fibers that stabilize the ciliary pocket of the light-sensitive photoreceptors.²³⁵ Relatedly, the *D. melanogaster* ADGRL homolog Cirl contributes to the formation and function of photo- and mechano-sensory organs,^{195,211,379,380} and the C homolog Flamingo partakes in visual system development.^{342,381,382} Consistent with the subfamily L role in synaptogenesis,^{139,209,335} Cirl was identified as a player in the synaptic assembly of photoreceptor cells (R8 axons).³⁸⁰ Interestingly, L3 controls synaptic release from cone photoreceptors on horizontal cells in mice non-cell autonomously (Fig. 6C).²¹⁸

In the PNS, the subfamily L aGPCR Cirl is important for the physiology of mechanosensory neurons,^{195,379} providing the initial in vivo characterization of an aGPCR as metabotropic mechanosensory.³⁸³ Expressed in chordotonal organs of *D. melanogaster*, Cirl sensitizes mechanosensory neurons for the stimulation by proprioceptive, auditory, and tactile stimuli by acting upstream of mechanosensitive transient receptor potential channels (Fig. 8).³⁷⁹ Further investigations demonstrated that Cirl modulates responses to innocuous and noxious mechanical

stimuli in opposing directions. By sensitizing low-threshold mechanoreceptors and dampening high-threshold nociceptors, Cirl facilitates the separation of mechanosensory signals carrying different physiological information.¹⁹⁴ Moreover, the antinociceptive action of Cirl suggests a possible target for peripheral analgesic therapy.¹⁹⁴ Recent work showed that interaction of different Cirl isoforms enables the discrimination between distinct mechanical stimulus intensities through a $G\alpha_o$ /cAMP-dependent signaling route.²¹¹

In addition, vertebrate aGPCRs serve as critical components in mechanosensitive sensory organs, where they link mechanical force stimulation to ion channel function and intracellular signaling. Equilibrioception, the sense of balance, relies on rapid mechanoelectrical transduction in vestibular hair cells. L2, expressed at the apical surface of utricular hair cells, is required for normal vestibular function in mice.³⁸⁴ Loss of L2 impairs balance behavior and abolishes mechanoelectrical transduction currents independent of tip links. L2 conveys sensitivity to force stimuli to hair cells by enhancing the open probability of the ion channel TMC1, thereby driving glutamate release and calcium signaling.³⁸⁴ D1 serves a similar function as a key force sensor in utricular hair cells.³⁸⁵ D1 converts mechanical stimuli into altered intracellular cAMP signaling via $G\alpha_i$ signaling, which, in turn, regulates plasma membrane excitability and is coupled to CNGA3 ion channel activity in a subset of hair cells. Reconstitution experiments and structural analyses confirmed the D1-mediated mechanotransduction pathway.³⁸⁵

3. Vasculature

The formation of new blood vessels through sprouting angiogenesis is a highly coordinated and multistep collective cell migration event. aGPCRs regulate angiogenesis at various key steps. Endothelial cell-enriched G6 promotes angiogenesis in a cell autonomous manner by stimulating VEGFR2 transcription³⁸⁶ or by interacting with and enhancing LRP1 expression.³⁸⁷ The stimulation of endothelial cell proliferation or survival contributes to the angiogenic functions of G6 and A2.^{61,386,387} In contrast, promotion of endothelial cell migration via small GTPase activation (Fig. 6A), which results in the modulation of cellular adhesion, filopodia, or lamellipodia, seems to constitute a more generic proangiogenic function of aGPCRs. Promigratory aGPCRs include E5, which regulates expression of the Rho GTPase Cdc42,³⁸⁸ via its soluble NTF that acts as a chemoattractant for endothelial cells through integrin receptors.⁹⁹ Similarly, G3 and A2 activate endothelial cell migration by acting on the small GTPases Rac, RhoA, or Cdc42.^{58,276,389} Rac, in turn, upregulates A2 expression during capillary-like network formation.³⁹⁰ A link between A2 and Cdc42 has also been detected in pericytes.³⁹¹ By contrast, L4 promotes angiogenesis without affecting endothelial cell migration, instead participating in VEGF/Notch-dependent tip cell specification.^{392,393} A2, an essential receptor for brain vascularization,^{58,394,395} also acts specifically in tip cells¹⁷⁹ by regulating the WNT/ β -catenin-dependent expression of MMP25.³⁹⁶

Reflecting their pleiotropic functions in the physiological angiogenic cascade, aGPCRs also affect tumor vascularization. L4^{392,397} and A2^{398,399} are enriched in tumor endothelial cells and their genetic inactivation reduces tumor growth and vessel density. G1, E2, and E5 expression in tumor cells stimulates tumor angiogenesis by increasing intratumoral levels of key angiogenic molecules like VEGF and MMP9.^{282,400} By contrast, B1, B2, and B3 act as antiangiogenic and antitumorigenic factors, at least in part through their NTF, with the NTF of B1 termed vasculostatin (Fig. 6C).^{70,189,192,401,402}

The vascular functions of aGPCRs extend beyond the regulation of angiogenesis. F5 has been implicated in patterning

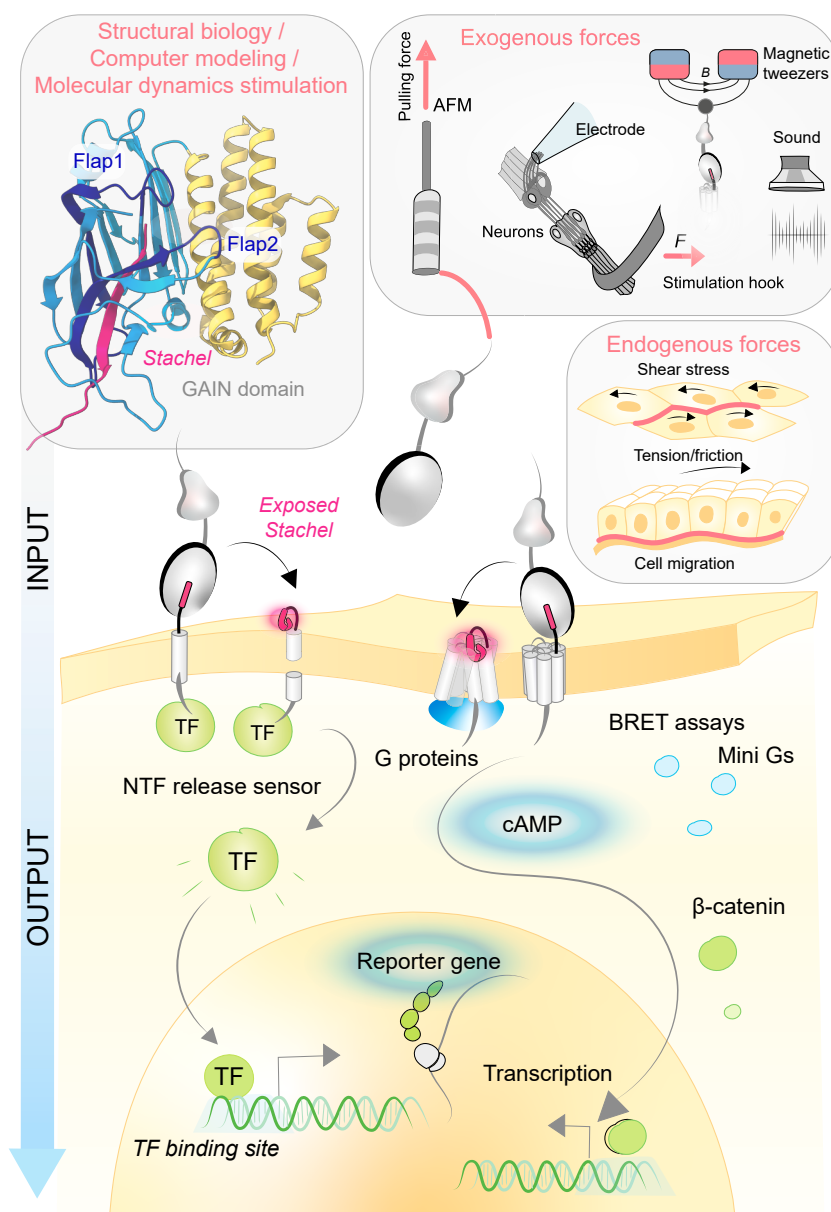


Fig. 8. Experimental technologies for aGPCR research. With the finding that aGPCRs are prone to detect adhesive ligands and mechanical stimuli, the field has begun to explore and adapt existing technologies and establish new experimental strategies to mechanically activate aGPCRs and capture the respective mechanoreponse. Some mechanical stimulation paradigms are shown including AFM, magnetic tweezers, acute application of sound stimuli, piezo element-driven pulling forces, and shear stress. Sophisticated computer-based simulations in combination with crystal structures enables directed experimental strategies to investigate structural dynamics and conformational states of specific aGPCR domains. The NTF release sensor (NRS) is a transgenic system that converts the physical NTF separation into visible reporter gene signal and can thus provide quantitative spatiotemporal information of NTF release of a given aGPCR. Technologies such as mini-Gs, cAMP, and BRET assays have been used to track and quantify metabotropic activity of mechanically-stimulated aGPCRs. See section XV.

the retinal vasculature⁴⁰³ and genetically interacts with L4 to shape the aortic arch arteries and the cardiac outflow tract, functions that may not be endothelial-autonomous.⁴⁰⁴ F5 and L2 contribute to flow and fluid shear stress mechano-transduction.^{405,406} C1 controls lymphatic endothelial cell movements during valve formation by inhibiting the maturation of adherens junctions.⁴⁰⁷ L2, A2, and G6 contribute to the control of vascular permeability,⁴⁰⁸ the latter 2 especially at the blood-brain barrier.^{387,408,409} L4 overexpression triggers endothelial-mesenchymal transition, linked to an increase in chemokine and cytokine expression,⁴¹⁰ while its silencing markedly affects endothelial metabolism.⁴¹¹

4. Lymphatic vessels

The lymphatic vasculature plays key roles in interstitial fluid balance, immune surveillance, and lipid absorption. Lymphatic endothelial cells (LEC) exhibit unique mechanosensitive properties and specialized cell-cell junctions, enabling them to adapt their permeability and regulate lymph flow.^{412–414} These features, along with their “puzzle” morphology, make LEC an attractive model for exploring the function of aGPCRs. To date, C1 and G3 have been studied in human lymphatics.^{389,407,415–419} C1 regulates lymphatic valve formation through endothelial cell rearrangements and junction maturation via VE-cadherin stabilization.⁴⁰⁷ In disease, C1 is implicated in hereditary lymphedema, a lymphatic

vascular disorder characterized by chronic swelling.^{415,416} However, the effects of C1 lymphedema-associated genetic variants on receptor function remain unclear. Similarly, G3 regulates cytoskeletal organization, cellular adhesion, junctional integrity, and migration of LECs via activity modulation of the small GTPases Cdc42 and RhoA.³⁸⁹ Other aGPCRs, including A2, L4, G1, E5, and F5, are abundantly expressed in human LEC (Fig. 5).^{389,420,421} However, their specific functions in lymphatic biology remain unexplored.

Given the critical role of aGPCRs in other conditions such as cancer metastasis and obesity, where lymphatic dysfunction is implicated,^{321,422} exploring the role of aGPCRs in lymphatics will have broad implications.

5. Skin

Human single-cell RNA sequencing (scRNA-seq) data show moderate levels of C1, C2, F4, G1, L1, L2, and V1 in basal and suprabasal keratinocytes that form the epidermis, the squamous (cornified) epithelium of the skin (Fig. 5). These transcripts are also present in squamous (uncornified) epithelial cells covering other organs, such as the oral cavity, tongue, esophagus, and vagina. Among these, only F4 has been confirmed at the protein level in humans.²⁴⁷ A few basal and all suprabasal, uncornified keratinocytes express F4. In psoriatic skin, F4 expression is diminished, suggesting its involvement in epidermal differentiation. Deletion of F4 reduced the number of keratinocyte layers in organotypic cocultures and abolished expression of keratin 1. Endogenous F4 exhibits unexpected close intracellular colocalization with keratin 1.²⁴⁷ In mice, not only F4 is present in the skin and other squamous cornified epithelia but also F2,⁴²³ suggesting specific functions in these epithelia. Notably, F2 is completely missing in humans (Fig. 5). Members of the AC subfamily are, among others, expressed in a wide range of epithelia in human and mouse, where especially C1 controls the establishment of epithelial PCP,⁴²⁴ a process that polarizes epithelial cells within the plane of a tissue. For instance, mammalian C1 is responsible for the coordinated alignment of hair follicles across the skin surface.⁷⁹

6. Heart

Adhesion GPCRs are expressed in the heart during development (F5⁴⁰⁴, G6^{319,425,426}, L2^{427,428}, and L4⁴⁰⁴) and adulthood (F5⁴⁰⁴, G6^{319,425}, L2⁴²⁸, L4⁴⁰⁴, and G1^{429,430}) in endocardial cells (G6³¹⁹, F5⁴⁰⁴, and L4⁴⁰⁴), vascular endothelial cells (F5⁴⁰⁴ and L4⁴⁰⁴), cardiomyocytes (G1^{429,430} and L2^{427,428}), and cardiac cushions (L2⁴²⁷) (Fig. 5).

KO studies have demonstrated their relevance. Analysis of global L2^{KO} mice, which are embryonic lethal, and L2 knockdown in chicken and stem cells indicates that L2 specifies cardiac lineage commitment^{431,432} and controls endothelial-to-mesenchymal transition within cardiac cushions.⁴²⁷ Postnatally induced cardiomyocyte-specific L2-KO caused dilated cardiomyopathy, serious arrhythmia, and death, which could be rescued with p38-MAPK activators.⁴³³ Similarly, global G6 deletion is embryonic lethal, causing a thinned ventricular wall, hypotrabeculation, bradycardia, arrhythmia, abnormal mitochondria, and/or circulatory failure.^{319,426,434} Recent data suggest these phenotypes may be secondary to placental defects.⁴³⁴ However, another study reported normal placenta,⁴²⁶ and data in zebrafish (no placenta) showed that G6 is required for trabeculation.^{319,338} Increased perinatal lethality, ventricular septum defects, and/or malformed large vessels⁴⁰⁴ have been reported for global double L4/F5 double KO, which alone causes no or a mild phenotype.⁴³⁵ Surprisingly, similar to G6,⁴³⁴ endothelial-specific deletion of L4/F5 did not cause a heart phenotype. These data indicate that aGPCRs in different cardiac cell types play important roles in heart

development, but more work is required to resolve current controversies.

Studies also emphasize the importance of aGPCRs in adulthood. Cardiomyocyte-specific G1-KO and global L4-KO each caused little to no cardiac phenotype in unstressed hearts but an accelerated cardiac dysfunction upon chronic pressure overload.^{430,436} Cardiomyocyte-specific G1-KO mice displayed increased LV dilation and heart weight with no increase in wall thickness, indicating impaired hypertrophy, although cardiomyocyte cross-sectional area was only slightly and not significantly decreased. Impaired hypertrophy would be in line with previous reports that G1-KO/knockdown^{437,438} or PCBP2-mediated G1-mRNA degradation⁴³⁸ attenuated induced hypertrophy in skeletal muscle or neonatal cardiomyocytes. In contrast, L4^{KO} mice displayed increased pressure overload-induced LV wall thickness, fibrosis, and cardiomyocyte cross-sectional area.⁴³⁶ Collectively, there remains uncertainty about which signaling pathways and cellular behaviors are controlled by aGPCRs in the heart.

7. Lung

Transcripts of 12 aGPCR genes (L1, L2, E5, A3, C1, C2, D1, F1, F5, G1, G6, and V1) are expressed in specialized epithelial cells throughout the respiratory tract including ciliated cells, basal respiratory cells, club cells, ionocytes, alveolar type 1 (AT1), and alveolar type 2 (AT2) cells (Fig. 5). However, a role for most of these receptors in lung function has not been reported. F5 is the most abundantly expressed aGPCR in AT1 and AT2 cells, and several research groups generated loss-of-function mice to determine its role in vivo. The most striking phenotype in F5^{KO} mice was a marked accumulation of pulmonary surfactant in the distal lung,^{112,266,267} resulting in progressive immune cell-mediated alveolar simplification.^{112,435,439–441} Mechanistically, AT2 cell-specific F5 expression regulates surfactant secretion and uptake in AT2 cells via Gα_{q/11} signaling.^{281,440} Coimmunoprecipitation studies identified surfactant protein D as a putative F5 ligand.¹¹² However, functional ligand-dependent receptor activation studies have not been reported.

Several aGPCRs have emerged as hits from unbiased screening approaches and genome-wide association studies in chronic lung diseases. For example, in idiopathic pulmonary fibrosis, E5 has been proposed as a marker for quiescent fibroblasts⁴⁴² and reduced G1 expression was observed in fibroblasts cultured from IPF patients.⁴⁴³ In chronic obstructive pulmonary disease (COPD), single nucleotide polymorphisms (SNPs) in the G6 locus have been reproducibly associated with reduced lung function, a pathological hallmark of tissue destruction in COPD.^{444–447} In addition, decreased lung G6 expression in COPD patients supports a common SNP as being causal for disease.⁴⁴⁵ In the context of idiopathic pulmonary arterial hypertension, G6 expression was increased in human airway smooth muscle cells,⁴⁴⁸ and novel SNPs suggest potential causal variants affecting G6 expression and/or function.⁴⁴⁹ Furthermore, TIA-mediated activation of G6 in human airway smooth muscle cells suggested a role in cell proliferation and airway remodeling.⁴⁴⁹ Finally, G6 knockdown in iPSC-derived human AT2 cells alters cellular responses to injury, demonstrating a role for this receptor in postinjury epithelial cell repair in the distal lung.⁴⁵⁰

In summary, future studies are necessary to elucidate the function of many aGPCR family members expressed in pulmonary epithelial and other respiratory tract cell types, including fibroblasts, endothelial cells, and smooth muscle cells.

8. Musculoskeletal system

The musculoskeletal system, comprising bones, muscles, tendons, and joints, is essential for structural support, movement, and

metabolism. Dysfunctions in this system can lead to conditions such as osteoporosis, muscle atrophy, and arthritis. aGPCRs have emerged as key regulators of musculoskeletal function, influencing development, repair, and mechanotransduction.⁴⁵¹

Genetic studies link *D1* and *G6* to human height, weight, and skeletal frame size.^{1,452,453} Notably, *G6* maintains growth plate homeostasis via the PTHrP/IHH pathway, with mutations implicated in adolescent idiopathic scoliosis.^{454–458} Similarly, *D1* acts as a membrane receptor for androgens, activating the G_{α_s} /cAMP/PKA pathway to enhance muscle strength and growth. The development of the selective androgen analogs, such as AP503, targeting *D1* without binding nuclear androgen receptors, offers a promising treatment for muscle atrophy with minimal side effects, broadening the scope of androgen therapy.⁸⁸ *D1* has recently been identified as a regulator of bone formation, acting simultaneously on osteoblasts and osteoclasts. The receptor is activated by mechanical forces and interaction with its ligand PTK7.^{254,459}

Beyond these roles, *G1* plays a significant role in protein synthesis and muscle hypertrophy. Its function is driven by PGC-1 α or mechanical loading, which activates the $G_{\alpha_{12/13}}$ pathway.⁴³⁷ Interestingly, *G1* expression is upregulated during early differentiation of human cultured myoblasts. Although *G1*-deficient myoblasts show impaired fusion in vitro, *G1*^{KO} mice exhibit no overt phenotype, suggesting that compensatory mechanisms may mitigate its loss during muscle development.⁴⁶⁰ Furthermore, *B1* and *B3* promote myoblast fusion. *B1* promotes myoblast fusion by recognizing phosphatidylserine on apoptotic cells through its thrombospondin repeats, initiating the ELMO/Dock180/Rac1 pathway.³²⁶ Similarly, *B3* interacts with ELMO to activate Rac1 (Fig. 6A), driving embryonic myoblast fusion processes.²⁷⁷

Other aGPCRs also contribute to musculoskeletal function. *E5* deletion results in abnormal sarcoplasmic reticulum structure, although skeletal muscle function remains unaffected, indicative of its impact on structure rather than function.²⁴⁹ Meanwhile, *V1* has been identified as a regulator of bone density in humans and mice, linking it to osteoporosis susceptibility.⁴⁶¹

Collectively, these findings solidify the role of aGPCRs as mechanosensors and signaling hubs in the musculoskeletal system, with significant implications for treating conditions like adolescent idiopathic scoliosis, osteoporosis, and muscle degeneration.

9. Immune system and spleen

The immune system-associated aGPCRs are primarily clustered in 2 subfamilies, E and G (Fig. 5). Notably, several E and G receptors exhibit restricted expression within specific immune cell populations, making them selective biomarkers for distinct immune cell subsets.²⁵³ For example, *E1* (F4/80) serves as a well established marker for mouse tissue macrophages, whereas *E1* was identified as a specific marker for human eosinophils.^{462–464} Individual aGPCRs are key markers of human mature polymorphonuclear granulocytes (*E3*) and pancytotoxic lymphocytes, as well as microglia (*G1*).^{251,465,466} Furthermore, aGPCRs have unique pathophysiological roles in regulating innate and adaptive immune responses, owing to their dual functions in cell adhesion and signaling.⁴⁶⁷ Thus, myeloid-restricted aGPCRs, such as *E2* and *G3*, are involved in necrotic-like cell recognition and specific activation of protease-activated receptor 2, respectively, leading to inflammatory activation of macrophages and neutrophils.^{48,91,313} *G1* is an NK-cell inhibitory receptor that suppresses cellular cytotoxicity, cytokine production, and cell migration.^{251,279,468} *E5*-deficient mice exhibited mild granulocytosis and enhanced antibacterial activity, whereas *E1* was found to promote regulatory T cell-mediated peripheral immune tolerance.^{469,470}

Compelling evidence supporting the role of aGPCRs as metabolic mechanosensors has initially emerged from studies on immune aGPCRs. The *E2*^{C492Y} missense mutation, altering the GAIN domain of the receptor (Fig. 4), results in a less stable receptor complex that readily releases its NTF upon vibratory stimulation in the presence of its ligand, triggering excessive histamine release by mast cells to cause a rare dermal allergic disorder known as vibratory urticaria.⁸⁹ Similarly, *E5* functions as a shear stress-dependent mechanosensor on leukocytes by interacting with CD55 (Fig. 3C).⁴⁷¹ Notably, *E5*-mediated mechanosensing of CD55 on red blood cells is crucial for maintaining proper compartmentalization, homeostasis, and adaptive immune functions of type 2 conventional dendritic cells and marginal zone B cells in the spleen.^{94,97} Likewise, *G1* plays a critical role in platelet shape change during hemostasis by acting as a specific collagen receptor that responds to shear forces in blood circulation.²⁸⁶

In addition, some aGPCRs are expressed in several differentiation stages of hematopoietic stem and progenitor cells, suggesting their potential involvement in normal hematopoietic development and leukemogenesis.^{472–475} Finally, immune aGPCRs, including *G1*, *E2*, and *E5*, are implicated in various (patho)physiological processes and immunological disorders, highlighting their role in immune (dys)function.^{476–479} For instance, *E2* is temporarily upregulated on neutrophils in the posttraumatic course,^{479,480} and its expression is higher on neutrophils from sepsis compared with noninfectious patients with a systemic inflammatory response syndrome.⁴⁷⁸ In conclusion, specific aGPCRs are actively involved in modulating diverse immune responses, with a crucial contribution to immune dysfunction and disorders.

10. Kidney

Numerous aGPCRs are expressed in the murine metanephric kidney in a variety of cell types (Fig. 5), including glomerular endothelial cells (*F5*⁴⁸¹, *G1*^{482,483}, *G3*⁴⁸⁴, and possibly *L4*^{404,485}), mesangial cells (*G3*⁴⁸⁴), parietal epithelial cells (*G6*⁴⁸⁶), and podocytes (*A2*⁴⁸⁷, *C1*: embryo⁴⁸⁸, and *G3*⁴⁸⁴), as well as cells of the proximal tubules (*B1*⁴⁸⁹, *C1*⁴⁸⁸, *G1*²⁵², and *G3*⁴⁸⁴), distal tubules (*B1*⁴⁸⁹ and *G1*²⁵²), collecting ducts (*C1*: embryo⁴⁸⁸, *F5*^{490,491}, *G6*^{425,486}, *G3*⁴⁸⁵, and *F1*⁴⁸⁵), and renal pelvis/urothelium (*F1*^{423,492} and *G6*^{325,486}). This expression pattern has in part also been observed in zebrafish⁴⁹³ and humans⁴⁹⁴ (*F1*⁴⁹², *G1*²⁵², and *G6*⁴⁸⁶).

Transcriptomic and proteomic data suggest another 7 aGPCRs to be expressed in the murine nephron.⁴⁹⁵ Notably, polycystin-1, the protein product of the *PKD1* gene whose mutation causes autosomal dominant polycystic kidney disease, can be regarded as an atypical aGPCR^{193,496} containing a GAIN domain and being responsive to a TIA (Figs. 4 and 6A).^{497,498} A variety of kidney diseases are associated with altered expression levels or patterns of a number of aGPCRs⁴⁹⁴ (*A2*⁴⁸⁷, *G1*⁴⁸³, *G3*⁴⁸⁴, and *G6*⁴⁹⁹). Although these descriptive data indicate that aGPCRs play an important role in kidney development and physiology, our understanding of their relevance is limited. *C1* is the best-characterized aGPCR in kidney development with *C1*^{KO} mice exhibiting uretric bud branching defects, growth retardation, dilated cortical tubules, and mitotic spindle misorientation.⁵⁰⁰ Adult global *F5*^{KO} exhibit impaired function with compromised basement membrane composition and morphological defects in the glomeruli.⁴⁸¹ Kidney-specific *F5*^{KO} have a significantly reduced urine pH, attributable to an increased V-ATPase accumulation.⁴⁹⁰ Combined *F5*;*L4*^{DKO} results in ~50% perinatal lethality. Alive-born *F5*;*L4*^{DKO} mice exhibit loss of endothelial fenestration and fusion of podocyte foot processes, resulting in proteinuria, uremia, and death at 4 weeks.⁴⁰⁴ However, endothelial-specific *F5*;*L4*^{DKO} animals display no renal defects. Also, global *F1*^{KO} does not result in overt defects.³²³ Finally, it has been shown that deletion of aGPCRs

can be protective (G3: acute kidney injury,⁴⁸⁴ hypertensive nephropathy⁵⁰¹; and G1: diabetes⁴⁸³) or detrimental (A2: diabetes⁴⁸⁷) in kidney disease.

11. Pancreas

Adhesion GPCRs are increasingly recognized as regulators of glucose metabolism, acting at multiple levels including pancreatic islets, insulin-sensitive tissues, and local inflammatory environments. In human pancreatic islets, expression of several aGPCRs, such as A2, A3, B3, C2, C3, E5, F1, F4, F5, G1, L1, L2, and L4, has been reported (Fig. 5).^{502,503} Their roles range from pancreatic development to insulin secretion. For instance, G1 enhances β -cell mitochondrial function and insulin release via collagen III-mediated ECM sensing, although its deletion does not impair glucose tolerance in mice.^{504–506} L1 and L3 exert opposing effects on insulin secretion,²¹⁵ whereas B3, via C1ql3 activation, suppresses insulin secretion by lowering cAMP levels.⁵⁰⁷

12. Metabolism, fat, and liver

Activation and signaling of aGPCRs change the physiological function of adipocytes, hepatocytes, and myocytes, thereby influencing whole-body energy homeostasis. Indeed, it has been demonstrated that more than one-third of aGPCRs are among the most abundantly expressed GPCRs in white adipose tissue.⁵⁰⁸ Several members, namely A2, A3, D1, G1, G2, G6, L2, and F5, are involved in preadipocyte differentiation into mature adipocytes.^{508–511} Besides, aGPCRs can also directly influence adipocyte function: G2 activation increases lipolysis⁵⁰⁸ and modulates insulin-stimulated glucose uptake.⁵⁰⁸ Regulation of insulin sensitivity has also been found for F5.^{113,509}

Additionally, aGPCRs can affect the thermogenic program as documented for B3⁵¹² and specifically impact adipocytes as observed for A3, which is highly expressed in human adipocytes and murine brown fat. A3 knockdown in mice reduces uncoupling protein 1 and other thermogenic markers and exacerbates obesity, whereas A3 overexpression induces beige adipocyte biogenesis and increases energy expenditure, improving metabolic homeostasis.⁵¹³ G2 expression is upregulated when brown adipose undergoes “whitening,” suggesting that it negatively regulates brown/beige fat thermogenic capacity.⁵¹⁴ In a KO mouse model, it was shown that B3 reduces thermogenesis; however, it is still uncertain if this is mediated by its adipocyte-specific function.⁵¹²

Differential expression of several aGPCRs in the liver has been reported in hepatocytes (A3, G6, G7, G8, F5, L2, and L4) and cholangiocytes (A3, E5, G1, G2, G6, F1, and L2) (Fig. 5).⁵¹⁵ However, their functions remain incompletely understood. Emerging evidence links them to liver metabolism and injury. As such, F5 affects lipid metabolism⁴⁵⁸ and ferroptosis in sepsis-induced liver injury.⁵¹⁶ Furthermore, its deletion alleviates sepsis- and acetaminophen-induced liver injury.⁵¹⁷ F1 regulates hepatic lipid metabolism,⁵¹⁸ and its absence mitigates steatosis and fibrosis in mice.⁵¹⁹ C2 affects LDL cholesterol levels⁵²⁰ and lipid accumulation via the modulation of reactive oxygen species.⁵²¹ G1 sensing of 17 α -hydroxypregnenolone protects against ferroptosis-induced liver injury.⁵²²

Taken together, these findings highlight critical roles for aGPCRs in metabolism and energy homeostasis.

13. Gastrointestinal tract

A closer examination of the human scRNA-seq data for aGPCRs (Fig. 5) reveals that several aGPCRs (A3, E5, G1, G4, G6, and G7) exhibit moderate expression across various (glandular) epithelial cell types in the gastrointestinal tract. Additionally, qRT-PCR analysis of 12 rat gastrointestinal segments identified 28 aGPCRs, some of which displayed restricted expression patterns along the

gastrointestinal tract axis, likely associated with specific gut functions.⁵²³ Similarly, an analysis of 4 mouse gastrointestinal canal subsegments detected low-abundance aGPCRs, with B1-3 localized in the muscle-myenteric nerve layer and G4 found in the duodenal, jejunal, and ileal mucosa.⁵²⁴

Several aGPCRs are specifically expressed in specialized cell types of the epithelial layer. Human E5 localizes at adherens junctions, interacting with β -catenin,²⁷⁴ although it is located intracellularly in colorectal cancer.⁵²⁵ Human G1 colocalizes with pepsinogen at the gastric gland base and may support colonic stem cell expansion.^{121,252} Mouse G2 has been reported to be selectively expressed in mature chemosensory cells,⁵²⁶ whereas human G4 is enriched in enterochromaffin and neuroendocrine carcinoma cells, serving as a potential biomarker.⁵²⁷ Furthermore, G4 pentraxin-domain facilitated receptor homodimerization has been suggested to be critical to endogenous activation, although its function remains unknown (Fig. 3D).¹⁶⁹

In gastrointestinal tract development, the aGPCR Mayo of *D. melanogaster* shows midgut hyperplasia, hyperkalemia, and tachycardia.³³⁹ In mice, overexpression of E5 causes a dose-dependent megaintestine with normal microscopic morphology, providing a model for postnatal intestinal growth.⁵²⁸ Expression of E5 and B1 in the colon was found to similarly protect mice from dextrane sulfate sodium-induced colitis, but likely via different mechanisms.⁵²⁹ G7, found predominantly in intestinal epithelial cells in mice and humans, may aid in nutrient absorption.⁵³⁰

Although the cellular distribution in the gastrointestinal tract of certain aGPCRs has been recently characterized and offers insight into their roles in (patho)physiological processes, several receptors like A3 and G6 remain largely uncharacterized, highlighting the need for a comprehensive investigation of their protein expression patterns and gastrointestinal tract function.

14. Female reproductive system

Congenital abnormalities of the female reproductive tract affect 10% of women, often with severe consequences.⁵³¹ aGPCRs are crucial in the development of these tissues, aiding in cell positioning and organization.^{532,533} They facilitate cell-ECM interactions, essential for tissue integrity and function. Additionally, aGPCRs are involved in developmental signaling pathways, including the WNT signaling pathways, which regulate tissue morphogenesis and differentiation.^{153,534–538}

The *C. elegans* L homolog LAT-1 is important for the hermaphrodite nematode ovulation, sperm guidance, and germ cell apoptosis, through a *trans*-mechanism independent of its CTF (Fig. 6C).^{156,219}

In mice, half of A3-deficient females fail to develop a vaginal opening during puberty; correspondingly, A3 is expressed in the female urogenital system, with the highest prepubertal expression and with a rapid drop after sexual maturation.⁵³² A3 deficiency impairs estradiol-dependent vaginal canalization by unbalancing apoptotic regulators, potentially driven by the PCP WNT pathway,⁵³² an established pathway for A3.^{63,262,271,273,539–542} Aligned with the idea that A subfamily members interact with the WNT pathway is the finding that reduced postpubertal A3 expression coincides with upregulated A2 expression—also active in WNT pathway signaling—in the female reproductive tract.⁵³² Curiously, also G protein-dependent signaling (Fig. 6A), although weak, was recently described for A3.⁵³⁹

Birds display high expression of G1 and its ligand, collagen III, in the Müllerian duct, which gives rise to the fallopian tubes, uterus, and upper vagina in human females, and the oviducts in the chick (Fig. 7).⁵³³ Knockdown of G1 results in truncated ducts, suggesting a central role of G1 in the developmental elongation process, potentially via PAX2 signaling.⁵³³ Intriguingly, G1 also

modulates cellular β -catenin levels and regulates the canonical WNT pathway, possibly via its ligand transglutaminase-2.⁵⁴³

G2 and G6 are both linked to uterus and placental development during pregnancy.^{434,544} G2 regulates the decidualization of endometrial stromal cells during implantation and early gestation, likely involving the PI3K/Akt/mTOR signaling pathway.⁵⁴⁵ For G6, G protein signaling by progesterone promotes breast cancer¹³⁶ and likely also female reproductive system development. Likewise, D1, expressed in the murine oviduct, regulates ductal fluid flow and embryo transit, possibly via *Plxdc2*.⁸⁷

aGPCRs involved in female reproduction have also been linked to male fertility, for example, A3,⁵⁴⁶ G1,⁵⁴⁷ and G2,⁵⁴⁸ supporting their fundamental roles in development.

15. Male reproductive system

aGPCRs involved in the male reproductive tract are A2³¹⁴ A3⁵⁴⁶ G2 is highly expressed in the male reproductive system, primarily localized in the efferent ducts and proximal epididymis.^{549,550} G2 plays a critical role in sperm maturation. G2^{KO} mice exhibit reduced sperm count or motility, and morphological abnormalities (such as head defects)⁵⁵¹ while also causing downregulation of genes related to sperm maturation in the epididymis (including cystatin, lipocalins, β -defensins, Adam28, Crisp1, and Enpp2).⁵⁴⁸ G2 couples with the anion channel CFTR in a $G\alpha_q$ -dependent manner to regulate Cl^- and pH homeostasis. The G2- $G\alpha_q$ signaling axis maintains the baseline outward rectifying current of CFTR, which is essential for fluid reabsorption and sperm maturation. G2, CFTR, β -arrestin1, and $G\alpha_q$ form a supercomplex localized to the apical membrane of nonciliated cells, acting as a regional signaling hub to regulate fluid reabsorption and ion homeostasis (Fig. 6A, B).³¹⁴

Clinical studies have identified various G2 mutations (such as *p.Glu516Ter*, *p.Leu668ArgfsTer21*, *p.Arg814Ter*, and *p.Lys818Ter*) associated with male infertility and closely linked to congenital bilateral absence of the vas deferens. These mutations result in the deletion or truncation of the 7-transmembrane domain, disrupting the coupling of G2 with downstream $G\alpha_q/G\alpha_s$ proteins and β -arrestins (Fig. 6A).^{552–554}

L2 interacts with its ligand LRG1 to ameliorate vascular and neurological abnormalities and restore diabetic erectile function.¹⁵⁰

B. Diseases

Adhesion GPCRs are recognized in numerous disease contexts by contributing to monogenic diseases and complex pathologies—including cancer, diabetes, and neurological disorders—and by targeting structures for viral components.

1. Cancer

E5 was the first aGPCR reported to be regulated during tumorigenesis.⁵⁵⁵ Over the past decades, many more aGPCRs have been implicated in cancer. Members of all 9 aGPCR subfamilies are now considered to partake in tumorigenesis and/or the tumor microenvironment, influencing cancer growth and metastasis. Somatic mutations in aGPCRs have been detected in multiple cancers, but whether they drive or accompany tumorigenesis remains unclear. Alterations in aGPCR expression and/or signaling can contribute to key oncogenic processes (cancer hallmarks), such as tumor cell growth (proliferation and survival), motility and spread (migration, invasion, and metastasis), access to vasculature (vascular cooption, angiogenesis, and vasculogenesis), tumor-promoting inflammation (immune cell recruitment), immune escape, and therapeutic resistance. Below is a nonexhaustive selection of key examples of aGPCR involvement in cancer:

a. Tumor progression and growth. Adhesion GPCRs can either suppress or promote tumor growth depending on their expression level and signaling context. Several studies have profiled the aGPCR expression in individual malignancies and assessed their prognostic impact.^{100,556–561}

For example, G1 is overexpressed in acute myeloid leukemia, colorectal, and prostate cancers and sustains *in vivo* tumor growth, invasion, and/or therapeutic resistance.⁵⁶² Conversely, the interaction of G1 with its ECM ligand, transglutaminase-2, blocks the growth and metastasis of melanoma¹⁶⁶ and exerts tumor-suppressive functions in glioma.⁵⁶³

Similarly, F1 in HER2⁺ breast cancer promotes tumorigenesis but switches to a tumor-suppressive role upon interacting with laminin-111, leading to decreased receptor signaling, tumor cell senescence, increased HER2 expression, and enhanced sensitivity to anti-HER2 therapies.¹¹¹

D1, a $G\alpha_s$ -coupled aGPCR known to be regulated by ESYT1 in a Ca^{2+} -dependent manner, is allosterically activated by its ligand PTK7 to promote glioblastoma growth and brain invasion.^{86,280,333,564,565} D1 has also been implicated in a few other malignancies, including lung and gastric adenocarcinoma, and leukemia,^{559,566–568} although its exact function in those settings has not been clearly determined.

Several members of the E subfamily, most notably E5, have also been implicated in a plethora of malignancies, where they contribute to cancer stem cell maintenance, tumor cell migration, invasion, apoptosis, proliferation, and response to therapy.^{100,569–593}

A2 was shown to regulate glioblastoma proliferation through effects on mitotic assembly and progression.⁵⁹⁴ A3 was identified as a marker of stem cells in breast tissue, which are greatly expanded upon oncogenic transformation.⁵⁹⁵

B family members are transcriptionally downregulated or frequently mutated in various cancers, including brain, breast, and lung, suggesting a tumor-suppressive role.^{402,595–598} In brain malignancies, B1 undergoes epigenetic silencing, and reactivating its expression inhibits tumor cell proliferation, angiogenesis, and tumor growth *in vivo*, further supporting its tumor-suppressive function.^{329,599}

b. Tumor cell migration/invasion and metastasis. Many aGPCRs, such as E1, E2, E5, L1, and G1, mediate ECM interactions and/or promote epithelial-to-mesenchymal transition,^{102,587,600–614} whereas L4 is associated with endothelial-to-mesenchymal transition.⁴¹⁰ By triggering changes in cell adhesion and motility, these receptors enable cancer cells to adopt invasive mesenchymal-like properties, promoting metastasis.

A2 expressed on pericyte-like cells derived from lung adenocarcinoma stem cells enables them to initiate brain metastases through *trans*-endothelial migration.⁵⁵⁶ This effect of A2 is mediated by its ability to act as a WNT coreceptor, thus promoting canonical WNT7/b-catenin signaling.^{59,261,601}

L1-3, whose expression is induced by nuclear androgen receptor signaling, promote prostate cancer growth.⁶¹⁵ A similar effect is noted for L3 in urothelial cancer.⁶¹⁶ Cancer-linked mutations affecting the L3 GAIN domain impair its adhesion functions and $G\alpha_{13}$ signaling, leading to altered cell motility and cytoskeletal organization that may contribute to tumor progression.⁶¹⁷ L3 knockdown reduces bladder cancer cell migration.⁶¹⁸

G1 localizes to the leading edge of glioblastomas, supporting cell adhesion and invasive behavior of tumor cells.⁶¹⁹ G1 also promotes hepatocellular carcinoma metastasis.^{477,617} L4 promotes migration in glioblastoma, colorectal cancer, retinoblastoma, and neuroblastoma.^{620–623}

C1 promotes migration in ovarian cancer,⁶²⁴ whereas C3 knockdown in lung adenocarcinoma⁶²⁵ and neuroendocrine prostate cancer⁶²⁶ suppresses migration.

c. Immune evasion. Several aGPCRs are expressed in immune lineages of the tumor microenvironment. Members of the E subfamily (E1, E2, E3, and E5) can modulate the immune microenvironment by influencing immune cell infiltration to the tumor site and controlling the function of tumor-associated immune cells.^{100,577,627–631}

L4 overexpression in breast cancer cells is linked to an immunosuppressive tumor environment, marked by fewer cytotoxic T cells and more M2-like macrophages.⁶³²

G1 is upregulated in exhausted, tumor-reactive T cells in cholangiocarcinoma, renal cell carcinoma, lung cancer, and the bone marrow in AML,^{633–637} suggesting a broader role in immune suppression.

B3 regulates F-actin in T cells, reducing traction force and impairing cytotoxicity in melanoma and colorectal cancer.⁶³⁸ These receptors may promote immune evasion by recruiting immune suppressor cells to the tumor or by inhibiting antitumor immune responses.

d. Angiogenesis. Some aGPCRs, including L4^{392,393,639} and G1,⁵⁶² are involved in tumor angiogenesis. By stimulating the tumor's ability to form blood vessels, aGPCRs directly contribute to cancer progression and are potential therapeutic targets.

The angiogenic actions of aGPCRs can be exploited therapeutically. For example, the use of anti-L4 antibodies or scFVs in glioblastoma xenografts normalizes tumor vessels and improves survival in comparison to untreated controls or those treated with anti-VEGF antibody (bevacizumab) alone.^{640,641} G1 can inhibit VEGF-induced angiogenesis in melanoma,²⁸² whereas B1 acts as a negative regulator of angiogenesis through N-terminal cleavage events that release vasculostatin.¹⁹² In addition, E2 and E5 may also play a role in regulating tumor angiogenesis.⁴⁰⁰ Finally, A2 expressed on tumor endothelial cells is necessary for VEGF-induced tumor angiogenesis.³⁹⁹

2. Type 2 diabetes

Adhesion GPCRs regulate systemic insulin sensitivity through actions in adipose tissue and muscle. F5 mediates insulin-sensitizing effects of the hepatokine FNDC4 in adipose tissue. Its deletion impairs adipokine release and promotes systemic insulin resistance.^{113,509} A3, activated by the flavonoid hesperetin, also contributes to improved insulin sensitivity in adipose tissue.⁵¹³ Although aGPCRs are highly expressed in myoblasts, their function in skeletal muscle insulin sensitivity remains unexplored.

Importantly, aGPCRs also influence diabetes pathophysiology through immune-metabolic crosstalk. G3 expression in adipose tissue macrophages promotes proinflammatory signaling; its deletion dampens macrophage activation and reduces obesity-induced adipose inflammation.⁶⁴² These findings collectively point to aGPCRs as context-dependent regulators of insulin secretion, sensitivity, and inflammation—key elements in diabetes development and progression.

3. Viral infection

Viruses either encode GPCRs (viral vGPCRs)^{643,644} or exploit host GPCRs⁶⁴⁵ to manipulate cellular processes and enhance their control over the host environment. In response, hosts continually adapt their GPCRs to counter these viral strategies. Consequently, it is not surprising that viruses regulate or interact with aGPCRs, given their crucial roles in cell

signaling,²⁹³ maintaining host physical barriers,^{79,387,646–648} and immune surveillance.^{167,253,467,468,649,650}

During severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, several aGPCRs are implicated. Bioinformatic analysis revealed an interaction between the SARS-CoV-2 spike subunit and L4 mRNA levels, which are consistently downregulated in infected cells.⁶⁵¹ Additionally, D1 and G6 are upregulated in SARS-CoV-2-infected epithelial cell models. Targeted downregulation of these receptors reduces the release of free virus particles.⁶⁵¹

Adhesion GPCRs also play a role in latent viral infections. G1 is upregulated in human immunodeficiency virus-positive CD4⁺ T cells⁶⁵² and in cytomegalovirus-positive CD8⁺ T cells.¹⁵⁰ Viruses also directly interact with aGPCRs, for example, binding of the mumps virus small hydrophobic protein to A3, triggering epithelial barrier dysfunction.^{653,654}

Studying interactions between viral proteins and aGPCRs is key to developing antiviral therapies and understanding viral pathogenesis. Despite being an emerging field, the few interactions discovered so far suggest that much remains to be uncovered.

4. Bacterial infections

B1 recognizes phosphatidylserine on the surface of apoptotic cells and bacteria, promoting their engulfment by macrophages and other phagocytes through the activation of downstream signaling pathways.^{67,655} B2 and B3 are implicated in modulating immune responses^{650,656,657} and cellular interactions during pathogen clearance.^{658–661} Together, these receptors contribute to efficient immune surveillance and removal of infectious agents, enhancing host defense mechanisms.

5. Neurodevelopmental, neurodegenerative, and neuropsychiatric disorders

B receptors play critical roles in brain development and synaptic architecture. B1 is essential for dendritic spine formation and excitatory synaptogenesis, and its absence in mice leads to social deficits, reduced brain weight, increased neuronal apoptosis, and heightened susceptibility to seizures; phenotypes relevant to autism spectrum disorder and epilepsy.^{299,662} Additionally, B1 interacts with autism-linked proteins such as neuroligin 1 and IRSp53, and autism spectrum disorder-relevant B1 variants have been reported in patients.⁶⁶² Decreased B1 expression is observed in the substantia nigra of Parkinson disease patients as well as the substantia nigra and striatum of Parkinson disease animal models,⁶⁶³ correlating with dopaminergic neuron loss. B2 is implicated in mood regulation and emotional behavior.⁶⁶⁴ B2^{KO} mice exhibit antidepressant-like behavior.^{663,665} Variants in B3, including polymorphism and copy number variations, are linked to schizophrenia-related disorganization,^{666,667} addiction,⁶⁶⁸ epilepsy, and bipolar disorder.⁶⁶⁹ Mice lacking full-length B3 have reduced brain and body weights, augmented energy expenditure, and deficits in social interaction.^{512,670}

Recent insights into the genetic basis of craniorachischisis, a severe neural tube defect characterized by complete failure of neural tube closure have identified several potentially pathogenic variants in components that govern PCP establishment and maintenance including C1.²²¹ Functional studies revealed that although these variants did not disrupt known PPIs, they significantly impaired proper subcellular localization caused by reduced protein expression and defective plasma membrane trafficking, mechanisms consistent with phenotypes observed in analogous mouse mutants.³⁴⁴

G1 has verified roles in spermatogonia,⁵⁴⁷ skeletal muscle^{437,547} and brain development,³⁴⁵ CNS myelination,^{362,363} and hemostasis.²⁸⁶ Mutations in G1 cause bilateral frontoparietal

polymicrogyria, a recessive cortical malformation disorder characterized by severe developmental issues, intellectual disability, and seizures.^{345,347} In adults, *G1* mRNA levels are upregulated in patients who respond to antidepressant treatment.^{671,672} Reduced *G1* expression is linked to suicide, potentially due to a *G1* splice variant affecting synaptic pruning.^{220,673}

L3 is the most studied latrophilin homolog in neuropsychiatric disorders. Variants are not only linked to childhood attention deficit hyperactivity disorder^{674,675} but also connected to autism spectrum disorder^{674–676} and substance use disorder.⁶⁷⁷ L2 variants are associated with microcephaly with severely reduced sulcation and rhombencephalosynapsis,⁶⁷⁸ and with cocaine use disorder.⁶⁷⁹ L1 haploinsufficiency has been linked to intellectual disability and developmental delay in a small cohort of 10 individuals³⁵² and to developmental and epileptic encephalopathy.⁶⁸⁰

Pathogenic variants in V1 cause human USH2C, a common form of combined deaf-blindness.⁶⁸¹ V1 mouse models suffer from progressive deafness and show increased susceptibility to audiogenic seizures.⁶⁸² Recent studies have linked heterozygous variation in V1 to various forms of epilepsy in humans.^{683,684} In the CNS, defects in V1 cause alterations in myelination³¹⁰ and dysfunctions in hippocampal astrocytes.³⁷⁴

Critical synopsis and outlook: The extensive repertoire of aGPCRs in model organisms and humans has been complemented by a tremendous increase in our understanding of the physiological functions these receptors support. A unifying theme across many recent findings is the role of aGPCRs as mechanosensors in diverse organ systems and cellular contexts. Given their unusual molecular architecture and the autolytic processing characteristic of many family members, mechanical stimuli are natural physiological inputs for aGPCR activation. Importantly, such cues appear to be essential for multiple developmental programs during and after embryogenesis. It is therefore unsurprising that germline and somatic mutations in aGPCR loci are associated with, and in some cases causal for, human developmental disorders and cancers. Future research must decipher the specific contributions of impaired aGPCR signaling to individual pathological conditions, both to understand disease mechanisms and to identify opportunities where therapeutic targeting of these receptors may benefit patients. The systematic delineation of defined signaling pathways, activating conditions, and expression patterns of individual aGPCR homologs will greatly enhance and likely accelerate this emerging translational branch of aGPCR research in the years ahead.

XIII. Adhesion G protein–coupled receptors as drug targets

Adhesion GPCRs are emerging as promising drug targets because they integrate mechanical and chemical signals, control key physiological processes, and are involved in several pathologies. The identification of pharmacological actuators of individual aGPCR functions is an urgent need to fully exploit their immense therapeutic potential.

A. ADGRA

A3 signaling can induce adipose thermogenesis, and the proposed A3 agonistic ligand hesperetin may represent an obesity treatment.⁵¹³ Engineered WNT ligands, designed as specific A2/RECK agonists, enable blood-brain barrier repair in neurological disorders (Fig. 6B).⁴⁰⁹

B. ADGRB

Herpes simplex-derived oncolytic viruses engineered to express the B1 NTF-derived vasculostatin proteolytic fragment had

potent antiangiogenic and tumor-suppressive effects in brain cancer models.^{685–688} Additionally, small molecules inhibiting the epigenetic reader MBD2 and the writer EZH2 target B1 gene epigenetic silencing and present a promising strategy to restore B1 expression and its tumor-suppressive functions.^{329,689}

C. ADGRD

A role for D1 in glioblastoma progression is supported by several studies. The identification of PTK7 as an allosteric modulator of D1, along with the development of antibodies targeting the D1 NTF, provides impetus to investigate these as potential therapeutic modalities.^{86,291} D1 was also implicated as a receptor for the androgen 5 α -DHT in muscle cells, where its action to raise cAMP levels was proposed to enhance muscle strengthening. A small molecule D1 activator, AP503, may serve as a drug lead for its beneficial actions with limited side effects.⁸⁸

D. ADGRE

Monoclonal antibody 1B2 directed against E5 proved efficacious in a mouse model of experimental arthritis and was proposed to work by neutralizing E5 through a combination of receptor internalization and induced NTF shedding.⁶⁹⁰ However, later in-depth analyses of its mode of action in vivo revealed that the antibody depletes granulocytes in mice under conditions of acute inflammation via a Fc receptor-dependent mechanism.⁶⁹¹ An antibody-drug conjugate against E5 demonstrated efficacious killing of human glioblastoma cells, in which E5 plays a tumorigenic role.¹⁰⁰ Moreover, an afucosylated monoclonal antibody to E1 efficiently depletes eosinophilic granulocytes.⁴⁶⁴ E2 may regulate serum factor H-related protein FHR1-related antibody-associated vasculitis,⁹¹ and E2 genetic variants are associated with vibratory urticaria.⁸⁹ Immune targeting E2⁴⁷⁵ or E5^{593,692} with engineered T cells expressing chimeric antigen receptors are promising novel pharmacotherapeutic tools capitalizing on the specific cellular expression patterns of aGPCRs that may prove useful in the future.

E. ADGRF

Synaptamide is an endogenous lipid that binds to the F1 GAIN domain and reduces lysophosphatidic acid–induced inflammation in mice. It elevates cAMP levels in cultured microglia and suppresses proinflammatory cytokine levels, suggesting that F1 activation by synaptamide holds therapeutic potential to ameliorate brain and peripheral tissue inflammation.⁶⁹³

F. ADGRG

G1 has varied roles in physiology and cancer progression. Small molecule antagonists, the partial agonist 3- α -DOG, and modulatory antibodies target the receptor. Pharmacological studies indicate that the small molecules occupy the orthosteric site in lieu of the TIA^{125–127} and exhibit selectivity for G subfamily members.^{263,287} Individual G1 antibodies inhibited glioma cell migration⁶⁹⁴ and promoted RhoA signaling in breast cancer cells.⁶⁹⁵ A G1-targeted antibody-drug conjugate proved efficacious in colorectal cancer cell models.⁶⁹⁶

G6 is involved in axon myelination. In vivo phenotypic screening of small molecules was performed to correct mutant G6 Zebrafish Schwann cell development, otic, and myelination defects and lead to the identification of potential agonists that are undergoing further characterization.^{138,263,697} G2/CFTR signaling is required for sperm maturation, representing a potential therapeutic target for male infertility.³¹⁴

G. ADGRL

L2 may play a role in equilibrioception and represents a potential therapeutic target for balance disorders such as vertigo. A small molecule termed D11 was reported to block the c-mesenchymal-to-epithelial transition mediated by L2-TMC1, thereby avoiding side effects associated with traditional vestibular suppressants.³⁸⁴

Critical synopsis and outlook: The current landscape of drug-targeting strategies for aGPCRs remains limited and fragmented, reflecting our still emerging understanding of receptor- and ortholog-specific working principles. This immaturity is further compounded by the intersection of multiple input modalities—adhesive ligands, mechanical forces, and steroid hormones—that aGPCRs are capable of integrating or distinguishing. Only once we understand in molecular detail how an individual receptor parses these diverse cues, and which structural elements enable or bias one mode of activation over another, can a focused and rational development of pharmacological agents truly begin. A major challenge lies in identifying intervention points that selectively modulate defined signaling routes without perturbing others, a task complicated by the multifunctional nature of aGPCRs. Structural elucidation of ligand-binding sites, mechanosensitive receptor states, and allosteric interfaces will therefore be indispensable. In parallel, systematic pathway deconvolution and isoform-resolved expression studies will help reveal which signaling outputs are most physiologically or pathologically relevant, thereby guiding where pharmacological precision is needed most. As these mechanistic foundations solidify, new opportunities will emerge for designing small molecules, allosteric modulators, or engineered biologicals that can intervene with unprecedented selectivity. Ultimately, the maturation of our conceptual and structural understanding of aGPCR signaling will transform the currently fragmented therapeutic landscape into a more coherent framework for targeted drug discovery.

XIV. Phylogeny of adhesion G protein–coupled receptor(s) and model organisms

A. Phylogenetic relationships of adhesion G protein–coupled receptor(s) subfamilies and homologs

aGPCRs have been present in Metazoa for at least 750 million years⁶⁹⁷ and are classified into 9 families (A, B, C, D, E, F, G, L, and V) based on the phylogenetic relationships of their 7TMD¹ (Fig. 7). This classification, however, has been challenged by recent studies, which highlight ambiguities in the hierarchical organization of GPCRs and call for a revised system based on phylogenetically supported levels.⁷¹⁵

Notably, the secretin-like receptor class is now considered to have evolved from aGPCRs, most likely from the D subfamily.^{715,44,45} The evolutionary conservation of aGPCRs is evident, as at least 1 member of each family has a fish ortholog, indicating that all aGPCR families were already present by the Silurian period, approximately 419 million years ago. In vertebrates, no additional independent aGPCR families have been identified beyond the known 9, and sequences with a 1-to-1 orthology to human aGPCRs exist in at least one species from each major mammalian lineage (Monotremata, Marsupialia, and Eutheria), suggesting that the full aGPCR repertoire was already established before the rise of mammals over 178 million years ago.¹⁵

However, despite this conservation, aGPCRs exhibit notable gene losses, duplications, and expansions across different taxa. For example, F3 and E5 are absent in birds, whereas multiple paralogs

of certain aGPCRs, such as E2, exist in species like felids, marmots, and artiodactyls.^{15,698} These variations reflect the genomic plasticity of aGPCRs, influenced by whole-genome duplications and local gene duplication events. Such dynamics have led to neofunctionalization or subfunctionalization of gene duplicates, which must be considered when studying aGPCR function in model organisms, as their roles may differ significantly from those in humans.

B. Model organisms for adhesion G protein–coupled receptor(s) research

Research with animal models is a foundation of aGPCR research and has promoted insights into many of the physiological roles that are currently attributed to them.^{292,293,699–701} In the following section, the main model species currently in use and their individual utility for questions pertaining to aGPCRs are introduced.

1. Choanoflagellates

As the closest living relatives of animals, choanoflagellates provide a window into the early evolution of GPCRs, and aGPCRs in particular.^{702,703} Systematic analyses of GPCR repertoires in 23 choanoflagellate species, including *Salpingoeca rosetta*, have revealed that aGPCRs constitute the largest GPCR family in most choanoflagellates, with up to 41 aGPCRs predicted in some species.^{44,704–706} Interestingly, the abundance and diversity of protein domains in the NTFs of choanoflagellate aGPCRs rival those found in metazoans, suggesting that the number of aGPCRs likely increased and their protein domain architectures diversified in the stem lineage leading to both metazoans and choanoflagellates.

Eighteen of the 19 choanoflagellate aGPCR subfamilies detected appear to have diversified independently from metazoan aGPCRs, with the exception of the V subfamily.⁴⁴ Nonetheless, choanoflagellate and metazoan aGPCRs share key structural features in the form of the HormR/GAIN/7TMD layout along with additional extracellular domains.⁷⁰⁶ Thus, the HormR/GAIN/7TMD and diversity of other NTF domains evolved before the divergence of choanoflagellates and metazoans and were, therefore, foundational to the subsequent evolution of metazoan aGPCRs.

Future efforts to reconstruct the premetazoan functions of aGPCRs will benefit from the study of aGPCR functions and regulation in phylogenetically relevant organisms, including choanoflagellates and diverse early branching animals.

2. Fruit fly (*Drosophila melanogaster*)

The aGPCR family in *D. melanogaster* contains 5 homologs allocated to subfamilies ADGRA (Remoulade), ADGRC (Flamingo/Starry night), ADGRL/A (Cirl), and 1 group equally evolutionarily related to all known aGPCR subfamilies termed ADGRX (Mayo, Ketchup).⁷

Remoulade/CG15744 (remo). The predicted ENT of Remo is structurally homologous to that of vertebrate A2 (Fig. 1A). Notably, its irregular GPS ($H^{-2}R^{-1}T^{+1}$) suggests that it is not self-cleavable.¹⁵³ Structure predictions of the *remo* gene product indicate coiled-coil elements in its ICT. Unlike A2, Remo lacks a C-terminal PBM. Recent observations have connected Remo signal transduction to Rac1, a member of the Rho family of small GTPases, and axon growth guidance in the CNS of the fly.⁷⁰⁷ It is unclear whether Remo can also work akin to A2 as a WNT coreceptor in complex with RECK, Frizzled, and Lrp5/6 (Fig. 6B).

Flamingo/Starry night/CG11895 (Fmi or Stan) shares the same basic domain structure of ADGRC homologs, consisting of cadherin repeats, an EGF-LamG region, HormR, GAIN domain and 7TMDs,

and a long intracellular domain (Fig. 1A).^{259,708} It is most extensively characterized for its function in the “core” PCP pathway, controlling the orientation of epithelial structures, such as hairs, bristles, and the ommatidial units of the compound eye.^{259,708,709} Here, Fmi interacts homophilically at cell-cell contacts, binding asymmetrically with the Frizzled 7TMD receptor in 1 cell and the Stbm/Vang 4TM protein in the opposing cell, thus apparently acting as both ligand and receptor for itself.^{259,332,710–713} Flamingo also functions extensively in *Drosophila* peripheral and CNS development. This includes dendritic patterning,^{714,715} photoreceptor target selection in the brain,^{381,716} and mushroom body development.^{717–719} Notably, both cell autonomous functions involving unidentified ligands^{715,720} and homophilic functions involving Fmi-Fmi binding^{342,720} have been reported. Moreover, although these functions appear to be independent of planar polarity pathway function,^{381,715} in several contexts, planar polarity proteins also appear to act together with Fmi in the nervous system.^{718,719,721,722}

Cirl/CG8639. Similar to other ADGRL homologs, Cirl contains an extracellular RBL, HormR, and GAIN domains but lacks an OLF domain (Fig. 1A).³⁷⁹ Deletion of Cirl results in a broad reduction in the mechanosensitivity of larvae, including tactile sensitivity to gentle touch, auditory, proprioceptive, and nociceptive stimuli.^{194,195,211,379} This is explained by the expression of Cirl in dendrites and cilia of chordotonal neurons,^{195,723} which serve as the main mechanosensory nerve cells in insects and nociceptive nerve cells.¹⁹⁴ In addition, Cirl is required for setting the number of neurons generated during central brain neurogenesis, where the aGPCR functions together with the TLR Tollo/Toll-8.¹⁵³ For this function as a metabotropic mechanosensory, Cirl self-cleavage is necessary,¹⁵³ whereas its mechanosensory role in the periphery does not require GAIN domain-mediated receptor autoproteolysis.^{194,195} The Cirl-Tollo interaction is also required for the planar cell polarization of contractile cell-cell contacts in embryonic ectoderm.¹⁵⁴ In the visual system, Cirl appears to affect activity-dependent synaptic assembly.³⁸⁰

Mayo/CG11318 and *Ketchup/CG15556 (ktch)*. Mayo and Ketchup are minimalist aGPCRs whose structure predictions only indicate the presence of GAIN and 7TM domains in each.⁷ Both proteins contain a canonical GPS and are self-proteolysed.^{153,339} Mayo is expressed in the epithelia of the midgut and anal plate of third instar larvae.⁷²⁴ Genetic removal of *mayo* impacts enterocyte proliferation in the larval midgut, leading to a non-cell autonomous increase in potassium concentration in the hemolymph, which results in tachycardia.³³⁹ Ketchup is expressed in the proventriculus of the gastrointestinal canal and Malpighian tubules, which function as the kidney equivalent in insects.⁷²⁴ Ketchup's function in these organs, which regulate ion and water homeostasis, is unknown at the present time.

3. Roundworm (*Caenorhabditis elegans*)

In the nematode *C. elegans*, the following 3 aGPCRs exist: the L homologs LAT-1 and LAT-2, and the C homolog FMI-1.

Like its mammalian homologs (Fig. 1A), LAT-1 plays a role in the neuronal system of *C. elegans*. Here, it is essential for neuronal morphogenesis, affecting sensory structures such as the male sensory rays and head sensilla. Consistent with this, the absence of LAT-1 leads to defective male copulation behavior.³⁴¹ Beyond its neuronal role, LAT-1 regulates anterior-posterior division plane orientations in the early embryo via $G\alpha_s$ signaling^{295,534} and contributes to fertility by modulating sperm guidance, ovulation, and germ cell apoptosis.^{219,294} Furthermore, LAT-1 modulates Notch signaling in the stem cell niche of the *C. elegans* gonad via direct

interaction with the DSL ligand, thereby regulating germ cell proliferation to ensure the correct number of germ cells.¹⁵⁶

LAT-2, in contrast, remains less understood. Expression analyses revealed its presence in the pharyngeal primordium during embryogenesis and later in the pharynx and excretory system, suggesting roles in feeding and waste regulation.⁵³⁴

Unlike in other species, the role of FMI-1 in PCP has not been described in *C. elegans* yet. The receptor is involved in neuronal circuit formation by controlling axon growth and pioneer-dependent axon navigation independently of PCP pathways.^{343,725,726} It also regulates dendrite self-avoidance by antagonizing the PCP component VANG-1/van Gogh.⁷²⁷ Additionally, FMI-1 has been linked to body size regulation and ECM composition, together with other PCP components.⁷²⁸

4. Zebrafish (*Danio rerio*)

The zebrafish aGPCR repertoire contains close to 60 members that represent homologs of 24 of the mammalian 33 aGPCR (Fig. 1A).⁴⁹³ Missing homologs are restricted to subfamilies E, F, and G, which also exhibit zebrafish-specific expansions. These expansions, combined with the genome-wide duplication event that occurred within the teleost lineage, explain the larger number of zebrafish aGPCRs. Many true orthologs of human aGPCRs exist in zebrafish, making this model organism powerful to study their function.

L2 has been found to mediate shear stress mechanotransduction⁴⁰⁶ and control vascular permeability in zebrafish endothelial cells.⁴⁰⁸ CRISPR-Cas9 mutants and morphants of L3.1 (*lphn3*), the ortholog of L3, have been used to investigate its role in attention-deficit/hyperactivity and other externalizing disorders, revealing altered dopaminergic neuron distributions, hyperactive motor phenotypes, potential new therapeutic targets, and therapeutic and metabolic effects of existing and emerging drugs.^{729–737}

The zebrafish paralogs of C1 (*adgrc1a* and *b*) regulate convergence and extension (CE) and epiboly movements during gastrulation,^{738,739} as well as tissue homeostasis and aging phenotypes in adults.⁶⁹⁹ Besides its role in CE,⁷³⁹ C2 controls facial motor neuron migration in the developing hindbrain.⁷⁴⁰ C3 is required for the development of GABA and acoustic startle circuits in the inner retina⁷⁴¹ and hindbrain.⁷⁴²

Zebrafish A2 has been investigated for its role in promoting WNT/ β -catenin signaling during brain angiogenesis and dorsal root ganglia formation, contributing to the identification of its coreceptor RECK,⁵³ the delineation of its mechanism in WNT ligand-specific signaling,^{54,56} the identification of highly specific pathway agonists,³⁵⁶ and its downstream angiogenic effector (Fig. 6B).³⁴³ The closely related A3 was found to regulate PCP during zebrafish VE movements by binding Dishevelled,²⁷³ an interaction shared with zebrafish A2.⁵⁴

The role of G1 in oligodendrocyte development and peripheral myelination was revealed by the analysis of zebrafish G1 mutants.^{123,362} Microglial-derived transglutaminase 2 was identified as a relevant ligand for A1 during CNS myelination, a finding supported by somatic gene disruptions in zebrafish.³⁶⁵ Morpholino knockdown studies further implicated this receptor in the formation of hematopoietic stem cells,⁷⁴³ a process that could be compensated by the ectopic expression of G3.⁴⁷²

Forward genetic screens in zebrafish revealed the essential role of G6 in PNS myelination.³⁶⁷ Additional roles of this receptor in zebrafish include spine ossification,⁴⁵⁴ cardiac trabeculation,³¹⁹ and inner ear morphogenesis.⁷⁴⁴ The zebrafish model also contributed to elucidating the context-dependent mechanisms of G6 signaling, defining its ligands, and identifying potential small-molecule agonists and posttranscriptional regulators.^{32,132,134,135,137,138,263,319,745}

Zebrafish V1 models have been generated for the analysis of V1 functions and disease mechanisms associated with mutations in V1.^{746–748} The *adgrv1^{rmc22}* zebrafish is the first V1 mutant model for Usher syndrome type 2C that displays an early retinal dysfunction, which can be used as outcome measures in the evaluation of therapeutic strategies.⁷⁴⁷

5. Chick (*Gallus gallus*)

In the chick embryo (avian) model for developmental biology studies, the ability to fenestrate the eggshell provides ease of access to the embryo and enables temporal manipulation of live embryo development. Thus, changes can be made to tissue position through grafting,⁷⁴⁹ gene expression,^{749,750} and cell signaling pathways.⁷⁵¹ Overall, the chick model has contributed knowledge of C1 function in key gastrulation events⁷⁵² as well as in neural tube closure mechanisms.²⁷² The rich vascular network of the chick embryo chorioallantoic membrane also provides a unique assay system,⁷⁵³ offering efficient screening for antiangiogenic drugs^{754,755} as well as for studying cancer biology.^{400,756,757} A sterile environment can be easily maintained following tumor cell inoculation in vivo, and since the avian immune system is not mature until day 15 postgestation, immune rejection of xenografted cells is prevented. Indeed, a chorioallantoic membrane assay-based drug screen recently identified Dub as an angiogenesis inhibitor for breast cancer, which acts via the regulation of B1.⁷⁵⁸

6. Mouse (*Mus musculus*) and rat (*Rattus norvegicus*)

Mice and rats offer several advantages for studying the complex roles of aGPCRs, including their genetic similarity to humans, the wide availability of genetic models, and their relevance to humans. The average protein identity between human and mouse aGPCRs is approximately 81%, with a minimum of 60% (G4) and a maximum of 98.5% (L1).

Due to the large exon-intron structure and numerous splice variants of aGPCRs,²⁰⁴ rodent KO models require careful design. Global KO of several aGPCRs, such as A2, F5, and G6, leads to severe phenotypes including embryonic lethality,^{58,394} surfactant accumulation,^{112,266,267} and perinatal death.^{368,426} In such cases, tissue-specific KO models can uncover more subtle receptor functions. Indeed, except for an *L3^{KO}* rat model,^{759,760} most aGPCR^{KOs} were generated in mice and use Cre-loxP systems for tissue-specific or temporally controlled receptor deletions (Table 2).^{761–785}

Some studies have used knock-in models to introduce tags (eg, GFP, mCherry, HA, and Myc) to facilitate receptor visualization in live cells or tissues.^{210,223,350} This is especially valuable, given the challenges in developing antibodies for aGPCRs.

In addition to null models, disease mouse models help investigate how mutations disrupt protein function and cellular processes. For example, the human Y6244fsX1 mutation in V1, a key component of the ankle-link complex essential for cochlear hair cell development, was modeled in V1 Y6236fsX1 mice. These mice recapitulated Usher syndrome type 2, demonstrating the relevance of mutant mice for studying disease mechanisms.⁶⁸¹ Notably, no humanized aGPCR rodent models exist, suggesting a promising area for future research.

Critical synopsis and outlook: *Evolutionary analyses of aGPCRs have both supported and propelled research into their underlying working principles. The recent discovery of a broad aGPCR repertoire in unicellular species at the brink of multicellularity underscores the importance of their molecular design in mediating cell-cell communication, likely by enabling the exchange of adhesive and mechanical cues within cell communities. Looking back into the evolutionary history of aGPCRs will continue to guide the recognition—and*

experimental interrogation, in both invertebrate and vertebrate models—of functional features that have remained conserved for at least 600 million years. Studies of the coevolution of extracellular aGPCR-ligand-binding domains and their cognate ligands have not yet been widely initiated, even though this line of inquiry may reveal the determinants of receptor-ligand specificity and thereby inform strategies for selectively modulating aGPCR function pharmacologically. Moreover, deciphering the evolutionary logic by which extracellular domains and ligands coadapted to enable the diverse mechanochemical signaling modes characteristic of aGPCRs may offer important insights into how receptor architectures became tailored to the environmental and biomechanical properties of their cellular expression sites across different organisms, organs, and tissues.

XV. Experimental technologies for adhesion G protein-coupled receptor(s) interrogation

A. Molecular dynamics studies

Studies of how aGPCR proteins behave and move using molecular dynamic (MD) simulations have mainly focused on the GAIN domain (Fig. 4) and have uncovered 2 dynamic regions near the GPS, termed flap 1 and flap 2 (Fig. 8).³⁰ Expanding on this perspective, MD simulations supported investigations into the GPS cleavage mechanism, validating the presence of a T-shaped π - π interaction of the catalytic triad histidine as a key determinant of GPS cleavage competence in the GAIN domain.⁵² In a biophysical study on CTF-NTF dissociation at the GAIN domain using single-molecule atomic force spectroscopy, MD was used to investigate GAIN mechanical stability and force propagation determinants of G1 mechanosensing.^{786,787}

With the characterization of 7TMD structures of several aGPCRs, future MD investigations are bound to uncover dynamics of *Stachel*-binding and *Stachel*-dependent signal transduction (Fig. 6), as well as using first GAIN/7TMD complexes^{27,50} to investigate the dynamic continuum of *Stachel* release off the GAIN domain and transition into the 7TMD binding pocket (Fig. 4).

B. Homology modeling

Homology modeling serves as a critical computational tool for resolving aGPCR structures by leveraging conserved TMH frameworks from known homologous templates to predict the 3-dimensional conformations of target receptors.⁷⁸⁸ Its core workflow encompasses template selection, backbone mapping of transmembrane regions, side-chain optimization, and loop modeling, supplemented by MD simulations to refine dynamic conformations, such as the outward movement of the TMH6 in activated states.^{789,790}

However, traditional homology modeling faces limitations in accuracy due to challenges, including template scarcity for aGPCRs and deviations in side-chain orientations within ligand-binding pockets. Deep learning-based protein structure prediction has emerged as a powerful technique for resolving the conformations of membrane proteins, including GPCRs. Recent advances in deep learning models, such as AlphaFold and RoseTTAFold, have surpassed the accuracy limitations of traditional homology modeling, achieving near-experimental resolution for full-sequence structure prediction.^{791,792} These approaches primarily rely on multiple sequence alignments and coevolutionary analysis, utilizing neural networks to learn spatial constraints and contact maps between residues, thereby inferring protein folding patterns.¹⁰ For highly flexible membrane proteins like aGPCRs, deep learning enables precise prediction of TMH topology. However, challenges remain

Table 2
Currently available mouse models with associated publications from the Mouse Genome Informatics, International Mouse Strain Resource, and The Jackson Laboratory databases

Receptor	Strain	Repository/Depositor	Description	References
ADGRA1	<i>Adgra1^{em1(IMPC)}</i>	The Jackson Laboratory	Null/KO	761
	<i>Adgra1^{tm1b(EUCOMM)Hmgu}</i>	Helmholtz Zentrum Muenchen GmbH	Null/KO	762
ADGRA2	<i>Adgra2^{tm1.1Bstc}</i>	JAX 016881	Targeted (conditional ready); Exon 1 flanked by loxP sites for Cre-mediated excision	395
ADGRA3	<i>Gpr124 null</i>	Velocigene	Null/KO; Exons 3–13 targeted	394
	<i>Adgra3^{tm1.1(HBEGF,-cre/ERT2)Pac}</i>	JAX 068344	Tamoxifen-inducible; Exon 1 targeted for null/KO	595
	<i>Adgra3^{tm1Lex}</i>	Lexicon Pharmaceuticals	Null/KO	762
ADGRB1	<i>Adgrb1^{tm2a(EUCOMM)Wtsi}</i>	Wellcome Trust Sanger Institute	Targeted (conditional ready); exons targeted for Cre-mediated excision	763
	<i>Adgrb1^{+/−}</i>	Erwin G. Van Meir	Constitutive Null/knockout of full-length isoform; exon 2 targeted; short Bai1 isoforms remains expressed from the alternative promoter	328
ADGRB2	<i>Bai1^{−/−}</i>	University of Virginia	Gene-trap mutation between exons 2 and 3	529
	<i>Adgrb2^{tm1b(KOMP)Mbp}</i>	UC Davis	Null/KO	764
ADGRB3	<i>Adgrb3^{em1(IMPC)Bay}</i>	Baylor College of Medicine	Null/KO	761
	<i>Bai3^{Flax}</i>	Michisuke Yuzaki	Targeted (conditional ready); exons targeted for Cre-mediated excision	77
ADGRB3	<i>Adgrb3^{Δ7/Δ7}</i>	Erwin G. Van Meir	Constitutive null/knockout of full-length isoform; exon 10 targeted; short Bai3 isoforms remain expressed from the alternative promoter	670
	<i>Bai3^{+/−}</i>	Sushant Bhatnagar	Constitutive null/knockout of full-length and short isoforms; exons 2 and 18 targeted	512
	<i>Adgrb3^{Tn(sb-lacZ,GFP)PV449Jtak}</i>	Junji Takeda	Transposon insertion	765
	<i>Celsr1^{ctb}</i>	JAX 016111	Spontaneous null/knockout; single G deletion results in a frameshift mutation	766
	<i>Celsr1^{Crsh}</i>		Single-point mutation, D1040G	344
ADGRB3	<i>Celsr1^{Scy}</i>		Single-point mutation, N1110K	767
	<i>Celsr1^{em1(IMPC)Mbp}</i>	IMPC UC Davis	Null/KO	761
	<i>Celsr1^{KO}</i>		Null/KO; exons 26–29 targeted	768
	<i>Celsr2^{tm1Dgen}</i>	JAX 005779	Null/KO; exon 23 targeted for insertion of bacterial lacZ	769
	<i>Celsr2^{KO}</i>		Null/KO; exons 16–28 targeted	770
ADGRB3	<i>Celsr3^{KO}</i>		Null/KO; exons 19–27 targeted	771
ADGRD1	<i>Adgrd1^{tm1a(EUCOMM)Wtsi}</i>	Wellcome Trust Sanger Institute	Targeted (conditional ready); exons targeted for Cre-mediated excision	763,772
ADGRD2	<i>Adgrd1^{tm1b(EUCOMM)Wtsi}</i>	Wellcome Trust Sanger Institute	Null/knockout	772
	No current mouse models - ADGRD2 is a pseudogene in mice and is therefore non-functional			
ADGRE1	<i>Adgre1^{tm1(cre)Kpf}</i>	Klaus Pfeffer	Targeted; endogenous coding sequence replaced with Cre and Neo	773
	<i>Adgre1^{tm1.1Mrl}</i>	Merck Research Laboratory	Targeted (conditional ready); Exon 16–17 flanked by loxP sites for Cre-mediated excision	774
ADGRE2	No mouse orthologs			
ADGRE3	No mouse orthologs			
ADGRE4	<i>Adgre4^{tm1b(EUCOMM)Hmgu}</i>	Helmholtz Zentrum Muenchen GmbH	Null/knockout; target exon flanked by loxP sites for Cre-mediated excision, reporter tagged	761
ADGRE5	<i>Adgre5^{tm1Dgen}</i>	JAX 005788, Deltagen	Null/knockout; exons 2–5 targeted	774
	<i>Adgre5^{tm1Kake}</i>	Kathleen Kelly	Null/knockout; exons 2–12 replaced with PGKneo cassette	470
	<i>Adgre5^{em2Cys}</i>	Jason C. Cyster	Null/knockout; exons 2–3 targeted using CRISPR-Cas9 for intragenic deletion	94
ADGRF1	<i>Adgrf1^{tm1Tcam}</i>	Takeda Cambridge	Null/knockout; exon 12 targeted	423
	<i>Adgrf1^{tm1Smoc}</i>	Shanghai Model Organisms Center	Null/knockout; exons 11–13 targeted	519
	<i>Adgrf1^{tm1a(KOMP)Wtsi}</i>	Wellcome Trust Sanger Institute	Targeted (conditional ready); exons targeted for Cre-mediated excision	763
ADGRF2	<i>Adgrf2^{tm1Tcam}</i>	Andreas P Russ/Takeda Pharmaceuticals	Null/knockout; exon 7 targeted	423
ADGRF3	<i>Adgrf2^{em1Iwto}</i>	Tsutomu Iwamoto	Null/knockout; exon 3 targeted	775
	<i>Adgrf3^{em1(IMPC)J}</i>	JAX 042379	Null/knockout; exon 8 targeted	761
	<i>Adgrf3^{tm1Lex}</i>	Lexicon Pharmaceuticals	Null/knockout	762
ADGRF4	<i>Adgrf3^{em1Kzt}</i>	Keizo Tokuhira	Null/KO; exons 7–10 targeted	776
	<i>Adgrf4^{tm1Tcam}</i>	Takeda Cambridge	Null/knockout; exon 6 targeted	423
	<i>Adgrf4^{tm1a(KOMP)Wtsi}</i>	Wellcome Trust Sanger Institute	Targeted (conditional ready); exons targeted for Cre-mediated excision	763
ADGRF4	<i>Adgrf4^{tm2a(EUCOMM)Wtsi}</i>	Wellcome Trust Sanger Institute	Targeted (conditional ready); exons targeted for Cre-mediated excision	763
	<i>Adgrf5^{tm1.1Bstc}</i>	JAX 022505	Targeted (conditional ready); exon 2 targeted	266
	<i>Adgrf5^{tm1Shiro}</i>	Shigehisa Hirose	Null/knockout; exon 2 targeted	112
ADGRF5	<i>Adgrf5^{tm1.1pbs}</i>	James P Bridges	Targeted (conditional ready); exon 17 targeted for Flp-mediated recombination	267
	<i>Adgrf5^{tm1.2pbs}</i>	James P Bridges	Null/knockout; exon 17 targeted	267
	<i>Adgrf5^{tm1a(KOMP)Wtsi}</i>	Wellcome Trust Sanger Institute	Targeted (conditional ready)	763
ADGRG1	<i>Adgrf5^{tm1b(KOMP)Wtsi}</i>	Wellcome Trust Sanger Institute	Cre-excision of the tm1a allele	772
	<i>Adgrg1^{tm1Lex}</i>	Lexicon Pharmaceuticals	Null/knockout; exons 2–3 targeted	307
	<i>Tg(Adgrg1-EGFP)HC35Gsat</i>	Rockefeller University	Transgenic; EGFP reporter gene inserted at the initiating codon of the first coding exon	121

(continued on next page)

Table 2 (continued)

Receptor	Strain	Repository/Depositor	Description	References
ADGRG2	HE6 ^{KO}		Null/knockout; exons 22-25 targeted	551
ADGRG3	Adgrg3 ^{tm1Fwa}	Frederick W Alt	Null/knockout; exons 2-8 targeted	777
	Adgrg3 ^{tm1Smoc}	Shanghai Model Organisms Center	Null/knockout; exons 1-2 targeted	642
ADGRG4	Adgrg4 ^{em1(IMPC)}	JAX 051244	Null/knockout; exon 3 targeted	761
ADGRG5	Adgrg5 ^{tm1Lex}	Lexicon Pharmaceuticals	Null/knockout	762
	Adgrg5 ^{tm1a(EUCOMM)Wtsi}	Wellcome Trust Sanger Institute	Targeted (conditional ready); exons targeted for Cre-mediated excision	763
	Adgrg5 ^{tm1b(EUCOMM)Wtsi}	Wellcome Trust Sanger Institute	Null/knockout	761
ADGRG6	Adgrg6 ^{tm1Apr}	Andreas P Russ/Takeda Pharmaceuticals	Null/knockout; exon 18 targeted	426
	Adgrg6 ^{tm1Taki}	Tetsu Akiyama	Null/KO; exon 2 targeted	319
	Adgrg6 ^{tm1Smoc}	Shanghai Model Organisms Center	Targeted (conditional ready); exon 2 targeted	778
	Adgrg6 ^{em1Jlp}	Jose Luis de la Pompa	Intragenic deletion of exons 3 and 4 producing an N-terminal fragment lacking the CUB and PTX domains	434
	Adgrg6 ^{em2Jlp}	Jose Luis de la Pompa	Null/knockout; exon 7 targeted	434
	Adgrg6 ^{tm1a(EUCOMM)Hmgu}	Helmholtz Zentrum Muenchen GmbH	Targeted (conditional ready)	425
	Gpr126 ^{-/-}	Lexicon Pharmaceuticals	Conditional ready	310
ADGRG7	Adgrg7 ^{tm1Wfro}	Wei-Fang Rong	Null/knockout; exons 10-12 targeted	530
	Adgrg7 ^{tm1b(EUCOMM)Hmgu}	Helmholtz Zentrum Muenchen GmbH	Null/knockout	761
ADGRL1	Adgrl1 ^{tm1Sud}	JAX 006393	Null/knockout; exons 1-2 targeted	779
	Adgrl1 ^{tm2.1Sud}	JAX 035181	Null/knockout; Myc-tagged mouse ADGRL1 with floxed exon 2 for Cre-mediated excision	223
	Adgrl1 ^{tm2c(EUCOMM)Hmgu}	JAX 035185	Targeted (conditional ready)	223
	Adgrl1 ⁻		Null/knockout; exons 1-3 targeted	352
ADGRL2	Lphn2 ^{tm1Dgen}	HAR/EMMA	Null/knockout	1,678
	Adgrl2 ^{tm1Sud}	JAX 023401	Targeted (conditional ready) contains Frt sites and a part of loxP sites for Cre-mediated excision or expression of an alternative transcript fused to mVenus	350
ADGRL3	Adgrl3 ^{tm1Sud}	JAX 026684	Conditional; exon 6 flanked by loxP sites for Cre-mediated excision	351
	Adgrl3 ^{Gt(S17-5H1)Sor}	Texas A&M Institute for Genomic Medicine	Null/knockout	780
	Adgrl3 ^{tm1(KOMP)Vlbg}	Velocigene	Null/knockout	218
	Adgrl3 ^{tm1.1(KOMP)Vlbg}	Velocigene	Null/knockout	772
ADGRL4	Adgrl4 ^{tm1Dgen}	DeltaGen, European Mouse Mutant Archive, HAR	Null/knockout	436
	Adgrl4 ^{tm1Lex}	Lexicon Pharmaceuticals	Null/knockout; exons 4-6 targeted	762
	Adgrl4 ^{em1(IMPC)Mbp}	IMPC UC Davis	Null/knockout	761
ADGRV1	Adgrv1 ^{tm1Pwh}	Perrin C White, JAX 009379	Null/knockout; exon 82 targeted	682
	Adgrv1 ^{tm1Msat}	Makoto Sato	Null/knockout; exons 2-4 targeted	781
	Adgrv1 ^{tm2Msat}	Makoto Sato	Null/knockout; exons 2-4 targeted, insertion of YFP	782
	Adgrv1 ^{tm1.1(KOMP)Vlbg}	Velocigene	Null/knockout	772
	Adgrv1 ^{m1}		Spontaneous Null/knockout; deletions in Exon 31 causes frameshift and premature stop codon	783
	Adgrv1 ^{frings}		Spontaneous intragenic deletion; single nucleotide deletion that results in a nonsense mutation in Exon 27	784,785

in loop modeling, conformational dynamics, and fine-grained predictions of ligand-binding pockets.⁷⁹³

C. Acute receptor activation

Acute activation strategies have enabled investigation of the intracellular signaling activity of aGPCRs in vitro and are emerging as tools to study aGPCR functions in vivo (Fig. 8). Two main approaches, one relying on addition of ligands (Table 1) and the other on controlled exposure of the *Stachel*, have been explored.

Addition of soluble small molecules^{88,108,125,126,136,137,230} or synthetic peptides derived from the *Stachel* sequence,^{32,33,77,174,176,216,281,287,312,701} combined with measurements of G protein activation, GTP turnover, or second messenger regulation, has been used to interrogate aGPCR signaling in a manner analogous to classical GPCR agonists (Fig. 6A). However, ligand specificity and solubility remain a challenge in these approaches.

For 4 aGPCRs (G1, G6, D1, and L3), naturally occurring adhesive ligands (derived from the ECM or membrane-anchored) have also been shown to induce second messenger regulation upon acute

presentation as purified proteins in solution^{117,132,133} or when presented on coated substrates or through cell mixing.^{86,87,322} Antibodies binding the NTF of G6 and D1 have been shown to induce cAMP production.^{291,794} In future assay development, testing the impact of adhesive ligands in a more physiological setting, for example, in a 3D matrix or in coculture while simultaneously applying an acute stimulus such as mechanical stress, will be informative. This can be supported by acute membrane anchoring of secreted ligand forms by exploiting genetic code expansion technology combined with biorthogonal integration of unnatural AAs within the ligand. When expressed in coculture with cognate receptor-expressing cells, such acute membrane ligand fixation can aid in investigating adhesion-dependent aGPCR activation.⁷⁹⁵

Signaling profiling, which systematically screens the 4 main G protein pathways and directly measures G protein coupling, is now possible through strategies that acutely expose the *Stachel*, thereby circumventing ligand solubility issues. One of the first approaches used urea to dissociate the NTF and expose the *Stachel*.³³

In recent years, the strategy of engineering a protease site N-terminal to the *Stachel* to acutely trigger its exposure upon

protease addition^{188,226,284,290,300,796–798} has paved the way for using live cell BRET readouts to monitor direct G protein activation and downstream effector interactions (Fig. 6A, B).

D. Force assays

A wide range of aGPCRs are involved in mechanotransduction, that is, the conversion of mechanical forces into biochemically and physiologically actionable information.^{292,383,471,799,800} Experimental approaches to define forces that are transmitted between aGPCRs and their adhesive ligands (Table 1) during mechanical stimulation, which affect individual aGPCR during signal transduction and influence cellular responses to aGPCR activation, are a rapidly emerging area in aGPCR research (Fig. 8). These efforts are essential for determining the specific role of a given aGPCR within the distinct phases of mechanotransduction: mechanotransmission, the transfer of forces to and between molecules and cells; mechanosensation, the detection of such forces by conformational changes within membrane proteins; and mechanoresponse,⁸⁰¹ the cellular signaling reaction triggered by this molecular level of force detection. However, for many aGPCRs and their observed functions, these roles have yet to be clearly defined.

Techniques that enable direct application of force to receptors while simultaneously measuring intracellular signaling will pave the way for directly linking GAIN domain force load to GPCR signaling output. One such method combines optical tweezers and confocal microscopy, using a highly focused laser beam to manipulate (hold, pull, or push) living cells mechanically^{802,803} while simultaneously monitoring fluorescent signals. This approach leverages reporters that detect G protein recruitment, cAMP production,⁸⁰⁴ calcium mobilization,⁸⁰⁵ or Rho kinase activity⁸⁰⁶ downstream of aGPCR activation (Figs. 6 and 8).

Magnetic tweezers apply physiologically relevant force-loading rates (~pN/s) to measure conformational changes and GAIN domain dissociation of aGPCRs (Figs. 4, 6, and 8).^{807,808} Recent studies show that the GAIN B subdomain of self-cleaved receptors such as G1, L1, and L3 undergoes partial unfolding at low forces before dissociating at 10–20 pN. Similar partial unfolding was also observed in noncleavable B3. These findings reveal conserved mechanical responses of the GAIN B subdomain across aGPCR subfamilies.

Single-molecule atomic force microscopy (AFM) is a valuable tool for characterizing the mechanical properties of individual protein domains and PPIs⁸⁰⁹ and has been used extensively for studying GPCR (Fig. 8).⁸¹⁰ However, its application to aGPCRs is more limited, with only a single report documenting GAIN-*Stachel* dissociation forces for isolated GAIN domains lacking the 7TMD in a range of ~95–160 pN at loading rates of 2000–20,000 pN/s.⁷⁸⁶

The activation of G6 through its endogenous ligands, laminin 211 and collagen IV, in combination with pulling or pushing forces were studied using AFM with a coated cantilever.⁷⁹⁴ A fluorescent cAMP sensor enabled measurement of this second messenger at the single-cell level, revealing distinct activation modes for these ligands.

A high-throughput mechanical stimulation assay utilizing a magnetic tweezer system, integrated with a GPCR biosensor platform, was developed to examine the mechanosensitivity of selected aGPCRs.³⁸⁴ In these assays, HEK293 cells expressing N-terminal Flag-tagged aGPCR and G protein BRET probes were incubated with paramagnetic beads, which were coated with anti-Flag M2 antibody. Forces were applied to the receptor-bound magnetic beads, enabling a real-time detection of force-induced G protein activation via a G protein dissociation BRET assay (Fig. 8). Using this method, 5 aGPCRs—D1, G6, L2, L3, and V1—were found to trigger $G\alpha_s$ or $G\alpha_i$ signaling in response to force

stimulation. The platform's versatility extends to endogenous aGPCR studies by leveraging the magnetic beads coated with antibodies specifically recognizing the extracellular regions of the target receptors.³⁸⁴ The force-induced changes in secondary messengers, such as cAMP and Ca^{2+} , or other cellular signals, could also be quantified.

Vibration and shaking of heterologous cell cultures expressing aGPCRs G6,¹³⁴ D1,¹⁷² and G5²¹⁶ have also been used to study the impact of broad mechanical forces on receptor activity (Fig. 8).

Physiological force-dependency of cellular aGPCR functions were first observed in flies³²⁵ and mice.⁴³⁷ Increased G1 expression was shown to modulate skeletal muscle hypertrophy as a target in a transcriptional cascade active during exercise. Similarly, anabolic effects of G1 on skeletal muscle mass in vivo were achieved through wheel-running and muscle overload by stretching.⁴³⁷ Through direct sensory neuronal stimulation via Piezo-actuated glass probes operated between 100 and 1500 Hz showed Cirl-dependent suppression of cAMP levels using a transgenic EPAC sensor.^{195,811} Through electrophysiological recordings of proprioceptive neurons, Cirl-dependent maintenance of neuronal current amplitudes and frequency were demonstrated, which underlie mechanical stimulus-instructed organ functions and behaviors such as hearing, tactile perception, animal movement, and nociception.^{194,195,211,379} Additional technical efforts provided transgenic sensors to investigate physiological ligand- and force-dependent receptor dissociation as observed in proprioceptive neurons during joint motion or central brain neurogenesis,^{153,723} collectively placing Cirl within the processes of mechano-transmission and -sensing.

Recently, similar physiological approaches demonstrated the mechanosensing contribution of L2³⁸⁴ and D1³⁸⁵ to equilibrium in mice. A fluid jet system was used to directly apply mechanical stimuli to the cell surface of hair cells.⁸¹² When integrated with BRET-based biosensors (Fig. 8), this system confirmed the mechanosensitivity of selected aGPCRs identified by a magnetic tweezer assay. Furthermore, the fluid jet system has been utilized to explore the physiological roles of aGPCR in the inner ear hair cells. Specifically, activation of L2 by the fluid jet stimulation increases intracellular Ca^{2+} levels and promotes glutamate secretion in mouse vestibular hair cells, a response that is severely impaired in L2-deficient hair cells.^{384,812} Therefore, this multimodal methodology bridges molecular-scale force application with systems-level physiological outputs, offering high resolution for dissecting aGPCR roles in mechanobiology.

E. Receptor dissociation

In most aGPCRs, the GAIN domain is autoproteolytically active, although, for any given aGPCR, self-cleavage may be contextual depending on cell type^{25,185,306,813} or other factors such as receptor glycosylation.¹⁸⁵ The autoproteolytic cleavage of aGPCRs and thus receptor dissociation can be suppressed by point mutations immediately adjacent to the GPS²⁶ or within the intradomain environment of the cleavage site.⁵² For example, mutations of a highly conserved histidine at the −2 position of the GPS abolishes cleavage and dissociation.^{26,32,281,294,296,379}

Detecting NTF-CTF dissociation events (Figs. 4 and 6), especially at high spatial and/or temporal resolution, is important for understanding aGPCR function but technically challenging. A biochemical approach used to characterize aGPCR dissociation involves affinity purification/immunoprecipitation of receptors using NTF- or CTF-specific antibodies or epitope tags to assess whether the 2 fragments remain noncovalently bound or have dissociated. As was demonstrated for D1 using this approach and subcellular fractionation,²²⁶ cleavage occurs in the ER, but the NTF

and CTF remain noncovalently bound until they reach the plasma membrane. Once localized at the plasma membrane dissociation can take place.

A recent advance is the development of an NRS system, which enables transcriptional detection and quantification of NTF dissociation from any given aGPCR in cell culture, and at cellular resolution, also in vivo (Fig. 8).^{153,723} Its utility was demonstrated using NRS reporters for the *Drosophila* receptors Cirl, Mayo, and Ketchup. In particular, analysis of Cirl-NTF release conditions in the developing brain revealed important biological functions of Cirl dissociation at the interface between glial and neural progenitor cells.¹⁵³

Critical synopsis and outlook: *The adaptation of emerging technologies for the study of molecular, cellular, physiological, and pathophysiological aspects has significantly improved the analyses of aGPCR properties. Specific focus is currently warranted to emulate the native environment, in which aGPCR natively receive and respond to their adequate stimuli, in in vitro assays. This requires different approaches than the pharmacological and cell biological analyses of non-aGPCRs and is hampered by the lack of detailed information on the ligand spectrum of individual homologs, the properties of mechanical stimuli they are activated by, and the potential crosstalk with other agonistic conditions such as steroid agonists. To complete our knowledge on these determinants of aGPCR signals, an increasing number of biophysical approaches, such as the ones pioneered for the investigation of motor proteins, adhesion molecules, and other mechanoresponsive molecules, are required and need to be adapted to aGPCR questions. Also, structural studies that aim at characterizing full-length aGPCR in their native tissue environment including cryo-ET analyses, and molecular modeling techniques to grasp the dynamics of aGPCR systems without and with interactors are needed from here on out to continue the successful characterization of aGPCR-dependent signals.*

XVI. Perspectives

The decade that has passed since the last comprehensive review on aGPCRs published in this journal¹ has witnessed tremendous scientific progress across all aspects of these receptors, including their structure, signaling, biochemistry, and the diverse cell, tissue, and organ functions they regulate, and the consequences of their dysfunction. This progress has been driven by the concerted efforts of the international research community dedicated to aGPCRs, as represented by the Adhesion GPCR Consortium (<https://www.adhesiongpcr.org>). This collaborative network has played a pivotal role in advancing methodological innovations, standardizing aGPCR nomenclature to ensure precise communication, and fostering interdisciplinary dialog among structural and cellular biologists, pharmacologists, biochemists, physiologists, geneticists, and clinicians. As a result, our mechanistic understanding of aGPCR activation and signaling paradigms has advanced significantly, laying the foundation for a more comprehensive understanding of aGPCR function and paving the way for novel therapeutic approaches targeting these complex receptors. However, many fundamental questions remain unanswered, new scientific challenges are emerging, and the technological toolbox for aGPCR research remains incomplete. Major knowledge gaps include endogenous receptor expression patterns, receptor-specific ligands, context-dependent signaling pathways, isoform-specific functions, and the integration of aGPCR functions within broader cellular and physiological networks. Technological advances, including the development of specific antibodies, protocols for the application of mechanical stimuli, and assays to read and quantify their mechanoresponses, are highly sought after. Addressing these

scientific and technological challenges will require sustained collaboration, further technological advances in structural and functional assays, both in silico, in vitro, and in vivo development of fragment- and isoform-specific antibodies, and the translation of basic discoveries into clinically relevant strategies. Considering the remarkable achievements to date, aGPCR research stands well positioned to capitalize on these insights, deepen our biological understanding, and ultimately harness the therapeutic potential of aGPCRs in a wide range of diseases in which they play critical roles. We look forward with great anticipation to the advances and insights that the coming decade of aGPCR research will bring.

Abbreviations

1TM, single-pass transmembrane; 7TM, 7-pass transmembrane; 7TMD, 7-pass transmembrane domain; AA, amino acid; ADGR, Adhesion G protein-coupled receptor; AFM, atomic force microscopy; aGPCR, adhesion GPCR; AIS, adolescent idiopathic scoliosis; AT1, alveolar type 1; AT2, alveolar type 2; BRET, bioluminescence energy transfer; CAM, chorioallantoic membrane; CE, convergence and extension; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CRN, craniorachischisis; cryo-EM, cryogenic electron microscopy; CTF, C-terminal fragment; DHEA, dehydroepiandrosterone; ECL, extracellular loop; EGF, epidermal growth factor-like; EMT, epithelial-to-mesenchymal transition; EndMT, endothelial-to-mesenchymal transition; ENT, extracellular N-terminus; ER, endoplasmic reticulum; GAIN, GPCR autoproteolysis-inducing; GPCR, G protein-coupled receptor; GPS, GPCR proteolysis site; GRKs, G protein receptor kinases; GRN, generic residue numbering; hASMC, human airway smooth muscle cells; HIV, human immunodeficiency virus; HormR, hormone receptor motif; ICL, intracellular loop; ICT, intracellular C-terminus; IPF, idiopathic pulmonary fibrosis; KO, knockout; KRT1, keratin 1; LEC, lymphatic endothelial cells; MAGUK, membrane-associated guanylate kinase; MD, molecular dynamics; NK, natural killer; NRS, NTF release sensor; NTF, N-terminal fragment; PBM, PDZ-binding motif; PC1, polycystin-1; PCP, planar cell polarity; PKD1, polycystic kidney disease 1; PNS, peripheral nervous system; PR3, proteinase 3; PTK7, protein tyrosine kinase 7; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNP, single nucleotide polymorphism; TG2, transglutaminase-2; TIA, tethered/intramolecular agonist; TLR, Toll-like receptor; TMH, transmembrane helix; Treg, regulatory T cells.

Acknowledgments

We thank Ivana Henry, Cambridge, for her collaboration on the illustrations. We apologize to authors whose work was not referenced in this manuscript.

Financial support

This work was supported by the Deutsche Forschungsgesellschaft (DFG) to Langenhan (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, project 542631574); Aust (FOR 2149 project number 246212759, project 432108769); Blanco-Redondo (DFG project number 574945774); Bridges (R01HL177550); Engel (FOR 2149 project number 246212759 and EN453/15-1 project number 522261482); Georgiadis (project 450149205-TRR333/1 (BATenergy) (project P03)); Hamann (FOR 2149 project number 246212759); Hildebrand (CRC1423 project number 421152132, subprojects C01, Z04); Kittel (KFO 5001 project number 426503586); Kleinau (EXC 311 2008/1

(UniSysCat)—390540038 (Research Unit E)); Liebscher (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, subproject B05; Prömel (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, subproject C04); Scheerer (CRC1423, project number 421152132, subproject A01, A05, Z03 and EXC 311 2008/1 (UniSysCat)—390540038 (Research Unit E)); Scholz (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, subproject B06); Schöneberg (FOR 2149 project number 246212759 and CRC 1423 project number 421152132); Sträter (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, project 542631574); Vallon (project number 440925599); Wolfrum (FOR 2149 project number 246212759); the National Institutes of Health (NIH) to Caron and Avila-Zozaya (HD060860); Blacklow (2R35CA220340, 1R01CA272484 and 1R01AI172846); Duman (R01-CA283569 and R01-MH137505); Hall (R21-NS133638 and R21-NS142860); Sando (00MH117235 and DP2MH1401324); Tall (R35 GM149539); Tilley (HL134608); Tolias (MH137505 and 2RF1NS062829); Van Meir (NS117666 and NS144449); Zaidman (R00DK127215); the National Institute of Mental Health (NIMH) to Südhof (R01MH126929); the Wellcome Trust to Del Toro and Seiradake (226647/Z/22/Z); Strutt (210630/Z/18/Z and 305132/Z/23/Z); the Novo Nordisk Foundation to Chung (NNF23OC008432); Gloriam (NNF23OC0082561); the European Research Council (ERC) to Del Toro and Seiradake (Synergy grant SUNRISE: 101167188); Vanhollebeke (Ctrl-BBB 865176); the Federal Ministry of Research, Technology and Space (BMFT) to Scholz (03VP11220); Langenhan (03VP11220); the NWO to Hamann (Gravitation Program 024.006.009); FRFS-WELBIO (CR-2017S-05R) to Vanhollebeke; the Secretaría de Educación, Ciencia, Tecnología e Innovación de la Ciudad de México to Boucard (SECTEI/165/2023; CONAHCYT PN2017-4687, CB221568, INFRA302758); Mitacs accelerate program IT29484 to Moreno-Salinas; the National Research Foundation (NRF) Singapore to Yan (MID-SIZED GRANT (MSG)(NRF-MSG-2023-0001)); the German Academic Exchange Service (DAAD) to Singh (reference number 91897195); the Alfred Sloan Foundation to Sando; the Leipzig University, Faculty of Medicine to Blanco-Redondo (Junior research grant); the Foundation Fighting Blindness (FFB) to Wolfrum (PPA-0717-0719-RAD); the Independent Research Fund Denmark to Mathiasen (Sapere Aude 1054-00086B) and (NNF23OC0081901); the National Science and Technology Council (NSTC), Taiwan to Lin (NSTC-113-2320-B-182-009); the University of California, Howard Hughes Medical Institute to Garcia De Las Bayonas; the Cancer Research UK (CRUK) and UK Research and Innovation (UKRI) to Favara; and the Deutsche Herzstiftung e.V., Manfred Roth Stiftung, and Research Foundation Medicine at the University Clinic Erlangen to Engel.

Conflict of interests

Dimitris G. Placantonakis holds patents on the therapeutic targeting of ADGRE5 and ADGRD1 in GBM. Marie-Gabrielle Ludwig is an employee of Novartis Pharma AG. Laurent Sabbagh is an employee of Domain Therapeutics. Erwin G. Van Meir is co-founder, CSO, and shareholder of OncoSpherix, Inc. Giselle R. Wiggan is Employee of and shareholder in Nxera Pharma UK Limited. Norbert Sträter and Tobias Langenhan are coinventors of a pending patent covering NTF release sensors for aGPCRs (WO/2022/063915; priority application: EP 3974535; applicant: Leipzig University). David E. Gloriam is a part-time employee and warrant-holder at Kvantify. Benoit Vanhollebeke is shareholder and founder of NeuVasQ Biotechnologies. Stephen C. Blacklow is on the board of directors for the nonprofit Revson Foundation and nonprofit Institute for Protein Innovation, is on the scientific advisory board for Erasca, Inc. and MPM Capital, is head of the

scientific advisory board with equity in Odyssey Therapeutics, and is a consultant for Scorpion Therapeutics.

Data availability

Transcriptome data on aGPCRs shown in Figure 5 was extracted from the Human Protein Atlas (HPA) consortium.

CRediT authorship contribution statement

Tobias Langenhan and Nicole Scholz: Conceptualization, Supervision, Writing, Reviewing and Editing, Visualization, Project Administration, and Funding Acquisition. **Garret R. Anderson, Demet Araç, Gabriela Aust, Monserrat Avila-Zozaya, Sofie Morsing Bagger, Patrick Barth, Sandra Berndt, Stephen C. Blacklow, Beatriz Blanco-Redondo, Antony A. Boucard, James P. Bridges, Lara-Sophie Brodmerkel, Kathleen M. Caron, Yin Kwan Chung (鍾炫坤), Andrew N. Dates, Virginea de Araujo Farias, Daniel Del Toro, Joseph G. Duman, Felix B. Engel, David M. Favara, Caroline J. Formstone, Chaoyu Fu, Alain Garcia De Las Bayonas, Anastasia Georgiadi, David E. Gloriam, Randy A. Hall, Jörg Hamann, Peter W. Hildebrand, Cheng-Chih Hsiao, Bill X. Huang, Jonathan A. Javitch, Hee-Yong Kim, Robert J. Kittel, Gunnar Kleinau, Richard Leduc, Ines Liebscher, His-Hsien Lin, Joshua Linnert, Marie-Gabrielle Ludwig, David C. Martinelli, Signe Mathiasen, Daniel Matús, Mariam Melkumyan, Ana L. Moreno-Salinas, Jan Mulder, Michael A. Nash, Kasturi Pal, Daniel T. Pederick, Nicole A. Perry-Hauser, Xianhua Piao, Yu-Qi Ping, Dimitris G. Placantonakis, Fabian Pohl, Simone Prömel, Mette M. Rosenkilde, Laurent Sabbagh, Richard C. Sando, Patrick Scheerer, Torsten Schöneberg, Elena Seiradake, Mareike Selcho, Florian Seufert, Abhishek K. Singh, Georgios Skiniotis, Katja Spiess, Norbert Sträter, David Strutt, Thomas C. Südhof, Jinpeng Sun, Gregory G. Tall, Doreen Thor, Douglas G. Tilley, Kimberley F. Tolias, Mario Vallon, Erwin G. Van Meir, Benoit Vanhollebeke, Giselle R. Wiggan, Uwe Wolfrum, Jie Yan, Nathan A. Zaidman, and Yimin Zou:** Visualization, Writing — Review and Editing. **Gabriela Aust, Jörg Hamann, Cheng-Chih Hsiao, and Jan Mulder:** Formal Analysis.

Declaration of AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

References

- Hamann J, Aust G, Araç D, et al. International union of basic and clinical pharmacology. XCIV. Adhesion G protein-coupled receptors. *Pharmacol Rev.* 2015;67(2):338–367. <https://doi.org/10.1124/pr.114.009647>
- Fredriksson R, Lagerström MC, Lundin LG, Schiöth HB. The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogue groups, and fingerprints. *Mol Pharmacol.* 2003;63(6):1256–1272. <https://doi.org/10.1124/mol.63.6.1256>
- Harmar AJ. Family-B G-protein-coupled receptors. *Genome Biol.* 2001;2(12):REVIEWS3013. <https://doi.org/10.1186/gb-2001-2-12-reviews3013>
- Lagerström MC, Schiöth HB. Structural diversity of G protein-coupled receptors and significance for drug discovery. *Nat Rev Drug Discov.* 2008;7(4):339–357. <https://doi.org/10.1038/nrd2518>
- Langenhan T, Aust G, Hamann J. Sticky signaling—adhesion class G protein-coupled receptors take the stage. *Sci Signal.* 2013;6(276):re3. <https://doi.org/10.1126/scisignal.2003825>
- Liebscher I, Schöneberg T, Prömel S. Progress in demystification of adhesion G protein-coupled receptors. *Biol Chem.* 2013;394(8):937–950. <https://doi.org/10.1515/hsz-2013-0109>

7. Scholz N, Langenhan T, Schöneberg T. Revisiting the classification of adhesion GPCRs. *Ann N Y Acad Sci*. 2019;1456(1):80–95. <https://doi.org/10.1111/nyas.14192>
8. Wang J, Chitsaz F, Derbyshire MK, et al. The conserved domain database in 2023. *Nucleic Acids Res*. 2023;51(D1):D384–D388. <https://doi.org/10.1093/nar/gkac1096>
9. Sigrist CJ, de Castro E de, Cerutti L, et al. New and continuing developments at PROSITE. *Nucleic Acids Res*. 2012;41:D344–D347. <https://doi.org/10.1093/nar/gks1067>
10. Jumper J, Evans R, Pritzel A, et al. Highly accurate protein structure prediction with AlphaFold. *Nature*. 2021;596(7873):583–589. <https://doi.org/10.1038/s41586-021-03819-2>
11. van Kempen M, Kim SS, Tumescheit C, et al. Fast and accurate protein structure search with Foldseek. *Nat Biotechnol*. 2024;42(2):243–246. <https://doi.org/10.1038/s41587-023-01773-0>
12. Tawfeeq C, Wang J, Khaniya U, et al. IgStrand: a universal residue numbering scheme for the immunoglobulin-fold (Ig-fold) to study Ig-proteomes and Ig-interactomes. *PLoS Comput Biol*. 2025;21(4):e1012813. <https://doi.org/10.1371/journal.pcbi.1012813>
13. Bandekar SJ, Garbett K, Kordon SP, et al. Structural basis for regulation of CELSR1 by a compact module in its extracellular region. *Nat Commun*. 2025;16(1):3972. <https://doi.org/10.1038/s41467-025-59319-8>
14. Seufert F, Pérez-Hernández G, Pándy-Szekeres G, et al. Generic residue numbering of the GAIN domain of adhesion GPCRs. *Nat Commun*. 2025;16(1):246. <https://doi.org/10.1038/s41467-024-55466-6>
15. Wittlake A, Prömel S, Schöneberg T. The evolutionary history of vertebrate adhesion GPCRs and its implication on their classification. *Int J Mol Sci*. 2021;22(21):11803. <https://doi.org/10.3390/ijms222111803>
16. Kleinau G, Ali AH, Wiechert F, et al. Intramolecular activity regulation of adhesion GPCRs in light of recent structural and evolutionary information. *Pharmacol Res*. 2023;197:106971. <https://doi.org/10.1016/j.phrs.2023.106971>
17. Jackson VA, del Toro D, Carrasquero M, et al. Structural basis of latrophilin-FLRT interaction. *Structure*. 2015;23(4):774–781. <https://doi.org/10.1016/j.str.2015.01.013>
18. Ranaivoson FM, Liu Q, Martini F, et al. Structural and mechanistic insights into the Latrophilin3-FLRT3 complex that mediates glutamatergic synapse development. *Structure*. 2015;23(9):1665–1677. <https://doi.org/10.1016/j.str.2015.06.022>
19. Lu YC, Nazarko OV, Sando R, et al. Structural basis of latrophilin-FLRT-UNC5 interaction in cell adhesion. *Structure*. 2015;23(9):1678–1691. <https://doi.org/10.1016/j.str.2015.06.024>
20. Jackson VA, Mehmood S, Chavent M, et al. Super-complexes of adhesion GPCRs and neural guidance receptors. *Nat Commun*. 2016;7(1):11184. <https://doi.org/10.1038/ncomms11184>
21. Del Toro D del, Carrasquero-Ordaz MA, Chu A, et al. Structural basis of teneurin-latrophilin interaction in repulsive guidance of migrating neurons. *Cell*. 2020;180(2):323–339.e19. <https://doi.org/10.1016/j.cell.2019.12.014>
22. Li J, Xie Y, Cornelius S, et al. Alternative splicing controls teneurin-latrophilin interaction and synapse specificity by a shape-shifting mechanism. *Nat Commun*. 2020;11(1):2140. <https://doi.org/10.1038/s41467-020-16029-7>
23. Seiradake E, del Toro D, Nagel D, et al. FLRT structure: balancing repulsion and cell adhesion in cortical and vascular development. *Neuron*. 2014;84(2):370–385. <https://doi.org/10.1016/j.neuron.2014.10.008>
24. Knapp B, Roedig J, Roedig H, et al. Affinity proteomics identifies interaction partners and defines novel insights into the function of the adhesion GPCR VLGR1/ADGRV1. *Molecules*. 2022;27(10):3108. <https://doi.org/10.3390/molecules27103108>
25. Araç D, Boucard AA, Bolliger MF, et al. A novel evolutionarily conserved domain of cell-adhesion GPCRs mediates autophagy. *EMBO J*. 2012;31(6):1364–1378. <https://doi.org/10.1038/emboj.2012.26>
26. Lin HH, Chang GW, Davies JQ, Stacey M, Harris J, Gordon S. Autocatalytic cleavage of the EMR2 receptor occurs at a conserved G protein-coupled receptor proteolytic site motif. *J Biol Chem*. 2004;279(30):31823–31832. <https://doi.org/10.1074/jbc.m402974200>
27. Mao C, Zhao RJ, Dong YJ, et al. Conformational transitions and activation of the adhesion receptor CD97. *Mol Cell*. 2024;84(3):570–583.e7. <https://doi.org/10.1016/j.molcel.2023.12.020>
28. Gray JX, Haino M, Roth MJ, et al. CD97 is a processed, seven-transmembrane, heterodimeric receptor associated with inflammation. *J Immunol*. 1996;157(12):5438–5447. <https://doi.org/10.4049/jimmunol.157.12.5438>
29. Krasnoperov VG, Bittner MA, Beavis R, et al. α -Latrotoxin stimulates exocytosis by the interaction with a neuronal G-protein-coupled receptor. *Neuron*. 1997;18(6):925–937. [https://doi.org/10.1016/s0896-6273\(00\)80332-3](https://doi.org/10.1016/s0896-6273(00)80332-3)
30. Beliu G, Altrichter S, Guixà-González R, et al. Tethered agonist exposure in intact adhesion/class B2 GPCRs through intrinsic structural flexibility of the GAIN domain. *Mol Cell*. 2021;81(5):905–921.e5. <https://doi.org/10.1016/j.molcel.2020.12.042>
31. Ferré S, Casadó V, Devi LA, et al. G protein-coupled receptor oligomerization revisited: functional and pharmacological perspectives. *Pharmacol Rev*. 2014;66(2):413–434. <https://doi.org/10.1124/pr.113.008052>
32. Liebscher I, Schön J, Petersen SC, et al. A tethered agonist within the ectodomain activates the adhesion G protein-coupled receptors GPR126 and GPR133. *Cell Rep*. 2014;9(6):2018–2026. <https://doi.org/10.1016/j.celrep.2014.11.036>
33. Stoveken HM, Hajduczuk AG, Xu L, Tall GG. Adhesion G protein-coupled receptors are activated by exposure of a cryptic tethered agonist. *Proc Natl Acad Sci U S A*. 2015;112(19):6194–6199. <https://doi.org/10.1073/pnas.1421785112>
34. Stacey M, Lin HH, Gordon S, McKnight AJ. LNB-TM7, a group of seven-transmembrane proteins related to family-B G-protein-coupled receptors. *Trends Biochem Sci*. 2000;25(6):284–289. [https://doi.org/10.1016/s0968-0004\(00\)01583-8](https://doi.org/10.1016/s0968-0004(00)01583-8)
35. Chang GW, Stacey M, Kwakkenbos MJ, Hamann J, Gordon S, Lin HH. Proteolytic cleavage of the EMR2 receptor requires both the extracellular stalk and the GPS motif. *FEBS Lett*. 2003;547(1–3):145–150. [https://doi.org/10.1016/s0014-5793\(03\)00695-1](https://doi.org/10.1016/s0014-5793(03)00695-1)
36. Seufert F, Chung YK, Hildebrand PW, Langenhan T. TTM domain structures of adhesion GPCRs: what's new and what's missing? *Trends Biochem Sci*. 2023;48(8):726–739. <https://doi.org/10.1016/j.tibs.2023.05.007>
37. Kuhn CK, Stenzel U, Berndt S, Liebscher I, Schöneberg T, Horn S. The repertoire and structure of adhesion GPCR transcript variants assembled from publicly available deep-sequenced human samples. *Nucleic Acids Res*. 2024;52(7):3823–3836. <https://doi.org/10.1093/nar/gkac145>
38. Ballesteros JA, Weinstein H. [19] Integrated methods for the construction of three-dimensional models and computational probing of structure-function relations in G protein-coupled receptors. In: Sealfon SC, Vol 25, eds. *Methods in Neurosciences*. Elsevier; 1995:366–428. [https://doi.org/10.1016/s1043-9471\(05\)80049-7](https://doi.org/10.1016/s1043-9471(05)80049-7)
39. Wootten D, Simms J, Miller LJ, Christopoulos A, Sexton PM. Polar transmembrane interactions drive formation of ligand-specific and signal pathway-biased family B G protein-coupled receptor conformations. *Proc Natl Acad Sci U S A*. 2013;110(13):5211–5216. <https://doi.org/10.1073/pnas.1221585110>
40. de Graaf C, Nijmeijer S, Wolf S, Ernst OP. TTM domain structure of adhesion GPCRs. *Handb Exp Pharmacol*. 2016;234:43–66. https://doi.org/10.1007/978-3-319-41523-9_3
41. Isberg V, de Graaf C de, Bortolato A, et al. Generic GPCR residue numbers—aligning topology maps while minding the gaps. *Trends Pharmacol Sci*. 2015;36(1):22–31. <https://doi.org/10.1016/j.tips.2014.11.001>
42. Isberg V, Vroeling B, van der Kant R, Li K, Vriend G, Gloriam D. GPCRDB: an information system for G protein-coupled receptors. *Nucleic Acids Res*. 2014;42:D422–D425. <https://doi.org/10.1093/nar/gkt1255>
43. Pándy-Szekeres G, Caroli J, Mamyrbekov A, et al. GPCRdb in 2023: state-specific structure models using AlphaFold2 and new ligand resources. *Nucleic Acids Res*. 2023;51(D1):D395–D402. <https://doi.org/10.1093/nar/gkac1013>
44. Nordström KJV, Lagerström MC, Waller LMJ, Fredriksson R, Schiöth HB. The Secretin GPCRs descended from the family of adhesion GPCRs. *Mol Biol Evol*. 2009;26(1):71–84. <https://doi.org/10.1093/molbev/msn228>
45. Krishnan A, Dnyansagar R, Almén MS, et al. The GPCR repertoire in the demosponge Amphimedon queenslandica: insights into the GPCR system at the early divergence of animals. *BMC Evol Biol*. 2014;14(1):270. <https://doi.org/10.1186/s12862-014-0270-4>
46. Krasnoperov V, Lu Y, Buryanovsky L, Neubert TA, Ichtchenko K, Petrenko AG. Post-translational proteolytic processing of the calcium-independent receptor of alpha-latrotoxin (CIRL), a natural chimera of the cell adhesion protein and the G protein-coupled receptor. Role of the G protein-coupled receptor proteolysis site (GPS) motif. *J Biol Chem*. 2002;277(48):46518–46526. <https://doi.org/10.1074/jbc.m206415200>
47. Salzman GS, Ackerman SD, Ding C, et al. Structural basis for regulation of GPR56/ADGRG1 by its alternatively spliced extracellular domains. *Neuron*. 2016;91(6):1292–1304. <https://doi.org/10.1016/j.neuron.2016.08.022>
48. Chu TY, Zheng-Gérard C, Huang KY, et al. GPR97 triggers inflammatory processes in human neutrophils via a macromolecular complex upstream of PAR2 activation. *Nat Commun*. 2022;13(1):6385. <https://doi.org/10.1038/s41467-022-34083-1>
49. Wang F, Wang Y, Qiu W, Zhang Q, Yang H, Song G. Crystal structure of the extracellular domains of GPR110. *J Mol Biol*. 2023;435(6):167979. <https://doi.org/10.1016/j.jmb.2023.167979>
50. Kordon SP, Cechova K, Bandekar SJ, et al. Conformational coupling between extracellular and transmembrane domains modulates holo-adhesion GPCR function. *Nat Commun*. 2024;15(1):10545. <https://doi.org/10.1038/s41467-024-54836-4>
51. Leon K, Cunningham RL, Riback JA, et al. Structural basis for adhesion G protein-coupled receptor Gpr126 function. *Nat Commun*. 2020;11(1):194. <https://doi.org/10.1038/s41467-019-14040-1>
52. Pohl F, Seufert F, Chung YK, et al. Structural basis of GAIN domain autoproteolysis and cleavage-resistance in the adhesion G-protein coupled receptors. *Nat Commun*. 2026. <https://doi.org/10.1038/s41467-026-71225-1>
53. Vanhollenbeke B, Stone OA, Bostaille N, et al. Tip cell-specific requirement for an atypical Gpr124- and Reck-dependent Wnt/ β -catenin pathway during brain angiogenesis. *eLife*. 2015;4:e06489. <https://doi.org/10.7554/elife.06489>
54. Eubelen M, Bostaille N, Cabochette P, et al. A molecular mechanism for Wnt ligand-specific signaling. *Science*. 2018;361(6403):eaat1178. <https://doi.org/10.1126/science.aat1178>
55. Vallon M, Yuki K, Nguyen TD, et al. A RECK-WNT7 receptor-ligand interaction enables isoform-specific regulation of Wnt bioavailability. *Cell Rep*. 2018;25(2):339–349.e9. <https://doi.org/10.1016/j.celrep.2018.09.045>

56. America M, Bostaille N, Eubelen M, Martin M, Stainier D, Vanhollebeke B. An integrated model for Gpr124 function in Wnt7a/b signaling among vertebrates. *Cell Rep.* 2022;39(9):110902. <https://doi.org/10.1016/j.celrep.2022.110902>
57. Heiden R, Hannig L, Kuo CJ, Ergün S, Braunger BM, Vallon M. WNT7A/B assemble a GPR124-RECK-LRP5/6 co-receptor complex to activate β -catenin signaling in brain endothelial cells. *J Biol Chem.* 2025;301(10):110682. <https://doi.org/10.1016/j.jbc.2025.110682>
58. Kuhnert F, Mancuso MR, Shamloo A, et al. Essential regulation of CNS angiogenesis by the orphan G protein-coupled receptor GPR124. *Science.* 2010;330(6006):985–989. <https://doi.org/10.1126/science.1196554>
59. Posokhova E, Shukla A, Seaman S, et al. GPR124 functions as a WNT7-specific coactivator of canonical β -catenin signaling. *Cell Rep.* 2015;10(2):123–130. <https://doi.org/10.1016/j.celrep.2014.12.020>
60. Alok A, Lei Z, Jagannathan NS, et al. Wnt proteins synergize to activate β -catenin signaling. *J Cell Sci.* 2017;130(9):1532–1544. <https://doi.org/10.1242/jcs.198093>
61. Vallon M, Essler M. Proteolytically processed soluble tumor endothelial marker (TEM) 5 mediates endothelial cell survival during angiogenesis by linking integrin $\alpha\beta3$ to glycosaminoglycans. *J Biol Chem.* 2006;281(45):34179–34188. <https://doi.org/10.1074/jbc.m605291200>
62. Chong ZS, Ohnishi S, Yusa K, Wright GJ. Pooled extracellular receptor-ligand interaction screening using CRISPR activation. *Genome Biol.* 2018;19(1):205. <https://doi.org/10.1186/s13059-018-1581-3>
63. Yamamoto Y, Irie K, Asada M, Mino A, Mandai K, Takai Y. Direct binding of the human homologue of the Drosophila disc large tumor suppressor gene to seven-pass transmembrane proteins, tumor endothelial marker 5 (TEM5), and a novel TEM5-like protein. *Oncogene.* 2004;23(22):3889–3897. <https://doi.org/10.1038/sj.onc.1207495>
64. Wang J, Miao Y, Wicklein R, et al. RTN4/NoGo-receptor binding to BAI1 adhesion-GPCRs regulates neuronal development. *Cell.* 2021;184(24):5869–5885.e25. <https://doi.org/10.1016/j.cell.2021.10.016>
65. Wang J, Miao Y, Wicklein R, et al. RTN4/NoGo-receptor binding to BAI1 adhesion-GPCRs regulates neuronal development. *Cell.* 2022;185(1):218. <https://doi.org/10.1016/j.cell.2021.12.017>
66. Tu YK, Duman JG, Tolias KF. The adhesion-GPCR BAI1 promotes excitatory synaptogenesis by coordinating bidirectional trans-synaptic signaling. *J Neurosci.* 2018;38(39):8388–8406. <https://doi.org/10.1523/jneurosci.3461-17.2018>
67. Park D, Tosello-Tramont AC, Elliott MR, et al. BAI1 is an engulfment receptor for apoptotic cells upstream of the ELMO/Dock180/Rac module. *Nature.* 2007;450(7168):430–434. <https://doi.org/10.1038/nature06329>
68. Lala T, Doan JK, Takatsu H, Hartzell HC, Shin HW, Hall RA. Phosphatidylserine exposure modulates adhesion GPCR BAI1 (ADGRB1) signaling activity. *J Biol Chem.* 2022;298(12):102685. <https://doi.org/10.1016/j.jbc.2022.102685>
69. Das S, Owen KA, Ly KT, et al. Brain angiogenesis inhibitor 1 (BAI1) is a pattern recognition receptor that mediates macrophage binding and engulfment of Gram-negative bacteria. *Proc Natl Acad Sci U S A.* 2011;108(5):2136–2141. <https://doi.org/10.1073/pnas.1014775108>
70. Koh JT, Kook H, Kee HJ, et al. Extracellular fragment of brain-specific angiogenesis inhibitor 1 suppresses endothelial cell proliferation by blocking $\alpha\beta5$ integrin. *Exp Cell Res.* 2004;294(1):172–184. <https://doi.org/10.1016/j.yexcr.2003.11.008>
71. Oda K, Shiratsuchi T, Nishimori H, et al. Identification of BAIAP2 (BAI-associated protein 2), a novel human homologue of hamster IRSp53, whose SH3 domain interacts with the cytoplasmic domain of BAI1. *Cytogenet Cell Genet.* 1999;84(1–2):75–82. <https://doi.org/10.1159/000015219>
72. Shiratsuchi T, Oda K, Nishimori H, et al. Cloning and characterization of BAP3 (BAI-associated protein 3), a C2 domain-containing protein that interacts with BAI1. *Biochem Biophys Res Commun.* 1998;251(1):158–165. <https://doi.org/10.1006/bbrc.1998.9408>
73. Okajima D, Kudo G, Yokota H. Brain-specific angiogenesis inhibitor 2 (BAI2) may be activated by proteolytic processing. *J Recept Signal Transduct Res.* 2010;30(3):143–153. <https://doi.org/10.3109/10799891003671139>
74. Zencir S, Ovee M, Dobson MJ, Banerjee M, Topcu Z, Mohanty S. Identification of brain-specific angiogenesis inhibitor 2 as an interaction partner of glutaminase interacting protein. *Biochem Biophys Res Commun.* 2011;411(4):792–797. <https://doi.org/10.1016/j.bbrc.2011.07.029>
75. Sticco MJ, Palomino PAP, Lukacovich D, et al. C1QL3 promotes cell-cell adhesion by mediating complex formation between ADGRB3/BAI3 and neuronal pentraxins. *FASEB J.* 2021;35(1):e21194. <https://doi.org/10.1096/fj.202000351rr>
76. Bolliger MF, Martinelli DC, Südhof TC. The cell-adhesion G protein-coupled receptor BAI3 is a high-affinity receptor for C1q-like proteins. *Proc Natl Acad Sci U S A.* 2011;108(6):2534–2539. <https://doi.org/10.1073/pnas.1019577108>
77. Kakegawa W, Mitakidis N, Miura E, et al. Anterograde C1ql1 signaling is required in order to determine and maintain a single-winner climbing fiber in the mouse cerebellum. *Neuron.* 2015;85(2):316–329. <https://doi.org/10.1016/j.neuron.2014.12.020>
78. Hamoud N, Tran V, Aimi T, et al. Spatiotemporal regulation of the GPCR activity of BAI3 by C1ql4 and Stabilin-2 controls myoblast fusion. *Nat Commun.* 2018;9(1):4470. <https://doi.org/10.1038/s41467-018-06897-5>
79. Basta LP, Sil P, Jones RA, Little KA, Hayward-Lara G, Devenport D. Celsr1 and Celsr2 exhibit distinct adhesive interactions and contributions to planar cell polarity. *Front Cell Dev Biol.* 2023;10:1064907. <https://doi.org/10.3389/fcell.2022.1064907>
80. Devenport D, Oristian D, Heller E, Fuchs E. Mitotic internalization of planar cell polarity proteins preserves tissue polarity. *Nat Cell Biol.* 2011;13(8):893–902. <https://doi.org/10.1038/ncb2284>
81. Lei Y, Zhu H, Yang W, Ross ME, Shaw GM, Finnell RH. Identification of novel CELSR1 mutations in spina bifida. *PLoS One.* 2014;9(3):e92207. <https://doi.org/10.1371/journal.pone.0092207>
82. Salašová A, Yokota C, Potěšil D, Zdráhal Z, Bryja V, Arenas E. A proteomic analysis of LRRK2 binding partners reveals interactions with multiple signaling components of the WNT/PCP pathway. *Mol Neurodegener.* 2017;12(1):54. <https://doi.org/10.1186/s13024-017-0193-9>
83. Shima Y, Kawaguchi SY, Kosaka K, et al. Opposing roles in neurite growth control by two seven-pass transmembrane cadherins. *Nat Neurosci.* 2007;10(8):963–969. <https://doi.org/10.1038/nn1933>
84. Lindenmaier LB, Parmentier N, Guo C, Tissir F, Wright KM. Dystroglycan is a scaffold for extracellular axon guidance decisions. *eLife.* 2019;8:e42143. <https://doi.org/10.7554/eLife.42143>
85. Thakar S, Wang L, Yu T, et al. Evidence for opposing roles of Celsr3 and Vangl2 in glutamatergic synapse formation. *Proc Natl Acad Sci U S A.* 2017;114(4):E610–E618. <https://doi.org/10.1073/pnas.1612062114>
86. Frenster JD, Erdjument-Bromage H, Stephan G, et al. PTK7 is a positive allosteric modulator of GPR133 signaling in glioblastoma. *Cell Rep.* 2023;42(7):112679. <https://doi.org/10.1016/j.celrep.2023.112679>
87. Bianchi E, Sun Y, Almansa-Ordóñez A, et al. Control of oviductal fluid flow by the G-protein coupled receptor Adgrl1 is essential for murine embryo transit. *Nat Commun.* 2021;12(1):1251. <https://doi.org/10.1038/s41467-021-21512-w>
88. Yang Z, Ping YQ, Wang MW, et al. Identification, structure, and agonist design of an androgen membrane receptor. *Cell.* 2025;188(6):1589–1604.e24. <https://doi.org/10.1016/j.cell.2025.01.006>
89. Boyden SE, Desai A, Cruise G, et al. Vibratory urticaria associated with a missense variant in ADGRE2. *N Engl J Med.* 2016;374(7):656–663. <https://doi.org/10.1056/nejmoa1500611>
90. Stacey M, Chang GW, Davies JQ, et al. The epidermal growth factor–like domains of the human EMR2 receptor mediate cell attachment through chondroitin sulfate glycosaminoglycans. *Blood.* 2003;102(8):2916–2924. <https://doi.org/10.1182/blood-2002-11-3540>
91. Irmischer S, Brix SR, Zipfel SLH, et al. Serum FHR1 binding to necrotic-type cells activates monocyte inflammation and marks necrotic sites in vasculopathies. *Nat Commun.* 2019;10(1):2961. <https://doi.org/10.1038/s41467-019-10766-0>
92. Stacey M, Lin HH, Hilyard KL, Gordon S, McKnight AJ. Human epidermal growth factor (EGF) module-containing mucin-like hormone Receptor 3 is a new member of the EGF-TM7 family that recognizes a ligand on human macrophages and activated neutrophils. *J Biol Chem.* 2001;276(22):18863–18870. <https://doi.org/10.1074/jbc.m101147200>
93. Stacey M, Chang GW, Sanos SL, et al. EMR4, a novel epidermal growth factor (EGF)-TM7 molecule up-regulated in activated mouse macrophages, binds to a putative cellular ligand on B lymphoma cell line A20. *J Biol Chem.* 2002;277(32):29283–29293. <https://doi.org/10.1074/jbc.m204306200>
94. Liu D, Duan L, Rodda LB, et al. CD97 promotes spleen dendritic cell homeostasis through the mechanosensing of red blood cells. *Science.* 2022;375(6581):eabi5965. <https://doi.org/10.1126/science.abi5965>
95. Hamann J, Stortelers C, Kiss-Toth E, Vogel B, Eichler W, van Lier RAW. Characterization of the CD55 (DAF)-binding site on the seven-span transmembrane receptor CD97. *Eur J Immunol.* 1998;28(5):1701–1707. [https://doi.org/10.1002/\(sici\)1521-4141\(199805\)28:05<1701::aid-immu1701>3.0.co;2-2](https://doi.org/10.1002/(sici)1521-4141(199805)28:05<1701::aid-immu1701>3.0.co;2-2)
96. Hamann J, Vogel B, van Schijndel GM, van Lier RA. The seven-span transmembrane receptor CD97 has a cellular ligand (CD55, DAF). *J Exp Med.* 1996;184(3):1185–1189. <https://doi.org/10.1084/jem.184.3.1185>
97. Liu D, Winer BY, Chou MY, et al. Dynamic encounters with red blood cells trigger splenic marginal zone B cell retention and function. *Nat Immunol.* 2024;25(1):142–154. <https://doi.org/10.1038/s41590-023-01690-z>
98. Kop EN, Kwakkenbos MJ, Teske GJD, et al. Identification of the epidermal growth factor–TM7 receptor EMR2 and its ligand dermatan sulfate in rheumatoid synovial tissue. *Arthritis Rheum.* 2005;52(2):442–450. <https://doi.org/10.1002/art.20788>
99. Wang T, Ward Y, Tian L, et al. CD97, an adhesion receptor on inflammatory cells, stimulates angiogenesis through binding integrin counterreceptors on endothelial cells. *Blood.* 2005;105(7):2836–2844. <https://doi.org/10.1182/blood-2004-07-2878>
100. Ravn-Boess N, Roy N, Hattori T, et al. The expression profile and tumorigenic mechanisms of CD97 (ADGRE5) in glioblastoma render it a targetable vulnerability. *Cell Rep.* 2023;42(11):113374. <https://doi.org/10.1016/j.celrep.2023.113374>
101. Wandel E, Saalbach A, Sittig D, Gebhardt C, Aust G. Thy-1 (CD90) is an interacting partner for CD97 on activated endothelial cells. *J Immunol.* 2012;188(3):1442–1450. <https://doi.org/10.4049/jimmunol.1003944>
102. Ward Y, Lake R, Yin JJ, et al. LPA receptor heterodimerizes with CD97 to amplify LPA-initiated RHO-dependent signaling and invasion in prostate cancer cells. *Cancer Res.* 2011;71(23):7301–7311. <https://doi.org/10.1158/0008-5472.can.11-2381>

103. Ward Y, Lake R, Martin PL, et al. CD97 amplifies LPA receptor signaling and promotes thyroid cancer progression in a mouse model. *Oncogene*. 2013;32(22):2726–2738. <https://doi.org/10.1038/ncr.2012.301>
104. Chang H, Hou P, Wang X, et al. CD97 negatively regulates the innate immune response against RNA viruses by promoting RNF125-mediated RIG-I degradation. *Cell Mol Immunol*. 2023;20(12):1457–1471. <https://doi.org/10.1038/s41423-023-01103-z>
105. Chen H, Rosen CE, González-Hernández JA, et al. Highly multiplexed bioactivity screening reveals human and microbiota metabolome-GPCRome interactions. *Cell*. 2023;186(14):3095–3110.e19. <https://doi.org/10.1016/j.cell.2023.05.024>
106. Cerny O, Godlee C, Tocci R, et al. CD97 stabilises the immunological synapse between dendritic cells and T cells and is targeted for degradation by the *Salmonella* effector SteD. *PLoS Pathog*. 2021;17(7):e1009771. <https://doi.org/10.1371/journal.ppat.1009771>
107. Hilbig D, Sittig D, Hoffmann F, et al. Mechano-dependent phosphorylation of the PDZ-binding motif of CD97/ADGRE5 modulates cellular detachment. *Cell Rep*. 2018;24(8):1986–1995. <https://doi.org/10.1016/j.celrep.2018.07.071>
108. Lee JW, Huang BX, Kwon H, et al. Orphan GPR110 (ADGRF1) targeted by N-docosahexaenoyl ethanolamine in development of neurons and cognitive function. *Nat Commun*. 2016;7(1):13123. <https://doi.org/10.1038/ncomms13123>
109. Huang BX, Hu X, Kwon HS, et al. Synaptamide activates the adhesion GPCR GPR110 (ADGRF1) through GAIN domain binding. *Commun Biol*. 2020;3(1):109. <https://doi.org/10.1038/s42003-020-0831-6>
110. Huang BX, Chen H, Joo Y, et al. Interaction between GPR110 (ADGRF1) and tight junction protein occludin implicated in blood-brain barrier permeability. *iScience*. 2023;26(4):106550. <https://doi.org/10.1016/j.isci.2023.106550>
111. Abdulkareem NM, Bhat R, Castillo M, et al. Interactions between ADGRF1 (GPR110) and extracellular matrix proteins govern its effects on tumorigenesis in HER2-positive breast cancer. *Br J Pharmacol*. 2025;182(11):2524–2541. <https://doi.org/10.1111/bph.17463>
112. Fukuzawa T, Ishida J, Kato A, et al. Lung surfactant levels are regulated by Ig-Hepta/GPR116 by monitoring surfactant protein D. *PLoS One*. 2013;8(7):e69451. <https://doi.org/10.1371/journal.pone.0069451>
113. Georgiadi A, Lopez-Salazar V, Merabhi RE, et al. Orphan GPR116 mediates the insulin sensitizing effects of the hepatokine FND4 in adipose tissue. *Nat Commun*. 2021;12(1):2999. <https://doi.org/10.1038/s41467-021-22579-1>
114. Li T, Chiou B, Gilman CK, et al. A splicing isoform of GPR56 mediates microglial synaptic refinement via phosphatidylserine binding. *EMBO J*. 2020;39(16). EMBJ2019104136:e104136. <https://doi.org/10.15252/embj.2019104136>
115. Xu L, Begum S, Hearn JD, Hynes RO. GPR56, an atypical G protein-coupled receptor, binds tissue transglutaminase, TG2, and inhibits melanoma tumor growth and metastasis. *Proc Natl Acad Sci U S A*. 2006;103(24):9023–9028. <https://doi.org/10.1073/pnas.0602681103>
116. Bauer L, Edwards J, Heil A, et al. Mesenchymal transglutaminase 2 activates epithelial ADAM17: link to G-protein-coupled receptor 56 (ADGRG1) signalling. *Int J Mol Sci*. 2024;25(4):2329. <https://doi.org/10.3390/ijms25042329>
117. Luo R, Jeong SJ, Jin Z, Stokes N, Li S, Piao X. G protein-coupled receptor 56 and collagen III, a receptor-ligand pair, regulates cortical development and lamination. *Proc Natl Acad Sci U S A*. 2011;108(31):12925–12930. <https://doi.org/10.1073/pnas.1104821108>
118. Zhu B, Luo R, Jin P, et al. GAIN domain-mediated cleavage is required for activation of G protein-coupled receptor 56 (GPR56) by its natural ligands and a small-molecule agonist. *J Biol Chem*. 2019;294(50):19246–19254. <https://doi.org/10.1074/jbc.ra119.008234>
119. Chen H, Nwe PK, Yang Y, et al. A forward chemical genetic screen reveals gut microbiota metabolites that modulate host physiology. *Cell*. 2019;177(5):1217–1231.e18. <https://doi.org/10.1016/j.cell.2019.03.036>
120. Chiang NY, Chang GW, Huang YS, et al. Heparin interacts with the adhesion GPCR GPR56, reduces receptor shedding, and promotes cell adhesion and motility. *J Cell Sci*. 2016;129(11):2156–2169. <https://doi.org/10.1242/jcs.174458>
121. Jin G, Sakitani K, Wang H, et al. The G-protein coupled receptor 56, expressed in colonic stem and cancer cells, binds progastrin to promote proliferation and carcinogenesis. *Oncotarget*. 2017;8(25):40606–40619. <https://doi.org/10.18632/oncotarget.16506>
122. Little KD, Hemler ME, Stipp CS. Dynamic regulation of a GPCR-tetraspanin-G protein complex on intact cells: central role of CD81 in facilitating GPR56-Ga α /11 association. *Mol Biol Cell*. 2004;15(5):2375–2387. <https://doi.org/10.1091/mbc.e03-12-0886>
123. Ackerman SD, Luo R, Poitelson Y, et al. GPR56/ADGRG1 regulates development and maintenance of peripheral myelin. *J Exp Med*. 2018;215(3):941–961. <https://doi.org/10.1084/jem.20161714>
124. Chatterjee T, Zhang S, Posey TA, et al. Anti-GPR56 monoclonal antibody potentiates GPR56-mediated Src-Fak signaling to modulate cell adhesion. *J Biol Chem*. 2021;296:100261. <https://doi.org/10.1016/j.jbc.2021.100261>
125. Stoveken HM, Bahr LL, Anders MW, Wojtovich AP, Smrcka AV, Tall GG. Dihydromunduletone is a small-molecule selective adhesion G protein-coupled receptor antagonist. *Mol Pharmacol*. 2016;90(3):214–224. <https://doi.org/10.1124/mol.116.104828>
126. Stoveken HM, Larsen SD, Smrcka AV, Tall GG. Gedunin- and Khivorin-derivatives are small-molecule partial agonists for adhesion G protein-coupled receptors GPR56/ADGRG1 and GPR114/ADGRG5. *Mol Pharmacol*. 2018;93(5):477–488. <https://doi.org/10.1124/mol.117.111476>
127. Vizurraga AL, Robertson MJ, Yu M, Skiniotis G, Tall GG. Hexahydroquinoline derivatives are selective agonists for the adhesion G protein-coupled receptor ADGRG1/GPR56. *Mol Pharmacol*. 2023;104(1):28–41. <https://doi.org/10.1124/molpharm.123.000688>
128. Lin H, Xiao P, Bu RQ, et al. Structures of the ADGRG2–Gs complex in apo and ligand-bound forms. *Nat Chem Biol*. 2022;18(11):1196–1203. <https://doi.org/10.1038/s41589-022-01084-6>
129. Ping YQ, Mao C, Xiao P, et al. Structures of the glucocorticoid-bound adhesion receptor GPR97–Go complex. *Nature*. 2021;589(7843):620–626. <https://doi.org/10.1038/s41586-020-03083-w>
130. Gupta J, Swaminath G, Danao J, Tian H, Li Y, Wu X. Signaling property study of adhesion G-protein-coupled receptors. *FEBS Lett*. 2012;586(8):1214–1219. <https://doi.org/10.1016/j.febslet.2012.03.014>
131. Southern C, Cook JM, Neetoo-Isselee Z, et al. Screening β -arrestin recruitment for the identification of natural ligands for orphan G-protein-coupled receptors. *J Biomol Screen*. 2013;18(5):599–609. <https://doi.org/10.1177/1087057113475480>
132. Paavola KJ, Sidik H, Zuchero JB, Eckart M, Talbot WS. Type IV collagen is an activating ligand for the adhesion G protein-coupled receptor GPR126. *Sci Signal*. 2014;7(338):ra76. <https://doi.org/10.1126/scisignal.2005347>
133. Wilde C, Chaudhry PM, Luo R, Simon KU, Piao X, Liebscher I. Collagen VI is a Gi-biased ligand of the adhesion GPCR GPR126/ADGRG6. *Cells*. 2023;12(11):1551. <https://doi.org/10.3390/cells12111551>
134. Petersen SC, Luo R, Liebscher I, et al. The adhesion GPCR GPR126 has distinct, domain-dependent functions in Schwann cell development mediated by interaction with Laminin-211. *Neuron*. 2015;85(4):755–769. <https://doi.org/10.1016/j.neuron.2014.12.057>
135. Küffer A, Lakkaraju AKK, Mogha A, et al. The prion protein is an agonistic ligand of the G protein-coupled receptor Adgrg6. *Nature*. 2016;536(7617):464–468. <https://doi.org/10.1038/nature19312>
136. An W, Lin H, Ma L, et al. Progesterone activates GPR126 to promote breast cancer development via the Gi pathway. *Proc Natl Acad Sci U S A*. 2022;119(15):e2117004119. <https://doi.org/10.1073/pnas.2117004119>
137. Bradley EC, Cunningham RL, Wilde C, et al. In vivo identification of small molecules mediating Gpr126/Adgrg6 signaling during Schwann cell development. *Ann N Y Acad Sci*. 2019;1456(1):44–63. <https://doi.org/10.1111/nyas.14233>
138. Asad A, Shahidan NO, De La Vega De León A, Wiggins GR, Whitfield TT, Baxendale S. A screen of pharmacologically active compounds to identify modulators of the Adgrg6/Gpr126 signalling pathway in zebrafish embryos. *Basic Clin Pharmacol Toxicol*. 2023;133(4):364–377. <https://doi.org/10.1111/bcpt.13923>
139. Silva JP, Leliana VG, Ermolyuk YS, et al. Latrophilin 1 and its endogenous ligand Lasso/teneurin-2 form a high-affinity transsynaptic receptor pair with signaling capabilities. *Proc Natl Acad Sci U S A*. 2011;108(29):12113–12118. <https://doi.org/10.1073/pnas.1019434108>
140. O'Sullivan ML, de Wit J, Savas JN, et al. FLRT proteins are endogenous latrophilin ligands and regulate excitatory synapse development. *Neuron*. 2012;73(5):903–910. <https://doi.org/10.1016/j.neuron.2012.01.018>
141. Boucard AA, Ko J, Südhof TC. High affinity neurexin binding to cell adhesion G-protein-coupled receptor CIRL1/Latrophilin-1 produces an intercellular adhesion complex. *J Biol Chem*. 2012;287(12):9399–9413. <https://doi.org/10.1074/jbc.m111.318659>
142. Zuko A, Oguro-Ando A, Post H, et al. Association of cell adhesion molecules Contactin-6 and Latrophilin-1 regulates neuronal apoptosis. *Front Mol Neurosci*. 2016;9:143. <https://doi.org/10.3389/fnmol.2016.00143>
143. Kreienkamp HJ, Zitzer H, Gundelfinger ED, Richter D, Böckers TM. The calcium-independent receptor for α -latrotoxin from human and rodent brains interacts with members of the ProSAP/SSTRIP/Shank family of multidomain proteins. *J Biol Chem*. 2000;275(42):32387–32390. <https://doi.org/10.1074/jbc.c000490200>
144. Popova NV, Plotnikov A, Deev IE, Petrenko AG. Interaction of calcium-independent latrotoxin receptor with intracellular adapter protein TRIP8b. *Dokl Biochem Biophys*. 2007;414:149–151. <https://doi.org/10.1134/s1607672907030155>
145. Popova NV, Plotnikov AN, Ziganshin RKH, Deyev IE, Petrenko AG. Analysis of proteins interacting with TRIP8b adapter. *Biochemistry (Mosc)*. 2008;73(6):644–651. <https://doi.org/10.1134/s0006297908060035>
146. Chhabra KH, Bathina S, Faniyan TS, et al. ADGLR1 is a glucose receptor involved in mediating energy and glucose homeostasis. *Diabetologia*. 2024;67(1):170–189. <https://doi.org/10.1007/s00125-023-06010-6>
147. Kordon SP, Dutka P, Adamska JM, et al. Isoform- and ligand-specific modulation of the adhesion GPCR ADGLR3/Latrophilin3 by a synthetic binder. *Nat Commun*. 2023;14(1):635. <https://doi.org/10.1038/s41467-023-36312-7>
148. Bittner MA, Krasnoperov VG, Stuenkel EL, Petrenko AG, Holz RW. A Ca $^{2+}$ -independent receptor for α -latrotoxin, CIRL, mediates effects on secretion via multiple mechanisms. *J Neurosci*. 1998;18(8):2914–2922. <https://doi.org/10.1523/jneurosci.18-08-02914.1998>
149. Jackson VA, Meijer DH, Carrasquero M, et al. Structures of teneurin adhesion receptors reveal an ancient fold for cell-cell interaction. *Nat Commun*. 2018;9(1):1079. <https://doi.org/10.1038/s41467-018-03460-0>
150. Yin GN, Kim DK, Kang JI, et al. Latrophilin-2 is a novel receptor of LRG1 that rescues vascular and neurological abnormalities and restores diabetic

- erectile function. *Exp Mol Med*. 2022;54(5):626–638. <https://doi.org/10.1038/s12276-022-00773-5>
151. Yang J, Yin GN, Kim DK, et al. Crystal structure of LRG1 and the functional significance of LRG1 glycan for LPHN2 activation. *Exp Mol Med*. 2023;55(5):1013–1022. <https://doi.org/10.1038/s12276-023-00992-4>
 152. Amisten S, Rezel M, Grossi M, et al. The DNA repair factor ku80 binds and activates the adhesion receptor ELTD1/ADGRL4. *Biochem Biophys Res Commun*. 2025;764:151785. <https://doi.org/10.1016/j.bbrc.2025.151785>
 153. Scholz N, Dahse AK, Kemkemmer M, et al. Molecular sensing of mechano- and ligand-dependent adhesion GPCR dissociation. *Nature*. 2023;615(7954):945–953. <https://doi.org/10.1038/s41586-023-05802-5>
 154. Lavalou J, Mao Q, Harmansa S, et al. Formation of polarized contractile interfaces by self-organized Toll-8/Cir1 GPCR asymmetry. *Dev Cell*. 2021;56(11):1574–1588.e7. <https://doi.org/10.1016/j.devcel.2021.03.030>
 155. Mühlhfeld S, Schmitt-Wrede HP, Harder A, Wunderlich F. Fmrfamide-like neuropeptides as putative ligands of the latrophilin-like HC110-R from *Haemonchus contortus*. *Mol Biochem Parasitol*. 2009;164(2):162–164. <https://doi.org/10.1016/j.molbiopara.2008.12.003>
 156. Post WB, Groß VE, Matúš D, et al. Notch activity is modulated by the aGPCR latrophilin binding the DSL ligand in *C. elegans*. *Nat Commun*. 2025;16(1):6461. <https://doi.org/10.1038/s41467-025-61730-0>
 157. Reiners J, van Wijk E, Märker T, et al. Scaffold protein harmonin (USH1C) provides molecular links between Usher syndrome type 1 and type 2. *Hum Mol Genet*. 2005;14(24):3933–3943. <https://doi.org/10.1093/hmg/ddi417>
 158. van Wijk E, van der Zwaag B, Peters T, et al. The DFNB31 gene product whirlin connects to the Usher protein network in the cochlea and retina by direct association with USH2A and VLGR1. *Hum Mol Genet*. 2006;15(5):751–765. <https://doi.org/10.1093/hmg/ddi490>
 159. Davletov BA, Shamotoienko OG, Lelianova VG, Grishin EV, Ushkaryov YA. Isolation and biochemical characterization of a Ca²⁺-independent α -latrotoxin-binding protein. *J Biol Chem*. 1996;271(38):23239–23245. <https://doi.org/10.1074/jbc.271.38.23239>
 160. Krasnoperov VG, Beavis R, Chepurny OG, Little AR, Plotnikov AN, Petrenko AG. The calcium-independent receptor of α -latrotoxin is not a neurexin. *Biochem Biophys Res Commun*. 1996;227(3):868–875. <https://doi.org/10.1006/bbrc.1996.1598>
 161. Lelianova VG, Davletov BA, Sterling A, et al. α -latrotoxin receptor, latrophilin, is a novel member of the secretin family of G protein-coupled receptors. *J Biol Chem*. 1997;272(34):21504–21508. <https://doi.org/10.1074/jbc.272.34.21504>
 162. Wei Z, Liao L, Han Y, et al. Structural basis of calcium-dependent C1q/BAI assemblies in synaptic connectivity. *Research Square*. 2025. <https://doi.org/10.21203/rs.3.rs-6014540/v1>
 163. Miao Y, Wang H, Jude KM, et al. Structure of the complex of C1q-like 3 protein with adhesion-GPCR BAI3. *Commun Biol*. 2025;8(1):693. <https://doi.org/10.1038/s42003-025-08112-w>
 164. Ressler S, Vu BK, Vivona S, Martinelli DC, Südhof TC, Brunger AT. Structures of C1q-like proteins reveal unique features among the C1q/TNF superfamily. *Structure*. 2015;23(4):688–699. <https://doi.org/10.1016/j.str.2015.01.019>
 165. Martinelli DC, Chew KS, Rohlmann A, et al. Expression of C1ql3 in discrete neuronal populations controls efferent synapse numbers and diverse behaviors. *Neuron*. 2016;91(5):1034–1051. <https://doi.org/10.1016/j.neuron.2016.07.002>
 166. Elegheert J, Kakegawa W, Clay JE, et al. Structural basis for integration of GluR receptors within synaptic organizer complexes. *Science*. 2016;353(6296):295–299. <https://doi.org/10.1126/science.aae0104>
 167. Niu M, Xu S, Yang J, et al. Structural basis for CD97 recognition of the decay-accelerating factor CD55 suggests mechanosensitive activation of adhesion GPCRs. *J Biol Chem*. 2021;296:100776. <https://doi.org/10.1016/j.jbc.2021.100776>
 168. Abbott RJM, Spendlove I, Roversi P, et al. Structural and functional characterization of a novel T cell receptor co-regulatory protein complex, CD97-CD55. *J Biol Chem*. 2007;282(30):22023–22032. <https://doi.org/10.1074/jbc.M702588200>
 169. Kieslich B, Weiß RH, Brendler J, Ricken A, Schöneberg T, Sträter N. The dimerized pentraxin-like domain of the adhesion G protein-coupled receptor 112 (ADGRG4) suggests function in sensing mechanical forces. *J Biol Chem*. 2023;299(12):105356. <https://doi.org/10.1016/j.jbc.2023.105356>
 170. Dintzner E, Bandekar SJ, Leon K, Cechova K, Vafabakhsh R, Araç D. The far extracellular CUB domain of the adhesion GPCR ADGRG6/GPR126 is a key regulator of receptor signaling. *Preprint*. Posted online July 25, 2024. bioRxiv 580607. <https://doi.org/10.1101/2024.02.16.580607>
 171. Barros-Álvarez X, Nwokonko RM, Vizurraga A, et al. The tethered peptide activation mechanism of adhesion GPCRs. *Nature*. 2022;604(7907):757–762. <https://doi.org/10.1038/s41586-022-04575-7>
 172. Ping YQ, Xiao P, Yang F, et al. Structural basis for the tethered peptide activation of adhesion GPCRs. *Nature*. 2022;604(7907):763–770. <https://doi.org/10.1038/s41586-022-04619-y>
 173. Qu X, Qiu N, Wang M, et al. Structural basis of tethered agonism of the adhesion GPCRs ADGRD1 and ADGRF1. *Nature*. 2022;604(7907):779–785. <https://doi.org/10.1038/s41586-022-04580-w>
 174. Xiao P, Guo S, Wen X, et al. Tethered peptide activation mechanism of the adhesion GPCRs ADGRG2 and ADGRG4. *Nature*. 2022;604(7907):771–778. <https://doi.org/10.1038/s41586-022-04590-8>
 175. Gupta C, Bernadyn TF, Tall GG. Structural clarity is brought to adhesion G protein-coupled receptor tethered agonism. *Basic Clin Pharmacol Toxicol*. 2023;133(4):295–300. <https://doi.org/10.1111/bcpt.13831>
 176. Demberg LM, Rothmund S, Schöneberg T, Liebscher I. Identification of the tethered peptide agonist of the adhesion G protein-coupled receptor GPR64/ADGRG2. *Biochem Biophys Res Commun*. 2015;464(3):743–747. <https://doi.org/10.1016/j.bbrc.2015.07.020>
 177. Tesmer JJG. A GAIN in understanding autoprolytic G protein-coupled receptors and polycystic kidney disease proteins. *EMBO J*. 2012;31(6):1334–1335. <https://doi.org/10.1038/emboj.2012.51>
 178. Nieberler M, Kittel RJ, Petrenko AG, Lin HH, Langenhan T. Control of adhesion GPCR function through proteolytic processing. *Handb Exp Pharmacol*. 2016;234:83–109. https://doi.org/10.1007/978-3-319-41523-9_5
 179. VanHook AM. GAINing autoprolytic activity. *Sci Signal*. 2012;5(217):ec93–ec93. <https://doi.org/10.1126/scisignal.2003072>
 180. Yona S, Lin HH, Siu WO, Gordon S, Stacey M. Adhesion-GPCRs: emerging roles for novel receptors. *Trends Biochem Sci*. 2008;33(10):491–500. <https://doi.org/10.1016/j.tibs.2008.07.005>
 181. Lin HH, Stacey M, Yona S, Chang GW. GPS proteolytic cleavage of adhesion-GPCRs. *Adv Exp Med Biol*. 2010;706:49–58. https://doi.org/10.1007/978-1-4419-7913-1_4
 182. Wei W, Hackmann K, Xu H, Germino G, Qian F. Characterization of cis-autoproteolysis of Polycystin-1, the product of human polycystic kidney disease 1 gene. *J Biol Chem*. 2007;282(30):21729–21737. <https://doi.org/10.1074/jbc.M703218200>
 183. Abe J, Fukuzawa T, Hirose S. Cleavage of Ig-hepta at a “SEA” module and at a conserved G protein-coupled receptor proteolytic site. *J Biol Chem*. 2002;277(26):23391–23398. <https://doi.org/10.1074/jbc.M110877200>
 184. Chung YK, Ihling CH, Zielke L, Mathiasen S, Sinz A, Langenhan T. Self-cleavage of the GAIN domain of adhesion G protein-coupled receptors requires multiple domain-extrinsic factors. *Nat Commun*. 2025;16(1):8736. <https://doi.org/10.1038/s41467-025-64589-3>
 185. Hsiao CC, Cheng KF, Chen HY, et al. Site-specific N-glycosylation regulates the GPS auto-proteolysis of CD97. *FEBS Lett*. 2009;583(19):3285–3290. <https://doi.org/10.1016/j.febslet.2009.09.001>
 186. Jayachandran A, Annadurai P, Upadhyay M, et al. Domain-specific N-glycosylation of the adhesion G-protein-coupled receptor ADGRG6 N-terminal fragment regulates trafficking, proteolytic processing, and signaling. *Mol Biol Cell*. 2025;36(8):ar101. <https://doi.org/10.1091/mbc.e25-02-0060>
 187. Seufert F, Chung YK, Schick R, et al. Mechanistic insights into adhesion GPCR autoproteolysis by a multiscale computational approach. *Research Square*. 2025. <https://doi.org/10.21203/rs.3.rs-7121662/v1>
 188. Perry-Hauser NA, Du Rand JRD, Lee KH, Shi L, Javitch JA. N-terminal fragment shedding contributes to signaling of the full-length adhesion receptor ADGRL3. *J Biol Chem*. 2025;301(2):108174. <https://doi.org/10.1016/j.jbc.2025.108174>
 189. Cork SM, Kaur B, Devi NS, et al. A proprotein convertase/MMP-14 proteolytic cascade releases a novel 40 kDa vasculostatin from tumor suppressor BAI1. *Oncogene*. 2012;31(50):5144–5152. <https://doi.org/10.1038/onc.2012.1>
 190. Lehmann L, Groß VE, Behlendorf R, Prömel S. The N terminus-only function of adhesion GPCRs: emerging concepts. *Trends Pharmacol Sci*. 2025;46(3):231–248. <https://doi.org/10.1016/j.tips.2025.01.004>
 191. Vallon M, Aubele P, Janssen KP, Essler M. Thrombin-induced shedding of tumour endothelial marker 5 and exposure of its RGD motif are regulated by cell-surface protein disulfide-isomerase. *Biochem J*. 2012;441(3):937–944. <https://doi.org/10.1042/bj20111682>
 192. Kaur B, Brat DJ, Devi NS, Van Meir EG. Vasculostatin, a proteolytic fragment of Brain Angiogenesis Inhibitor 1, is an antiangiogenic and antitumorigenic factor. *Oncogene*. 2005;24(22):3632–3642. <https://doi.org/10.1038/sj.onc.1208317>
 193. Prömel S, Langenhan T, Araç D. Matching structure with function: the GAIN domain of adhesion-GPCR and PKD1-like proteins. *Trends Pharmacol Sci*. 2013;34(8):470–478. <https://doi.org/10.1016/j.tips.2013.06.002>
 194. Dannhäuser S, Lux TJ, Hu C, et al. Antinociceptive modulation by the adhesion GPCR C1RL promotes mechanosensory signal discrimination. *eLife*. 2020;9:e56738. <https://doi.org/10.7554/eLife.56738>
 195. Scholz N, Guan C, Nieberler M, et al. Mechano-dependent signaling by latrophilin/C1RL quenches cAMP in proprioceptive neurons. *eLife*. 2017;6:e28360. <https://doi.org/10.7554/eLife.28360>
 196. Yu S, Hackmann K, Gao J, et al. Essential role of cleavage of Polycystin-1 at G protein-coupled receptor proteolytic site for kidney tubular structure. *Proc Natl Acad Sci U S A*. 2007;104(47):18688–18693. <https://doi.org/10.1073/pnas.0708217104>
 197. Kurbegovic A, Kim H, Xu H, et al. Novel functional complexity of Polycystin-1 by GPS cleavage in vivo: role in polycystic kidney disease. *Mol Cell Biol*. 2014;34(17):3341–3353. <https://doi.org/10.1128/mcb.00687-14>
 198. Mengerink KJ, Moy GW, Vacquier VD. suREJ3, a Polycystin-1 protein, is cleaved at the GPS domain and localizes to the acrosomal region of sea urchin sperm. *J Biol Chem*. 2002;277(2):943–948. <https://doi.org/10.1074/jbc.M109673200>
 199. Folts CJ, Giera S, Li T, Piao X. Adhesion G protein-coupled receptors as drug targets for neurological diseases. *Trends Pharmacol Sci*. 2019;40(4):278–293. <https://doi.org/10.1016/j.tips.2019.02.003>
 200. Chiang NY, Hsiao CC, Huang YS, et al. Disease-associated GPR56 mutations cause bilateral frontoparietal polymicrogyria via multiple mechanisms. *J Biol*

- Chem. 2011;286(16):14215–14225. <https://doi.org/10.1074/jbc.m110.183830>
201. Jin Z, Tietjen I, Bu L, et al. Disease-associated mutations affect GPR56 protein trafficking and cell surface expression. *Hum Mol Genet.* 2007;16(16):1972–1985. <https://doi.org/10.1093/hmg/ddm144>
 202. Trudel M, Yao Q, Qian F. The role of G-protein-coupled receptor proteolysis site cleavage of polycystin-1 in renal physiology and polycystic kidney disease. *Cells.* 2016;5(1):3. <https://doi.org/10.3390/cells5010003>
 203. Lin HH, Stacey M, Saxby C, et al. Molecular analysis of the epidermal growth factor-like short consensus repeat domain-mediated protein-protein interactions DISSECTION OF THE CD97-CD55 COMPLEX. *J Biol Chem.* 2001;276(26):24160–24169. <https://doi.org/10.1074/jbc.m101770200>
 204. Knierim AB, Röhre J, Çakir MV, et al. Genetic basis of functional variability in adhesion G protein-coupled receptors. *Sci Rep.* 2019;9(1):11036. <https://doi.org/10.1038/s41598-019-46265-x>
 205. Parag RR, Yamamoto T, Saito K, Zhu D, Yang L, Van Meir EG. Novel isoforms of adhesion G protein-coupled receptor B1 (ADGRB1/BAI1) generated from an alternative promoter in Intron 17. *Mol Neurobiol.* 2025;62(1):900–917. <https://doi.org/10.1007/s12035-024-04293-3>
 206. Uhlén M, Fagerberg L, Hallström BM, et al. Proteomics. Tissue-based map of the human proteome. *Science.* 2015;347(6220):1260419. <https://doi.org/10.1126/science.1260419>
 207. Hamann J, Kwakkenbos MJ, de Jong EC, Heus H, Olsen AS, van Lier RAW. Inactivation of the EGF-TM7 receptor EMR4 after the Pan-Homo divergence. *Eur J Immunol.* 2003;33(5):1365–1371. <https://doi.org/10.1002/eji.200323881>
 208. Caminschi I, Vandenabeele S, Sofi M, et al. Gene structure and transcript analysis of the human and mouse EGF-TM7 molecule, FIRE. *DNA Seq.* 2006;17(1):8–14. <https://doi.org/10.1080/10425170500355737>
 209. Wang S, DeLeon C, Sun W, Quake SR, Roth BL, Südhof TC. Alternative splicing of latrophilin-3 controls synapse formation. *Nature.* 2024;626(7997):128–135. <https://doi.org/10.1038/s41586-023-06913-9>
 210. Sando R, Jiang X, Südhof TC. Latrophilin GPCRs direct synapse specificity by coincident binding of FLRTs and teneurins. *Science.* 2019;363(6429):eaav7969. <https://doi.org/10.1126/science.aav7969>
 211. Bormann A, Körner MB, Dahse AK, et al. Intron retention of an adhesion GPCR generates 1TM isoforms required for 7TM-GPCR function. *Cell Rep.* 2025;44(1):115078. <https://doi.org/10.1016/j.celrep.2024.115078>
 212. Garbett K, Zheng C, Drube J, Hoffmann C, Gurevich VV, Sando RC. Cytoplasmic tail composition modulates the G protein and arrestin-3 signaling bias of the adhesion GPCR LPHN2. Preprint. Posted online July 6, 2025. bioRxiv 663222. <https://doi.org/10.1101/2025.07.04.663222>
 213. Ovando-Zambrano JC, Arias-Montaño JA, Boucard AA. Alternative splicing event modifying ADGRL1/latrophilin-1 cytoplasmic tail promotes both opposing and dual cAMP signaling pathways. *Ann N Y Acad Sci.* 2019;1456(1):168–185. <https://doi.org/10.1111/nyas.14198>
 214. Boucard AA, Maxeiner S, Südhof TC. Latrophilins function as heterophilic cell-adhesion molecules by binding to teneurins: regulation by alternative splicing. *J Biol Chem.* 2014;289(1):387–402. <https://doi.org/10.1074/jbc.m113.504779>
 215. Röhre J, Thor D, Winkler J, et al. Involvement of the adhesion GPCRs latrophilins in the regulation of insulin release. *Cell Rep.* 2019;26(6):1573–1584.e5. <https://doi.org/10.1016/j.celrep.2019.01.040>
 216. Wilde C, Fischer L, Lede V, et al. The constitutive activity of the adhesion GPCR GPR114/ADGRG5 is mediated by its tethered agonist. *FASEB J.* 2016;30(2):666–673. <https://doi.org/10.1096/fj.15-276220>
 217. Hamann J, Eichler W, Hamann D, et al. Expression cloning and chromosomal mapping of the leukocyte activation antigen CD97, a new seven-span transmembrane molecule of the secretion receptor superfamily with an unusual extracellular domain. *J Immunol.* 1995;155(4):1942–1950. <https://doi.org/10.4049/jimmunol.155.4.1942>
 218. Wang Y, Cao Y, Hays CL, et al. Adhesion GPCR latrophilin 3 regulates synaptic function of cone photoreceptors in a trans-synaptic manner. *Proc Natl Acad Sci U S A.* 2021;118(45):e2106694118. <https://doi.org/10.1073/pnas.2106694118>
 219. Matúš D, Post WB, Groß VE, et al. The N terminus-only (trans) function of the adhesion G protein-coupled receptor latrophilin-1 controls multiple processes in reproduction of *Caenorhabditis elegans*. *G3 (Bethesda).* 2024;14(11):jkæ206. <https://doi.org/10.1093/g3journal/jkæ206>
 220. Li T, Luo R, Schmidt R, et al. GPR56 S4 variant is required for microglia-mediated synaptic pruning. *Glia.* 2023;71(3):560–570. <https://doi.org/10.1002/glia.24293>
 221. Robinson A, Escuin S, Doudney K, et al. Mutations in the planar cell polarity genes CELSR1 and SCRIB are associated with the severe neural tube defect craniorachischisis. *Hum Mutat.* 2012;33(2):440–447. <https://doi.org/10.1002/humu.21662>
 222. Duman JG, Tzeng CP, Tu YK, et al. The adhesion-GPCR BAI1 regulates synaptogenesis by controlling the recruitment of the Par3/Tiam1 polarity complex to synaptic sites. *J Neurosci.* 2013;33(16):6964–6978. <https://doi.org/10.1523/jneurosci.3978-12.2013>
 223. Matúš D, Lopez JM, Sando RC, Südhof TC. Essential role of latrophilin-1 adhesion GPCR nanoclusters in inhibitory synapses. *J Neurosci.* 2024;44(23):e1978232024. <https://doi.org/10.1523/jneurosci.1978-23.2024>
 224. Volynski KE, Silva JP, Lelanova VG, Rahman MA, Hopkins C, Ashkaryov YA. Latrophilin fragments behave as independent proteins that associate and signal on binding of LTXN4C. *EMBO J.* 2004;23(22):4423–4433. <https://doi.org/10.1038/sj.emboj.7600443>
 225. Malaker SA, Riley NM, Shon DJ, et al. Revealing the human mucinome. *Nat Commun.* 2022;13(1):3542. <https://doi.org/10.1038/s41467-022-13062-4>
 226. Frenster JD, Stephan G, Ravn-Boess N, et al. Functional impact of intramolecular cleavage and dissociation of adhesion G protein-coupled receptor GPR133 (ADGRD1) on canonical signaling. *J Biol Chem.* 2021;296:100798. <https://doi.org/10.1016/j.jbc.2021.100798>
 227. Huang YS, Chiang NY, Chang GW, Lin HH. Membrane-association of EMR2/ADGRE2-NTF is regulated by site-specific N-glycosylation. *Sci Rep.* 2018;8(1):4532. <https://doi.org/10.1038/s41598-018-22849-x>
 228. Kishore A, Hall RA. Disease-associated extracellular loop mutations in the adhesion G protein-coupled receptor G1 (ADGRG1; GPR56) differentially regulate downstream signaling. *J Biol Chem.* 2017;292(23):9711–9720. <https://doi.org/10.1074/jbc.m117.780551>
 229. Ke N, Ma H, Diedrich G, et al. Biochemical characterization of genetic mutations of GPR56 in patients with bilateral frontoparietal polymicrogyria (BFP). *Biochem Biophys Res Commun.* 2008;366(2):314–320. <https://doi.org/10.1016/j.bbrc.2007.11.071>
 230. Hsiao CC, Chen HY, Chang GW, Lin HH. GPS autoproteolysis is required for CD97 to up-regulate the expression of N-cadherin that promotes homotypic cell-cell aggregation. *FEBS Lett.* 2011;585(2):313–318. <https://doi.org/10.1016/j.febslet.2010.12.005>
 231. Ojeda-Muñiz EY, Rodríguez-Hernández B, Correoso-Braña KG, Segura-Landa PL, Boucard AA. Biased signalling is structurally encoded as an auto-proteolysis event in adhesion G protein-coupled receptor latrophilin-3/ADGRL3. *Basic Clin Pharmacol Toxicol.* 2023;133(4):342–352. <https://doi.org/10.1111/bcpt.13927>
 232. Singh J, Elhabashy H, Muthukuttiappan P, et al. Cross-linking of the endolysosomal system reveals potential flotillin structures and cargo. *Nat Commun.* 2022;13(1):6212. <https://doi.org/10.1038/s41467-022-33951-0>
 233. Azimzadeh P, Talamantez-Lyburn SC, Chang KT, Inoue A, Balenga N. Spatial regulation of GPR64/ADGRG2 signaling by β -arrestins and GPCR kinases. *Ann N Y Acad Sci.* 2019;1456(1):26–43. <https://doi.org/10.1111/nyas.14227>
 234. Spiess K, Bagger SO, Torz LJ, et al. Arrestin-independent constitutive endocytosis of GPR125/ADGRA3. *Ann N Y Acad Sci.* 2019;1456(1):186–199. <https://doi.org/10.1111/nyas.14263>
 235. Maerker T, van Wijk E van, Overlack N, et al. A novel Usher protein network at the periciliary reloading point between molecular transport machineries in vertebrate photoreceptor cells. *Hum Mol Genet.* 2008;17(1):71–86. <https://doi.org/10.1093/hmg/ddm285>
 236. Linnert J, Knapp B, Güler BE, Boldt K, Ueffing M, Wolfrum U. Usher syndrome proteins ADGRV1 (USH2C) and CIB2 (USH1J) interact and share a common interactome containing TRIC/CCT-BBS chaperonins. *Front Cell Dev Biol.* 2023;11:1199069. <https://doi.org/10.3389/fcell.2023.1199069>
 237. Linnert J, Kusuluri DK, Güler BE, Patnaik SR, May-Simera HL, Wolfrum U. The BBS/CCT chaperonin complex ensures the localization of the adhesion G protein-coupled receptor ADGRV1 to the base of primary cilia. *Front Cell Dev Biol.* 2025;13:1520723. <https://doi.org/10.3389/fcell.2025.1520723>
 238. Kusuluri DK, Güler BE, Knapp B, et al. Adhesion G protein-coupled receptor VLGR1/ADGRV1 regulates cell spreading and migration by mechanosensing at focal adhesions. *iScience.* 2021;24(4):102283. <https://doi.org/10.1016/j.isci.2021.102283>
 239. Güler BE, Linnert J, Wolfrum U. Monitoring paxillin in astrocytes reveals the significance of the adhesion G protein coupled receptor VLGR1/ADGRV1 for focal adhesion assembly. *Basic Clin Pharmacol Toxicol.* 2023;133(4):301–312. <https://doi.org/10.1111/bcpt.13860>
 240. Krzysko J, Maciag F, Mertens A, et al. The adhesion GPCR VLGR1/ADGRV1 regulates the Ca²⁺ homeostasis at mitochondria-associated ER membranes. *Cells.* 2022;11(18):2790. <https://doi.org/10.3390/cells11182790>
 241. Linnert J, Güler BE, Krzysko J, Wolfrum U. The adhesion G protein-coupled receptor VLGR1/ADGRV1 controls autophagy. *Basic Clin Pharmacol Toxicol.* 2023;133(4):313–330. <https://doi.org/10.1111/bcpt.13869>
 242. Krishnan A, Nijmeijer S, de Graaf C de, Schiöth HB. Classification, nomenclature, and structural aspects of adhesion GPCRs. *Handb Exp Pharmacol.* 2016;234:15–41. https://doi.org/10.1007/978-3-319-41523-9_2
 243. Kuznetsov D, Tegenfeldt F, Manni M, et al. OrthoDB v11: annotation of orthologs in the widest sampling of organismal diversity. *Nucleic Acids Res.* 2023;51(D1):D445–D451. <https://doi.org/10.1093/nar/gkac998>
 244. Bjarnadóttir TK, Fredriksson R, Höglund PJ, Gloriam DE, Lagerström MC, Schiöth HB. The human and mouse repertoire of the adhesion family of G-protein-coupled receptors. *Genomics.* 2004;84(1):23–33. <https://doi.org/10.1016/j.ygeno.2003.12.004>
 245. Bjarnadóttir TK, Gloriam DE, Hellstrand SH, Kristiansson H, Fredriksson R, Schiöth HB. Comprehensive repertoire and phylogenetic analysis of the G protein-coupled receptors in human and mouse. *Genomics.* 2006;88(3):263–273. <https://doi.org/10.1016/j.ygeno.2006.04.001>
 246. Haitina T, Olsson F, Stephansson O, et al. Expression profile of the entire family of Adhesion G protein-coupled receptors in mouse and rat. *BMC Neurosci.* 2008;9:43. <https://doi.org/10.1186/1471-2202-9-43>
 247. Winkler R, Quaaas M, Glasmacher S, et al. The adhesion G-protein-coupled receptor GPR115/ADGRF4 regulates epidermal differentiation and associates with cytoskeletal KRT1. *Cells.* 2022;11(19):3151. <https://doi.org/10.3390/cells11193151>

248. Aust G, Wandel E, Boltze C, et al. Diversity of CD97 in smooth muscle cells. *Cell Tissue Res.* 2006;324(1):139–147. <https://doi.org/10.1007/s00441-005-0103-2>
249. Zyrjanova T, Schneider R, Adams V, et al. Skeletal muscle expression of the adhesion-GPCR CD97: CD97 deletion induces an abnormal structure of the sarcoplasmic reticulum but does not impair skeletal muscle function. *PLoS One.* 2014;9(6):e100513. <https://doi.org/10.1371/journal.pone.0100513>
250. Chiesa MD, Falco M, Parolini S, et al. GPR56 as a novel marker identifying the CD56dull CD16+ NK cell subset both in blood stream and in inflamed peripheral tissues. *Int Immunol.* 2010;22(2):91–100. <https://doi.org/10.1093/intimm/dxp116>
251. Peng YM, van de Garde MDB, Cheng KF, et al. Specific expression of GPR56 by human cytotoxic lymphocytes. *J Leukoc Biol.* 2011;90(4):735–740. <https://doi.org/10.1189/jlb.0211092>
252. Kaiser F, Morawski M, Krohn K, et al. Adhesion GPCR GPR56 expression profiling in human tissues. *Cells.* 2021;10(12):3557. <https://doi.org/10.3390/cells10123557>
253. Lin HH, Hsiao CC, Pabst C, Hébert J, Schöneberg T, Hamann J. Adhesion GPCRs in regulating immune responses and inflammation. *Adv Immunol.* 2017;Chapter Five;136:163–201. <https://doi.org/10.1016/bs.ai.2017.05.005>
254. Lehmann J, Lin H, Zhang Z, et al. The mechanosensitive adhesion G protein-coupled receptor 133 (GPR133/ADGRD1) enhances bone formation. *Signal Transduct Target Ther.* 2025;10(1):199. <https://doi.org/10.1038/s41392-025-02291-y>
255. Hsiao CC, van der Poel M, van Ham TJ, Hamann J. Macrophages do not express the phagocytic receptor BAI1/ADGRB1. *Front Immunol.* 2019;10:962. <https://doi.org/10.3389/fimmu.2019.00962>
256. Kwakkenbos MJ, Pouwels W, Matmati M, et al. Expression of the largest CD97 and EMR2 isoforms on leukocytes facilitates a specific interaction with chondroitin sulfate on B cells. *J Leukoc Biol.* 2005;77(1):112–119. <https://doi.org/10.1189/jlb.0704402>
257. Wobus M, Vogel B, Schmücking E, Hamann J, Aust G. N-glycosylation of CD97 within the EGF domains is crucial for epitope accessibility in normal and malignant cells as well as CD55 ligand binding. *Int J Cancer.* 2004;112(5):815–822. <https://doi.org/10.1002/ijc.20483>
258. Südhof TC. α -Latrotoxin and its receptors: neuroligins and CIRL/latrophilins. *Annu Rev Neurosci.* 2001;24(1):933–962. <https://doi.org/10.1146/annurev.neuro.24.1.933>
259. Usui T, Shima Y, Shimada Y, et al. Flamingo, a seven-pass transmembrane cadherin, regulates planar cell polarity under the control of frizzled. *Cell.* 1999;98(5):585–595. [https://doi.org/10.1016/s0092-8674\(00\)80046-x](https://doi.org/10.1016/s0092-8674(00)80046-x)
260. McGee J, Goodyear RJ, McMillan DR, et al. The very large G-protein-coupled receptor VLGR1: a component of the ankle link complex required for the normal development of auditory hair bundles. *J Neurosci.* 2006;26(24):6543–6553. <https://doi.org/10.1523/jneurosci.0693-06.2006>
261. Sun JP, Li R, Ren HZ, Xu AT, Yu X, Xu ZG. The very large G protein coupled receptor (VLGR1) in hair cells. *J Mol Neurosci.* 2013;50(1):204–214. <https://doi.org/10.1007/s12031-012-9911-5>
262. Knapp B, Roedig J, Boldt K, et al. Affinity proteomics identifies novel functional modules related to adhesion GPCRs. *Ann N Y Acad Sci.* 2019;1456(1):144–167. <https://doi.org/10.1111/nyas.14220>
263. Diamantopoulou E, Baxendale S, De La Vega De León A, et al. Identification of compounds that rescue otic and myelination defects in the zebrafish adgrg6 (gpr126) mutant. *eLife.* 2019;8:e44889. <https://doi.org/10.7554/eLife.44889>
264. Li J, Shalev-Benami M, Sando R, et al. Structural basis for teneurin function in circuit-wiring: a toxin motif at the synapse. *Cell.* 2018;173(3):735–748.e15. <https://doi.org/10.1016/j.cell.2018.03.036>
265. Cruz-Ortega JS, Boucard AA. Actin cytoskeleton remodeling defines a distinct cellular function for adhesion G protein-coupled receptors ADGRL/latrophilins 1, 2 and 3. *Biol Open.* 2019;8(4):bio039826. <https://doi.org/10.1242/bio.039826>
266. Yang MY, Hilton MB, Seaman S, et al. Essential regulation of lung surfactant homeostasis by the orphan G protein-coupled receptor GPR116. *Cell Rep.* 2013;3(5):1457–1464. <https://doi.org/10.1016/j.celrep.2013.04.019>
267. Bridges JP, Ludwig MG, Mueller M, et al. Orphan G protein-coupled receptor GPR116 regulates pulmonary surfactant pool size. *Am J Respir Cell Mol Biol.* 2013;49(3):348–357. <https://doi.org/10.1165/rcmb.2012-0439oc>
268. Knapp B, Wolfrum U. Adhesion GPCR-related protein networks. *Handb Exp Pharmacol.* 2016;234(10):147–178. https://doi.org/10.1007/978-3-319-41523-9_8
269. Südhof TC. Signaling by latrophilin adhesion-GPCRs in synapse assembly. *Neuroscience.* 2025;575:150–161. <https://doi.org/10.1016/j.neuroscience.2025.03.041>
270. Stephenson JR, Paavola KJ, Schaefer SA, Kaur B, Van Meir EG, Hall RA. Brain-specific angiogenesis inhibitor-1 signaling, regulation, and enrichment in the postsynaptic density. *J Biol Chem.* 2013;288(31):22248–22256. <https://doi.org/10.1074/jbc.m113.489757>
271. Sakurai T, Kamakura S, Hayase J, Kohda A, Nakamura M, Sumimoto H. GPR125 (ADGRA3) is an autocleavable adhesion GPCR that traffics with Dlg1 to the basolateral membrane and regulates epithelial apicobasal polarity. *J Biol Chem.* 2022;298(10):102475. <https://doi.org/10.1016/j.jbc.2022.102475>
272. Nishimura T, Honda H, Takeichi M. Planar cell polarity links axes of spatial dynamics in neural-tube closure. *Cell.* 2012;149(5):1084–1097. <https://doi.org/10.1016/j.cell.2012.04.021>
273. Li X, Roszko I, Sepich DS, et al. Gpr125 modulates Dishevelled distribution and planar cell polarity signaling. *Development.* 2013;140(14):3028–3039. <https://doi.org/10.1242/dev.094839>
274. Hilbig D, Dietrich N, Wandel E, et al. The interaction of CD97/ADGRE5 with β -catenin in adherens junctions is lost during colorectal carcinogenesis. *Front Oncol.* 2018;8:182. <https://doi.org/10.3389/fonc.2018.00182>
275. Weng Z, Situ C, Lin L, Wu Z, Zhu J, Zhang R. Structure of BAI1/ELMO2 complex reveals an action mechanism of adhesion GPCRs via ELMO family scaffolds. *Nat Commun.* 2019;10(1):51. <https://doi.org/10.1038/s41467-018-07938-9>
276. Hernández-Vásquez MN, Adame-García SR, Hamoud N, et al. Cell adhesion controlled by adhesion G protein-coupled receptor GPR124/ADGRA2 is mediated by a protein complex comprising intersectins and Elmo–Dock. *J Biol Chem.* 2017;292(29):12178–12191. <https://doi.org/10.1074/jbc.m117.780304>
277. Hamoud N, Tran V, Croteau LP, Kania A, Côté JF. G-protein coupled receptor BAI3 promotes myoblast fusion in vertebrates. *Proc Natl Acad Sci U S A.* 2014;111(10):3745–3750. <https://doi.org/10.1073/pnas.1313886111>
278. Lanoue V, Usardi A, Sigoillot SM, et al. The adhesion-GPCR BAI3, a gene linked to psychiatric disorders, regulates dendrite morphogenesis in neurons. *Mol Psychiatry.* 2013;18(8):943–950. <https://doi.org/10.1038/mp.2013.46>
279. Chang GW, Hsiao CC, Peng YM, et al. The adhesion G protein-coupled receptor GPR56/ADGRG1 is an inhibitory receptor on human NK cells. *Cell Rep.* 2016;15(8):1757–1770. <https://doi.org/10.1016/j.celrep.2016.04.053>
280. Stephan G, Haddock S, Wang S, et al. Modulation of GPR133 (ADGRD1) signaling by its intracellular interaction partner extended synaptotagmin 1. *Cell Rep.* 2024;43(5):114229. <https://doi.org/10.1016/j.celrep.2024.114229>
281. Bridges JP, Safina C, Pirard B, et al. Regulation of pulmonary surfactant by the adhesion GPCR GPR116/ADGRF5 requires a tethered agonist-mediated activation mechanism. *eLife.* 2022;11:e69061. <https://doi.org/10.7554/eLife.69061>
282. Yang L, Chen G, Mohanty S, et al. GPR56 regulates VEGF production and angiogenesis during melanoma progression. *Cancer Res.* 2011;71(16):5558–5568. <https://doi.org/10.1158/0008-5472.can.10-4543>
283. Paavola KJ, Stephenson JR, Ritter SL, Alter SP, Hall RA. The N terminus of the adhesion G protein-coupled receptor GPR56 controls receptor signaling activity. *J Biol Chem.* 2011;286(33):28914–28921. <https://doi.org/10.1074/jbc.m111.247973>
284. Dates AN, Jones DTD, Smith JS, et al. Heterogeneity of tethered agonist signaling in adhesion G protein-coupled receptors. *Cell Chem Biol.* 2024;31(8):1542–1553.e4. <https://doi.org/10.1016/j.chembiol.2024.03.004>
285. Silva JP, Ushkaryov YA. Adhesion-GPCRs, structure to function. *Adv Exp Med Biol.* 2010;706:59–75. https://doi.org/10.1007/978-1-4419-7913-1_5
286. Yeung J, Adili R, Stringham EN, et al. GPR56/ADGRG1 is a platelet collagen-responsive GPCR and hemostatic sensor of shear force. *Proc Natl Acad Sci U S A.* 2020;117(45):28275–28286. <https://doi.org/10.1073/pnas.2008921117>
287. Bernadyn TF, Vizurraga A, Adhikari R, Kwarciński F, Tall GG. GPR114/ADGRG5 is activated by its tethered peptide agonist because it is a cleaved adhesion GPCR. *J Biol Chem.* 2023;299(10):105223. <https://doi.org/10.1016/j.jbc.2023.105223>
288. Liebscher I, Schön J, Petersen SC, et al. A tethered agonist within the ecto-domain activates the adhesion G protein-coupled receptors GPR126 and GPR133. *Cell Rep.* 2015;10(6):1021. <https://doi.org/10.1016/j.celrep.2015.01.065>
289. Qian Y, Ma Z, Liu C, et al. Structural insights into adhesion GPCR ADGRL3 activation and Gq, Gs, Gi, and G12 coupling. *Mol Cell.* 2022;82(22):4340–4352.e6. <https://doi.org/10.1016/j.molcel.2022.10.009>
290. Mathiasen S, Palmisano T, Perry NA, et al. G12/13 is activated by acute tethered agonist exposure in the adhesion GPCR ADGRL3. *Nat Chem Biol.* 2020;16(12):1343–1350. <https://doi.org/10.1038/s41589-020-0617-7>
291. Stephan G, Frenster JD, Liebscher I, Placantonakis DG. Activation of the adhesion G protein-coupled receptor GPR133 by antibodies targeting its N-terminus. *J Biol Chem.* 2022;298(6):101949. <https://doi.org/10.1016/j.jbc.2022.101949>
292. Vizurraga A, Adhikari R, Yeung J, Yu M, Tall GG. Mechanisms of adhesion G protein-coupled receptor activation. *J Biol Chem.* 2020;295(41):14065–14083. <https://doi.org/10.1074/jbc.rev120.007423>
293. Lala T, Hall RA. Adhesion G protein-coupled receptors: structure, signaling, physiology, and pathophysiology. *Physiol Rev.* 2022;102(4):1587–1624. <https://doi.org/10.1152/physrev.00027.2021>
294. Prömel S, Frickenhaus M, Hughes S, et al. The GPS motif is a molecular switch for bimodal activities of adhesion class G protein-coupled receptors. *Cell Rep.* 2012;2(2):321–331. <https://doi.org/10.1016/j.celrep.2012.06.015>
295. Müller A, Winkler J, Fiedler F, et al. Oriented cell division in the C. elegans embryo is coordinated by G-protein signaling dependent on the adhesion GPCR LAT-1. *PLoS Genet.* 2015;11(10):e1005624. <https://doi.org/10.1371/journal.pgen.1005624>
296. Bohnenkamp J, Schöneberg T. Cell adhesion receptor GPR133 couples to Gs protein. *J Biol Chem.* 2011;286(49):41912–41916. <https://doi.org/10.1074/jbc.c111.265934>
297. Kishore A, Purcell RH, Nassiri-Toosi Z, Hall RA. Stalk-dependent and stalk-independent signaling by the adhesion G protein-coupled receptors GPR56 (ADGRG1) and BAI1 (ADGRB1). *J Biol Chem.* 2016;291(7):3385–3394. <https://doi.org/10.1074/jbc.m115.689349>
298. Peeters MC, Fokkelman M, Boogaard B, et al. The adhesion G protein-coupled receptor G2 (ADGRG2/GPR64) constitutively activates SRE and NF κ B and is

- involved in cell adhesion and migration. *Cell Signal*. 2015;27(12):2579–2588. <https://doi.org/10.1016/j.celsig.2015.08.015>
299. Duman JG, Tu YK, Toliaas KF. Emerging roles of BAI adhesion-GPCRs in synapse development and plasticity. *Neural Plast*. 2016;2016(1):8301737. <https://doi.org/10.1155/2016/8301737>
 300. Bui DLH, Roach A, Li J, et al. The adhesion GPCRs CELSR1–3 and LPHN3 engage G proteins via distinct activation mechanisms. *Cell Rep*. 2023;42(6):112552. <https://doi.org/10.1016/j.celrep.2023.112552>
 301. Salzman GS, Zhang S, Gupta A, Koide A, Koide S, Araç D. Stachel-independent modulation of GPR56/ADGRG1 signaling by synthetic ligands directed to its extracellular region. *Proc Natl Acad Sci U S A*. 2017;114(38):10095–10100. <https://doi.org/10.1073/pnas.1708810114>
 302. Tissir F, Goffinet AM. Nine atypical cadherins Celsr1–3 and planar cell polarity in vertebrates. *Prog Mol Biol Transl Sci*. 2013;116:193–214. <https://doi.org/10.1016/b978-0-12-394311-8.00009-1>
 303. Langenhan T, Piao X, Monk KR. Adhesion G protein-coupled receptors in nervous system development and disease. *Nat Rev Neurosci*. 2016;17(9):550–561. <https://doi.org/10.1038/nrn.2016.86>
 304. Syrovatkina V, Alegre KO, Dey R, Huang XY. Regulation, signaling, and physiological functions of G-proteins. *J Mol Biol*. 2016;428(19):3850–3868. <https://doi.org/10.1016/j.jmb.2016.08.002>
 305. Gilman AG. G proteins: transducers of receptor-generated signals. *Annu Rev Biochem*. 1987;56(1):615–649. <https://doi.org/10.1146/annurev.bi.56.070187.003151>
 306. Iguchi T, Sakata K, Yoshizaki K, Tago K, Mizuno N, Itoh H. Orphan G protein-coupled receptor GPR56 regulates neural progenitor cell migration via a Gα12/13 and rho pathway. *J Biol Chem*. 2008;283(21):14469–14478. <https://doi.org/10.1074/jbc.m708919200>
 307. Li S, Jin Z, Koirala S, et al. GPR56 regulates pial basement membrane integrity and cortical lamination. *J Neurosci*. 2008;28(22):5817–5826. <https://doi.org/10.1523/jneurosci.0853.08.2008>
 308. Jeong SJ, Luo R, Li S, Strokes N, Piao X. Characterization of G protein-coupled receptor 56 protein expression in the mouse developing neocortex. *J Comp Neurol*. 2012;520(13):2930–2940. <https://doi.org/10.1002/cne.23076>
 309. Moers A, Nürnberg A, Goebbels S, Wettschureck N, Offermanns S. Gα12/Gα13 deficiency causes localized overmigration of neurons in the developing cerebellar and cerebral cortices. *Mol Cell Biol*. 2008;28(5):1480–1488. <https://doi.org/10.1128/mcb.00651-07>
 310. Mogha A, Benesh AE, Patra C, et al. Gpr126 functions in Schwann cells to control differentiation and myelination via G-protein activation. *J Neurosci*. 2013;33(46):17976–17985. <https://doi.org/10.1523/jneurosci.1809-13.2013>
 311. Hu QX, Dong JH, Du HB, et al. Constitutive Gai coupling activity of very large G protein-coupled receptor 1 (VLGR1) and its regulation by PDZD7 protein. *J Biol Chem*. 2014;289(35):24215–24225. <https://doi.org/10.1074/jbc.M114.549816>
 312. Demberg LM, Winkler J, Wilde C, et al. Activation of adhesion G protein-coupled receptors: agonist specificity of Stachel sequence-derived peptides. *J Biol Chem*. 2017;292(11):4383–4394. <https://doi.org/10.1074/jbc.M116.763656>
 313. Hsiao CC, Chu TY, Wu CJ, et al. The adhesion G protein-coupled receptor GPR97/ADGRG3 is expressed in human granulocytes and triggers antimicrobial effector functions. *Front Immunol*. 2018;9:2830. <https://doi.org/10.3389/fimmu.2018.02830>
 314. Zhang DL, Sun YJ, Ma ML, et al. Gq activity- and β-arrestin-1 scaffolding-mediated ADGRG2/CFTR coupling are required for male fertility. *eLife*. 2018;7:e33432. <https://doi.org/10.7554/eLife.33432>
 315. Guo P, Tai Y, Wang M, et al. Gα12 and Gα13: versatility in physiology and pathology. *Front Cell Dev Biol*. 2022;10:809425. <https://doi.org/10.3389/fcell.2022.809425>
 316. Worzfeld T, Wettschureck N, Offermanns S. G12/G13-mediated signalling in mammalian physiology and disease. *Trends Pharmacol Sci*. 2008;29(11):582–589. <https://doi.org/10.1016/j.tips.2008.08.002>
 317. Suzuki N, Hajicek N, Kozasa T. Regulation and physiological functions of G12/13-mediated signaling pathways. *Neurosignals*. 2009;17(1):55–70. <https://doi.org/10.1159/000186690>
 318. Sénéchal C, Fujita R, Jamet S, et al. The adhesion G-protein-coupled receptor Gpr116 is essential to maintain the skeletal muscle stem cell pool. *Cell Rep*. 2022;41(7):111645. <https://doi.org/10.1016/j.celrep.2022.111645>
 319. Patra C, van Amerongen MJ van, Ghosh S, et al. Organ-specific function of adhesion G protein-coupled receptor GPR126 is domain-dependent. *Proc Natl Acad Sci U S A*. 2013;110(42):16898–16903. <https://doi.org/10.1073/pnas.1304837110>
 320. Purcell RH, Toro C, Gahl WA, Hall RA. A disease-associated mutation in the adhesion GPCR BAI2 (ADGRB2) increases receptor signaling activity. *Hum Mutat*. 2017;38(12):1751–1760. <https://doi.org/10.1002/humu.23336>
 321. Dietzsch AN, Al-Hasani H, Altschmied J, et al. Dysfunction of the adhesion G protein-coupled receptor latrophilin 1 (ADGRL1/LPHN1) increases the risk of obesity. *Signal Transduct Target Ther*. 2024;9(1):103. <https://doi.org/10.1038/s41392-024-01810-7>
 322. Moreno-Salinas AL, Holleran BJ, Ojeda-Muniz EY, et al. Convergent selective signaling impairment exposes the pathogenicity of latrophilin-3 missense variants linked to inheritable ADHD susceptibility. *Mol Psychiatry*. 2022;27(5):2425–2438. <https://doi.org/10.1038/s41380-022-01537-3>
 323. McDonald PH, Chow CW, Miller WE, et al. β-arrestin 2: a receptor-regulated MAPK scaffold for the activation of JNK3. *Science*. 2000;290(5496):1574–1577. <https://doi.org/10.1126/science.290.5496.1574>
 324. DeFea KA, Zalevsky J, Thoma MS, Déry O, Mullins RD, Bunnett NW. β-arrestin-dependent endocytosis of proteinase-activated receptor 2 is required for intracellular targeting of activated ERK1/2. *J Cell Biol*. 2000;148(6):1267–1281. <https://doi.org/10.1083/jcb.148.6.1267>
 325. Zeghal M, Laroche G, Freitas JD, Wang R, Giguère PM. Profiling of basal and ligand-dependent GPCR activities by means of a polyvalent cell-based high-throughput platform. *Nat Commun*. 2023;14(1):3684. <https://doi.org/10.1038/s41467-023-39132-x>
 326. Hochreiter-Hufford AE, Lee CS, Kinchen JM, et al. Phosphatidylserine receptor BAI1 and apoptotic cells as new promoters of myoblast fusion. *Nature*. 2013;497(7448):263–267. <https://doi.org/10.1038/nature12135>
 327. Duman JG, Mulherkar S, Tu YK, et al. The adhesion-GPCR BAI1 shapes dendritic arbors via Bcr-mediated RhoA activation causing late growth arrest. *eLife*. 2019;8:e47566. <https://doi.org/10.7554/eLife.47566>
 328. Zhu D, Li C, Swanson AM, et al. BAI1 regulates spatial learning and synaptic plasticity in the hippocampus. *J Clin Invest*. 2015;125(4):1497–1508. <https://doi.org/10.1172/jci74603>
 329. Zhu D, Osuka S, Zhang Z, et al. BAI1 suppresses medulloblastoma formation by protecting p53 from Mdm2-mediated degradation. *Cancer Cell*. 2018;33(6):1004–1016.e5. <https://doi.org/10.1016/j.ccell.2018.05.006>
 330. Cho C, Smallwood PM, Nathans J. Reck and Gpr124 are essential receptor cofactors for Wnt7a/Wnt7b-specific signaling in mammalian CNS angiogenesis and blood-brain barrier regulation. *Neuron*. 2017;95(5):1056–1073.e5. <https://doi.org/10.1016/j.neuron.2017.07.031>
 331. Yuki K, Vallon M, Ding J, et al. GPR124 regulates murine brain embryonic angiogenesis and BBB formation by an intracellular domain-independent mechanism. *Development*. 2024;151(11):dev202794. <https://doi.org/10.1242/dev.202794>
 332. Chen WS, Antic D, Matis M, et al. Asymmetric homotypic interactions of the atypical cadherin flamingo mediate intercellular polarity signaling. *Cell*. 2008;133(6):1093–1105. <https://doi.org/10.1016/j.cell.2008.04.048>
 333. Bayin NS, Frenster JD, Kane JR, et al. GPR133 (ADGRD1), an adhesion G-protein-coupled receptor, is necessary for glioblastoma growth. *Oncogenesis*. 2016;5(10):e263–e263. <https://doi.org/10.1038/oncsis.2016.63>
 334. Frenster JD, Inocencio JF, Xu Z, et al. GPR133 promotes glioblastoma growth in hypoxia. *Neurosurgery*. 2017;64(CN_suppl_1):177–181. <https://doi.org/10.1093/neuros/nyx227>
 335. Moreno-Salinas AL, Avila-Zozaya M, Ugalde-Silva P, Hernández-Guzmán DA, Missirlis F, Boucard AA. Latrophilins: a neuro-centric view of an evolutionary conserved adhesion G protein-coupled receptor subfamily. *Front Neurosci*. 2019;13:700. <https://doi.org/10.3389/fnins.2019.00700>
 336. Kaur B, Cork SM, Sandberg EM, et al. Vasculostatin inhibits intracranial glioma growth and negatively regulates in vivo angiogenesis through a CD36-dependent mechanism. *Cancer Res*. 2009;69(3):1212–1220. <https://doi.org/10.1158/0008-5472.can-08-1166>
 337. Sheldon H, Zhang W, Bridges E, et al. ELTD1 is present in extracellular vesicles derived from endothelial cells as a cleaved extracellular domain which induces in vivo angiogenesis. *J Extracell Biol*. 2022;1(8):e52. <https://doi.org/10.1002/jex2.52>
 338. Srivastava S, Gunawan F, Vergarajaregui S, et al. Adgrg6/Gpr126 is required for compact wall integrity and establishing trabecular identity during cardiac trabeculation. *Nat Commun*. 2026;17:1484. <https://doi.org/10.1038/s41467-026-69292-5>
 339. Vieira Contreras F, Auger GM, Müller L, et al. The adhesion G-protein-coupled receptor mayo/CG11318 controls midgut development in *Drosophila*. *Cell Rep*. 2024;43(1):113640. <https://doi.org/10.1016/j.celrep.2023.113640>
 340. Carmona-Rosas G, Li J, Smith JJ, et al. Structural basis and functional roles for Toll-like receptor binding to latrophilin in *C. elegans* development. *Nat Struct Mol Biol*. Published online. 2025;32(9):1–14. <https://doi.org/10.1038/s41594-025-01592-8>
 341. Matúš D, Post WB, Horn S, Schöneberg T, Prömel S. Latrophilin-1 drives neuron morphogenesis and shapes chemo- and mechanosensation-dependent behavior in *C. elegans* via a trans function. *Biochem Biophys Res Commun*. 2022;589:152–158. <https://doi.org/10.1016/j.bbrc.2021.12.006>
 342. Chen PL, Clandinin TR. The cadherin flamingo mediates level-dependent interactions that guide photoreceptor target choice in *Drosophila*. *Neuron*. 2008;58(1):26–33. <https://doi.org/10.1016/j.neuron.2008.01.007>
 343. Najarro EH, Ackley BD. *C. elegans* fmi-1/flamingo and Wnt pathway components interact genetically to control the anteroposterior neurite growth of the VD GABAergic neurons. *Dev Biol*. 2013;377(1):224–235. <https://doi.org/10.1016/j.ydbio.2013.01.014>
 344. Curtin JA, Quint E, Tsipouri V, et al. Mutation of Celsr1 disrupts planar polarity of inner ear hair cells and causes severe neural tube defects in the mouse. *Curr Biol*. 2003;13(13):1129–1133. [https://doi.org/10.1016/s0960-9822\(03\)00374-9](https://doi.org/10.1016/s0960-9822(03)00374-9)
 345. Piao X, Hill RS, Bodell A, et al. G protein-coupled receptor-dependent development of human frontal cortex. *Science*. 2004;303(5666):2033–2036. <https://doi.org/10.1126/science.1092780>
 346. Bae BI, Tietjen I, Atabay KD, et al. Evolutionarily dynamic alternative splicing of GPR56 regulates regional cerebral cortical patterning. *Science*. 2014;343(6172):764–768. <https://doi.org/10.1126/science.1244392>

347. Bahi-Buisson N, Poirier K, Boddaert N, et al. GPR56-related bilateral frontoparietal polymicrogyria: further evidence for an overlap with the cobblestone complex. *Brain*. 2010;133(11):3194–3209. <https://doi.org/10.1093/brain/awq259>
348. Pederick DT, Lui JH, Gingrich EC, et al. Reciprocal repulsions instruct the precise assembly of parallel hippocampal networks. *Science*. 2021;372(6546):1068–1073. <https://doi.org/10.1126/science.abg1774>
349. Pederick DT, Perry-Hauser NA, Meng H, He Z, Javitch JA, Luo L. Context-dependent requirement of G protein coupling for Latrophilin-2 in target selection of hippocampal axons. *eLife*. 2023;12:e83529. <https://doi.org/10.7554/elife.83529>
350. Anderson GR, Maxeiner S, Sando R, Tsetsenis T, Malenka RC, Südhof TC. Postsynaptic adhesion GPCR latrophilin-2 mediates target recognition in entorhinal-hippocampal synapse assembly. *J Cell Biol*. 2017;216(11):3831–3846. <https://doi.org/10.1083/jcb.201703042>
351. Zhang RS, Liakath-Ali K, Südhof TC. Latrophilin-2 and latrophilin-3 are redundantly essential for parallel-fiber synapse function in cerebellum. *eLife*. 2020;9:e54443. <https://doi.org/10.7554/elife.54443>
352. Vitobello A, Mazel B, Lelianaova VG, et al. ADGRL1 haploinsufficiency causes a variable spectrum of neurodevelopmental disorders in humans and alters synaptic activity and behavior in a mouse model. *Am J Hum Genet*. 2022;109(8):1436–1457. <https://doi.org/10.1016/j.ajhg.2022.06.011>
353. Sigoillot SM, Iyer K, Binda F, et al. The secreted protein C1QL1 and its receptor BA13 control the synaptic connectivity of excitatory inputs converging on cerebellar Purkinje cells. *Cell Rep*. 2015;10(5):820–832. <https://doi.org/10.1016/j.celrep.2015.01.034>
354. Aimi T, Matsuda K, Yuzaki M. C1ql1-Bai3 signaling is necessary for climbing fiber synapse formation in mature Purkinje cells in coordination with neuronal activity. *Mol Brain*. 2023;16(1):61. <https://doi.org/10.1186/s13041-023-01048-4>
355. Wang CY, Liu Z, Ng YH, Südhof TC. A synaptic circuit required for acquisition but not recall of social transmission of food preference. *Neuron*. 2020;107(1):144–157.e4. <https://doi.org/10.1016/j.neuron.2020.04.004>
356. Zhou Q, Qin J, Liang Y, et al. Celsr3 is required for Purkinje cell maturation and regulates cerebellar postsynaptic plasticity. *iScience*. 2021;24(7):102812. <https://doi.org/10.1016/j.isci.2021.102812>
357. Li C, Wei JA, Wang D, et al. Planar cell polarity protein Celsr2 maintains structural and functional integrity of adult cortical synapses. *Prog Neurobiol*. 2022;219:102352. <https://doi.org/10.1016/j.pneurobio.2022.102352>
358. Donohue JD, Amidon RF, Murphy TR, et al. Parahippocampal latrophilin-2 (ADGRL2) expression controls topographical presubiculum to entorhinal cortex circuit connectivity. *Cell Rep*. 2021;37(8):110031. <https://doi.org/10.1016/j.celrep.2021.110031>
359. Feng B, Freitas AE, Gorodetski L, et al. Planar cell polarity signaling components are a direct target of β -amyloid-associated degeneration of glutamatergic synapses. *Sci Adv*. 2021;7(34):eab2307. <https://doi.org/10.1126/sciadv.abh2307>
360. Sando R, Südhof TC. Latrophilin GPCR signaling mediates synapse formation. *eLife*. 2021;10:e65717. <https://doi.org/10.7554/elife.65717>
361. Zhang X, Chen X, Matúš D, Südhof TC. Reconstitution of synaptic junctions orchestrated by teneurin-latrophilin complexes. *Science*. 2025;387(6731):322–329. <https://doi.org/10.1126/science.adq3586>
362. Ackerman SD, Garcia C, Piao X, Gutmann DH, Monk KR. The adhesion GPCR Gpr56 regulates oligodendrocyte development via interactions with Gα12/13 and RhoA. *Nat Commun*. 2015;6(1):6122. <https://doi.org/10.1038/ncomms7122>
363. Giera S, Deng Y, Luo R, et al. The adhesion G protein-coupled receptor GPR56 is a cell-autonomous regulator of oligodendrocyte development. *Nat Commun*. 2015;6(1):6121. <https://doi.org/10.1038/ncomms7121>
364. Piao X, Chang BS, Bodell A, et al. Genotype–phenotype analysis of human frontoparietal polymicrogyria syndromes. *Ann Neurol*. 2005;58(5):680–687. <https://doi.org/10.1002/ana.20616>
365. Giera S, Luo R, Ying Y, et al. Microglial transglutaminase-2 drives myelination and myelin repair via GPR56/ADGRL1 in oligodendrocyte precursor cells. *eLife*. 2018;7:e33385. <https://doi.org/10.7554/elife.33385>
366. Shin D, Lin ST, Fu YH, Ptáček LJ. Very large G protein-coupled receptor 1 regulates myelin-associated glycoprotein via Gαs/Gαq-mediated protein kinases A/C. *Proc Natl Acad Sci U S A*. 2013;110(47):19101–19106. <https://doi.org/10.1073/pnas.1318501110>
367. Monk KR, Naylor SG, Glenn TD, et al. A G protein-coupled receptor is essential for Schwann cells to initiate myelination. *Science*. 2009;325(5946):1402–1405. <https://doi.org/10.1126/science.1173474>
368. Monk KR, Oshima K, Jörs S, Heller S, Talbot WS. Gpr126 is essential for peripheral nerve development and myelination in mammals. *Development*. 2011;138(13):2673–2680. <https://doi.org/10.1242/dev.062224>
369. Mogha A, Harty BL, Carlin D, et al. Gpr126/Adgrg6 has Schwann cell autonomous and nonautonomous functions in peripheral nerve injury and repair. *J Neurosci*. 2016;36(49):12351–12367. <https://doi.org/10.1523/jneurosci.3854-15.2016>
370. Yu D, Li T, Delpech JC, et al. Microglial GPR56 is the molecular target of maternal immune activation-induced parvalbumin-positive interneuron deficits. *Sci Adv*. 2022;8(18):eabm2545. <https://doi.org/10.1126/sciadv.abm2545>
371. Zhu B, Wangzhou A, Yu D, et al. Adhesion G protein-coupled receptor ADGRL1 promotes protective microglial response in Alzheimer's disease. Preprint. Posted online October 18, 2024. bioRxiv 618329. <https://doi.org/10.1101/2024.10.15.618329>
372. Zhang Y, Chen K, Sloan SA, et al. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J Neurosci*. 2014;34(36):11929–11947. <https://doi.org/10.1523/jneurosci.1860-14.2014>
373. Soto JS, Jami-Alahmadi Y, Chacon J, et al. Astrocyte–neuron subproteomes and obsessive-compulsive disorder mechanisms. *Nature*. 2023;616(7958):764–773. <https://doi.org/10.1038/s41586-023-05927-7>
374. Güler BE, Zorin M, Linnert J, Nagel-Wolfrum K, Wolfrum U. The adhesion GPCR ADGRL1 controls glutamate homeostasis in hippocampal astrocytes supporting neuron development: first insights into to pathophysiology of ADGRL1-associated epilepsy. Preprint. Posted online April 28, 2024. bioRxiv 591120. <https://doi.org/10.1101/2024.04.25.591120>
375. Leng X, Zhang T, Guan Y, Tang M. Genotype and phenotype analysis of epilepsy caused by ADGRL1 mutations in Chinese children. *Seizure*. 2022;103:108–114. <https://doi.org/10.1016/j.seizure.2022.11.005>
376. Fuster-García C, García-Bohórquez B, Rodríguez-Muñoz A, et al. Usher syndrome: genetics of a human ciliopathy. *Int J Mol Sci*. 2021;22(13):6723. <https://doi.org/10.3390/ijms22136723>
377. Reiners J, Nagel-Wolfrum K, Jürgens K, Märker T, Wolfrum U. Molecular basis of human Usher syndrome: deciphering the meshes of the Usher protein network provides insights into the pathomechanisms of the Usher disease. *Exp Eye Res*. 2006;83(1):97–119. <https://doi.org/10.1016/j.exer.2005.11.010>
378. Lefèvre G, Michel V, Weil D, et al. A core cochlear phenotype in USH1 mouse mutants implicates fibrous links of the hair bundle in its cohesion, orientation and differential growth. *Development*. 2008;135(8):1427–1437. <https://doi.org/10.1242/dev.012922>
379. Scholz N, Gehring J, Guan C, et al. The adhesion GPCR latrophilin/CIRL shapes mechanosensation. *Cell Rep*. 2015;11(6):866–874. <https://doi.org/10.1016/j.celrep.2015.04.008>
380. Osaka J, Yasuda H, Watanuki Y, et al. Identification of genes regulating stimulus-dependent synaptic assembly in *Drosophila* using an automated synapse quantification system. *Genes Genet Syst*. 2023;97(6):297–309. <https://doi.org/10.1266/ggs.22-00114>
381. Lee RC, Clandinin TR, Lee CH, Chen PL, Meinertzhagen IA, Zipursky SL. The protocadherin Flamingo is required for axon target selection in the *Drosophila* visual system. *Nat Neurosci*. 2003;6(6):557–563. <https://doi.org/10.1038/nn1063>
382. Hakeda-Suzuki S, Berger-Müller S, Tomasi T, et al. Golden Goal collaborates with Flamingo in conferring synaptic-layer specificity in the visual system. *Nat Neurosci*. 2011;14(3):314–323. <https://doi.org/10.1038/nn.2756>
383. Scholz N, Monk KR, Kittel RJ, Langenhan T. Adhesion GPCRs as a putative class of metabotropic mechanosensors. *Handb Exp Pharmacol*. 2016;234:221–247. https://doi.org/10.1007/978-3-319-41523-9_10
384. Yang Z, Zhou SH, Zhang QY, et al. A force-sensitive adhesion GPCR is required for equilibrium. *Cell Res*. 2025;35(4):243–264. <https://doi.org/10.1038/s41422-025-01075-x>
385. Yang Z, Zhou SH, Wang MW, et al. Force sensing GPR133 is essential for normal balance and modulates vestibular hair cell membrane excitability via Gi signaling and CNGA3 coupling. Preprint. Posted online October 27, 2023. bioRxiv 563882. <https://doi.org/10.1101/2023.10.24.563882>
386. Cui H, Wang Y, Huang H, et al. GPR126 protein regulates developmental and pathological angiogenesis through modulation of VEGFR2 receptor signaling. *J Biol Chem*. 2014;289(50):34871–34885. <https://doi.org/10.1074/jbc.m114.571000>
387. Kakogiannis N, Scalise AA, Martini E, et al. GPR126 is a specifier of blood–brain barrier formation in the mouse central nervous system. *J Clin Invest*. 2024;134(15):e165368. <https://doi.org/10.1172/jci165368>
388. Zhao W, Wang Z, Sun Z, Wang S, Wu M, Zheng L. Lentivirus-mediated overexpression of CD97/ADGRE5 reverses dysregulated high glucose-induced endothelial cell migration. *Mol Med Rep*. 2017;15(5):3048–3054. <https://doi.org/10.3892/mmr.2017.6417>
389. Valtcheva N, Primorac A, Jurisic G, Hollmén M, Detmar M. The orphan adhesion G protein-coupled receptor GPR97 regulates migration of lymphatic endothelial cells via the small GTPases RhoA and Cdc42. *J Biol Chem*. 2013;288(50):35736–35748. <https://doi.org/10.1074/jbc.m113.512954>
390. Vallon M, Rohde F, Janssen KP, Essler M. Tumor endothelial marker 5 expression in endothelial cells during capillary morphogenesis is induced by the small GTPase Rac and mediates contact inhibition of cell proliferation. *Exp Cell Res*. 2010;316(3):412–421. <https://doi.org/10.1016/j.yexcr.2009.10.013>
391. Chen DY, Sun NH, Lu YP, et al. GPR124 facilitates pericyte polarization and migration by regulating the formation of filopodia during ischemic injury. *Thrombostasis*. 2019;9(20):5937–5955. <https://doi.org/10.7150/thno.34168>
392. Masiero M, Simões FC, Han HD, et al. A core human primary tumor angiogenesis signature identifies the endothelial orphan receptor ELTD1 as a key regulator of angiogenesis. *Cancer Cell*. 2013;24(2):229–241. <https://doi.org/10.1016/j.ccr.2013.06.004>
393. Favara DM, Liebscher I, Jazayeri A, et al. Elevated expression of the adhesion GPCR ADGRL4/ELTD1 promotes endothelial sprouting angiogenesis without activating canonical GPCR signalling. *Sci Rep*. 2021;11(1):8870. <https://doi.org/10.1038/s41598-021-85408-x>

394. Anderson KD, Pan L, Yang XM, et al. Angiogenic sprouting into neural tissue requires Gpr124, an orphan G protein-coupled receptor. *Proc Natl Acad Sci U S A*. 2011;108(7):2807–2812. <https://doi.org/10.1073/pnas.1019761108>
395. Cullen M, Elzarrad MK, Seaman S, et al. GPR124, an orphan G protein-coupled receptor, is required for CNS-specific vascularization and establishment of the blood-brain barrier. *Proc Natl Acad Sci U S A*. 2011;108(14):5759–5764. <https://doi.org/10.1073/pnas.1017192108>
396. Schevenels G, Cabochette P, America M, et al. A brain-specific angiogenic mechanism enabled by tip cell specialization. *Nature*. 2024;628(8009):863–871. <https://doi.org/10.1038/s41586-024-07283-6>
397. Dieterich LC, Mellberg S, Langenkamp E, et al. Transcriptional profiling of human glioblastoma vessels indicates a key role of VEGF-A and TGFβ2 in vascular abnormalization. *J Pathol*. 2012;228(3):378–390. <https://doi.org/10.1002/path.4072>
398. Carson-Walter EB, Watkins DN, Nanda A, Vogelstein B, Kinzler KW, Croix BS. Cell surface tumor endothelial markers are conserved in mice and humans. *Cancer Res*. 2001;61(18):6649–6655.
399. Wang Y, Cho SG, Wu X, Sivko S, Liu M. G-protein coupled Receptor 124 (GPR124) in endothelial cells regulates vascular endothelial growth factor (VEGF)-induced tumor angiogenesis. *Curr Mol Med*. 2014;14(4):543–554. <https://doi.org/10.2174/1566524014666140414205943>
400. Tjong WY, Lin HH. The role of the RGD motif in CD97/ADGRE5-and EMR2/ADGRE2-modulated tumor angiogenesis. *Biochem Biophys Res Commun*. 2019;520(2):243–249. <https://doi.org/10.1016/j.bbrc.2019.09.113>
401. Kee HJ, Koh JT, Kim MY, et al. Expression of brain-specific angiogenesis inhibitor 2 (BAI2) in normal and ischemic brain: involvement of BAI2 in the ischemia-induced brain angiogenesis. *J Cereb Blood Flow Metab*. 2002;22(9):1054–1067. <https://doi.org/10.1097/00004647-200209000-00003>
402. Kee HJ, Ahn KY, Choi KC, et al. Expression of brain-specific angiogenesis inhibitor 3 (BAI3) in normal brain and implications for BAI3 in ischemia-induced brain angiogenesis and malignant glioma. *FEBS Lett*. 2004;569(1–3):307–316. <https://doi.org/10.1016/j.febslet.2004.06.011>
403. Niaudet C, Petkova M, Jung B, et al. Adgrf5 contributes to patterning of the endothelial deep layer in retina. *Angiogenesis*. 2019;22(4):491–505. <https://doi.org/10.1007/s10456-019-09674-0>
404. Lu S, Liu S, Wietelmann A, et al. Developmental vascular remodeling defects and postnatal kidney failure in mice lacking Gpr116 (Adgrf5) and Eltd1 (Adgrf4). *PLoS One*. 2017;12(8):e0183166. <https://doi.org/10.1371/journal.pone.0183166>
405. Qiu D, Xu K, Chung N, et al. Identification and validation of G protein-coupled receptors modulating flow-dependent signaling pathways in vascular endothelial cells. *Front Mol Biosci*. 2023;10:1198079. <https://doi.org/10.3389/fmolb.2023.1198079>
406. Tanaka K, Chen M, Prendergast A, et al. Latrophilin-2 mediates fluid shear stress mechanotransduction at endothelial junctions. *EMBO J*. 2024;43(15):3175–3191. <https://doi.org/10.1038/s44318-024-00142-0>
407. Tatin F, Taddei A, Weston A, et al. Planar cell polarity protein Celsr1 regulates endothelial adherens junctions and directed cell rearrangements during valve morphogenesis. *Dev Cell*. 2013;26(1):31–44. <https://doi.org/10.1016/j.devcel.2013.05.015>
408. Camillo C, Facchinello N, Villari G, et al. LPHN2 inhibits vascular permeability by differential control of endothelial cell adhesion. *J Cell Biol*. 2021;220(11):e202006033. <https://doi.org/10.1083/jcb.202006033>
409. Martin M, Vermeiren S, Bostaille N, et al. Engineered Wnt ligands enable blood-brain barrier repair in neurological disorders. *Science*. 2022;375(6582):eabm4459. <https://doi.org/10.1126/science.abm4459>
410. Sheldon H, Alexander J, Bridges E, et al. ELTD1 activation induces an endothelial-EMT transition to a myofibroblast phenotype. *Int J Mol Sci*. 2021;22(20):11293. <https://doi.org/10.3390/ijms222011293>
411. Favara DM, Zois CE, Haider S, et al. ADGRL4/ELTD1 silencing in endothelial cells induces ACLY and SLC25A1 and alters the cellular metabolic profile. *Metabolites*. 2019;9(12):287. <https://doi.org/10.3390/metabo9120287>
412. Davis RB, Kechele DO, Blakeney ES, Pawlak JB, Caron KM. Lymphatic deletion of calcitonin receptor-like receptor exacerbates intestinal inflammation. *JCI Insight*. 2017;2(6):e92465. <https://doi.org/10.1172/jci.insight.92465>
413. Petrova TV, Koh GY. Organ-specific lymphatic vasculature: from development to pathophysiology. *J Exp Med*. 2018;215(1):35–49. <https://doi.org/10.1084/jem.20171868>
414. Schoofs H, Daubel N, Schnabelhner S, et al. Dynamic cytoskeletal regulation of cell shape supports resilience of lymphatic endothelium. *Nature*. 2025;641(8062):465–475. <https://doi.org/10.1038/s41586-025-08724-6>
415. Gonzalez-Garay ML, Aldrich MB, Rasmussen JC, et al. A novel mutation in CELSR1 is associated with hereditary lymphedema. *Vasc Cell*. 2016;8(1):1. <https://doi.org/10.1186/s13221-016-0035-5>
416. Erickson RP, Lai LW, Mustachich DJ, Bernas MJ, Kuo PH, Witte MH. Sex-limited penetrance of lymphedema to females with CELSR1 haploinsufficiency: a second family. *Clin Genet*. 2019;96(5):478–482. <https://doi.org/10.1111/cge.13622>
417. Seo SH, Lee S, Park JKH, et al. Clinical staging and genetic profiling of Korean patients with primary lymphedema using targeted gene sequencing. *Sci Rep*. 2022;12(1):13591. <https://doi.org/10.1038/s41598-022-17958-7>
418. Rogerson D, Alkelai A, Giordano J, et al. Investigation into the genetics of fetal congenital lymphatic anomalies. *Prenat Diagn*. 2023;43(6):703–716. <https://doi.org/10.1002/pd.6345>
419. Xia S, Liu Z, Yan H, et al. Lymphedema complicated by protein-losing enteropathy with a 22q13.3 deletion and the potential role of CELSR1: a case report. *Medicine*. 2021;100(24):e26307. <https://doi.org/10.1097/md.00000000000026307>
420. Xu W, Nelson-Maney NP, Bálint L, et al. Orphan G-protein coupled receptor GPRC5B is critical for lymphatic development. *Int J Mol Sci*. 2022;23(10):5712. <https://doi.org/10.3390/ijms23105712>
421. Manolis D, Hasan S, Maraveyas A, et al. Quantitative proteomics reveals CLR interactome in primary human cells. *J Biol Chem*. 2024;300(6):107399. <https://doi.org/10.1016/j.jbc.2024.107399>
422. Karakousi T, Mudianto T, Lund AW. Lymphatic vessels in the age of cancer immunotherapy. *Nat Rev Cancer*. 2024;24(6):363–381. <https://doi.org/10.1038/s41568-024-00681-y>
423. Prömel S, Waller-Evans H, Dixon J, et al. Characterization and functional study of a cluster of four highly conserved orphan adhesion-GPCR in mouse. *Dev Dyn*. 2012;241(10):1591–1602. <https://doi.org/10.1002/dvdy.23841>
424. Goffinet AM, Tissir F. Seven pass cadherins CELSR1-3. *Semin Cell Dev Biol*. 2017;69:102–110. <https://doi.org/10.1016/j.semcdb.2017.07.014>
425. Musa G, Cazorla-Vázquez S, van Amerongen MJ, et al. Gpr126 (Adgrg6) is expressed in cell types known to be exposed to mechanical stimuli. *Ann N Y Acad Sci*. 2019;1456(1):96–108. <https://doi.org/10.1111/nyas.14135>
426. Waller-Evans H, Prömel S, Langenhan T, et al. The orphan adhesion-GPCR GPR126 is required for embryonic development in the mouse. *PLoS One*. 2010;5(11):e14047. <https://doi.org/10.1371/journal.pone.0014047>
427. Doyle SE, Scholz MJ, Greer KA, et al. Latrophilin-2 is a novel component of the epithelial-mesenchymal transition within the atrioventricular canal of the embryonic chicken heart. *Dev Dyn*. 2006;235(12):3213–3221. <https://doi.org/10.1002/dvdy.20973>
428. Lee CS, Cho HJ, Lee JW, et al. The G protein-coupled receptor Latrophilin-2, A marker for heart development, induces myocardial repair after infarction. *Stem Cells Transl Med*. 2022;11(3):332–342. <https://doi.org/10.1093/stcltm/ztzab015>
429. Liu M, Parker RMC, Darby K, et al. GPR56, a novel secretin-like human G-protein-coupled receptor gene. *Genomics*. 1999;55(3):296–305. <https://doi.org/10.1006/geno.1998.5644>
430. Einspahr J, Xu H, Roy R, et al. Loss of cardiomyocyte-specific adhesion G-protein-coupled receptor G1 (ADGRG1/GPR56) promotes pressure overload-induced heart failure. *Biosci Rep*. 2024;44(9):BSR20240826. <https://doi.org/10.1042/bsr20240826>
431. Lee CS, Cho HJ, Lee JW, et al. Identification of latrophilin-2 as a novel cell-surface marker for the cardiomyogenic lineage and its functional significance in heart development. *Circulation*. 2019;139(25):2910–2912. <https://doi.org/10.1161/circulationaha.119.040826>
432. Lee CS, Cho HJ, Lee JW, Son H, Chai J, Kim HS. Adhesion GPCR Latrophilin-2 specifies cardiac lineage commitment through CDK5, Src, and p38MAPK. *Stem Cell Rep*. 2021;16(4):868–882. <https://doi.org/10.1016/j.stemcr.2021.03.003>
433. Kang M, Lee CS, Son H, et al. Latrophilin-2 deletion in cardiomyocyte disrupts cell junction, leading to D-CMP. *Circ Res*. 2024;135(11):1098–1115. <https://doi.org/10.1161/circresaha.124.324670>
434. Torregrosa-Carrión R, Piñero-Sabaris R, Siguero-Álvarez M, et al. Adhesion G protein-coupled receptor Gpr126/Adgrg6 is essential for placental development. *Sci Adv*. 2021;7(46):eabj5445. <https://doi.org/10.1126/sciadv.abj5445>
435. Niaudet C, Hofmann JJ, Mãe MA, et al. Gpr116 receptor regulates distinctive functions in pneumocytes and vascular endothelium. *PLoS One*. 2015;10(9):e0137949. <https://doi.org/10.1371/journal.pone.0137949>
436. Xiao J, Jiang H, Zhang R, et al. Augmented cardiac hypertrophy in response to pressure overload in mice lacking ELTD1. *PLoS One*. 2012;7(5):e35779. <https://doi.org/10.1371/journal.pone.0035779>
437. White JP, Wrann CD, Rao RR, et al. G protein-coupled receptor 56 regulates mechanical overload-induced muscle hypertrophy. *Proc Natl Acad Sci U S A*. 2014;111(44):15756–15761. <https://doi.org/10.1073/pnas.1417898111>
438. Zhang Y, Si Y, Ma N, Mei J. The RNA-binding protein PCBP2 inhibits Ang II-induced hypertrophy of cardiomyocytes through promoting GPR56 mRNA degradation. *Biochem Biophys Res Commun*. 2015;464(3):679–684. <https://doi.org/10.1016/j.bbrc.2015.06.139>
439. Ariestanti DM, Ando H, Hirose S, Nakamura N. Targeted disruption of Ighepta/Gpr116 causes emphysema-like symptoms that are associated with alveolar macrophage activation. *J Biol Chem*. 2015;290(17):11032–11040. <https://doi.org/10.1074/jbc.m115.648311>
440. Brown K, Filuta A, Ludwig MG, et al. Epithelial Gpr116 regulates pulmonary alveolar homeostasis via Gq/11 signaling. *JCI Insight*. 2017;2(11):e93700. <https://doi.org/10.1172/jci.insight.93700>
441. Kubo F, Ariestanti DM, Oki S, et al. Loss of the adhesion G-protein coupled receptor ADGRF5 in mice induces airway inflammation and the expression of CCL2 in lung endothelial cells. *Respir Res*. 2019;20(1):11. <https://doi.org/10.1186/s12931-019-0973-6>
442. Heinzlmann K, Lehmann M, Gerckens M, et al. Cell-surface phenotyping identifies CD36 and CD97 as novel markers of fibroblast quiescence in lung fibrosis. *Am J Physiol, Lung Cell Mol Physiol*. 2018;315(5):L682–L696. <https://doi.org/10.1152/ajplung.00439.2017>
443. Yang J, Wang Z, Leng D, et al. G protein-coupled receptor 56 regulates matrix production and motility of lung fibroblasts. *Exp Biol Med*. 2014;239(6):686–696. <https://doi.org/10.1177/1535370214529395>

444. Sakornsakolpat P, Prokopenko D, Lamontagne M, et al. Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. *Nat Genet.* 2019;51(3):494–505. <https://doi.org/10.1038/s41588-018-0342-2>
445. Terzikhan N, Sun F, Verhamme FM, et al. Heritability and genome-wide association study of diffusing capacity of the lung. *Eur Respir J.* 2018;52(3):1800647. <https://doi.org/10.1183/13993003.00647-2018>
446. Shrine N, Izquierdo AG, Chen J, et al. Multi-ancestry genome-wide association analyses improve resolution of genes and pathways influencing lung function and chronic obstructive pulmonary disease risk. *Nat Genet.* 2023;55(3):410–422. <https://doi.org/10.1038/s41588-023-01314-0>
447. Shrine N, Guyatt AL, Erzurumluoglu AM, et al. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. *Nat Genet.* 2019;51(3):481–493. <https://doi.org/10.1038/s41588-018-0321-7>
448. Gorr MW, Sriram K, Muthusamy A, Insel PA. Transcriptomic analysis of pulmonary artery smooth muscle cells identifies new potential therapeutic targets for idiopathic pulmonary arterial hypertension. *Br J Pharmacol.* 2020;177(15):3505–3518. <https://doi.org/10.1111/bph.15074>
449. Hall RJ, O'Loughlin J, Billington CK, Thakker D, Hall IP, Sayers I. Functional genomics of GPR126 in airway smooth muscle and bronchial epithelial cells. *FASEB J.* 2021;35(7):e21300. <https://doi.org/10.1096/fj.202002073r>
450. Werder RB, Berthiaume KA, Merritt C, et al. The COPD GWAS gene ADGRG6 instructs function and injury response in human iPSC-derived type II alveolar epithelial cells. *Am J Hum Genet.* 2023;110(10):1735–1749. <https://doi.org/10.1016/j.ajhg.2023.08.017>
451. Sreepada A, Tiwari M, Pal K. Adhesion G protein-coupled receptor gluing action guides tissue development and disease. *J Mol Med.* 2022;100(10):1355–1372. <https://doi.org/10.1007/s00109-022-02240-0>
452. Chan YF, Jones FC, McConnell E, Bryk J, Bünger L, Tautz D. Parallel selection mapping using artificially selected mice reveals body weight control loci. *Curr Biol.* 2012;22(9):794–800. <https://doi.org/10.1016/j.cub.2012.03.011>
453. Kim JJ, Park YM, Baik KH, et al. Exome sequencing and subsequent association studies identify five amino acid-altering variants influencing human height. *Hum Genet.* 2012;131(3):471–478. <https://doi.org/10.1007/s00439-011-1096-4>
454. Kou I, Takahashi Y, Johnson TA, et al. Genetic variants in GPR126 are associated with adolescent idiopathic scoliosis. *Nat Genet.* 2013;45(6):676–679. <https://doi.org/10.1038/ng.2639>
455. Liu Z, Hussien AA, Wang Y, et al. An adhesion G protein-coupled receptor is required in cartilaginous and dense connective tissues to maintain spine alignment. *eLife.* 2021;10:e67781. <https://doi.org/10.7554/eLife.67781>
456. Karner CM, Long F, Solnica-Krezel L, Monk KR, Gray RS. Gpr126/Adgrg6 deletion in cartilage models idiopathic scoliosis and pectus excavatum in mice. *Hum Mol Genet.* 2015;24(15):4365–4373. <https://doi.org/10.1093/hmg/ddv170>
457. Soranzo N, Rivadeneira F, Chinapen-Horsley U, et al. Meta-analysis of genome-wide scans for human adult stature identifies novel loci and associations with measures of skeletal frame size. *PLoS Genet.* 2009;5(4):e1000445. <https://doi.org/10.1371/journal.pgen.1000445>
458. Bian F, Hansen V, Feng HC, et al. The G protein-coupled receptor ADGRG6 maintains mouse growth plate homeostasis through IHH signaling. *J Bone Miner Res.* 2024;39(11):1644–1658. <https://doi.org/10.1093/jbmr/zjae144>
459. He L, Zhang Q, You Y, et al. Exogenous activation of the adhesion GPCR ADGRD1/GPR133 protects against bone loss by negatively regulating osteoclastogenesis. *Sci Adv.* 2025;11(28):eads3829. <https://doi.org/10.1126/sciadv.ads3829>
460. Wu MP, Doyle JR, Barry B, et al. G-protein coupled receptor 56 promotes myoblast fusion through serum response factor- and nuclear factor of activated T-cell-mediated signalling but is not essential for muscle development in vivo. *FEBS J.* 2013;280(23):6097–6113. <https://doi.org/10.1111/febs.12529>
461. Urano T, Shiraki M, Yagi H, et al. GPR98/Gpr98 gene is involved in the regulation of human and mouse bone mineral density. *J Clin Endocrinol Metab.* 2012;97(4):E565–E574. <https://doi.org/10.1210/jc.2011-2393>
462. Austyn JM, Gordon S. F4/80, a monoclonal antibody directed specifically against the mouse macrophage. *Eur J Immunol.* 1981;11(10):805–815. <https://doi.org/10.1002/eji.1830111013>
463. Hamann J, Koning N, Pouwels W, et al. EMR1, the human homolog of F4/80, is an eosinophil-specific receptor. *Eur J Immunol.* 2007;37(10):2797–2802. <https://doi.org/10.1002/eji.200737553>
464. Legrand F, Tomasevic N, Simakova O, et al. The eosinophil surface receptor epidermal growth factor-like module containing mucin-like hormone receptor 1 (EMR1): a novel therapeutic target for eosinophilic disorders. *J Allergy Clin Immunol.* 2014;133(5):1439–1447.e8. <https://doi.org/10.1016/j.jaci.2013.11.041>
465. Matmati M, Pouwels W, van Bruggen R, et al. The human EGF-TM7 receptor EMR3 is a marker for mature granulocytes. *J Leukoc Biol.* 2007;81(2):440–448. <https://doi.org/10.1189/jlb.0406276>
466. van der Poel M, Ulas T, Mizze MR, et al. Transcriptional profiling of human microglia reveals grey–white matter heterogeneity and multiple sclerosis-associated changes. *Nat Commun.* 2019;10(1):1139. <https://doi.org/10.1038/s41467-019-08976-7>
467. Tseng WY, Stacey M, Lin HH. Role of adhesion G protein-coupled receptors in immune dysfunction and disorder. *Int J Mol Sci.* 2023;24(6):5499. <https://doi.org/10.3390/ijms24065499>
468. Palacios D, Majhi RK, Szabo EK, et al. The G protein-coupled receptor GPR56 is an inhibitory checkpoint for NK cell migration. *J Immunol.* 2024;213(9):1349–1357. <https://doi.org/10.4049/jimmunol.2400228>
469. Lin HH, Faunce DE, Stacey M, et al. The macrophage F4/80 receptor is required for the induction of antigen-specific effector regulatory T cells in peripheral tolerance. *J Exp Med.* 2005;201(10):1615–1625. <https://doi.org/10.1084/jem.20042307>
470. Wang T, Tian L, Haino M, et al. Improved antibacterial host defense and altered peripheral granulocyte homeostasis in mice lacking the adhesion class G protein receptor CD97. *Infect Immun.* 2006;75(3):1144–1153. <https://doi.org/10.1128/iai.00869-06>
471. Karpus ON, Veninga H, Hoek RM, et al. Shear stress-dependent down-regulation of the adhesion-G protein-coupled receptor CD97 on circulating leukocytes upon contact with its ligand CD55. *J Immunol.* 2013;190(7):3740–3748. <https://doi.org/10.4049/jimmunol.1202192>
472. Maglito A, Mariani SA, de Pater E, et al. Unexpected redundancy of Gpr56 and Gpr97 during hematopoietic cell development and differentiation. *Blood Adv.* 2021;5(3):829–842. <https://doi.org/10.1182/bloodadvances.202003693>
473. Pabst C, Bergeron A, Lavallée VP, et al. GPR56 identifies primary human acute myeloid leukemia cells with high repopulating potential in vivo. *Blood.* 2016;127(16):2018–2027. <https://doi.org/10.1182/blood-2015-11-683649>
474. Martin GH, Roy N, Chakraborty S, et al. CD97 is a critical regulator of acute myeloid leukemia stem cell function. *J Exp Med.* 2019;216(10):2362–2377. <https://doi.org/10.1084/jem.20190598>
475. Haubner S, Mansilla-Soto J, Nataraj S, et al. Cooperative CAR targeting to selectively eliminate AML and minimize escape. *Cancer Cell.* 2023;41(11):1871–1891.e6. <https://doi.org/10.1016/j.ccell.2023.09.010>
476. Tseng WY, Jan Wu YJ, Yang TY, et al. High levels of soluble GPR56/ADGRG1 are associated with positive rheumatoid factor and elevated tumor necrosis factor in patients with rheumatoid arthritis. *J Microbiol Immunol Infect.* 2017;51(4):485–491. <https://doi.org/10.1016/j.jmii.2016.11.010>
477. Luo Y, Lu J, Lei Z, et al. GPR56 facilitates hepatocellular carcinoma metastasis by promoting the TGF- β signaling pathway. *Cell Death Dis.* 2024;15(10):715. <https://doi.org/10.1038/s41419-024-07095-6>
478. Lewis SM, Treacher DF, Edgeworth J, et al. Expression of CD11c and EMR2 on neutrophils: potential diagnostic biomarkers for sepsis and systemic inflammation. *Clin Exp Immunol.* 2015;182(2):184–194. <https://doi.org/10.1111/cei.12679>
479. Zheng L, Rang M, Fuchs C, et al. The posttraumatic increase of the adhesion GPCR EMR2/ADGRE2 on circulating neutrophils is not related to injury severity. *Cells.* 2023;12(22):2657. <https://doi.org/10.3390/cells12222657>
480. Zheng L, Fuchs C, Kleber C, Osterhoff G, Aust G. Long-lasting changes in circulating dendritic cell and monocyte subsets, and altered expression of EMR2, CD97 and EMR3 on these cells in the posttraumatic course. *Clin Transl Immunology.* 2025;14(6):e70040. <https://doi.org/10.1002/cti2.70040>
481. Nagase M, Ando H, Beppu Y, et al. Glomerular endothelial cell receptor adhesion G-protein-coupled receptor F5 (ADGRF5) and the integrity of the glomerular filtration barrier. *J Am Soc Nephrol.* 2024;35(10):1366–1380. <https://doi.org/10.1681/asn.0000000000000427>
482. Fu J, Wei C, Zhang W, et al. Gene expression profiles of glomerular endothelial cells support their role in the glomerulopathy of diabetic mice. *Kidney Int.* 2018;94(2):326–345. <https://doi.org/10.1016/j.kint.2018.02.028>
483. Wu J, Wang Z, Cai M, et al. GPR56 promotes diabetic kidney disease through eNOS regulation in glomerular endothelial cells. *Diabetes.* 2023;72(11):1652–1663. <https://doi.org/10.2337/db23-0124>
484. Fang W, Wang Z, Li Q, et al. Gpr97 exacerbates AKI by mediating Sema3A signaling. *J Am Soc Nephrol.* 2018;29(5):1475–1489. <https://doi.org/10.1681/asn.2017080932>
485. Steichen H, Xue J, Zaidman NA. Identification and localization of adhesion G protein-coupled receptor expression in the murine kidney. *Am J Physiol Ren Physiol.* 2025;329(1):F11–F19. <https://doi.org/10.1152/ajprenal.00134.2025>
486. Cazorla-Vázquez S, Kösters P, Bertz S, et al. Adhesion GPCR Gpr126 (Adgrg6) expression profiling in Zebrafish, mouse, and human kidney. *Cells.* 2023;12(15):1988. <https://doi.org/10.3390/cells12151988>
487. Li Y, Duan Y, Chu Q, et al. G-protein coupled receptor GPR124 protects against podocyte senescence and injury in diabetic kidney disease. *Kidney Int.* 2025;107(4):652–665. <https://doi.org/10.1016/j.kint.2024.12.013>
488. Yates LL, Papakrivopoulou J, Long DA, et al. The planar cell polarity gene Vangl2 is required for mammalian kidney-branching morphogenesis and glomerular maturation. *Hum Mol Genet.* 2010;19(23):4663–4676. <https://doi.org/10.1093/hmg/ddq397>
489. Izutsu T, Konda R, Sugimura J, Iwasaki K, Fujioka T. Brain-specific angiogenesis inhibitor 1 is a putative factor for inhibition of neovascular formation in renal cell carcinoma. *J Urol.* 2011;185(6):2353–2358. <https://doi.org/10.1016/j.juro.2011.02.019>
490. Zaidman NA, Tomilin VN, Khayyat NH, et al. Adhesion-GPCR Gpr116 (ADGRF5) expression inhibits renal acid secretion. *Proc Natl Acad Sci U S A.* 2020;117(42):26470–26481. <https://doi.org/10.1073/pnas.2007620117>
491. Abe J, Suzuki H, Notoya M, Yamamoto T, Hirose S. Ig-hepta, a novel member of the G protein-coupled hepta-helical receptor (GPCR) family that has immunoglobulin-like repeats in a long N-terminal extracellular domain and defines a new subfamily of GPCRs. *J Biol Chem.* 1999;274(28):19957–19964. <https://doi.org/10.1074/jbc.274.28.19957>

492. Lum AM, Wang BB, Beck-Engeser GB, Li L, Channa N, Wabl M. Orphan receptor GPR110, an oncogene overexpressed in lung and prostate cancer. *BMC Cancer*. 2010;10(1):40. <https://doi.org/10.1186/1471-2407-10-40>
493. Hartly BL, Krishnan A, Sanchez NE, Schiöth HB, Monk KR. Defining the gene repertoire and spatiotemporal expression profiles of adhesion G protein-coupled receptors in zebrafish. *BMC Genom*. 2015;16(1):62. <https://doi.org/10.1186/s12864-015-1296-8>
494. Cazorla-Vázquez S, Engel FB. Adhesion GPCRs in kidney development and disease. *Front Cell Dev Biol*. 2018;6:9. <https://doi.org/10.3389/fcell.2018.00009>
495. Poll BG, Chen L, Chou CL, Raghuram V, Knepper MA. Landscape of GPCR expression along the mouse nephron. *Am J Physiol, Ren Physiol*. 2021;321(1):F50–F68. <https://doi.org/10.1152/ajprenal.00077.2021>
496. Sussman CR, Wang X, Chebib FT, Torres VE. Modulation of polycystic kidney disease by G-protein coupled receptors and cyclic AMP signaling. *Cell Signal*. 2020;72:109649. <https://doi.org/10.1016/j.cellsig.2020.109649>
497. Pawnikar S, Magenheimer BS, Munoz EN, Maser RL, Miao Y. Mechanism of tethered agonist-mediated signaling by polycystin-1. *Proc Natl Acad Sci U S A*. 2022;119(19):e2113786119. <https://doi.org/10.1073/pnas.2113786119>
498. Pawnikar S, Magenheimer BS, Joshi K, et al. Activation of polycystin-1 signaling by binding of stalk-derived peptide agonists. *eLife*. 2024;13:RP5992. <https://doi.org/10.7554/eLife.95992>
499. Kösters P, Cazorla-Vázquez S, Krüger R, et al. Adhesion G protein-coupled receptor Gpr126 (Adgrg6) expression profiling in diseased mouse, rat, and human kidneys. *Cells*. 2024;13(10):874. <https://doi.org/10.3390/cells13100874>
500. Brzóska HL, d'Esposito AM, Kolatsi-Joannou M, et al. Planar cell polarity genes Celsr1 and Vangl2 are necessary for kidney growth, differentiation, and rostrocaudal patterning. *Kidney Int*. 2016;90(6):1274–1284. <https://doi.org/10.1016/j.kint.2016.07.011>
501. Wu JC, Wang XJ, Zhu JH, et al. GPR97 deficiency ameliorates renal interstitial fibrosis in mouse hypertensive nephropathy. *Acta Pharmacol Sin*. 2023;44(6):1206–1216. <https://doi.org/10.1038/s41401-022-01041-y>
502. Amisten S, Salehi A, Rorsman P, Jones PM, Persaud SJ. An atlas and functional analysis of G-protein coupled receptors in human islets of Langerhans. *Pharmacol Ther*. 2013;139(3):359–391. <https://doi.org/10.1016/j.pharmthera.2013.05.004>
503. Kaczmarek I, Suchý T, Prömel S, Schöneberg T, Liebscher I, Thor D. The relevance of adhesion G protein-coupled receptors in metabolic functions. *Biol Chem*. 2022;403(2):195–209. <https://doi.org/10.1515/hsz-2021-0146>
504. Mohammad Al-Amily IM, Sjögren M, Duner P, Tariq M, Wollheim CB, Salehi A. Ablation of GPR56 causes β -cell dysfunction by ATP loss through mistargeting of mitochondrial VDAC1 to the plasma membrane. *Bio-molecules*. 2023;13(3):557. <https://doi.org/10.3390/biom13030557>
505. Duner P, Al-Amily IM, Soni A, et al. Adhesion G protein-coupled receptor G1 (ADGRG1/GPR56) and pancreatic β -cell function. *J Clin Endocrinol Metab*. 2016;101(12):4637–4645. <https://doi.org/10.1210/jc.2016-1884>
506. Olaniiru OE, Pingitore A, Giera S, et al. The adhesion receptor GPR56 is activated by extracellular matrix collagen III to improve β -cell function. *Cell Mol Life Sci*. 2018;75(21):4007–4019. <https://doi.org/10.1007/s00018-018-2846-4>
507. Gupta R, Nguyen DC, Schaid MD, et al. 1q-like-3 protein inhibits insulin secretion from pancreatic β -cells via the cell adhesion G protein-coupled receptor BA13. *J Biol Chem*. 2018;293(47):18086–18098. <https://doi.org/10.1074/jbc.ra118.005403>
508. Suchý T, Zieschang C, Popkova Y, et al. The repertoire of Adhesion G protein-coupled receptors in adipocytes and their functional relevance. *Int J Obes*. 2020;44(10):2124–2136. <https://doi.org/10.1038/s41366-020-0570-2>
509. Nie T, Hui X, Gao X, et al. Adipose tissue deletion of Gpr116 impairs insulin sensitivity through modulation of adipose function. *FEBS Lett*. 2012;586(20):3618–3625. <https://doi.org/10.1016/j.febslet.2012.08.006>
510. Al Hasan MA, Roy P, Dolan S, Martin PE, Patterson S, Bartholomew C. Adhesion G-protein coupled receptor 56 is required for 3T3-L1 adipogenesis. *J Cell Physiol*. 2020;235(2):1601–1614. <https://doi.org/10.1002/jcp.29079>
511. Ye C, Wang X, Lin J, et al. Systematical identification of regulatory GPCRs by single-cell trajectory inference reveals the role of ADGRD1 and GPR39 in adipogenesis. *Sci China Life Sci*. 2025;68(4):1057–1072. <https://doi.org/10.1007/s11427-024-2732-8>
512. Alsharif H, Latimer MN, Perez KC, et al. Loss of brain angiogenesis Inhibitor-3 (BAI3) G-protein coupled receptor in mice regulates adaptive thermogenesis by enhancing energy expenditure. *Metabolites*. 2023;13(6):711. <https://doi.org/10.3390/metabo13060711>
513. Zhao Z, Hu L, Song B, et al. Constitutively active receptor ADGRA3 signaling induces adipose thermogenesis. *eLife*. 2024;13:RP100205. <https://doi.org/10.7554/eLife.100205>
514. Harms MJ, Ishibashi J, Wang W, et al. Prdm16 is required for the maintenance of Brown adipocyte identity and function in adult mice. *Cell Metab*. 2014;19(4):593–604. <https://doi.org/10.1016/j.cmet.2014.03.007>
515. Fagerberg L, Hallström BM, Oksvold P, et al. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Mol Cell Proteomics*. 2013;13(2):397–406. <https://doi.org/10.1074/mcp.m113.035600>
516. Wang Y, Wang T, Xiang Q, et al. GPR116 promotes ferroptosis in sepsis-induced liver injury by suppressing system Xc. *Cell Biol Toxicol*. 2023;39(6):3015–3030. <https://doi.org/10.1007/s10565-023-09815-8>
517. Xiang Q, Li N, Zhang Y, Wang T, Wang Y, Bian J. GPR116 alleviates acetaminophen-induced liver injury in mice by inhibiting endoplasmic reticulum stress. *Cell Mol Life Sci*. 2024;81(1):299. <https://doi.org/10.1007/s00018-024-05313-0>
518. Wu M, Lo TH, Li L, et al. Amelioration of non-alcoholic fatty liver disease by targeting adhesion G protein-coupled receptor F1 (Adgrf1). *eLife*. 2023;12:e85131. <https://doi.org/10.7554/eLife.85131>
519. Ma B, Zhu J, Tan J, et al. Gpr110 deficiency decelerates carcinogen-induced hepatocarcinogenesis via activation of the IL-6/STAT3 pathway. *Am J Cancer Res*. 2017;7(3):433–447.
520. Kathiresan S, Melander O, Guiducci C, et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat Genet*. 2008;40(2):189–197. <https://doi.org/10.1038/ng.75>
521. Tan J, Che Y, Liu Y, et al. CELSR2 deficiency suppresses lipid accumulation in hepatocyte by impairing the UPR and elevating ROS level. *FASEB J*. 2021;35(10):e21908. <https://doi.org/10.1096/fj.202100786rr>
522. Lin H, Ma C, Zhuang X, et al. Sensing steroid hormone 17 α -hydroxypregnenolone by GPR56 enables protection from ferroptosis-induced liver injury. *Cell Metab*. 2024;36(11):2402–2418.e10. <https://doi.org/10.1016/j.cmet.2024.09.007>
523. Badiali L, Cedernaes J, Olszewski PK, Nylander O, Vergoni AV, Schiöth HB. Adhesion GPCRs are widely expressed throughout the subsections of the gastrointestinal tract. *BMC Gastroenterol*. 2012;12(1):134. <https://doi.org/10.1186/1471-230x-12-134>
524. Ito J, Ito M, Nambu H, et al. Anatomical and histological profiling of orphan G-protein-coupled receptor expression in gastrointestinal tract of C57BL/6J mice. *Cell Tissue Res*. 2009;338(2):257–269. <https://doi.org/10.1007/s00441-009-0859-x>
525. Becker S, Wandel E, Wobus M, et al. Overexpression of CD97 in intestinal epithelial cells of transgenic mice attenuates colitis by strengthening adherens junctions. *PLoS One*. 2010;5(1):e8507. <https://doi.org/10.1371/journal.pone.0008507>
526. Grunddal KV, Tonack S, Egerod KL, et al. Adhesion receptor ADGRG2/GPR64 is in the GI-tract selectively expressed in mature intestinal tuft cells. *Mol Metab*. 2021;51:101231. <https://doi.org/10.1016/j.molmet.2021.101231>
527. Leja J, Essaghir A, Essand M, et al. Novel markers for enterochromaffin cells and gastrointestinal neuroendocrine carcinomas. *Mod Pathol*. 2009;22(2):261–272. <https://doi.org/10.1038/modpathol.2008.174>
528. Hofmann F, Thalheim T, Rother K, et al. How to obtain a mega-intestine with normal morphology: in silico modelling of postnatal intestinal growth in a CD97-transgenic mouse. *Int J Mol Sci*. 2021;22(14):7345. <https://doi.org/10.3390/ijms22147345>
529. Lee CS, Penberthy KK, Wheeler KM, et al. Boosting apoptotic cell clearance by colonic epithelial cells attenuates inflammation in vivo. *Immunity*. 2016;44(4):807–820. <https://doi.org/10.1016/j.immuni.2016.02.005>
530. Ni YY, Chen Y, Lu SY, et al. Deletion of Gpr128 results in weight loss and increased intestinal contraction frequency. *World J Gastroenterol*. 2014;20(2):498–508. <https://doi.org/10.3748/wjg.v20.i2.498>
531. Acien M, Acien P. Female genital tract congenital malformations, classification, diagnosis and management. Published online 2014:3-14. doi:10.1007/978-1-4471-5146-3_1.
532. Kvam JM, Nybo ML, Torz L, et al. High incidence of imperforate vagina in ADGRA3-deficient mice. *BMC Biol*. 2024;22(1):77. <https://doi.org/10.1186/s12915-024-01873-6>
533. Roly ZY, Major AT, Fulcher A, Estermann MA, Hirst CE, Smith CA. Adhesion G-protein-coupled receptor, GPR56, is required for Müllerian duct development in the chick. *J Endocrinol*. 2020;244(2):395–413. <https://doi.org/10.1530/joe-19-0419>
534. Langenhan T, Prömel S, Mestek L, et al. Latrophilin signaling links anterior-posterior tissue polarity and oriented cell divisions in the *C. elegans* embryo. *Dev Cell*. 2009;17(4):494–504. <https://doi.org/10.1016/j.devcel.2009.08.008>
535. vandenBerg AL, Sassoon DA. Non-canonical Wnt signaling regulates cell polarity in female reproductive tract development via van gogh-like 2. *Development*. 2009;136(9):1559–1570. <https://doi.org/10.1242/dev.034066>
536. Murata T, Ishitsuka Y, Karouji K, et al. β -catenin/C429S mice exhibit sterility consequent to spatiotemporally sustained Wnt signalling in the internal genitalia. *Sci Rep*. 2014;4(1):6959. <https://doi.org/10.1038/srep06959>
537. Steinhart Z, Angers S. Wnt signaling in development and tissue homeostasis. *Development*. 2018;145(11):dev146589. <https://doi.org/10.1242/dev.146589>
538. St-Jean G, Boyer A, Zamberlam G, Godin P, Paquet M, Boerboom D. Targeted ablation of Wnt4 and Wnt5a in Müllerian duct mesenchyme impedes endometrial gland development and causes partial Müllerian agenesis. *Biol Reprod*. 2019;100(1):49–60. <https://doi.org/10.1093/biolre/iy160>
539. Bagger SM, Schihada H, Walser ALS, et al. Complex G-protein signaling of the adhesion GPCR, ADGRA3. *J Biol Chem*. 2025;301(5):108441. <https://doi.org/10.1016/j.jbc.2025.108441>
540. Fu JF, Yen TH, Chen Y, et al. Involvement of Gpr125 in the myeloid sarcoma formation induced by cooperating MLL/AF10(OM-L2) and oncogenic KRAS in a mouse bone marrow transplantation model. *Int J Cancer*. 2013;133(8):1792–1802. <https://doi.org/10.1002/ijc.28195>
541. James RG, Biechele TL, Conrad WH, et al. Bruton's tyrosine kinase revealed as a negative regulator of Wnt- β -catenin signaling. *Sci Signal*. 2009;2(72):ra25. <https://doi.org/10.1126/scisignal.2000230>

542. Wu Y, Chen W, Gong L, Ke C, Wang H, Cai Y. Elevated G-protein Receptor 125 (GPR125) expression predicts good outcomes in colorectal cancer and inhibits Wnt/ β -catenin signaling pathway. *Med Sci Monit*. 2018;24:6608–6616. <https://doi.org/10.12659/msm.910105>
543. Ganesh RA, Venkataraman K, Sirdeshmukh R. GPR56 signaling pathway network and its dynamics in the mesenchymal transition of glioblastoma. *J Cell Commun Signal*. 2023;17(4):1527–1535. <https://doi.org/10.1007/s12079-023-00792-5>
544. Yoo JY, Ahn JI, Kim TH, et al. G-protein coupled receptor 64 is required for decidualization of endometrial stromal cells. *Sci Rep*. 2017;7(1):5021. <https://doi.org/10.1038/s41598-017-05165-8>
545. Shen H, Jin M, Gu S, Wu Y, Yang M, Hua X. CD97 is decreased in preclamping placentas and promotes human trophoblast invasion through PI3K/Akt/mTOR signaling pathway. *Reprod Sci*. 2020;27(8):1553–1561. <https://doi.org/10.1007/s43032-020-00183-w>
546. Nybo ML, Kvam JM, Nielsen JE, et al. Loss of Adgr3 causes obstructive azoospermia with high penetrance in male mice. *FASEB J*. 2023;37(2):e22781. <https://doi.org/10.1096/fj.202200762r>
547. Chen G, Yang L, Begum S, Xu L. GPR56 is essential for testis development and male fertility in mice. *Dev Dyn*. 2010;239(12):3358–3367. <https://doi.org/10.1002/dvdy.22468>
548. Davies B, Behnen M, Cappallo-Obermann H, Spiess AN, Theuring F, Kirchhoff C. Novel epididymis-specific mRNAs downregulated by HE6/Gpr64 receptor gene disruption. *Mol Reprod Dev*. 2007;74(5):539–553. <https://doi.org/10.1002/mrd.20636>
549. Kirchhoff C, Osterhoff C, Samalecos A. HE6/GPR64 adhesion receptor colocalizes with apical and subapical F-actin scaffold in male excurrent duct epithelia. *Reproduction*. 2008;136(2):235–245. <https://doi.org/10.1530/rep-08-0078>
550. Obermann H, Samalecos A, Osterhoff C, Schröder B, Heller R, Kirchhoff C. HE6, a two-subunit heptahelical receptor associated with apical membranes of efferent and epididymal duct epithelia. *Mol Reprod Dev*. 2003;64(1):13–26. <https://doi.org/10.1002/mrd.10220>
551. Davies B, Baumann C, Kirchhoff C, et al. Targeted deletion of the epididymal receptor HE6 results in fluid dysregulation and male infertility. *Mol Cell Biol*. 2004;24(19):8642–8648. <https://doi.org/10.1128/mcb.24.19.8642-8648.2004>
552. Khan MJ, Pollock N, Jiang H, et al. X-linked ADGRG2 mutation and obstructive azoospermia in a large Pakistani family. *Sci Rep*. 2018;8(1):16280. <https://doi.org/10.1038/s41598-018-34262-5>
553. Patat O, Pagnin A, Siegfried A, et al. Truncating mutations in the adhesion G protein-coupled receptor G2 gene ADGRG2 cause an X-linked congenital bilateral absence of vas deferens. *Am J Hum Genet*. 2016;99(2):437–442. <https://doi.org/10.1016/j.ajhg.2016.06.012>
554. Yuan P, Liang ZK, Liang H, et al. Expanding the phenotypic and genetic spectrum of Chinese patients with congenital absence of vas deferens bearing CFTR and ADGRG2 alleles. *Andrology*. 2019;7(3):329–340. <https://doi.org/10.1111/andr.12592>
555. Aust G, Eichler W, Laue S, et al. CD97: a dedifferentiation marker in human thyroid carcinomas. *Cancer Res*. 1997;57(9):1798–1806.
556. Shi W, Xu C, Lei P, et al. A correlation study of adhesion G protein-coupled receptors as potential therapeutic targets for breast cancer. *Breast Cancer Res Treat*. 2024;207(2):417–434. <https://doi.org/10.1007/s10549-024-07373-z>
557. Gad AA, Balenga N. The emerging role of adhesion GPCRs in cancer. *ACS Pharmacol Transl Sci*. 2020;3(1):29–42. <https://doi.org/10.1021/acscptsci.9b00093>
558. Yang J, Wu S, Alachkar H. Corrigendum to "Characterization of upregulated adhesion GPCRs in acute myeloid leukemia" [Transl Res. 2019 Oct;212:26–35. doi: 10.1016/j.trsl.2019.05.004. Epub 2019 May 17.] *Transl Res*. 2025;275:62. <https://doi.org/10.1016/j.trsl.2024.11.003>
559. Yang J, Wu S, Alachkar H. Characterization of upregulated adhesion GPCRs in acute myeloid leukemia. *Transl Res*. 2019;212:26–35. <https://doi.org/10.1016/j.trsl.2019.05.004>
560. Stephan G, Ravn-Boess N, Placantonakis DG. Adhesion G protein-coupled receptors in glioblastoma. *Neurooncol Adv*. 2021;3(1):vdab046. <https://doi.org/10.1093/oaajnl/vdab046>
561. Lei P, Wang H, Yu L, et al. A correlation study of adhesion G protein-coupled receptors as potential therapeutic targets in uterine corpus endometrial cancer. *Int Immunopharmacol*. 2022;108:108743. <https://doi.org/10.1016/j.intimp.2022.108743>
562. Ng KF, Chen TC, Stacey M, Lin HH. Role of ADGRG1/GPR56 in tumor progression. *Cells*. 2021;10(12):3352. <https://doi.org/10.3390/cells10123352>
563. Moreno M, Pedrosa L, Paré L, et al. GPR56/ADGRG1 inhibits mesenchymal differentiation and radioresistance in glioblastoma. *Cell Rep*. 2017;21(8):2183–2197. <https://doi.org/10.1016/j.celrep.2017.10.083>
564. Frenster JD, Kader M, Kamen S, et al. Expression profiling of the adhesion G protein-coupled receptor GPR133 (ADGRD1) in glioma subtypes. *Neurooncol Adv*. 2020;2(1):vdad053. <https://doi.org/10.1093/oaajnl/vdad053>
565. Zhang S, Zhang Y, Sun X. Targeting GPR133 via miR-106a-5p inhibits the proliferation, invasion, migration and epithelial-mesenchymal transition (EMT) of glioma cells. *Int J Neurosci*. 2024;134(9):991–1002. <https://doi.org/10.1080/00207454.2023.2201873>
566. Wu G, Zhai D, Xie J, et al. N6-methyladenosine (m6A) RNA modification of G protein-coupled receptor 133 increases proliferation of lung adenocarcinoma. *FEBS Open Bio*. 2022;12(3):571–581. <https://doi.org/10.1002/2211-5463.13244>
567. Zhou LL, Jiao Y, Chen HM, et al. Differentially expressed long noncoding RNAs and regulatory mechanism of LINC02407 in human gastric adenocarcinoma. *World J Gastroenterol*. 2019;25(39):5973–5990. <https://doi.org/10.3748/wjg.v25.i39.5973>
568. Lv M, Li X, Tian W, Yang H, Zhou B. ADGRD1 as a potential prognostic and immunological biomarker in non-small-cell lung cancer. *BioMed Res Int*. 2022;2022(1):5699892. <https://doi.org/10.1155/2022/5699892>
569. Jaspars LH, Vos W, Aust G, van Lier RAW, Hamann J. Tissue distribution of the human CD97 EGF-TM7 receptor. *Tissue Antigens*. 2001;57(4):325–331. <https://doi.org/10.1034/j.1399-0039.2001.057004325.x>
570. Safaee M, Ivan ME, Oh MC, et al. The role of epidermal growth factor-like module containing mucin-like hormone receptor 2 in human cancers. *Oncol Rep*. 2014;31(1):242. <https://doi.org/10.4081/oncol.2014.242>
571. Tjong WY, Lin HH. The RGD motif is involved in CD97/ADGRE5-promoted cell adhesion and viability of HT1080 cells. *Sci Rep*. 2019;9(1):1517. <https://doi.org/10.1038/s41598-018-38045-w>
572. Hsiao CC, Keysselt K, Chen HY, et al. The adhesion GPCR CD97/ADGRE5 inhibits apoptosis. *Int J Biochem Cell Biol*. 2015;65:197–208. <https://doi.org/10.1016/j.biocel.2015.06.007>
573. Buzatu IM, Costachi A, Docea AO, Manea EV, Zlatian O. Research progress of EMR2 receptor function in glioma and its potential application as therapeutic target. *Curr Health Sci J*. 2024;50(4):467–477. <https://doi.org/10.12865/CHSJ.50.04.02>
574. Safaee M, Fakurnejad S, Bloch O, et al. Proportional upregulation of CD97 isoforms in glioblastoma and glioblastoma-derived brain tumor initiating cells. *PLoS One*. 2015;10(2):e0111532. <https://doi.org/10.1371/journal.pone.0111532>
575. Liu JK, Lubelski D, Schonberg DL, et al. Phage display discovery of novel molecular targets in glioblastoma-initiating cells. *Cell Death Differ*. 2014;21(8):1325–1339. <https://doi.org/10.1038/cdd.2014.65>
576. Safaee M, Clark AJ, Oh MC, et al. Overexpression of CD97 confers an invasive phenotype in glioblastoma cells and is associated with decreased survival of glioblastoma patients. *PLoS One*. 2013;8(4):e62765. <https://doi.org/10.1371/journal.pone.0062765>
577. Yang R, Zhang W, Shang X, et al. Neutrophil-related genes predict prognosis and response to immune checkpoint inhibitors in bladder cancer. *Front Pharmacol*. 2022;13:1013672. <https://doi.org/10.3389/fphar.2022.1013672>
578. Feliciano A, García-Mayea Y, Jubierre L, et al. miR-99a reveals two novel oncogenic proteins E2F2 and EMR2 and represses stemness in lung cancer. *Cell Death Dis*. 2017;8(10):e3141. <https://doi.org/10.1038/cddis.2017.544>
579. Davies JQ, Lin HH, Stacey M, et al. Leukocyte adhesion-GPCR EMR2 is aberrantly expressed in human breast carcinomas and is associated with patient survival. *Oncol Rep*. 2011;25(3):619–627. <https://doi.org/10.3892/or.2010.1117>
580. Mirkowska P, Hofmann A, Sedek L, et al. Leukemia surfaceome analysis reveals new disease-associated features. *Blood*. 2013;121(25):e149–e159. <https://doi.org/10.1182/blood-2012-11-468702>
581. Santorelli L, Capitoli G, Chinello C, et al. In-depth mapping of the urinary N-Glycoproteome: distinct signatures of ccRCC-related progression. *Cancers*. 2020;12(1):239. <https://doi.org/10.3390/cancers12010239>
582. Wu J, Lei L, Wang S, Gu D, Zhang J. Immunohistochemical expression and prognostic value of CD97 and its ligand CD55 in primary gallbladder carcinoma. *J Biomed Biotechnol*. 2012;2012(1):587672. <https://doi.org/10.1155/2012/587672>
583. He Y, Wang W, Xu L, et al. Immunohistochemical expression and prognostic significance of CD97 and its ligand DAF in human cervical squamous cell carcinoma. *Int J Gynecol Pathol*. 2015;34(5):473–479. <https://doi.org/10.1097/pgp.0000000000000200>
584. Mustafa T, Eckert A, Klonisch T, et al. Expression of the epidermal growth factor seven-transmembrane member CD97 correlates with grading and staging in human oral squamous cell carcinomas. *Cancer Epidemiol Biomarkers Prev*. 2005;14(1):108–119. <https://doi.org/10.1158/1055-9965.108.14.1>
585. Mustafa T, Klonisch T, Hombach-Klonisch S, et al. Expression of CD97 and CD55 in human medullary thyroid carcinomas. *Int J Oncol*. 2004;24(2):285–294. <https://doi.org/10.3892/ijo.24.2.285>
586. Rutkowski MJ, Sughrue ME, Kane AJ, Kim JM, Bloch O, Parsa AT. Epidermal growth factor module-containing mucin-like receptor 2 is a newly identified adhesion G protein-coupled receptor associated with poor overall survival and an invasive phenotype in glioblastoma. *J Neuro-oncol*. 2011;105(2):165–171. <https://doi.org/10.1007/s11060-011-0576-7>
587. Slepak TI, Guyot M, Walters W, Eichberg DG, Ivan ME. Dual role of the adhesion G-protein coupled receptor ADRGE5/CD97 in glioblastoma invasion and proliferation. *J Biol Chem*. 2023;299(9):105105. <https://doi.org/10.1016/j.jbc.2023.105105>
588. Zhang X, Zhang X, Yang Q, et al. Comprehensive analysis of ADGRE5 gene in human tumors: clinical relevance, prognostic implications, and potential for personalized immunotherapy. *Heliyon*. 2024;10(6):e27459. <https://doi.org/10.1016/j.heliyon.2024.e27459>
589. Aust G, Steinert M, Schütz A, et al. CD97, but not its closely related EGF-TM7 family member EMR2, is expressed on gastric, pancreatic, and esophageal carcinomas. *Am J Clin Pathol*. 2002;118(5):699–707. <https://doi.org/10.1309/a6ab-v3f3-7m88-c0ej>

590. Steinert M, Wobus M, Boltze C, et al. Expression and regulation of CD97 in colorectal carcinoma cell lines and tumor tissues. *Am J Pathol.* 2002;161(5): 1657–1667. [https://doi.org/10.1016/s0002-9440\(10\)64443-4](https://doi.org/10.1016/s0002-9440(10)64443-4)
591. Yin Y, Xu X, Tang J, et al. CD97 promotes tumor aggressiveness through the traditional G protein–coupled receptor–mediated signaling in hepatocellular carcinoma. *Hepatology.* 2018;68(5):1865–1878. <https://doi.org/10.1002/hep.30068>
592. Li C, Liu DR, Li GG, et al. CD97 promotes gastric cancer cell proliferation and invasion through exosome-mediated MAPK signaling pathway. *World J Gastroenterol.* 2015;21(20):6215–6228. <https://doi.org/10.3748/wjg.v21.i20.6215>
593. Zhou S, Lin W, Jin X, et al. CD97 maintains tumorigenicity of glioblastoma stem cells via mTORC2 signaling and is targeted by CAR Th9 cells. *Cell Rep Med.* 2024;5(12):101844. <https://doi.org/10.1016/j.xcrm.2024.101844>
594. Cherry AE, Vicente JJ, Xu C, et al. GPR124 regulates microtubule assembly, mitotic progression, and glioblastoma cell proliferation. *Glia.* 2019;67(8): 1558–1570. <https://doi.org/10.1002/glia.23628>
595. Spina E, Simundza J, Incassati A, et al. Gpr125 is a unifying hallmark of multiple mammary progenitors coupled to tumor latency. *Nat Commun.* 2022;13(1):1421. <https://doi.org/10.1038/s41467-022-28937-x>
596. Kaur B, Brat DJ, Calkins CC, Van Meir EG. Brain angiogenesis Inhibitor 1 is differentially expressed in normal brain and glioblastoma independently of p53 expression. *Am J Pathol.* 2003;162(1):19–27. [https://doi.org/10.1016/s0002-9440\(10\)63794-7](https://doi.org/10.1016/s0002-9440(10)63794-7)
597. Shiratsuchi T, Nishimori H, Ichise H, Nakamura Y, Tokino T. Cloning and characterization of BAI2 and BAI3, novel genes homologous to brain-specific angiogenesis inhibitor 1 (BAI1). *Cytogenet Cell Genet.* 1997;79(1–2): 103–108. <https://doi.org/10.1159/000134693>
598. Kan Z, Jaiswal BS, Stinson J, et al. Diverse somatic mutation patterns and pathway alterations in human cancers. *Nature.* 2010;466(7308):869–873. <https://doi.org/10.1038/nature09208>
599. Zhu D, Hunter SB, Vertino PM, Van Meir EG. Overexpression of MBD2 in glioblastoma maintains epigenetic silencing and inhibits the antiangiogenic function of the tumor suppressor gene BAI1. *Cancer Res.* 2011;71(17): 5859–5870. <https://doi.org/10.1158/0008-5472.CAN-11-1157>
600. Meng ZW, Zhang L, Cai XR, Wang X, She FF, Chen YL. Author Correction: IL-8 is a novel prometastatic chemokine in intrahepatic cholangiocarcinoma that induces CXCR2-PI3K/AKT signaling upon CD97 activation. *Sci Rep.* 2024;14(1):8478. <https://doi.org/10.1038/s41598-024-58952-5>
601. Huang Q, Liu L, Xiao D, et al. CD44+ lung cancer stem cell-derived pericyte-like cells cause brain metastases through GPR124-enhanced transendothelial migration. *Cancer Cell.* 2023;41(9):1621–1636.e8. <https://doi.org/10.1016/j.ccell.2023.07.012>
602. Hsiao CC, Wang WC, Kuo WL, et al. CD97 inhibits cell migration in human fibrosarcoma cells by modulating TIMP-2/MT1- MMP/MMP-2 activity—role of GPS autoproteolysis and functional cooperation between the N- and C-terminal fragments. *FEBS J.* 2014;281(21):4878–4891. <https://doi.org/10.1111/febs.13027>
603. Wobus M, Huber O, Hamann J, Aust G. CD97 overexpression in tumor cells at the invasion front in colorectal cancer (CC) is independently regulated of the canonical Wnt pathway. *Mol Carcinog.* 2006;45(11):881–886. <https://doi.org/10.1002/mc.20262>
604. Liu D, Li C, Trojanowicz B, et al. CD97 promotion of gastric carcinoma lymphatic metastasis is exosome dependent. *Gastric Cancer.* 2016;19(3): 754–766. <https://doi.org/10.1007/s10120-015-0523-y>
605. Eichberg DG, Slepak TI, Pascoini AL, Komotar RJ, Ivan ME. Genetic manipulation of adhesion GPCR CD97/ADGRE5 modulates invasion in patient-derived glioma stem cells. *J Neuro-oncol.* 2021;153(3):383–391. <https://doi.org/10.1007/s11060-021-03778-8>
606. Meng ZW, Zhang L, Cai XR, Wang X, She FF, Chen YL. IL-8 is a novel prometastatic chemokine in intrahepatic cholangiocarcinoma that induces CXCR2-PI3K/AKT signaling upon CD97 activation. *Sci Rep.* 2023;13(1):18711. <https://doi.org/10.1038/s41598-023-45496-3>
607. Galle J, Sittig D, Hanisch I, et al. Individual cell-based models of tumor-environment interactions multiple effects of CD97 on tumor invasion. *Am J Pathol.* 2006;169(5):1802–1811. <https://doi.org/10.2353/ajpath.2006.060006>
608. Chidambaram A, Fillmore HL, van Meter TE, Dumur CI, Broaddus WC. Novel report of expression and function of CD97 in malignant gliomas: correlation with Wilms tumor 1 expression and glioma cell invasiveness. *J Neurosurg.* 2012;116(4):843–853. <https://doi.org/10.3171/2011.11.jns111455>
609. Ward Y, Lake R, Faraji F, et al. Platelets promote metastasis via binding tumor CD97 leading to bidirectional signaling that coordinates transendothelial migration. *Cell Rep.* 2018;23(3):808–822. <https://doi.org/10.1016/j.celrep.2018.03.092>
610. Garofano K, Rashid K, Smith M, et al. Prostate cancer cell-platelet bidirectional signaling promotes calcium mobilization, invasion and apoptotic resistance via distinct receptor-ligand pairs. *Sci Rep.* 2023;13(1):2864. <https://doi.org/10.1038/s41598-023-29450-x>
611. Liu Y, Chen L, Peng S, et al. The expression of CD97EGF and its ligand CD55 on marginal epithelium is related to higher stage and depth of tumor invasion of gastric carcinomas. *Oncol Rep.* 2005;14(6):1413–1420. <https://doi.org/10.3892/or.14.6.1413>
612. Ali H, Olsson L, Lindmark G, Hammarström ML, Hammarström S, Sitohy B. The myeloid cell biomarker EMR1 is ectopically expressed in colon cancer. *Tumour Biol.* 2021;43(1):209–223. <https://doi.org/10.3233/tub-200082>
613. Aust G, Zheng L, Quas M. To detach, migrate, adhere, and metastasize: CD97/ADGRE5 in cancer. *Cells.* 2022;11(9):1538. <https://doi.org/10.3390/cells11091538>
614. Akter R, Park R, Lee SK, et al. Upregulation of EMR1 (ADGRE1) by tumor-associated macrophages promotes colon cancer progression by activating the JAK2/STAT1,3 signaling pathway in tumor cells. *Int J Mol Sci.* 2024;25(8): 4388. <https://doi.org/10.3390/ijms25084388>
615. Teramoto Y, Najafi MAE, Matsukawa T, Sharma A, Goto T, Miyamoto H. Latrophilins as downstream effectors of androgen receptors including a splice variant, AR-V7, induce prostate cancer progression. *Int J Mol Sci.* 2024;25(13):7289. <https://doi.org/10.3390/ijms25137289>
616. Goto T, Yasui M, Teramoto Y, Nagata Y, Mizushima T, Miyamoto H. Latrophilin-3 as a downstream effector of the androgen receptor induces urothelial tumorigenesis. *Mol Carcinog.* 2024;63(10):1847–1854. <https://doi.org/10.1002/mc.23783>
617. Avila-Zozaya M, Rodríguez-Hernández B, Monterrubio-Ledezma F, Cisneros B, Boucard AA. Thwarting of Lphn3 functions in cell motility and signaling by cancer-related GAIN domain somatic mutations. *Cells.* 2022;11(12):1913. <https://doi.org/10.3390/cells11121913>
618. Goto T, Teramoto Y, Nagata Y, Miyamoto H. Latrophilin-3 as a downstream effector of the androgen receptor induces bladder cancer progression. *Discov Oncol.* 2024;15(1):440. <https://doi.org/10.1007/s12672-024-01324-2>
619. Shashidhar S, Lorente G, Nagavarapu U, et al. GPR56 is a GPCR that is overexpressed in gliomas and functions in tumor cell adhesion. *Oncogene.* 2005;24(10):1673–1682. <https://doi.org/10.1007/sj.onc.1208395>
620. Geng G, Zhang L, Yu Y, Guo X, Li Q, Ming M. ADGLR4 promotes cell growth, aggressiveness, EMT, and angiogenesis in neuroblastoma via activation of ERK/STAT3 pathway. *Curr Mol Med.* 2025;25(1):45–55. <https://doi.org/10.2174/0115665240254765231117122210>
621. Guihurt Santiago JG, Burgos-Tirado N, Lafontaine DD, et al. Adhesion G protein-coupled receptor, ELTD1, is a potential therapeutic target for retinoblastoma migration and invasion. *BMC Cancer.* 2021;21(1):53. <https://doi.org/10.1186/s12885-020-07768-3>
622. Li J, Shen J, Wang Z, et al. ELTD1 facilitates glioma proliferation, migration and invasion by activating JAK/STAT3/HIF-1 α signaling axis. *Sci Rep.* 2019;9(1):13904. <https://doi.org/10.1038/s41598-019-50375-x>
623. Sun J, Zhang Z, Chen J, Xue M, Pan X. ELTD1 promotes invasion and metastasis by activating MMP2 in colorectal cancer. *Int J Biol Sci.* 2021;17(12): 3048–3058. <https://doi.org/10.7150/ijbs.62293>
624. Zuo J, Zheng A, Wang X, et al. Upregulation of CELSR1 expression promotes ovarian cancer cell proliferation, migration, and invasion. *Méd Oncol.* 2023;41(1):10. <https://doi.org/10.1007/s12032-023-02232-1>
625. Li Y, Zhu L, Hao R, Li Y, Zhao Q, Li S. Systematic expression analysis of the CELSR family reveals the importance of CELSR3 in human lung adenocarcinoma. *J Cell Mol Med.* 2021;25(9):4349–4362. <https://doi.org/10.1111/jcmm.16497>
626. Van Emmen LV, Ku SY, Gayvert K, et al. The identification of CELSR3 and other potential cell surface targets in neuroendocrine prostate cancer. *Cancer Res Commun.* 2023;3(8):1447–1459. <https://doi.org/10.1158/2767-9764.crc-22-0491>
627. Li J, Meng Z, Cao Z, et al. ADGRE5-centered Tsurv model in T cells recognizes responders to neoadjuvant cancer immunotherapy. *Front Immunol.* 2024;15: 1304183. <https://doi.org/10.3389/fimmu.2024.1304183>
628. Su Q, Li L, Li X, et al. CD97 serves as a novel biomarker of immune cell infiltration in hepatocellular carcinoma. *World J Surg Oncol.* 2022;20(1):382. <https://doi.org/10.1186/s12957-022-02829-2>
629. Vogl UM, Öhler L, Rasic M, Frischer JM, Modak M, Stöckl J. Evaluation of prognostic immune signatures in patients with breast, colorectal and pancreatic cancer receiving chemotherapy. *Anticancer Res.* 2017;37(4): 1947–1955. <https://doi.org/10.21873/anticancer.11535>
630. Xiang S, Li J, Shen J, et al. Identification of prognostic genes in the tumor microenvironment of hepatocellular carcinoma. *Front Immunol.* 2021;12: 653836. <https://doi.org/10.3389/fimmu.2021.653836>
631. Yoon JW, Kim KM, Cho S, et al. Th1-poised naive CD4 T cell subpopulation reflects anti-tumor immunity and autoimmune disease. *Nat Commun.* 2025;16(1):1962. <https://doi.org/10.1038/s41467-025-57237-3>
632. Sheldon H, Bridges E, Silva I, et al. ADGLR4/ELTD1 expression in breast cancer cells induces vascular normalization and immune suppression. *Mol Cancer Res.* 2021;19(11):1957–1969. <https://doi.org/10.1158/1541-7786.MCR-21-0171>
633. Liu C, Liu T, Hu Y, et al. G protein–coupled receptor 56 characterizes CTLs and reflects the progression of lung cancer patients. *J Immunol.* 2023;211(4): 683–692. <https://doi.org/10.4049/jimmunol.2101048>
634. Mei Y, Liu Y, Liu W, et al. Identifying ADGRG1 as a specific marker for tumor-reactive T cells in acute myeloid leukemia. *Exp Hematol Oncol.* 2024;13(1):92. <https://doi.org/10.1186/s40164-024-00560-0>
635. Mathioudaki A, Wang X, Sedloev D, et al. The remission status of AML patients after allo-HCT is associated with a distinct single-cell bone marrow T-cell signature. *Blood.* 2024;143(13):1269–1281. <https://doi.org/10.1182/blood.2023021815>

636. Zheng C, Fass JN, Shih YP, et al. Transcriptomic profiles of neoantigen-reactive T cells in human gastrointestinal cancers. *Cancer Cell*. 2022;40(4):410–423.e7. <https://doi.org/10.1016/j.ccell.2022.03.005>
637. Jacquier A, Lambert T, Delattre JF, et al. Tumor infiltrating and peripheral CD4+ILT2+ T cells are a cytotoxic subset selectively inhibited by HLA-G in clear cell renal cell carcinoma patients. *Cancer Lett*. 2021;519:105–116. <https://doi.org/10.1016/j.canlet.2021.06.018>
638. Yang Y, Wen D, Lin F, et al. Suppression of non-muscle myosin II boosts T cell cytotoxicity against tumors. *Sci Adv*. 2024;10(44):eadp0631. <https://doi.org/10.1126/sciadv.adp0631>
639. Favara DM, Banham AH, Harris AL. A review of ELTD1, a pro-angiogenic adhesion GPCR. *Biochem Soc Trans*. 2014;42(6):1658–1664. <https://doi.org/10.1042/bst20140216>
640. Zalles M, Smith N, Saunders D, et al. A tale of two multi-focal therapies for glioblastoma: an antibody targeting ELTD1 and nitron-based OKN-007. *J Cell Mol Med*. 2022;26(2):570–582. <https://doi.org/10.1111/jcmm.17133>
641. Zalles M, Smith N, Saunders D, et al. ELTD1 as a multi-focal target for malignant gliomas: preclinical studies. *Neurooncol Adv*. 2021;3(1):vdab132. <https://doi.org/10.1093/oaajnl/vdab132>
642. Shi J, Zhang X, Wang S, et al. Gpr97 is dispensable for metabolic syndrome but is involved in macrophage inflammation in high-fat diet-induced obesity in mice. *Sci Rep*. 2016;6(1):24649. <https://doi.org/10.1038/srep24649>
643. Rosenkilde MM, Tsutsumi N, Knerr JM, Kildedal DF, Garcia KC. Viral G protein-coupled receptors encoded by β - and γ -herpesviruses. *Annu Rev Virol*. 2022;9(1):329–351. <https://doi.org/10.1146/annurev-virology-100220-113942>
644. Spiess K, Rosenkilde MM. Functional properties of virus-encoded and virus-regulated G protein-coupled receptors. In: Stevens C, ed. *G Protein-Coupled Receptor Genetics, Research and Methods in the Post-Genomic Era*. Humana Press; 2014:45–65. https://doi.org/10.1007/978-1-62703-779-2_3
645. Dragic T, Litwin V, Allaway GP, et al. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature*. 1996;381(6584):667–673. <https://doi.org/10.1038/381667a0>
646. Chang J, Mancuso MR, Maier C, et al. Gpr124 is essential for blood-brain barrier integrity in central nervous system disease. *Nat Med*. 2017;23(4):450–460. <https://doi.org/10.1038/nm.4309>
647. Pickering C, Hägglund M, Szymdynger-Chodobska J, et al. The Adhesion GPCR GPR125 is specifically expressed in the choroid plexus and is upregulated following brain injury. *BMC Neurosci*. 2008;9(1):97. <https://doi.org/10.1186/1471-2202-9-97>
648. Karki P, Ke Y, Zhang C, et al. GPR68 mediates lung endothelial dysfunction caused by bacterial inflammation and tissue acidification. *Cells*. 2024;13(24):2125. <https://doi.org/10.3390/cells13242125>
649. Nijmeijer S, Vischer HF, Leurs R. Adhesion GPCRs in immunology. *Biochem Pharmacol*. 2016;114:88–102. <https://doi.org/10.1016/j.bcp.2016.04.013>
650. Hamann J, Hsiao CC, Lee CS, Ravichandran KS, Lin HH. Adhesion GPCRs as modulators of immune cell function. *Handb Exp Pharmacol*. 2016;234(4):329–350. https://doi.org/10.1007/978-3-319-41523-9_15
651. Nahalka J. 1-L transcription of SARS-CoV-2 spike protein S1 subunit. *Int J Mol Sci*. 2024;25(8):4440. <https://doi.org/10.3390/ijms25084440>
652. Wanjalla CN, McDonnell WJ, Barnett L, et al. Adipose tissue in persons with HIV is enriched for CD4+ T effector memory and T effector memory RA+ cells, which show higher CD69 expression and CD57, CX3CR1, GPR56 co-expression with increasing glucose intolerance. *Front Immunol*. 2019;10:408. <https://doi.org/10.3389/fimmu.2019.00408>
653. Woznik M, Rödner C, Lemon K, Rima B, Mankertz A, Finsterbusch T. Mumps virus small hydrophobic protein targets ataxin-1 ubiquitin-like interacting protein (ubiquitin 4). *J Gen Virol*. 2010;91(11):2773–2781. <https://doi.org/10.1099/vir.0.024638-0>
654. Rosenkilde MM, Spiess K, Pedersen LJT, Henningsen MLN, Qvortrup K. *Small hydrophobic protein drug conjugates and uses thereof*. 2022. WO2022223837.
655. Elliott MR, Zheng S, Park D, et al. Unexpected requirement for ELM01 in clearance of apoptotic germ cells in vivo. *Nature*. 2010;467(7313):333–337. <https://doi.org/10.1038/nature09356>
656. Penberthy KK, Ravichandran KS. Apoptotic cell recognition receptors and scavenger receptors. *Immunol Rev*. 2016;269(1):44–59. <https://doi.org/10.1111/imr.12376>
657. Mathema VB, Na-Bangchang K. Regulatory roles of brain-specific angiogenesis inhibitor 1(BAI1) protein in inflammation, tumorigenesis and phagocytosis: a brief review. *Crit Rev Oncol Hematol*. 2017;111:81–86. <https://doi.org/10.1016/j.critrevonc.2017.01.006>
658. Mazaheri F, Breus O, Durdu S, et al. Distinct roles for BAI1 and TIM-4 in the engulfment of dying neurons by microglia. *Nat Commun*. 2014;5(1):4046. <https://doi.org/10.1038/ncomms5046>
659. Das S, Sarkar A, Ryan KA, et al. Brain angiogenesis inhibitor 1 is expressed by gastric phagocytes during infection with *Helicobacter pylori* and mediates the recognition and engulfment of human apoptotic gastric epithelial cells. *FASEB J*. 2014;28(5):2214–2224. <https://doi.org/10.1096/fj.13-243238>
660. Morioka S, Kajioka D, Yamaoka Y, et al. Chimeric efferocytic receptors improve apoptotic cell clearance and alleviate inflammation. *Cell*. 2022;185(26):4887–4903.e17. <https://doi.org/10.1016/j.cell.2022.11.029>
661. Zhou X, Zhu D, Wu D, et al. Microneedle delivery of CAR-M-like engineered macrophages alleviates intervertebral disc degeneration through enhanced efferocytosis capacity. *Cell Rep Med*. 2025;6(4):102079. <https://doi.org/10.1016/j.xcrim.2025.102079>
662. Shiu FH, Wong JC, Yamamoto T, et al. Mice lacking full length Adgrb1 (Bai1) exhibit social deficits, increased seizure susceptibility, and altered brain development. *Exp Neurol*. 2022;351:113994. <https://doi.org/10.1016/j.expneurol.2022.113994>
663. Choi JS, Bae WY, Nam S, Jeong JW. New targets for Parkinson's disease: adhesion G protein-coupled receptor B1 is downregulated by AMP-activated protein kinase activation. *OMICS A J Integr Biol*. 2018;22(7):493–501. <https://doi.org/10.1089/omi.2018.0047>
664. Moon SY, Shin SA, Oh YS, Park HH, Lee CS. Understanding the role of the BAI subfamily of adhesion G protein-coupled receptors (GPCRs) in pathological and physiological conditions. *Genes*. 2018;9(12):597. <https://doi.org/10.3390/genes9120597>
665. Okajima D, Kudo G, Yokota H. Antidepressant-like behavior in brain-specific angiogenesis inhibitor 2-deficient mice. *J Physiol Sci*. 2011;61(1):47–54. <https://doi.org/10.1007/s12576-010-0120-0>
666. Liao HM, Chao YL, Huang AL, et al. Identification and characterization of three inherited genomic copy number variations associated with familial schizophrenia. *Schizophr Res*. 2012;139(1–3):229–236. <https://doi.org/10.1016/j.schres.2012.05.015>
667. DeRosier P, Lencz T, Burdick KE, Siris SG, Kane JM, Malhotra AK. The genetics of symptom-based phenotypes: toward a molecular classification of schizophrenia. *Schizophr Bull*. 2008;34(6):1047–1053. <https://doi.org/10.1093/schbul/sbn076>
668. Liu QR, Drgon T, Johnson C, Walther D, Hess J, Uhl GR. Addiction molecular genetics: 639,401 SNP whole genome association identifies many “cell adhesion” genes. *Am J Med Genet B Neuropsychiatr Genet*. 2006;141B(8):918–925. <https://doi.org/10.1002/ajmg.b.30436>
669. McCarthy MJ, Nievergelt CM, Kelsoe JR, Welsh DK. A survey of genomic studies supports association of circadian clock genes with bipolar disorder spectrum illnesses and lithium response. *PLoS One*. 2012;7(2):e32091. <https://doi.org/10.1371/journal.pone.0032091>
670. Shiu FH, Wong JC, Bhattacharya D, et al. Generation and initial characterization of mice lacking full-length BAI3 (ADGRB3) expression. *Basic Clin Pharmacol Toxicol*. 2023;133(4):353–363. <https://doi.org/10.1111/bcpt.13917>
671. Belzeaux R, Gorgievski V, Fiori LM, et al. GPR56/ADGRG1 is associated with response to antidepressant treatment. *Nat Commun*. 2020;11(1):1635. <https://doi.org/10.1038/s41467-020-15423-5>
672. Qi W, Guan W. GPR56: a potential therapeutic target for neurological and psychiatric disorders. *Biochem Pharmacol*. 2024;226:116395. <https://doi.org/10.1016/j.bcp.2024.116395>
673. Lion M, Ibrahim EC, Caccamo-Garcia E, et al. A specific GPR56/ADGRG1 splicing isoform is associated with antidepressant response in major depressive disorder. *Eur Neuropsychopharmacol*. 2025;93:5–14. <https://doi.org/10.1016/j.euroneuro.2025.01.001>
674. Bruxel EM, Moreira-Maia CR, Akutagawa-Martins GC, et al. Meta-analysis and systematic review of ADGRL3 (LPHN3) polymorphisms in ADHD susceptibility. *Mol Psychiatry*. 2021;26(6):2277–2285. <https://doi.org/10.1038/s41380-020-0673-0>
675. Domené S, Stanescu H, Wallis D, et al. Screening of human LPHN3 for variants with a potential impact on ADHD susceptibility. *Am J Med Genet B Neuropsychiatr Genet*. 2011;156B(1):11–18. <https://doi.org/10.1002/ajmg.b.31141>
676. Kappel DB, Schuch JB, Rovaris DL, et al. ADGRL3 rs6551665 as a common vulnerability factor underlying attention-deficit/hyperactivity disorder and autism spectrum disorder. *NeuroMolecular Med*. 2019;21(1):60–67. <https://doi.org/10.1007/s12017-019-08525-x>
677. Arcos-Burgos M, Vélez JL, Martínez AF, et al. ADGRL3 (LPHN3) variants predict substance use disorder. *Transl Psychiatry*. 2019;9(1):42. <https://doi.org/10.1038/s41398-019-0396-7>
678. Vezain M, Lecuyer M, Rubio M, et al. A de novo variant in ADGRL2 suggests a novel mechanism underlying the previously undescribed association of extreme microcephaly with severely reduced sulcation and rhombencephalosynapsis. *Acta Neuropathol Commun*. 2018;6(1):109. <https://doi.org/10.1186/s40478-018-0610-5>
679. Sun J, Kranzler HR, Gelernter J, Bi J. A genome-wide association study of cocaine use disorder accounting for phenotypic heterogeneity and gene-environment interaction. *J Psychiatry Neurosci*. 2020;45(1):34–44. <https://doi.org/10.1503/jpn.180098>
680. Lei W, Xiong Y, Shi Y, et al. ADGRL1 variants: from developmental and epileptic encephalopathy to genetic epilepsy with febrile seizures plus. *Dev Med Child Neurol*. 2025;67(1):119–125. <https://doi.org/10.1111/dmcn.16005>
681. Guan Y, Du HB, Yang Z, et al. Deafness-associated ADGRV1 mutation impairs USH2A stability through improper phosphorylation of WHRN and WDSUB1 recruitment. *Adv Sci (Weinh)*. 2023;10(16):e2205993. <https://doi.org/10.1002/adv.202205993>
682. McMillan DR, White PC. Loss of the transmembrane and cytoplasmic domains of the very large G-protein-coupled receptor-1 (VLGR1 or Mass1) causes audiogenic seizures in mice. *Mol Cell Neurosci*. 2004;26(2):322–329. <https://doi.org/10.1016/j.mcn.2004.02.005>
683. Myers KA, Nasioulas S, Boys A, et al. ADGRV1 is implicated in myoclonic epilepsy. *Epilepsia*. 2018;59(2):381–388. <https://doi.org/10.1111/epi.13980>
684. Zhou P, Meng H, Liang X, et al. ADGRV1 variants in febrile seizures/epilepsy with antecedent febrile seizures and their associations with audio-visual

- abnormalities. *Front Mol Neurosci*. 2022;15:864074. <https://doi.org/10.3389/fnmol.2022.864074>
685. Nair M, Bolyard C, Lee TJ, Kaur B, Yoo JY. Therapeutic application of brain-specific angiogenesis inhibitor 1 for cancer therapy. *Cancers*. 2021;13(14):3562. <https://doi.org/10.3390/cancers13143562>
 686. Meisen WH, Dubin S, Sizemore ST, et al. Changes in BAI1 and Nestin expression are prognostic indicators for survival and metastases in breast cancer and provide opportunities for dual targeted therapies. *Mol Cancer Ther*. 2015;14(1):307–314. <https://doi.org/10.1158/1535-7163.mct-14-0659>
 687. Hardcastle J, Kurozumi K, Dmitrieva N, et al. Enhanced antitumor efficacy of vasculostatin (Vstat120) expressing oncolytic HSV-1. *Mol Ther*. 2010;18(2):285–294. <https://doi.org/10.1038/mt.2009.232>
 688. Bolyard C, Meisen WH, Banasavadi-Siddegowda Y, et al. BAI1 orchestrates macrophage inflammatory response to HSV infection—implications for oncolytic viral therapy. *Clin Cancer Res*. 2016;23(7):1809–1819. <https://doi.org/10.1158/1078-0432.ccr-16-1818>
 689. Zhang H, Zhu D, Zhang Z, et al. EZH2 targeting reduces medulloblastoma growth through epigenetic reactivation of the BAI1/p53 tumor suppressor pathway. *Oncogene*. 2020;39(5):1041–1048. <https://doi.org/10.1038/s41388-019-1036-7>
 690. de Groot DM de, Vogel G, Dulos J, et al. Therapeutic antibody targeting of CD97 in experimental arthritis: the role of antigen expression, shedding, and internalization on the pharmacokinetics of anti-CD97 monoclonal antibody 1B2. *J Immunol*. 2009;183(6):4127–4134. <https://doi.org/10.4049/jimmunol.0901253>
 691. Veninga H, de Groot DM de, McCloskey N, et al. CD97 antibody depletes granulocytes in mice under conditions of acute inflammation via a Fc receptor-dependent mechanism. *J Leukoc Biol*. 2011;89(3):413–421. <https://doi.org/10.1189/jlb.0510280>
 692. Shang K, Huang D, Liu J, et al. CD97-directed CAR-T cells with enhanced persistence eradicate acute myeloid leukemia in diverse xenograft models. *Cell Rep Med*. 2025;6(6):102148. <https://doi.org/10.1016/j.xcrm.2025.102148>
 693. Park T, Chen H, Kim HY. GPR110 (ADGRF1) mediates anti-inflammatory effects of N-docosahexaenoylethanolamine. *J Neuroinflamm*. 2019;16(1):225. <https://doi.org/10.1186/s12974-019-1621-2>
 694. Ohta S, Sakaguchi S, Kobayashi Y, Mizuno N, Tago K, Itoh H. Agonistic antibodies reveal the function of GPR56 in human glioma U87-MG cells. *Biol Pharm Bull*. 2015;38(4):594–600. <https://doi.org/10.1248/jbpb.b14-00752>
 695. Jallouli R, Moreno-Salinas AL, Laniel A, et al. G protein selectivity profile of GPR56/ADGRG1 and its effect on downstream effectors. *Cell Mol Life Sci*. 2024;81(1):383. <https://doi.org/10.1007/s00018-024-05416-8>
 696. Jacob J, Francisco LE, Chatterjee T, et al. An antibody–drug conjugate targeting GPR56 demonstrates efficacy in preclinical models of colorectal cancer. *Br J Cancer*. 2023;128(8):1592–1602. <https://doi.org/10.1038/s41416-023-02192-3>
 697. Erwin DH. Early metazoan life: divergence, environment and ecology. *Philos Trans R Soc B Biol Sci*. 2015;370(1684):20150036. <https://doi.org/10.1098/rstb.2015.0036>
 698. Schöneberg T. Modulating vertebrate physiology by genomic fine-tuning of GPCR functions. *Physiol Rev*. 2025;105(1):383–439. <https://doi.org/10.1152/physrev.00017.2024>
 699. Langenhan T, Barr MM, Bruchas MR, et al. Model organisms in G protein–coupled receptor research. *Mol Pharmacol*. 2015;88(3):596–603. <https://doi.org/10.1124/mol.115.098764>
 700. Monk KR, Hamann J, Langenhan T, Nijmeijer S, Schöneberg T, Liebscher I. Adhesion G protein–coupled receptors: from in vitro pharmacology to in vivo mechanisms. *Mol Pharmacol*. 2015;88(3):617–623. <https://doi.org/10.1124/mol.115.098749>
 701. Liebscher I, Cevheroglu O, Hsiao CC, et al. A guide to adhesion GPCR research. *FEBS J*. 2022;289(24):7610–7630. <https://doi.org/10.1111/febs.16258>
 702. Richter DJ, Fozouni P, Eisen MB, King N. Gene family innovation, conservation and loss on the animal stem lineage. *eLife*. 2018;7:e34226. <https://doi.org/10.7554/elife.34226>
 703. King N, Westbrook MJ, Young SL, et al. The genome of the choanoflagellate *Monosiga brevicollis* and the origin of metazoans. *Nature*. 2008;451(7180):783–788. <https://doi.org/10.1038/nature06617>
 704. Krishnan A, Almén MS, Fredriksson R, Schiöth HB. The origin of GPCRs: identification of mammalian like Rhodopsin, Adhesion, Glutamate and Frizzled GPCRs in fungi. *PLoS One*. 2012;7(1):e29817. <https://doi.org/10.1371/journal.pone.0029817>
 705. de Mendoza A de, Sebé-Pedrós A, Ruiz-Trillo I. The evolution of the GPCR signaling system in eukaryotes: modularity, conservation, and the transition to metazoan multicellularity. *Genome Biol Evol*. 2014;6(3):606–619. <https://doi.org/10.1093/gbe/evu038>
 706. Garcia De Las Bayonas A, King N. G protein–coupled receptor diversity and evolution in the closest living relatives of Metazoa. *eLife*. 2025;14:RP107467. <https://doi.org/10.7554/elife.107467.2>
 707. Yang X, Pan C, Ye M, et al. *Drosophila* adhesion GPCR Remoulade regulates axon growth, branching, and guidance by modulating Rac1 GTPase. *J Genet Genomics*. 2024;51(4):458–461. <https://doi.org/10.1016/j.jgg.2023.11.006>
 708. Chae J, Kim MJ, Goo JH, et al. The *Drosophila* tissue polarity gene starry night encodes a member of the protocadherin family. *Development*. 1999;126(23):5421–5429. <https://doi.org/10.1242/dev.126.23.5421>
 709. Lu B, Usui T, Uemura T, Jan L, Jan YN. Flamingo controls the planar polarity of sensory bristles and asymmetric division of sensory organ precursors in *Drosophila*. *Curr Biol*. 1999;9(21):1247–1250. [https://doi.org/10.1016/s0960-9822\(99\)80505-3](https://doi.org/10.1016/s0960-9822(99)80505-3)
 710. Strutt H, Warrington S, Madathil ACK, Langenhan T, Strutt D. Molecular symmetry breaking in the Frizzled-dependent planar polarity pathway. *Curr Biol*. 2023;33(24):5340–5354.e6. <https://doi.org/10.1016/j.cub.2023.10.071>
 711. Strutt H, Strutt D. Differential stability of flamingo protein complexes underlies the establishment of planar polarity. *Curr Biol*. 2008;18(20):1555–1564. <https://doi.org/10.1016/j.cub.2008.08.063>
 712. Lawrence PA, Casal J, Struhl G. Cell interactions and planar polarity in the abdominal epidermis of *Drosophila*. *Development*. 2004;131(19):4651–4664. <https://doi.org/10.1242/dev.01351>
 713. Strutt D, Strutt H. Differential activities of the core planar polarity proteins during *Drosophila* wing patterning. *Dev Biol*. 2007;302(1):181–194. <https://doi.org/10.1016/j.ydbio.2006.09.026>
 714. Gao FB, Brenman JE, Jan LY, Jan YN. Genes regulating dendritic outgrowth, branching, and routing in *Drosophila*. *Genes Dev*. 1999;13(19):2549–2561. <https://doi.org/10.1101/gad.13.19.2549>
 715. Gao FB, Kohwi M, Brenman JE, Jan LY, Jan YN. Control of dendritic field formation in *Drosophila*: the roles of flamingo and competition between homologous neurons. *Neuron*. 2000;28(1):91–101. [https://doi.org/10.1016/s0896-6273\(00\)00088-x](https://doi.org/10.1016/s0896-6273(00)00088-x)
 716. Senti KA, Usui T, Boucke K, Greber U, Uemura T, Dickson BJ. Flamingo regulates R8 axon-axon and axon-target interactions in the *Drosophila* visual system. *Curr Biol*. 2003;13(10):828–832. [https://doi.org/10.1016/s0960-9822\(03\)00291-4](https://doi.org/10.1016/s0960-9822(03)00291-4)
 717. Reuter JE, Nardine TM, Penton A, et al. A mosaic genetic screen for genes necessary for *Drosophila* mushroom body neuronal morphogenesis. *Development*. 2003;130(6):1203–1213. <https://doi.org/10.1242/dev.00319>
 718. Shimizu K, Sato M, Tabata T. The Wnt5/planar cell polarity pathway regulates axonal development of the *Drosophila* mushroom body neuron. *J Neurosci*. 2011;31(13):4944–4954. <https://doi.org/10.1523/jneurosci.0154-11.2011>
 719. Ng J. Wnt/PCP proteins regulate stereotyped axon branch extension in *Drosophila*. *Development*. 2012;139(1):165–177. <https://doi.org/10.1242/dev.068668>
 720. Kimura H, Usui T, Tsubouchi A, Uemura T. Potential dual molecular interaction of the *Drosophila* 7-pass transmembrane cadherin Flamingo in dendritic morphogenesis. *J Cell Sci*. 2006;119(6):1118–1129. <https://doi.org/10.1242/jcs.02832>
 721. Li X, Wang Y, Wang H, et al. Epithelia-derived wingless regulates dendrite directional growth of drosophila ddaE neuron through the Fz-Fmi-Dsh-Rac1 pathway. *Mol Brain*. 2016;9(1):46. <https://doi.org/10.1186/s13041-016-0228-0>
 722. Matsubara D, Horiuchi SY, Shimono K, Usui T, Uemura T. The seven-pass transmembrane cadherin Flamingo controls dendritic self-avoidance via its binding to a LIM domain protein, Espinas, in *Drosophila* sensory neurons. *Genes Dev*. 2011;25(18):1982–1996. <https://doi.org/10.1101/gad.16531611>
 723. Buhlan M, Ljaschenko D, Scholz N, Langenhan T. Experimental modulation of physiological force application on leg joint neurons in intact *Drosophila melanogaster*. *Nat Protoc*. 2024;19(1):113–126. <https://doi.org/10.1038/s41596-023-00907-7>
 724. Blanco-Redondo B, Langenhan T. Parallel genomic engineering of two *Drosophila* genes using orthogonal attB/attP sites. *G3*. 2018;8(9):3109–3118. <https://doi.org/10.1534/g3.118.200565>
 725. Najarro EH, Wong L, Zhen M, et al. *Caenorhabditis elegans* Flamingo cadherin fmi-1 regulates GABAergic neuronal development. *J Neurosci*. 2012;32(12):4196–4211. <https://doi.org/10.1523/jneurosci.3094-11.2012>
 726. Steimel A, Wong L, Najarro EH, Ackley BD, Garriga G, Hutter H. The Flamingo ortholog FMI-1 controls pioneer-dependent navigation of follower axons in *C. elegans*. *Development*. 2010;137(21):3663–3673. <https://doi.org/10.1242/dev.054320>
 727. Hsu HW, Liao CP, Chiang YC, Syu RT, Pan CL. *Caenorhabditis elegans* Flamingo FMI-1 controls dendrite self-avoidance through F-actin assembly. *Development*. 2020;147(14):dev179168. <https://doi.org/10.1242/dev.179168>
 728. Schön JL, Groß VE, Post WB, et al. The adhesion GPCR and PCP component flamingo (FMI-1) alters body size and regulates the composition of the extracellular matrix. *Matrix Biol*. 2024;128:1–10. <https://doi.org/10.1016/j.matbio.2024.02.005>
 729. Lange M, Norton W, Coolen M, et al. The ADHD-susceptibility gene lphn3.1 modulates dopaminergic neuron formation and locomotor activity during zebrafish development. *Mol Psychiatry*. 2012;17(9):946–954. <https://doi.org/10.1038/mp.2012.29>
 730. Lange M, Froc C, Grunwald H, Norton WHJ, Bally-Cuif L. Pharmacological analysis of zebrafish lphn3.1 morphant larvae suggests that saturated dopaminergic signaling could underlie the ADHD-like locomotor hyperactivity. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;84(A):181–189. <https://doi.org/10.1016/j.pnpbp.2018.02.010>
 731. Reuter I, Knaup S, Romanos M, Lesch KP, Drepper C, Lillesaar C. Developmental exposure to acetaminophen does not induce hyperactivity in zebrafish larvae. *J Neural Transm*. 2016;123(8):841–848. <https://doi.org/10.1007/s00702-016-1556-z>
 732. Fontana BD, Reichmann F, Tilley CA, et al. adgrl3.1-deficient zebrafish show noradrenaline-mediated externalizing behaviors, and altered expression of externalizing disorder-candidate genes, suggesting functional targets for treatment. *Transl Psychiatry*. 2023;13(1):304. <https://doi.org/10.1038/s41398-023-02601-4>

733. Þorsteinsson H, Baukman HA, Sveinsdóttir HS, et al. Validation of L-type calcium channel blocker amlodipine as a novel ADHD treatment through cross-species analysis, drug-target Mendelian randomization, and clinical evidence from medical records. *Neuropsychopharmacology*. 2025;50(7):1145–1155. <https://doi.org/10.1038/s41386-025-02062-x>
734. Grzymala B, Þorsteinsson H, Halldórsdóttir Dp, et al. Metabolomic and lipidomic profiling reveals convergent pathways in attention deficit hyperactivity disorder therapeutics: insights from established and emerging treatments. *J Pharmacol Exp Ther*. 2025;392(4):103403. <https://doi.org/10.1016/j.jpet.2025.103403>
735. Fontana BD, Alnassar N, Norton WHJ, Parker MO. Social isolation intensifies adgrl3.1-related externalizing and internalizing behaviors in zebrafish. *Prog Neuropsychopharmacol Biol Psychiatry*. 2025;136:111193. <https://doi.org/10.1016/j.pnpbp.2024.111193>
736. Sveinsdóttir HS, Christensen C, Þorsteinsson H, et al. Novel non-stimulants rescue hyperactive phenotype in an adgrl3.1 mutant zebrafish model of ADHD. *Neuropsychopharmacology*. 2023;48(8):1155–1163. <https://doi.org/10.1038/s41386-022-01505-z>
737. Martínez AF, Abe Y, Hong S, et al. An ultraconserved brain-specific enhancer within ADGRL3 (LPHN3) underpins attention-deficit/hyperactivity disorder susceptibility. *Biol Psychiatry*. 2016;80(12):943–954. <https://doi.org/10.1016/j.biopsych.2016.06.026>
738. Formstone CJ, Mason I. Combinatorial activity of Flamingo proteins directs convergence and extension within the early zebrafish embryo via the planar cell polarity pathway. *Dev Biol*. 2005;282(2):320–335. <https://doi.org/10.1016/j.ydbio.2005.03.026>
739. Carreira-Barbosa F, Kajita M, Morel V, et al. Flamingo regulates epiboly and convergence/extension movements through cell cohesive and signalling functions during zebrafish gastrulation. *Development*. 2009;136(3):383–392. <https://doi.org/10.1242/dev.026542>
740. Wada H, Tanaka H, Nakayama S, Iwasaki M, Okamoto H. Frizzled3a and Celsr2 function in the neuroepithelium to regulate migration of facial motor neurons in the developing zebrafish hindbrain. *Development*. 2006;133(23):4749–4759. <https://doi.org/10.1242/dev.02665>
741. Lewis A, Wilson N, Stearns G, Johnson N, Nelson R, Brockerhoff SE. Celsr3 is required for normal development of GABA circuits in the inner retina. *PLoS Genet*. 2011;7(8):e1002239. <https://doi.org/10.1371/journal.pgen.1002239>
742. Meserve JH, Navarro MF, Ortiz EA, Granato M. Celsr3 drives development and connectivity of the acoustic startle hindbrain circuit. *PLoS Genet*. 2024;20(10):e1011415. <https://doi.org/10.1371/journal.pgen.1011415>
743. Solaimani Kartalaei PS, Yamada-Inagawa T, Vink CS, et al. Whole-transcriptome analysis of endothelial to hematopoietic stem cell transition reveals a requirement for Gpr56 in HSC generation. *J Exp Med*. 2015;212(1):93–106. <https://doi.org/10.1084/jem.20140767>
744. Geng FS, Abbas L, Baxendale S, et al. Semicircular canal morphogenesis in the zebrafish inner ear requires the function of gpr126 (lauscher), an adhesion class G protein-coupled receptor gene. *Development*. 2013;140(21):4362–4374. <https://doi.org/10.1242/dev.098061>
745. Musa G, Srivastava S, Petzold J, Cazorla-Vázquez S, Engel FB. miR-27a/b is a posttranscriptional regulator of Gpr126 (Adgrg6). *Ann N Y Acad Sci*. 2019;1456(1):109–121. <https://doi.org/10.1111/nyas.14245>
746. Ebermann I, Phillips JB, Liebau MC, et al. PDZD7 is a modifier of retinal disease and a contributor to digenic Usher syndrome. *J Clin Invest*. 2010;120(6):1812–1823. <https://doi.org/10.1172/jci39715>
747. Stermerink M, Broekman S, Peters T, Kremer H, de Vrieze E de, van Wijk E van. Generation and characterization of a zebrafish model for ADGRV1-associated retinal dysfunction using CRISPR/Cas9 genome editing technology. *Cells*. 2023;12(12):1598. <https://doi.org/10.3390/cells12121598>
748. Xiao X, Zheng H, Xiong M, Chen X, Jiang L, Hu Y. Genotypic and phenotypic characteristics of ADGRV1 mutations in four children and functional validation in a zebrafish model. *Gene*. 2025;942:149246. <https://doi.org/10.1016/j.gene.2025.149246>
749. Rashidi H, Sottile V. The chick embryo: hatching a model for contemporary biomedical research. *BioEssays*. 2009;31(4):459–465. <https://doi.org/10.1002/bies.200800168>
750. Itasaki N, Bel-Vialar S, Krumlauf R. 'Shocking' developments in chick embryology: electroporation and in ovo gene expression. *Nat Cell Biol*. 1999;1(8):E203–E207. <https://doi.org/10.1038/70231>
751. Poopalasundaram S, Richardson J, Graham A. Key separable events in the remodelling of the pharyngeal arches. *J Anat*. 2023;243(1):100–109. <https://doi.org/10.1111/joa.13850>
752. Voiculescu O, Bertocchini F, Wolpert L, Keller RE, Stern CD. The amniote primitive streak is defined by epithelial cell intercalation before gastrulation. *Nature*. 2007;449(7165):1049–1052. <https://doi.org/10.1038/nature06211>
753. Ribatti D. The chick embryo chorioallantoic membrane (CAM). A multifaceted experimental model. *Mech Dev*. 2016;141:70–77. <https://doi.org/10.1016/j.mod.2016.05.003>
754. As MN, Deshpande R, Kale VP, Bhone RR, Datar SP. Establishment of an in ovo chick embryo yolk sac membrane (YSM) assay for pilot screening of potential angiogenic and anti-angiogenic agents. *Cell Biol Int*. 2018;42(11):1474–1483. <https://doi.org/10.1002/cbin.11051>
755. Öztürk AA, Kıyan HT. Treatment of oxidative stress-induced pain and inflammation with dexketoprofen trometamol loaded different molecular weight chitosan nanoparticles: formulation, characterization and anti-inflammatory activity by using in vivo HET-CAM assay. *Microvasc Res*. 2020;128:103961. <https://doi.org/10.1016/j.mvr.2019.103961>
756. Patiño-Morales CC, Jaime-Cruz R, Ramírez-Fuentes TC, Villavicencio-Guzmán L, Salazar-García M. Technical implications of the chicken embryo chorioallantoic membrane assay to elucidate neuroblastoma biology. *Int J Mol Sci*. 2023;24(19):14744. <https://doi.org/10.3390/ijms241914744>
757. Murphy JB, Rous P. The behavior of chicken sarcoma implanted in the developing embryo. *J Exp Med*. 1912;15(2):119–132. <https://doi.org/10.1084/jem.15.2.119>
758. Cao J, Liu X, Yang Y, et al. Decylubiquinone suppresses breast cancer growth and metastasis by inhibiting angiogenesis via the ROS/p53/BAI1 signaling pathway. *Angiogenesis*. 2020;23(3):325–338. <https://doi.org/10.1007/s10456-020-09707-z>
759. Regan SL, Hufgard JR, Pitzer EM, et al. Knockout of latrophilin-3 in Sprague-Dawley rats causes hyperactivity, hyper-reactivity, under-response to amphetamine, and disrupted dopamine markers. *Neurobiol Dis*. 2019;130:104494. <https://doi.org/10.1016/j.nbd.2019.104494>
760. Regan SL, Pitzer EM, Hufgard JR, Sugimoto C, Williams MT, Vorhees CV. A novel role for the ADHD risk gene latrophilin-3 in learning and memory in Lphn3 knockout rats. *Neurobiol Dis*. 2021;158:105456. <https://doi.org/10.1016/j.nbd.2021.105456>
761. Adams DJ, Barlas B, McIntyre RE, et al. Genetic determinants of micronucleus formation in vivo. *Nature*. 2024;627(8002):130–136. <https://doi.org/10.1038/s41586-023-07009-0>
762. Tang T, Li L, Tang J, et al. A mouse knockout library for secreted and transmembrane proteins. *Nat Biotechnol*. 2010;28(7):749–755. <https://doi.org/10.1038/nbt.1644>
763. Skarnes WC, Rosen B, West AP, et al. A conditional knockout resource for the genome-wide study of mouse gene function. *Nature*. 2011;474(7351):337–342. <https://doi.org/10.1038/nature10163>
764. Specia DJ, Trimmer JS, Peterson AS, Díaz E. Whole exome sequencing reveals a functional mutation in the GAIN domain of the Bai2 receptor underlying a forward mutagenesis hyperactivity QTL. *Mamm Genome*. 2017;28(11–12):465–475. <https://doi.org/10.1007/s00335-017-9716-5>
765. Horie K, Yusa K, Yae K, et al. Characterization of sleeping beauty transposition and its application to genetic screening in mice. *Mol Cell Biol*. 2003;23(24):9189–9207. <https://doi.org/10.1128/mcb.23.24.9189-9207.2003>
766. Fairfield H, Srivastava A, Ananda G, et al. Exome sequencing reveals pathogenic mutations in 91 strains of mice with Mendelian disorders. *Genome Res*. 2015;25(7):948–957. <https://doi.org/10.1101/gr.186882.114>
767. Nolan PM, Peters J, Strivens M, et al. A systematic, genome-wide, phenotype-driven mutagenesis programme for gene function studies in the mouse. *Nat Genet*. 2000;25(4):440–443. <https://doi.org/10.1038/78140>
768. Ravi A, Qu Y, Goffinet AM, Tissir F. Planar cell polarity adherin Celsr1 regulates skin hair patterning in the mouse. *J Invest Dermatol*. 2009;129(10):2507–2509. <https://doi.org/10.1038/jid.2009.84>
769. Qu Y, Glasco DM, Zhou L, et al. Atypical cadherins Celsr1-3 differentially regulate migration of facial branchiomotor neurons in mice. *J Neurosci Atyp*. 2010;30(28):9392–9401. <https://doi.org/10.1523/jneurosci.0124-10.2010>
770. Boutin C, Labedan P, Dimidschstein J, et al. A dual role for planar cell polarity genes in ciliated cells. *Proc Natl Acad Sci U S A*. 2014;111(30):E3129–E3138. <https://doi.org/10.1073/pnas.1404988111>
771. Tissir F, Bar I, Jossin Y, De Backer O, Goffinet AM. Protocadherin Celsr3 is crucial in axonal tract development. *Nat Neurosci*. 2005;8(4):451–457. <https://doi.org/10.1038/nn1428>
772. Dickinson ME, Flenniken AM, Ji X, et al. High-throughput discovery of novel developmental phenotypes. *Nature*. 2016;537(7621):508–514. <https://doi.org/10.1038/nature19356>
773. Schaller E, Macfarlane AJ, Rupec RA, Gordon S, McKnight AJ, Pfeffer K. Inactivation of the F4/80 glycoprotein in the mouse germ line. *Mol Cell Biol*. 2002;22(22):8035–8043. <https://doi.org/10.1128/mcb.22.22.8035-8043.2002>
774. Veninga H, Becker S, Hoek RM, et al. Analysis of CD97 expression and manipulation: antibody treatment but not gene targeting curtails granulocyte migration. *J Immunol*. 2008;181(9):6574–6583. <https://doi.org/10.4049/jimmunol.181.9.6574>
775. Chiba Y, Yoshizaki K, Sato H, et al. Deficiency of G protein-coupled receptor Gpr111/Adgrf2 causes enamel hypomineralization in mice by alteration of the expression of kallikrein-related peptidase 4 (Klk4) during pH cycling process. *FASEB J*. 2023;37(4):e22861. <https://doi.org/10.1096/fj.202202053r>
776. Suzuki A, Yabuta N, Shimada K, et al. Individual disruption of 12 testis-enriched genes via the CRISPR/Cas9 system does not affect the fertility of male mice. *J Reprod Immunol*. 2024;163:104252. <https://doi.org/10.1016/j.jri.2024.104252>
777. Sleckman BP, Khan WN, Xu W, et al. Cloning and functional characterization of the early-lymphocyte-specific Pb99 gene. *Mol Cell Biol*. 2000;20(12):4405–4410. <https://doi.org/10.1128/mcb.20.12.4405-4410.2000>
778. Sun P, He L, Jia K, et al. Regulation of body length and bone mass by Gpr126/Adgrg6. *Sci Adv*. 2020;6(12):eaaz0368. <https://doi.org/10.1126/sciadv.aaz0368>
779. Tobaben S, Südhof TC, Stahl B. Genetic analysis of α -latrotoxin receptors reveals functional interdependence of CIRL/latrophilin 1 and neuroligin 1a. *J Biol Chem*. 2002;277(8):6359–6365. <https://doi.org/10.1074/jbc.M111231200>

780. Wallis D, Hill DS, Mendez IA, et al. Initial characterization of mice null for *Lphn3*, a gene implicated in ADHD and addiction. *Brain Res.* 2012;1463: 85–92. <https://doi.org/10.1016/j.brainres.2012.04.053>
781. Yagi H, Takamura Y, Yoneda T, et al. *Vlgr1* knockout mice show audiogenic seizure susceptibility. *J Neurochem.* 2005;92(1):191–202. <https://doi.org/10.1111/j.1471-4159.2004.02875.x>
782. Yagi H, Tokano H, Maeda M, et al. *Vlgr1* is required for proper stereocilia maturation of cochlear hair cells. *Genes Cells.* 2007;12(2):235–250. <https://doi.org/10.1111/j.1365-2443.2007.01046.x>
783. Yao L, Zhang L, Qi LS, et al. The time course of deafness and retinal degeneration in a Kunming Mouse model for Usher syndrome. *PLoS One.* 2016;11(5):e0155619. <https://doi.org/10.1371/journal.pone.0155619>
784. Klein BD, Fu YH, Ptacek LJ, White HS. Auditory deficits associated with the *Frings Mgr1* (*Mass1*) mutation in mice. *Dev Neurosci.* 2005;27(5):321–332. <https://doi.org/10.1159/000086712>
785. Johnson KR, Zheng QY, Weston MD, Ptacek LJ, Noben-Trauth K. The *Mass1* mutation underlies early onset hearing impairment in *BUB/BnJ* mice, a model for the auditory pathology of Usher syndrome IIC. *Genomics.* 2005;85(5):582–590. <https://doi.org/10.1016/j.ygeno.2005.02.006>
786. Dumas L, Marfoglia M, Yang B, et al. Uncovering and engineering the mechanical properties of the adhesion GPCR ADGRG1 GAIN domain. *Preprint.* Posted online April 6, 2023. bioRxiv 535724. <https://doi.org/10.1101/2023.04.05.535724>
787. Marfoglia M, Guirardel L, AlloPool BP. An adaptive graph neural network for dynamic allosteric network prediction in protein systems. *Preprint.* Posted online November 3, 2024. bioRxiv 621466. <https://doi.org/10.1101/2024.11.01.621466>
788. Zhang Y, DeVries ME, Skolnick J. Structure modeling of all identified G protein-coupled receptors in the human genome. *PLoS Comput Biol.* 2006;2(2):e13. <https://doi.org/10.1371/journal.pcbi.0020013>
789. Lebon G, Warne T, Edwards PC, et al. Agonist-bound adenosine A2a receptor structures reveal common features of GPCR activation. *Nature.* 2011;474(7352):521–525. <https://doi.org/10.1038/nature10136>
790. Brunskole I, Strasser A, Seifert R, Buschauer A. Role of the second and third extracellular loops of the histamine H4 receptor in receptor activation. *Naunyn-Schmiedeberg's Arch Pharmacol.* 2011;384(3):301–317. <https://doi.org/10.1007/s00210-011-0673-3>
791. Abramson J, Adler J, Dunger J, et al. Accurate structure prediction of biomolecular interactions with AlphaFold 3. *Nature.* 2024;630(8016):493–500. <https://doi.org/10.1038/s41586-024-07487-w>
792. Krishna R, Wang J, Ahern W, et al. Generalized biomolecular modeling and design with RoseTTAFold All-Atom. *Science.* 2024;384(6693):eadl2528. <https://doi.org/10.1126/science.adl2528>
793. He XH, Li JR, Shen SY, Xu HE. AlphaFold3 versus experimental structures: assessment of the accuracy in ligand-bound G protein-coupled receptors. *Acta Pharmacol Sin.* 2025;46(4):1111–1122. <https://doi.org/10.1038/s41401-024-01429-y>
794. Mitgau J, Franke J, Schinner C, et al. The N terminus of adhesion G protein-coupled receptor GPR126/ADGRG6 as allosteric force integrator. *Front Cell Dev Biol.* 2022;10:873278. <https://doi.org/10.3389/fcell.2022.873278>
795. Streit M, Hemberger M, Häfner S, Knote F, Langenhan T, Beliu G. Optimized genetic code expansion technology for time-dependent induction of adhesion GPCR-ligand engagement. *Protein Sci.* 2023;32(4):e4614. <https://doi.org/10.1002/pro.4614>
796. Lizano E, Hayes JL, Willard FS. A synthetic method to assay adhesion-family G-protein coupled receptors. Determination of the G-protein coupling profile of ADGRG6(GPR126). *Biochem Biophys Res Commun.* 2020;534:317–322. <https://doi.org/10.1016/j.bbrc.2020.11.086>
797. Perry-Hauser NA, VanDyck MW, Lee KH, Shi L, Javitch JA. Disentangling autoproteolytic cleavage from tethered agonist-dependent activation of the adhesion receptor ADGRL3. *J Biol Chem.* 2022;298(12):102594. <https://doi.org/10.1016/j.jbc.2022.102594>
798. Garbett K, Tosun B, Lopez JM, Smith CM, Honkanen K, Sando RC. Synaptic Gα12/13 signaling establishes hippocampal PV inhibitory circuits. *Proc Natl Acad Sci U S A.* 2024;121(52):e2407828121. <https://doi.org/10.1073/pnas.2407828121>
799. Wilde C, Mitgau J, Suchý T, Schöneberg T, Liebscher I. Translating the force—mechano-sensing GPCRs. *Am J Physiol, Cell Physiol.* 2022;322(6): C1047–C1060. <https://doi.org/10.1152/ajpcell.00465.2021>
800. Sun S, Wang W. Mechanosensitive adhesion G protein-coupled receptors: insights from health and disease. *Genes Dis.* 2025;12(3):101267. <https://doi.org/10.1016/j.gendis.2024.101267>
801. Hoffman BD, Grashoff C, Schwartz MA. Dynamic molecular processes mediate cellular mechanotransduction. *Nature.* 2011;475(7356):316–323. <https://doi.org/10.1038/nature10316>
802. Arbore C, Perego L, Sergides M, Capitanio M. Probing force in living cells with optical tweezers: from single-molecule mechanics to cell mechanotransduction. *Biophys Rev.* 2019;11(5):765–782. <https://doi.org/10.1007/s12551-019-00599-y>
803. Català-Castro F, Schäffer E, Krieg M. Exploring cell and tissue mechanics with optical tweezers. *J Cell Sci.* 2022;135(15):jcs259355. <https://doi.org/10.1242/jcs.259355>
804. Klarenbeek J, Goedhart J, van Batenburg A van, Groenewald D, Jalink K. Fourth-generation Epac-based FRET sensors for cAMP feature exceptional brightness, photostability and dynamic range: characterization of dedicated sensors for FLIM, for ratiometry and with high affinity. *PLoS One.* 2015;10(4): e0122513. <https://doi.org/10.1371/journal.pone.0122513>
805. Feng Y, Brazil KN, Kobayashi E, Mallis RJ, Reinherz EL, Lang MJ. Mechano-sensing drives acuity of αβ T-cell recognition. *Proc Natl Acad Sci U S A.* 2017;114(39):E8204–E8213. <https://doi.org/10.1073/pnas.1703559114>
806. Fritz RD, Letzelter M, Reimann A, et al. A versatile toolkit to produce sensitive FRET biosensors to visualize signaling in time and space. *Sci Signal.* 2013;6(285):rs12. <https://doi.org/10.1126/scisignal.2004135>
807. Fu C, Huang W, Tang Q, et al. Unveiling mechanical activation: GAIN domain unfolding and dissociation in adhesion GPCRs. *Nano Lett.* 2023;23(20): 9179–9186. <https://doi.org/10.1021/acs.nanolett.3c01163>
808. Zhong BL, Lee CE, Vachharajani VT, Bauer MS, Südhof TC, Dunn AR. Piconewton forces mediate GAIN domain dissociation of the latrophilin-3 adhesion GPCR. *Nano Lett.* 2023;23(20):9187–9194. <https://doi.org/10.1021/acs.nanolett.3c03171>
809. Yang B, Liu Z, Liu H, Nash MA. Next generation methods for single-molecule force spectroscopy on polyproteins and receptor-ligand complexes. *Front Mol Biosci.* 2020;7:85. <https://doi.org/10.3389/fmolb.2020.00085>
810. Zocher M, Bippes CA, Zhang C, Müller DJ. Single-molecule force spectroscopy of G-protein-coupled receptors. *Chem Soc Rev.* 2013;42(19):7801–7815. <https://doi.org/10.1039/c3cs60085h>
811. Nikolaev VO, Bünnemann M, Hein L, Hannawacker A, Lohse MJ. Novel single chain cAMP sensors for receptor-induced signal propagation. *J Biol Chem.* 2004;279(36):37215–37218. <https://doi.org/10.1074/jbc.c400302200>
812. Caprara GA, Peng AW. Mechanotransduction in mammalian sensory hair cells. *Mol Cell Neurosci.* 2022;120:103706. <https://doi.org/10.1016/j.mcn.2022.103706>
813. Yang LY, Liu XF, Yang Y, et al. Biochemical features of the adhesion G protein-coupled receptor CD97 related to its auto-proteolysis and HeLa cell attachment activities. *Acta Pharmacol Sin.* 2017;38(1):56–68. <https://doi.org/10.1038/aps.2016.89>