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Letter: ACE2, IBD and COVID-19—why IBD patients may be at reduced risk of COVID-19

We read with interest the excellent single-centre observational case series by Taxonera et al,[1] evaluating the clinical characteristics and incidence rates of COVID-19 in IBD patients. Although limited by a small sample size, they demonstrated that IBD patients were less likely to acquire COVID-19 than the general population, with an odds ratio of 0.74 (95% CI 0.70-0.77; $P < 0.001$),[1] with no significant observed difference in standardised mortality risk or case mortality rate.[1] They questaioned whether this lower infection rate may be a consequence of improved adherence with shielding recommendations.[1] We speculate that differential serum angiotensin-converting enzyme-2 (ACE2) levels observed in patients with IBD may contribute.

Large datasets support the findings of Taxonera's study of comparatively low rates of COVID-19 in patients with IBD.[1,2] Experience from Wuhan reported no cases among 318 IBD patients.[3] Additionally, despite over 18 million COVID-19 cases worldwide, as of 5 August 2020, an international IBD COVID-19 registry reported only 1,925 cases in IBD patients.[4]

Although undoubtedly multifactorial, there is biological plausibility to this finding. ACE2 and angiotensin (Ang)II play important roles in the blood pressure and volume regulating renin-angiotensin system (RAS) (Figure 1).[5] ACE2 catalyses the conversion of AngII to Angiotensin 1-7 and negatively regulates the RAS. ACE2 has two isoforms: a membrane-bound glycoprotein expressed widely on mucosal surfaces of healthy people including ileum, colon and lungs, and a distinct soluble circulating form.[5] SARS-CoV-2 enters cells via the former, but can be bound in circulation to the latter.[6]

In mouse models, ACE2 expression in lungs is significantly decreased following SARS-CoV-2 infection, while Ang II levels increase.[7] These changes are purported as an underlying mechanism of acute respiratory distress syndrome (ARDS). Supporting this, recombinant human ACE2 protein protects mice from ARDS.[7] Additionally, preliminary evidence suggests that recombinant ACE2 is safe in human ARDS patients, with biomarker-based suggestion of efficacy—surfactant protein D, a determinant of lung injury, and interleukin-6, an important mediator of the cytokine storm, both decrease following ACE2 therapy.[8]

Since SARS-CoV-2 has high affinity for ACE2,[6] minor changes in expression of membrane-bound ACE2 on mucosal surfaces are unlikely to significantly alter an individual's susceptibility to COVID-19. However, soluble ACE2 may competitively inhibit circulating SARS-CoV-2. Plasma ACE2 activity is higher in IBD patients when compared to healthy controls, with a trend towards higher levels in patients with Crohn's disease (CD) than ulcerative colitis (UC).[5] ACE2 activity is significantly higher in non-inflamed biopsies of IBD patients than unaffected controls, but levels are lower in inflamed segment biopsies.[5] Interestingly, rates of ICU/ventilator requirement/death are higher in UC than CD patients (10% vs 6%) and in those with moderate/severe disease activity compared to mild/no disease activity in the SECURE-IBD registry.[4] This observation is speculatively contributed to by the higher serum ACE2 activity in CD patients.[5] Clinical trials investigating the benefit of recombinant ACE2 have already been proposed and may provide further evidence for the central role of ACE2 in the pathogenesis of COVID-19.

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LINKED CONTENT

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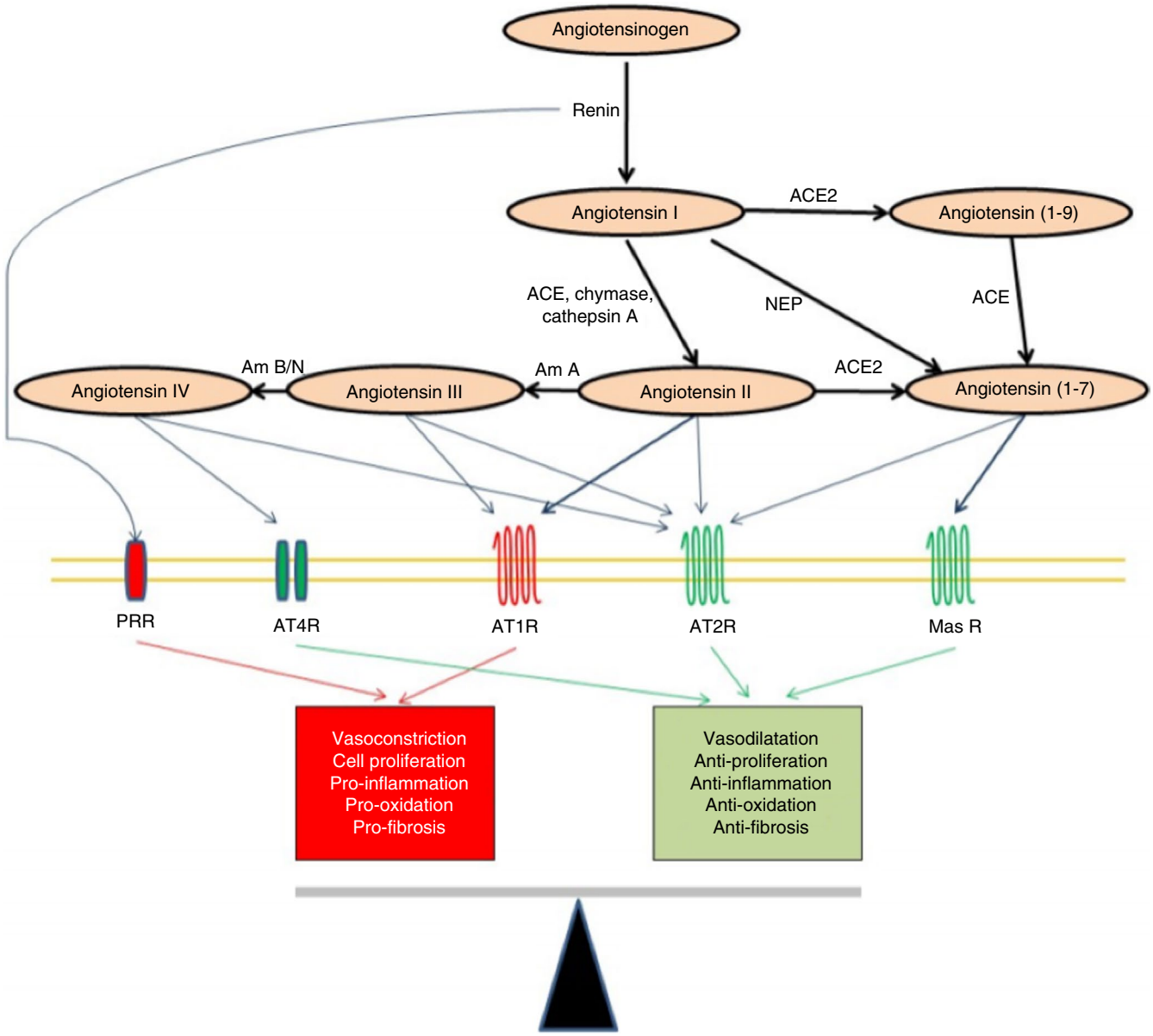

FIGURE 1 The renin-angiotensin system pathway.[5] Am, aminopeptidase; AT1R angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; AT4R, angiotensin type 4 receptor; NEP, neutral endopeptidase; PPR, (pro)renin receptor; RAS, renin-angiotensin system

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