Immune system response to COVID 19: A review article

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Abstract

SARS-CoV-2 is a newly emerged coronavirus that has been widely transmitted since late 2019. It has caused a pandemic and infected roughly 750 million people globally. It mainly promotes the immune system, which is vital as a barrier against COVID-19. Humoral immunity (antibody-mediated immunity), among the various functions of the immune system against the coronavirus, plays an outstanding role in preventing infection. This review presents a brief overview of the immune system regarding its protection of the human body from COVID-19; illustrates the process of the immune system, how it works, and its mechanism to fight virus. A systematic search was conducted in PubMed, Embase, Cochrane Library and Web of Science databases, and grey literature was searched through Google Scholar included all scientific literature published from 2020 until 2023.

Keywords: SARS-CoV-2, COVID 19, immune system, immunity, antibody.

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Introduction

COVID-19 is a horrible pandemic that spread worldwide, resulting in hundreds of millions of infected cases and millions of fatalities. The disease initially appeared in Wuhan, China, spread quickly, and eventually became a pandemic (1). Fever, dry cough, and exhaustion are the most common symptoms of this disease. A large number of infected individuals get severe pneumonia, and some develop acute respiratory distress syndrome (ARDS) (2)

An efficient immune response against SARS-CoV-2 may be considered fundamental for the resolution of COVID-19. However, some studies have shown a significant relationship between the disease severity and the levels of proinflammatory cytokines and subsets of immune cells (3,4). It has been suggested that during the response to SARS-CoV-2, the immune dysregulation and the high level of proinflammatory cytokines could be the main cause of tissue injury. Eventually, the exact pathophysiologic mechanism of COVID-19 remains still largely unknown.

SARS-CoV-2 is a linear positive-sense (+) single stranded RNA (ssRNA) virus and a significant member of the large coronaviruses group {4}. Coronaviruses have caused three epidemics in the past two decades namely, COVID-19, SARS, and Middle East respiratory syndrome (MERS) (5).

Interaction of SARS-CoV-2 with the host cells occurs via attachment of viruses spike (S) protein to the host angiotensin-converting enzyme 2 (ACE2) receptor, processed by transmembrane protease serine 2 (TMPRSS2). TMPRSS2 is a critical fusion peptide for fusing the virus into the host cells (6). SARS-CoV-2 and other coronaviruses encode several non-structural manipulating virulence proteins that interact with the host immune system, causing alteration of host cells' physiology (7). Although the interaction between SARS-CoV-2 with the host immune system, underlying molecular immune mechanisms, and the cause of the differences in clinical symptoms have been studying since the virus identification, the means by which the virus causes immune evasion and exhaustion has not entirely been elucidated (8).

Notably, the distribution and replication of SARS-Cov-2 were found in the respiratory system and the genitourinary, gastrointestinal, and even central neural systems (9). Therefore, SARS-CoV-2 can be detected in urine and stool, except in samples from the respiratory tract, which increased the risk of

infection via sewage networks and wastewater systems (10)

Immune responses

The immune system is the best defense because it supports the body's natural ability to defend against pathogens (eg, viruses, bacteria, fungi, protozoan, and worms (11)) and resists infections. As long as the immune system is functioning normally, infections such as COVID-19 goun noticed. The three types of immunity are innate immunity (rapid response), adaptive immunity (slow response), and passive immunity . Passive immunity has two types: natural immunity, received from the maternal side, and artificial immunity, received from medicine. Skin and inflammatory responses begin when the body is affected (12,13). However, when the body encounters germs or viruses for the first time, the immune system cannot work properly, and illness can occur. This scenario is what has occurred in the case of COVID-19 (14).

Protective SARS-CoV-2-specific antibodies and cell-mediated responses are induced following infection. Evidence suggests that some of these responses can be detected for at least a year following infection **(15).**

●Humoral immunity

After primary COVID-19 infection, the humoral immune system was activated through stimulation by CD4+ T helper cells or direct interaction with SARS-CoV-2. However, patients indicate a different algorithm during COVID-19 infection (16). B-cells-secreted antibodies can contribute to the clearance of infected host cells through binding to viral antigens and directing natural killer (NK) cells to kill them via antibody-dependent cell cytotoxicity (ADCC) (17). Subsequently, memory B-cells are formed, an essential component of long-lasting immunity after viral clearance. Although antibodies are vital components in the release of viral pathogens, some antibodies may lead to abnormal B cell activation and the progression of infection (18). Since the secretory immunoglobulin A (IgA) protects the mucosal respiratory tract against SARS-CoV-2, it is typically considered the most critical immunoglobulin in neutralizing SARS-CoV-2. In patients with COVID19 infection, IgA released earlier than other Immunoglobulins, remains longer than IgM, and stimulates the production of pro-inflammatory cytokines such as monocyte chemoattractant proteins (MCPs) and interleukin-6 (IL-6) (19,20). In addition, anti-SARS-CoV-2 IgA was identified in patients' saliva and remained for approximately three months after symptoms appearance (21). High levels of both IgG and IgA are associated with severe COVID-19 infection (22). Interestingly, although IgA and IgG were detected in breast milk with Covid19, other body fluids lacked these antibodies. However, seronegative patients mean no immunity (23).

Following infection with SARS-CoV-2, the majority of patients develop detectable serum antibodies to the receptor-binding domain of the viral spike protein and associated neutralizing activity **(24).**

However, the magnitude of antibody response may be associated with severity of disease, and patients with mild infection may not mount detectable neutralizing antibodies **(25)**. When neutralizing antibodies are elicited, they generally decline over several months after infection, although studies have reported detectable neutralizing activity up to 12 months **(15)** .In one study of 121 convalescent plasma donors with initial spike-binding titers ≥1:80, titers declined slightly over five months but remained ≥1:80 in the vast majority, and neutralizing titers correlated with the binding titers **(26)**.Other studies have also identified spike- and receptor-binding domain memory B cells that increased over the few months after infection as well as spike protein-specific plasma cells, and these findings suggest the potential for a long-term memory humoral response **(27).**

Neutralizing activity has been associated with protection from subsequent infection **(28).** Detectable binding antibodies, which generally correlate with neutralizing activity, are also associated with a reduced risk of SARS-CoV-2 reinfection **(29).**

●Cell-mediated immunity

Given the high number of infiltrated CD8+ T cells (80%) recruited to the infected area, the researchers believe cellular immunity is the first line of defense against SARSCoV-2 infection (30). However, the exhausted infiltrated T cells cause the reduction of non-exhausted CD8+ T-cells in patients with severe COVID-19 (31).

Studies have also identified SARS-CoV-2-specific CD4 and CD8 T cell responses in patients who had recovered from COVID-19 and in individuals who had received COVID-19 vaccination, which suggest the potential for a durable T cell immune response **(32).**

The first study on patients with COVID-19 revealed that low levels of IFN-γ and TNF-α in

CD4+ T cells are associated with severity. Consistently, in CD8+ T cells, the frequency of the exhausted (PD-1+CTLA-4+TIGIT+) subset was significantly higher in the severe group (33). Consequently, the no (low) functionality of CD8+ T cells in severe patients could impact an efficient control of infection (31), as previously described in SARS-CoV infection (34). Furthermore, COVID-19 was associated with a significant decrease of T cell activation, determined by CD25, CD28, and CD69 expression on CD4+ and CD8+ T cell subsets (34). Despite a wave of information on the specific T cell responses to many other pathogens, less is known about respiratory CoV infections. CD8+ T cells are typically required for the control of influenza virus and other respiratory viruses (34). Furthermore, T resident memory cells (TRM) are critical in preventing re-infection from influenza virus (35). Their role in SARS-Co-V2 infection should be, however, more finely determined. In senescent mice infected by SARS-CoV, CD8+ CTLs alone are not sufficient to clear the virus in the absence of both CD4+ T cells and specific Abs (36).

Serological follow up of post covid condition

Similar to other viral respiratory infections, patients infected by SARS-CoV-2 generally mount an immune response with virus-specifc IgM, IgA and IgG antibodies, but anti-SARS-CoV-2 antibody titers appear to vary considerably between individuals **(37).**

Furthermore, it is so far unknown how long immunity against SARS-CoV-2 persists in patients who recovered from the infection. Previous investigations have shown that respiratory coronaviruses causing common colds usually elicit only weak immune responses that wane rapidly **(38)** . In contrast, immunity against the SARS-CoV-1 and MERS-coronaviruses that are more related to SARS-CoV-2, appear to be more sustained **(39).** Investigations of the course of antibody responses against SARS-CoV-2 showed conflicting results so far. While some reports indicated rapidly waning antibody titers **(40)** others found a slower decline **(41).**

Antibody assays have a significant benefit over Quantitative reverse transcription **PCR** (qRT-PCR) so that they can identify people who had SARS-CoV-2 infection even if they have never undergone testing while acutely ill **(42).** Serological tests can be completed more quickly, cheaply, and with fewer steps than molecular approaches **(43,44).** Nucleic acid amplification tests (NAATs) can be performed in conjunction with serological diagnostics when the viral load of patients is below the detection limit of qRT-PCR assays **(44,45).**

Furthermore, serological tests can be practical in the following situations: (1) diagnosing patients with negative qRT-PCR results and strong clinical evidence suggesting infection, (2) diagnosis of patients more than 1 week after the onset of symptoms, and (3) figuring out the potential immunity and the likelihood of protection against a reinfection **(46,47).**

IgM is the earliest immunoglobulin raised against viral invasion. Then IgG levels begin to grow, with higher specificity and viral neutralizing activity **(48).** The antibody assay is a confirmed test to detect the presence and trend of COVID-19 disease. **(49)** developed a 15-min point-of-care lateral flow immunoassay to detect IgM and IgG in human blood. According to their primary research, the total testing sensitivity and specificity were 88.66, and 90.63%, respectively **(49).**

Some studies have revealed that IgM and IgG antibodies against SARS-CoV-2 rise nearly four days after the appearance of the COVID-19 symptoms and peak one month later **(50,51).** It has been established that the neutralizing properties of anti-SARSCoV-2 IgG antibody have a regular pattern, in which antibody increases rapidly within the first 3 weeks and then decreases 6 months after the onset of symptoms (52). Another study reported that the serum levels of anti-SARS-CoV-2 RBD-specific IgM, IgG, and IgA antibodies were rapidly reduced in serum of convalescent patients 4–14 weeks after discharge (53). Accordingly, it can be inferred that the production pattern of anti-SARS-COV-2 antibodies in COVID-19 patients is different (54). However, a longitudinal study reported that recovered patients with both low peak infection dose (ID50 < 10,000) and high peak infective dose (ID50 > 10,000) maintained a titer of SARS-COV-2-neutralizing antibody up to 60 days POS (55). In addition, Wajnberg et al., have shown that the anti-spike IgG antibody will be stable in individuals with a mild-to-moderate COVID-19 for up to 5 months (56)

Conclusion

The immune system is the best defense of the body against different infection .The process and mechanism of the immune system can be a good source of knowledge for immune system

development. The tracking of COVID-19 antibodies durability in eligible volunteers after infection demonstrated that their levels declined significantly over 6 months.

Further research prospectives

Further research could focus on the most recent observations regarding COVID-19 treatment. Also research on nutrition (eg, dietary recommendations) to boost the immune system should be explored and recommended because no registered medicine is available for COVID-19 treatment.

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