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Insights into the virologic and immunologic features of SARS-COV-2

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Abstract

The host immunity is crucial in determining the clinical course and prognosis of coronavirus disease 2019, where some systemic and severe manifestations are associated with excessive or suboptimal responses. Several antigenic epitopes in spike, nucleocapsid and membrane proteins of severe acute respiratory syndrome coronavirus 2 are targeted by the immune system, and a robust response with innate and adaptive components develops in infected individuals. High titer neutralizing antibodies and a balanced T cell response appears to constitute the optimal immune response to severe acute respiratory syndrome coronavirus 2, where innate and mucosal defenses also contribute significantly. Following exposure, immunological memory seems to develop and be maintained for substantial periods. Here, we provide an overview of the main aspects in antiviral immunity involving innate and adaptive responses with insights into virus structure, individual variations pertaining to disease severity as well as long-term protective immunity expected to be attained by vaccination.

Key Words: SARS-CoV-2; Immune response; Neutralizing antibodies; Spike protein

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Core Tip: Robust cellular and humoral responses are elicited in immunocompetent individuals with severe acute respiratory syndrome coronavirus 2 infection that remain detectable for several months following exposure. A balanced T cell response and neutralizing antibodies in circulation and mucosal surfaces are pivotal in controlling virus infection and for protection. Particular impairments in innate and adaptive immune responses are associated with pathogenesis and severe disease.

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INTRODUCTION

An outbreak of pneumonia was reported in Wuhan City, Hubei Province, China in December 2019. In a short time, the World Health Organization declared the epidemic as a public health emergency of international concern[1]. The agent was subsequently named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, and the World Health Organization named the disease caused by SARS-CoV-2 as coronavirus disease-2019 (COVID-19)[2].

SARS-CoV-2 is the third zoonotic human coronavirus that emerged in this century following SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) [3]. Overall, SARS-CoV-2 is less pathogenic than SARS-CoV and MERS-CoV but more transmissible[4].

STRUCTURAL HALLMARKS OF SARS-COV-2

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus, classified in the *Coronaviridae* family, *Betacoronavirus* genus[5,6]. It is phylogenetically-related to SARS-CoV and bat SARS-like coronavirus strain BatCov RaTG13, with 79.6% and 96.2% identities, respectively[7]. However, the origin of SARS-CoV-2 is yet to be confirmed. Although betacoronaviruses from Malayan pangolins share sequence similarities in the receptor binding domain (RBD) of the spike (S) gene, they are more distantly-related[8,9]. Therefore, pangolins are suggested as the intermediate host for SARS-CoV-2[8].

The genome size of SARS-CoV-2 is approximately 29.9 kb with 14 open reading frames encoding 27 proteins[5,10]. These include four structural (nucleocapsid (N), envelope (E), membrane (M) and S), as well as 16 nonstructural (nsp1-16) and seven accessory (ORF3a-ORF8) proteins (Figure 1).

The proteins encoded by the SARS-CoV-2 genome have various functions in virus replication and packaging. The S protein interacts with the host cell receptors and is essential for virus entry into host cells[11]. It is also a major antigen targeted by the immune response. The subunit S1 involves the RBD and binds to the host cell, while S2 fuses the viral and cellular membranes for penetration[12,13]. The RBD of the S protein recognizes the cellular receptor, angiotensin-converting enzyme 2 on the host cell, and SARS-CoV-2 enters into the target cell. The E and M proteins, major components of the virus structure, participate in virion assembly and release[14]. M protein binds to the N and accessory proteins 3a and 7a for the budding of viral particles[15]. Virus capsid formed by the N protein encapsulates the viral genome and contributes to replication and the cell signal pathway[16]. Main features and known functions of the viral nonstructural proteins are provided in Table 1.

IMMUNE RESPONSE IN COVID-19

Similar to many other respiratory viruses, a robust immune response with innate and adaptive components develops in individuals infected with SARS-CoV-2[36]. Nearly a year following the declaration of the pandemic, it is now established that SARS-CoV-2 infections produce prolonged immunity with cellular and humoral responses, detectable for several months after exposure. However, the duration and patterns of this response in exposed and vaccinated persons need further elucidation as hallmarks for assessment of protective immunity in individuals and populations. Moreover, the association of variations in individual immune responses and their impact in pathogenesis also need in-depth investigation to fully understand and control severe manifestations of COVID-19[37].

In general, the initial response upon viral infection involves the components of the innate immunity such as induction of type I interferon, the inflammation process, complement, neutrophils and natural killer cells, which are subsequently taken over by adaptive responses involving T and B lymphocytes. Various viral proteins processed by the antigen-presenting cells such as dendritic cells are recognized by T and B cells in lymphoid tissues, resulting in activation of humoral and cellular

Table 1 Functions of the severe acute respiratory syndrome coronavirus 2 non-structural proteins

Protein	Function
Nsp 1	RNA processing Fixing of the replication complex to cellular membranes[17]
Nsp 2	p65 homolog Host cell survival[18]
Nsp 3	Proteolytic cleavage[19]
Nsp 4	Stabilization of the viral replication-transcription complex[20]
Nsp 5	Polyprotein processing[21]
Nsp 6	Autophagosome expansion inhibition[22]
Nsp 7/8	Primase[23,24] RNA-dependent RNA polymerase (RdRp) cofactor[25]
Nsp 9	ssRNA-binding protein[26]
Nsp 10	Cap methylation of viral mRNAs[27]
Nsp 12	Catalytic subunit of the RdRp[25,28]
Nsp 13	Helicase (Hel) and NTPase activity[29,30] Interferon antagonist[31]
Nsp 14	Exoribonuclease (ExoN) and methyltransferase activity[32] Interferon antagonist[31]
Nsp 15	Nidoviral RNA uridylylate-specific endoribonuclease (NendoU)[33] Interferon antagonist[31]
Nsp 16	2'-O-ribose methyltransferase mRNA capping[34,35]

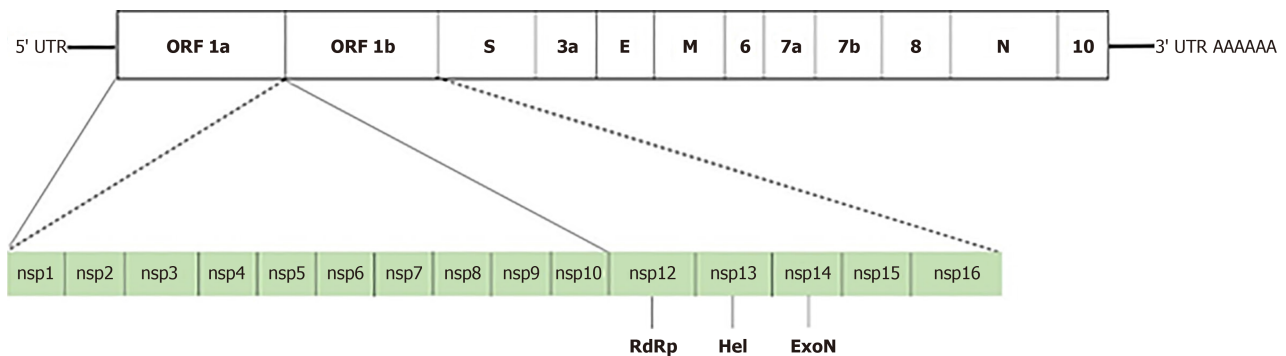


Figure 1 Organization of the severe acute respiratory syndrome coronavirus 2 genome[11]. Open reading frame (ORF)1a encodes nsp1-10 and ORF1b encodes nsp11-16. Structural proteins are encoded by spike (S), envelope (E), membrane (M) and nucleocapsid (N). A poly(A) tail is located at the 3' untranslated region (UTR).

components of the adaptive response that produce highly-specific defense mechanisms to control ongoing or future infections[36,38]. Here, main findings in antiviral immunity involving particular components of the innate and adaptive immune response are revisited.

Hallmarks of innate immunity

As the first line of defense against virus infection, appropriately elicited innate immunity is crucial to control SARS-CoV-2 infections as well as for an optimal adaptive response. Reduced type I interferon responses due to various factors such as mutations in the genome or autoantibodies are associated with severe disease[39-41].

Interestingly, an excessive response has also been observed to exacerbate clinical symptoms, where an overproduction of proinflammatory cytokines, which may be coupled with impaired type I interferon response, is present. Here, the signature cytokines have been identified as interleukin-6 (IL-6), IL-10 and C-reactive protein[42, 43]. IL-6 has attracted particular interest due to its involvement as a potential contributing factor in SARS-CoV-2-associated acute respiratory distress syndrome[44]. It regulates dendritic cell differentiation, plasma cell maturation and is associated with ischemic injury. In SARS-CoV-2 infections, excessive macrophage activation and IL-6 production may result in the cytokine storm with subsequent endothelial cell damage, capillary leak and development of acute respiratory distress syndrome. Therefore, the inhibition of IL-6 or receptor binding has been investigated as potential therapeutic options to reduce morbidity and mortality with inconclusive findings so far[38,45-47].

In conjunction with IL-6 and other proinflammatory cytokines, the complement system also contributes to the pathogenesis in severe COVID-19 disease, including thrombotic events. Findings in infected individuals as well as acute lung injury models in mice indicate the involvement of the C5a-C5a receptor axis[48,49]. SARS-CoV-2 N protein is suggested to activate the mannose binding-lectin pathway, which in turn may be a triggering event in acute respiratory distress syndrome development[50]. Hence, complement inhibitors, especially those that can suppress coagulation pathway activation, such as C1 esterase inhibitor, are currently being investigated as novel approaches for treatment of SARS-CoV-2 pneumonia[38,51]. Complement system activation *via* alternate or classic pathways is also involved in COVID-19 disease, especially following antibody response and may be a key contributor in the immune complex-related injury[38,49].

In addition to the aforementioned contributors, changes in the expression of interferon receptor gene *IFNAR2*, tyrosine kinase 2, monocyte/macrophage chemotactic receptor CCR2 and particular antiviral restriction enzyme activators (OAS1, OAS2, OAS3) were documented in infected individuals, some associated with disease severity[42,43,52].

Despite aimed to prevent *Mycobacterium tuberculosis* infections, the Bacillus Calmette-Guérin vaccine has been proposed to affect COVID-19 infections in regions where it has been used in population vaccination[53-54]. Although reduced disease severity and mortality were observed in some reports, a beneficial effect is not universally documented[55-59]. The proposed mechanism of action is the enhanced reactivity of monocytes/macrophages and natural killer cells by epigenetic reprogramming (also termed as “trained immunity”), in the presence of proinflammatory cytokines[60]. Currently, the impact of heterologous protection provided by the Bacillus Calmette-Guérin vaccine in COVID-19 lacks concrete evidence, which is likely to be provided by the ongoing clinical trial[59].

Hallmarks of adaptive immunity

The humoral and cellular components of the adaptive immune response, mainly involving various T and B cell subsets, provides specific defenses for controlling ongoing virus infection as well as neutralizing immunity upon re-exposure. Therefore, information on the mechanisms and dynamics of the adaptive response in COVID-19 is crucial to understand pathogenesis and to develop successful preventive measures [36].

Cellular responses: A robust and enduring CD4+ and CD8+ T cell response is elicited in the majority of SARS-CoV-2-infected individuals, targeting multiple virus epitopes including S, N and M proteins[61,62]. It is detectable from the second week of symptom onset and at the convalescent stage[62,63]. Although the duration and degree of protection is not clear, virus-specific T cells remain detectable 6-8 mo following infection[64,65]. Variations in breadth and magnitude of the T cell response and associations with disease severity is reported in some cohorts[61,63,66,67]. In SARS-CoV-2 infections, virus-specific CD4+ T cells produce tumor necrosis factor, IL-2 and interferon, where CD4+ T cell response is correlated with anti-spike/anti-nucleocapsid IgG/IgA and neutralizing antibody titers[63,64,68-70]. Similarly, CD8+ T cells are commonly present in convalescent plasma of COVID-19 patients in which activated cytotoxic and polyfunctional/stem-like cells prevalent at acute and convalescent stages, respectively[62,63,66,69,71]. Single cell transcriptome investigations provided insights into T cell subsets in different groups of infected individuals, indicating that a coordinated and focused immune response is crucial for successful elimination of the virus[72]. It is also noteworthy that the virus-specific T cell repertoire is maintained following infection for extended periods despite declines in humoral immunity and can swiftly be activated upon recurrent exposure and antigen

presentation[63,73]. A polyfunctional and persistent SARS-CoV-2 specific memory develops in recovered patients, which can contribute to a rapid anamnestic response upon re-exposure[74,75]. Interestingly, a prolonged viral RNA positivity in pharyngeal mucosa with reduced risk for transmission was associated with increased SARS-CoV-2-specific CD8+ T cells, suggesting that low-level viral persistence supports immune stimulation and maturation[76].

During acute SARS-CoV-2 infections in adults, a peripheral T cell depletion resulting in lymphopenia might occur[61]. A transient condition that coincides with clinical recovery, it is associated with extensive T cell activation, altered differentiation and diminished function possibly involving proinflammatory cytokines, which in turn may prolong viral clearance and increase morbidity[73,77].

An intriguing observation is the detection of pre-existing CD4+ and CD8+ T cells in persons with no documented virus exposure[73,78,79]. Involving several T-cell epitopes, it suggests that previous exposures to endemic coronaviruses causing seasonal upper respiratory tract infections induce some sort of cross-reactive immunity to SARS-CoV-2[79,80]. The extent and potential impact of the cross-protection is not currently well-defined, but it is probably among the contributing factors to the varying clinical presentations in COVID-19 disease[81].

Humoral responses: In SARS-CoV-2, a polyclonal humoral response with antibodies, mainly targeting virus S and N proteins is mounted[82,83]. Despite the presence of IgM, IgG and IgA antibodies in acute and convalescent COVID-19 patients, virus serology is not practical in diagnosis, as antibodies increase only slightly during early symptomatic disease and are detectable in a portion of the patients[68,82,84]. Subsequently, a gradual increase in virus-specific IgG and IgM levels are observed with IgA dynamics similar to IgM, having attained peak levels before IgG. Most of the patients will have detectable seroconversion within 20 d after the onset of symptoms with a median time of 12 d[82,85,86]. Then, IgM levels begin to decrease in approximately 3 wk after symptom onset, while IgG continues to elevate, peaking at 50-60 d post infection and may last up to 10 mo[87,88]. Despite decreasing antibody levels, memory B cells remain and activate to produce antibodies upon virus re-exposure[89]. In COVID-19 patients, antibody levels are negatively correlated with viral RNA, which indicates their importance in eliminating the viruses in circulation[82,90]. In the respiratory tract, mucosal immunity provided by IgA antibodies and local T cells can effectively abolish SARS-CoV-2 infection and prevent systemic dissemination and further transmission[37].

Neutralizing antibodies are capable of suppressing virus entry into host cells. Therefore, they are pivotal in protection from reinfections. They are produced in human infections as well as animal infection models and observed to persist for 6 mo following infection[87,89,91]. Among antibodies against the S protein, RBD as well as S1 and S2 domains are targeted by neutralizing antibodies[83,89,91,92]. Anti-RBD antibodies have been reported to persist longer, possibly related to the preferential detection of higher-affinity antibodies[91]. Furthermore, despite variations in antibody titers, the number of RBD-specific memory B cells is shown to remain stable over time, producing antibodies with increased potency and resistance to mutations in the virus genome, suggesting ongoing evolution of the humoral response. This is likely to be fueled by persistent B cell exposure to antigens trapped as immune complexes on follicular dendritic cells[89].

Similar to cellular immunity, some form of cross-reactivity between SARS-CoV-2 and other human coronaviruses seem to occur. This is particularly observed in N protein and S1-S2 subunits of the spike protein but not in the RBD region for SARS-CoV and follows genomic similarities in these regions[86,92-94]. The impact of cross-reactive antibodies, especially those induced by endemic respiratory coronaviruses in SARS-CoV-2 immune response remains to be elucidated.

The impact of the virus-specific humoral immune response has led to the practice of administration of convalescent plasma as a therapeutic option, especially in severe disease to benefit from immediate effects of preformed polyclonal antibodies[37,82]. Such therapies have previously been used in particular viral pathogens such as Ebola virus, SARS-CoV and MERS-CoV[82,95]. Currently, sufficient data is lacking to establish the effectiveness as well as indications/limitations of convalescent plasma therapy in COVID-19 disease[82]. Many factors including the timing of administration during clinical course, patient selection criteria and antibody titers in the donor plasma seem to influence the outcome. Due to limited availability of convalescent plasma from donors, monoclonal neutralizing antibodies, antibody cocktails and antibody designs to increase efficiency are currently in clinical trials[95-98].

CONCLUDING REMARKS AND INSIGHTS FOR VACCINATION

An optimal immune response to SARS-CoV-2 appears to include high-titer neutralizing antibodies and a balanced T cell response. Factors affecting innate and mucosal immunity also contribute substantially to infection control[37,38]. Currently used vaccines have been approved for population immunization with Emergency Use Authorization in several countries, based on the findings of the interim Phase III clinical trials. Current vaccine prototypes utilize various antigen delivery strategies based on DNA, mRNA or adenovirus-based platforms, recombinant viral subunits/protein and inactivated virus as well as other approaches. The reports on preclinical efficacy, phase I-III clinical trials and the immune responses induced by these vaccines have been extensively reviewed and can be found in detail elsewhere [37]. Protective immunity induced by different vaccine platforms may be based on different immune mechanisms and may require booster administrations to maintain long-term immunity. Therefore, a thorough understanding of immune responses induced by each platform and subsequent outcomes in preventing transmission and controlling infection must be monitored and optimal boosting strategies should be determined.

CONCLUSION

Robust cellular and humoral responses are elicited in immunocompetent individuals with SARS-CoV-2 infection that remain detectable for several months following exposure. Impaired type I interferon response, imbalances in complement components and production of excessive proinflammatory cytokines such as IL-6 are associated with pathogenesis and severe disease. Several antigenic epitopes in virus S, N and M proteins are recognized by the immune system. A balanced T cell response and neutralizing antibodies in circulation and mucosal surfaces are pivotal in controlling virus infection and for protection. Despite reductions in antibody levels in months following infection, the maintained memory cells can be activated to produce antibodies upon virus re-exposure. Cross-reactive immunity due to previous exposure to other coronaviruses is documented, with currently unknown implications for SARS-CoV-2 infections.

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