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Cell Mediated Immunity as a Weapon to Fight Against COVID19: A Brief Review

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Abstract

COVID-19 is not the first severe respiratory disease outbreak caused by the coronavirus. Just in the past two decades, coronaviruses have caused three epidemic diseases, namely, COVID-19, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). At present, the cases of COVID-19 have been found in many countries around the world. Here, we provide an outline of the pathophysiology of SARS-CoV-2 infection. Also, we describe the interaction of SARS-CoV-2 with the cell mediated immune system and the subsequent contribution of dysfunctional immune responses to disease progression. Understanding the immunological response to the SARS-CoV-2 viral infection will help us to develop successful treatments and vaccines, identify vulnerable groups and help inform public health measures to control the coronavirus outbreak.

Keywords: COVID19; Respiratory disease; Respiratory Syndrome

Introduction

Coronavirus disease 2019 (COVID-19) is a kind of viral pneumonia which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The emergence of SARS-CoV-2 has been marked as the third introduction of a highly pathogenic coronavirus into the human population after the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) in the twenty-first century. By May 2020, SARS-CoV-2 had infected more than 26,49,542 people across 215 countries/regions and killed more than 4,3960: a pandemic as declared by the World Health Organization [1]. Daily reports of sharp rises in the number of new cases continue to emerge from many countries/regions, but efforts to overcome the virus are hampered by a lack of knowledge of several important aspects of SARS-CoV-2 infection, ranging from pathogen biology to host response and treatment options. Therefore, there is an urgent need to better understand the host–pathogen biology of COVID-19 as this will offer important insights into treatment and management of the disease, including identification of new therapies [2]. Everyday reports of sharp rises in the number of new cases continue to emerge from many countries/regions, but efforts to overcome the virus are hampered by a lack of knowledge of several important aspects of SARS-CoV-2 infection, ranging from pathogen biology to host response and treatment options. Therefore,

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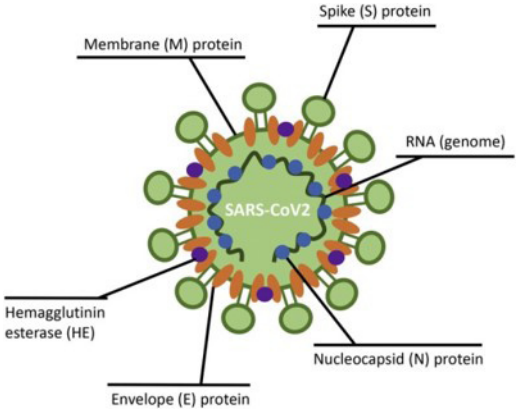
there is an urgent need to better understand the host–pathogen biology of COVID-19 as this will offer important insights into treatment and management of the disease, including identification of new therapies. Here, we review the literature on SARS-CoV-2 pathophysiology, its interaction with target cells and the immune response to the virus, including the contribution of dysfunctional immune responses to disease progression. Specifically, we highlight the implications of specific features of the infection for promising therapeutic interventions that could target the virus or the dysfunctional immune response. Moreover, we discuss about how studies focused on the pathogenesis and immune response will be essential for the development of vaccines and therapeutic purposes.

Structure of the COVID 19

Coronaviruses (CoVs) are large enveloped viruses with a single-stranded, nonsegmented, positive sense RNA genome that spans approximately 30 kilobases, making it the largest known genome of any RNA virus. Being RNA viruses, CoVs readily evolve by mutation and homologous and non-homologous recombination, which expands their host range and facilitates crossing of species barriers. Extensive animal reservoirs, especially among bats, genetic recombination among CoVs, and their plasticity in terms of receptor use renders CoVs highly effective at host switching, sometimes across wide taxonomic distances [3,4].

Coronaviruses are spherical in shape. Their most prominent feature are club-like projections on the virus surface which are referred to as "spikes". The virus membrane contains four structural components, the spike (S), envelope (E), membrane (M) and nucelocapsid (N) protein(5) (Figure 1). For SARS-CoV and SARS-CoV2, the S protein is the primary determinant for host tropism and pathogenicity. It is the main target for neutralizing antibodies and therefore of great interest in terms of immunological response and vaccine design (6). The spike structure is formed by homotrimers of S-glycoproteins, each of which consists of two subunits, whereby S1 forms the part involved in receptor recognition, and S2 is highly conserved, anchors the protein in the viral membrane and facilitates viral fusion [7,8]. S1 contains a hypervariable loop which differs greatly between betacoronaviruses on both size and sequence. Viral entry requires the proteolysis of the S protein in two locations, a process that utilizes host proteases, and results in irreversible conformational changes of the S protein. Some anti-SARS-CoV antibodies in humans mimic receptor engagement, thus modeling conformational S protein changes upon antigen-antibody interaction. The amino acid sequence of receptor binding sites of SARS-CoV2 is 74% homologous to that of SARS- CoV suggesting similar or even identical cell entry mechanisms for both viruses [9].



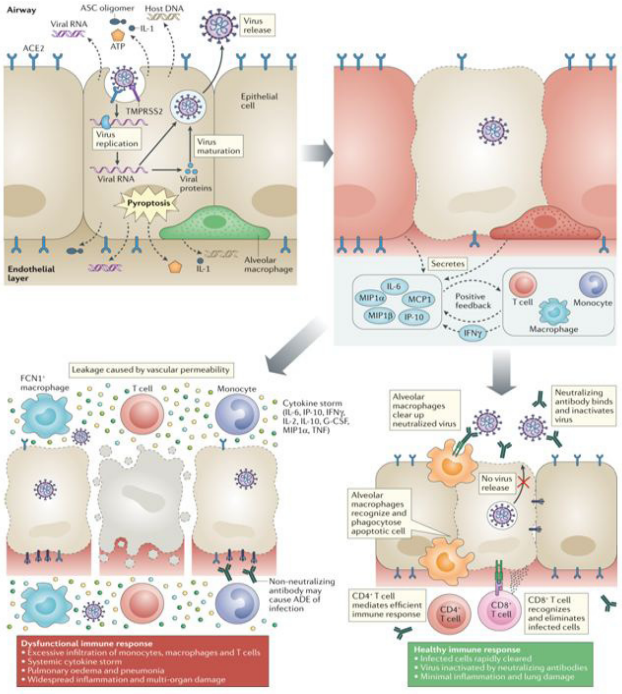
Pathogenesis of COVID 19

Patients with COVID-19 show clinical manifestations including fever, nonproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia [10], which are similar to the symptoms of SARS-CoV and MERS-CoV infections [11]. Hence, although the pathogenesis of COVID-19 is poorly understood, the similar mechanisms of SARS-CoV and MERS-CoV still can give us a lot of information on the pathogenesis of SARS-CoV-2 infection to facilitate our recognition of COVID-19.

Like the other respiratory coronaviruses, SARS-CoV-2 is transmitted primarily via respiratory droplets, with a possible, but unproven, faecal–oral transmission route. On infection, the median incubation period is approximately 4–5 days before symptom onset [11,12], with 97.5% of symptomatic patients developing symptoms within 11.5 days. At the point of hospital admission, patients with COVID-19 typically exhibit a fever and dry cough; less commonly, patients also experience difficulty in breathing, muscle and/or joint pain, headache/dizziness, diarrhoea, nausea and the coughing up of blood [13,15]. Within 5–6 days of symptom onset, SARS-CoV-2 viral load reaches its peak significantly earlier than that of the related SARS-CoV, where viral load peaks at about 10 days after symptom onset [16,17]. Severe COVID-19 cases progress to Acute Respiratory Distress Syndrome (ARDS), on average around 8–9 days after symptom onset [18] [20]. The pathophysiology of SARS-CoV-2 infection very closely resembles that of SARS-CoV infection, with aggressive inflammatory responses strongly implicated in the resulting damage to the airways. Hence, disease severity in patients is due to not only the viral infection but also the host response. The pattern of increasing severity with age is also broadly consistent with the epidemiology of SARS-CoV and MERS-CoV [21]. ARDS seen in severe COVID-19 is characterized by difficulty in breathing and low blood oxygen level. As a result, some patients may succumb to secondary bacterial and fungal infections. ARDS may lead directly to respiratory failure, which is the cause of death in 70% of fatal COVID-19 cases. In addition, the vast release of cytokines by the immune system in response to the viral infection and/or secondary infections can result in a cytokine storm and symptoms of sepsis that are the cause of death in 28% of fatal COVID-19 cases [21]. In these cases, uncontrolled inflammation inflicts multi-organ damage leading to organ failure, especially of the cardiac, hepatic and renal systems (Figure 2). Most patients with SARS-CoV infection who progressed to renal failure eventually died [22]. Research on real-life immunity to SARS-CoV-2 is in its preliminary stages, and uncertainties remain. It is possible that the antibodies that someone develops against the virus could actually increase the risk of the disease becoming worse.

When severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells expressing the surface receptors angiotensin-converting enzyme 2 (ACE2) and TMPRSS2, the active replication and release of the virus cause the host cell to undergo pyroptosis and release damage-associated molecular patterns, including ATP, nucleic acids and ASC oligomers. These are recognized by neighbouring epithelial cells, endothelial cells and alveolar macrophages, triggering the generation of pro-inflammatory cytokines and chemokines (including IL-6, IP-10, macrophage inflammatory protein 1α (MIP1α), MIP1β and MCP1). These proteins attract monocytes, macrophages and T cells to the site of infection, promoting further inflammation (with the addition of IFNγ produced by T cells) and establishing a pro-

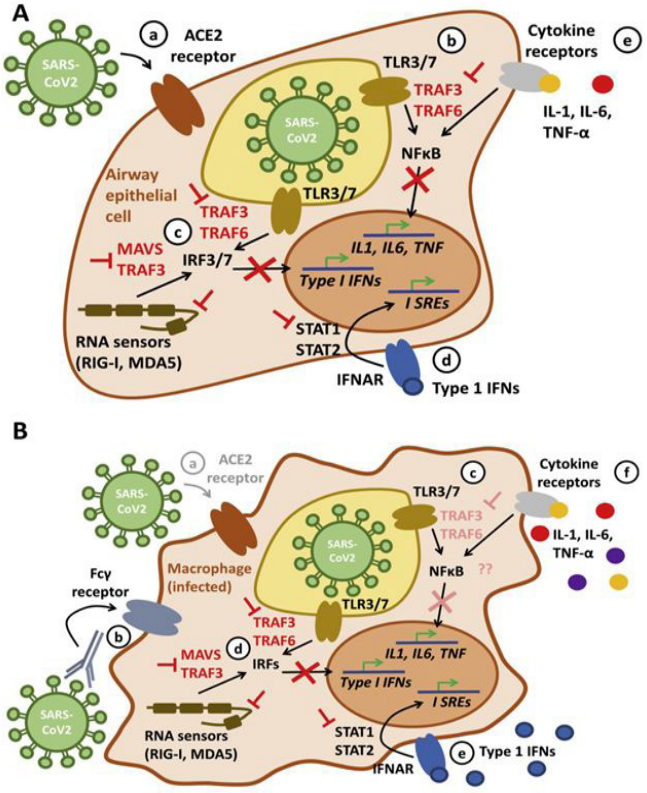
inflammatory feedback loop. In a defective immune response (left side) this may lead to further accumulation of immune cells in the lungs, causing overproduction of pro-inflammatory cytokines, which eventually damages the lung infrastructure. The resulting cytokine storm circulates to other organs, leading to multi-organ damage. In addition, non-neutralizing antibodies produced by B cells may enhance SARS-CoV-2 infection through Antibody-Dependent Enhancement (ADE), further exacerbating organ damage. Alternatively, in a healthy immune response (right side), the initial inflammation attracts virus-specific T cells to the site of infection, where they can eliminate the infected cells before the virus spreads. Neutralizing antibodies in these individuals can block viral infection, and alveolar macrophages recognize neutralized viruses and apoptotic cells and clear them by phagocytosis. Altogether, these processes lead to clearance of the virus and minimal lung damage, resulting in recovery. G-CSF, granulocyte colony-stimulating factor; TNF, tumour necrosis factor (Figure 2).



Development of immune elusion strategy (Figure 3)

SARS-CoV-specific $CD4^+$ T cells express IFNγ, TNF and IL-2, which suggests that patients with SARS-CoV infection exhibit a T_H1 cell response and mainly use cellular immunity to control the infection [24,25]. Although this pro-inflammatory profile may be an aggravating factor for immunepathogenesis, $CD4^+$ T cells have been hypothesized to control SARS, as depletion of these cells in mice resulted in slower clearance of the virus from the host and severer lung inflammation. With the use of a mouse-adapted strain of SARS-CoV, immunization with dendritic cells bearing SARS-CoV peptides resulted in higher numbers of virus-specific $CD4^+$ and $CD8^+$ T cells that accumulated in the lungs and increased survival [26] [27]. Also, transfer of SARS-CoV-specific $CD4^+$ and $CD8^+$ T cells into immunodeficient mice resulted in better protection against a mouse-adapted strain of SARS-CoV [28].

Despite evidence for an important role of T cells in controlling infection, several vaccine formulations against SARS-CoV previously tested in animal models showed signs of immunopathology associated with T_H2 cell-mediated eosinophil infiltration [29]. In particular, aged mice that were vaccinated seemed to display increased immunopathology rather than protection. Further study of the nature of protective versus detrimental T cell responses is critically needed to determine the optimal T cell engagement strategies for vaccines [30].



Immune evasion strategies of SARS-CoV2.

Cell-mediated immunity is essential in recovery from and control of viral infections, especially infections involving oncogenic viruses or viruses that spread directly from cell to contiguous cell. In these situations antibody cannot reach the virus but virally induced antigens on the surface of the infected cell can be recognized by different effector cells (e.g., cytotoxic T cells) , If the virus reaches target organs, it is more difficult to control. The host defenses that may play important roles in target organs are initially inflammation, fever, and interferon and subsequently cell-mediated immunity. Together with reports of lymphopenia and reduced peripheral T cell levels in patients, these findings suggest that T cells are attracted away from the blood and into the infected site to control the viral infection. In patients with COVID-19, increased T cell exhaustion and reduced functional diversity predicted severe disease. Despite the impaired response, patients who recovered from SARS-CoV infection developed coronavirus-specific memory T cells, which were found up to 2 years after recovery.

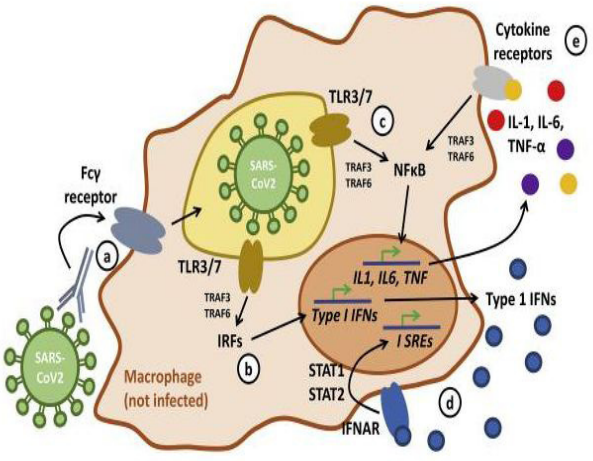
Soluble mediators include immune interferon, chemotactic factors, macrophage migration inhibitory factor, and lymphotoxin; other lymphokines and monokines are not depicted. Cytotoxic effector lymphocytes, macrophages, and natural killer cells play complex but important roles in host defense. PMNs, Polymorphonuclear leukocytes. In some situations, cell-mediated immunity may develop before antibody production begins. For example, cytotoxic effector T cells have been found in bronchial washings 3 to 4 days after initiation of intranasal infection in mice; at this time, antibody cannot yet be detected. Cell-mediated immune responses can cause tissue damage; the lung lesions produced in influenza may be examples. Both T and B cell responses against SARS-CoV-2 are detected in the blood around 1 week after the onset of COVID-19 symptoms. $CD8^+$ T cells are important for directly attacking and killing virus-infected cells,

whereas $CD4^+$ T cells are crucial to prime both $CD8^+$ T cells and B cells. $CD4^+$ T cells are also responsible for cytokine production to drive immune cell recruitment. The first autopsy of a patient with COVID-19 revealed an accumulation of mononuclear cells (likely monocytes and T cells) in the lungs, coupled with low levels of hyperactive T cells in the peripheral blood [23].

Fig-A describes the SARS-CoV2 infects airway epithelial cells through interactions with the trans-membrane enzyme ACE2 (a). While RNA viruses usually activate TLR3 and/or 7 in endosomes (b) and cytosolic RNA sensors RIG-I and MDA-5 (c), SARS-COV2 effectively suppresses the activation of TNF receptor-associated factors (TRAF) 3 and 6, thereby limiting activation of the transcription factors NFκB and IRF3 and 7, thereby suppressing early pro-inflammatory responses through type I interferons (IFN) and pro-inflammatory effector cytokines IL-1, IL-6 and TNF-α (red symbols). Furthermore, novel CoVs inhibit the activation of STAT transcription factors (d) in response to type I IFN receptor activation, which further limits antiviral response mechanisms. Altogether, this prohibits virus containment through activation of anti-viral programs and the recruitment of immune cells.

Fig-B shows the tissue monocytes/macrophages express ACE2 to a significantly lower extent, making infection through this route less likely (a). However, immune complexes consisting of ineffective antibodies against e.g. seasonal CoVs and virus particles may be taken up by macrophages through Fcγ receptors resulting in their infection (b). In a process referred to as Antibody Directed Enhancement (ADE), virions inhibit type I IFN signaling in infected macrophages while allowing pro-inflammatory IL-1, IL-6 and TNF-α expression, which may contribute to hyperinflammation and cytokine storm syndrome (c,d). Inhibited type 1 IFN signaling suppresses anti-viral programs, while increased IL-1, IL-6 and TNF-α expression auto-amplifies itself through positive feedback loops (f).

Cytokine strom in SARS-CoV2 (Figure 4).



Inflammatory response through monocytes macrophages. Uninfected monocytes/macrophages from the blood stream invade the lungs where they detect virus particles and/or cytoplasmic and nuclear components. Within immune complexes, these particles are taken up into the cell (a) where they are presented to TLRs, activating NFκB and/or IRF dependent pro-inflammatory pathways (b,c). As a result, uninfected monocytes/macrophages produce significant amounts of pro-inflammatory cytokines (d,e) which recruit additional innate and adaptive immune cells and cause additional tissue damage (Figure 4).

Coronavirus-specific T cells are clearly important in eliminating the virus and controlling disease development and should be considered in vaccine strategies. However, whether T cell responses alone are capable of preventing infection in human settings remains to be investigated. This knowledge will be important for vaccine development.

Conclusion

As immunity does not exist and a considerable proportion of humans develop severe disease, the novel coronavirus SARS-CoV2 is a threat to millions globally. SARS-CoV2 has the capacity to escape innate immune responses, which allows the pathogen to produce large copy numbers in primarily infected tissues, usually airway epithelia. Through the infection of innate immune cells, the conscription of uninfected cells from the circulation to the primary site of infection, massive immune reactions may induce hyperinflammation that can result in a cytokine storm and many life-threatening complications. Researchers are still uncertain about what level of long-term immune memory is adequate to protect against future coronavirus infection, and how long it takes for the immune system to drop below that level. It is not even clear as of now whether someone with immunity could spread the coronavirus to others while fighting off a second infection. If the immune response were strong enough to crush the virus quickly, the person probably wouldn't transmit it further. A weaker immune response that allowed some viral replication might not prevent transmission, though, particularly since people without symptoms are known to pass the coronavirus around. We are only beginning to understand host factors, such as differential expression of cell surface proteins that may determine infection risk, disease presentation and outcomes. Unveiling tissue and stage specific factors contributing to pathology will result in new, effective and disease stage specific therapeutic approaches that control virus replication while limiting inflammatory damage until vaccinations become available. The association between immune dysfunction and outcome of disease severity in patients with COVID-19 should serve as a note of caution in vaccine development. Further studies of the host immune response to SARS-CoV-2 are necessary, including a in depth investigation of the determinants of healthy versus dysfunctional outcomes. These will also help to identify biomarkers to define immune correlates of protection and disease severity for effective triage of patients.

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