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Review article

Recent advance of ACE2 and microbiota dysfunction in COVID-19 pathogenesis

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the coronavirus disease 2019 (COVID-19) and has become the world's most pressing public health threat. Although not as common as respiratory symptoms, a substantial proportion of patients with COVID-19 presented the gastrointestinal symptoms. ACE2, as the receptor of SARS-CoV and SARS-CoV-2, is highly expressed in the epithelia of the epithelium cells in lung and intestine. In addition, ACE2 is essential for the innate immunity, amino acid transportation and the homeostasis of intestinal microecology. The composition of gut microbiota in COVID-19 patients was altered and concordant with inflammatory, which may explain the gastrointestinal symptoms in patients. Here we reviewed and discussed the evolving role for ACE2 and gut microbiota in SARS-CoV-2 infection which might provide innovative approaches to targeting ACE2 and gut microbiota for the COVID-19 therapy.

1. Introduction

Coronaviruses, a large diverse family of viruses, contain a positive-sense and single-stranded RNA (ssRNA) genome (27–32 kb) and are members of the subfamily *Coronavirinae*. According to the phylogenetic relationships and genomic structures, coronaviruses can be classified into four genera, including *Alpha-*, *Beta-*, *Gamma-*, and *Delta* coronavirus. Coronaviruses are highly pathogenic to vertebrate hosts and cause upper respiratory tract illnesses and gastroenteritis [1, 2]. At the beginning of 21st century, two highly pathogenic human beta-coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), caused severe respiratory illness and high mortality. SARS-CoV infected more than 8,096 people worldwide including 774 deaths in 2003, and MERS-CoV has infected more than 2,500 people with a case-fatality rate of about 36% since 2012 [3]. Since the end of 2019, a novel transmissible coronavirus (severe acute respiratory syndrome-related coronavirus 2, SARS-CoV-2) was noted to cause the coronavirus disease 2019 (COVID-19) with the symptoms ranging from mild respiratory symptoms to severe lung injury, muti-organ failure, and death [4, 5, 6]. SARS-CoV-2 was first detected and reported in Wuhan, China and then spread worldwide, thus causing a global panic.

The clinical typical symptoms of COVID-19 include fever, dry cough, myalgia or fatigue, and dyspnea [7]. Previous studies have shown gastrointestinal symptom is a common presenting symptom of SARS during the course of illness [8]. Similar to SARS, a majority of patients with COVID-19 presented the gastrointestinal symptoms, including diarrhea, nausea, vomiting, and abdominal pain [9, 10, 11]. In addition, evidence showed that the samples of feces and anal swabs from patients with COVID-19 detected viral nucleic acids, indicating that gastrointestinal tract may be a potential way of fecal-oral transmission in COVID-19 [11, 12, 13]. The gut-lung axis may play an important role in composition and function of the gut microbiome, which modulate inflammatory responses and worsen outcomes in viral or bacterial respiratory infection [14]. Preliminary evidence showed that the changes of gut microbiota in COVID-19 patients may in turn contribute to the uncontrolled inflammation [15, 16].

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Angiotensin-converting enzyme 2 (ACE2) has been identified to serve as a receptor for SARS-CoV [17]. The spike protein of SARS-CoV has a high affinity for binding to ACE2 in human cells, which was a determinant factor for SARS-CoV to enter the cellular, thus increasing the replication rate and disease severity [1, 3]. The external subdomain of the SARS-CoV-2 receptor-binding domain has a high sequence homology with SARS-CoV, indicating that SARS-CoV-2 may bind the receptor ACE2 to enter cells [18, 19, 20]. It is known that the expression of ACE2 is abundant in the epithelia of intestine in humans. In the intestine, ACE2 is important for modulating the intestinal immunity by maintaining amino acid homeostasis, antimicrobial peptide expression and influencing the gut microbiota [21]. Growing evidence showed that human intestinal epithelial cells are a productive site for SARS-CoV-2 infection, replication and production of infectious *de novo* virus particles, which is mediated by an extremely robust intrinsic immune response to participate in the pathologies [22]. Gut microbiota is linked with host immune responses and homeostasis that influence the progress of airway diseases [23]. Maintaining the balance of intestinal microecology will have a beneficial effect on preventing or alleviating lung diseases. In this review, we discussed the recent developments for understanding the gastrointestinal symptoms observed in patients with COVID-19. Our effort is to reveal the relation between ACE2 and gut microbiota in SARS-CoV-2 infection, in order to provide new insights into the disease pathogenesis.

2. The role of ACE2 in intestine

ACE2, a homolog of ACE, is a kind of transmembrane carboxymonopeptidase containing a short intracellular cytoplasmic tail and a longer extracellular domain that exhibits carboxymonopeptidase activity [24]. As a component of renin–angiotensin system (RAS), ACE2 plays an important role in anti-proliferative, anti-fibrotic, anti-inflammatory, modulating blood pressure (BP) and maintaining fluid balance in the body. ACE2 is most widely expressed in epithelial cells of heart, kidney, lungs and gut. Research in the past few years has demonstrated that the expression of ACE2 was in a high level within the human gastrointestinal tract, suggesting that ACE2 possessed an important function in the gastrointestinal system [25, 26]. In the previous studies, researchers paid more attention to the carboxymonopeptidase activity of ACE2. However, the noncatalytic role of ACE2 was found to regulate neutral amino acid transporters with the discovery of collectrin which possessed a high sequence homology to the carboxyterminal end of ACE2 [27]. The noncatalytic activity of collectrin is associated with the Slc6 family of neutral amino acid transporters B^0AT1 (*Slc6a19*) to control polarized expression in the kidney required for renal reabsorption of amino acids [28].

Similar to collectrin, ACE2 can co-localize and interact with the neutral amino acid transporter B^0AT1 in the small intestine where collectrin is absent [29]. In the small intestine, ACE2 is primarily located in the differentiated epithelial cells, binds and stabilizes to B^0AT1. The transport activity of B^0AT1 in the small intestine seems to rely on the expression of ACE2. In the ACE2 knock-out mice, the enterocyte of small intestine cannot express B^0AT1, thus reducing the level of essential amino acid tryptophan in plasma [29]. The uptake of tryptophan mainly depends on B^0AT1 and regulated by the activation of mTOR pathway, resulting in the secretion of antimicrobial peptides from Paneth cells [30, 31]. The secretion of antimicrobial peptides in turn influenced the composition of the gut microbiota, thus increased the susceptibility to colitis. Moreover, ACE2 deficient mice treated with chemical irritants were highly susceptible to develop into diarrhea and colitis, and the propensity of germ-free mice developing severe colitis was increased after transplantation of the gut microbiota from ACE2 deficient mice [31]. Therefore, ACE2 and B^0AT1 co-localize on enterocyte of the small intestine to mediate the amino acid transport and tryptophan uptake, further contributing to local intestinal inflammation and diarrhea. ACE2 as a key regulator of RAS system plays a critical role in diarrhea and intestinal inflammation of malnutrition which is a major global health burden. ACE2 is a direct mediator of the intestinal amino acid homeostasis and RAS system, which provide the connection of dietary amino acid homeostasis, innate immunity, gut microbial ecology [31, 32]. Consequently, ACE2 plays an essential role in gut function and biology, regulating of antimicrobial peptide expression, and regulating local and systemic immune responses against pathogenic agents, hence providing a molecular explanation for how amino acid malnutrition can cause intestinal inflammation and diarrhea.

3. ACE2 and SARS-CoV-2 infection

Viral infections are dependent on cell membrane receptors to enter cells for the replication. There is growing evidence that SARS-CoV-2 can infect the intestinal epithelial cells which fully support the replication and production of infectious de novo virus particles [33]. It has been identified that ACE2 was the receptor of SARS-CoV, which caused acute lung failure in humans by infecting ciliated bronchial epithelial cells and type II pneumocytes [34, 35]. The entry of SARS-CoV to host cells is mediated by spike (S) protein which is functionally divided into a receptor-binding unit S1 and a membrane-fusion unit S2. S1 is responsible for receptor binding with the cellular membrane and composed of the amino-terminal domain (S1-NTD) and the carboxy-terminal domain (S1-CTD). S1-CTD is identified as the receptor-binding domain (RBD) which is essential for the infection of SARS-CoV mediated by ACE2 [35, 36, 37]. S2 is a fusion unit for the cellular and viral membranes, providing a way for the viral genomes to enter host cells.

Recent reports demonstrated that SARS-CoV and SARS-CoV-2 share a homology of 79% and bind with similar affinities to host cell receptor ACE2 [38, 39, 40]. SARS-CoV-2 recognizes ACE2 at the cellular membrane using a receptor-binding unit S1 of S protein, which shares about 75% overall amino acid sequence identity with the SARS-CoV S1 [41]. However, SARS-CoV-2 appears to be more readily transmitted from human to human than SARS-CoV [42, 43]. Biophysical and structural evidence showed that SARS-CoV-2 S protein binds ACE2 with higher affinity than does S protein of SARS-CoV [44]. The S protein in SARS-CoV and SARS-CoV-2 reflect the high degree of structural homology, with the difference of their RBDs position [45]. Sequence analysis of SARS-CoV-2 S illustrated that there is a four amino acid residue insertion at the boundary between the S1 and S2 subunits, which is a furin cleavage site apart from SARS-CoV S [46]. Yan et al. reported the structural basis for the recognition of SARS-CoV-2 by full-length human ACE2 [44]. The overall interface between SARS-CoV-2 and ACE2 is mediated mainly through polar interactions divided into three clusters, including two ends of the bridge interact with the N and C termini, small areas on the α2 helix and loop 3–4. When the S1 subunit binds to a host cell receptor of ACE2, the prefusion structure of SARS-CoV-2 S protein undergoes a substantial structural rearrangement. The entry of SARS-CoV-2 requires cellular proteases to cleavage S protein at the S1/S2 boundary, following the fusion of viral and cellular membranes mediated by S2 subunit [40]. A furin cleavage site in SARS-CoV-2 resulted in the efficient proteolytic processing in human cells.

Single-cell RNA-sequencing (scRNA-seq) datasets across health and disease revealed that small intestinal ileal absorptive enterocyte express host factors used by SARS-CoV-2 [26]. Furthermore, research reported that the SARS-CoV-2 receptor of ACE2 was highly expressed in oesophageal epithelial cells and the absorptive enterocyte from ileum and colon [13, 47]. These findings may explain the gastrointestinal symptoms in patients with SARS-CoV-2 infection and provide a way of faecal transmission. Moreover, the domain of SARS-CoV-2 S bound to ACE2 with ~15 nM affinity, which is about 10- to 20-fold higher than the affinity of SARS-CoV binding to ACE2, thus contributing to the efficient spread from human to human [44, 48].

4. Gut microbiota dysbiosis and SARS-CoV-2

The gut microbiome plays a critical role in health and disease. Microbiota in the intestine has great influence on host immune system by promoting the local homeostatic interactions. The relationship between

the distal (gastrointestinal tract) immune and respiratory tract is considered as the gut-lung axis [49, 50, 51]. Changes in the composition and function of the gut microbiome are linked with altered immune responses and homeostasis in the respiratory tract. The gut-lung axis has been identified several gut microbe-derived components and metabolites to mediated the immune response during respiratory disease. The specific microbiota strains (such as probiotics) showed beneficial effects on the host immunity and/or against pathogens by the successful treatment of intestinal disorders [52].

ACE2 expression in the intestine is positively associated with suppressing intestinal inflammation by maintaining amino acid homeostasis, antimicrobial peptide expression and ecology of the gut microbiome. In addition, ACE2 regulates the infection and transcription of virus, and is essential for the amino acid transportation, innate immunity and the composition of the gut microbiota [17, 31, 32, 40]. Previous studies have uncovered gut dysfunction is related to the respiratory infections and results in the more severe clinical course of the disease [53]. SARS-CoV-2 infected human with ACE2^{+} mature and gut microbiota dysbiosis by TMPRSS2 and TMPRSS4 proteases [54]. Patients hospitalized with SARS-CoV-2 infection showed co-bloom of opportunistic fungal pathogens, *Candida species* and *Aspergillus species*, in the gut compared with healthy individuals, resulting in a long disease course than nasopharyngeal clearance of SARS-CoV-2 [22]. These researches provided a reasonable explanation to gastrointestinal symptom and intestinal inflammation in patients with COVID-19.

Over 60% of patients with SARS-CoV-2 exhibited the gastrointestinal symptoms, including diarrhea, nausea and vomiting, thus caused higher severity of diseases [11, 55, 56]. Researchers have isolated the active replication SARS-CoV-2 from the stool specimen of patients with diarrhea, suggesting the human intestinal tract might be a transmission route [57]. Electron-microscopy and mRNA expression analysis demonstrated that enterocyte were readily infected by SARS-CoV and SARS-CoV-2, and illustrated strong induction of a generic viral response program supporting SARS-CoV-2 replication [58]. Additionally, Fecal metabolomic analysis showed potential amino acid-related pathways were associated with gut microbiota and inflammation, thus suggesting the important role of fecal metabolites in mediating the effect of the core gut microbiota on host metabolism and inflammation [15]. Intestinal epithelial cells participate in the pathologies of SARS-CoV-2 by contributing to increase patient viremia and fuel an exacerbated cytokine response [33]. It is known that ACE2 is an important receptor of SARS-CoV-2 and regulator of amino acid malnutrition to influence the microbial ecology and intestinal inflammation [31, 40, 59]. Significantly, Accumulating research has focused on the dysbiosis of gut microbiota in COVID-19 patients. The composition of gut microbiome in patients with COVID-19 was significantly altered and characterized by enrichment of opportunistic pathogens (e.g. *Clostridium hathewayi* and *Clostridium ramosum*), and an inverse correlation between the probiotic bacteria (e.g. *Lactobacillus* and *Bifidobacterium*) and anti-inflammatory bacterium (*Faecalibacterium prausnitzii*) [60, 61, 62] (Figure 1). These changes of gut microbiome composition are concordant with disease severity and concentrations of several inflammatory cytokines by depleting the immunomodulatory potential gut bacteria [63]. Moreover, the expression of ACE2 in murine gut can be downregulated by the bacteria of Bacteroidetes members which inversely correlated with the SARS-CoV-2 load in fecal samples of patients [60]. The coronaviruses infect the host through recognizing several pattern recognition receptors (PRRs) of host cells to trigger the production of immune system cell effectors [64]. The loss of ACE2-protective functions upon SARS-CoV-2 infection contributed to the gut microbiota dysbiosis, altered permeability of gut barrier and subsequently disabled priming of local and systemic immunity [60, 65, 66]. These may explain the poor outcomes and a potential link between ACE2 functions and gut microbiota of COVID-19 patients. Taken together, the disruption of the corresponding gut microbiome features may underlie the potential predisposition of healthy individuals to the susceptibility and severity of SARS-CoV-2.

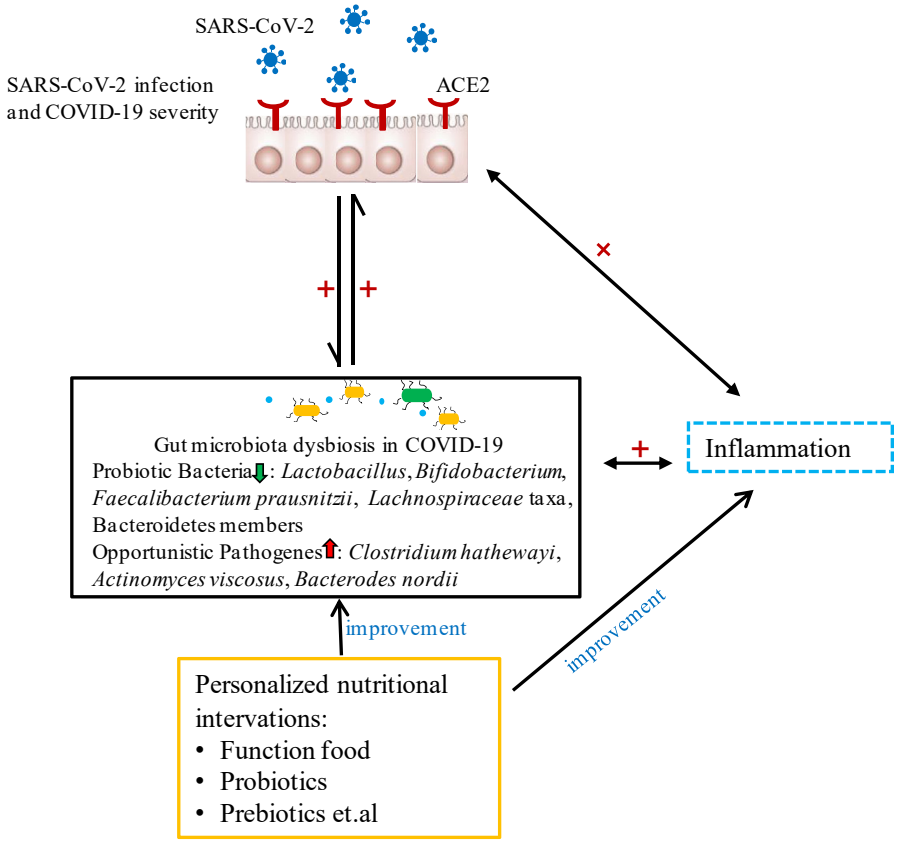

Figure 1. Personalized nutritional strategies for the prevention and treatment of SARS-CoV-2. Human with dysbiosis of gut microbiota is vulnerable to attack by SARS-CoV-2 thereby increasing the inflammation. In turn, COVID-19 infection changed the balance of gut microbiota and increased the inflammation. The opportunistic pathogens (*Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi*) were found in more abundance and correlation with COVID-19 severity. The anti-inflammatory bacterium of *Faecalibacterium prausnitzii* showed an inverse correlation. Four Bacteroidetes members could downregulate the expression of ACE2 and were decreased in COVID-19 patients. Personalized nutritional strategies could improve the gut dysbiosis and immune response in patients with SARS-CoV-2.

The rapid development of COVID-19 cases through out the world promotes the research of specific therapeutic drugs and vaccines. ACE2, as the receptor for SARS-CoV-2 entry cells, has raised the use of ACE inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) to potentially treat COVID-19 [41]. However, the benefits and risks have been discussed and studied during the past months, which showed that there was no association between ACEIs/ARBs exposure and a higher risk of SARS-CoV-2 infection [67, 68]. Among the range of therapeutic options in treating COVID-19 patients, modulating the intestinal microbiota suggested a potentially useful in combating COVID-19 or its associated symptoms [66, 69, 70]. The core gut microbial features and related metabolites provide a potential preventive/treatment target for regulating the susceptibility of SARS-CoV-2 infection. Probiotics or prebiotics may regulate the balance gut microbiota and exert beneficial immunomodulatory and direct antiviral effects. In recent years, probiotic strains have been considered as useful agents to prevent and reduce respiratory tracts infections [70, 71]. On the other hand, probiotics have been reported to produce peptides which possessed the inhibitory effect on the activity of ACE [72]. Therefore, the use of probiotics or prebiotics based on these data seems credible in the prevention and treatment of COVID-19.

Gut microbiota dysbiosis within SARS-CoV-2 infection altered permeability of gut barrier and subsequently influenced systemic inflammation, thus worsening outcomes. It is worth noting that the appearance of gastrointestinal impairments is earlier than the respiratory symptoms [15, 73]. Although the modulation mechanism of gut microbiota in the therapy of COVID-19 have yet to be fully elucidated, related research raised the possibility of maintaining gut homeostasis to be a new therapeutic option for COVID-19. In early February of 2020, National Health Commission of China published the "Diagnosis and Treatment Plan of Corona Virus Disease 2019 (Tentative Sixth Edition)" which suggested probiotics might be used to modulate/maintain the homeostasis intestinal microecology and prevent secondary bacterial infection (National Health Commission (NHC) of the PRC, 2020). Therefore, it is apparent that diet, especially probiotics, may prevent or accelerate recovery and improve clinical outcomes of patients affected with COVID-19. However, further studies are needed to investigate the regulation mechanism of gut microbiota on the intestinal inflammation in SARS-CoV-2 infected patients.

5. Conclusion

SARS-CoV-2 is a novel transmissible and the third highly pathogenic coronavirus. The function of ACE2 has attracted increasing attention toward the therapies, vaccine research and development of SARS-CoV and SARS-CoV-2. ACE2 also couples diet to modulate gut microbiota via regulation of intestinal amino acid transport and intestinal immunity. Given that patients with COVID-19 showed gut dysfunction or secondary gut dysfunction complications, modulating gut microbiota seems credible in altering the gastrointestinal symptoms favorably and reducing ventilator-associated pneumonia. Therefore, study of the interaction between the ACE2 and gut microbiota in the patients with SARS-CoV-2 infection may provide insights into the therapy of the virus.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data included in article/supp. material/referenced in article.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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