Minireview *Highlight article*

Pathology and pathogenicity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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Impact statement

The current survey of studies outlines the direct and indirect effects of SARS-CoV-2 on the specific body systems and summarizes the SARS-CoV-2 main pathogenicity mechanisms that require attention during patient hospitalization and for further research.

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a beta coronavirus that causes infectious respiratory disease, named as coronavirus disease of 2019 (COVID-19). While extensive studies have provided basic information on clinical characteristics of COVID-19, the disease pathology is not fully known. The SARS-CoV-2 virus structural studies and biochemical experiments have also indicated that the virus receptor-binding domain (RBD) binds with a high affinity to angiotensin-converting enzyme-2 (ACE-2) receptor from humans; however, the mechanism remains unclear. Hereunder, a summary of relevant findings in the SARS-CoV-2 virus pathology and major pathogenicity mechanisms are discussed. This review of studies provides additional enlightenments on the way forward to prevent further spread or even cure for the SARS-CoV-2 virus-caused COVID-19 disease, either-or should a similar viral plague occur in the future.

Keywords: SARS-CoV-2, Coronavirus, COVID-19, pathology, pathogenicity

***Experimental Biology and Medicine* 2020; 245: 1299–1307. DOI: 10.1177/1535370220942126**

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan city of China's Hubei Province in December 2019 and was then characterized as a pandemic in March 2020.[1] The genomic characterization of SARS-CoV-2 shares 79.5% of the genetic sequence of the SARS-CoV coronavirus that caused the 2002–2003 epidemic.[2,3] All coronaviruses that have caused diseases to humans (SARS-CoV, MERS-CoV, HKU1, HCoV-NL63, HCoV-OC43, and HCoV-229E) have had spillover from animals[4]; however, there is no evidence to support such a zoonotic theory for the origin of SARS-CoV-2 to-date. Of note, in addition to these viruses, studies indicate that other several known coronaviruses are circulating in animals that have not yet spillover to infect humans.[5,6]

These coronaviruses, named for the crown-like protein spikes on their surface, belong to a family of positive-sense, single-stranded RNA viruses called Coronaviridae.[7,8] Coronaviridae are infectious viruses known to cause illnesses ranging from mild respiratory symptoms, even asymptomatic in immunocompetent cases, to more severe diseases such as the SARS-CoV-2 virus-caused 2019 novel coronavirus disease (abbreviated as COVID-19). The SARS-CoV-2 virus is an emerging respiratory beta coronavirus, like SARS-CoV (China, 2002) and MERS-CoV (Saudi Arabia, 2012).[9] The SARS-CoV-2 virus-caused COVID-19 disease, with droplets and close contact as the main modes of transmission,[10] is clinically characterized with the patient flu-like symptoms including fever, cough, and shortness of breath during the first 2 to 14 days of the viral incubation period.[11] As the COVID-19 disease advances, hypoxic respiratory failure and even death are notable in older adults and people of any age who have severe underlying medical conditions such as chronic lung disease and diabetes.[12–15] Noteworthy, some COVID-19 cases have also been observed to remain asymptomatic while they are likely contagious.[16,17]

Although extensive studies have provided basic information on clinical characteristics of COVID-19 disease, many relevant features of the pathogenicity mechanisms of the disease-causing SARS-CoV-2 virus are not fully known. This review of studies provides enlightenment on the SARS-CoV-2 virus pathology in reference to published literature findings on the effects of the virus in different human body systems. Moreover, this survey summarizes the SARS-CoV-2 virus major pathogenicity mechanisms that may play a role in the way forward to prevent further spread or even cure for the SARS-CoV-2 virus-caused COVID-19 disease, either-or should a similar viral plague occur in the future.

Pathology

The pathological lesions of SARS-CoV-2 in the body systems of COVID-19 cases are not fully known. The preliminary data acquired from the studies on clinical characteristics of COVID-19 suggest that the effect of the SARS-CoV-2 is not confined to the respiratory tract, rather may also invade multi-body systems that warrant a need for multidisciplinary attention on the way forward to compact the pandemic. This section of the study summarizes the human body system pathological features (Table 1) and results of examination procedures (Table 2) used to confirm the diagnosis for the SARS-CoV-2 virus-caused COVID-19 disease that have been reported incompletely.

Respiratory system

Several studies have reported that the SARS-CoV-2 virus infection causes a highly proportionate debilitation and pneumonia to those seen in SARS-CoV and MERS-CoV infections.[52,53] This pathological lesion is particularly notable in older adults and people of any age with underlying medical conditions such as lung disease (asthma, chronic obstructive pulmonary disease, etc.). The COVID-19 clinical symptoms including fever, cough, and myalgias often resemble more of influenza than that of the common cold. Radiographic abnormalities on COVID-19 cases chest computed tomography (CT) scan are featured by bilateral pulmonary parenchymal ground-glass opacity with pulmonary consolidation in a bilateral diffuse distribution, sometimes with a rounded morphology in a peripheral lung distribution.[54] Consistent with the pathology of SARS-CoV and MERS infections,[52,53] histopathological studies in the lungs of patients who died from SARS-CoV-2 infection demonstrated damages of pneumocytes with hyaline membrane formation, interstitial lymphocyte infiltration, and multinucleated syncytial cells.[18,19] Additionally, congestion of alveolar septal vessels with alveolar edema, infiltration of monocytes and lymphocytes in alveolar cavity and micro-thrombosis, alveolar exudate organization, pulmonary interstitial fibrosis, desquamation of mucosal epithelium, and mucus concealed bronchi have also been reported as prominent features of COVID-19.[20,55] However, the pathogenicity mechanism of the SARS-CoV-2 to induce COVID-19 pneumonia and the pulmonary limitations in COVID-19 cases after their recovery from pneumonia remains to be determined.

Cardiovascular system

The SARS-CoV-2 infection-associated cardiovascular dysfunction in COVID-19 patients has been reported by several lines of clinical studies.[11,21–25] The findings of these studies suggest the causality of the SARS-CoV-2 to the myocardium and blood vessels injury as the highest risk of mortality in COVID-19 patients, next to pulmonary injury. Analysis of SARS-CoV-2 infection-associated death cases, including an observational study of 52 COVID-19 patients whereby 19 (36.5%) of them showed acute myocardial injury,[25] substantiate cardiovascular dysfunction as one of the major medical conditions in SARS-CoV-2 pathology. Moreover, other clinical studies have also reported coagulation aberrations in severe and critical COVID-19 patients[11,21,24] that may lead to deep vein thrombosis and disseminated intravascular coagulation. However, whether the cardiac injury in COVID-19 patients is the direct or indirect pathogenic consequence of the SARS-CoV-2 infection remains largely unclear.

Immune system

In general, the entire human population remains susceptible to a novel virus and therefore lacks immunity to SARS-CoV-2. Only after the virus enters the host, the innate immune system of the host recognizes the virus through activation of pattern recognition receptors (PRRs) including the Toll-like receptor,[56] nucleotide-binding oligomerization domain-like receptor,[57] and retinoic acid-inducible gene-I-like receptor.[58] The activation of the PRRs initiates a signaling cascade that induces the expression of type I interferons and other inflammatory cytokines to limit viral replication through different pathways. A delay in the expression of type I interferons has been reported to cause a loss to prevent viral replication and subsequently lead inflammatory cytokine storm in older adults and in aged experimental mouse models.[59,60] Although yet unknown, it is plausible that SARS-CoV-2 follows similar escape mechanisms. Upon the virus entry, ordinarily, the host immune response recognizes and presents the virus to $CD4^+$-T-helper cells, which subsequently stimulate the $CD8^+$-T-killer cells and the B-cells to target any virally infected cells and to produce the virus-specific antibodies, respectively. However, it seems that the SARS-CoV-2 compromises the host immune system leading to lymphopenia, a significant reduction of lymphocytes, and exacerbated inflammation with a yet unknown etiology.

Digestive system

Gastrointestinal symptoms among COVID-19 patients has been reported by several cohort clinical studies.[11,12,15,21,24,25,27,60–65] These studies detailed that COVID-19 gastrointestinal symptoms mainly include loss of appetite, nausea, vomiting, diarrhea, and abdominal discomfort. These gastrointestinal symptoms of COVID-19 were also common in SARS-CoV-1[66] and MERS-CoV[67]-infected patients but with more frequency than in SARS-CoV-2-infected COVID-19 patients, presumably due to the differences among the coronaviruses tropism to the

Table 1. Pathological features of the SARS-CoV-2 virus in the body systems of COVID-19 cases.

Body system	Pathological features	References
Respiratory	A damage of pneumocytes with hyaline membrane formation, interstitial lymphocyte infiltration, and multinucleated syncytial cells in the lungs.	18–20
Cardiovascular	Myocardial and blood vessels injury.	11,21–25
Immune	Lymphopenia and exacerbated inflammation.	12,24,26
Digestive	Fecal sample positive for SARS-CoV-2 RNA.	27–29
Urinary	Proteinuria, elevated levels of serum creatinine and blood urea nitrogen, tubular necrosis, luminal brush border sloughing, and vacuole degeneration.	30–33
Reproductive	Decreased serum testosterone to luteinizing hormone ratio in male patients.	34
Skeletal	Joint problems such as arthritis.	35
Integumentary	Ischemic changes in the fingers and toes.	36
Nervous	Viral encephalitis, acute toxic encephalitis, and acute cerebrovascular disease.	20,37–41
Other	Abnormal levels of alanine aminotransferase and aspartate aminotransferase in serum bilirubin.	12,25,42,43

Table 2. Examination procedures used to confirm SARS-CoV-2 virus infection.

Test	Positive test characteristics	References
RT-PCR	Detecting the SARS-CoV-2 virus unique sequences of RNA in sputum, throat swabs, and/or secretions of the lower respiratory tract samples.	44,45
Ab	Detecting IgM, IgA, IgG, or total antibodies against SARS-CoV-2 via serology.	44,45
ELISA	Detecting IgM and IgG antibodies based on recombinant SARS-CoV-2 nucleocapsid protein and spike protein via serology.	46
IHC	A damage of pneumocytes with hyaline membrane formation, interstitial lymphocyte infiltration, and multinucleated syncytial cells in the lungs.	18,19
CXR	Shows multiple small patchy shadows and interstitial changes in the lung periphery that gradually spread to the bronchi and then the whole lung with infrequent interlobar pleural thickening and pleural effusion.	47
CT Scan	Presentation of bilateral pulmonary parenchymal ground-glass opacity with pulmonary consolidation in a bilateral diffuse distribution, sometimes with a rounded morphology in a peripheral lung distribution.	21,48,49
FDG-PET Scan	Detect lung lesions characterized by increased FDG uptake in lymph node.	50,51

RT-PCR: reverse transcriptase-polymerase chain reaction; Ab: antibody; ELISA: enzyme-linked immunosorbent assay; IHC: immunohistochemistry; CXR: chest X-ray; CT: computed tomography; FDG-PET: fluorodeoxyglucose-positron emission tomography.

gastrointestinal tract. Remarkably, a reverse transcriptase-polymerase chain reaction (RT-PCR) diagnostic test has revealed the presence of the SARS-CoV-2 RNA in the stool of confirmed COVID-19 patients,[27–29] which sensitizes a new possibility of the fecal-oral route of SARS-CoV-2 transmission. Moreover, this presence of SARS-CoV-2 in the COVID-19 cases stool enlightens a need for considering rectal swab RT-PCR diagnostic test alongside the nasopharyngeal swab test to confirm the diagnosis of COVID-19 and before discharging hospitalized COVID-19 patients. There are several hypotheses on SARS-CoV-2 infection-induced gastrointestinal symptoms including the possible SARS-CoV-2 interaction with the angiotensin-converting enzyme-2 (ACE-2) receptor found in the human gastrointestinal tract (discussed in the next section), but the exact pathogenicity mechanism needs yet to be investigated.

Urinary system

Clinical studies of severe COVID-19 patients have shown evidence on the possible implications of SARS-CoV-2 infection that may induce urinary complications, including acute kidney impairment.[11,21,24,30–33] These studies indicated that proteinuria, and elevated levels of serum creatinine and blood urea nitrogen, suggesting renal injury, have been observed in severe COVID-19 patients. Moreover, another report of histopathological examination on autopsy kidney from deceased COVID-19 patients[33] determined acute renal tubular damage, including tubular necrosis, luminal brush border sloughing, and vacuole degeneration. Similar pathological features were also observed in autopsy kidney samples from SARS-CoV[68] and MERS-CoV[69]-infected patients, suggesting that coronaviruses may have similar pathogenicity mechanisms. These pathological features provide insights that the urinary system is susceptible to damage by SARS-CoV-2 infection; however, the mechanisms remain unclear.

Reproductive system

Consistent with the findings of previous related studies,[70,71] studies of COVID-19 patients on the vulnerability of human gonad to SARS-CoV-2 infection have determined the virus in the testis of male patients,[34] but not in the females' ovary or uterus.[72] These studies suggest that the SARS-CoV-2 infection may cause impairment of sex hormones in males; however, the pathogenicity mechanism and also the virus contagions in the genital system remain unknown. Of note, an investigational study of women with severe COVID-19 illness to detect

SARS-CoV-2 in their vaginal fluid reported negative results,[72] suggesting low to no risk of the virus transmission to their sexual partner. Moreover, another published study has also reported that no SARS-CoV-2 was found in the amniotic fluid or umbilical cord blood of COVID-19 women patients and their neonatal throat swabs.[73] Altogether, the studies suggest that the risk of SARS-CoV-2 transmission from mother to a newborn baby during pregnancy and childbirth is low.

Skeletal system

Skeletal joints problem such as arthritis associated with SARS-CoV-2 infection has been reported in severe COVID-19 patients.[35] Of note, SARS-CoV-2 in people with rheumatoid arthritis (RA) has been observed to cause severe symptoms than in their counterparts who never experienced RA.[35] The reason for the severity of the COVID-19 symptoms in people with RA is mostly because of their compromised immune system and thus increasing both the risk and the disease development further. However, whether the joint injury associated with the SARS-CoV-2 infection is caused by the direct effect of the virus or subjected to immune reaction is not yet known. Moreover, studies indicate that certain drugs such as corticosteroids used for the management of SARS-CoV-2-related infections, including SARS-CoV[74] and MERS-CoV[75] infection, have documented negative effects; therefore, drugs applied for the therapeutics of COVID-19 patients particularly those who have RA require extra caution.

Integumentary system

Specific integumentary change due to SARS-CoV-2 infection has not been reported aside from the intravascular coagulation-associated ischemic changes[11,21,24] that may occur in the fingers and toes of severe COVID-19 patients.[36] However, several skin injuries from long-term contact to personal protective equipment (PPE) and exaggerated personal hygiene (hand washing) have been mainly common among healthcare workers.[76,77] These studies further underlined that prolonged use of PPE such as masks, gloves, and goggles, and the excessive hand washing may cause various degrees of cutaneous diseases, even dermatitis. Therefore, the commonly reported skin injuries among health professionals including burning, itching, and stinging are attributable to the prolonged use of PPE, not SARS-CoV-2 infection unless diagnosed. However, the potential effect of SARS-CoV-2 infection on the hydro-lipid mantle of the skin surface requires further elucidation.

Nervous system

Evidence on the neurological effects of SARS-CoV-2 is not yet studied appropriately. However, the neurological manifestations of neuroinvasion and neurotropism that have been reported as common characteristics for human coronaviruses[78–80] may also be applicable for SARS-CoV-2. Reports on studies of SARS-CoV[81,82] and MERS-CoV[83] have shown a positive test of the SARS-CoV-1 in the SARS patients cerebrospinal fluid and an altered mental status in 26% of studied patients, respectively. Moreover, other studies using transgenic mice models, SARS-CoV[84,85] or MERS-CoV,[86] revealed that the virus could enter the brain through the olfactory nerves. Concerning SARS-CoV-2, a study on 214 patients with moderate to severe COVID-19 indicated that 36.4% of the patients revealed neuropathic-related clinical findings including headache, dizziness, ataxia, myopathy, acute cerebrovascular problems, depressed level of consciousness, and impairment of senses of smell and taste.[87] Other studies on COVID-19 patients have also suggested possible pathological lesions of SARS-CoV-2 in the nervous system including viral encephalitis,[40] acute toxic encephalitis,[20,38] and acute cerebrovascular disease.[37,39,41] Whether these neurological manifestations are subject to the direct effect of the SARS-CoV-2 virus infection or are consequences to COVID-19 disease is yet to be determined in future studies.

Other systems

Published data reporting clinical features of SARS-CoV-2 infected patients have delineated various degrees of liver injury during the course of the COVID-19 disease[11,12,21,24,25,42,43,63,64,88] involving abnormal levels of alanine aminotransferase and aspartate aminotransferase alongside elevated serum bilirubin.[12,25,42,43] Additionally, a histological study on a deceased COVID-19 patient, liver biopsy, reported microvesicular steatosis and lobular activity,[70] which requires medical attention. The liver injury in COVID-19 patients is presumed to be caused by either SARS-CoV-2 direct infection of hepatocytes for the virus may directly bind to the angiotensin-converting enzyme-2 (ACE-2) receptor found in the cholangiocytes (discussed in the next section), or following to an immune-related inflammation, or drug-mediated hepatotoxicity. However, the pathogenicity mechanism of SARS-CoV-2 infection associated liver injury remains to be studied.

Pathogenicity

The to-date available reports describing clinical characteristics of COVID-19 disease have contributed to a better understanding of the disease pathology in the individual cases body systems. However, further study on the pathogenicity of the SARS-CoV-2 virus is required to obtain additional insights on the way forward to control COVID-19 pandemic or should a similar viral plague occur in the future. Pathogenicity characteristics of the SARS-CoV-2 virus (Figure 1) are highly complex, with multiple factors leading to severe injury in the respiratory tract and several other body systems (Figure 2).

Coronaviruses are morphologically characterized by the crown-shaped protein spikes on their surface. According to structural studies[89–91] and biochemical experiments,[2,91,92] the SARS-CoV-2 virus surface protein spikes contain a variable receptor-binding domain (RBD) that allows the virus to bind with a high affinity to the angiotensin-converting enzyme-2 (ACE-2) receptor found in the human respiratory tract, lungs, gastrointestinal tract, kidneys, and the heart; however, the mechanism remains unclear. In addition to the ACE-2 receptor, the presence of type 2 transmembrane

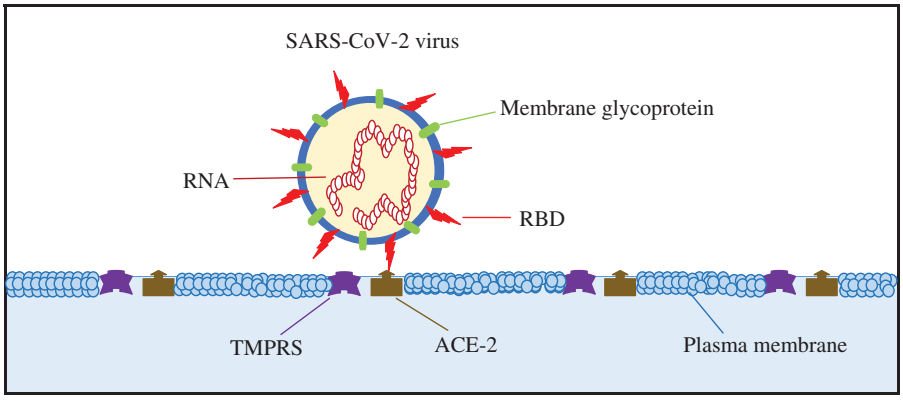

Figure 1. Schematic representation of the SARS-CoV-2 virus pathogenicity characteristics. The entry of the virus into the target cell depends on the binding of the virus surface protein spikes, variable receptor-binding domain (RBD), to the angiotensin-converting enzyme-2 (ACE-2) receptor augmented by type 2 transmembrane serine protease (TMPRSS2). (A color version of this figure is available in the online journal.)

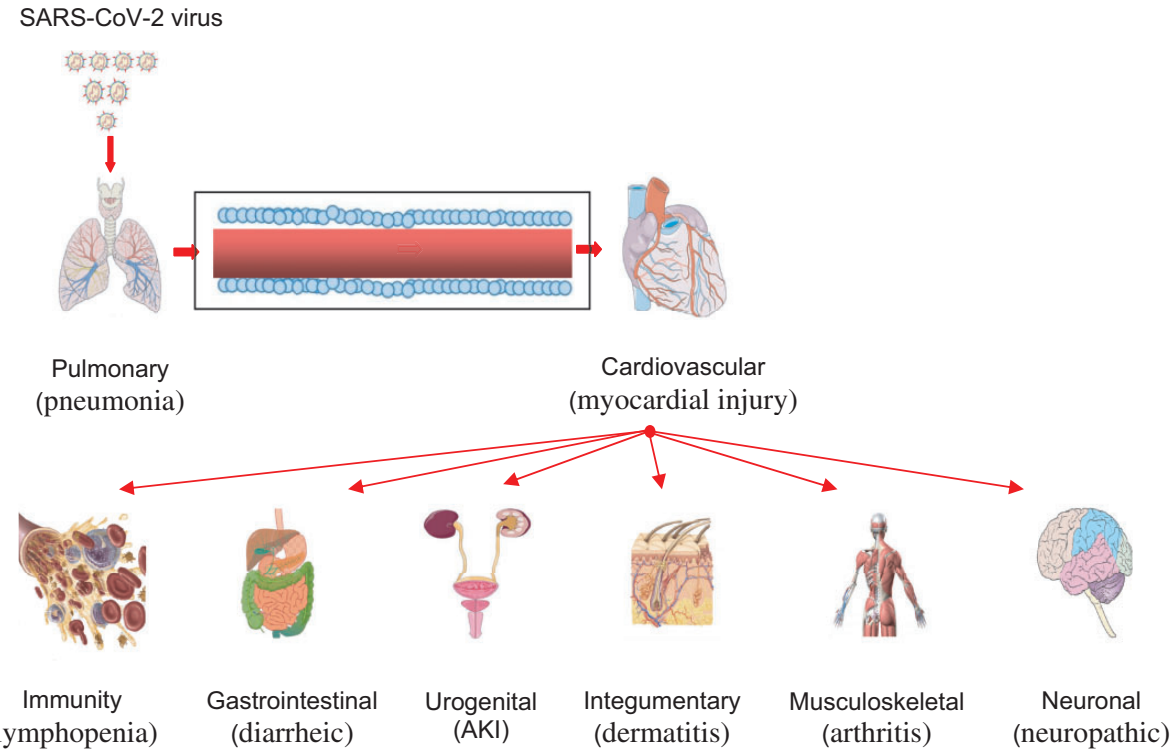

Figure 2. Outline of the SARS-CoV-2 virus pathophysiology and pathogenicity. The virus has direct or indirect effects on multi-body systems that warrant a need for multidisciplinary attention during patient hospitalization and further research. The most common COVID-19 features to a body system include pneumonia (pulmonary), myocardial injury (cardiovascular), lymphopenia (immunity), diarrheic (gastrointestinal), acute kidney impairment, AKI, (urogenital), dermatitis (integumentary), arthritis (musculoskeletal), and neuropathic (neuronal). (A color version of this figure is available in the online journal.)

serine protease (TMPRSS2) in the target cells have been suggested to augment the SARS-CoV-2 viral entry as is the case in influenza and human metapneumovirus.[93–96] Briefly, the TMPRSS2 proteolysis to the complex formed following the binding of the SARS-CoV-2 RBD with the host ACE-2 receptor, and thereby enhances cleavage of the host target cell receptor and activates the virus surface protein. It may be premature to reach into conclusion with the aforementioned concepts at this stage; however, it is worth noticing that the presence of both ACE-2 receptor and TMPRSS2 in the target cell determines the host susceptibility to the SARS-CoV-2 virus.

The SARS-CoV-2 virus entry into the target cell compromises the host immune system leading to lymphopenia, a significant reduction of lymphocytes and exacerbates inflammation as the COVID-19 disease advances[12,24,26]; however, the mechanism is not fully known. In brief, following the SARS-CoV-2 virus infection, mainly people in an immune-impaired state, such as the old aged and individuals of any age but who have severe underlying medical conditions, show significantly lower white blood cell count in their peripheral blood. While the T lymphocytes and B lymphocytes significantly reduce in the peripheral blood of the patient, the inflammatory factors such as IL-6 are

significantly increased contributing to the aggravation of the COVID-19 disease. Ordinarily, in an infection process, the host immune response mediated by antigen-presenting cells (APCs) recognizes and presents the foreign antigen to $CD4^+$-T-helper cells, which subsequently stimulate the $CD8^+$-T-killer cells and the B-cells to target any that specific foreign antigen containing cell and to produce the antigen-specific antibodies, respectively. Interestingly, aside from the symptomatic COVID-19 cases, reports have indicated that there are some people with effective immune function, immunocompetent, capable of withstanding the SARS-CoV-2 virus infection and that even remain asymptomatic while they are likely contagious.[16,17]

Concluding remarks

In conclusion, there is no vaccine to prevent SARS-CoV-2 virus infection or specific medicine to treat COVID-19 disease to-date. The acquired basic information on clinical characteristics of COVID-19 has contributed to thus far adoption of symptomatic treatment and oxygen therapy to enhance the patient immune function. Worthy of note is that the SARS-CoV-2 virus virulence depends on the presence of ACE-2 receptor and TMPRSS2 in the host target cell. Advanced *in vitro* and *in vivo* experiments in the fields of pathogenicity of the SARS-CoV-2 virus is crucial to fully elucidate the pathogenesis of COVID-19 disease or should a similar viral plague occur in the future.

DECLARATION OF CONFLICTING INTERESTS

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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