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SARS-CoV-2–A Tough Opponent for the Immune System

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OPINION

SARS-CoV-2–A Tough Opponent for the Immune System

There are about 30 coronaviruses that can affect humans and animals, and their respiratory complications are common to both human and animal species. However, coronaviruses correlate with specific manifestations in animals, including diarrhea, encephalomyelitis, peritonitis, and hepatitis (1). Before SARS-CoV and MERS-CoV occurred, coronaviruses were only referred to as a possible cause of the common cold and mild localized respiratory infections in humans. SARS-CoV (Severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus) were the two epidemics that appeared in 2002 and 2012, respectively. MERS-CoV and SARS-CoV infection could cause manifestations of pneumonia, renal inadequacy, or even death and therefore made coronaviruses a global concern.

Coronaviruses recently returned with a new one, SARS-CoV-2, related to a potentially severe respiratory disease–called the coronavirus disease (COVID-19). The condition has raised considerable concerns due to its widespread and rapid distribution.

SARS-CoV-2 is Probably the Result of a Zoonotic Spillover

Zoonotic Spillover

Zoonotic spillover, also known as animal-to-human transmission, is referred to as when a pathogen is

transmitted from a non-human animal to a human. It is the result of the continuous processes of modifying an animal pathogen to become a zoonotic one. These processes help an animal pathogen to handle obstacles it will likely face as it becomes a zoonotic pathogen. The obstacles mainly correlate with specific pathogen attributes (prevalence, release, and survival), the exposure, and the reservoir-host interactions (2).

Human SARS-CoV-2 and Bat SARS-like Coronavirus Share Considerable Similarities

Research shows that the SARS-CoV-2 can be clustered with the 2015 isolated Bat SARS-like coronavirus. It supports the hypothesis that the novel coronavirus most likely originated from bats and reached to humans. Protein structure analysis reveals that the nucleocapsid protein (N) and the spike-like nucleoprotein (S) in SARS-CoV-2 share significant similarities with those of bat-like SARS coronavirus. However, some differences do exist which, given the importance of these two proteins in the efficiency of viral assembly and the fusion of cell membrane, may account for enhanced pathogenicity of the novel coronavirus compared with that of bat-like SARS (3). On the other hand, recent research suggests a possible intermediate host. Pangolin-CoV, found in Malayan pangolins, shares 91.02% similarity with SARS-CoV-2 at the genome level. However, neither Bat-CoV nor Pangolin-CoV possesses a furin cleavage site at the S1/S2 margin on the S glycoprotein, setting them apart from SARS-CoV-2 (4).

Bat's Unique Immune System Facilitates Cross-species Transmission of Viruses

Bats can play a role as a reservoir host for a variety of viruses due to their unique immune system.

Interferons (IFNs) are the immunomodulatory, antiviral agents that can promote phagocytosis by macrophage and restrain the spread and inhibit replication of the virus. Therefore, inhibition of IFN production would weaken the first line of defense and aid virus survival (5). Not only bats can regulate IFN type I response but also have adopted specific strategies to minimize virus-induced pro-inflammatory reactions (6). In this manner, bats have evolved towards an efficient antiviral immune response.

More interestingly, environmental stressors may reactivate the virus from latency, resulting in higher viral levels in perpetually infected bats. Elevated viral levels provide a suitable environment for viral replication leading to viral persistence. Viral persistence, in turn, might bring about new viral strains (7).

Taken together, we can assume that bats possess an additional, innate ability for antiviral defense, and, on the other hand, the potential to go hand-in-hand with the virus to generate variability. Consequently, bat viruses are highly capable of overcoming multiple barriers to become a zoonotic pathogen.

The Immunopathogenesis of Coronavirus Outbreaks: from SARS-CoV and MERS-CoV to SARS-CoV-2

The family of Coronaviridae comprises four genera: α, β, γ, and δ. The three aggressive coronaviruses, i.e., MERS-CoV, SARS-CoV, and the novel SARS-CoV-2, are all of the genus β (5,8) and have been found in bats (8). The interaction between receptor binding domain (RBD) of Spike (S) glycoprotein and the host cell surface receptor begins the coronavirus infection. For instance, the critical elements in coronavirus entrance are angiotensin-converting enzyme 2 (ACE2) for SARS-

CoV and SARS-CoV-2 and dipeptidyl peptidase-4 (DPP4) for MERS-CoV (9). The most common immunopathological consequence of the three highly pathogenic CoVs is the acute respiratory distress syndrome (ARDS) (10).

SARS-CoV

The SARS outbreak of 2002–2003 first occurred in southern China. Its spread to 25 other countries caused up to 8000 cases, with over 700 deaths. SARS-CoV infection presents with mild respiratory symptoms that can progress to atypical pneumonia (11). Male and elderly patients are more likely to develop severe forms of the disease (12). Histopathological investigation in SARS-CoV infected cases has described the possible role of inflammatory mechanisms in causing damage to the alveolar septa and pulmonary arteriole epithelium (5). A sudden drop in T lymphocytes is present as an acute phase response of SARS-CoV, which returns to normal later throughout the disease. However, the lymphocyte levels were still lower than those of healthy controls were. The release of SARS-CoV-specific IgG antibodies usually occurs 10–14 d after the onset of infection (13). SARS-CoV-specific IgM and IgA responses in recovered SARS patients are under six months-long, though virus-specific IgG levels persist for one year. Additionally, a consistent SARS-CoV-specific memory T cell response remains remarkable for six years, but virus-specific memory B cell response is absent in recovered SARS patients (14).

MERS-CoV

The MERS outbreak arose from Saudi Arabia and affected more than 2500 cases from 27 countries

by the end of 2019. Although MERS-CoV can affect a variety of human cell lines, its main target is epithelial cells of the lower respiratory tract (15). As for SARS-CoV infection, patients with MERS-CoV infection show high levels of serum pro-inflammatory cytokines along with lung injury (16). Even though lymphocytopenia is present in MERS infection, the levels are not as striking as SARS (13).

MERS-CoV and SARS-CoV remain considerably pathogenic despite being vulnerable to the IFN response. However, there is no complete grasp of the mechanism through which these viruses win over the immune system. The most likely hypothesis is that MERS-CoV and SARS-CoV interfere with the flow of IFN production, indeed as impairing both the innate and adaptive immune responses (5,6,17,18). Replication in virus-induced double-membrane vesicles that lack pattern recognition receptors (PRRs) is another strategy of SARS-CoV and MERS-CoV to hide from the immune system (10).

SARS-CoV-2

The 2019–2020 outbreak of COVID-19 has originated from Wuhan in China. Infection, severe, and death cases are more likely to belong to male and older people (15,19) and are mostly in those who have an underlying disease, e.g., hypertension, diabetes, and cardiovascular disease (20,21). The pattern of acute lung damage in cases with COVID-19 is alike that of SARS and MERS. Computed tomography (CT) scan features include a bilateral and peripheral consolidative opacity in the lung (22). As mentioned, SARS-CoV-2 entrance and pathogenesis rely on binding to the ACE2 receptor (13). However, possessing furin cleavage site by S glycoprotein and the expression of furin-like proteases in host cells on top of ACE2 expressing tissues broadens the SARS-CoV-2 tissue tropis

(23). Similar to SARS-CoV, levels of peripheral CD4+ and CD8+ T lymphocytes markedly decline in COVID-19 infection. One of the shortcomings of innate immunity is the aggressive systemic inflammatory response known as “cytokine storm” which is one of the elemental mechanisms of ARDS (10). Peripheral blood levels of inflammatory cytokines in patients with COVID-19 are high as for patients with SARS and MERS. However, COVID-19 has associated with elevation of T-helper-2 (Th2) cytokines as well. Given the anti-inflammatory properties of Th2 cytokines, it seems there is a tendency in COVID-19 to revert inflammatory response (16). This phenomenon can be used as a possible therapy since IL-10 seems to deviate the immune response from Th1 to Th2, therefore, minimize the detrimental impact of cytokine storm on lungs (24).

Lessons we can Learn from SARS-CoV and a Look at a SARS-CoV-2 Vaccine

DNA-mediated immunization using a plasmid DNA encoding the SARS-CoV S glycoprotein could lead to the induction of humoral and cellular immunity in mice (18). Precisely, it has shown to increase the number of both CD4+ and CD8+ SARS-CoV S-specific T-cells, the antibody levels, and also, the ability to produce neutralizing antibodies. Interestingly, vaccine-mediated immunity was influenced by neither the adoptive transfer of T cells nor the depletion of CD4+ and CD8+ cells. While the passive transfer of IgG to mice was successful in generating an effective immune response. These findings point that during viral infection and replication in the lung, the individual is protected by his humoral immunity, and the value of cell-mediated protection seems to be of no importance. It should be, however, remembered that viral clearance is a laborious task where cell-mediated protection will tend to become prominent over its counterpart–the humoral immunity. If viral removal is incomplete, the infectious virus persists in his home–the lung–as represented in stable high levels

of inflammatory mediators and also a high number of CD8+ T cells (25).

Efforts have commenced for the development of an epitope-based vaccine for the novel coronavirus and led to the recognition of 933 non-self viral pentapeptides (26). Among which, 107 pentapeptides belong to the protein S, and of these, 66 epitopes have previously been validated as immunogenic peptides and so are of high importance for the design of novel coronavirus vaccine.

In conclusion, virus-host interactions are capable of unleashing tremendous amounts of cytokines that, in turn, are involved in the pathogenesis of COVID-19. Besides the high potential of the novel coronavirus in compromising the respiratory system, its rapid transmission and ability to engage many hosts in severe forms of infections or immunopathological complications make it a tough opponent for the immune system.

Declarations

Ethics approval and consent to participate

Competing interests

The authors declare that they have no competing interests

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