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Covid-19, Coronavirus, SARS-CoV-2 and the small bowel

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ABSTRACT

Although SARS-CoV-2 may primarily enter the cells of the lungs, the small bowel may also be an important entry or interaction site, as the enterocytes are rich in angiotensin converting enzyme (ACE)-2 receptors. The initial gastrointestinal symptoms that appear early during the course of Covid-19 support this hypothesis. Furthermore, SARS-CoV virions are preferentially released apically and not at the basement of the airway cells. Thus, in the setting of a productive infection of conducting airway epithelia, the apically released SARS-CoV may be removed by mucociliary clearance and gain access to the GI tract via a luminal exposure. In addition, post-mortem studies of mice infected by SARS-CoV have demonstrated diffuse damage to the GI tract, with the small bowel showing signs of enterocyte desquamation, edema, small vessel dilation and lymphocyte infiltration, as well as mesenteric nodes with severe hemorrhage and necrosis. Finally, the small bowel is rich in furin, a serine protease which can separate the S-spike of the coronavirus into two “pinchers” (S1 and 2). The separation of the S-spike into S1 and S2 is essential for the attachment of the virion to both

the ACE receptor and the cell membrane. In this special review, we describe the interaction of SARS-CoV-2 with the cell and enterocyte and its potential clinical implications.

Key words: SARS-CoV-2. Coronaviruses. Coronavirus. Colitis. Pellagra. Enterocyte. angiotensin converting enzyme.

INTRODUCTION

The coronaviruses (CoV) are a large family of enveloped, positive single-stranded RNA viruses that lead to respiratory, enteric and hepatic infectious diseases in animals and humans (1,2). From the mid-1960s onwards, only two human (H) CoV species were believed to infect humans; HCoV-229E and HCoV-OC43. In 2003, a novel member of the coronavirus family was identified that caused an aggressive lung disease with a high mortality, the SARS-CoV (3,4). Human coronaviruses NL63 and HCoV-HKU1 were subsequently described in 2004 and 2005, respectively and MERS appeared in 2013, which also induced an aggressive lung disease (2,5,6). In December 2019, the latest human Coronavirus SARS-CoV-2 appeared (7). In some series, traditional HCoV account for up to 30 % of influenza negative upper respiratory tract infections and up to 8.1 % of enteritis (5,6). Interestingly, the novel SARS-CoV-2 may result in gastrointestinal (GI) symptoms in up to one third of patients (7,8). Furthermore, SARS-CoV-2 may present primarily with GI complaints such as diarrhea, abdominal pain and hematochezia (9). In addition, Zhang et al. showed that SARS-CoV-2 is excreted in the feces, thus raising the possibility of fecal oral transmission (10). The authors collected specimens from the oropharynx, anus and serum in 39 patients infected with SARS-CoV-2. Of the 15 patients who recovered, they found RNA material from the virus in the stools in 26.7 % of patients (10). Until now, no viral cultures or experiments that fulfill Koch's postulates have been performed with viral material found in feces and thus no definitive conclusions can be made regarding the fecal-oral transmission route.

SARS-Cov-2 AND ANGIOTENSIN CONVERTING ENZYME 2 (ACE2) RECEPTORS

Whereas more research is underway to elucidate the transmission mechanism of SARS-CoV-2, there are also important aspects of the virus and the gastrointestinal tract that deserve close attention. This includes the interaction of SARS-CoV-2 with the small bowel, specifically with the angiotensin-converting enzyme 2 (ACE2) receptors located on the brush border of

enterocytes (11-13). Cells expressing ACE 2 receptors are found in the nose, oropharynx, bronchial tree, lungs, kidney and intestines, mainly the small bowel (11-16). ACE2 receptors act as negative regulators of the RAS-angiotensin system, counterbalancing the multiple functions of ACE, primarily metabolizing angiotensinogen II. The latter has deleterious effects on the cardiovascular, renal and respiratory systems leading to heart, lung and kidney pathologies, including chronic hypertension, pulmonary and renal failure (17). D ownregulation or blockage of ACE2 receptors and function by the SARS-CoV strongly contributes to the pathogenesis of severe lung failure and ARDS in SARS (11-17).

SARS-CoV-2 AND THE SMALL BOWEL

Although SARS-CoV-2 may primarily enter the cells of the lungs, the small bowel may also be an important entry or interaction site, as the enterocytes are rich in ACE2 receptors (11,12,16). First, the initial GI symptoms that occur early during the course of Covid-19 support this hypothesis (7-9). Second, SARS-CoV virions are preferentially released apically and not at the basement of the airway cells (18). Thus, in the setting of a productive infection of conducting airway epithelia, the apically released SARS-CoV may be removed by mucociliary clearance and gain access to the gastrointestinal tract via a luminal exposure (17,18). Third, post-mortem studies of mice infected by SARS-CoV have demonstrated diffuse damage to the GI tract, with the small bowel showing signs of enterocyte desquamation, edema, small vessel dilation and lymphocyte infiltration, as well as mesenteric nodes with severe hemorrhage and necrosis. Finally, the small bowel is rich in furin, a serine protease.

ENDOGENOUS HUMAN SERINE PROTEASES AND THE MECHANISM OF VIRAL ENTRY INTO THE CELL

Endogenous serine proteases such as furin and transmembrane serine protease (TMPRSS2) are essential to separate the S-spike of the virus so it can attach itself efficiently to the cell membrane. These serine proteases separate the S-spike of the coronavirus into two “pinchers” (S1 and 2). In fact, the separation of the S-spike into the S1 and S2 is essential for the attachment of the virion to both the ACE receptor and the cell membrane, as subsequently explained (19,20) (Fig. 1). An important misconception is that SARS-CoV-2 attaches only to ACE2. However, attachment to only this receptor would not enable the

virion to deliver the RNA into the cell, as attachment to *both* the ACE2 receptor (S1-part of spike) and the membrane (S2-part of spike) are necessary for a successful viral entry. Thus, human serine proteases are a key factor that change the configuration of the S-spike for a successful viral attachment.

SARS-CoV-2 BINDS WITH A HIGHER AFFINITY TO THE CELL

Recently, Wrapp et al. provided novel biophysical and structural evidence that the SARS-CoV-2 S protein binds angiotensin-converting enzyme 2 (ACE2) with 10-fold higher affinity than the previous SARS-CoV (20). Interestingly in SARS-CoV-2, the S-spike that is formed by the S1 and S2 segments and is more disordered than in SARS-CoV, having a solvent exposed loop (i. e. "crack") held by polybasic RRAR bonds in between S1 and S2. This "crack" facilitates the influx of human proteases, such as the serine proteases (transmembrane protease serine 2) TMPRSS2 and furin, which cleave this polybasic RRAR site at the junction of S1 and S2 (21) (Fig. 1). This cleavage results in a separation of both arms (i.e. "pinchers") of the S-spike. S1 contains the receptor-binding domain, which directly binds to the peptidase domain of ACE2. Whereas S2 is responsible for cell membrane fusion (19-21). As with TMPRSS, the enzyme furin may enable the S-spike to separate into two pinching structures. Interestingly, furin is a widely distributed enzyme in the small bowel and is a key enzyme in the process of activation of other enteric toxins from the following bacteria: *Clostridium difficile* exotoxin and Shiga, diphtheria and anthrax (22,23).

POTENTIAL IMPLICATIONS OF SARS-CoV-2 BINDING WITH THE ENTEROCYTE

In summary, SARS-Cov-2 attaches itself very effectively onto the cell with its "tweezer"-like S-spike onto two spots: a) the ACE2 receptor (using the S1 domain); and b) the outer cell membrane (using the S2 domain) (Fig. 1). After the tight attachment onto these structures, the virion is engulfed by the cell and the viral RNA enters the cytoplasm via endocytosis. In addition to further increasing viral endocytosis and subsequent replication, ACE2 blockage by a large SARS-CoV-2 viral load may further impair the hosts´ nutrition and abilities to mount a balanced immune response. In fact, various elegant studies have demonstrated that ACE2 also functions as the chaperone for the membrane bound amino acid transporter B^0 AT1 (12) (Fig. 1). B^0AT1 is essential for trafficking amino acids into the cells. When SARS-CoV-2 blocks ACE2, it also blocks B^0AT1, thus shutting down amino acid transport in the intestines

(12) (Fig. 1). Insight into the interaction of ACE2 and B^0AT1 started more than a decade ago, when collectrin (a type 1 transmembrane protein homologous to ACE2) was shown to regulate amino acid transport on the brush border membranes of the renal tubules via the non-covalent association with a neutral amino acid transporter B^0AT1 (26). This Hartnup amino acid transporter, B^0AT1, is also the major luminal sodium-dependent neutral amino acid transporter of both the small intestine and the proximal tubule of the kidneys (12,25). The B^0AT1 receptor is present in the small bowel brush border membrane, side-by-side with ACE2 receptors (12,26). Mutations in B^0AT1 lead to Hartnup disease, which is a defective uptake of amino acids through the kidneys and small intestine (24,26). Patients with Hartnup disease develop pellagra-like symptoms under stress conditions, such as a rash, cerebellar ataxia and diarrhea (11). ACE2 deficient mice do not express B^0AT1 in the small bowel and therefore exhibit a dramatically reduced level of tryptophan, which also leads to colitis (12,26). Hashimoto et al. has shown that colitis in ACE2 deficiency of the small bowel occurs due to tryptophan deficiency, leading to aberrant mTOR activation. This results in impaired expression of antimicrobial peptides from Paneth cells of the small bowel (26) (Fig. 1). A lack of these antimicrobial peptides leads to an abnormal composition of the gut microbiome. More importantly, their studies showed that these abnormalities and the colitis were rapidly restored by the administration tryptophan or nicotinamide (vitamin B3), the latter is the standard therapy for pellagra (26).

COULD SARS-Cov-2 ALSO INVOLVE THE GI TRACT IN HUMANS?

The likely answer is yes. First, there are clinical data showing a large number of GI symptoms in Covid-19 patients that support this notion (7-9,27). Up to 30 % of patients with pneumonia have diarrhea (27). In addition, gastrointestinal tract symptoms may be the sole manifestation of Covid-19 (9). Second, a recent case report demonstrated nonspecific colitis in a patient with Covid-19, which further underscores the need to elucidate the possible mechanisms of this colitis. This may be due to direct viral infection or due to a systemic response in Covid-19, such as hypotension and vasculitis (ischemia), or simply be due to this pellagra like state from the blockage of amino-acid transport and derangement of the microbiome (https://journals.lww.com/ajg/Documents/COVID19_Carvalho_et_al_AJG_Preproof.pdf).

Third, Wei et al recently showed that diarrhea was associated with a worse fever and

dyspnea in patients with Covid-19 (27). In addition, in this study of 82 SARS. CoV-2 patients with pneumonia, the presence of diarrhea was associated with decreased viral clearance. Thus, suggesting that GI tract involvement leads to a higher viral load and/or more prolonged viral shedding (https://www.cghjournal.org/article/S1542-3565(20)30526-7/pdf). Histologic data of the small bowel and colon of patients with SARS during the 2003 epidemic showed that small bowel villi were covered with SARS. However, the colon mucosa did not show significant damage, suggesting that the colitis may be toxic or nutritional (27) (Fig. 2). This has also been demonstrated in mice with a pellagra-like state (26).

THE SMALL BOWEL AS POTENTIAL SOURCE OF SYSTEMIC INFLAMMATORY RESPONSE

There is a potential interaction of SARS-CoV-2 with the enterocytic ACE2/B^0AT1 receptors, which can lead to a disruption of the gut microbiome. Furthermore, a massive inflammatory response (cytokine storm) may also have its origins or perpetuation in the small bowel. In fact, the small bowel has the largest mass of lymphoid tissue in the human body. The gut-associated lymphoid tissue consists of lymphoid elements such as Peyer's patches, submucosal lymphangiectasias, mesenteric lymph nodes and lymphatics within the submucosa. Furthermore, there is a dense population of various types of white blood cells such T cells, plasma cells, mast cells, dendritic cells and macrophages located primarily in the lamina propria but also within the crypts (28-30). Epithelial cells also act as microbial sensors by secreting factors such as IL-8, MCP-1, RANTES, TNF and IL-6 in response to microbial entry (28). This results in the recruitment of neutrophils, eosinophils, monocytes, phagocytic macrophages and T cells, which may also result in aberrant, uncontrolled responses such as the cytokine storm known to occur in SARS and Covid-19.

HOW DO WE PLACE THESE FINDINGS IN THE CONTEXT OF Covid-19?

We hypothesize that ACE2 receptors in the small bowel have an important function in the life cycle, pathogenicity and body damage of SARS-CoV-2 via several mechanisms:

1. ACE2 receptors of the enterocytes provide an entrance site for SARS-CoV-2, either primary or after the virus has circulated systemically, allowing it to re-enter the body ("re-entry" or "second hit hypothesis").

2. Partial or complete blockage of ACE2 by SARS-CoV-2 results in a malfunction of the amino acid transport of the gut, leading to a malnutrition, or a pellagra-like state. Furthermore,

patients with underlying malnourishment or a vitamin deficiency such as the elderly may be more susceptible to the detrimental ACE2 blockage effects of SARS-CoV-2.

3. Small bowel malfunction leads to colitis, inflammation and an altered gut microbiome. This inflammation results in increased intercellular spaces between the enterocytes, leading to increased intestinal permeability. Thus, allowing enhanced uptake of bacterial antigens and other toxins, further complicating the septic state of Covid-19 patients.

4. Small bowel lymphocytes, dendritic cells and macrophages may initiate or propagate the cytokine storm.

5. Small bowel and colon inflammation and the alteration of the gut microbiome ("altered inflammasome") lead to more systemic inflammation and an imbalance of the innate immune system of the gut.

POTENTIAL THERAPEUTIC IMPLICATIONS

The ACE2 receptors are used by SARS-CoV-2, therefore potential approaches would be to supply the host with additional ACE2 receptors. Thus leaving endogenous ACE2 receptors free for physiological functioning and providing the virus with "false" ACE2 receptors. This concept was proven in animal experiments and in early human trials. Therapy with recombinant ACE2 protein rescued the severe lung injury in ACE2 knock out mice (31). In a phase 2 study using recombinant ACE2, Khan et al. found that this therapy decreased angiotensinogen and interleukin-6 levels (32). Unfortunately, no further studies using recombinant ACE2 have been published. Another interesting clinical observation is that patients taking monoclonal antibodies such as Tocilizumab for rheumatism or adalimumab or infliximab for inflammatory bowel disease were not more frequently affected by SARS-CoV-2. In fact, most large studies of Covid-19 do not list these patients as victims of SARS-CoV-2, despite their theoretical immune suppressed status. We suspect that these monoclonal antibodies block the S-spike of the virus, decreasing its ability to bind to the ACE2 receptor and cell membrane. Hoffmann et al. recently demonstrated that inhibition of the TMPSSR (the serine protease responsible for the splitting of the S-spike) using camostat mesylate blocks the infection of cells by SARS-CoV-2 (21). In the meantime, it would be important to evaluate whether there is a tryptophan or B3 deficiency in Covid-19 patients. If so, rapid substitution of tryptophan or niacinamide could help to prevent or ameliorate the vicious circle of the malnutrition-inflammation-immunodeficiency cascade.

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CONCLUSION

SARS-CoV-2 uses the ACE2 receptor as its main attachment point to invade human cells. ACE2 receptors are present in various tissues including the oropharynx, nose, lungs, kidneys, pancreas and the small bowel. SARS-CoV-2 enters the cell by endocytosis. Endocytosis is only possible if the virus attaches itself to both the ACE2 receptor and the cell membrane. Attachment to the cell occurs via the viral S-spike. The S-spike must be separated into two parts, S-1 and S-2, for a successful cell attachment. This separation of the S-spike into "tweezers" occurs via the action of endogenous serine proteases such as furin and TMPRSS2. Furin is widely distributed in the small bowel and is used by other microorganisms for pathogenicity enhancement, such the activation of bacterial toxins and other viruses. Thus, the small bowel may serve as a viral entry site or as a potentiating organ, including magnification of the systemic inflammatory response, since the small bowel is the largest lymphoid organ of the body. A significant proportion of Covid-19 patients with gastrointestinal symptoms clearly support the involvement of the small bowel by SARS-Cov-2. The ACE2 receptor is closely bound and acting as chaperone, directly influences the transport of essential amino-acids via the enterocyte into the body. Thus, there may be nutritional colitis and a deregulated inflammatory response due to an abnormal inflammasome.

Thus, as gastroenterologists, we need to be aware of these important aspects and be vigilant when evaluating patients with gastrointestinal symptoms. We must look into the potential interactions of SARS-CoV-2 with the gut, to further expand our prophylactic and therapeutic armamentarium for Covid-19. Finally, a well-performed endoscopic inspection and appropriate biopsy specimens (including samples for electron microscopy) from the small bowel and colon in patients with Covid-19 may shed light on the pathogenesis of this novel respiratory-enteric coronavirus.

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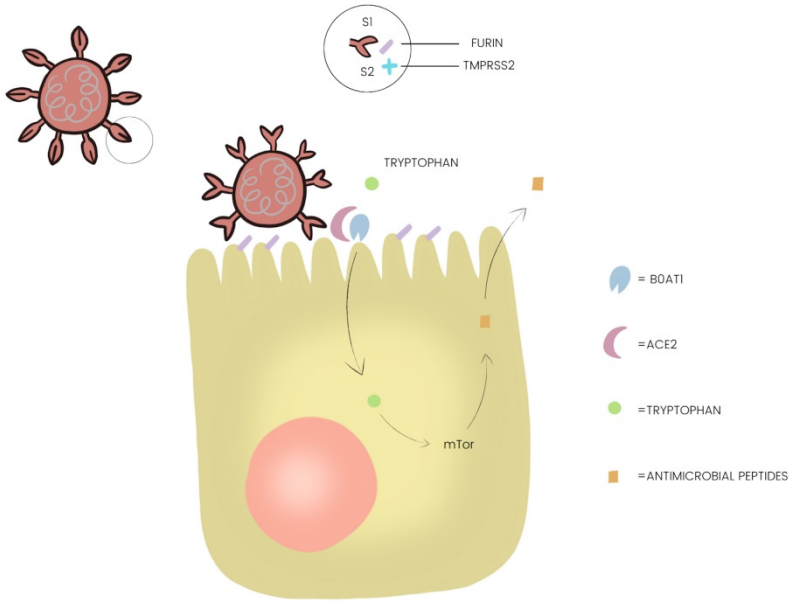

Fig. 1. The key attachment structures of the SARS-CoV-2 are the S-spikes, which form its "crown". The S-spike consists of two elements, S1 and S2. On its approach to the cell, the S-spike is held together by a polybasic bond. Various enzymes such as TMPRSS2 and furin enter into the space between S1 and S2 and separate it into a "claw-like" structure. This allows the virus to attach to both the ACE2 receptor with the S1 part and to the cell membrane with the S2 part of the S-spike. This dual attachment is essential to ensure effective viral endocytosis. Moreover, the ACE2 receptor lies side-by-side with the amino acid transporter B^0AT1, which is an essential transporter of amino acids into the enterocyte. In fact, ACE2 functions as a chaperone for this membrane bound amino acid transporter, B^0 AT1. Blockage of the ACE2 receptor results in a malfunction of amino acid transport, leading to tryptophan deficiency and a decreased production of antimicrobial peptides via the serine-threonine kinase mTOR pathway (mechanistic target of rapamycin). Various data support the occurrence of colitis as a result of tryptophan deficiency microbiome deregulation from a lack of antimicrobial peptides (figure drawn by Kirsten O. Tucker, USA).

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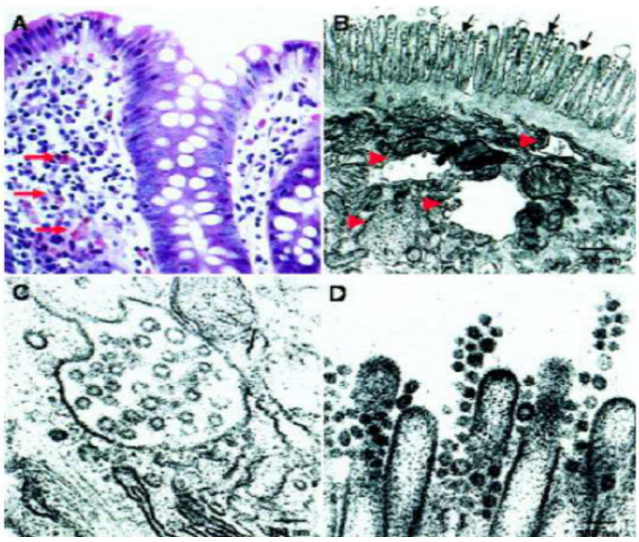

Fig. 2. Histologic and ultrastructural appearances of the colon in a patient with a SARS-CoV infection. A. Endoscopic colonic biopsy specimens with scattered lipofusin-ladened macrophages in the lamina propria, indicative of melanosis coli. The macrophages are indicated by the *red arrows* and there are no significant inflammatory cell infiltrates (H&E; original magnification 200×). B. Dilated cytoplasmic vesicles, which are consistent with a dilated endoplasmic reticulum, are seen toward the apical cytoplasm (indicated by *red arrowheads*) and some are filled with viral particles. A number of viral particles were also seen on the surface the microvilli (indicated by *black arrows*). C. Higher magnification of the virus-containing vesicles. The viral particles had a mild variation in size and ranged from 60 to 90 nm, which is consistent with the coronavirus morphology. D. Viral particles were found on the luminal surface of the enterocytes. Some viral particles appeared to attach onto the microvilli, whereas some appeared to be detached from the cell (from Leung et al. Gastroenterology 2003 1251011-1017DOI:10.1016/j.gastro.2003.08.001, Elsevier, with permission).