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## BRIEF REVIEW

## The Role of Angiotensin Converting Enzyme 2 in Modulating Gut Microbiota, Intestinal Inflammation, and Coronavirus Infection

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**The role of angiotensin converting enzyme 2 has expanded from regulating the renin angiotensin system to regulating intestinal amino acid homeostasis and the gut microbiome. Recently, angiotensin converting enzyme 2 was identified as a primary receptor for severe acute respiratory syndrome coronaviruses 1 and 2 being expressed in multiple tissues including the luminal surface of the gut. In this brief perspective, we examine the role of angiotensin converting enzyme 2 as the receptor for severe acute respiratory syndrome coronavirus 2 and the impact of coronavirus disease 19 infection on the gut microbiome and on the gut epithelium.**

**Keywords:** ACE2; SAR-CoV-2; Gut Microbiota.

Angiotensin converting enzyme 2 (ACE2) has emerged as a critical regulator of the renin angiotensin system (RAS) by metabolizing angiotensin (Ang) II into the beneficial peptide Ang 1-7.<sup>1</sup> ACE2, which has 400-fold higher catalytic efficiency against Ang II than Ang I,<sup>2</sup> is part of both the systemic RAS, a central hormonal circuit responsible for regulating extracellular fluid volume and blood pressure, and as a component of the local RAS, such as in the lung, heart, kidney, or gut. ACE2 has also been identified as the key receptor for severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2.

The systemic RAS involves multiple organs, with juxtaglomerular cells in the kidney producing renin, which cleaves liver-derived angiotensinogen to produce Ang I. Ang I is converted to Ang II by ACE. Ang II in turn activates the G-protein-coupled AT1 receptors AT1R and AT2R.<sup>3</sup> A dysregulated RAS, as seen in hypertension, diabetes, and cardiovascular disease, leads to an increase in Ang II that, via AT1R, can cause a plethora of harmful effects, including vasoconstriction, inflammation, cardiovascular damage, or increased oxidative stress. Although ACE/Ang II/AT1R have been considered the deleterious arm of the RAS, ACE2, and Ang 1-7 acting through its receptor Mas oppose the effects of Ang II. The ACE2–Ang 1-7–Mas axis is considered to be a negative regulator of the RAS, opposing the activity of ACE–Ang II–AT1 axis.<sup>3</sup>

We have previously shown that infection of mice with SARS-CoV reduces ACE2 expression in the lung and other tissues due to spike protein-mediated down-regulation of

ACE2.<sup>4</sup> Spike treatment further led to increased Ang II and pulmonary edema, which was mediated by AT1R. Given the similarities between SARS-CoV and SARS-CoV-2 spike proteins,<sup>5</sup> a similar mechanism of spike-mediated ACE2 down-regulation most likely underlies tissue damage in coronavirus disease 2019 (COVID-19) by skewing the RAS.

ACE2 has critical roles in multiple organs, including heart, kidney, lungs, or gut.<sup>5–9</sup> ACE2 knockout mice have impaired cardiac function and elevated levels of Ang II in heart, kidney, and plasma,<sup>6</sup> although pretreatment with exogenous ACE2 could prevent Ang II-induced hypertension and heart injury.<sup>7</sup> Loss of ACE2 exacerbated kidney injury in diabetic mice, and treatment with ACE2 reduced diabetic nephropathy, accompanied by an increase in Ang 1-7.<sup>8</sup> Furthermore, in a mouse model of acute lung injury, acid inspiration and other injury modalities led to decreased levels of ACE2 and increased levels of Ang II in the lungs,<sup>9</sup> which was further exacerbated in ACE2 knockout mice. However, treatment with ACE2 reduced the degree of acid-induced lung injury in both wild-type and knockout mice.

Importantly, in the gut, ACE2 has a completely different function independent of the RAS; ACE2 stabilizes neutral amino acid transporters, such as B<sup>0</sup>AT1 and loss of ACE2 compromises intestinal uptake of certain dietary amino acids, such as tryptophan. Because tryptophan plays an important role in immunity, ACE2 knockout mice exhibited altered gut microbiota and developed more severe dextran sulfate sodium-induced colitis compared with wild-type control mice.<sup>10</sup> Therefore, down-regulation of ACE2 by SARS-CoV-2 could explain multi-organ failure in COVID-19, and restoration of ACE2 is a rational therapeutic strategy.

In this brief perspective, we examine the role of ACE2 in the gut and propose a model for how SARS-CoV-2 could impact the gut microbiome and intestinal epithelium.

**Abbreviations used in this paper:** ACE2, angiotensin converting enzyme 2; ACEI, angiotensin converting enzyme inhibitor; Ang, angiotensin I; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; LP, *Lactobacillus paracasei*; RAS, renin angiotensin system; rh, recombinant human; SARS-CoV, severe acute respiratory syndrome coronavirus.

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## Gastrointestinal Manifestations of SARS and COVID-19

Although SARS and COVID-19 typically present with a respiratory illness, a significant proportion of patients have reported gastrointestinal symptoms, including diarrhea, vomiting, and abdominal pain.<sup>11</sup> ACE2, being the natural receptor in the lung alveolar epithelium and intestinal epithelium for the spike protein of both SARS-CoV and SARS-CoV-2, has been correlated to not only the severity of respiratory disease but also that of gastrointestinal conditions.

Diarrhea was a common symptom of SARS, found in up to 20% of patients during the 2003 epidemic.<sup>12,13</sup> Most of the diarrhea was self-limiting, but gastrointestinal symptoms were correlated with more severe pulmonary disease as patients required ventilatory support. Intestinal biopsies obtained by colonoscopy showed minimal architectural disruption with no villous atrophy of the colonic epithelium.<sup>14</sup> Electron microscopy showed the presence of actively replicating virus on the microvilli of the luminal surface of enterocytes within both small and large intestines.

In the outbreak of COVID-19 infection in Wuhan, China, diarrhea was reported in 3.8% and nausea and vomiting in 5% of patients.<sup>15</sup> SARS-CoV-2 RNA was detected in 38% (with diarrhea) and 8.7% (without diarrhea) of the stool from patients with COVID-19.<sup>16</sup> Patients with diarrhea, however, were found to have a higher viral load. A recent systematic review pooled findings from 35 studies, including 6686 patients with COVID-19; among these, 29 studies reported 4% of patients had gastrointestinal symptoms and 19% had abnormal liver function tests.<sup>17</sup> Gastrointestinal and hepatic manifestations are also found frequently in children, as in adults. As in the case of SARS, those who had higher viral load tended to have higher rates of gastrointestinal symptoms and liver injury. Approximately 10% of patients with COVID-19 actually presented with gastrointestinal manifestations only, without any respiratory symptoms, in which case the diagnosis could have been delayed.

Interestingly, in a retrospective study investigating the clinical and virologic characteristics of COVID-19 in China, individuals with hypertension receiving treatment of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) exhibited a lower risk of gastrointestinal symptoms and lower mortality compared with those who did not receive these medications.<sup>18</sup> However, this study is limited by its retrospective nature and the small number of patients (100 in total) involved.

Nevertheless, not all coronavirus used ACE2 as receptor, as Middle East respiratory syndrome coronavirus, which also causes diarrhea in some patients, acts independent of ACE2.

### SARS-CoV-2 in Stool and Fecal Microbiome

More than one-half of patients with COVID-19 infection tested positive for fecal RNA according to a study by Gupta et al.<sup>19</sup> The duration of fecal viral shedding ranged from 1 to 33 days after symptomatic recovery of lung injury and even after a negative nasopharyngeal swab. In a group of pediatric

patients infected with SARS-CoV-2, rectal swabs were found positive for SARS-CoV-2 even after the nasopharynx was cleared of the virus, suggesting that viral shedding from the digestive tract might be more durable than that from the respiratory tract.<sup>20</sup> In the laboratory, an expandable organoid culture system of bat intestinal epithelium confirmed that SARS-CoV-2 can infect enterocytes of bats.<sup>21</sup> Furthermore, SARS-CoV and SARS-CoV-2 replication has also been demonstrated in human intestinal organoids.<sup>21,22</sup> Intestinal epithelium supports SARS-CoV 2 and fecal-oral transmission is possible.<sup>22,23</sup>

Infection by SARS-CoV-2 has been shown to alter the fecal microbiome during hospitalization.<sup>24</sup> In a small group of 15 patients, depletion of opportunistic pathogens and depletion of commensals was documented during SARS-CoV-2 infection. *Coprobacillus*, *Clostridium ramosum*, and *Clostridium mathewayi* were found more commonly in patients with severe COVID-19. On the other hand, the presence of *Faecalibacterium prausnitzii* was correlated with milder disease. Loss of salutary species in COVID-19 persisted in the majority of patients in spite of clearance of virus, suggesting that exposure to SARS-CoV-2 might be associated with more long-lasting deleterious effects to the gut microbiome. Although this is an interesting observation, validation of these findings with a larger sample that has baseline gut microbiome data and long-term follow-up of the fecal microbiome will be needed.

### Angiotensin Converting Enzyme 2 in Colitis

To understand what SARS-CoV-2 is doing in the gut, investigators also looked at the role of ACE2 in intestinal inflammation. Krzysztof et al<sup>25</sup> reported that ACE2 expression in the inflamed ileum in Crohn's disease was 60% lower than in healthy individuals. However, colonic ACE2 expression in patients with Crohn's disease was found to be increased. Burgueno et al<sup>26</sup> studied patients with inflammatory bowel disease (IBD) and confirmed that ACE2 and TMPRSS2 were expressed abundantly in the ileum and colon. Yet inflammation correlates with significant down-regulation of epithelial ACE2.<sup>26</sup> During active inflammation in IBD, there was no significant increase in expression of ACE2 or TMPRSS2 in the intestinal mucosa, suggesting that patients with IBD are not more susceptible to SARS-CoV-2. Treatment of IBD, using anti-TNF agents, vedolizumab, ustekinumab, and corticosteroid, leads to a trend toward decreased ACE2 and control of inflammation.<sup>27</sup> Based on the limited data available, additional monitoring of IBD disease activity and ACE2 expression in intestine, with or without the use of immunomodulatory and biologic therapies, should be warranted.

As we described, deficiency in murine ACE2 results in highly increased susceptibility to intestinal inflammation induced by epithelial damage.<sup>10</sup> This is independent of enzymatic activity and is instead regulated by intestinal amino acid homeostasis, expression of antimicrobial peptides, and changes to the gut microbiome.<sup>10</sup> In an animal study of stress-induced intestinal inflammation, irbesartan, an ARB, reduced inflammation, which was correlated with increased ACE2.<sup>28</sup> ARB-treated mice showed reduced stress-induced

biomarkers of oxidative injury and cytokines, such as TLR-4 and IL1- $\beta$ , in colonic epithelium, and hence had less severe inflammation. Therefore, ACE2 in the intestine is a critical regulator of intestinal inflammation via its role in amino acid absorption. In addition, hyperactivation of the RAS might be involved in driving intestinal inflammation.

## A Model of SARS-CoV-2 Interaction With Angiotensin Converting Enzyme 2 and Renin Angiotensin System in the Gut

ACE2 is central to intestinal infection with SARS-CoV-2 and is highly expressed in the gut.<sup>1</sup> As shown in [Figure 1](#), gut luminal ACE2 could be “hijacked” as a receptor for SARS-CoV-2 to promote viral infection in the intestine. After replication and packaging, the virus can be released into the abluminal side of the enterocyte and taken into the circulation. However, in contrast to fecal–oral transmission, evidence supporting systemic infection from gut-derived SARS-CoV-2 has not been described to our knowledge. Viremia was detected in 6 of 10 individuals that succumbed to fatal COVID-19 infection<sup>29</sup>; and the presence of viremia is irrefutable in severely ill subjects,<sup>30</sup> as well as more likely to occur in individuals with compromised immune systems.<sup>31</sup> During infection in the gut, SARS-CoV-2 could have multiple effects on the RAS, as the local RAS of the gut epithelium has all the components of the systemic RAS. ACE2 on enterocytes generates Ang 1-7 from luminal Ang II. Ang 1-7 binding to Mas receptor could block glucose transport in the gut by specifically modulating luminal glucose transporters, SGLT1 (luminal) and GLUT-2 (abluminal), similar to what has been described in the pancreas<sup>32</sup> ([Figure 1](#)). ACE is also present on the luminal surface of enterocytes.<sup>33–35</sup> ACE participates in degradation of digestive enzymes yielding free amino acids and also influences bacterial metabolism generating bioactive peptide fragments, including Ang II.<sup>36</sup> As shown in [Figure 1](#), Ang II is an agonist of enterocyte apical membrane AT1R, which stimulates the absorption of dietary sodium via up-regulation of NHE3 activity.<sup>37–39</sup> When SARS-CoV-2 down-regulates luminal ACE2, there would be less enzyme to cleave Ang II and lower levels of Ang 1-7 and reduced Mas activation. More Ang II (and therefore less Ang 1-7) results in luminal AT1R activation and enhanced permeability, leading to so-called leaky gut syndrome<sup>40</sup> ([Figure 1](#)).

ACE2 has been found previously to control expression of B<sup>0</sup>AT1 in the intestine.<sup>41</sup> B<sup>0</sup>AT1 is the primary apical membrane transporter in the intestine, which functions in Na<sup>+</sup>-coupled uptake of neutral amino acids, such as tryptophan.<sup>42</sup> Importantly, B<sup>0</sup>AT1 substrates, notably tryptophan and glutamine, signal to down-regulate lymphoid proinflammatory cytokines, promote tight junction formation, activate the release of antimicrobial peptides, and modulate mucosal cell autophagy as defense mechanisms<sup>40,43</sup> ([Figure 2](#)), all of which can be disturbed by COVID-19 infection and lead to leaky gut. It is intriguing to consider that SARS-CoV-2 disruption of the gut barrier could lead to elevation of systemic bacterial lipopolysaccharide and

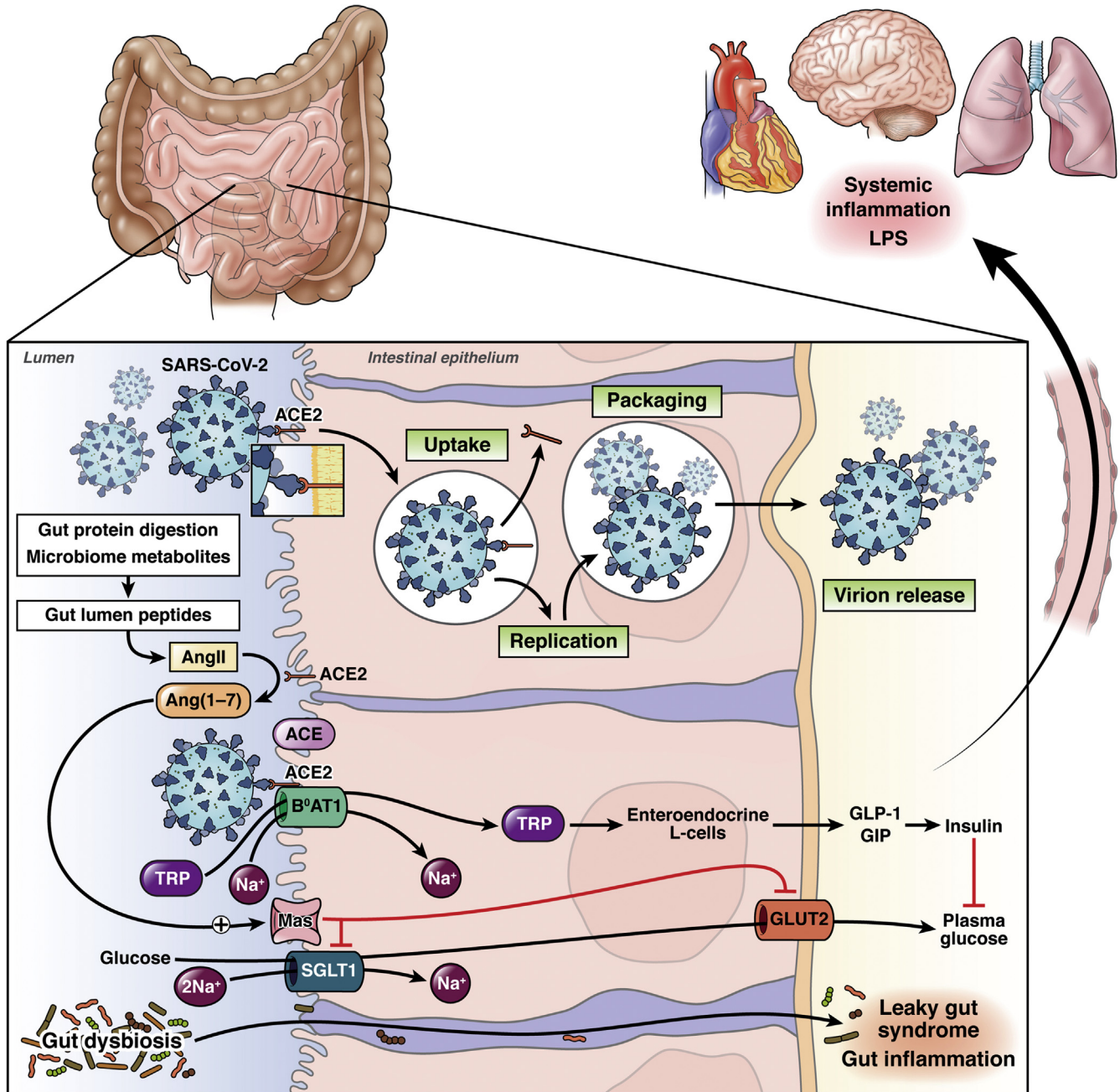
peptidoglycan and enhancement of inflammation. Therefore, leaky gut and microbial dysbiosis can contribute to cytokine storm in patients severely ill with COVID-19 ([Figure 2](#)).

A recent study has shown how the spike protein of SARS-CoV-2 (S1) could interact with a complex of ACE2 and the tryptophan amino acid transporter B<sup>0</sup>AT1.<sup>44</sup> On S1 binding, the ACE2:B<sup>0</sup>AT1 complex is internalized in the intestine. The virus-induced internalization of ACE2, by reducing the function of a critical amino acid transporter, could adversely impact glucose homeostasis ([Figure 1](#)). In healthy gut, tryptophan transported by B<sup>0</sup>AT1 activates mucosal enteroendocrine L cells to release incretins, such as GLP-1 and GIP. Incretins enter the circulation to modulate glucose homeostasis. This key regulatory pathway can be disturbed in patients with COVID-19 and might explain, in part, the hyperglycemia in patients who are not diabetic. SARS-CoV-2 can readily infect ACE2-expressing intestinal epithelial cells, resulting in an altered local gut RAS and possibly down-regulated intestinal ACE2-B<sup>0</sup>AT1 cell surface expression, which could then lead to a series of downstream sequelae to promote leaky gut syndrome and elevated plasma bacterial lipopolysaccharides and/or peptidoglycans enhancing systemic inflammation in patients with COVID-19.

### Possible Therapeutics That Modulate Angiotensin Converting Enzyme 2

As we have detailed, virus-mediated reduction of ACE2 expression in the gut could shift the RAS from the protective arm (ACE2–Ang 1-7–Mas) toward the deleterious arm (ACE–Ang II–AT1R), which has previously been shown in the lung to have deleterious effects.<sup>4</sup> Conceptually, one could consider that restoration of epithelial ACE2 levels would serve to restore balance of the disturbed RAS and intestinal amino acid uptake and benefit patients with COVID-19. Rodent studies support that ACEI and ARB increase the expression of ACE2 messenger RNA in heart, kidney, and the aorta.<sup>45–47</sup> The ARB losartan, as well as olmesartan, increase ACE2 expression in a rat model of myocardial infarction.<sup>48</sup> Restoring intestinal ACE2 expression by the administration of ACEI and ARB might represent an effective therapeutic strategy in individuals infected with COVID-19.<sup>49</sup> At the same time, there is no clinical evidence suggesting that ACEI or ARB, by increasing cellular receptors for SARS-CoV-2, would alter susceptibility to viral infection or increase risk for severe disease in those already infected.

Yisireyli et al<sup>28</sup> reported that the ARB, irbesartan, inhibited RAS activation and restored ACE2 expression to suppress stress-induced intestinal inflammation.<sup>28</sup> ARBs have anti-inflammatory properties via inhibition of Ang II/AT1R and by increasing ACE2, which activates the Ang (1-7)–Mas pathway to counteract inflammatory signaling. Stress due to oxidative injury directly down-regulated ACE2/B<sup>0</sup>AT-1 activity by modulation of intestinal mTOR and p70 S6 kinase (p70S6K), lowered the levels of  $\alpha$ -defensins, changed the intestinal microbiota and increased expression of enzymes in the kynurenine pathway, important in tryptophan metabolism. These results suggest that irbesartan and ARB as a class might represent therapeutic agents for intestinal

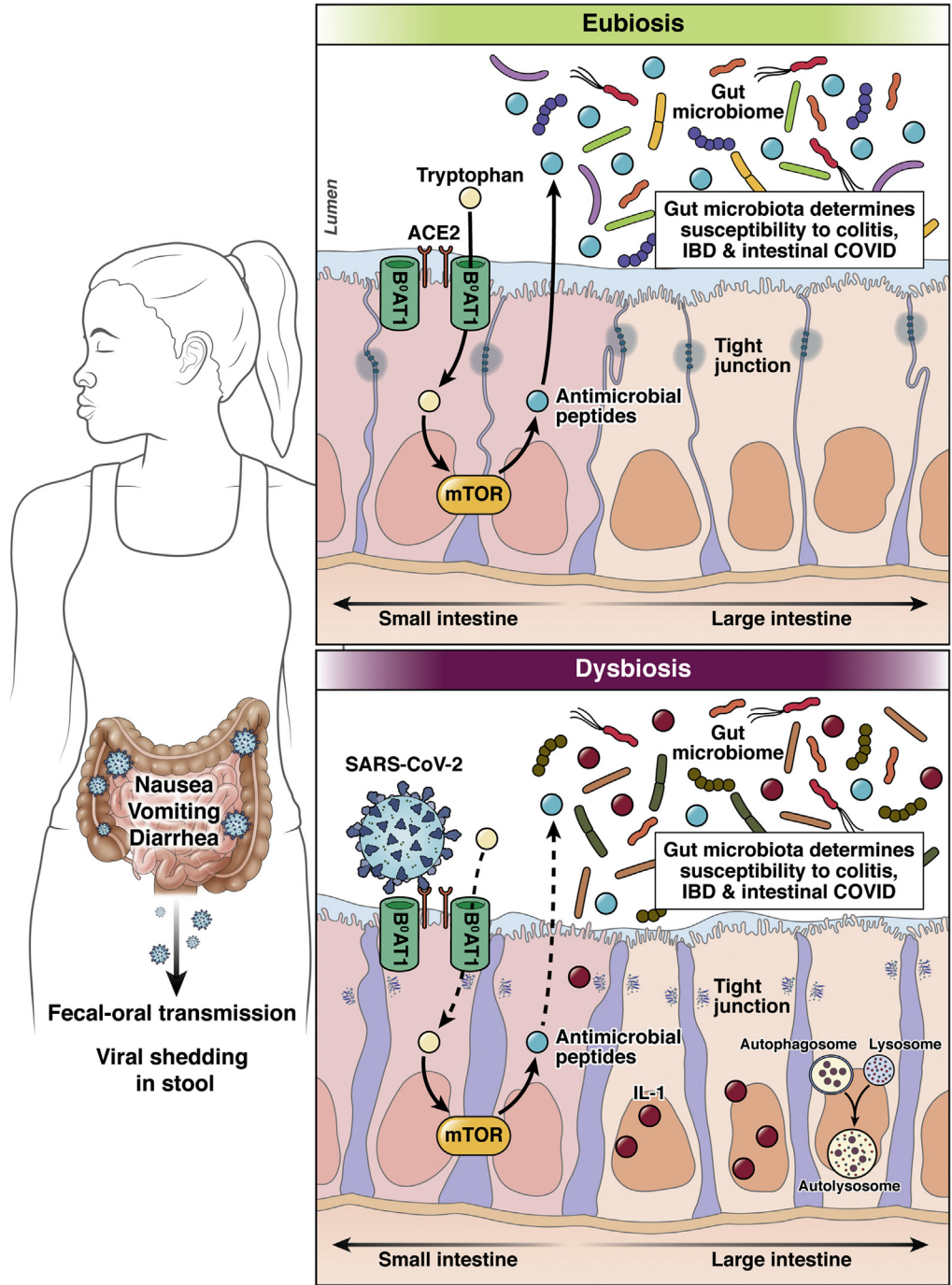


**Figure 1.** The dysregulated RAS in the gut of patients with COVID-19. All RAS components are recapitulated locally in the gut. ACE2 serves as the receptor for SARS-CoV-2 to promote viral infection and replication. Spike S-protein of SARS-CoV-2 binding to the extracellular domain of ACE2 can lead to internalization of ACE2/B<sup>0</sup>AT1. B<sup>0</sup>AT1 serves as an amino acid transporter for tryptophan. Tryptophan stimulates enteroendocrine L cells to release GLP-1 and GIP, key incretins that regulate pancreatic insulin-producing  $\beta$  cells and inhibit glucagon-producing  $\alpha$  cells thereby modulating plasma glucose levels. SARS-CoV-2 by down-regulating intestinal ACE2-B<sup>0</sup>AT1 would disrupt glucose and sodium homeostasis. Reduced levels of ACE2 could result in a dysbiotic gut by diminishing the generation of Ang 1-7 and activation of the Mas receptor, resulting in unimpeded and increased absorption of glucose from the gut. Dysbiosis can lead to disruption of the gut barrier, resulting in release of microbial products into the circulation. These changes in an already compromised patient with COVID-19 can lead to enhanced systemic inflammation.

inflammation perhaps even in patients with COVID-19.<sup>25</sup> Vuille-dit-Bille et al<sup>37</sup> reported that use of ACEI in human subjects increased duodenal ACE2 messenger RNA expression levels by 1.9-fold compared with nontreated controls. Clinical data are now rapidly becoming available from patients

infected with COVID-19, and soon the impact of ACEI or ARB administration on outcomes might be established.<sup>20</sup>

Monteil et al<sup>50</sup> showed that recombinant human ACE2 (rhACE2) can effectively block SARS-CoV-2 infection in VeroE6 cells and human blood vessel and kidney organoid



**Figure 2.** Individuals with COVID-19 infection might experience diarrhea, nausea, and vomiting. This can lead to viral shedding in the stool, ultimately contributing to fecal-oral transmission of SARS-CoV-2. An individual’s gut microbiome can determine susceptibility to IBD and perhaps COVID-19 infection. In the small intestine, reduced tryptophan uptake by epithelial cells results in diminished release of antimicrobial peptides via reduced mTOR activation. In the large intestinal epithelial cells, the dysbiotic gut microbiome results in increased release of proinflammatory cytokines, loss of tight junction formation, and changes in mucosal cell autophagy.

models. This finding was supported by a subsequent study by Lei et al,<sup>51</sup> which showed a similar effect using the extracellular domain of ACE2 attached to the Fc region of IgG. Batlle et al<sup>52</sup> reviewed the use of rhACE2 for patients severely ill with COVID-19. Currently in phase 2 clinical trials in Europe ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04335136) ID NCT04335136), rhACE2 was well tolerated in healthy volunteers and human subjects with acute respiratory distress syndrome and pulmonary arterial hypertension.<sup>53</sup> In addition, Hemnes et al<sup>54</sup> provided strong support for consideration of rhACE2 in pulmonary

dysfunction demonstrating Mas activation in a phase 2a, open-label pilot study of a single infusion of rhACE2 (0.2 or 0.4 mg·kg<sup>-1</sup> intravenously). rhACE2 was well tolerated with significant improvement in cardiac output and pulmonary vascular resistance. rhACE2 infusion was also associated with reduced plasma markers of inflammation within 2–4 hours and with increases in plasma SOD2 at 2 weeks.<sup>54</sup> Taken together, evidence supports the concept that ACE2 is a critical molecule that protects from pulmonary injury (and injury of multiple other tissues, such as the heart, kidneys, blood

vessels, or gut). However, it is unclear what impact rhACE2 given systemically would have on the gut. One could postulate that intravenous ACE2 would enhance the generation of systemic Ang 1-7 that would serve to activate Mas in the gut endothelium and restore gut vascular barrier integrity resulting in reduced leakage of microbial products into the circulation; however, this has to be tested experimentally.

Although not yet a US Food and Drug Administration–approved biologic, the use of genetically modified bacteria that express ACE2 might in the future serve as a therapeutic strategy that would directly target the gut. To overcome the challenges of large-scale production of high-quality ACE2 (hrACE2), Verma et al<sup>55</sup> developed an expression and delivery system based on the use of probiotic species *Lactobacillus paracasei* (LP) to serve as a live vector for oral delivery of human ACE2. They showed that codon-optimized ACE2 can be efficiently expressed in LP. They developed recombinant LP expressing the secreted ACE2 in fusion with the nontoxic subunit B of cholera toxin, which acted as a carrier to facilitate transmucosal transport. LP increased ACE2 activities in serum and tissues and chronic gavage administration of LP reduced microvascular complications in 2 diabetic mouse models. These results provide proof of concept for feasibility of using engineered probiotic species as live vectors for delivery of human ACE2 and might in the future represent a strategy to correct gut dysbiosis while simultaneously increasing serum levels of ACE2. As a caveat, ACE2 is heavily glycosylated and the binding between ACE2 and the SARS-CoV-2 spike glycoprotein appears to be highly dependent on sugar modification, which will be fundamentally different in bacterial-derived ACE2.

## Conclusions

In summary, as the global COVID-19 pandemic unfolds, there is an urgent need for additional basic and clinical studies to address the unanswered questions that threaten lives and cause morbidity. This brief perspective has directed attention to the SARS-CoV-2 receptor ACE2, which is highly expressed on the luminal surface of intestinal epithelial cells. In the gut, ACE2 stabilizes expression amino acid transporter B<sup>0</sup>AT1 and thereby controls amino acid uptake. SARS-CoV-2, by down-regulating intestinal ACE2, could promote leaky gut syndrome with elevated plasma bacterial lipopolysaccharides and/or peptidoglycans, modifying the gut microbiome and enhancing systemic inflammation. Targeting of the RAS axis, by inhibition of ACE or by enhancing intestinal ACE2 by providing rhACE2 or adding genetically modified bacteria that express ACE2, may be rational strategies for improving clinical outcomes in patients with COVID-19.

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**Conflicts of interest**

The authors disclose no conflicts.