Review

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Features of the Immune Response in COVID-19

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BACKGROUND This review is devoted to the analysis of the features of the immune response in COVID-19. The review indicates the clinical manifestations of COVID-19, modern data on the immunopathogenesis of the disease and its complications are considered.

AIM OF STUDY To clarify some pathogenetic mechanisms of the immune response in COVID-19, which can help in creating an algorithm for examining patients for early prognosis and prevention of severe course and complications of the disease.

MATERIAL AND METHODS To achieve this goal, the results of domestic and foreign scientific studies on the pathogenesis, diagnosis and treatment of COVID-19 were analysed. The literature search was carried out in electronic search engines Scopus and PubMed. For the analysis, scientific articles published in the period from 2019 to 2021 were selected; 88% of analysed works are not older than 5 years.

CONCLUSION The late production of type I IFN, an increase in the level of pro-inflammatory monocytes, a decrease in the expression of HLA-DR on monocytes, violation of the presentation of the virus and the formation of specific lymphocytes, the death of T-lymphocytes and profound immunosuppression are of greatest importance for the development of a severe form of COVID-19.

Keywords: COVID-19, cytokine storm, antigen-presenting cells, monocytes, HLA-DR, T-lymphocytes, IL, IFN

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ACE - angiotensin converting enzyme
APC - antigen presenting cells
ARDS - acute respiratory distress syndrome
CRP - C -reactive protein
CTL - cytotoxic lymphocytes
G-CSF - granulocyte colony stimulating factor
GM-CSF - granulocyte-macrophage colony-stimulating factor
HLA - human leukocyte antigen
HLA-DR - human leukocyte antigen
HLH - hemophagocytic lymphohistiocytosis
IFN - interferon
Ig - immunoglobulin
IL - interleukin
MV - mechanical ventilation
MAS - macrophage activation syndrome
MCP 1 - monocytic chemoattractant protein 1
MHC - major histocompatibility complex
MIP 1α - macrophage inflammatory protein 1α
Th-I - t-helper cells type I
TLR 7 - Toll-like receptor 7
TNFα - tumor necrosis factor α
TSP 2 - transmembrane serine protease type 2

INTRODUCTION

COVID-19 is a severe acute respiratory illness caused by the novel coronavirus SARS-CoV-2. Its first outbreak was recorded in Wuhan (China) in December 2019 [1]. The COVID-19 epidemic quickly spread around the world, and already on March 11, 2020, the World Health Organization officially announced the beginning of a pandemic [2].

The causative agent of the disease is an enveloped zooanthroponotic RNA virus SARS-CoV-2 from the Coronaviridae family of the Betacoronavirus genus, which is transmitted by airborne droplets, airborne dust and contact routes [3]. After introduction into the human body, the main target for SARS-CoV-2 is the cell membrane protein angiotensin-converting enzyme 2 (ACE2) [4, 5]. ACE2 is located on the membranes of alveolocytes, enterocytes, vascular endothelial cells, and smooth muscle cells of most organs. The cellular transmembrane serine protease type 2 (TSP2) promotes the binding of the virus to ACE2, activating its S-protein, which is necessary for the penetration of SARS-CoV-2 into the cell [5].

The incubation period of COVID-19 is quite long and lasts up to 14 days, during which an infected person can shed the virus. Active shedding of the virus during the incubation period, which is not accompanied by clinical symptoms, contributes to an increase in the incidence of COVID-19. The introduction of the virus into the body induces an immune response associated with the production of interferons (IFN-α and IFN-β) [6]. It is the base level of interferons that determines whether the spread of the virus will stop at the level of the upper respiratory tract [6].

CLINICAL MANIFESTATIONS

According to statistics, about 80% of patients suffer from mild COVID-19 [7, 8]. Clinically, this is manifested by fever, dry cough, fatigue, dizziness, anosmia. When the virus enters the gastrointestinal tract, the first symptoms are nausea, vomiting, abdominal pain, and diarrhea. Patients with a mild form of coronavirus infection do not require hospitalization [7, 8].

However, in some patients, there is a decrease or slowdown in IFN α/β production at an early stage of infection, leading to a late and excessive immune response and severe COVID-19, acute lung injury and the development of acute respiratory distress syndrome (ARDS). Descending down the respiratory tract, the virus enters type II pneumocytes responsible for the production of surfactant and maintaining surface tension in the alveoli [9]. The progressive replication of the virus and its cytopathic action cause a generalized hyperinflammatory process in the lungs, diffuse alveolar damage and impaired gas exchange, which is clinically manifested as ARDS.

SEVERE COVID-19

The most vulnerable to COVID-19 are people over 60 years of age with concomitant cardiovascular pathology (hypertension, atherosclerosis, cardiopathy), diabetes, obesity, autoimmune diseases and a number of other types of pathology. Most often, they have a severe form of coronavirus infection — bilateral pneumonia, respiratory failure, ARDS, hypercoagulability with thrombosis and thromboembolism, heart failure, sepsis, and septic shock [7, 8, 10].

One of the complications of severe COVID-19 is a “cytokine storm”, which manifestations are similar to the course of hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS). At the same time, activation of innate and acquired immunity, dysregulation of the synthesis of pro- and anti-inflammatory, immunoregulatory cytokines, interleukins (IL): IL-1, 2, 6, 7-10, 12, 17, 18, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), tumor necrosis factor α (TNFα), IFNγ, IFNα and IFNβ , monocytic chemoattractant protein 1 (MCP 1) and macrophage inflammatory protein 1α (MIP 1α) [7, 10].

LABORATORY DATA

Laboratory data play an important role in determining the severity of the disease and identifying complications. In a clinical blood test, normocytosis or leukopenia, lymphopenia are usually noted, with neutrophilia if bacterial infection occurs. The hemoglobin level does not change or decreases. The level of C-reactive protein (CRP) and the erythrocyte sedimentation rate increase in proportion to the severity. If thrombotic complications develop, the level of D-dimer in the blood and the content of platelets increase. In a “cytokine storm”, the level of IL-6 is

elevated. Patients with severe COVID-19 have high levels of inflammatory markers (CRP, ferritin, procalcitonin) [6–8, 10].

IMMUNE RESPONSE TO COVID-19

To fully understand the mechanism of the development of the disease, it is necessary to take a closer look at the immune response to SARS-CoV-2. A virus-infected cell begins to express a modified major histocompatibility complex MHC I, recognized by Toll-like receptor 7 (TLR 7), which is located in the endosomes of antigen-presenting cells (APC) [11, 12]. For a full-fledged immune response, a sufficient base level of IFN at this stage of the disease is extremely important, since it stimulates the phagocytic activity of macrophages and prevents the virus from multiplying. At a high baseline level of IFN, macrophages phagocytize infected cells, process and present antigens to T cells using the HLA complex . This induces the differentiation of naive T-lymphocytes into antigen-specific CD4+ T -type I helper cells (Th-I). Th-lymphocytes initiate the production of pro-inflammatory cytokines of Th-tumor necrosis factor, IL-6, IL-1β, IL -2, which has a stimulating effect on both macrophages and CD8+-cytotoxic lymphocytes (CTL) [14].

In addition, a humoral response is triggered. T-helper cells stimulate the differentiation of B-lymphocytes into plasma cells, which then produce antibodies specific for the viral antigen. Neutralizing antibodies effectively block the penetration of the virus into body cells, opsonize infected cells, and prevent recurrence of infection in convalescents [14].

Compared to other respiratory viruses, SARS-CoV-2 elicits a lower antiviral transcriptional response characterized by low levels of type I IFN and increased cytokine expression. Also, in patients with severe COVID-19, there is an impaired response to type I IFN and a lower clearance of the virus [9]. In people over 60 years of age, there is a decrease in the production of IFN by dendritic cells, and, on the contrary, an increase in the production of cytokines, which perverts the immune response and aggravates the course of the disease [11, 13].

ROLE OF MONOCYTES

COVID-19 is characterized by diffuse alveolar lesion and focal reactive pneumocyte hyperplasia with signs of intravascular thrombosis and inflammatory cell infiltration [15]. Inflammatory infiltrate of the lung tissue prevents effective alveolar gas exchange [16, 17]. The pulmonary interstitium is infiltrated by immunocompetent cells: macrophages, lymphocytes, and monocytes [15–17].

An important role in the development of the inflammatory process is played by cells of the monocyte-macrophage series. Human blood monocytes are a population of cells that develop from myeloid precursors in the bone marrow and express various markers on their surface [16]. One of them, HLA-DR (human leukocyte antigen-DR), is a class II MHC molecule, a glycosylated transmembrane protein of antigen-presenting cells. Expression of HLA-DR on monocytes (mHLA-DR) is extremely important for antigen presentation, since T -helper cells react to foreign antigens presented on the surface of macrophages only in combination with HLA-DR [18]. The loss of this molecule is clinically manifested as the phenomenon of immunoparalysis [18, 19] — tolerance to endotoxins, characterized by a reduced response to secondary infection after the first inflammatory stress [18–20]. Low expression of mHLA-DR also reflects reduced antigen presentation ability.

The inhibition of mHLA-DR expression in patients with severe infections and sepsis is an early sign of immunosuppression. This change can be used as a predictive criterion for death. Since IL-6 can suppress HLA-DR expression [21], it can be assumed that excessive production of IL-6 is associated with reduced HLA-DR expression in COVID-19 [22, 23].

Depending on the level of expression of the surface markers CD14 and CD16, human monocytes are divided into two main subgroups with different characteristics. Classical monocytes express the CD14+ and CD16- markers. The second subtype is the CD16+ monocyte population, which, depending on the level of expression, consists of intermediate (CD14++, CD16+) and non-classical (CD14+, CD16++) monocytes [24–26]. In healthy people, more than 95% of peripheral blood monocytes are classical (CD14+, CD16–) [27, 28]. Monocytes that express CD16 receptors on their surface and have the phenotype CD14++, CD16+ and CD14+, CD16+ are considered to be pro-inflammatory monocytes that secrete cytokines and are involved in the development of chronic inflammation [27, 29]. In turn, the microenvironment in the focus of infection also induces an increase in the content of inflammatory monocytes expressing CD16+ and supports the inflammatory response [30]. At the same time, in older people and patients with chronic diseases, regardless of etiology, the number of classical monocytes decreases, while the

number of intermediate ones increases to 20% or more [28, 31]. Also, in a number of studies, it was noted that monocytes of patients expressing CD16+ carried out an increased production of pro-inflammatory cytokines TNF-α [32], IL-6 [33] and IL-1β [32] compared with the data of the control group. At the same time, from the point of view of a number of authors, an excess of TNF-α in the blood was a triggering factor for the generalization of inflammation [27, 34] and subsequently a "cytokine storm".

CYTOKINE STORM

"Cytokine storm" is a formidable complication of coronavirus infection caused by systemic hyperinflammation, an uncontrolled increase in the number and continuous activation of immune cells, lymphocytes and macrophages, and an imbalance of pro- and anti-inflammatory cytokines [35–37]. The exact mechanism of this phenomenon is not yet understood, but recent research suggests that the "cytokine storm" in COVID-19 is the result of a failed immune response to the virus. Late secretion of type I IFN at the stage of active viral replication leads to increased activation of immune cells and hypersecretion of proinflammatory cytokines by mononuclear macrophages [38–41]. Clinically, this is manifested by damage not only to the lungs, but also to other organs: the heart, kidneys, and liver, which leads to multiple organ failure and death [42, 43].

One of the main pro-inflammatory cytokines is IL-1. It consists of two types of ligands, IL-1α and IL-1ß, of which IL-1ß has a systemic pro-inflammatory effect. IL-1 is produced by macrophages and monocytes and has a pro-inflammatory effect by triggering the proliferation of immune cells and inducing the secondary production of cytokines [44]. In addition, some autoimmune diseases, such as Still disease and gouty arthritis, are associated with elevated levels of IL-1.

In the development of the "cytokine storm" the level of IL-6 is of great importance, which is a pro-inflammatory cytokine with a pleiotropic effect. It induces differentiation of B- and T-cells, promotes the production of various acute phase proteins by hepatocytes, such as C-reactive protein, serum amyloid A, fibrinogen, and hepcidin, and also promotes inhibition of albumin synthesis [44, 45]. IL-6 is the main trigger of the "cytokine storm" [46]. According to researchers, the values of its level in peripheral blood can be used as a prognostic factor for the progression of COVID-19, so the role of IL-6 in this disease deserves special attention [47].

A unique feature of the "cytokine storm" in COVID-19 is the paradoxical role of IL-10 [48]. This interleukin has an anti-inflammatory effect, regulating the production of pro-inflammatory IL-1, IL-6, IL-8, IL-12, TNF-α, GM-CSF, IFN-γ , and increases the activity of cytotoxic T-lymphocytes. But in viral sepsis in patients with COVID-19, a sharp increase in IL-10 can increase inflammation due to its ability to induce the proliferation of cytotoxic effector CD8+ T cells and hyperactivation of adaptive immunity [49].

An important pro-inflammatory cytokine is IL-18, which is produced by cells of the monocyte-macrophage series in response to activation of the inflammasome by viral components. IL-18 is responsible for inducing an adaptive immune response after innate activation. According to the latest data, the content of IL-18 in the blood correlates with the levels of ferritin, procalcitonin, and biochemical markers of cytolysis in it [50].

Along with other cytokines, TNF-α is also pro-inflammatory and is produced by various cell types such as monocytes, macrophages and T- cells. TNF-α is involved in the regulation of inflammatory processes, infectious diseases, and malignant tumors [51]. Tumor necrosis factor induces T-cell apoptosis by interacting with its TNFR-1 receptor, which is overexpressed in old T-cells, which exacerbates the lymphopenia characteristic of COVID-19 [52].

CHANGES IN IMMUNOCOMPETENT CELLS

Patients with severe COVID-19 requiring mechanical ventilation (MV) have lymphopenia and significant depletion of effector CD4+, CD8+ lymphocytes, and NK cells. According to a number of studies, in patients with severe COVID-19, lymphopenia correlates with high serum levels of IL-6, IL-10 and TNF-α, there is a decrease in the level of IL-2 and IL-7 that affect the proliferation of lymphocytes, which is a poor prognostic sign. Lymphopenia can also develop as a result of direct death of T-lymphocytes infected with the virus [53-55]. A number of authors have published data on high expression levels of programmed cell death markers — PD-1 (PD-1L ligand) on lymphocytes in severe COVID-19 infection. Previously, high expression of PD-1 was recorded in patients with sepsis, oncology, and severe viral infections, including human immunodeficiency virus [56–58].

All these changes in the immune response during infection with the COVID-19 virus lead to the suppression of adaptive immunity: a decrease in proliferative and antiviral activity and the formation of deep immunosuppression.

Rajendra Karki et al. showed that lymphopenia and death of T-lymphocytes in severe COVID-19 infection is the result of increased synthesis of TNF-α and IFN-γ . The increased production of TNF-α and IFN-γ seen in COVID-19 patients may be related to several cell types. The results of sequencing of peripheral blood cells in patients with COVID-19 showed an increased expression of TNF-α and IL-1α on mononuclear cells and an increased expression of IFN-γ on NK - and CD8 T-lymphocytes compared with data from healthy donors [59]. As the authors point out, the synergism of TNF-α and IFN-γ plays an important role in the pathogenesis of not only COVID-19 infection, but also a number of diseases and syndromes, such as sepsis and hemophagocytic lymphohistiocytosis, which are characterized by hyperactivation of the immune system, synthesis of a wide range of cytokines, massive death of immunocompetent cells and the formation of multiple organ failure [60].

The study of the peripheral pool of lymphocytes showed that COVID-19 induces lymphopenia and remodels antigen-presenting cells with the formation of a pool of non-classical and intermediate types of monocytes, which affects the formation of adaptive immunity in patients with COVID-19. This is especially pronounced in aged patients with signs of immune dysregulation and impaired function of circulating monocytes. The relative number of intermediate (CD14++, CD16+) and non-classical (CD14+, CD16++) monocytes in these patients, according to studies, can be up to 20–45% of the entire population, while in healthy donors - only up to 5% [27, 28, 53, 54]. The decrease in HLA-DR expression on monocytes and other antigen-presenting cells also disrupts the formation of an adaptive immune response during acute infection, reducing the formation of specific CD4+ and CD8+ cytotoxic lymphocytes. The formation of lymphopenia contributes to further replication of the virus, expansion of infection zones and aggravation of the patient's clinical condition.

At the same time, in patients with a mild form of COVID- 19 Virus presentation by classical monocytes results in clonal proliferation of SARS-CoV-2 virus-specific T cells. Further formation of CD8+ and CD4+ T cells of the adaptive immune system of patients with COVID-19 and clonal increase in specific effector CD8+ cells and NK cells leads to the destruction of infected cells, the cessation of viral replication and the formation of long-lived T - and B - memory cells. Recent studies have shown a robust adaptive immune response in patients with mild COVID-19, suggesting a critical role for adaptive immunity in the elimination of SARS-CoV-2 [30, 52, 54]. Indirect evidence of successful presentation of the viral antigen and a milder course of COVID-19 is an increase in the level of specific immunoglobulins IgM and IgG in patients with a higher relative number of T-lymphocytes, CD4+ lymphocytes and NK cells [61].

CONCLUSION

At the moment, the accumulated knowledge about the pathogenesis of COVID-19 shows that the greatest importance for the implementation of the severe course of the inflammatory process is, first of all, the late production of type I IFN, which is necessary to stop the replication of the virus. The next factor that enhances the inflammatory immune response is an increase in the level of pro-inflammatory monocytes (intermediate and non-classical). The suppression of the adaptive immune response leads to a decrease in the expression of HLA-DR on monocytes, a violation of the presentation of the virus, and, as a result, a violation of the formation of a pool of specific lymphocytes, the death of T-lymphocytes and profound immunosuppression.

The use of modern knowledge about the immunopathogenesis of COVID-19 can help create an immunological algorithm for early prediction and prevention of complications of severe infection. Conducting an immunological examination of patients admitted to the hospital, including, in addition to a clinical blood test, such indicators of the state of the immune system as CRP, analysis of the level of IL-6, IL-10, the spectrum of monocytes and HLA-DR expression activity, the expression level of PD-1 on lymphocytes will help assess the risk of severe infection and the possible development of complications, which will allow timely effective pathogenetic therapy.

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