Overview of the pathogenesis of COVID-19 (Review)

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Abstract. At present, the pathogenesis of the novel coronavirus disease 2019 (COVID-19) has not been fully elucidated. Clinical and experimental findings from studies investigating COVID-19 have suggested that the immune-inflammatory response has a crucial role in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The present article aimed to systematically review the available literature on the pathogenesis of COVID-19. Severe COVID-19 is characterized by organ dysfunction, hypercytokinemia and lymphopenia. It is assumed that the direct cytopathological damage of host cells and the dysregulated immune response caused by SARS-CoV-2 may be the primary underlying mechanisms of COVID-19. Based on the published literature, this review attempts to provide an integrated view of the immunological mechanisms and the potential pathogenesis of COVID-19, providing an in-depth summary of the host-pathogen interaction and host immune responses. It is of great importance to elucidate the possible pathogenesis of COVID-19 to determine the direction of future research.

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1. Introduction

The ongoing outbreak of the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be a potentially once-in-a-century pandemic (1). The crude mortality rate of COVID-19 is estimated at 3%; however, the mortality rate of critical patients was at one point as high as 61.5% (2). No effective antiviral drugs specific for treating SARS-CoV-2 infection are currently available. Early identification of patients with severe COVID-19 and active organ support remain the most efficient strategies for preventing its progression and improving clinical outcomes (3). Additionally, strict preventative measures to lower the risk of further disease transmission, including social distancing and self-isolation, were adopted quickly in a number of countries, which had a profoundly negative impact on the physical and mental health and well-being of individuals (4,5). Hence, there is strong concern regarding the pathogenesis of COVID-19 amongst healthcare professionals due to its high infectivity and lethality.

At present, the pathogenic mechanisms of human COVID-19 remain to be fully elucidated. Recently, accumulating evidence from clinical trials and experimental studies *in vitro* and *in vivo* have increased our knowledge of the potential molecular mechanisms of COVID-19 (6-18). Additionally, previous work with other highly pathogenic β-coronaviruses, such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) may provide insights that could improve our understanding of the underlying mechanisms of COVID-19. SARS, MERS and COVID-19 share various clinical, laboratory and histopathological characteristics (11). Similar to SARS and MERS, there are no significant distinguishing clinical characteristics of COVID-19 and symptoms overlap largely with other severe acute lower respiratory infections (19). SARS-CoV-2 has 75-80% genomic similarity to the SARS-CoV, and 50% to the MERS-CoV (20,21). Moreover, SARS-CoV and SARS-CoV-2 attach to the same receptor, angiotensin-converting enzyme 2 (ACE2), suggesting a similar tissue tropism and route of entry (8,22). A recent autopsy study revealed that pathological changes in patients with COVID-19 are highly similar to features observed in patients with SARS and MERS (23). Lymphopenia is a common event that can predict pneumonia development and progression to respiratory failure in patients with SARS, MERS and COVID-19 (6,24,25). More importantly, although SARS-CoV-2 infection and host immune patterns are incompletely characterized, elevated plasma levels of TNF-α, IL-2, IL-7, IL-10, granulocyte colony stimulating factor (G-CSF), interferon γ-induced protein 10 (IP10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory

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protein 1 α (MIP-1A) and C-reactive protein (CRP) may be markers of severe status in the early stages of infection (6,24), suggesting that hypercytokinemia-related immunopathology may serve a fundamental role in severe COVID-19. Although COVID-19, SARS and MERS resemble each other clinically, *in vitro* studies have highlighted notable differences between these viruses with respect to their growth characteristics, receptor utilization and host responses, suggesting that their pathogenesis may also significantly differ. Additionally, dysregulation of the cholinergic anti-inflammatory pathway may be involved in severe COVID-19. Of note, it is speculated that as the SARS-CoV-2 virus replicates, cell and viral debris or virions may interact with the nicotinic acetylcholine receptors, thus blocking the action of the cholinergic anti-inflammatory pathway (26-30).

It is difficult to elaborate the exact pathogenesis of COVID-19. A growing body of studies have suggested the pivotal role of a dysregulated or exacerbated immune response against SARS-CoV-2, leading to an intense inflammatory response (6,18). This dysregulated inflammatory response is systemic, but primarily affects the lungs. The present review discusses and summarizes the possible pathogenesis of SARS-CoV-2-mediated dysregulated immune responses and the possible pathogenetic mechanisms of SARS-CoV-2-mediated dysregulated immune inflammatory responses (Fig. 1). Further virus and immune-related research is urgently required to improve our understanding of the exact pathogenesis of COVID-19, and ultimately lead to improvements in precise diagnosis, treatment and effective vaccine design to manage COVID-19.

2. Overview of SARS-CoV-2

Coronaviruses (CoV) are a large family of enveloped single positive-strand RNA viruses, which include α, β, γ and δ genera with varying degrees of pathogenicity and immunogenicity (31). Most CoVs only cause self-limiting respiratory tract infections (32). By contrast, SARS-CoV, SARS-CoV-2 and MERS-CoV, belong to the β-CoV genera, and may cause acute respiratory distress syndrome (ARDS) and extrapulmonary manifestations, such as diarrhea, shock, severe renal and liver dysfunction, and multiple organ dysfunction syndrome (MODS) (32).

The genomic structure of SARS-CoV-2 provides important information regarding the pathogenicity and related virulent factors. The entire genome of SARS-CoV-2 has been sequenced, and has been demonstrated to contain 29,903 nucleotides (21). The SARS-CoV-2 is genetically similar to SARS-CoV and bat SARS-like coronaviruses. Chan *et al* (32) found that the genome of SARS-CoV-2 has 82% nucleotide similarity with that of human SARS-CoV. Further genetic analysis confirmed that SARS-CoV-2 was ~79% homologous to SARS-CoV and ~50% homologous to MERS-CoV (20).

Structural proteins, including spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins, serve a crucial role in the pathogenesis of viruses, as well as virion assembly and structure (33). The S glycoprotein has a very potent influence on viral tropism and pathogenic phenotype. It has been confirmed that the S protein is the primary protein that mediates the binding of SARS-CoV-2 to the receptor ACE2 of the host cells and causes membrane fusion, which serves a key role in viral entry into cells (7,8). The S protein is the primary target of neutralizing antibodies (Abs) and the focus of treatment and vaccine development. In SARS-CoV, the nucleocapsid (N) protein binds to viral RNA and participates in viral replication, M protein serves an important role in stabilizing the viral structure, envelope formation, as well as viral budding and release. The E protein has been demonstrated to be a virulence domain that activates immunopathology in SARS-CoV infection (34). However, it is currently unclear whether these structural proteins undergo similar functions in COVID-19.

It appears that SARS-CoV-2 may be less pathogenic than MERS-CoV and is closer to that of SARS-CoV. The basic reproductive number 'R0' is defined as the number of additional individuals one case infects during the course of their illness. The estimated average R0 for COVID-19 ranges between 2 and 6.47 (35-40). In comparison, the estimated average R0 for SARS was 2, and 1.3 for MERS (36). The mean serial interval, in the epidemiology of infectious diseases, refers to the duration between symptom onset of a secondary case and that of its primary case (37). A recent study reported that the mean serial interval (the duration between symptom onset of a secondary case and that of its primary case) of COVID-19 was 3.96 days, considerably shorter than that for SARS (8.4 days) or MERS (14.6 days), suggesting that SARS-CoV-2 spreads far more rapidly than SARS-CoV and MERS-CoV. SARS-CoV-2 appears to have higher transmissibility (a higher R0) and a similar case fatality rate to that of SARS-CoV (40,41).

There are some differences in the viral load kinetics between SARS-CoV, MERS-CoV and SARS-CoV-2 infections (42). For the majority of patients with COVID-19, the peak viral load of SARS-CoV-2 is very high at presentation, and declines steadily. By contrast, the viral load of SARS-CoV peaks at ~10 days, and that of MERS-CoVin the second week after symptom onset (43). Of note, the peak viral load of SARS-CoV-2 is positively correlated with age (43). High viral loads in the upper respiratory tract samples in patients with COVID-19 are suggestive of a significant shedding of SARS-CoV-2 and a potentially high risk of transmissibility during the first few days of clinical symptoms (44).

3. Pathogenesis of COVID-19

The pathogenic phases of COVID-19 remain incompletely understood. Previous studies have proposed SARS may consist of three phases: Viral replication, immune hyperactivity and pulmonary destruction (45). The clinical phases of COVID-19 have been recently proposed: Viremia phase, acute phase and recovery phase (14). It is generally hypothesized that the course of infection goes through the following stages (33,45-48): Viral invasion and replication, dysregulated immune response, multiple organ damage and recovery. Firstly, the virus enters the host cells, where it replicates, assembles and is released extracellularly to target cells, and this directly causes the damage and destruction of parenchymal cells such as alveolar epithelial cells. At the same time, a large number of pathogen associated molecular pattern (PAMP) and damage associated molecular pattern (DAMP) molecules are released to stimulate

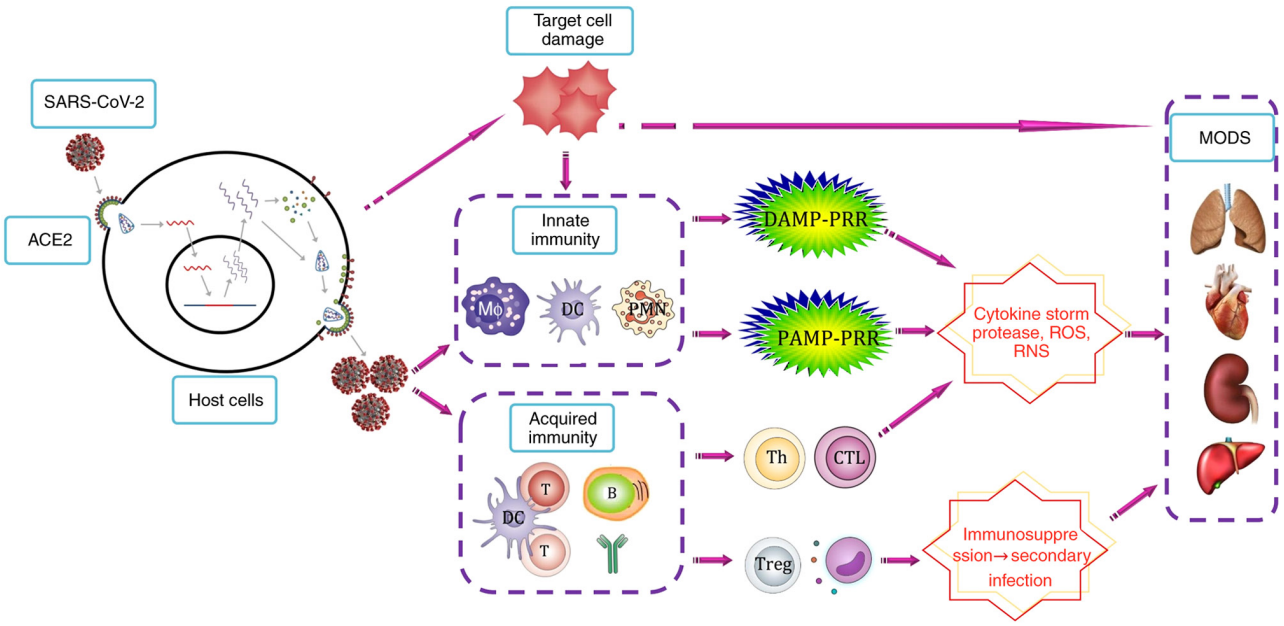

Figure 1. Hypothetical pathogenesis of COVID-19. Severe acute respiratory syndrome coronavirus 2 targets cells through the S protein that binds to the ACE2 receptor, replicating and assembling in target cells before being released extracellularly. Inflammatory signaling molecules are released by infected cells and may induce organ injury through innate and acquired immunity. COVID-19, coronavirus disease 2019; S, spike; ACE2, angiotensin converting enzyme 2.

the innate immune response, induce inflammatory cell infiltration, release large quantities of cytokines, chemokines, proteases and free radicals, causing ARDS, sepsis and MODS. It has been observed that the pathological findings of COVID-19-induced pneumonia appear to resemble those seen in SARS-CoV and MERS-CoV infection including bilateral acute changes with diffuse alveolar damage and vascular congestion, patchy inflammatory cellular infiltration, intra-alveolar edema, hemorrhage, proteinaceous exudate, denudation and reactive hyperplasia of pneumocytes, as well as the presence of multinucleated giant cells, but hyaline membrane formation was is not prominent observed (49,50). After the initial critical stage, the inflammatory response is gradually resolved, the damaged organ gradually recovers, and some of the damaged organs enter fibrosis and chronic stage, such as chronic critical illness, persistent inflammation, immunosuppression and catabolism syndrome.

It is speculated that the major pathological alterations that take place in the vital organs during COVID-19 may be caused directly by the cytopathic effect mediated by SARS-CoV-2, and indirectly as a result of the harmful immune responses induced by SARS-CoV-2, but the relative importance of each of these requires further study. There is some evidence supporting the more important role of an abnormal immune response (rather than a direct viral cytopathic effect) in the effects of COVID-19. It has been observed that patients with COVID-19 had the highest viral load during the early stage (43). The timeline of COVID-19 infection showed that the median time from onset of symptoms to first hospital admission was 7 days, 9 days till ARDS, and 10.5 days till ICU (24). The association of worsening clinical progression with declining viral loads (42) and the onset of an immunological response, plus the presence of significantly elevated cytokines levels suggested that severe lung damage was largely immunopathological in nature (6,24,42,44).

SARS-CoV-2 invades host cells. It is widely accepted that human CoV transmissibility and pathogenesis primarily depends on the interactions between the virus and specific host cells (46,51). Receptor recognition and entry is the first step of viral infection and is the key determinant of tissue tropism. Enhanced binding affinity between SARS-CoV-2 and ACE2 has been proposed to correlate with elevated virus transmissibility and disease severity in humans (7,52). CoV entry into host cells is a multi-step process involving several distinct domains in the S protein that mediates viral attachment to the target cell surface, receptor engagement, protease processing and membrane fusion. Subsequently, the viral genome is released into the cytoplasm, and the virus replicates within the host cells (53). Notably, three CoV (human CoV-NL63, SARS-CoV and SARS-CoV-2) that bind to the same receptor (ACE2) cause diseases of varying severity, indicating that there may be other pathogenic factors underlying the differences between these three coronaviruses (54). It has been demonstrated that the overall ACE2-binding mode of the SARS-CoV-2 S receptor-binding domain (RBD) is nearly identical to that of the SARS-CoV RBD, but SARS-CoV-2 RBD takes a more compact conformation, which enhances its ACE2-binding affinity (8,9). Walls *et al* (7) showed that the RBD of SARS-CoV-2 S protein and SARS-CoV S protein bind with similar affinities to human ACE2 to enter cells. However, another study observed that SARS-CoV-2 and ACE2 have an affinity that is 10-20 times that of SARS-CoV, which may be related to the higher transmissibility seen in SARS-CoV-2 (55).

The characteristic distribution of SARS-CoV-2 and ACE2 may contribute to revealing the pathogenic mechanisms of COVID-19. SARS-CoV-2 viral RNA can be detected in respiratory secretions, peripheral blood, urine and stool specimens of some patients with COVID-19, which coincides with various transmission pathways in SARS-CoV-2 infection (56). Virions in the blood that are released from the primary target

(for example the lung) may circulate and infect host cells in the remote secondary organs and tissues.

On the other hand, ACE2 is expressed in the lungs, heart, renal system and gastrointestinal tract, of which it is abundantly present in the epithelia of the human lungs and small intestines (57-59). These observations may indicate that ACE2 serves an important role in extrapulmonary manifestations of COVID-19, such as gastrointestinal symptoms (57,60,61). It is noteworthy that gut-lung crosstalk may be involved in the pathogenesis of COVID-19; however, the potential efficacy of probiotics as one of the novel therapeutic approaches of COVID-19 requires further exploration (62). In addition, ACE2 is widely expressed in the vascular endothelial cells and smooth muscle cells in all organs, which may cause extensive vascular endothelial cell injury and this may be the molecular basis by which multiple organ lesions are formed in COVID-19-infected patients (59,63). Cardiac injury has been reported in 7-23% of patients with COVID-19, which is associated with a higher mortality (64). A more recent study showed that patients with basic heart failure disease showed increased ACE2 expression, suggesting that cardiac cells with high expression of ACE2 may act as the target cells of SARS-CoV-2 (65).

Direct cytopathic effect of SARS-CoV-2. After entering the host cells, the virus can replicate and survive within the target cells. It is speculated that the life cycle of SARS-CoV-2 may be similar to other single positive-strand RNA coronaviruses to a certain extent (33,66,67). After replication is complete, new virus particles are assembled in the endoplasmic reticulum, after which they are released outside of the cell. At the same time, target cells lyse or form syncytia and other lesions occur. SARS-CoV-2 may induce a substantial cytopathic effect on host cells, thus early effective antiviral treatment may reduce the risk of progression, and thereby mortality (68). It is unclear whether SARS-CoV-2 interferes with target cells in other ways to cause host cell damage or apoptosis, including mitochondrial damage, endoplasmic reticulum stress, intracellular environment alterations (such as pH changes) or enzyme dysfunction.

In view of the expression of ACE2 in immune cells, including monocytes/macrophages and lymphocytes (59), it is unclear whether SARS-CoV-2 can directly infect certain immune cells to cause immune cell damage. More importantly, immune cells may migrate within the body. Therefore, the SARS-CoV-2-infected immune cells may allow the virus to disseminate systemically. Pathological studies using COVID-19 models have shown that the common type of damage caused by SARS-CoV-2 infection also occurs in the immune system, and spleen and lymphoid atrophy have been shown to be associated with marked cytokine activation, suggesting that SARS-CoV-2 might directly damage immune cells (6,24,25,69).

Initiation of the innate immune response. The innate immune response, which uses various pattern recognition receptors (PRRs) to recognize and respond to viruses, is an important barrier to viral infection (70). The intensity of the host immune and inflammatory responses are closely related to the type of invading virus, the viral load, and the age and immune status of the host (71). In general, host innate immune cells are stimulated to produce antiviral and proinflammatory cytokines and chemokines to eliminate the invading viruses (71,72).

PAMP-PRR pathway. The viral RNA that is present within the infected cells is detected by various PRRs in the immune cells, which leads to the secretion of type I interferons (IFNs), proinflammatory cytokines and chemokines (70,73). Previous studies have demonstrated that key components of the innate immune signaling pathways serve important roles as protective factors against SARS-CoV disease, including STAT1 and myeloid differentiation primary response protein MyD88 (74). Gralinski *et al* (75) identified an adaptor protein (TIR domain-containing adapter molecule 2) in the toll-like receptor signaling pathway that may be involved in the development of SARS. The IFN response, a key component of antiviral innate immunity, is initiated by retinoic acid-inducible gene-I-like receptor-mediated recognition of viral replicative intermediates in the cytosol (73). However, Channappanavar *et al* (76) showed that robust SARS-CoV replication and delayed IFN-I signaling promotes severe SARS, as IFN-I could promote the accumulation of pathogenic macrophages, thus causing lung immunopathology and vascular leakage. In this regard, the specific pathogenic PAMPs of SARS-CoV-2 and the corresponding PRRs and signaling pathways remain to be systemically identified.

Macrophages are crucial components of innate immunity and potential mediators of immunopathology (77). Moreover, macrophages are the main target cells for SARS-CoV replication (78). MERS-CoV and SARS-CoV can easily infect and robustly replicate in human macrophages and dendritic cells, inducing the aberrant production of proinflammatory cytokines and chemokines (77,79,80). In SARS-CoV infection, viroporin 3a has also been shown to induce the activation of nucleotide oligomerization domain-like receptor protein 3 inflammasome and the secretion of IL-1β in macrophages, suggesting that PAMP-PRR signaling in macrophages may result in the release of proinflammatory cytokines in COVID-19 (15).

DAMP-PRR pathway. Following cellular injury and necrosis, endogenous DAMPs can be released, such as DNA, RNA, ATP, heat shock proteins, high mobility group protein B1 and the extracellular matrix, which could be recognized and activated by corresponding PRRs, and promote the release of cytokines and chemokines, and this may further aggravate the inflammatory response and tissue damage, forming a vicious cycle (81). It is speculated that both DAMPs and PAMPs may also contribute to the systemic dysregulation of the innate immune response and may be involved in the development of MODS in COVID-19. After SARS-CoV-2 activates PRRs, it may induce the antiviral innate immune response, and also lead to cell damage and organ dysfunction.

Adaptive immune response. Antigen-presenting cells present antigen peptides to T and B cells for recognition, thereby inducing cellular and humoral immunity. Ni *et al* (82) characterized SARS-CoV-2-specific humoral and cellular immunity in recovered patients with Covid-19. Both T cells and B cells were detected in newly discharged patients (82). In addition, Spearmen's correlation showed that the neutralizing antibody titers were significantly positively correlated with the numbers of NP-specific T cells (82).

These findings suggested both B and T cells participate in immune-mediated protection to viral infection.

Cellular immune response. The role of T cells and its subsets in resisting COVID-19 remains unclear. Previous studies have confirmed that the S protein of SARS-CoV is the primary antigen protein that induces the host immune response, and serves an important role in activating cytotoxic T cell responses and causing humoral immune responses. Xu *et al* (23) found that the proportions of circulating $CD4^+$ and $CD8^+$ T cells were substantially decreased in patients infected with COVID-19, but their status was hyperactivated. In addition, there is an increased percentage of highly proinflammatory T helper 17 (Th17) cells and high numbers of cytotoxic $CD8^+$ T cells, indicating that the overactivation of T cells may partly account for the severe inflammatory response (23). However, the disease is more severe when lymphocytopenia is present in COVID-19, suggesting that the T cell response may be necessary for SARS-CoV-2 clearance. Diao *et al* (83) observed that in addition to a reduction in the number of T cells, surviving T cells are functionally exhausted in COVID-19. In addition, T cell subpopulation differentiation and functional imbalance are key factors in the development of some inflammatory diseases. Therefore, an imbalance in the ratio of Th1/Th2 and Th17/regulatory T cells in COVID-19 may be a research topic that requires further study.

Humoral immune response. The host humoral response against SARS-CoV-2 comprises specific IgA, IgM and IgG responses. Most patients with COVID-19 have a specific Ab response ≥10 days following the onset of symptoms (41). In a recent study of 82 confirmed and 58 probable COVID-19 cases, the specific IgM and IgA Abs were detected on day 5 (IQR 3-6), while IgG was detected on day 14 (IQR 10-18) after symptom onset (84). However, the persistence of neutralizing Abs for SARS-CoV-2 requires further study.

Antiviral neutralizing Abs play a pivotal role in viral clearance. The S protein RBD is specific for SARS-CoV-2 and may be the direct target for neutralizing Abs (43). Tian *et al* (17) assessed the cross-reactivity of anti-SARS-CoV Abs with SARS-CoV-2 S protein. This previous study revealed that the epitope of CR3022, a SARS-CoV-specific human monoclonal Ab, which does not overlap with the ACE2 binding site, could bind potently with SARS-CoV-2 RBD. Most recently, the neutralizing Ab from three convalescent SARS patients was reported to reduce SARS-CoV-2-driven cell entry, although with lower efficiency compared with SARS-CoV, suggesting that Ab responses raised against SARS-CoV S protein during infection or vaccination could at least partially protect against SARS-CoV-2 infection (22). It has also been suggested that convalescent plasma in patients with COVID-19 might be useful as a potential therapy (85). On the other hand, Ab-dependent cell-mediated cytotoxicity may also be involved in cellular damage and organ injury (15). The Fc receptor-mediated Ab-dependent enhancement of SARS-CoV-2 infection may additionally lead to inflammatory responses (15).

Hypercytokinemia and organ damage. COVID-19 can cause both pulmonary and systemic inflammation, leading to MODS in high risk patients (86). Organ dysfunction is the key diagnostic criterion for severe or critical SARS-CoV-2 pneumonia (87,88). The most frequent organ dysfunction in patients with severe and critical COVID-19 includes ARDS, shock, acute myocardial injury, liver injury, kidney injury and MODS (2,25,86,88-90). The most frequent type of organ dysfunction in patients with severe and critical COVID-19 admitted to the ICU includes ARDS (61.1%), arrhythmia (44.4%), shock (30.6%), myocardial injury (22.2%) and acute kidney injury (8.3%) (82). Another clinical trial indicated that the majority of critically ill patients with COVID-19 had organ function injury, including ARDS (67%), acute kidney injury (29%), liver dysfunction (29%) and cardiac injury (23%), and 71% of these patients required mechanical ventilation (2). It is generally assumed that the fundamental pathophysiology of critical COVID-19 is severe ARDS (2).

The involvement of multiple organs may be related to the direct damage of target cells by SARS-CoV-2 and improper host responses, such as the immune-inflammatory response (Fig. 1). The effects of the host immune response are a double-edged sword, both protecting the host (immunity) by clearing the infection, and harming the host by inducing tissue and cell damage, resulting in immunopathology and worse clinical outcomes (91). In other words, cytokines and chemokines released from activated immune cells not only participate in the antiviral immune response, but can also cause cell damage and organ dysfunction. The optimal objective is to achieve a careful balance in the immune response, which could eliminate the virus, whilst avoiding inflammatory-mediated organ injury.

Hypercytokinemiais an uncontrolled host inflammatory state that is characterized by fulminant MOD and elevated proinflammatory cytokine responses (92). Hypercytokinemia serves a key role in pathogenic inflammation both in severe SARS and COVID-19 (11,92-96). The cytokines and chemokines found in MERS-CoV-infected cells share a similar expression profile to SARS-CoV-infected cells (56). Several studies from humans who succumbed to highly pathogenic human CoV infections, such as SARS and MERS, have also suggested that a dysregulated immune response and immunopathology occurred, resulting in excessive inflammation and lethal consequences during human CoV infections (92,95). Macrophages in the lung tissue are proposed to be the primary inducer of hypercytokinemiaand underlie the pathogenesis of MERS and SARS (54). In serum from patients with COVID-19 with a poor outcome, there was a significant increase in CRP, IL-2, IL-7, IL-10, G-CSF, IP10, MCP-1, MIP-1A and TNF-α, characterized as hypercytokinemia (24). Chen *et al* (6) also demonstrated elevated cytokine levels (IL-6, IL-10 and TNF-α) in severe COVID-19. A recent study reported that COVID-19 is associated with an elevated cytokine profile that is similar to that observed in secondary hemophagocytic lymphohistiocytosis (97). Findings from autopsies and serum of patients with COVID-19 suggest a crucial immune-inflammatory implication in the progression to ARDS and MODS (23). ARDS caused by SARS-CoV-2 infection seems to primarily result from exaggerated and uncontrollable inflammation initiated by viral replication. High levels of proinflammatory cytokines may lead to tissue damage in the heart, liver, kidney and the central nervous system, causing sepsis, shock or multiple organ failure (92).

The detailed expression profile of the cytokine and chemokine responses in COVID-19 requires further investigation and comparison with that in MERS and SARS.

Acquired immune-induced proinflammatory reactions (including Th17 and cytotoxic T lymphocyte accumulation) may also serve an important role in tissue damage caused by hypercytokinemia (23). This exacerbated detrimental inflammatory response towards invading viruses is termed sepsis (98). It is suggested that appropriate immunomodulatory treatments according to the changes of patients' immune status may be the key breakthrough in treatment. Most recently, preliminary data have shown that dexamethasone resulted in lower 28-day mortality amongst patients hospitalized with COVID-19 who were receiving respiratory support (99). In addition, proteolytic enzymes (such as elastase, collagenase, cathepsin and matrix metalloproteinase) released at the site of inflammation may also mediate tissue and organ damage (100). Oxidative stress (such as increased reactive oxygen species and reactive nitrogen species) is an important pathway that contributes to numerous inflammatory pathological processes, including in patients infected with COVID-19. The oxidative damage imposed on host tissues via polymorphonuclear cells and macrophage activation may lead to tissue damage and organ dysfunction (101-103). Considering the harmful effects of oxidative stress in COVID-19, antioxidant therapies using bioactive compounds, as well as encouraging healthy lifestyles as a potential treatment is an attractive and practical strategy that warrants further study in the treatment of COVID-19 (103-106).

Immunosuppression. It has been observed that lymphopenia (defective acquired immunity) is a common feature in patients with COVID-19, and it is related to disease severity and mortality (10,87,88,107). Immunosuppression may lead to difficulty in removing the virus or secondary infections. Hospital-acquired secondary infection is frequent in patients with severe COVID-19 (5-15.5%) (2,24,108). A recent meta-analysis (109), including 3,448 patients from 28 studies, showed that secondary bacterial infection was identified in 14.3% of patients with COVID-19. Moreover, it has been suggested that immunocompromised patients may have a higher viral load of SARS-CoV-2, prolonged viral shedding and impaired Ab responses (10,43). Liang *et al* (110) found that patients with cancer may be more susceptible to infection with SARS-CoV-2 than healthy individuals, and had a worse prognosis, as their immune systems were suppressed by the effects of the tumors and anticancer treatment.

The reason for significant lymphopenia in patients with severe COVID-19 remains unclear. It is speculated that the underlying mechanisms of lymphopenia may include hemopoietic tissue depression, as well as direct invasion by viral particles, which damages the lymphocytes and results in its destruction (2). It has been postulated that SARS-CoV-2 may directly infect T cells and lead to T cell depletion (79). Pathological studies on biopsy tissues from patients with COVID-19 have revealed that the cell damage caused by SARS-CoV-2 infection often occurs in the immune system (50). Furthermore, it is hypothesized that the underlying mechanism includes increased apoptosis or necrosis of immune cells (2), and lymphocyte recruitment and sequestration in the infection sites or lymphoid tissues (lymphocyte redistribution). However, these speculations require experimental confirmation. In addition, several other factors may also contribute to the development of immune suppression, such as a reduction in the number or function of antigen presenting cells, increased anti-inflammatory cytokines (such as IL-10 and TGF-β), neuroendocrine responses (such as glucocorticoids), elevated regulatory T cells and myeloid-derived suppressor cells (111). Of note, lymphopenia and hypercytokinemia were observed in patients with critical SARS-CoV in 2003, Swine flu in 2009, and COVID-19 in 2019, which may indicate that there is a particular dysregulated immunological phenotype associated with significantly elevated severity (25).

Renin-angiotensin system in COVID-19. ACE2 is an important component of the renin-angiotensin-aldosterone system, which converts angiotensin II into angiotensin 1-7 and angiotensin I into angiotensin 1-9 (112). Notably, in addition to mediating viral entry, the SARS-CoV S protein also has effects on the downregulated expression of ACE2, leading to aggravated lung injury (33). These results have led to the hypothesis that the binding of SARS-CoV-2 S protein is a virulence factor for COVID-19 outside of its role in viral attachment and entry.

Our previous data and other studies have demonstrated that angiotensin II is involved in the pathophysiological processes of pulmonary inflammation, pulmonary edema, pulmonary fibrosis and parenchymal cell apoptosis in a lipopolysaccharide-induced ARDS animal model (Fig. 2) (113-117). Blocking the angiotensin II receptor may inhibit the function of mature lung dendritic cells, reducing lipopolysaccharide-induced ARDS (118), and thus guide the development of potentially beneficial drugs.

4. Recovery of immune homeostasis and repair of organ damage

There are distinct long-term outcomes observed in patients with COVID-19, including recovery, organ fibrosis and dysfunction, chronic critical illness or persistent inflammation, immunosuppression and catabolism syndrome, and possibly even death. A retrospective study of 1,591 consecutive patients with COVID-19 referred to ICU for admission in Italy revealed that 58% of patients were still in the ICU, 16% patients were discharged, and 26% succumbed to the disease whilst in ICU (119). The long-term prognosis of patients with COVID-19 depends on a variety of factors, including whether the virus is cleared in time, and whether the inflammatory response subsides and inflammatory cells and cytokines are cleared. During the recovery of COVID-19, the number of $CD4^+$ T cells, $CD8^+$ T cells, B cells and NK cells, and the markers of $CD8^+$ T cell exhaustion may gradually normalize. Additionally, SARS-CoV-2-specific Abs can be identified. Long-term prognosis also depends on the regeneration and repair of parenchymal cells in damaged organ tissues. Pulmonary fibrosis appears frequently in COVID-19, including in patients who survived the infection (23,120,121). However, at present it is unknown whether patients with COVID-19 will develop chronic critical illnesses or persistent inflammation-immunosuppression and catabolism syndrome. There are a number of problems that require solving even after the patient clears the acute phase. For example, how can chronic critical illness, persistent inflammation, immunosuppression

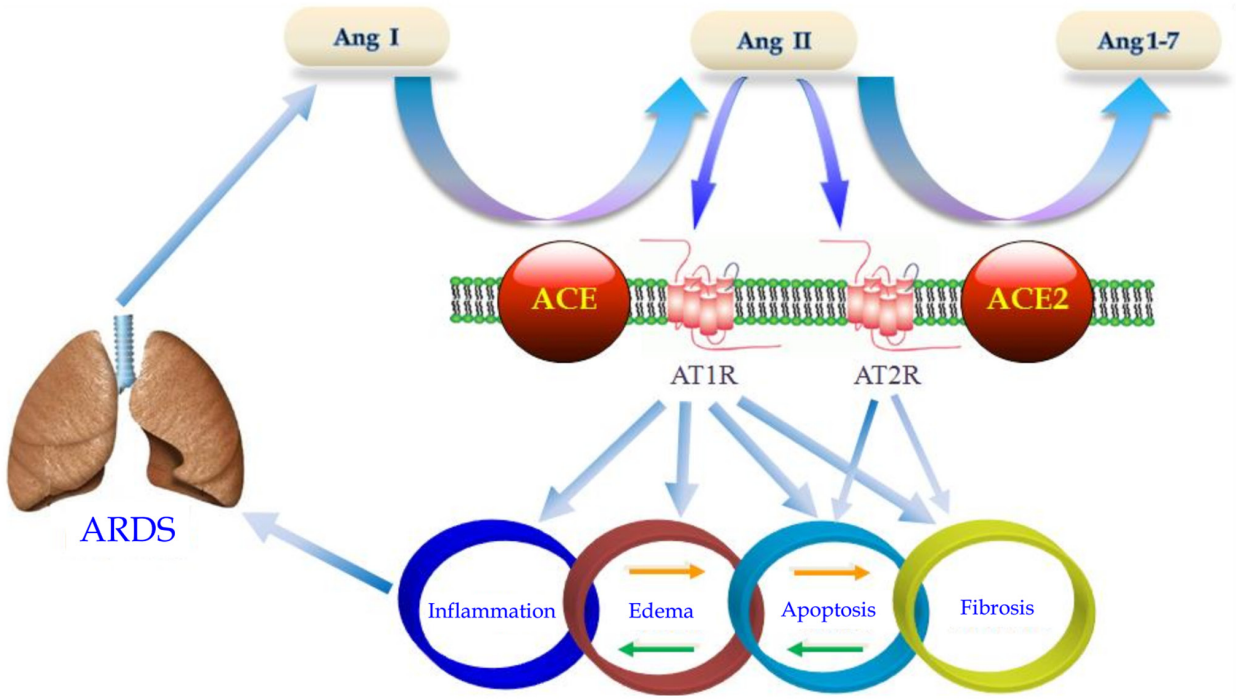

Figure 2. Schematic diagram of the proposed role of angiotensin II and ACE2 in the development of ARDS. Angiotensin II may be involved in the pathophysiological processes of pulmonary inflammation, pulmonary edema, pulmonary fibrosis and parenchymal cell apoptosis in ARDS. SARS-CoV2 spike proteins may result in downregulated expression of ACE2, therefore increasing local angiotensin II levels and aggravating lung injury. ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; SARS-CoV2, severe acute respiratory syndrome coronavirus 2.

and catabolism syndrome be avoided? What are the roles and mechanisms of specialized pro-resolving mediators in COVID-19? These gaps in our knowledge urgently require further investigation in order to contribute to an improved understanding of the pathogenesis of COVID-19.

Of note, patients with COVID-19 can relapse or become reinfected. Relapse in patients with COVID-19 refers to the reappearance of symptoms in survivors due to the persistence of the SARS-CoV-2 at immunologically segregated body sites. Reinfection refers to survivors being susceptible to acquiring new infections after recovery. Patients reinfected with a strain determined to be of a different genotype or subtype than the previous strain they were originally infected with can easily be identified using genotyping assays. Elsayed *et al* (122) reported that there were 11 cases of relapse for COVID-19 at the time of study. The reason for this is currently unknown, but it may involve factors such as age and immune status of the host, the presence of underlying lung disease, and the severity of SARS-CoV2 infection, all of which could affect the elimination of the virus (122). It is noteworthy to speculate that an inflammatory rebound triggered by an inappropriate immune response could constitute a probable explanation of the recurrence of clinical symptoms (123).

5. Conclusions

In summary, the pathogenic mechanisms of COVID-19 as a novel severe respiratory infectious disease are not yet fully determined, which is largely due to the novelty this disease. Although a number of crucial questions remain unanswered at present, it is obvious that we are only beginning to understand the pathogenic mechanisms of COVID-19. The present review discussed the pathogenesis of COVID-19. It is assumed that SARS-CoV-2 dysregulates the immune inflammatory response in a manner similar to SARS-CoV and MERS-CoV infections. Severe COVID-19 is characterized by organ dysfunction, hypercytokinemia and lymphopenia. Immune dysfunction in patients with COVID-19, including lymphopenia, decreased numbers of $CD4^+$ T cells and abnormal cytokine levels, is a common feature and may be a crucial factor associated with disease severity and worse outcomes (6,117). The direct damage and lysis of host target cells by the virus and the inappropriate innate and acquired immune responses of the host may be the key pathogenic mechanisms underlying the severity of SARS-CoV-2. The molecular determinants that may account for the important differences in pathogenesis between the highly pathogenic human coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV-2) are currently unknown. Further in-depth studies on the pathogenesis of COVID-19 will be crucial for devising novel treatment strategies and designing effective vaccines for this highly fatal emerging infectious disease. As our knowledge of the pathogenesis improves, a more reasonable approach to therapeutic treatments and vaccine development can be designed in order to combat this novel and fatal illness.

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JL conceived the subject of the review. CL and QH drafted the manuscript, and JL and HQ revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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