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A Review on New Coronavirus Mechanism of Action

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Abstract

The new coronavirus outbreak caused by the severe acute respiratory syndrome coronavirus2 (SARS-CoV2) has resulted in more than 126750 deaths worldwide so far and billions of expenses for the governments. SARS-CoV2, similar to SARS, was transmitted from bats and spread via human to human closed contacts. The virus uses its spike protein to bind to angiotensin-converting enzyme 2 receptors on target cells to replicate. Consequently, it spreads from infected cells to contaminate other cells. The body's first response toward the virus is to activate the innate immune system, leading to the synthesis of inflammatory mediators. In the next step, the adaptive immune system appears where B lymphocytes produce antibodies specific for the virus, and CD8+ cells kill the infected cells directly. In this article, we try to explain the virus mechanism of action and immune response in detail. Although many questions remain unanswered, we expect this review could help in vaccine and treatment progression,

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Introduction

Coronaviruses (CoVs) are a subgroup of enveloped and positive-sense single-stranded RNA viruses that can cause respiratory and enteric symptoms ranging from mild to severe and even life-threatening infections (1). According to the disease manifestations and the involved site, infective coronaviruses are divided into low and highly pathogenic CoVs. Low pathogenic viruses are responsible for seasonal common cold with mild to moderate upper respiratory symptoms, while highly pathogenic CoVs, such as severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), can invade the lower respiratory tract and cause pneumonia (2). CoVs were behind two significant epidemics in the past twenty years: SARS-CoV in 2003 originated in southern China and MERS-CoV in 2012 in Saudi Arabia, resulting in a terrifying outbreak with high levels of mortality (3). SARS-CoV-2, the third outbreak of coronaviruses, was firstly diagnosed in Wuhan in the Hubei Province of China and rapidly spread to all countries of the world (4). So far (4/15/2020), 2,000,066 infected cases and 126,754 deaths have been recorded (5). Previous studies revealed that direct virus invasion and the body's immune response play a key role in disease severity; however, more recent studies of patients who died of SARS-CoV showed that the host's dysregulated immune system could cause more fatality (6). In this review article, we try to summarize the SARS-CoV2 mechanism of action in the human body and discuss what we have already known about the ways it causes illness in patients.

Main:

Origin and animal reservoir of COVID-19

In December 2019, patients with acute respiratory symptoms of unknown etiology were admitted to local hospitals of Wuhan in Hubei province of China. Four were employees in South China Seafood Wholesale Market, and many others declared a frequent exposure to the same market (7). Samples taken from the patients were analyzed in the Wuhan Institute of Virology for its probable etiology. On January 7th 2020, Coronavirus was reported to be the initial cause of the disease with more

than 70% similarity with the previous SARS-CoV (8), this virus was reported as coronavirus disease 2019 (COVID-19). The number of infected cases started to increase; of them, many did not report any exposure to the seafood market, suggesting the human to human transmission (9). Investigations in live animal markets revealed that masked palm civets carry SARS-CoV-like viruses similar to SARS-CoV (10), but subsequent studies showed that they only serve as intermediate hosts (11). Further research was conducted to find the natural host for SARS-CoV, and by extracting anti-SARS-CoV antibodies from horseshoe bats, they reported to be the host emerging human pathogens (12).

Virus structure and invasion

Coronavirus uses the spike (S) protein on its surface to detect the proper receptor and enter the cells to transmit the infection to the host. The S protein is composed of two subunits: The N-terminal S1 for binding to the appropriate receptor and the C-terminal S2 to fuse with the hosts' cellular membrane. These two subunits help the virus to attach to the target cell and fuse its membrane with the cellular membrane, leading to viral entry (13). The S1 subunit of SARS-CoV2, similar to SARS-CoV, links the virus with the angiotensin-converting enzyme 2 (ACE2) receptor on the cell's surface (14). Most viruses use their host's endocytosis machinery system by clathrin-dependent or independent pathways to pass into the cells (15). SARS-CoV, like vesicular stomatitis virus and influenza virus, uses a clathrin-dependent pathway where they can translocate into endosomes by endocytosed receptors such as growth factor receptors (16). Subsequently, viruses attached to the endocytosed receptors will be carried into tiny vesicles called early endosomes. Then, early endosomes become mature and more acidic to form late endosomes for SARS-CoV which requires a low pH in intracytoplasmic vesicles (15). Different CoVs such as MERS and SARS have been reported to use the endocytic pathway as their primary mechanism for their entry into various types of cells, however the exact mechanism is still unspecified (17). As mentioned before, one way is the clathrin-dependent pathway, but a more recent study by Wang et al. (18) reported a completely different way: the clathrin-independent pathway. The reason for such an inconsistency may be the cell type used in different studies; therefore, more investigation is required. The endocytic mechanism of SARS-CoV2 has not directly been described, but as we know, it uses the same receptor of SARS-CoV for entrance (19). Experiments, in line with lab explorations, revealed that the new coronavirus is susceptible to lysosomotropic drugs such as chloroquine, suggesting they may use the same endocytic pathway as SARS-CoV for cell entry (20). While the ACE2 receptor is a crucial part of the virus entry, the next step for infection depends on the cell type. Based on experiments done by Zuo X. et al.(21), the primary cells infected by the virus are lung cells purified with ACE2 receptors. However, other organs vulnerable to SARS-CoV2 are heart, esophagus, ileum, kidney, and bladder. A recent study also indicates the presence of ACE2 receptors in oral mucosa, especially on tongue cells indicating that the oral cavity is a high-risk place for virus entry (22). Coronaviruses use a wide variety of pathways to complete their gene expressions. After the virus entry, its genome becomes uncoated, and the ribosomes start to translate mRNA to produce RNA-dependent RNA-polymerase (RdRp). Then, the RdRp uses the negative strand to create a new RNA. Therefore, there are more positive RNA strands than negative ones (1:10 to 1:100) (23). On the other hand, after the deposition of nucleocapsids in the cell cytoplasm, the viral genome becomes ready for translation. The synthesized proteins are transported Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection into the endoplasmic reticulum from where they can aim for the Golgi compartment. Here, nucleocapsids proteins encapsulate the genomes and form nucleocapsids. Finally, these new viruses are exported from infected cells through the plasma membrane (24).

Immune system response

So far, there has been no comprehensive study reporting the exact mechanism of the immune system toward SARS-CoV2, and we can only rely on previous experiments performed on SARS-CoV and MERS. Generally, soon after the virus invasion, the human innate immune system is activated to battle the organism by pattern recognition receptors (PRRs). PRRs like C-type lectin receptors, Toll-like receptors, and RIG-I-like receptors trigger the intracellular signaling cascades, leading to the synthesis of inflammatory mediators. Inflammatory factors, dendritic cells, and interferons' (IFNs) production consequently activate macrophage phagocytosis (25). Macrophages infected by the virus represent delayed and excessive levels of inflammatory cytokines which is believed to be responsible for a dysregulated immune response to SARS-CoV infection (6). This explains why patients with severe forms of the disease show higher levels of pro-inflammatory cytokines and chemokines (26). After that, the adaptive immune system appears. T cells, including CD4+ and CD8+, are crucial for this step. CD4+ T lymphocytes call for B lymphocytes to produce antibodies specific for the virus, and CD8+ cells kill the infected cells directly (27). T cells not only destroy the virus to prevent further destruction but also regulate the immune system to prohibit its overactivity (28). However, SARS-CoV seems to break this mechanism by initiating TNF-mediated T cell apoptosis resulting in an uncontrolled immune response. One early outcome of the virus

invasion and cytokine/chemokine release is lung epithelial and endothelial cell apoptosis. This proceeding leads to vascular leakage and alveolar edema, causing respiratory distress (29). In patients with a more prolonged SARS-CoV infection, pneumocyte hyperplasia and interstitial fibrosis were reported. Also, in infected mice pathological features, infiltration of macrophages, neutrophils, and fibroblasts were observed (30). Inflammatory cytokines such as IL-6, IL-8, IL-1β, and GM-CSF along with chemokines like CCL-2, CCL-3, CCL-5, and IP-10 play a crucial role in acute respiratory distress syndrome (ARDS) and higher mortality rate in patients (31,32).

Clinical features

The SARS-CoV2 is believed to infect the older population (median age 49) or patients with underlying disease. The mean incubation period in a study done on 7736 patients was reported being four days (ranging from 2-7 days) (33). The initial and more common symptom of SARS-CoV2 is fever, which was detected in 48.7% of patients on presentation and reached up to 88.7% after hospitalization (33). Fever could be the only symptom or in combination with other manifestations such as dry cough (76%), dyspnea (55%), myalgia (44%), and headache (8%). Gastrointestinal symptoms such as nausea, vomiting, and diarrhea were also reported in 3% of the infected population (9). Also, 14-20% of patients required ventilation support (34), and by February 14th, the mortality rate was estimated to be 2.2% (35). Tang B. et al. studied the transmission risk of SARS-CoV2 and reported an R0 of 6.47, while SARS-CoV R0 was between 2 to 4, and its mortality rate was 10% (36). These findings suggest that SARS-CoV2 has a higher transmission risk and a lower lethal rate, indicating the importance of its epidemiologic control.

Conclusion

Understanding the mechanism of action of SARS-CoV2 and the body immune response to it is a crucial factor in vaccine development and treatment finding. However, we need more detailed knowledge about the SARS-CoV2 life cycle and pathophysiology to accelerate its treatment development process.

Conflict of Interest

The authors declare no conflicts of interest.

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