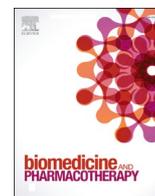




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Review

COVID-19 and inflammatory bowel disease: A pathophysiological assessment

Chunxiu Yang^{a,b}, Shu-Yuan Xiao^{a,b,c,*}

^a Department of Pathology, Zhongnan Hospital of Wuhan University, Wuhan, China

^b Wuhan University Center for Pathology and Molecular Diagnostics, Wuhan, China

^c Department of Pathology, University of Chicago Medicine, Chicago, IL, United States



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ABSTRACT

Coronavirus disease-2019 (COVID-19), caused by SARS-CoV-2, has led to the ongoing global pandemic. Although most patients experience no or only mild symptoms, some patients can develop severe illness, such as progressive pneumonia, acute respiratory distress syndrome, secondary hemophagocytic lymphohistiocytosis and multiple organ failure caused by cytokine release syndrome. A majority of COVID-19 patients also develop gastrointestinal symptoms. These can present special challenges to the management of patients with inflammatory bowel disease (IBD) due to potential interactions between the immune response related to SARS-CoV-2 infection and dysregulated immunity associated with IBD. In this context, the pathogenesis of COVID-19 is reviewed in order to address these questions regarding immune interactions between COVID-19 and IBD.

1. Introduction

Patients with unexplained pneumonia started to appear in December 2019 in Wuhan, China. Subsequently, the etiologic pathogen was identified to be a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Currently, coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has spread globally, with tens of thousands of deaths worldwide related to it. The main symptoms of COVID-19 patients include fever, fatigue, cough, myalgia and dyspnea. In addition, digestive symptoms have also manifested in many patients [1]. Some studies showed that 16 % cases presented with gastrointestinal (GI) symptoms only, with men slightly outnumbering women. The main GI symptoms included diarrhea, abdominal pain, loss of appetite, nausea and vomiting [2]. Therefore, it is important to further elucidate the pathogenesis of GI involvement by COVID-19 in patients with inflammatory bowel disease (IBD), a population with immune dysregulation and immune related therapies. The purpose of this review is to summarize current understanding of the GI involvement by COVID-19, immune dysregulation related to COVID-19 as well as in IBD pathogenesis, and to address the potential interaction between COVID-19 and IBD.

2. The characteristics of novel coronavirus

As of now, there are seven coronaviruses that can cause human diseases [3]. SARS-CoV-2 belongs to the β -coronavirus family with granules. Its origin is unknown. As an RNA virus, SARS-CoV-2 readily evolves through gene mutation and recombination, potentially facilitating its ability to cross barriers between species and resulting in wide spreading throughout the world [4]. The envelope of the virion contains three glycoproteins: namely the spike, membrane and envelope proteins [5]. The spike protein (S protein) is the receptor binding domain and the main antigen site (Fig. 1A), and is composed of two subunits. The S1 subunit is the receptor recognition site, and the S2 subunit promotes fusion between the viral envelope and host cell membrane [6,7]. This process depends on the interaction between the S protein, the angiotensin converting enzyme 2 (ACE2) receptor, and transmembrane protease serine type 2 (TMPRSS2). The cleavage of S protein, which regulates the viral entry into target cells, is itself regulated by TMPRSS2, a key enzyme in priming this process [6,8] (Fig. 1B). The structure of TMPRSS2 includes an extracellular domain, a membrane domain and an intracellular domain, of which the extracellular domain is the main catalytic domain [9].

The transmissibility and pathogenicity of novel coronavirus mainly depend on the affinity between the S protein and ACE2 receptor. It has

* Corresponding author at: Department of Pathology, Zhongnan Hospital of Wuhan University, Wuhan, China.

E-mail address: syxiao@whu.edu.cn (S.-Y. Xiao).

been shown that the affinity of SARS-CoV-2 to ACE2 is significantly higher than that of SARS-CoV [10]. Compared with SARS-CoV, the major differences in SARS-CoV-2 are three short insertions in the N-terminal domain [11]. A previous study has indicated that this insertion sequence may increase the efficiency of spike protein cleavage by protease TMPRSS2 [9]. Another bioinformatic study indicated that the genomic mutations of SARS-CoV-2 with methylation of the 5'-cap structure may affect the binding of spike protein to ACE2 and allow viral RNA to escape the recognition by the host's innate immune system [12].

3. GI involvement in COVID-19

3.1. Expression of ACE2 and TMPRSS2 in tissues

The entry of SARS-CoV-2 into target cells mainly depends on receptor recognition and protease cleavage. Therefore, the target cells should express both ACE2 and TMPRSS2. In addition to lung type 2 alveolar pneumocytes (AT2 cells) [6,13], ACE2 is widely expressed in other tissues (Fig. 2; data are from the Human Protein Atlas, <https://www.proteinatlas.org/>). ACE2 mRNA is found in the gastrointestinal tract, especially in the duodenum and other parts of the small intestine, and colon (Fig. 2A), and protein expression is more abundant in intestinal tissue than in other tissues (Fig. 2B). Some studies have found that ACE2 mRNA and protein expression in intestinal cell line were higher than those in lung [14], suggesting that the expression of ACE2 may be related to the gastrointestinal symptoms in patients with COVID-19.

Notably, since ACE2 and TMPRSS2 are co-localized in the host cell [8], the expression of TMPRSS2 mRNA is also higher in the gastrointestinal system, especially the small intestine, colon and stomach (Fig. 2C), with the corresponding protein expression increase (Fig. 2D). Intestinal ACE2 is involved in amino acid uptake and regulation of gut

microbiome homeostasis [15]. These findings provide evidence for gastrointestinal infection by SARS-CoV-2.

3.2. GI symptoms in COVID-19

As referred to in the Introduction, in addition to fever, cough, or dyspnea, some COVID-19 patients present with abdominal pain, diarrhea, nausea, vomiting and loss of appetite [2]. Laboratory examinations have shown leukopenia, lymphocytopenia, increased C-reactive protein (CRP) levels and serum transaminases. The characteristics of severe COVID-19 include acute respiratory distress syndrome (ARDS), lymphopenia, elevated CRP, pro-inflammatory cytokines, serum ferritin and D-dimer, in which lymphocytopenia correlates with clinical severity [16,17]. A case-control study from the US had shown that 35 % of patients had gastrointestinal symptoms, and patients with gastrointestinal symptoms were more likely to have an illness duration over one week, while most patients had an illness duration less than one week [18]. Other studies have shown that the incidence of diarrhea ranges from 2 % to 50 % [2,19–21] (overall 10.4 % [10]), and is higher in severe cases compared to mild cases [22]. A study from China in hospitalized patients with COVID-19 has shown a relationship between diarrhea and worsening of COVID-19 symptoms [18]. Patients with diarrhea were older and were more likely to have severe symptoms of pneumonia than patients without diarrhea, and patients with diarrhea required more ventilator support and needed admission to the intensive care units [20].

However, the pathogenesis of diarrhea in COVID-19 patients remains unknown, but it may be related to increased gastrointestinal mucosal permeability and poor absorption [8]. As well known, B⁰AT1 is a sodium-dependent neutral amino acid transporter and appears to be the major transport mechanism for tryptophan in enterocytes [23]. Expression of B⁰AT1 on intestinal epithelial cells depends on co-expression of ACE2 [24]. ACE2 functions as a chaperone for B⁰AT1 by

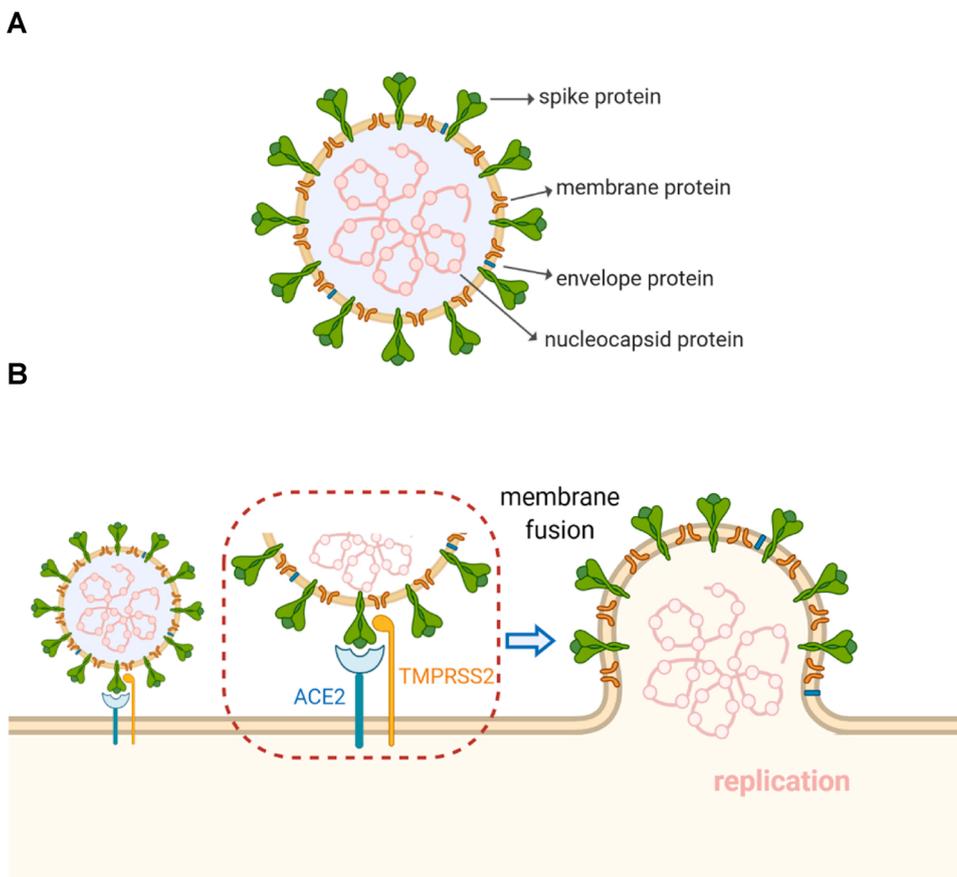


Fig. 1. The structure of SARS-CoV-2 (A) and the mechanism of SARS-CoV-2 entry into the target cell (B). (Diagram constructed using BioRender, <https://biorender.com/>).

A. The structure of SARS-CoV-2. The structural proteins of the virus include spike protein (S), membrane protein (M), envelope protein (E) and nucleocapsid protein (NP).

B. SARS-CoV-2 requires ACE2 and TMPRSS2 to enter the target cells. After the S protein binds to ACE2, cleavage of the S protein is regulated by TMPRSS2, and the fusion between viral envelope and host cell membrane occur to promote viral RNA entry into the target cells and replication.

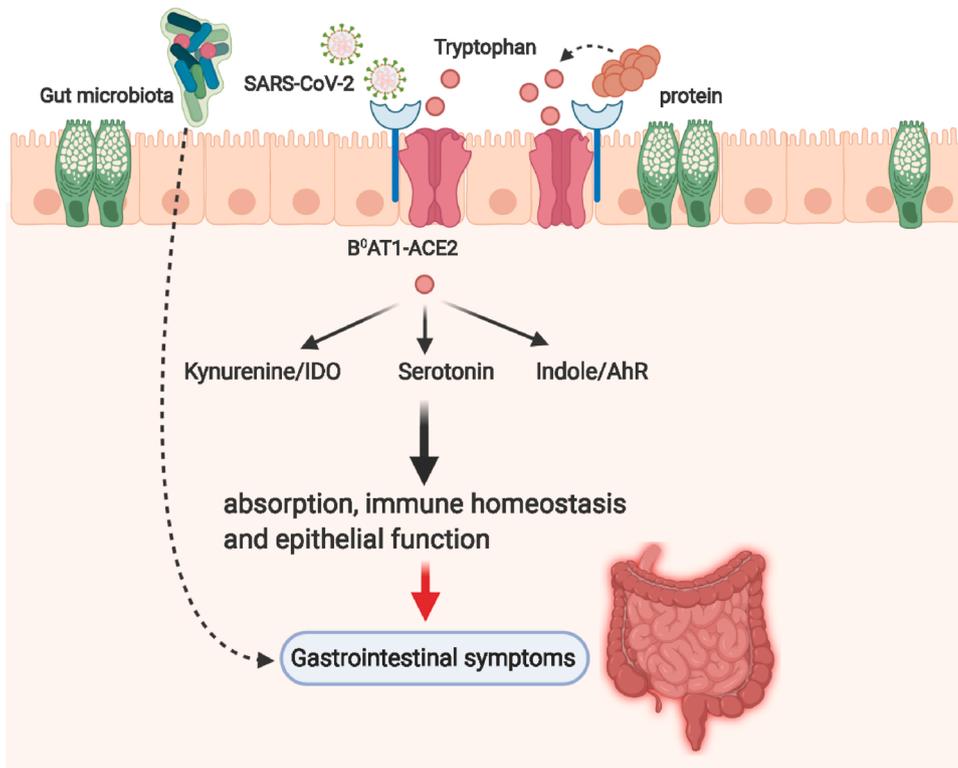


Fig. 3. Potential mechanism of GI symptoms in COVID-19. (Diagram constructed using Bio-Render, <https://biorender.com/>).

In the small intestine, ACE2 participates in protein digestion by cleaving the carboxy-terminal amino acids (AAs) from proteins or peptides and forming a complex with B⁰AT1 to mediate the absorption of tryptophan. Since the expression of ACE2 is upregulated with SARS-CoV-2 infection and ACE2 can affect the expression of B⁰AT1, SARS-CoV-2 infection may increase intestinal tryptophan metabolism. Meanwhile, virus infection can lead to gut microbiota imbalance. Together these factors may cause changes in intestinal permeability, leading to the GI symptoms seen in COVID-19 patients.

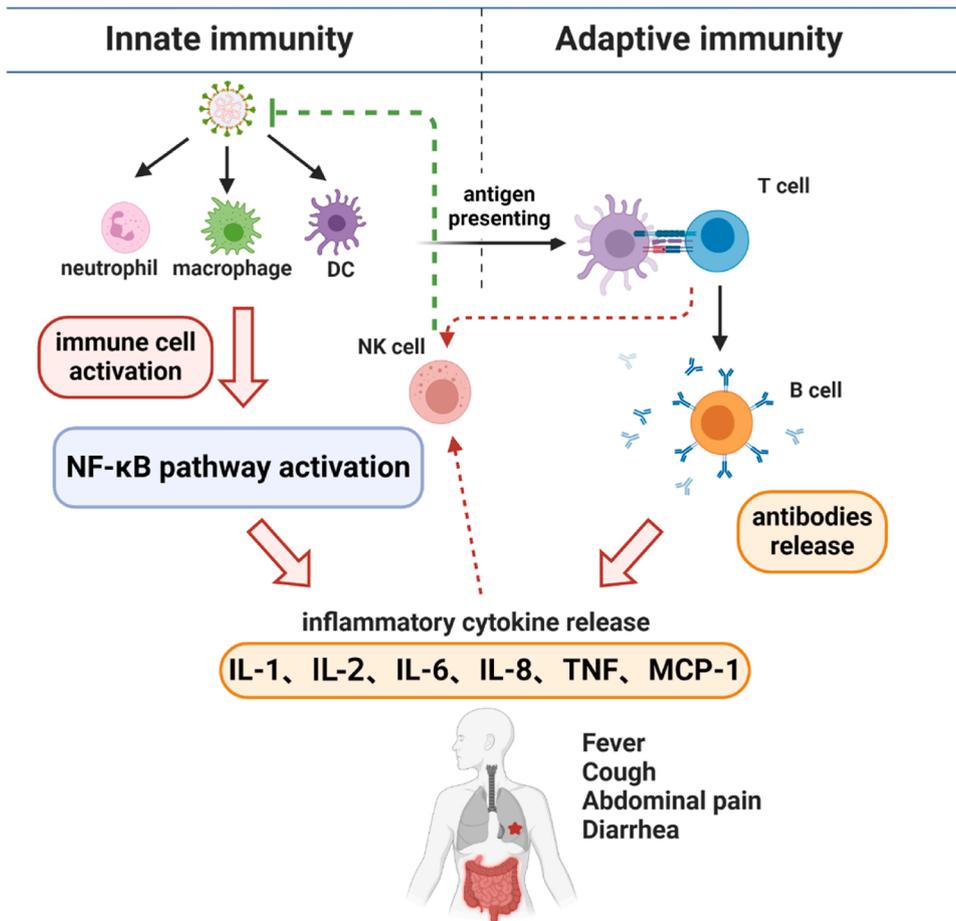


Fig. 4. Innate and adaptive immunity against novel coronavirus infection. (Diagram constructed using BioRender, <https://biorender.com/>).

The innate immune cells recognize the coronavirus and release a variety of inflammatory mediators and chemokines, leading to local accumulation of neutrophils in the infected area, with innate immunity is activated. Antigen-presenting cells (such as dendritic cells and macrophages) present viral antigen to T cell to activate adaptive immunity, leading to T cell activation and secretion of abundant pro-inflammatory cytokines. The activated T cells stimulate B cells to produce virus-specific antibodies. Moreover, activated T cells can release interferons (IFN) and activate natural killer cells (NK cells) to confer an anti-viral effect.

the gastric, duodenal and rectal glandular epithelial cell; viral RNA was also detected in feces of some COVID-19 patients even after negative conversion of the viral RNA in the respiratory tract [21], indicating a potential fecal-oral transmission.

3.3. Immune responses in COVID-19

Poor outcomes and mortality of COVID-19 are likely due to excessive inflammation and its corresponding tissue damage. Risk factors for poor outcomes include old age, male gender, and comorbidities such as obesity and chronic obstructive pulmonary disease [17,32,33]. The main causes of death include ARDS, cytokine release syndrome (CRS), CRS-induced macrophage activation syndrome (MAS), and secondary hemophagocytic histiocytosis (sHLH) [34–36]. CRS is characterized by elevated serum interleukin-6 (IL-6), tumor necrosis factor (TNF), IL-8 and IL-10 levels; in particular, the elevated IL-6 is related to ARDS, respiratory failure and poor outcome [31,37,38].

With high expression of ACE2 and TMPRSS2, the intestinal epithelial cells are the main target cells for the novel coronavirus in the GI tract. When the virus comes in contact with the intestinal epithelia cells, fusion between the viral envelope and host cell membrane occurs through the interaction of viral S protein and host cell ACE2 receptor and protease TMPRSS2. After viral entry and RNA replication in the target cells, a variety of inflammatory mediators and chemokines are released, leading to local accumulation of neutrophils in the infected area, with activation of innate immunity (Fig. 4). It has been reported that neutrophilia is a risk factor for the development of ARDS and progression to death in COVID-19 [39]. Meanwhile, the antigen-presenting cells (such as dendritic cells and macrophages) present viral antigens to CD4⁺T cell, leading to T cell activation and secretion of abundant

pro-inflammatory cytokines. The activated T cells also stimulate B cells to produce virus-specific antibodies. Moreover, activated T cells produce interferon (IFN) and activate natural killer cells (NK cells) to play an antiviral role (Fig. 4).

4. Immunomodulation in COVID-19 and inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disorder of the gastrointestinal tract. A study from Italy has shown that inflammatory bowel disease (IBD) affected the clinical outcome of COVID-19 infection. Active IBD, old age and comorbidities were associated with a worse COVID-19 outcome. Specifically, age over 65 years, active IBD and higher Charlson Comorbidity Index (CCI) score were all significantly associated with COVID-19-related death [40]. On another hand, a study of SARS-CoV-2 infection in 1918 adult patients with IBD has shown that the risk of COVID-19 associated mortality in IBD patients was lower than that of general population in the same region, and diarrhea was the only symptom at onset in some patients [41]. Therefore, the relationship between IBD and COVID-19 is complex.

The pathogenesis of IBD remains to be determined, but may be related to interactions among multiple pathogenic factors, including disease susceptibility gene variants, environmental stimulations, and abnormal gut microbial and immune factors [42], leading to dysregulated innate and adaptive immune responses. Multiple immune pathways have been shown to be dysregulated in IBD [42,43] (Fig. 5). IBD patients undergoing treatment with immunosuppressive drugs are often associated with malnutrition during the active phase, which makes them vulnerable to infection by SARS-CoV-2 [44]. Meanwhile, patients in the active phase of IBD may manifest fever, abdominal pain and diarrhea,

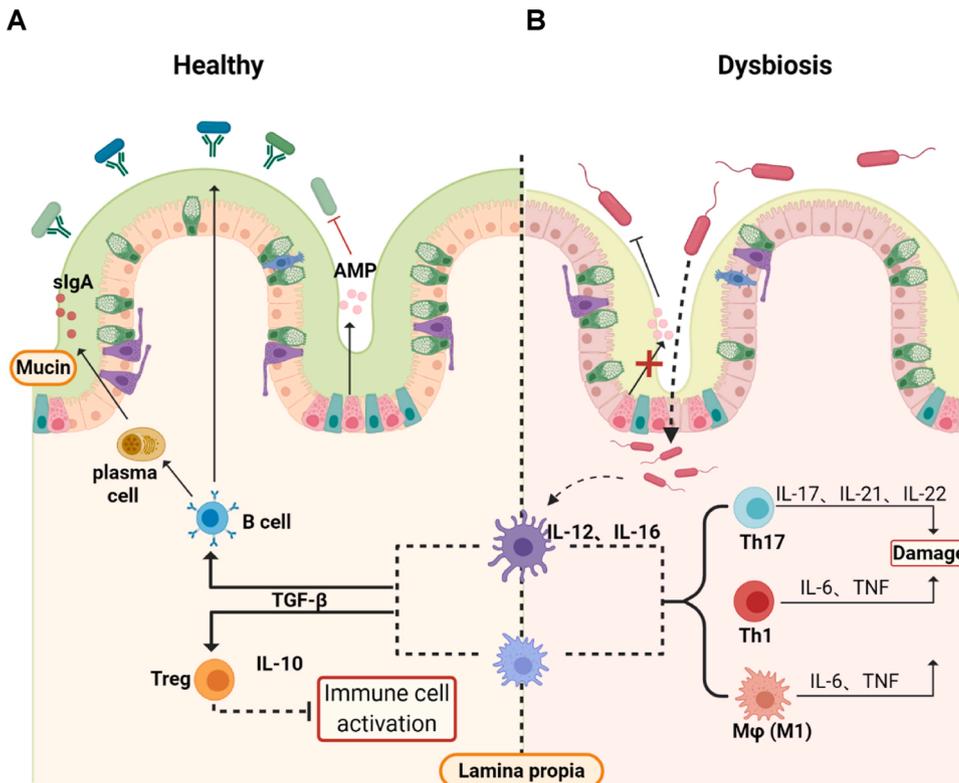


Fig. 5. Dysregulated immune response in inflammation bowel disease. (Diagram constructed using BioRender, <https://biorender.com/>).

A. In healthy states, the intestinal barrier consists of the mucosa including the surface mucus, epithelium and lamina propria, normal intestinal microbiota, secretory immunoglobulin, and intestinal associated lymphoid tissue. The intestinal mucus layer is secreted by goblet cells, which is an important barrier to separate intestinal tissue and immune system from the microbiota. Paneth cells secrete antimicrobial peptides (AMPs). Plasma cells produce and secrete protective sIgA. Microbe-related molecular patterns (MAMPs) induce epithelial cells to secrete cytokines and promote the development of tolerant DC and macrophages, the latter can regulate transforming growth factor β (TGF- β) and IL-10 secretion by Treg cells, and then inhibit the activation of immune cells to maintain intestinal immune homeostasis.

B. In the presence of intestinal microbiota disorders (such as decreased bacterial diversity, reduced number of protective microorganisms, and bacterial translocation), impaired intestinal epithelial integrity, decreased mucus secretion, disturbance of antimicrobial synthesis and secretion, and exogenous microbial infection, MAMPs stimulates DCs and macrophages to secrete pro-inflammatory cytokines (such as IL-6, IL-12 and IL-16), inducing T cells to differentiate into Th1 cells and Th17 cells. Th17 cells produce a variety of cytokines, including IL-21 and IL-22, promoting Th1 signaling activation, producing inflammatory cascade and persisting, and eventually leading to pathological changes in IBD.

which overlap with the GI symptoms of COVID-19, posing a diagnostic challenge clinically.

Since the intestinal barrier is damaged in patients with IBD, with mucosal architectural abnormalities, there is increased intestinal permeability, adhesion of intestinal microorganisms, activation of the mucosal immune system and production of pro-inflammatory cytokines. Therefore, when IBD patients are infected with SARS-CoV-2, the virus may enter the lamina propria through the damaged intestinal barrier and further aggravate the immune response, promoting increased release of inflammatory mediators, potentially resulting in CRS. T-helper 1 (Th1) effector cells promote the release of pro-inflammatory cytokines, such as IFN- γ and TNF- α , while the inhibition of Th2 cells reduces the production of anti-inflammatory cytokines is reduced, including IL-4 and IL-5 (Fig. 6). In IBD patients on immunosuppressive drugs, CRS is more likely to develop [45].

Cytokines expressed in IBD, such as IFN- γ , can potentially induce ACE2 expression [31]. Animal experiments have shown that blocking ACE2 expression can reduce the severity of colitis [31], although other studies have shown that ACE2 deficiency enhanced susceptibility to experimental colitis [15]. Since SARS-CoV-2 depends on ACE2 for its infection, inhibition of ACE2 may have effect on both COVID-19 and IBD. Given that the release of pro-inflammatory cytokines (such as TNF- α and IL-6) induces CRS in both IBD and COVID-19 patients, resulting in tissue damage and aggravated clinical manifestations, anti-cytokine therapies for IBD patients may have unintended effect on COVID-19. A recent case study [46] reported a male patient who was admitted to hospital for severe recurrence of UC had acquired SARS-CoV-2 infection. After treatment with infliximab, the patient's intestinal symptoms and pulmonary inflammation markedly improved, and two consecutive nasopharyngeal swab tests for SARS-CoV-2 were

negative. This suggests that anti-TNF- α agent may have a therapeutic effect for COVID-19 as well. Furthermore, since the release of IL-6 can trigger ARDS and lead to poor outcome, and intestinal macrophages in IBD patients also release abundant IL-6, agents such as Tocilizumab may have beneficial effects for both conditions. However, empirical evidence for their use is currently lacking [28].

Coinfections by other viruses are not uncommon in IBD patients, such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) [47]. The risk of EBV infection or reactivation increases in IBD patients after receiving immunosuppressive therapy for an extended period of time. Furthermore, infection with EBV increases the risk of developing lymphoproliferative disorders in the GI tract [48], as well as hemophagocytic lymphohistiocytosis (HLH) and EBV-associated mucocutaneous ulcers [49]. In patients with severe IBD, active EBV replication may aggravate histologic activity of the disease [50,51]. Similarly, superimposed CMV infection is common in IBD patients undergoing treatment, and may in turn exacerbate the severity and symptoms of IBD, with intensified inflammatory infiltration consisted of neutrophils, eosinophils and activated lymphocytes, in addition to plasma cells and small lymphocytes. The biological roles played by EBV and CMV in IBD patients are thus different from that played by COVID-19.

5. Management of IBD patients during COVID-19 outbreak in China

Many patients were using monotherapy with glucocorticoid, biologics or novel small molecule inhibitors to control intestinal inflammation. Although anti-TNF therapy can effectively relieve the inflammatory process in IBD, its side effects include infections (such as cytomegalovirus or reactivation of latent tuberculosis), injection site

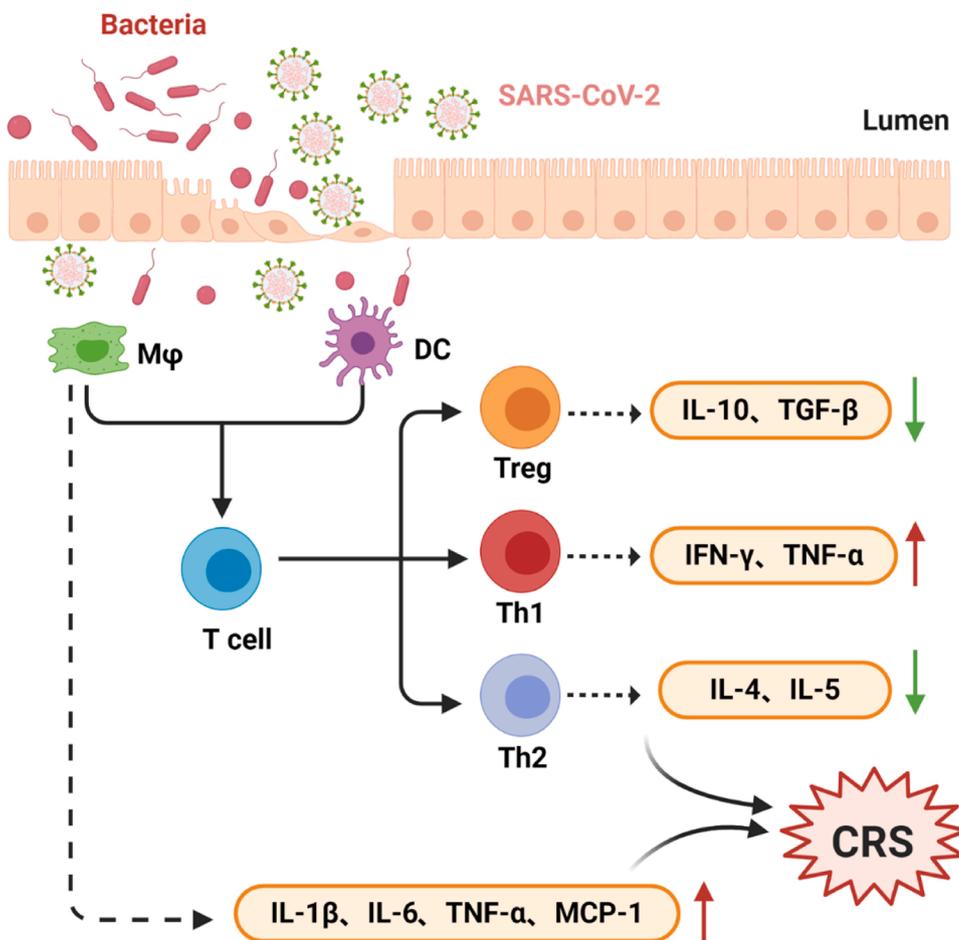


Fig. 6. Immune response in IBD patients with COVID-19. (Diagram constructed with BioRender, <https://biorender.com/>). The intestinal barrier is damaged in patients with IBD, resulting in increased intestinal permeability and adhesion of intestinal microorganisms, activation of mucosal immune system and production of pro-inflammatory cytokines. Subsequently, T cells differentiate into T-helper 1 (Th1) effector cells, which promote the release of pro-inflammatory cytokines, such as IFN- γ and TNF- α , while the inhibition of Th2 cells reduces the production of anti-inflammatory cytokines, including IL-4 and IL-5, making it more susceptible to SARS-Cov-2 infection.

reactions or other systemic side effects [52]; lymphoma may rarely occur. It should be noted that corticosteroid administration showed no effect on mortality but delayed the clearance of virus in both SARS and MERS patients. Therefore, the World Health Organization (WHO) recommended that routine corticosteroids should be avoided in IBD patients with COVID-19 [53]. Chloroquine is widely used for malaria and autoimmune diseases, and it has been reported that chloroquine can effectively inhibit SARS-CoV-2 infection *in vitro* [54]. However, the WHO stated that hydroxychloroquine had not been found to be effective in treating or preventing COVID-19, and had halted trials of hydroxychloroquine in the treatment of COVID-19 pneumonia due to safety concerns.

In the current COVID-19 outbreak, for IBD patients in the active phase of the disease, experts in China have recommended easy-to-digest food, and avoidance of alcohol, coffee and other cold drinks which may aggravate the clinical symptoms, in order to reduce intestinal burden. In addition, effort were made to reduce unnecessary endoscopic procedures and delay elective surgery as far as possible. It was also recommended that immunosuppressive drugs and biological agents be suspended in IBD patients with SARS-CoV-2 infection [44]. On another hand, drug delivery and telemedicine may be important measures for the management of IBD patients during such a pandemic, and mental health issues should be addressed during the follow-up of these patients during long period of lockdown or quarantine [55]. Regarding specific therapy, further evidence is needed in our understanding of the interactions between COVID-19 pathophysiology and altered immune status of IBD, in order to develop the best treatment strategy in IBD patients with COVID-19 infection.

Author contribution

Chunxiu Yang: outlining, literature search and writing.

Shu-Yuan Xiao: writing, editing, and final proof.

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Declaration of Competing Interest

There are no conflicts of interest to declare.

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