The Role of CD4+ and CD8+ T Cells in COVID-19 (Coronavirus Disease 2019)

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ABSTRACT

The SARS-CoV-2 virus mainly acts on lymphocytes, especially CD4+ and CD8+ T cells. Analysis of lymphocyte subsets can help in early screening of the critical course of the disease. An increase in proinflammatory cytokines and chemokines and a decrease in regulatory T cells contribute to an exaggerated inflammatory response (increased cytokine production, cytokine release syndrome) with loss of control over the deleterious immune response and increased tissue damage (e.g., in the lung). Sometimes the body's response to infection can be overwhelming. For example, when SARS-CoV-2 enters the lungs, it triggers an immune response, attracting immune cells to the area to attack the virus, resulting in local inflammation. In some patients, excessive/uncontrolled levels of cytokines will activate more immune cells, causing a hyperinflammation called a cytokine storm, a condition that can harm or kill a patient.

1. Introduction

T cells consist of CD4+, CD8+, and NK cells. Mature T cells that leave the thymus but have not been exposed to antigens are called naive T cells.1 When naive T cells are exposed to MHC-bound antigens that are presented by APCs or are said to stimulate specific cytokines, they develop into subsets of CD4+ and CD8+ T cells with different effector functions. Helper T cells direct the overall adaptive immune response, while cytotoxic T cells play an important role in the clearance and killing of virus-infected cells. T lymphocytes, including CD4+ and CD8+ T cells, play an important role in this defense.2 Cluster differentiation is a cell surface molecule that is expressed on various types of immune system cells, indicated by numbering. CD4 is a glycoprotein expressed on the surface of helper T cells, regulatory T cells, monocytes, macrophages, and dendritic cells. Antigen captured, processed, and presented by macrophages in the context of major histocompatibility complex II (MHC II) to CD4 cells.3
The CD4 count is reported as the number of cells in cubic millimeters of blood. In healthy people, the CD4 count ranges from 500 to 1500 cells per cubic millimeter. CD4 cell counts were considered to have good predictive value within no more than 6 months of examination. Like CD4, CD8 is a transmembrane glycoprotein. However, CD8 is predominantly expressed on the surface of cytotoxic T cells, but can also be found on natural killer (NK) cells, thymus cortical, and dendritic cells. These T-CD8 cells recognize the MHC-1 antigen complex presented by antigen-presenting cells (APCs). The CD8 count in healthy people is between 150 and 1000 cells per cubic millimeter. CD4+ T cells stimulate B cells to produce virus-specific antibodies, while CD8+ T cells are able to directly kill virus-infected cells. Helper T cells produce proinflammatory cytokines to help defense cells. However, SARS CoV-2 can inhibit T cells by inducing programmed cell death (apoptosis).

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Reported laboratory values associated with the development of SARS-CoV-2 Virus (decreased albumin, increased lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, cardiac troponin, D-dimer, procalcitonin, and CRP; Decreased lymphocyte count and eosinophils, with other compromised cellular immunity, can monitor disease course, symptoms and predict worst-case risk. Immunological studies in SARS-CoV-2 infection have shown lymphopenia, especially a decrease in the peripheral blood T cell.

Patients with severe disease have elevated plasma concentrations of proinflammatory cytokines, including interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP) 1α, CXCL, and tumor necrosis factor (TNF)-α (Figure 1). The more severe the patient's condition, the higher their IL-6 level. CD4+ and CD8+ T cells are activated in patients with SARS-CoV-2 infection. A higher percentage of CD4+ and CD8+ T cell receptors indicates reduced and absent T cells. T cell exhaustion leads to disease progression. The majority of adaptive immune cells are T cells, with a significant decrease in T cells, CD8+ T cells as the primary cytotoxic. Severe patients show pathological cytotoxic T cells that can kill the virus but can cause lung injury. Low peripheral lymphocyte count, there is atrophy of secondary lymphoid organs, including lymph nodes and spleen, found in patients with SARS-CoV-2 infection. In the lymph nodes, there is necrosis and atrophy of the spleen; significant degeneration of spleen cells; focal hemorrhagic necrosis; macrophage proliferation, and increased macrophage apoptosis in the spleen.
Immunohistochemical staining showed decreased numbers of CD4+ T cells and CD8+ T cells in lymph nodes and spleen. On the other hand, monocytes and macrophages were increased, which explains the increased number of cytokine cells. Proinflammatory agents such as interleukin (IL)-6, IL-1, tumor necrosis factor (TNF) α, and IL-8 in some patients as a cytokine storm. Most of the inflammatory cells that infiltrate the lungs are monocytes and macrophages, and a number of multinucleated giant cells are associated with diffuse alveolar injury. T lymphocytes, especially CD8+ cytotoxic T cells, are the most important immune cells for protecting against viral infections. One of the characteristics of SARS-CoV-2 infection is the decrease in the number of lymphocytes so that the number of lymphocytes can be used as a reference index in the diagnosis of SARS-CoV-2 infection. CD4+ and CD8+ T cells gradually decline with increasing disease severity. The substantial decrease in the number of lymphocytes indicates that SARS-CoV-2 produces immune cells and inhibits the body's cellular immune function.12

Damage to T lymphocytes is a factor that causes exacerbation in the patient. Late-stage lymphocyte function in SARS-CoV-2 patients is in an inhibitory state, as an exaggerated inflammatory response can increase T cell apoptosis. However, before this occurs, the lymphocytes are in a hyperfunctioning state. In the early stages of the disease, there is the migration of lymphocytes from the blood to the lungs, causing lymphocyte deficiency in the peripheral blood, which is mediated by antigenic stimulation.13

Lymphocyte function tests showed the ability to produce IFN-γ from CD8+ T cells was increased in patients with severe cases. If the activation of CD8+ T cells cannot eliminate the virus, CD4+ T cells will be activated to further enhance the immune response so that the ability of CD4+ T cells to produce IFN-γ is greatly increased in SARS-CoV-2 patients with severe cases of CD4+ T cell hyperfunction, which initiates the macrophage activation syndrome, resulting in a cytokine storm. An increase in IL-2R favors CD4+ T cell hyperfunction. The loss of natural T-regulation and an increase in the number of IL-10 cells also support immune hyperfunction in severe cases of

Figure 1. CD4+ and CD8+ responses in different severities of COVID-19 disease.
SARS-CoV-2 patients. Older people have a higher mortality rate after infection, partly because they have low numbers of lymphocytes, especially CD8+ T cells. As insufficient numbers of lymphocytes migrate to the site of infection, the host will increase the function of CD4+ T cells, which in turn causes a cytokine storm. Cytokines normally only function briefly and will stop when the body’s immune response arrives at the site of infection. In conditions of a cytokine storm, cytokines continue to send signals so that immune cells keep coming and reacting out of control. The lungs can become severely inflamed as the immune system tries to kill the virus. Inflammation of the lungs continues even after the infection is over.

T lymphocytes play a central role in protection against the coronavirus, so there is a relationship between lymphocytes and their subpopulations in the clinical course and complications of SARS-CoV-2 infection. A study in 752 patients analyzed the subpopulations of lymphocytes (CD3+, CD4+, CD8+), CD3+ lymphocytes below 900 cells/mm\(^3\), CD4+ cells below 500 cells/mm\(^3\), and CD8+ lymphocytes below 300 cells/mm\(^3\) were considered subjects at higher risk of infection. In addition, decreased production of IFN-γ by CD4+ T cells occurs in severe cases. In another study, non-intensive care unit patients had total T cell counts, CD4+ and CD8+ lower than 800, 400, and 300/µL, which required attention and intervention even though they were not accompanied by severe symptoms, but were at risk for further damage. The mean fluorescence intensity of CD8+ T cell expression on cytotoxic T cells was significantly increased, a sign of hyperactivity in response to SARS-CoV-2 infection. T-cell analysis showed laboratory results of 452 patients and 286 diagnosed with severe infection with decreased T cells, especially CD4+ T cells, and memory, CD8+ cells, and regulatory T cells.\(^{14-16}\)

2. Conclusion

The SARS-CoV-2 virus primarily acts on lymphocytes, especially CD4+ and CD8+ T cells. Analysis of lymphocyte subsets can assist in early screening of the critical course of the disease.

3. References


