Review Article

Immune Mechanisms in the Pathogenesis of Coronavirus Disease 2019

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Abstract

In December 2019, unknown pneumonia appeared in Wuhan, China. The virus was then identified as a beta-coronavirus and referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 2 March 2020, ICTV named its coronavirus disease 2019 (COVID-19). This virus rapidly spread to many countries and regions globally because of its human-to-human transmission route. COVID-19 was declared a pandemic on 11 March 2020. The average incubation period of the disease is 4 to 6 days, and the clinical features of the infection vary, ranging from asymptomatic, and mild to acute respiratory syndrome, multiple organ failure, and in people with underlying diseases, can lead to death. The pathogenesis of COVID-19 starts by binding the virus spike to the angiotensin-converting enzyme 2 (ACE2) cellular receptor that expresses in many tissues. SARS-CoV-2 can manipulate the host cell's immune elements by its specific proteins to evade the antiviral responses. Dysregulation in the host immune system activation can cause different disease outcomes. Although the exact mechanism of COVID-19 pathogenesis is still unclear, preventive and control measures are needed to inhibit the virus's rapid spreading. The present study will briefly review the different aspects of COVID-19 pathogenesis.

Keywords: SARS-CoV-2, Immune response, pathogenesis

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Introduction

On 2 March 2020, the *coronaviridae* study group of the international committee on taxonomy of viruses (ICTV) declared their decision regarding the change of the novel coronavirus name (formerly known as 2019-nCoV) to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is accountable for COVID-19 disease pandemic (1, 2). Beta coronaviruses comprise four lineages, A, B (SARS-CoV and SARS-CoV-2), C, and D (3, 4).

The pathogenesis of COVID-19 begins with binding the virus spike to the angiotensin-converting enzyme 2 (ACE2) receptor expressed in many tissues (5). This virus has developed various mechanisms for manipulating the antiviral response. Dysregulation of the immune response is a distinctive feature of severe SARS-CoV-2 infection. It leads to severe respiratory disease, pneumonia, and immune damage. Mortality due to SARS-CoV-2 infection occurs mainly due to the development of acute respiratory distress syndrome (ARDS) caused by viral pneumonia (6). Although

there are some studies around COVID-19 pathogenesis, our knowledge about this viral disease is minimal. As the COVID-19 pandemic progresses, it is increasingly necessary to understand the mechanisms of cellular and tissue damage and apply that knowledge to therapeutic strategies. This review tries to explain some aspects of COVID-19 immune mechanisms and pathogenesis.

Virology of SARS-CoV-2 and cell entry: Coronavirus, like other nidoviral families of viruses, their genomes are polycistronic. About two-thirds are occupied by two large ORFs (ORF1a and ORF1b), which encode 16 non-structural proteins (NSP1–NSP16), and one-third are comprised of genes that code the structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N), and nine accessory proteins (7).

Each SARS-CoV-2 structural protein has specific roles. The S protein is a homo-trimeric protein that utilizes an N-terminal signal sequence to access the endoplasmic reticulum (ER) and is heavily N-linked glycosylated, which binds to the ACE2 receptor (8). The M protein (~25–30 kDa) defines the shape of the viral envelope; it also inhibits the signal transducer and activator of transcription 1 (STAT1) phosphorylation in IFN signaling pathways (9). The E protein is the minor structural protein. This transmembrane protein has an N-terminal and a C-terminal endo-domain with ion channel activity either for positive or negative applied voltages (10). The N protein is the only protein that binds directly to the viral RNA genome. It is also involved in viral assembly and budding, resulting in complete virion formation (11). Each SARS-CoV-2 non-structural (nsp1-nsp16) and accessory protein has distinct functions.

Cell entry is an essential process for the onset of pathogenesis. All human coronaviruses encode a surface glycoprotein, spike, which binds to the host-cell receptor and mediates viral entry. The S protein comprises two subunits, S1 as the receptor-binding domain (RBD), and the S2 subunit has a role in fusing the viral membrane and the host cellular membrane. SARS-S1 attaches angiotensin-converting enzyme 2 (ACE2) as the entry receptor and employs the cellular Transmembrane serine protease 2 (TMPRSS2) and cathepsin for S protein priming to membrane fusion (12). After cellular entry, the virus releases its genome RNA into the host cell, translated into viral polyproteins (Figure 1) (13).

SARS-CoV-2 pathogenesis: The infection progression of SARS-CoV-2 in patients shows a biphasic pattern, including the viral response and inflammatory phases (14).

The first phase (The viral response phase): Upon the virus's entrance to the respiratory tract cells, peak SARS-CoV-2 load is observed at the time of symptom onset or in the first week of illness; after this time, it will be declined. It is most contagious just about the first five days of manifestations onset. The first phase is characterized by fever, cough, fatigue, and other systemic symptoms (15). In the viral response phase, it means in the early stage of infection, the immune system activation occurs. Cellular immune response and humoral immunity in humans have protective roles against SARS-CoV-2 infection (16).

The signals of the innate immune response can initiate following the recognition of SARS-CoV-2 S protein by membranous TLR2 and TLR4 via induction of nuclear factor k-B (NF-kB) pathways in macrophages, epithelial cells, and monocytes (17). After viral entry, SARS-CoV-2 ssRNA is available in the endosomes and activates the endosomal TLRs, typically TLR7 and TLR8 (18). following innate immunity system recognition, several defense mechanisms can be promptly initiated, which include: (A) the release of interferons (IFNs) alpha (α) and beta (β), which resulted in the prevention of viral replication, suppression of cellular protein synthesis, and limit the virus propagation (19-21). (B) NK cell-mediated cytotoxicity can control the disease progression. NK cells also promptly produce high levels of chemokines and IFN-γ when stimulated by respiratory viral infections (22).

The acquired immunity, also called adaptive immunity, consists of B-cell and T-cell responses. B lymphocytes can get activated directly or by the interaction of the TCD4+ cells. After B-cells activation, memory B-cell and plasmablast expansion occur in the early stage of infection. Plasmablasts

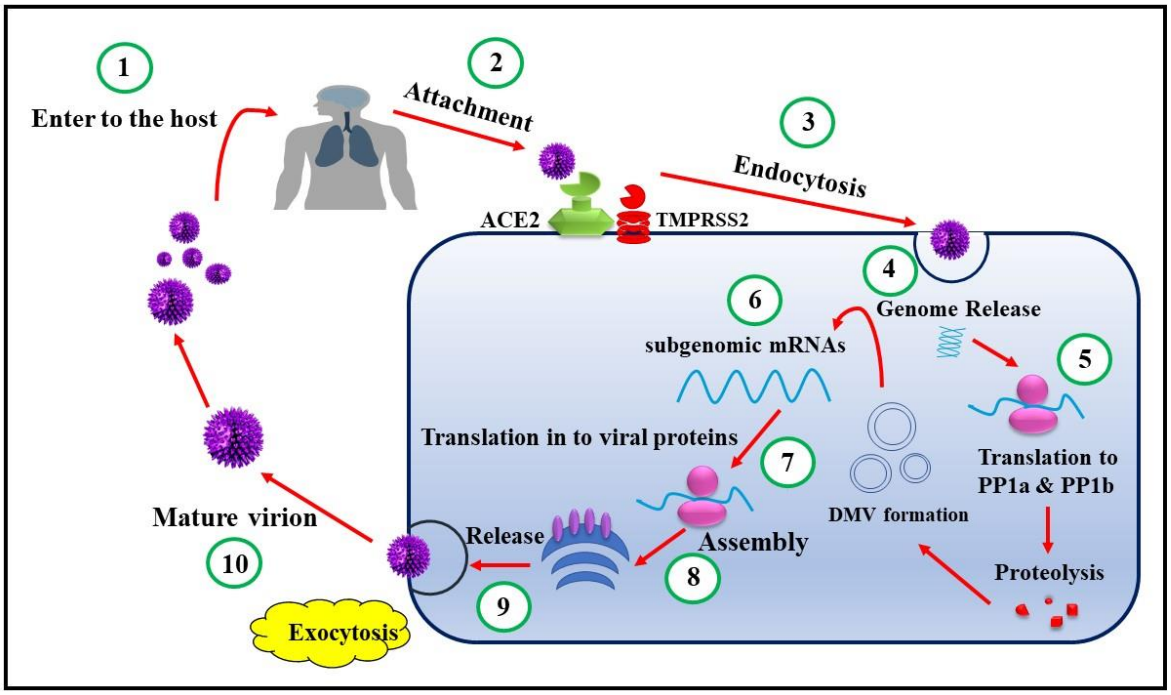

Figure 1. The replication cycle of SARS-CoV-2 in the infected cells; Upon SARS-CoV-2 attachment to its receptor, the virus enters the cell via endocytosis. Then viral genome directly translates into ribosomes and produces the non-structural proteins. Some of these proteins participate in DMV formation to protect viral RNA from host immune receptors. In DMVs, the subgenomic RNA is produced and this RNA translates to viral structural and accessory proteins in the cytoplasm. Then structural proteins will be localized in ER for virus assembly. At the end of this replication cycle, the virions release from cells by exocytosis. (Abbreviations: PP1a/1b: Poly Protein 1a/1b; DMV: Double Membrane Vesicle; ACE2: angiotensin-converting enzyme 2).

secrete serum IgM and IgA antibodies by day 5 to 7 and IgG by day 7 to 10 from the onset of the first signs of manifestations. The serum IgM and IgA titers decline after about 28 days, and IgG titer peaks at approximately 49 days (23-25). Overall, for providing an optimal immune response against viral infections, particularly SARS-CoV-2, the coordinated activity of cellular and humoral immunity is required.

Immune evasion: SARS-CoV-2 utilizes various tactics to evade the immune system to remain alive in infected host cells (26). Some of these mechanisms are: A) Interferences with the function of dendritic cells, B) Dysregulation in IFN-I production, C) overactivation of the NLRP3 inflammasome, and D) NK cell-mediated cytotoxicity exhaustion.

A) **Interferences with the function of dendritic cells:** The strategies used by SARS-CoV-2 with DC function interference activate an inadequate adaptive immune response by downregulating the expression of costimulatory receptors (CD80 and CD86) and human leukocyte antigen class II (HLA-II) molecules on the surface of the immature DCs, to disrupt the viral antigen presentation. This lack of maturation in DCs leads to slow antibody production and developing rises in SARS-CoV-2 viral load (22, 27).

B) **Dysregulation in IFN-I production:** Several SARS-CoV-2 non-structural and accessory proteins like nsp13, nsp14, and ORF6 can antagonize the IFN response and induces a delayed IFN-I response (28). double-membrane vesicles (DMV) encoded by NSP3, NSP4, and NSP6 are one of the virus evasion tools to avoid recognition of its dsRNA by innate immune sensors like RLRs, as in this way, dsRNA situated in DMV vesicles and protects from protein kinase R (PKR) and melanoma differentiation-associated

protein 5 (MDA5) recognition (29).

SARS-CoV-2 nsp1 protein is an essential pathogenic factor engaged in dysregulated IFN-I response. Nsp1 is located in the N-terminal region of the ORF 1 polyprotein produced after polyprotein 1a and 1ab cleavage during SARS-CoV-2 RNA translation. It binds to STAT1 and prevents its phosphorylation and its translocation to the cell nucleus so that it can suppress the production of antiviral proteins (30). Other SARS-CoV-2 proteins that contribute to Dysregulating the IFN-I production are nsp6, which binds TANK binding kinase 1 (TBK1) to suppress the phosphorylation of interferon regulatory factor 3 (IRF3), nsp13, which binds to TBK1 and blocks its phosphorylation SARS-CoV-2 ORF6 inhibits the nuclear translocation of IRF3 by binding to the importin Karyopherin a 2 (KPNA2) (30-32).

C) Overactivation of the NLRP3 inflammasome: SARS-CoV-2 ORF3a protein (viroporin), interaction with TRAF3 (Tumor necrosis factor receptor-associated factor 3) and ASC (Apoptosis-associated speck-like protein containing a CARD) results in activation of NF-κB and the NLRP3 inflammasome by inducing ubiquitination of p105 and ASC (33, 34). Another SARS-CoV protein that contributes to NLRP3 inflammasome overactivation is the SARS-CoV unique domain (SUD) of nsp3, which has three macrodomains (N, M, and C). The M and C domains are responsible for CXCL10 expression, and IL-1β secretion and induce the infiltration of macrophages and monocytes in lung epithelial cells (35).

D) NK cell-mediated cytotoxicity exhaustion: NKG2A is an NK-cell inhibitory receptor that contributes to NK-cell exhaustion. The increased expression of this receptor is responsible for NK cell exhaustion and reduces their capability to clear viral infections. The SARS-CoV-2 S protein with overexpression of the NKG2A receptor can modify NK-cell functions by leading to NK cell-mediated cytotoxicity exhaustion in COVID-19 patients (36, 37).

The second phase (The inflammation phase): After around 7 days of symptoms, the initial inflammatory reaction attracts virus-specific T lymphocytes to the site of infection. Usually, 10 days later, 50 percent of patients restore their average body temperature (14). In severe COVID-19 patients, SARS-CoV-2 induces an excessive immune response, resulting in a cytokine storm, ARDS, and even organ dysfunction (38-41).

In COVID-19 patients, elevated levels of pro-inflammatory cytokines like IL-1, IL2, IL-6, IL7, IL8, IL9, IL10, IL-12, Granulocyte-colony stimulating factor (G-CSF), Granulocyte-macrophage colony-stimulating factor (GM-CSF), Interferon gamma-induced protein 10 (IP10), macrophage inflammatory protein (MIP)1-alpha, monocyte chemoattractant protein (MCP)1, IFN-γ, and transforming growth factor (TGF), and also various chemokines such as chemokine (C-C motif) ligand 2 (CCL2), Chemokine (C-X-C motif) ligand 9 (CXCL9), and CXCL10 were detected in cases of severe COVID-19 compared to mild patients (13, 42, 43).

Conclusion

SARS-CoV-2 and its associated disease COVID-19 are among the most significant health and global economic burdens in the last 100 years. The SARS-CoV-2 showed an unexpectedly high transmission speed and global spreadability because of asymptomatic carriers, prolonged incubation time, specifically in old hosts, and super-spreaders. Based on many studies, COVID-19 represents different clinical forms from asymptomatic to mild, moderate, and very severe cases, but many unknowns exist. Although many aspects of COVID-19 immune mechanisms and pathogenesis are still unclear, we need global strategies to control the burden of this disease. As much as our knowledge in this area develops over time, we will see more improvements in vaccine developments and therapeutic strategies.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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