「An In-depth analysis of the immune response, inflammatory mechanism, and intervention strategy of COVID-19」

Updated 19 June, 2020.　Cellspect Co., Ltd

Recently, in a review article published in Nature Reviews Immunology, scientists from the Singapore A*STAR Institute provide an overview of the pathophysiology of SARS-CoV-2 infection, which causes coronavirus disease 2019 (COVID-19).

The researchers describe the interaction of SARS-CoV-2 with the immune system and the subsequent contribution of dysfunctional immune responses to disease progression. SARS-CoV-2 infection and destruction of lung cells will induce a series of local immune responses, and then macrophages and monocytes will be recruited to release cytokines and produce major adaptive T Cellular and B-cell immune responses. In most cases, this process can solve the infection problem. However, in some cases, a dysfunctional immune response occurs, which may cause severe lung damage and even systemic pathological response.

“The pathophysiology of SARS-CoV-2 infection closely resembles that of SARS infection, with aggressive inflammatory responses strongly implicated in the resulting damage to the airways. Therefore, disease severity in patients is due, not only to the viral infection, but also to the host response. The pattern of increasing severity with age is also broadly consistent with the epidemiology of SARS and MERS.” the author said.

About one week after symptom onset of COVID 19, researchers can detect T cells and B cell immune responses against SARS-CoV-2 from the patient's blood. CD8+ T (cytotoxic T cell) cells can directly attack and kill the virus infection while CD4+ (T helper cell) T cells are essential for turning on the function of CD8+ T cells and B cells. CD4+ T cells are also responsible for the production of cytokines to drive the recruitment of immune cells. The autopsy report of the first COVID-19 patient showed that monocytes accumulated in his lungs, and the level of hyperactive T cells in the peripheral blood was low. In addition, the researchers also reported that the level of lymphocytes and peripheral T cells in the patient's body has declined. Related research results have shown that T cells will be recruited to leave the blood and enter the infection site to control infection; while in COVID-19 patients, the increase of T cell depletion and the decrease of its functional diversity indicates the severity of the disease. Although the patient's response will be impaired, patients who had recovered from COVID-19 still developed coronavirus-specific memory T cells.

The B cell response of COVID-19 patients often occurs at the same time as the T helper cell response, that is, about one week after the patient's symptoms appear. In patients with SARS infection, the B cell response usually appears first to the nucleocapsid protein (N protein) reaction. Within 4-8 days after the patient's symptoms appear, the antibody reaction to the S protein will appear; the neutralizing antibody reaction will begin in the second week. Most patients will have neutralizing antibodies in the third week. Because the virus titer of SARS-CoV-2 reaches its peak earlier than SARS, its antibody response may appear earlier, so it seems that some patients do not produce persistent antibodies against SARS-CoV-2. At present, researchers are not clear whether these patients will be infected again. The antibodies are likely to be effective against SARS-CoV-2. The serum samples in the recovery phase have been COVID-19 has achieved promising results in the clinical application, and it has been successfully used in the treatment of SARS before.

In most individuals, recruited cells clear the infection in the lung, the immune response recedes, and patients recover. However, in some patients, a dysfunctional immune response occurs, which triggers a cytokine storm that mediates widespread lung inflammation and symptoms of sepsis that are the cause of death in 28% of fatal COVID-19 cases. In these cases, uncontrolled inflammation inflicts multi-organ damage leading to organ failure, especially of the cardiac, hepatic and renal systems. “It was observed that patients with severe COVID-19, requiring intensive care in hospitals, exhibited higher blood plasma levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, MCP1, macrophage inflammatory protein 1α (MIP1α), and tumor necrosis factor (TNF). IL-6 levels in these patients continue to increase over time and are relatively more elevated in non-survivors than survivors.” the author said. “Notably, there exists a highly inflammatory monocyte-derived FCN1+ macrophage population in the bronchoalveolar lavage fluid of patients with severe, but not mild, COVID-19. Also, patients with severe disease show a significantly higher percentage of CD14+CD16+ inflammatory monocytes in peripheral blood than patients with mild disease. These cells secrete inflammatory cytokines that contribute to the cytokine storm, including MCP1, IP-10, and MIP1α.”

The author also concluded several potential therapeutic approaches against SARS-CoV-2 besides drugs as following:

1. Blocking ACE2 receptor and/or TMPRSS2 protease
2. Targeting S-protein or TMPRSS2 protease
3. Antibodies & convalescent plasma therapeutics

Briefly, SARS-CoV-2 enter cells by binding its S protein (spike protein) to host cell ACE2 receptor. Moreover, the serine proteases TMPRSS2 can both cleave ACE2 and activate the S protein to facilitate the infection process. Blocking of ACE2 and TMPRSS2 have been clinically approved for many other indications. Monoclonal antibodies targeting the S-protein may also inhibit virus entry or fusion. An alternative strategy is to deliver high concentrations of a soluble form of ACE2 that could potentially

reduce virus entry into target host cells. In China, hospitals have initiated the use of convalescent plasma as a source of therapeutic polyclonal antibodies for treatment of COVID-19, and early data suggest a positive impact on respiratory viral load and mortality. There are many ongoing clinical trials using these methods and we look forward to good news in the near future.

At the end of their review, the authors conclude that “Controlling the inflammatory response may be as important as targeting the virus. Therapies inhibiting viral infection and regulation of dysfunctional immune responses may synergize to block pathologies at multiple steps. At the same time, 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 and evaluation. Further studies of the host immune response to SARS-CoV-2 are necessary, including a detailed investigation of the determinants of healthy versus dysfunctional outcomes. These will also help identify biomarkers to define immune correlates of protection and disease severity for effective triage of patients.”

Reference:

1. Matthew Zirui Tay et al., 28 April 2020 “The Trinity of COVID-19: Immunity, Inflammation, and Intervention” Nature Reviews Immunology, volume 20, pages363–374 (https://www.nature.com/articles/s41577-020-0311-8)