Angiotensin Converting Enzyme 2 May Mediate Disease Severity In COVID-19

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Abstract:

Identification of vulnerability to *severe* coronavirus disease 2019 (COVID-19) is extremely important and might allow optimised shielding and easing of lockdown. The disease is attributed to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which enters host cells through binding to angiotensin converting enzyme 2 (ACE2) on the cell surface. Clinical syndromes such as hypertension that display reduced ACE2 expression tend to correlate with a more severe disease course, whereas treatments which upregulate ACE2 such as the use of angiotensin converting enzyme inhibitors (ACE-i) appear to have a protective effect against COVID-19. Pre-clinical studies have shown that plasma soluble ACE2 could render SARS-CoV-2 inactive in a dose-dependent manner. The association of clinical syndromes or treatments that impact ACE2 expression and clinical severity of COVID-19 infection combined with the reduction in viral load with human recombinant serum ACE2 shown in pre-clinical studies indicate a key role for ACE2 in determining COVID-19 severity. In conclusion, we propose that measurement of ACE2 level may help identify individuals at risk of severe infection where targeted shielding can be used and could provide a novel therapeutic target.

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Identification of vulnerability to *severe* COVID-19 is extremely important, and might allow optimised shielding and easing of lockdown. We propose a pathological role for soluble angiotensin converting enzyme (sACE2) modulating COVID-19 disease severity, which could be used in screening and treatment.

Hypertension, diabetes and obesity are risk factors for severe disease.[1] SARS-CoV-2 enters the host cell through the spike (S) protein binding to ACE2,[2] and since ACE-inhibitors (ACE-i) and angiotensin-II receptor blockers (ARB) upregulate cellular ACE2 expression, this could theoretically facilitate SARS-CoV-2 binding and severe disease manifestation, while renin-angiotensin-aldosterone inhibition appears protective.[3]

After SARS-CoV-2 binds to host cells, ACE2 expression and enzymatic activity are significantly reduced through enhanced shedding, with the extracellular component of ACE2 cleaved and resultant soluble protein released. The resultant increased sACE2 may act as a 'dummy' receptor, binding the S protein on circulating virus. Thus, higher numbers of ACE2 receptors expressed prior to first binding event may lead to higher sACE2 level and reduced circulating SARS-CoV-2 with 'active' S protein sites, reduced numbers of affected host cells, and less systemic impact. Therefore, conditions that upregulate ACE2 may confer protection, whereas reduced ACE2 expression may result in more severe disease.

Clinical findings support such pathological role for reduced ACE2 levels in mediating disease severity. Patients with hypertension, exhibiting marked ACE up-regulation and ACE2 downregulation, are at higher risk of severe disease, whereas those taking ACE-i/ARB exhibit less disease severity and lower mortality.[3] The ACE2 gene is linked to metabolic syndrome and obesity.[4] ACE2 gene knockout leads to metabolic syndrome in mice. In patients with diabetic renal disease, ACE2 expression is reduced compared to patients with non-diabetic renal disease or controls. Lower ACE2 expression in obese patients and metabolic syndrome may explain worse outcomes with COVID-19.[1]

The ACE2 gene is located on the X-chromosome, and ACE2 activity and expression in rats was decreased by oophorectomy and restored by oestrogen. Thus, women would be expected to have higher ACE2 activity, which might explain better outcomes. Recent studies show that human recombinant sACE2 (hrsACE2) can bind and neutralise SARS-CoV-2 S protein,[5] reducing SARS-CoV-2 entry into cells in a dose-dependent manner.[2]

The association of clinical syndromes and treatments that impact ACE2 expression and the reduction in viral load with hrsACE2, indicate a key role for ACE2 in COVID-19 severity. We propose that measurement of ACE2 level may help identify individuals at risk of severe infection and provide a novel therapeutic target.

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