



COVID-19 Infection

REVIEW ARTICLE

Immune and Metabolic Response to COVID-19 Infection: Review for Molecular Pathways

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Abstract

The purpose of this review is a systematic analysis of data from clinical observations, international experience and reviews related to the pathogenetic aspects of the impact of a new coronavirus infection on the immune system. Information was searched in MEDLINE, PubMed, and RSCI databases. Some data for SARS-CoV-2 virus as etiological agent that provokes the development of COVID-19 are presented. Special attention was paid to immunity shifts, which were produced in patients under COVID-19 infection. The prevailing role of the “cytokine storm” in the development of severe forms of the disease is revealed in detail. Demonstrated and integrated into a single scheme of adjustment, innate and adaptive immunity is occurring with the new coronavirus infection. This information is supplemented by the characteristics of the metabolic response accompanying this pathology and by changes in the erythrocyte state under COVID-19 infection. Based on these pathogenetic mechanisms, potential variants of targeted correction of the disease are proposed and justified. (**International Journal of Biomedicine. 2020;10(3):177-181.**)

Key Words: COVID-19 • pathogenesis • immunity • cytokine storm

Introduction

Currently, it is difficult to overestimate the importance and relevance of a comprehensive review of various aspects of a new coronavirus infection (COVID-19),⁽¹⁻⁴⁾ which has become the cause of a global biological threat, as early as February 2020, classified by WHO as a pandemic.⁽⁵⁾ According to official statistics, the prevalence of COVID-19 in the world at the beginning of June is approaching 7 million people, of which about 400,000 have died. In the Russian Federation, the number of cases of infection is about half a million, with about 6,000 deaths due to this disease.

All of the above prompted us to closely study the features of the clinical picture and pathogenetic mechanisms that determine the course of this pathology, especially its

severe forms. Taking into account this circumstance, what comes to the fore is the assessment of the informativity of laboratory markers in relation to patients with COVID-19, which primarily include indicators that characterize the state of the blood system.⁽⁶⁻⁸⁾ On the other hand, the literature lacks a comprehensive description of the emerging shifts in SARS-CoV-2 infection: Attention is paid only to one of the components (disorders of the coagulation system, dysfunction of the body’s immunological defense links, etc.). In addition, it should be noted that, despite the obvious relevance and severity of the problem, there are only isolated generalizing works in the Russian literature, most of which are focused on the epidemiology of the disease,^(1,9-11) while only one publication is devoted to the disclosure of the pathogenetic aspects of the problem.⁽¹²⁾

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Some data for SARS-CoV-2 virus

Full-genome sequencing and phylogenetic analysis of the virus genome revealed that the coronavirus, which is an etiological agent that provokes the development of COVID-19, is a β -coronavirus. As a whole, coronaviruses contain single-stranded RNA and belong to the family *Coronaviridae* of the subfamily *Orthocoronavirinae*, which causes diseases in birds, mammals and humans. The viral genome consists of 27-32 thousand nucleotides encoding structural and non-structural proteins. The greatest pathogenetic value is found in the proteins of the membrane, capsid, nucleocapsid and spikes, which play an important role in the virus penetrating the host cell and replicating.^(15,28)

SARS-CoV-2 is genetically related (belongs to one subgenus) to the SARS virus, as well as a number of other coronaviruses, primarily isolated in bats. The structure of the receptor-binding gene region is almost identical to that of the SARS coronavirus. In addition, a common feature is that viruses use the angiotensin-converting enzyme 2, or ACE2 receptor, to enter the cell.⁽¹³⁾ In this regard, the group of the International Committee on virus taxonomy that studies coronaviruses proposed to name it SARS-CoV-2 (a coronavirus that causes Severe Acute Respiratory Syndrome Coronavirus 2).^(14,16)

It is interesting that the results of phylogenetic analysis of 103 SARS-CoV-2 strains isolated from Chinese patients identified two different serotypes of SARS-CoV-2, designated as type L (about 70% of circulating strains) and type S (about 30% of circulating strains).⁽¹⁷⁾ The authors note that type L showed a significant predominance at the initial stage of infection development in China, then in the course of its spread (outside of Wuhan district), the ratio changed towards an increased role of type S. However, the clinical significance of these results is still unclear, since the prevalence of these strains was not compared with laboratory shifts and symptoms of the disease.

Genetic “relatives” whose spread preceded the new coronavirus infection are SARS-CoV and MERS-CoV viruses, which are primarily zoonoses originating from bats.^(15,18) The first of them, transmitted to humans from cats and raccoon dogs, began in the province of Guangdong (China) and affected, according to official data, 8,096 patients, 774 of whom died, in 37 countries (mortality about 10%). The MERS-CoV virus, also primarily cultured in bats and transposed to humans via an intermediate host (camels), was more severe: 1,790 cases were identified with 640 deaths (mortality about 36%) in 27 countries.

MERS virus, also related to the genus of β -coronaviruses, is potentially more distantly related to SARS-CoV-2.^(2,16,18) Given that the RNA sequence of the considered coronavirus is similar to two other bat coronaviruses, it is assumed that bats were the primary source of the virus.^(17,18) On the other hand, it is not reliably established whether this transmission was carried out directly from bats, or whether any other mechanism or intermediate host was involved in this process.⁽⁴⁾

The experience gained by doctors and biologists in eliminating the foci of infection with SARS-CoV and MERS-CoV can be useful in the fight against the new coronavirus infection.

Immunity under COVID-19 infection

The state of the immune system in patients comes naturally under the close attention of specialists,^(6,18,19) since full disclosure of the nature of the immune response to the penetration of the coronavirus into the body is the key to creating the most effective and safe vaccine against this pathogen,⁽²⁰⁾ which can significantly limit its spread.

It should be noted that the common regularities of the immune response to the penetration of the COVID-19 pathogen into the body are consistent with ideas about the reaction to any viral agents.^(19,20) The integrative scheme of the immune response to the considered infectious agent is shown in Figure 1. Thus, when entering the internal environment of the body, the pathogen binds to low-specific, pattern-recognizing receptors, including Toll-(TLR), RIG-I-(RLR) and NOD-like (NLR) receptors, as well as lectin-type receptors and other soluble molecules (cGAS, IFI16, STING, DAI, etc.).⁽¹⁹⁾ TLRs perceive lipid, lipoprotein, protein, and nucleic antigens that are components of bacterial cells, viruses, and fungi.⁽²¹⁾ RIG-I-like receptors are more specific and can only bind complementarily to the nucleic acids of RNA-containing viruses.^(22,23) In turn, NOD-like receptors form complexes with protein antigens and participate in regulating the inflammatory response.^(24,25) Finally, lectin receptors provide implementation of phagocytic activity of immunocytes chemotaxis and stimulation of dendritic cells by involving NF- κ B and MAPK-dependent pathways.⁽²⁶⁾

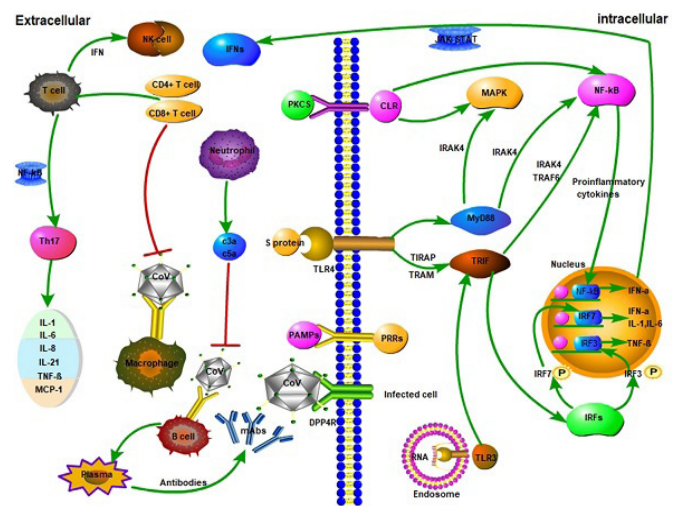


Fig. 1. Common scheme of immune response to SARS-CoV-2 infection (adapted from [19]).

Another feature of the interaction of SARS-CoV-2 with components of innate immunity is the ignoring of the inhibitory/viricidal function of defensins, endogenous peptides with pronounced antibiotic activity against a wide range of bacteria, fungi and viruses, and this effect is shown in vitro for neutrophil defensin obtained in humans (HNP1-3) and rabbits (RNP1-5).⁽²⁷⁾

More significant changes in COVID-19 infection occur in the composition of the acquired immunity. First of all, almost all researchers point to preferential shifts in the cellular

(T-dependent) link of the immune response, consisting of a decrease in the absolute number of CD4+ and CD8+ T cells,^(6,8) as well as an increase in the level of activation markers (HLA-DR and CD45RO) on these cells and a decrease in co-stimulating CD28 molecules.⁽⁸⁾ The severity of these disorders directly depends on the severity of the course of coronavirus infection, which is pathogenetically justified, since it is the T-cell component of the immune system that is responsible for the antiviral response. At the same time, a significant decrease in the level of T-regulatory lymphocytes was observed in patients with severe COVID-19 infection.⁽⁸⁾ Together, this led to the development of progressive lymphopenia. Clinicians differ in their views on the dynamics of γ IFN-producing CD4+ and CD8+ T cells: according to one, it is to increase, directly dependent on the severity of the condition;^(28,29) but to another— the dynamics is to reduce the numbers as well as IFN- γ production by CD4+ T cells on the background of maintaining the level of CD8+ T cells.⁽⁶⁾

Taking into account the phenomenon already established as one of the main pathogenetic mechanisms of a new coronavirus infection—the «cytokine storm»—it seems more logical to increase the number of interferon producers, which is confirmed by the undeniable extremely rapid hypercytokinemia, which plays a key role in the formation of severe forms of the disease (Fig.2).⁽²⁹⁾ It is the medicinal effect on individual cascades of the cytokine storm that can act as a targeted pathogenetic therapy for this life-threatening condition.⁽²⁹⁾ In this regard, there are several approaches:

- (1) Using exogenous gamma interferon and its direct inducers to stimulate components of innate immunity
- (2) Using immunomodulators to restore cytokine balance
- (3) Inhibiting cytokine production
- (4) Using cytokine traps
- (5) Inhibiting mononuclear mobilization and decontamination
- (6) Strengthening the vascular barrier by activating the Slit-Robo4 signaling mechanism

These paths are indicated by the respective numbers in Figure 2.

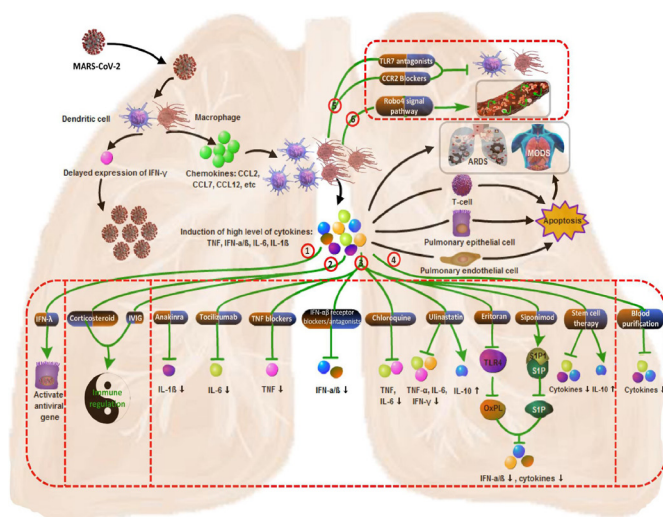


Fig. 2. “Cytokine storm” pathways and possibilities of its target therapy (adapted from [29]).

Interestingly, the B-dependent link of immunity also does not remain intact. It has been shown that COVID-19 infection reduces both the total number of B-lymphocytes and the level of their activation molecules.⁽⁸⁾ This trend also applies to dendritic cells, especially in severe patients.^(6,8)

Separately, we should focus on the ways this strain of coronavirus penetrates the cells of the macroorganism. Currently, it has been convincingly demonstrated that the main receptor providing COVID-19 internalization is ACE2, which combines it into SARS-CoV. On the contrary, the MERS-CoV virus uses dipeptyl-peptidase type 4 (DPP4) receptors for penetration.

At the same time, according to recent data, another receptor, CD147, plays an important role for the COVID-19 pathogen on the membrane of host cells, this receptor can act as an additional factor of virus invasion.⁽³⁰⁾ It has been shown that CD147 can independently bind to the virus spike protein, and its inhibition, or inhibition of expression, prevents internalization and spread of viral particles. In this regard, it is useful to use azithromycin, for which a similar effect based on inhibition of the CD147 cell receptor has been demonstrated on the example of malaria, as well as the use of high-affinity anti-CD147 antibodies.⁽³⁰⁾ In addition, azithromycin induces antiviral reactions in epithelial cells by increasing the level of interferons and proteins stimulated by its release, while reducing viral replication and virus release from the host cell. Additionally, this drug reduces the expression of metalloproteinases (MMPs) closely associated with CD147.

Metabolic shifts under COVID-19 infection

A number of other metabolic parameters reflecting signs of developing inflammation are pathogenetically associated with the dynamics of directly immunological indicators (Table 1).

Table 1.

Common characteristics of hematological and metabolic shifts, induced by COVID-19

Metabolic shifts	Clinical value
Leucopenia	Immune response
Leucocytosis	Bacterial superinfection
Neutrophylisis	Bacterial superinfection or/and cytokine storm
Trombocytopenia	Consumption coagulopathy
Elevation of C-reactive protein	Viremia, heavy course of disease
Calcitonin increasing	Bacterial superinfection
Elevation of LDH activity	Lung damage or multiorgan insufficiency
Bilirubin increasing	Liver damage
Elevation of aminotransferase activity	Liver damage or/and multiorgan insufficiency
High creatinine	Kidneys damage
Increasing of troponins	Heart damage
Hypoalbuminemia	Liver dysfunction
Trombine time prolongation	Consumption coagulopathy
Elevation of D-dimer or/and other products of fibrinogen degradation	Consumption coagulopathy

Thus, many authors note the formation of hypoalbuminemia, an increase in the concentrations of ferritin and C-reactive protein, and the activity of alanine aminotransferase and lactate dehydrogenase.^(1,6-8,31) A high-strength correlation between these parameters and the severity of the patients' condition was found.⁽⁶⁾

Thus, it is assumed that these parameters can act as Laboratory markers of infection and prognosis, can monitor the condition of patients and can perform topical diagnostics of lesions of individual organs and tissues in a new coronavirus infection.

COVID-induced changes in erythrocytes

The small amount of information in the literature about the state of red blood cells (RBCs) in coronavirus infection is available only from all components of the blood system. The main international databases of publications do not contain any articles directly devoted to the features of RBCs. Most of the information on this issue is indirect, and concerns the dynamics of general blood analysis.^(6,8,26) In particular, G. Lu and J. Wang⁽³²⁾ demonstrated a marked decrease in the absolute number of RBCs, depending on the severity of the disease, as well as their hypochromia, which persists even for 7-14 days after the clinical manifestation of infection. In addition, these shifts were naturally accompanied by a decrease in the concentration of hemoglobin, more pronounced than in seasonal flu outbreaks,^(32,33) combined with a progressive increase in the rate of erythrocyte sedimentation (ESR).^(34,35) Of particular interest is determining the level of glycosylated hemoglobin, a significant increase in the proportion of which, together with ESR, the concentration of fibrinogen and IL-6, may indicate the development of a systemic inflammatory response, hypercoagulation, and, as a result, a poor prognosis for patients with COVID-19.⁽³⁵⁾ Thus, in patients with diabetes mellitus, who are more likely than the general population to develop a severe course of the disease,^(11,13) when such signs were detected in 27.7% of them, the outcomes were fatal.⁽³⁵⁾ These data can be used as a target for targeted pathogenetic effects, as indicated by information about the protective properties of ascorbate in relation to oxidative modification and degradation of hemoglobin and albumin, demonstrated both in vitro and empirically in clinical conditions.⁽³⁶⁾ This fact can be useful as a way to preserve the oxygen transport function of the blood and, consequently, to increase the critical parameter-SaO₂, and so to stop the hypoalbuminemia present in the considered patient population.^(30,32)

In conclusion: On the whole, the etiological agent of a new coronavirus infection has a multi-faceted negative effect on the blood system of patients, which is expressed in the dysfunction of the immune system (mainly cellular) with the formation of a special syndrome, cytokine storm, as well as a decrease in the absolute amount of all the formed blood elements. Understanding the mechanisms of how these shifts develop creates opportunities for inventing new technologies for targeted therapy.

Competing Interests

The authors declare that they have no competing interests.

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