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Immune Responses to SARS-CoV-2

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Abstract

Since the onset of the COVID-19 pandemic, there have been over 100 million cases of the disease worldwide. Although the overall mortality rate of COVID-19 remains relatively low at approximately 2%, the highest mortality rate has been observed in patients with severe cases of COVID-19, reaching as high as 77%. Although researchers and clinicians continue developing treatments for severe COVID-19, the mechanisms that regulate the development of severe disease are complex and relatively unknown. The objective of this review is to summarize the differences between mild and severe cases of COVID-19 and their distinct effects on the immune system and its cells/proteins, including differences in the innate and adaptive immune responses triggered by varying degrees of disease severity. Identification of the mechanisms responsible for the development of severe COVID-19 may offer potential targets for future prevention and treatment methods that can reduce mortality rates from severe COVID-19. This review focuses on cytokine storm formation as the primary mechanism for severe COVID-19 development and explores alternative mechanisms that have been identified, such as how COVID-19-induced interferon loss inhibits the body's viral suppression capabilities and how different blood types may play a role in facilitating viral infection or protecting against it.

Keywords: Severe COVID-19; SARS-CoV-2; Immune system; Cytokine storm.

INTRODUCTION

The COVID-19 pandemic has impacted communities across the world in ways unprecedented in the modern era. As of June 2021, there have been over 150 million COVID-19 cases and 3.5 million deaths from COVID-19 worldwide, with >550,000 deaths in the United States alone. Patients who develop severe COVID-19 manifest acute symptoms, usually respiratory failure requiring ventilation. The make up about 15% of all cases [1] and have an estimated mortality rate of up to 77% [2], much higher than the mild-to-moderate disease mortality rate of 5.45% [3].

This review focuses on the differences between the innate and adaptive immunological mechanisms behind mild and severe cases of COVID-19. In identifying these differences, we aim to pinpoint the specific mechanisms responsible for the development of severe COVID-19. This may uncover potential targets for future treatments and preventive strategies that could reduce severe COVID-19 and related mortality.

SARS-CoV-2 Infection

COVID-19 is caused by infection with SARS-CoV-2, a novel coronavirus responsible for starting and maintaining the current worldwide pandemic. SARS-CoV-2 expresses a Spike protein on its surface that binds angiotensin-converting enzyme 2 (ACE2) on the membranes of host cells (Figure 1A) [4]. The virus mainly targets airway and alveolar epithelial cells that express ACE2. The serine protease TMPRSS2 is required for host cell infection, as it primes the S-protein and facilitates the virus's entry into host cells. Once infected, the virus replicates and matures within the host cell, eventually inducing pyroptosis, a highly inflammatory form of programmed cell death [5]. Viral RNA is released from the dead host cell, which then infects neighboring cells to repeat the cycle until full respiratory tract infection is achieved.

Innate Immune Response

The innate immune system includes monocytes, neutrophils, and macrophages that respond to infections

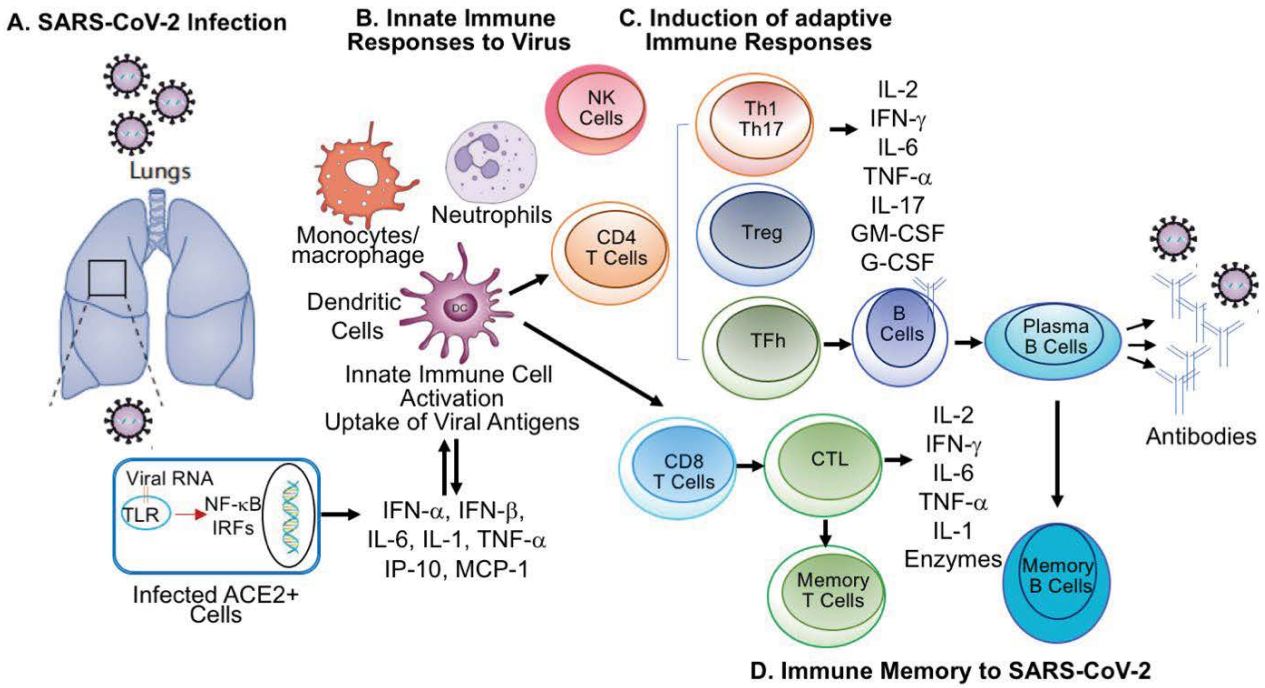

Figure 1. Host immune responses to SARS-CoV-2 infection. (A) Airborne SARS-CoV-2 infects ACE2-expressing target cells in the lungs. Cells infected by the virus may overcome the protective effect of type 1 interferons (IFN-α and IFN-β) to cause uncontrolled viral replication, resulting in pathologic respiratory injury that leads to pneumonia. **(B)** Recruited innate immune cells (neutrophils, monocytes/macrophages, and dendritic cells) are activated to produce pro-inflammatory cytokines (TNF-α, IFN-γ, IL-1, IL-6, IL-17). **(C)** The "cytokine storm" or "cytokine release syndrome (CRS)" may be enhanced by prolonged activation of $CD4^+$ and $CD8^+$ T cells. **(D)** B cells or plasma cells produce SARS-CoV-2 specific antibodies that help neutralize the virus, and memory T and B cells will initiate a rapid immune system response against potential future re-infection.

by releasing cytokines that signal and activate the cells of the adaptive immune system. In SARS-CoV-2 infection, a local immune response is initiated following the destruction of lung cells and the generation of damage-associated molecular patterns (DAMPs) that are released by host cells after pyroptosis [6]. This local immune response to SARS-CoV-2 recruits monocytes and neutrophils that respond to the infection by secreting pro-inflammatory cytokines and chemokines, such as IL-6, IFN-γ, and IP-10, which attract more monocytes, neutrophils, dendritic cells, and adaptive $CD4^+$ T cells and $CD8^+$ T cells from the blood to the infected site. These recruited cells clear up the lung infection, likely accounting for the full recovery in most COVID-19 cases.

In severe cases of COVID-19, it has been hypothesized that an abnormal immune response triggers a "cytokine storm" that mediates widespread lung inflammation1. The cytokine storm, including TNF-α, IL-1α, IL-1β, IL-16, and IL-17 causes a hyperinflammatory response as the concentration of pro-inflammatory cytokines secreted by immune cells increases, producing a pro-inflammatory feedback loop that continues to grow as both the numbers of immune cells and the production of cytokines continually increase. As immune cells accumulate in the lungs, pro-inflammatory cytokines (IL-1, IL-6, IL-17, TNF-α) and type 1 interferon (IFN-α and INF-β) are overproduced, causing additional damage to the lungs and accounting for increased disease severity (Figure 1B) [2,7]. When the cytokine storm is maintained in the lungs, it may spread to other organ systems and cause multi-organ damage, e.g., kidney damage and infection of intestinal epithelia, which has been observed in severe cases of COVID-19 [8].

Adaptive Immune Response

The adaptive immune system includes T lymphocytes and B lymphocytes, commonly referred to as T cells and B cells. T cells, which control the cell-mediated immune response, are classified as $CD4^+$ helper T cells that respond to antigen-presenting cells to facilitate B cell antibody production, and $CD8^+$ cytotoxic T cells, which interact directly with and kill infected cells (Figure 1C) [9]. The $CD8^+$ T cell response to SARS-CoV-2 is much more pronounced than the $CD4^+$ T cell response [10].

This finding is consistent with the concept that $CD8^+$ T cells lead to inflammation due to their cytotoxic nature, while $CD4^+$ T cells suppress the inflammatory immune response. While the role of T cells in response to SARS-CoV-2 has yet to be fully understood, T cells have been shown to target specific SARS-CoV-2-derived peptides such as HLA class I binding peptides, HLA class II binding peptides, and HLA-DR binding peptides [5,11]. In addition, T cell lymphopenia, characterized by decreased counts of both $CD4^+$ and $CD8^+$ T cells, has been observed in patients with both mild and severe COVID-19, suggesting that T cells may become exhausted and lose their functionality as the disease progresses [12]. The absolute number of T lymphocytes has been shown to be markedly reduced in severe cases of COVID-19 compared to moderate cases, and the $CD4^+$ expression of IFN-γ, an anti-inflammatory cytokine, was lower in severe cases than in moderate cases [7]. These findings suggest that lymphopenia may be an indicator of disease severity [13].

B cells mediate the production of antigen-specific antibodies that protect the host by limiting late-stage infection and preventing future re-infection. The main antibody response to SARS-CoV-2 involves the immunoglobulins IgA, IgM, and IgG [14]. In one study, the median duration of IgA and IgM antibody detection was found to be 5 days, while IgG antibodies were found to be detectable 14 days after symptom onset (Figure 1D) [10]. While the lifetime of SARS-CoV-2-specific IgG antibodies within a host has not been fully studied, IgG antibodies specific to SARS-CoV-1 can be detected in survivors up to six years after acute infection, suggesting that the SARS-CoV-2-specific IgG antibodies are expressed significantly longer than IgA and IgM antibodies [6]. Serological assays that detect SARS-CoV-2-specific antibodies, such as ELISAs, may play a potential role in diagnostic testing, but high specificity is required to avoid false-positive results [15]. In addition, it has been shown that the SARS-CoV-2 can destroy germinal centers in the lymph nodes where B cell-mediated antibody synthesis occurs, resulting in decreased antibody production and reducing the host's resistance to the virus [16].

Immune Memory to SARS-CoV-2

When a host is infected by an antigen, the adaptive immune system produces memory T cells and memory B cells that recognize specific antigens that the host has previously encountered, allowing the immune system to initiate a rapid response to potential re-infection. It has been shown that patients who recovered from SARS-CoV-1 have memory T cells specific to SARS-CoV-1 proteins that persisted for up to 11 years after infection (Figure 1D) [17]. Robust memory T cell responses specific for SARS-CoV-2 have also been detected in the blood of donors who have recovered from COVID-19 [18]. While the survival of memory T cells specific to SARS-CoV-2 cannot be accurately studied due to the abbreviated duration of the pandemic, it has been shown that memory T cells developed in response to mild COVID-19 infection can persist for at least three months after initial infection [19]. However, the percentage of memory T cells has been found to be significantly reduced in severe cases of COVID-19 [20]. Memory B cell count has also been found to be significantly decreased in patients with COVID-19 pneumonia compared to healthy control subjects [21]. While the functional differences between memory T cells and memory B cells are not entirely clear, a study of both cell types in COVID-19 patients showed that memory B cell counts were low, likely due to the destruction of germinal centers, while memory T cells were detectable in both symptomatic COVID-19 patients and in asymptomatic persons that lacked detectable SARS-CoV-2-specific antibodies [22]. These findings suggest that memory T cells may play a more significant role in COVID-19 than memory B cells.

Immunological memory serves as the basis for vaccine development and administration, as the purpose of a vaccine is to introduce an antigen to a host so that the immune system can produce memory T and B cells to develop acquired immunity against a disease. A study of memory T cells identified six immunodominant epitope groups that were frequently targeted by T cells across many COVID-19 patients, three of which were present in the S-protein of SARS-CoV-2 [18]. These findings explain the mechanisms of action of the COVID-19 vaccines from Pfizer-BioNTech and Moderna, mRNA vaccines that introduce a harmless piece of the virus's S-protein into a host. The S-protein mRNA gives the host the ability to produce the S-protein on its own, which the immune system recognizes as a foreign invader. The immune system then produces specific antibodies in response to the S-protein that can be reproduced by memory B cells in the case of future SARS-CoV-2 infection. These vaccines give patients acquired immunity to COVID-19 without the need for viral infection.

Alternative Mechanisms

Another widely discussed risk factor for SARS-CoV-2 infection and increased COVID-19 severity is blood type. At the beginning of the pandemic, studies from China and Europe suggested that blood type was a significant

biomarker for COVID-19 susceptibility, with blood type A increasing risk of infection and blood type O protecting against infection [23]. This finding was attributed to the fact that anti-A antibodies specifically inhibit the adhesion of SARS-CoV-1 S protein-expressing cells to ACE2-expressing cell lines [24]. However, more recent studies have questioned whether these differences between blood types play a role in determining disease susceptibility. While one study found that blood types B and AB and Rh+ factor were associated with increased odds for testing positive for COVID-19, the same researchers concluded that blood type was not associated with peak inflammatory markers, clinical outcomes (including intubation and death), or disease severity [25]. Another study found that COVID-19 patients with blood types A or AB have more severe disease and greater requirements for mechanical ventilation [26]. Other studies have concluded that blood type O protects against SARS-CoV-2 infection [25,27].

Therapies Based on Our Understanding of the SARS-CoV-2-Induced Cytokine Storm

Steroid therapy using corticosteroids may prevent the development of systemic inflammation and deleterious responses in COVID-19 patients with their potent anti-inflammatory effects [28]. Recent studies have examined the effectiveness of anti-cytokine therapies with a focus on IL-6 antagonists that have been used since the early days of the COVID-19 pandemic to treat the disease. Two recent studies on Tocilizumab, an IL-6 inhibitor commonly used to treat rheumatoid arthritis, found no effect on 28-day mortality in patients hospitalized with COVID-19 [29,30]. Another study showed that IL-6 levels in COVID-19 patients may be lower than initially thought, as IL-6 concentrations in critically ill patients with the disease were significantly lower than those of patients with acute respiratory distress syndrome (ARDS) and sepsis, possibly explaining the limited success of anti-IL-6 drugs [31]. Although inflammatory cytokines may not be the primary driving force behind severe COVID-19, they still play a role, as Tocilizumab reduced the risk of in-hospital mortality from COVID-19 in a study of 3924 patients when it was administered as early treatment (within the first two days of ICU admission) [32].

Many alternative mechanisms for COVID-19 disease progression have been suggested. One hypothesis involves interferons, a group of signaling proteins that play a role in antiviral activity and immunosuppression, and the observation that COVID-19 appears to lower the body's natural interferon response. Two studies tested the hypothesis that decreased interferon levels resulting from both autoantibodies and genetic mutations may adversely affect outcomes in COVID-19 patients. The presence of interferon-neutralizing autoantibodies correlated with life-threatening COVID-19 pneumonia in 2.6% of women and 12.5% of men [33]. Consistent with this study mutations in genes involved in interferon regulation, such as autosomal-recessive (AR) deficiencies (IRF7 and IFNAR1) and autosomal-dominant (AD) deficiencies (IRF7, IFNAR1, and IFNAR2), were identified in 3.5% of patients with life-threatening COVID-19 pneumonia [33,34]. While traditional interferon drugs have had a little suppressive effect against the virus, a new inhaled form of interferon increased the odds for improvement and rapid recovery in SARS-CoV-2 infection, further supporting the possibility that interferons may play a protective role in COVID-19 [35].

Future Directions

With the distribution of vaccines against COVID-19 from Pfizer-BioNTech, Moderna, and Johnson and Johnson along with the vaccines from AstraZeneca and Novavax that are still undergoing clinical trials, the future regarding the pandemic is looking brighter. While the end of this pandemic may be in sight, lessons learned from COVID-19 will impact disease research and treatment for years to come.

No matter what disease is being studied, the immune system will always play a major role in the body's response, making it a high-priority field of research when faced with life-threatening diseases. The research that has been conducted in response to COVID-19 will undoubtedly offer important insights into the pathogenesis and treatment of future emergent diseases to prevent this kind of worldwide state of emergency from occurring again. If a comparable disease does appear in the future, the research and clinical communities should be better equipped to handle the problem.

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