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Immune mechanisms of SARS-CoV-2 and potential drugs in the prevention and treatment of COVID-19

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Abstract

The lack of specific vaccines against SARS-CoV-2, as well as chemotherapy, significantly affected the spread of infection and the number of adverse outcomes of COVID-19. With the discovery of the pathogenesis of coronavirus infection, especially immune mechanisms, the important role of the innate immunity system in interacting with the virus is obvious. The presence of comorbid conditions, as well as the aging of the body, lead to disturbances in the immune response mechanism, low interferon induction, depletion of $CD8^+$-lymphocytes and natural killers and suppression of the effectiveness of both innate and adaptive immunity. The review discusses various mechanisms of antiviral activity associated with the induction of interferon (IFN) production, the use of direct IFN therapy, the use of antiviral drugs, and immunotropic therapy (synthetic immunomodulators), as promising in the prevention and treatment of COVID-19.

Key words: SARS-CoV-2, pathogenesis, COVID-19, innate immunity, adaptive immunity, interferon therapy.

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Иммунные механизмы SARS-CoV-2 и потенциальные препараты для профилактики и лечения COVID-19

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Резюме

Отсутствие специфических вакцин против SARS-CoV-2, как и химиопрепаратов, в значительной степени сказалось на распространении инфекции и количестве неблагоприятных исходов COVID-19. С раскрытием патогенеза коронавирусной инфекции, особенно иммунных механизмов, очевидна важная роль системы врожденного иммунитета при взаимодействии с вирусом. Коморбидные состояния, так же как и старение организма, приводят к нарушениям механизмов иммунного ответа, снижению интерфероноиндукции, истощению $CD8^+$-лимфоцитов и естественных киллеров и подавлению эффективности как врожденного, так и адаптивного иммунитета. В обзоре рассматриваются различные механизмы противовирусного действия, связанные с индукцией выработки интерферона (IFN), использованием прямой IFN-терапии, применением противовирусных препаратов, а также иммунотропной терапии (синтетических иммуномодуляторов) как перспективных средств для профилактики и лечения COVID-19.

Ключевые слова: SARS-CoV-2, патогенез, COVID-19, врожденный иммунитет, приобретенный иммунитет, интерферонотерапия.

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Due to epidemiological and clinical characteristics of the new coronavirus infection COVID-19, we have to continuously analyze the information on the pathogenesis of this infection. This is also important due to the absence of aetiotropic therapy and due to that the only option is a pathogenetic treatment.

Interaction of the virus and the human immune system includes the following two stages: internalization of the virus into the cell, virus multiplication with concurrent suppression of interferons (IFN) synthesis, induction of a systemic inflammatory response and "cytokine storm".

Each stage is characterized by its own distinctive key mechanisms that determine disease progression. The clinical aspect of COVID-19 disease is determined not only by a direct viral effect, but also depends on the individual response of the human body, thus determining broad disease variety in the population – varying from asymptomatic course of the disease or asymptomatic carrier state to severe course with a high probability of death.

The aim of our work was to analyze current understanding of new coronavirus infection COVID-19 pathogenesis in order to assess the perspectives for use of immune therapy in non-specific prevention and treatment of patients with COVID-19.

Like other respiratory coronaviruses, the primary route of COVID-19 transmission is airborne, but also the fecal-oral route cannot be excluded. In order to enter the cell the virus interacts with angiotensin-converting enzyme 2 (ACE2) receptor and membrane-bound serine protease 2 (TMPRSS2) required for protein S priming.

After binding of protein S to ACE2, direct fusion of the viral and cell membranes takes place, after which the protein undergoes partial cleavage and becomes active. The viral RNA enters the cell cytoplasm, where after its translation the active replication of the viral genome begins. Its interaction with the Golgi complex allows viral particles to be released into the blood plasma, thus continuing the cycle of the virus spreading throughout the body [1].

Considering the decreased ACE2 expression during COVID-19 infection, we can expect renin-angiotensin system failure, with subsequent dysregulation of blood pressure and water-electrolyte balance. At the same time, we cannot exclude that the observed change in ACE2 receptors expression can play an important role in COVID-19 pathogenesis itself [2]. Analysis of statistic data for COVID-19 cases among people living in highland areas showed a milder disease compared to residents of flat land areas. According to the authors' opinion [3], this may be due to both a decreased virus viability under low atmospheric pressure conditions, and due to decreased ACE2 expression in hypoxic environmental conditions.

Researchers demonstrate a lack of consensus on the role of ACE2 receptors in the disease pathogenesis. Experimental data showed a decreased viral load and replication in ACE2-mutant mice [2]. On the other hand, based on the similarity of lung damage observed in COVID-19 and in H5N1 avian influenza virus infection, one can assume a protective effect of exogenous ACE2 administration preventing acute respiratory distress syndrome (ARDS) development.

Mortality gender difference in COVID-19 was also attributed to ACE2, which is lower in women. It is presumably due to either genetic dimorphism, because the ACE2 gene is located on the X-chromosome, or due to different immunoregulatory effects of estrogens compared to testosterone [4].

At the stage of virus penetration into the cell, the viral antigen is presented to antigen-presenting cells (APC) and the virus is recognized by the innate immunity receptors. In the case of SARS-CoV-2 virus, like for all RNA-viruses, pathogen-associated molecular patterns (PAMP) are recognized by endosomal RNA-receptors, Toll-like receptors (TLR3 and TLR7), as well as by cytoplasmic receptors of RIG-I family (Retinoic-Acid-Inducible Gene I) and cytoplasmic helicase MDA-5 (Melanoma-Differentiation-Associated Protein 5, protein 5 associated with melanoma differentiation) [5]. Receptor activation should lead to a cascade response through the NF-kB transcription factor and IRF3 (regulatory IFN transcription factor), followed by the expression type I IFN and other pro-inflammatory cytokines. In addition to PAMP, damage-associated molecular patterns (DAMP), which respond to fragments of damaged cells produced as a result from the intense pyroptosis – characteristic manifestation of COVID-19, also play an important role.

A different response of pulmonary endothelial cells to damage is also linked to the role of DAMP [2]. Mice experiments demonstrated a different response to a protein belonging to a group of nuclear non-histone proteins HMGB1 (high-mobility group protein B1), which is a damage marker that can activate RAGE receptor (receptor for advanced glycation end products) actively expressed in the lung tissue. Researchers found *in vitro* necrosis of cells obtained from male animals, and apoptosis of cells from female animals. Results of experimental studies have already been presented on the efficacy of HMGB1/RAGE antagonists and TLR4 antagonists (also a functional HMGB1 receptor) in the treatment of severe lung damage-associated diseases [6].

Successful activation of interferon-producing cascade should limit the viral replication and suppress SARS-CoV-2 dissemination during the stage of disease onset [7]. However, given the inhibitory effect of the viral NSP1 (nonstructural RNA-binding protein) and rp6 (ribosomal protein S6) proteins, a low efficiency of interferon induction can be assumed, especially at the stage of active viral replication, while direct IFN therapy should demonstrate an adequate therapeutic effect. [8]. The work [9] presents a hypothesis of IFN production activation, associated with the level of intracellular ATP (adenosine triphosphate), the decrease of which, according to the authors opinion, plays one of the key roles in COVID-19 pathogenesis.

One of the most probable reasons for insufficient and tardy innate immunity response in COVID-19 disease is the possible immune evasion (escape) that is characteristic of this virus. Virus replication within cellular organelles prevents the virus from being recognized by cytoplasmic receptors. There is also evidence of a long "lag-period" (microorganisms growth initial phase), which leads to the retarded activation of the IFN cascade, that is too late to prevent viral dissemination. At the same time, a late increase of type I IFN level can potentiate the development of a "cytokine storm", thus prompting us to investigate the role of other IFNs with antiviral activity, e.g., IFN-λ. There is a variety of opinions regarding their role. On the one hand, there are published data [3] that a mutation of the *IFNL4* gene (TT-type), leading to the absence of this subtype, results in a faster and more complete viral load elimination. The authors suggest that this phenomenon results from deactivation of desensitization mechanism, which in other circumstances reduces IFN-α activity. On the other hand, IFN-λ, due to its organ-specificity effects, does not cause such a pronounced pro-inflamma-

tory response as type I IFN, and its presence in the early stages of the disease is able to suppress viral replication without the development of IFN-α lag-syndrome and without induction of "cytokine storm" [10]. In the case of innate immunity mechanisms failure, elements of the adaptive immune system are recruited as a defense, with the development of antibodies and a specific cellular immune response.

Hyperactivation of the innate immune response without a concomitant transition to an adaptive immune response is the important part of this infection pathogenesis. Patients with a severe course of the disease demonstrate a predominance of neutrophils, in contrast to the expected lymphocytes increase. This may be due to the ability of the virus to increase the expression of the membrane receptor of type 2 NK-cells (NKG2A), thus leading to functional depletion of $CD8^+$ lymphocytes and natural killer cells and leading to a suppression of both innate and adaptive immunity effectiveness [1]. The age-related dimorphism of symptoms may be associated with a change in the functional activity of the immune system. Aging-related T-cell lymphopenia, a decreased neutrophil and macrophage activity, a shift in the cytokine balance towards a pro-inflammatory response – all these factors aggravate the course of coronavirus infection. In addition, the phenomenon of antibody-dependent infection enhancement (ADE) suggests that in case of retarded period of antibody titer rise, which is typical for older people, the viral genetic shift can happen changing its antigenic structure, which leads to the accumulation of non-protective antibodies facilitating the viral penetration into cells. These data suggest that the virus, leading to a decrease in the number of ACE2 receptors, continues to spread via other mechanisms and pathways independent of the initial main entrance receptor [11].

In the case of adequate T-cell response, T-cells recruited to the site of infection exert a protective effect and limit the replication and spread of the virus. However, in the case of immune evasion, this accumulation of T-lymphocytes in the tissue leads to a hyperactive reaction, mainly type 1 reaction, with subsequent damage of organ tissues and the possible development of a "cytokine storm" [4], which is characterized by overproduction of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β. The increased levels of chemokines CXCL10, CCL7, an antagonist of the IL-1 receptor, are associated with increased viral load and loss of lung function [12]. Given the fact that the "cytokine storm" is probably the primary cause of body damage and death, a number of therapeutic strategies associated with inhibition of this process was proposed. The high-priority agents are probably monoclonal antibodies. However, other factors such as adequate vitamin D levels may also be important in achieving the control of this infection [6].

Haemodynamic disorders associated with both systemic inflammatory response and hypoxia are essential in the pathogenesis of COVID-19. Concurrently with the decrease in the level of functioning ACE2 responsible for vasodilation, vasoconstriction develops in the lungs with the resulting hypoxia. Hypoxia, in turn, affects the endothelium and provokes a pro-inflammatory response. In the setting of these processes, hypercoagulation is triggered, related to the release of the von Willebrand factor and to a high expression of tissue factor (TF). As a result, together with the activation of NETosis (the formation of extracellular neutrophil traps – that is a powerful neutrophil function, which is supposed to contribute to the development of multiple organ failure and lead to death), coagulation is initiated and the TF/VIIa pathway is activated. Subsequent microthrombosis in the lungs, which develops in the setting of hypercoagulation state, endothelial damage, and slowed blood perfusion, becomes a pathophysiological substrate for the development of ARDS [13]. Results of autopsies of patients who died from COVID-19 also confirm the presence of coagulation disorder: more than 70% of these cases were diagnosed with disseminated intravascular coagulation syndrome [6].

Consequently, in the pathogenesis of COVID-19, activation of innate immunity mechanisms, a cascade of interferon-producing reactions can facilitate the control of viral replication and suppression of SARS-CoV-2 dissemination during the onset of the disease and promote the involvement of the adaptive immune system with the formation of antibodies. Despite the different opinions regarding the spectrum of therapeutic strategies available, the immunotropic strategy among others is considered as promising for the prevention and treatment of COVID-19.

Synthetic immunomodulators

The synthetic immunomodulator azoximer bromide is one of the potential agents to be used at the early stages of COVID-19 infection development. It is characterizes by the complex mechanism of action – immunomodulatory, detoxifying and anti-inflammatory. Based on clinical studies results, we can discriminate three main roles of this agent in the immunopathogenesis of inflammatory diseases: it increases the effectiveness of innate immunity; it acts as an adjuvant in the development of a humoral immune response; it provides a pronounced pathogenetic and clinical effect in patients with severe inflammatory diseases.

The results of the study showed that incubation of cells with azoximer bromide increased the expression of innate immunity receptors, including MDA-5 [14–17]. High expression of MDA-5 ensures recognition of the virus at an early stage of infection – this is a prevention strategy; at a later stage, a strategy for activating a specific immune response is implemented. It is known that circulating plasmacytoid dendritic cells (pDCs) significantly prevent the spread of the virus in the body, and in particular viremia. These cells, when activated, produce type 1 IFN, thus blocking viral replication. It was found that an azoximer bromide-containing vaccine was significantly superior to nonadjuvant vaccines in increasing the number of pDC in blood plasma [18]. In addition, the drug increased the activity of NK-cells and CTLs – the main cells that provide the killing of virus-infected cells.

Azoximer bromide induces DC maturation, also increasing the expression of co-stimulating molecules $CD80^+/86^+$, ICOSL, required for the subsequent activation of T-follicular cells. These in turn are the key link

for the production of specific high-affinity antibodies by B-cells [19, 20]. Therefore, azoximer bromide provides a phase transition from innate to adaptive immune response – a step that is impaired in patients with severe COVID-19. The incorporation of this agent into a complex therapeutic strategy for patients with severe infectious pathological conditions (pneumonia, acute pancreatic necrosis, sepsis, etc.) was associated with a decrease of disease severity and a decrease in mortality; it provided a decrease of IL-6 concentration, an increase of lymphocytes count, and an increase in phagocytosis activity [1, 2] [21–25]. Decreased disease severity observed in the studies described above may also be due to the ability of azoxymer bromide to suppress NETosis, thus localizing the focus of inflammation and preventing the development of hemodynamic disorders, associated with blood clot formation and damage to the vascular endothelium. Thus, there is a rationale to consider azoximer bromide an effective component for therapeutic strategies in COVID-19 patients, that is effective both at the initial stage of infection and at the stage of systemic inflammation development. Currently, the drug has already been clinically tested in the setting of a new coronavirus infection and is included in the clinical guidelines in Slovakia for the treatment of COVID-19 patients aged ⩾ 65 years [26]. Elderly patients are at high risk of COVID-19 infection with a poor outcome. The physiological aging process also affects the immune system functioning. Aging slows down the timely response of nonspecific body defense mechanisms responsible for the recognition and removal of foreign agents. Studies in elderly and senile people have shown that the inclusion of azoxymer bromide into the treatment scheme for these categories of patients increased the relative and absolute content of T-lymphocytes with the $CD3^+$ and $CD4^+$ phenotypes, increased the ratio of $CD4^+/CD8^+$ lymphocytes, increased serum levels of immunoglobulins A and G, and normalized white blood cell counts [27–30]. This means that the drug can reduce the clinical manifestations of secondary immune deficiency by modulating immune mechanisms, which are essential in avoiding lymphopenia, suppression of type 1 INF, “cytokine storm”, and systemic inflammatory response.

Interferons

Currently, nine types of interferons were isolated in human, and according to their ability to interact with three types of receptors, they are grouped into three families:

- I – IFN-α, IFN-β, IFN-ε, IFN-ϰ, IFN-ω;
- II – IFN-γ;
- III – IFN-λ1, IFN-λ2, IFN-λ3.

IFN-α is widely used in medicine due to its pronounced antiviral, immunomodulatory and indirect antibacterial affect. IFN-α as a regulatory protein, enhances the synthesis of major histocompatibility complex molecules by antigen-presenting cells, securing the proper process of antigen presentation to immunocompeten T-cells. Interferon provides the expression of $CD4^+/CD8^+$ molecules on T-cells, which enables them to recognize the antigen and participate in the immune response. IFN-α, is the factor that enhances the expression of not only MHC molecules, but also other surface molecules. It increases the number of Fc receptors on the surface of immunocompeten T-cells, enabling the normal process of phagocytosis [31–33]. In Russia, a lot of IFN-α medicinal products are used in clinical practice [34–40]. The appropriateness of using IFN-β injectable forms in combination with antiviral drugs is also currently being discussed. However, the results of these studies have not yet been published [41]. In addition to IFN-α, the possibility of using IFN-λ is also discussed, as it has an antiviral effect distinct from that of type I IFNs. Unlike type I IFNs, IFN-λ exerts more organ-specific effects and participates in the maintenance of epithelial cells protective function, particularly in the respiratory tract [42]. Given the low rate of side effects associated with this therapy compared to type I and II interferons, the use of this therapy is potentially appropriate for the prevention of COVID-19.

Interferon inducers are substances of natural or synthetic origin that can induce type I and II IFNs synthesis in the body; they are characterized by immunomodulatory, antiviral, and anti-inflammatory activity [43, 44]. The main producers of IFN in response to the administration of IFN inducers are epithelial intestinal cells, hepatocytes, T-lymphocytes, neutrophils, and granulocytes. The mechanism of antiviral action is due to induction of IFN synthesis and, as a result, due to inhibition of virus-specific proteins translation in infected cells. Ultimately this results in virus reproduction suppression. Natural and synthetic IFN inducers are also able to induce the production of other cytokines: TNF-α, IL-1, IL-6, IL-8, IL-10, and colony stimulating factors. They are indicated in various infectious diseases, primarily viral diseases [45, 46].

Immunomodulatory drugs (for example, containing a polysaccharide complex obtained from a purified *Solanum tuberosum* shoots extract) may have a potential in COVID-19 prevention. An experimental animal study showed its activity against coronavirus, both in terms of clinical improvement and in reducing the estimated viral load. Panavir immunomodulatory activity is due to its effect on macrophage system, and due to induction of IFN synthesis, thus reducing viral infective activity and increasing the viability of the affected cells [47–49]. We are looking forward to clinical trials evidence.

Antiviral medicinal products. Imidazolyl ethanamide pentandioic acid (IEPA) is an original antiviral drug used in Russia, for treatment and prevention of influenza and other acute respiratory viral diseases. It was found that IEPA, being not an interferonogenic agent, increases IFN receptor (IFNAR) synthesis and enhances cell sensitivity to IFN signaling, which are initially suppressed by the

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influenza virus pathogenicity factor (non-structural protein NS1). The drug is able to stimulate the synthesis of antiviral effector proteins PKR and Mxa in infected cells, thus offsetting the suppressive effect of influenza virus on the IFN system. Theoretical assumptions of IEPA clinical efficacy were confirmed by the data regarding the effect on the innate immunity system under viral infection conditions [50, 51]. Clinical trials are needed to assess its efficacy in terms of new coronavirus infection treatment. Theoretical rationale is not sufficient in this setting.

Numerous studies, carried out both in the Russian Federation and in foreign laboratories, have shown that the medicinal product Umifenovir acts in the early stages of viral reproduction by inhibiting the fusion of the viral lipid envelope with intracellular membranes, thus preventing virus penetration into the cell. But the medicinal product does not affect viral transcription and translation, and it has no effect on neuraminidase (NA) activity and virus adsorption [52–54]. Umifenovir virus-specific mode of action differs from that of other anti-influenza drugs used: Amantadine and Remantadine are ion channel blockers, and Zanamivir and Oseltamivir are NA inhibitors. Umifenovir antiviral activity was confirmed in numerous *in vitro* and *in vivo* studies carried out in Russian core research centers and in independent laboratories in the USA, Great Britain, Australia, France, China, and other countries [55, 56]. In early February 2020, Chinese experts reported the possible efficacy of this medicinal product against coronavirus, but so far there is no confirmation from clinical studies.

Another antiviral and immunomodulatory agent is the sodium salt of the copolymer (1→4)-6-0-carboxymethyl-β-D-glucose, (1→4)-β-D-glucose and (21→24)-2.3,14,15,21,24,29,32-octahydroxy-23-(carboxymethoxymethyl)-7,10-dimethyl-4,13-di(2-propyl)-19,22,26,30,31-pentaoxaheptacyclo[23.3.2.216.20.05.28.08.27.09.18.012.17]dotriaconta-1,3,5(28),6.8(27),9 (18),10.12 (17),13,15-decaene. The primary mode of action of the drug is to induce IFN synthesis. In addition, it induces in the human body the synthesis of the so-called late IFN, which is a mixture of IFN-α and IFN-β, which possesses high antiviral activity. The drug induces IFN synthesis in almost all cells populations involved in the antiviral response of the body: T- and B-lymphocytes, macrophages, granulocytes, fibroblasts, and endothelial cells [57, 58]. There is still no confirmation of this drug effectiveness from clinical trials with COVID-19 patients.

Boceprevir is another potentially effective medicinal product. It is an inhibitor of 3CL protease (the main protease M^{pro}), which is important for the viability of the virus. Like other antiviral drugs with a similar effect (GC-376, calpain II and XII inhibitors), this drug suppressed viral replication in experimental studies. However, the clinical use of these agents is currently a subject of discussion [59].

The use of janus kinase inhibitors (JAKi) is also an issue in question.

The efficacy of these drugs in the treatment of patients with severe COVID-19 was confirmed in a number of randomized clinical studies. However, due to the possibility of further deterioration of coagulation disorders specific to COVID-19 patients, these drugs should be used with caution, after careful risk assessment for adverse effects of such a therapy [60, 61].

However, not only JAKi are able to block the virus internalization, but also inhibitors of CD147 receptor, which is, like JAK, the gateway for COVID-19. This mechanism among others is a target for azithromycin action. The antiviral effect of azithromycin was previously described in a series of scientific works. At the same time, cyclosporine capable of interaction with CD147 can also be used, or its analogs lacking immunosuppressive activity, such as cyclophilin A [62, 63].

Conclusion

The SARS CoV-2 pandemic has prompted researchers and medical practitioners to urgent search for drug therapies suitable for non-specific prevention and treatment aiming to reduce the incidence of adverse disease outcomes. The accumulated knowledge on SARS-CoV-2 immunopathogenesis, data from studies by our scientists searching the effective immunotropic drugs and investigating their mode of action, can serve as a theoretical background for experimental and clinical studies ultimately yielding treatment programs for patients suffering from COVID-19.

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