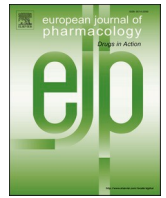




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Review



Gordian Knot: Gastrointestinal lesions caused by three highly pathogenic coronaviruses from SARS-CoV and MERS-CoV to SARS-CoV-2

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen of 2019 novel coronavirus disease (COVID-19), is currently spreading around the world. The WHO declared on January 31 that the outbreak of SARS-CoV-2 was a public health emergency. SARS-Cov-2 is a member of highly pathogenic coronavirus group that also consists of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Although respiratory tract lesions were regarded as main manifestation of SARS-Cov-2 infection, gastrointestinal lesions were also reported. Similarly, patients with SARS-CoV and MERS-CoV were also observed. Common gastrointestinal symptoms of patients mainly included diarrhea, vomiting and abdominal pain. Gastrointestinal lesions could be used as basis for early diagnosis of patients, and at the same time, controlling gastrointestinal lesions better facilitated to cut off the route of fecal-oral transmission. Hence, this review summarizes the characteristics and mechanism of gastrointestinal lesions caused by three highly pathogenic human coronavirus infections including SARS-CoV, MERS-CoV, as well as SARS-CoV-2. Furthermore, it is expected to gain experience from gastrointestinal lesions caused by SARS-CoV and MERS-CoV infections in order to be able to better relieve SARS-CoV-2 epidemic. Targeting gut microbiota to regulate the process of SARS-CoV-2 infection should be a concern. Especially, the application of nanotechnology may provide help for further controlling COVID-19.

1. Introduction

Coronavirus (CoV), with the largest genome of all known RNA viruses, is a positive-sense, single-stranded RNA (ssRNA) virus (Weiss and Navas-Martin, 2005). The term “coronavirus” is derived from the appearance of virus particles observed under electron microscopy. The sharp projections on viral membrane resemble king’s crown (Masters,

2006). About 50 years ago, CoVs in infected animals began to attract attention. On the one hand, several CoVs caused respiratory disease in animals such as dogs and chickens (Erles et al., 2003; Cavanagh, 2007; Biswas et al., 2016). On the other hand, human CoVs have begun to form pandemics many times around the world (Fig. 1).

Currently, various CoVs have been identified. In generally, they are divided into four genera according to phylogeny: alpha-CoV, beta-CoV,

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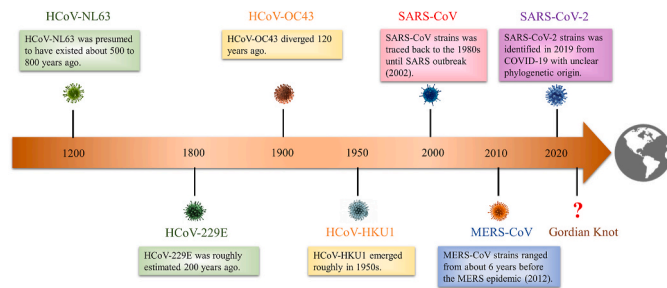


Fig. 1. The timeline of coronaviruses outbreak in human history. In human history, coronaviruses have formed seven major outbreaks worldwide. In terms of time, coronaviruses outbreak cycle is showing a shortening trend. The threat of coronavirus to humans needs to be relocated, and enough vigilance and attention should be given. This epidemic of SARS-CoV-2 has given us enough implications.

gamma-CoV and delta-CoV. Of particular concern is that alpha-CoV and beta-CoV are known to infect only mammals. Seven strains belonging to the alpha-CoV and beta-CoV usually cause respiratory and digestive illness in humans (Kin et al., 2015). The four strains (HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1) trigger only mild upper respiratory diseases in immunocompromised hosts (Forni et al., 2017). The other three highly pathogenic viruses, including the severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), induce respiratory and digestive diseases, and may lead to acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and even death in severe cases (Peiris et al., 2003a; Hui et al., 2018; Xu et al., 2020). The specific results are shown in Table 1.

Although respiratory symptoms are caused usually by CoVs, gastrointestinal symptoms are also reported. Common gastrointestinal symptoms include diarrhea, vomiting, and abdominal pain during course of the disease. In SARS patients, patients may be more prone to diarrhea symptoms during the first week of disease (Lee et al., 2003). In addition, gastrointestinal symptoms are also likely to occur in MERS patients (Arabi et al., 2014). Meanwhile, gastrointestinal symptoms of patients with SARS-CoV-2 infection seem to be more concerned. In the first patient in USA, the symptoms of nausea and vomiting (NV) appeared, and then diarrhea and abdominal discomfort also appeared (Holshue et al., 2020). NV are multifactorial and are regulated by the chemoreceptor trigger zone (CTZ). Through vagus nerve, emetogenic chemicals in gut or cerebrospinal fluid can stimulate CTZ and activate vomiting center (VC) (Anastasi and Capili, 2011; Törnblom and Abrahamsson, 2016). Also, some COVID-19 patients exhibited impaired brain function, such as anosmia and dysgeusia. Furthermore, Moriguchi et al. (2020)

confirmed the presence of SARS-CoV-2 in the COVID-19 patients' cerebrospinal fluid. Hence, presumably SARS-CoV-2 can infect brain, destroying CTZ and disrupting VC. Intestinal irritation can also induce NV through the gut-brain axis. Moreover, previous studies reported that CoV RNAs were detected in anal/rectal swabs and stool specimens from infected patients (Shi et al., 2005; Kipkorir et al., 2020). It can be speculated that gastrointestinal tract may be another target of CoV attacks after respiratory tract, and it may also become a large hiding place for viruses. Therefore, this review aims to elucidate the characteristics and mechanism of gastrointestinal lesions caused by SARS-CoV, MERS-CoV and SARS-CoV-2, and to explore new approaches for prevention and control, as well as treatment of COVID-19.

2. Overview of coronaviruses

The three highly pathogenic CoVs have similar genome structures (Fig. 2). Approximately two thirds of genome are occupied by two overlapping open reading frames (ORF1a and ORF1b), that could be translated into pp1a and pp1b polyproteins. Meanwhile, structural proteins (including spike, envelope, membrane, and nucleocapsid) are encoded by ORFs (Marra et al., 2003). Morphologically, the virion is mostly round, with a diameter of about 80–120 nm. Cell membrane is composed of at least three proteins, including spike glycoprotein, membrane protein, and envelope protein. Some CoVs also have hemagglutinin esterase (Suzuki et al., 2020). The virion contains a helical capsid formed by combining genome RNA and basic nucleocapsid protein (Fig. 3) (Bond et al., 1979). The particularity of structure is key to its ability to bind to host cell receptors and enter cell (Tortorici et al., 2019).

Human CoVs are zoonotic pathogens. About 70% of emerging pathogens that infect humans originate from animals. Most of them are deposited in animals and directly transmitted to humans. Specifically, almost all CoVs are thought to use bats as natural reservoir (Chan et al., 2013). Meanwhile, most of these highly pathogenic CoVs belong to RNA viruses characterized by higher mutation rates (Sola et al., 2015). These explain that CoVs could co-evolve with animal and human hosts, which may be reason why CoVs can break out in humans many times.

At present, SARS-CoV-2 infection has formed a pandemic worldwide. Recently, in term of phylogeny, clinical features and pathogenicity, SARS-CoV-2 showed partial similarities with SARS-CoV and MERS-CoV (Table 2). In genome structures, it has been widely elucidated that they have high homology, especially between SARS-CoV and SARS-CoV-2, suggesting that both two might have similar pathogenesis. The mean reproductive number (RO) of SARS-CoV-2 is estimated to be 2.71, which is higher than SARS (1.7–1.9) and MERS (<1), indicating that SARS-CoV-2 has a stronger ability to spread (Rahman et al., 2020; Wu et al., 2020b). This undoubtedly brings a huge test to global prevention and control of SARS-CoV-2. However, fortunately, the fatality rate of SARS-CoV-2 is estimated to be 3.8%, lower than SARS (9.6%) and MERS

Table 1
Comparison of clinical features of SARS-CoV-2, SARS-CoV and MERS-CoV.

	Classification	Original location	Epidemiology	Clinical symptoms	Incubation period	Total cases (global)	Total death (global)	Mortality	References
SARS-CoV-2	Beta-CoV	Wuhan, China	2019–2020 in China Globally thereafter	Fever, dry cough, dyspnea, myalgia, headache, diarrhea	3–6 days	18.4 million	697 thousand	3.8%	31986264
SARS-CoV	Beta-CoV	Guangdong, China	2002–2003 in China Globally thereafter	Fever, dry cough, dyspnea, myalgia, headache, diarrhea, malaise, respiratory distress	2–11 days	8096	774	9.6%	12734147
MERS-CoV	Beta-CoV	Jeddah, Saudi Arabia	2012 in Middle East 2015 in South Korea	Fever, cough, chills, sore throat, arthralgia, dyspnea, pneumonia, myalgia, diarrhea, vomiting	2–13 days	2519	866	34.3%	26049252

MERS-CoV, Middle East Respiratory Syndrome Coronavirus; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

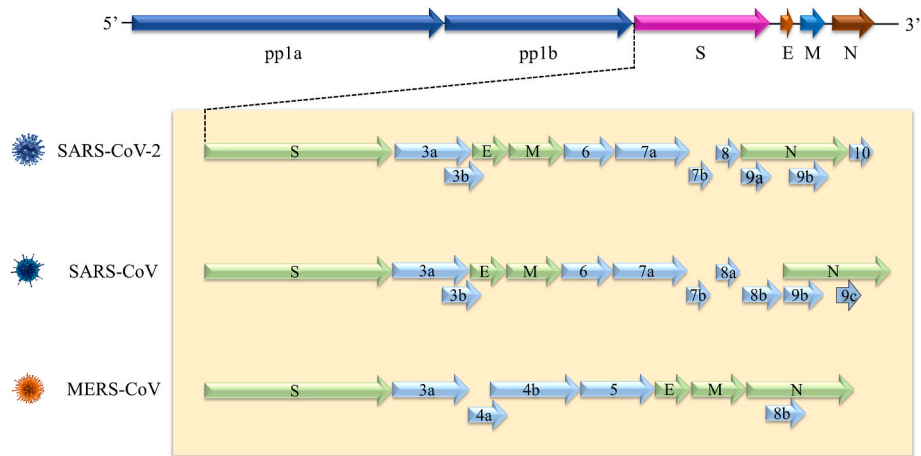


Fig. 2. 5' and 3' terminal sequences of SARS-CoV-2, SARS-CoV and MERS-CoV genomes. At the genomic level, the three coronaviruses have homology. SARS-CoV-2 and SARS-CoV have 82% structural similarity, however, it is 50% between SARS-CoV-2 and MERS-CoV. This suggests that experience can be gained from SARS-CoV and MERS-CoV outbreaks, which is very meaningful for better control of SARS-CoV-2 epidemic.

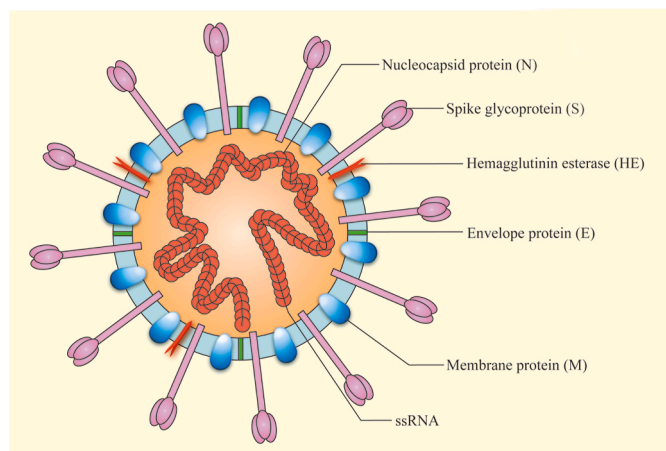


Fig. 3. The Schematic diagram of coronavirus virion structure. The virion is mostly round. The cell membrane is composed of several proteins, including spike (S) glycoprotein, the membrane (M) protein, envelope protein (E), and hemagglutinin esterase (HE). The genetic information is wrapped in the center.

(34.3%) (Table 1). It has been confirmed that individuals with SARS-CoV, MERS-CoV and SARS-CoV-2 may present obvious gastrointestinal lesions. Considering the similarities of the three coronaviruses, presumably measures against SARS-CoV and MERS-CoV could be used to control SARS-CoV-2, facilitating God to uncover Gordian knot and to close gate of epidemic.

3. Coronaviruses and gastrointestinal lesions

3.1. SARS-CoV and gastrointestinal lesions

SARS-CoV first broke out in China in November 2002, and soon spread throughout the world (Rota et al., 2003). According to WHO, SARS-CoV eventually infected 8096 individuals, of which 774 died, with case fatality ratio of 9.6% (WHO, 2003). SARS-CoV naturally resides in bats and infects humans through intermediate hosts, such as civets (He et al., 2004). Patients infected with SARS-CoV are characterized by lower respiratory tract disease, and may be accompanied by fever, headache and other symptoms (Peiris et al., 2003b). Gastrointestinal symptoms have also been observed in patients with SARS-CoV infections. In a retrospective analysis involving 138 SARS patients, 38.4% of patients developed diarrhea symptoms (Leung et al., 2003). By using monoclonal antibodies and probes specific for SARS-CoV, Ding et al. (2004) found that in addition to lungs and trachea, SARS-CoV also existed in stomach and small intestine. Electron microscopic observation also revealed that SARS-CoV particles were present in intestinal mucosa epithelial cells (Shi et al., 2005). This suggested that gastrointestinal tract may also be target of SARS-CoV attack. This also indicated that SARS-CoV can be transited through feces. Therefore, gastrointestinal symptoms may be common presenting symptom of SARS patients, which is of great significance to control viral transmission.

Using SARS-like pseudotyped lentiviruses, Simmons et al. (2004) confirmed that spike glycoproteins were a key structure for SARS-CoV to mediate infection of their target cells. A further research in mouse models revealed that spike glycoproteins could recognize the cell surface receptor, angiotensin-converting enzyme 2 (ACE2) (Kuba et al., 2005). It was worth noting that in addition to lungs, high expression of ACE2 was detected in gastrointestinal tract, suggesting gastrointestinal tract was a potential target for SARS-CoV (Hamming et al., 2004). After recognizing

Table 2
Phylogenetic, pathogenetic characteristics of SARS-CoV-2, SARS-CoV and MERS-CoV.

	Phylogenetic origin	Genome sequence homology to SARS-CoV-2	Animal reservoir	Intermediate host	Receptor	Disease	Route of transmission	References
SARS-CoV-2	Clade I, cluster IIa	-	Bats	Pangolin?	ACE2	COVID-19	Droplets, Contact	32075786
SARS-CoV	Clade I, cluster IIb	82%	Bats	Palm civets	ACE2	SARS	Droplets, Contact	12711465
MERS-CoV	Clade II	50%	Bats	Camels	DPP4	MERS	Contact	29680581

COVID-19, 2019 novel coronavirus disease; ACE2, Angiotensin-converting enzyme 2; DPP4, Dipeptidyl peptidase 4; MERS, Middle East Respiratory Syndrome; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; SARS, Severe Acute Respiratory Syndrome; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

ACE2, SARS-CoV interacted with transmembrane protease serine type 2 (TMPRSS2) to activate spike glycoproteins (Shulla et al., 2011). TMPRSS2, a member of type II transmembrane serine protease family, mediated the entry of SARS-CoV into targeted cells via facilitating virus-cell membrane fusion (Iwata-Yoshikawa et al., 2019). It can be concluded that spike/ACE2/TMPRSS2 was a key part of virus invading cells and spreading. In addition, spike glycoproteins can also bind dendritic cell specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGN). DC-SIGN was a C-type (calcium dependent) lectin highly expressed on dendritic cells (DCs), which can enhance virus invasion and promote virus dissemination (Yang et al., 2004; Gramberg et al., 2005). DC-SIGN was highly expressed in gastrointestinal tract (Geijtenbeek et al., 2000; Koning et al., 2015). Therefore, SARS-CoV can bind DCs, thereby promoting transfer of virus to susceptible cells. These further proved that SARS-CoV can directly attack gastrointestinal tissue and trigger gastrointestinal tract lesions.

Invading pathogens can activate cellular and humoral responses. Immune responses could lead to production of cytokines and chemokines, which in turn trigger inflammatory responses that attack pro-inflammatory cells (Perlman and Dandekar, 2005). The expression levels of cytokines and chemokines were abnormally expressed in serum of SARS-CoV-infected patients. Several studies have found that inflammatory cytokines (Interleukin (IL)-1, IL-6 and IL-12), chemokines (monocyte chemoattractant protein-1 (MCP-1) and interferon gamma-induced protein 10 (IP-10)) were significantly elevated (Wong et al., 2004; Zhang et al., 2004). The abnormal expression of these cytokines may explain inflammation and lesions of gastrointestinal tissues in SARS-CoV-infected patients. Furthermore, ACE2 was considered as a regulator of intestinal amino acid homeostasis and expression of antimicrobial peptides. It played a key role in intestinal inflammation (Hashimoto et al., 2012). Hence, in addition to directly invading targeted cells, SARS-CoV can also cause abnormalities in body's immune system, further aggravating gastrointestinal tract lesions.

3.2. MERS-CoV and gastrointestinal lesions

MERS-CoV is a zoonotic pathogen that was first isolated in Saudi Arabia (2012) (Zaki et al., 2012). As of Jan 2020, MERS-CoV eventually caused 2519 confirmed cases, including 866 deaths, with case fatality ratio of 34.3% (WHO, 2020a). The source of MERS-CoV received widespread attention. The natural reservoir of MERS-CoV was proved to be also bats (Lau et al., 2018). Yet, intermediate host was unclear. MERS-CoV strains isolated from humans were found to be highly consistent with those isolated from camels, suggesting MERS-CoV was most likely transmitted by camels to humans (Omrani et al., 2015). MERS-CoV-infected individuals had respiratory tract infection, including dry cough and sore throat (Memish et al., 2013a, 2013b). Gastrointestinal symptoms were also described as common symptoms in patients with MERS-CoV. One study showed that 35% of diagnosed patients had gastrointestinal symptoms (Assiri et al., 2013a). In a descriptive study, similar results were obtained. Of the 47 patients with MERS-CoV, 17% of patients had abdominal pain, 21% of patients had vomiting, and 26% of patients had diarrhea (Assiri et al., 2013b). At the same time, MERS-CoV can also be detected in stool samples of patients (Zhou et al., 2017), indicating it possessed a fecal-oral transmission ability.

Unlike SARS-CoV, MERS-CoV entered host cells by recognizing cell surface receptor dipeptidyl peptidase 4 (DPP4) (Raj et al., 2013). DPP4 was a serine exopeptidase, which can cut various substrates, enabling it to be engaged in multiple pathophysiological progresses (Enz et al., 2019). Mechanically, the attachment and fusion of virus and host cells were induced by the combination of MERS-CoV spike glycoproteins and β -propeller domain of DPP4 (Lu et al., 2013; Wang et al., 2013). Notably, a large amount of DPP4 expression was detected in intestinal epithelial tissue, suggesting gastrointestinal tract became a potential target of MERS-CoV (Nargis and Chakrabarti, 2018). MERS-CoV spike

glycoproteins can also recognize glycotopes in sialic acid whose function as an attachment factor to assist receptor DPP4 (Li et al., 2017). Moreover, spike glycoproteins were combined with some proteases (including TMPRSS2) of host cell to allow MERS-CoV to fuse with cell membrane, so that viral RNA was injected into cell to complete infection (Shirato et al., 2013; Millet and Whittaker, 2014; Earnest et al., 2017). The virus invasion induced by TMPRSS2 indicated that SARS-CoV and MERS-CoV have same infection mechanism, which provided approaches for clinical treatment.

There was increasing evidence that MERS-CoV infection often triggered high expression levels of inflammatory cytokines throughout body (Kindler et al., 2016). Meanwhile, cytokine storm could be induced by stimulation of a large number of cytokines, generating dramatic harmful consequences of inflammation responses (Clark and Vissel, 2017; Channappanavar and Perlman, 2017). The inflammation level of patients was positively correlated with degree of gastrointestinal lesions. Compared to healthy controls, Mahallawi et al. (2018) found pro-inflammatory cytokines (IFN- γ , TNF- α , IL-15 and IL-17) markedly increased in MERS-CoV patients. Furthermore, MERS-CoV infection was considered to promote Th17 cytokine production, thereby inducing expression of inflammation cytokines and chemokines (McGeachy et al., 2019). However, exact mechanism that MERS-CoV participates in gastrointestinal damage by regulating the expression levels of inflammatory cytokines remains to be further studied. Predictably, alleviating gastrointestinal symptoms by blocking abnormal release of inflammatory cytokines is an ideal choice for clinical treatment of MERS patients.

3.3. SARS-CoV-2 and gastrointestinal lesions

A previously unknown coronavirus, termed SARS-CoV-2, was firstly identified in December 2019 (Zhu et al., 2020; Wang et al., 2020a). It was known that SARS-CoV-2 was believed to be etiologic agent of atypical pneumonia (COVID-19) that caused globally nearly 18.4 million confirmed cases, including over 697,000 deaths, reported to WHO as of August 5, 2020 (WHO, 2020b). At the beginning of the outbreak, the source of SARS-CoV-2 received great attention. At whole-genome level, Zhou et al. (2020) found SARS-CoV-2 was 96% identical to a bat coronavirus, suggesting that natural reservoir was bats. Lam et al. (2020) tested pangolin samples and found that pangolin-associated coronaviruses were similar to SARS-CoV-2, indicating that pangolin may be intermediate host of SARS-CoV-2. COVID-19 patients showed typically fever and respiratory symptoms, nevertheless, some patients also presented with gastrointestinal manifestations, including diarrhea, vomiting and abdominal pain (Huang et al., 2020; Chen et al., 2020). Among 95 diagnosed patients, 24.2% had diarrhea, 17.9% had anorexia, and 17.9% had nausea (Lin et al., 2020). Furthermore, in a meta-analysis of involving 4243 patients with SARS-CoV-2 infection, 17.6% of patients had impaired gastrointestinal function, mainly in the form of anorexia, diarrhea and vomiting (Cheung et al., 2020). Notably, gastrointestinal symptoms of infected patients could appear early in disease course, indicating gastrointestinal symptoms can be first symptoms in some cases (Wang et al., 2020b; Song et al., 2020). Fascinatingly, Wan et al. (2020) indicated COVID-19 patients with gastrointestinal symptoms were susceptible to serious disease. Hence, it can provide a basis for predicting disease progression. Furthermore, gastrointestinal lesions caused by multiple drugs should also be taken seriously. Regrettably, there are no special drugs for COVID-19. However, excitingly, remdesivir and dexamethasone are confirmed to have therapeutic effects on COVID-19 to some extent (Wang et al., 2020c; News: Nature, 2020). Additionally, Gao et al. (2020) developed a purified inactivated SARS-CoV-2 virus vaccine candidate (PiCoVacc). The vaccine not only induced production of specific neutralizing antibodies, but also resisted attack of SARS-CoV-2. However, it will take some time for vaccine to be used clinically.

Through next-generation sequencing, it was found that SARS-CoV-2 was more similar to SARS-CoV (about 79%) than MERS-CoV (about

50%). The overlapping genome sequences between SARS-CoV and SARS-CoV-2 can encode and express spike glycoproteins that could bind to ACE2 to enter target cells (Lu et al., 2020). Meanwhile, ACE2 was also identified as a functional receptor for SARS-CoV-2 to invade gastrointestinal cells (Zhou et al., 2020; Wu et al., 2020a). After virus entered cell, TMPRSS2 cleaved hemagglutinin and then activated internalization of virus (Stopsack et al., 2020). TMPRSS4 also played a similar role. Hence, TMPRSS2 and TMPRSS4 were considered as crucial protease in SARS-CoV-2 intrusion and replication (Hoffmann et al., 2020; Matsuyama et al., 2020; Zang et al., 2020). Besides high expression of ACE2 receptors in gastrointestinal tissues (Garg et al., 2020), viral nucleocapsid protein was also detected in cytoplasm of gastric, duodenal and rectal epithelium (Xiao et al., 2020; Zhao et al., 2020; Lamers et al., 2020). TMPRSS2 was abundantly expressed in ileum and colon (Burguño et al., 2020). Increasingly, studies have shown that gut and lungs were somehow connected. In respiratory diseases, intestinal dysfunction was observed. Also, alterations in gut microbes affected lung function. For example, chronic obstructive pulmonary disease increased small intestinal permeability in patients (Sprooten et al., 2018). Moreover, when influenza struck, endogenous bifidobacterium from the gut could enhance host resistance to influenza (Zhang et al., 2020). This bi-directional communication network between the gut and the lung is called the “gut-lung axis”. Apparently, gut-lung axis existed in SARS-CoV-2 infection. After SARS-CoV-2 invaded the lung, host immune system was activated and inflammatory cytokines were released. Pulmonary permeability was increased with the release of inflammatory cytokines, which further led to viral invasion of the gut through the gut-lung axis, and vice versa (Ahlawat et al., 2020). In these processes, the intestinal flora acted as a “bridge”. Thus, regulating intestinal flora can improve intestinal lesions and even lung damage. However, another issue must be considered: whether excessive viral prophylaxis may disturb the patients’ flora balance and exacerbate gastrointestinal symptoms. For example, sodium hypochlorite is commonly used for daily disinfection. Hypochlorite, when dissolved in water, can form hypochlorous acid in the mucous membranes of the mouth and intestines. It is extremely unstable and rapidly breaks down into hydrochloric acid and free oxygen radicals, which in turn destroys cellular proteins, including gut microbes. Mild gastrointestinal reactions can occur in individuals after ingestion, including nausea, vomiting, and diarrhea (Slaughter et al., 2019). Thus, it is known that some disinfectants can disrupt intestinal microbial homeostasis and intestinal function through direct or indirect pathways. It is extremely important to use proper precautions against SARS-CoV-2.

The destruction of host immune function and formation of cytokine storm are considered to be crucial grounds for deterioration and even death of COVID-19 patients (Ye et al., 2020). Clinical observations found that in addition to typical symptoms of SARS-CoV-2 infection, some patients developed dramatical inflammatory responses. Inflammatory responses can be attributed to rapid viral replication, cellular damage and virus-induced ACE2 downregulation (Fu et al., 2020). Among them, rapid viral replication can promote cell death and activate immune cells, and then induce over-expressions of pro-inflammatory cytokines and chemokines (Cole and Ho, 2017). High expression levels of inflammatory cytokines have been detected in SARS-CoV-2 patients. Meanwhile, after infection with SARS-CoV-2, downregulation of ACE2 can facilitate expression of IL-6, which is main cytokine of cytokine storm. Granulocyte-macrophage colony-stimulating factor (GM-CSF) secreted by immune cells can activate inflammatory cells, thereby producing more cytokines, including IL-6 (Pedersen and Ho, 2020). When balance of pro-inflammatory and anti-inflammatory cytokines was broken, cytokine storm formed, triggering MOF eventually (Mehta et al., 2020). Severe patients with SARS-CoV-2 infection were observed to show cytokine storm that caused damage to organs throughout body, especially gastrointestinal tract. Therefore, blocking IL-6 signaling pathway to reduce occurrence of cytokine storm has a promising relief effect on COVID-19 patients’ gastrointestinal symptoms.

4. Apocalypse now from the past

At present, SARS-CoV-2 has posed a huge threat to the world. From brain to toes, most of body’s organs are targeted by CoVs (Fig. 4). In the largest autopsy results currently, virus particles are present in multiple organs, especially in gastrointestinal tract (Bian, 2020). It can be concluded that they could destroy gastrointestinal tract by directly infecting host cell or triggering body’s immune responses, thereby causing gastrointestinal symptoms. On the one hand, gastrointestinal symptoms can be regarded as the first symptom after SARS-CoV-2 infection. On the other hand, patients with gastrointestinal symptoms should also actively carry out symptomatic treatment in order to promote improvement of systemic symptoms and cut off fecal-oral transmission (Xie and Chen, 2020). Hence, it is necessary to gain experience in controlling gastrointestinal symptoms from SARS-CoV and MERS-CoV infections.

It should be noted, entire intestine should be considered as a steady state. Nevertheless, COVID-19 patients’ gastrointestinal conditions are not optimistic. Compared with healthy controls, COVID-19 patients’ opportunistic pathogens increased, and beneficial commensals decreased. At genus level, decreased levels of Clostridium and Bacteroides were observed in some COVID-19 patients. It was further found that Bacteroides dorei, Bacteroides thetaiotaomicron, Bacteroides massiliensis, and Bacteroides ovatus could downregulate expression level of ACE2, and was inversely correlated with SARS-CoV-2 load in fecal samples (Zuo et al., 2020; Yang et al., 2020). ACE2 downregulation increased abundance of opportunistic pathogens and gut dysbiosis via decreasing secretion of antimicrobial peptides (Dupont et al., 2014), which indicated that gut microbiota may affect SARS-CoV-2 ability to invade gastrointestinal tract. It is known that gut microbiota can participate in systemic health by regulating immune homeostasis (Meng et al., 2019). Consequently, it can be conjectured that gastrointestinal symptoms and imbalance of immune homeostasis triggered by SARS-CoV-2 can be partly mediated by gut microbiota. It could be a potential treatment strategy to relieve gastrointestinal symptoms via targeted regulation of intestinal species in COVID-19 patients.

Taking into account possible interactions between gut microbiota and SARS-CoV-2, dietary strategies to restore beneficial commensals have been gradually concerned, especially joint application of nanotechnology (Kalantar-Zadeh et al., 2020). In view of the similarity between size of SARS-CoV-2 and nanoparticles, nanotechnology can be used to design intelligent drugs that target problematic bacterial strains in gastrointestinal tract. Correspondingly, gut barriers against SARS-CoV could be enhanced and gastrointestinal symptoms could be relieved (Sportelli et al., 2020). Notably, nano-vaccines, with their unique advantages, have become a new option for treating SARS-CoV-2 (Fig. 5). Using nanotechnology to surface functionalization of nanoparticles, nano-vaccines can achieve strong immunogenicity (Nikaen et al., 2020; Nasrollahzadeh et al., 2020). Nanomaterials are versatile and can be used in all aspects of viruses. Nanomaterials for disinfection have also been explored. Metal nanoparticles, especially silver nanoparticles, can serve as an effective broad-spectrum antiviral agent (Rai et al., 2016). However, their antiviral activity is still to be explored in COVID-19. The rapid spread of viruses requires improved detection efficiency. The high surface and volume ratios of nanomaterials improves the sensor’s response, thereby increasing sensitivity. For example, specific probes functionalized with gold are able to form disulfide bonds with complementary RNA of the target virus. This can be used for rapid symptomatic and asymptomatic screening for COVID-19 (Li et al., 2020b). In addition to diagnostic screenings, nanomaterials can be used to design drugs. Virus-like particles (VLPs), a bionic nanoparticle that are commonly used for vaccine preparation, show considerable potential for application in COVID-19 (Pushko and Tretyakova, 2020). The VLP vaccine induces comprehensive humoral and cellular immunity. On the one hand, the VLP vaccine specifically recognizes B cell receptors and activates B cells. As a result, activated B cells further differentiate

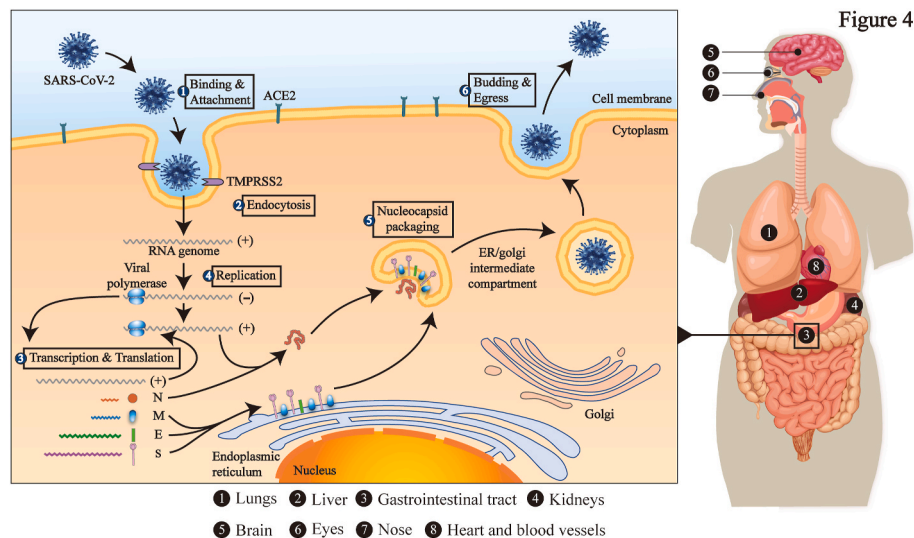


Fig. 4. The target organs attacked by SARS-CoV-2 and its infection mechanism. The whole-body organs of the human body may become the target of SARS-CoV-2 attack. Additionally, SARS-CoV-2 enters the target cell with the help of the ACE2 and TMPRSS2, and completes its own replication, eventually destroying the cell.

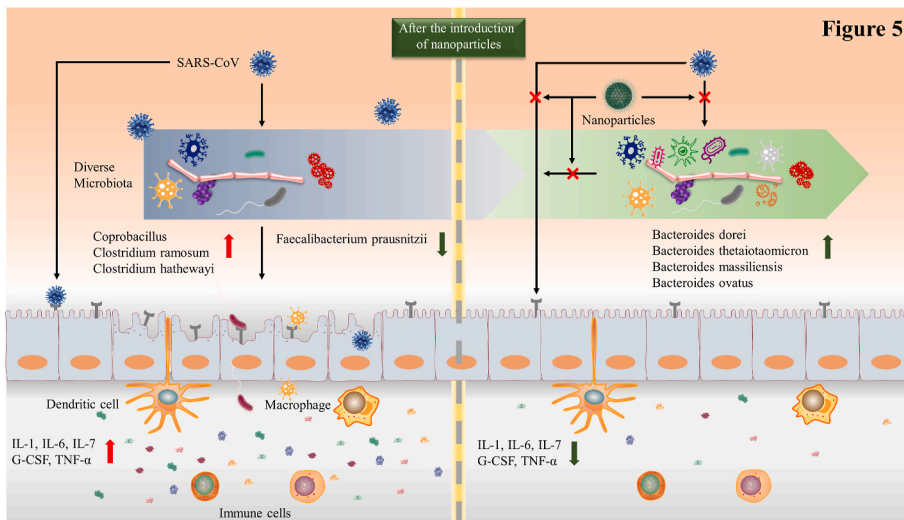


Fig. 5. Nanoparticles are used to strengthen the intestinal barrier against SARS-CoV-2 invasions. SARS-CoV-2 can interact with intestinal microbes, resulting in decreased microbial diversity. At the same time, intestinal microbes can regulate the expression level of ACE2 and affect the virus's ability to invade. Moreover, the expression levels of inflammatory cytokines also increase accordingly. However, targeted nanoparticles can block these pathways, and then restore intestinal microbial diversity, reduce inflammation levels, and improve intestinal barrier capabilities.

into plasma cells and produce antibodies, such as IgG and IgA (MacLennan et al., 2003). On the other hand, VLP vaccine promotes maturation of dendritic cells (DCs) and activates T cells subsequently, triggering cell-mediated immune response (Kwon et al., 2005). Antigen presentation and co-stimulatory molecules jointly induce DC maturation. In nano-vaccine, adjuvant acts as costimulatory molecules and viral proteins provides antigen. In another strategy, Wu et al. (2005) indicated that siRNA inhibited SARS-CoV replication in the Vero E6 cell line. Given the similarities between SARS-CoV and SARS-CoV-2, nanoparticles containing siRNA functional sequences could be hypothesized to be used for COVID-19. Thus, nanotechnology can mobilize the body's immunity in response to SARS-CoV-2 infections through multiple pathways.

However, conventional and subunit vaccines do not have these advantages. Vigilantly, secondary damages caused by nanoparticles have to be considered, including oxidative stress, genotoxicity and inflammation (Sivasankarapillai et al., 2020). These problems are still keys that should be resolved in present and future. Overall, nanoparticles can directly target SARS-CoV particles via immune system in gastrointestinal tract. Meanwhile, specific nanoparticles can interact with gut microbiota to relieve viral gastrointestinal damage. These applications

of nanotechnology may help us to prioritize to remodel homeostasis of gut microbes via targeting SARS-CoV-2 in order to reduce severity of gastrointestinal lesions.

5. Conclusions

The gastrointestinal lesions caused by three highly pathogenic coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) are clarified. SARS-CoV and SARS-CoV-2 not only exhibit similar clinical manifestations, but mechanism of infection of target cells, especially in gastrointestinal tissue. Currently, the application of the vaccine still takes a long time. Treatment strategies for SARS-CoV-2 infection considering gut microbiota has received great attention (Li et al., 2020a). The effects of SARS-CoV-2 on gastrointestinal tract could be mediated by gut microbiota, hence, it has become a potential treatment strategy for COVID-19 patients, whether to relieve gastrointestinal or systemic symptoms. It is worth mentioning application of nanotechnology targeting gut microbiota. However, it should still be warned that some drugs with therapeutic effects may become toxic after being metabolized by gut microbiota (Ke et al., 2020; Javdan et al., 2020). Therefore, patients with gastrointestinal lesions should be requested to be treated with

drugs that could both protect gastrointestinal functions. There are multiple important changes which need to be made so that God untie Gordian Knot and end the epidemic as soon as possible.

Declaration of competing interest

None.

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Abbreviations

COVID-19	2019 novel coronavirus disease
ARDS	Acute respiratory distress syndrome
ACE2	Angiotensin-converting enzyme 2
CoV	Coronavirus
DCs	Dendritic cells
DC-SIGN	Dendritic cell specific intercellular adhesion molecule-3 grabbing non-integrin
DPP4	Dipeptidyl peptidase 4
E	Envelope protein
HE	Hemagglutinin esterase
IP-10	Interferon gamma-induced protein 10
IL-1	Interleukin
GM-CSF	Granulocyte-macrophage colony-stimulating factor
M	Membrane protein
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MCP-1	Monocyte chemoattractant protein-1
MHV	Mouse hepatitis virus
MOF	Multiple organ failure
N	Nucleocapsid protein
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
ssRNA	Single-stranded RNA
S	Spike glycoprotein
TMPRSS2	Transmembrane protease serine type 2

Author statement

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