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Fibrotic Complications in the Lungs in Patients Who Have Had COVID-19 Pathogenesis of COVID-19

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Resume. Based on literature sources, the article presents up-to-date data on the main pathogenetic features of coronavirus infection associated with the SARS-CoV-2 virus, which caused a pandemic in 2019, according to the World Health Organization. The literature review covers in detail the processes of binding of the SARS-CoV-2 virus to the receptor of human cells that express angiotensin-converting enzyme 2 (ACE2), as well as internalization, replication of the virus, and the release of new virions from an infected cell that affect targeted organs (lungs, digestive tract, heart, central nervous system, and kidneys) and induce the development of a local and systemic inflammatory response. The existing methods of drug exposure that prevent human infection with the SARS-CoV-2 virus are described. The main epidemiological aspects of SARS-CoV-2 virus infection are highlighted, indicating a predominant lesion in elderly people and more often in males due to a higher level of ACE2 expression, to a greater extent in alveolocytes than in females. Mechanisms of development of the innate response are demonstrated. and the adaptive immune system of a macroorganism for infection with the SARS-CoV-2 virus. Therapeutic strategies related to the effect on various stages of the SARS-CoV-2 virus life activity are presented: internalization — the use of S-protein solute domains, anti-S-protein antibodies, a single-stranded variable fragment of antibodies to ACE2 or inhibition of glycosylation of cellular receptors, blocking the interaction of SARS-CoV-2 S-protein with ACE2 protein, and suppressing virus internalization by prescribing chloroquine and hydroxychloroquine; replication — inhibition of viral RNA-dependent RNA polymerase and the use of favipiravir, the non-nucleoside antiviral drug triazavirin, antiretroviral drugs (lopinavir in combination with ritonavir), nelfinavir, ribavirin, halidesivir, umifenovir, chymotrypsin-like protease inhibitors (cinanserin, flavonoids) and papain-like protease. In the near future, the above therapeutic methods will be aimed at preventing the development and treatment of both acute respiratory distress syndrome and conditions caused by damage to other targeted organs in COVID-19. Key words: coronavirus infection; acute respiratory distress syndrome; pathogenesis; immune response; angiotensin converting enzyme 2, tipepidine Pandemic of coronavirus disease 2019 (coronavirus disease 2019 — COVID-19; before — 2019nCoV) caused by the virus SARS-CoV-2, started in December 2019 in Hubei province, people's Republic of China, and on January 30, 2020 the emergency Committee of the world health organization (who) declared a global emergency health [6].

Coronaviruses are positive single-stranded large-envelope RNA-containing viruses that were first described in 1966 by Tyrell and Bynoe as causative agents of acute respiratory infections [19]. There are four subfamilies of coronaviruses: alpha, beta, gamma, and delta coronaviruses. The

SARS-CoV-2 virus is a beta-coronavirus. The genome of the SARS-CoV-2 virus is highly homologous with the genome of the SARS-CoV virus that caused acute respiratory failure.

Resume. Based on literature sources, the article presents up-to-date data on the main pathogenetic features of coronavirus infection associated with the SARS-CoV-2 virus, which caused a pandemic in 2019, according to the World Health Organization. The literature review covers in detail the processes of binding of the SARS-CoV-2 virus to the receptor of human cells that express angiotensin-converting enzyme 2 (ACE2), as well as internalization, replication of the virus, and the release of new virions from an infected cell that affect targeted organs (lungs, digestive tract, heart, central nervous system, and kidneys) and induce the development of a local and systemic inflammatory response. The existing methods of drug exposure that prevent human infection with the SARS-CoV-2 virus are described. The main epidemiological aspects of SARS-CoV-2 virus infection are highlighted, indicating a predominant lesion in elderly people and more often in males due to a higher level of ACE2 expression, to a greater extent in alveolocytes than in females. Mechanisms of development of the innate response are demonstrated. and the adaptive immune system of a macroorganism for infection with the SARS-CoV-2 virus. Therapeutic strategies related to the effect on various stages of the SARS-CoV-2 virus life activity are presented: internalization — the use of S-protein solute domains, anti-S-protein antibodies, a single-stranded variable fragment of antibodies to ACE2 or inhibition of glycosylation of cellular receptors, blocking the interaction of SARS-CoV-2 S-protein with ACE2 protein, and suppressing virus internalization by prescribing chloroquine and hydroxychloroquine; replication — inhibition of viral RNA-dependent RNA polymerase and the use of favipiravir, the non-nucleoside antiviral drug triazavirin, antiretroviral drugs (lopinavir in combination with ritonavir), nelfinavir, ribavirin, halidesivir, umifenovir, chymotrypsin-like protease inhibitors (cinanserin, flavonoids) and papain-like protease. In the near future, the above therapeutic methods will be aimed at preventing the development and treatment of both acute respiratory distress syndrome and conditions caused by damage to other targeted organs in COVID-19. Key words: coronavirus infection; acute respiratory distress syndrome; pathogenesis; immune response; angiotensin-converting enzyme type 2 acute respiratory distress syndrome (ARDS) thousands of people in 2003. However, COVID-19 is characterized by a lower severity and mortality rate than SARSCoV-associated ARDS. The SARS-CoV-2 virus mainly affects the elderly and more often men than women [12, 14]. Inoculation of SARS-CoV-2 into the human respiratory tract causes suppression of mucociliary clearance activity by inhibiting the mobility of epithelial cilia and is accompanied by death of epithelial cells. The SARSCoV-2 virus penetrates the nasal, laryngeal, and bronchial tree mucosa into the peripheral blood [9] and subsequently infects target organs — the lungs, digestive tract, heart, and kidneys, whose cells express angiotensin-converting enzyme 2 (ACE2). It is assumed that the main target of the SARSCoV-2 virus is lung epithelial cells. Initially, the SARS-CoV-2 virus binds by surface spines organized by the S protein to the ACE2 protein, which is located on the cell membrane of the macroorganism, This is followed by internalization, virus replication, and the release of new virions from the infected cell, which affect the target organs and induce the development of a local and systemic inflammatory response (Fig. 1) [16, 24, 33,].Binding of the SARS-CoV-2 virus to the eleto-human receptor, the main cell receptor to which the spike S protein of the SARSCoV-2 virus binds, the ACE2 enzyme was identified [9] S-protein The spike S-protein anchored in the coronavirus envelope is a three-dimensional pointed glycoprotein, the molecule of which consists of three domains: ectodomain, membrane anchor domain, and short intracellular tail (Figure 2) [62]. The ectodomain consists of a receptor-binding subunit S1 and a membrane-bound subunit S2. The S1 receptor-binding subunit contains two independent domains: N — (N-terminal domain-NTD) and C-terminal domain (C-domain — CD). The CD S-protein domain of the SARS-CoV-2 virus is a receptor - binding domain (RBD) that recognizes the ACE2 protein as its receptor. It

should be noted that the RBD region of SARS-CoV-2 is the main target for neutralizing antibodies [1, 6].

Angiotensin-converting enzyme 2 Protein ACE2 is a zinc-dependent peptidase that is an enzyme of the renin-angiotensin system and plays a key role in the regulation of blood pressure. The human ACE2 gene was mapped on the X chromosome. The ACE2 protein is a Type I transmembrane glycoprotein whose molecule contains two domains: the catalytic extracellular N-terminal peptidase (PD) and the transmembrane C-terminal domains (Figure 3). The catalytic domain contains the active site of zinc-metallopeptidase, the human zinc — binding motif. Assume, that glutamylaminopeptidase (ENPEP) is the second probable human CoV receptor [45]. The ACE2 protein functions as a monocarboxypeptidase that catalyzes the cleavage of angiotensin II (Ang II) to form angiotensin 1-7 (Ang 1-7). Vasoactive peptide Ang II, which is generated from Ang I by ACE, which is responsible for systemic vasoconstriction and aldosterone release, the Ang 1-7 peptide resists the action of the Ang II peptide, causing vasodilating, antiproliferative, and antifibrotic effects [2]. ACE2 protein is involved not only in the regulation of human blood pressure. In addition to being a potent inhibitor of the activity of the renin-angiotensin system, ACE2 protein induces vasodilation, causes natriuresis, and inhibits the activity of the inflammatory process by catalyzing the conversion of Ang II to Ang 1-7, it is also a receptor for the SARS-CoV and SARS-CoV-2 coronaviruses and interacts with amino acid transporters and integrins [27].

Interaction of SARS-CoV-2 virus S-protein with ACE2 The interaction of SARS-CoV with ACE2 is initiated by the penetration of RBD trimers of the S-protein of the SARSCoV-2 virus into the hydrophobic pocket of the catalytic domain of the ACE2 protein. Analyzing the full-length structure of the ACE2 protein, Zhou Qiang's lab discovered that the protein exists in the form of a dimer, which in both open and closed conformations contains an interface that interacts with coronaviruses. The RBD domain of the SARSCoV-2 S-protein recognizes the extracellular peptidase domain of the ACE2 protein mainly by polar amino acid residues [23]. It should be noted that the ACE2 protein functions as a SARS-CoV-2 virus receptor independently of the peptidase activity of PD. Attachment of the S-protein trimer of the SARS-CoV-2 virus to the structure of the ACE2 dimer implies simultaneous binding of two S-protein trimers to the ACE2 dimer [73]. The amino acid sequence of the RBD S protein of the SARS-CoV and SARS-CoV-2 viruses is 72% homologous. Comparison of the interaction of SARS-CoV-2 and SARS-CoV S-protein RBD domains with ACE2 protein revealed some variations in the structure of S-proteins of various coronaviruses. Thus, the RBD S-protein of the SARS-CoV-2 virus differs in the presence of

The RBD loop contains flexible glycyl residues, while the SARS-CoV S-protein RBD loop contains rigid prolyl residues. Molecular modeling has shown that the RBD of the S protein of the SARSCoV-2 virus has a significantly higher affinity for the ACE2 protein than the RBD of the S protein of the SARS-CoV virus [7]. The degree of affinity of the SARS-CoV-2 S protein to ACE2 is 10-20 times higher than that of the S protein of its closely related SARS-CoV virus [69]. A high level of affinity is associated with the presence of a phenylalanine F486 residue in the flexible RBD loop, which provides free penetration into the deep hydrophobic pocket of ACE2 [7, 23]. Mutations in the S-protein gene may be accompanied by a change in the affinity of the coronavirus for the ACE2 protein. Thus, a single N501T mutation (corresponding to the S487T mutation of the SARS-CoV virus) is accompanied by a significant increase in the level of affinity of the RBD S protein to human ACE2 [63]. Binding of the SARS-CoV-2 virus to the ACE2 protein induces an increased expression of the latter, which can lead to damage to AEC type II, which, in turn, can cause a number of systemic pathological reactions [24]. Drug counteraction to the process of binding of S-protein to membrane-associated protein ACE2 is one of the therapeutic areas that prevent human infection with the SARS-CoV-2 virus. In particular, it is believed that the use of soluble ACE2 receptors [3] or the extracellular ACE2 domain as a bait for binding to S-protein; antibodies

directed against ACE2, or a single-stranded antibody fragment (scFv); a complex consisting of the Fc antibody fragment and the ACE2 extracellular domain blocks the binding of the SARS-CoV-2 virus to the receptor and prevents infection of cells [26, 25]. Target cells expressing ACE2 in the human body mainly located in the tissues of the lungs and digestive tract. A large S-protein on the surface of the coronavirus binds to ACE2 on infected cells, which leads to the penetration of the SARS-CoV-2/ACE2 complex into the cell. The use of S-protein RBD solute domains, anti-S-protein antibodies, and a single-stranded variable fragment of anti-ACE2 antibodies (scFv) can block this interaction and prevent infection of the macroorganism cell. The synthetic S protein solute receptor-binding domain, or scFv, binds to ACE2 and prevents the virus from binding to membrane-bound ACE2. The extracellular domain of ACE2, fused with a fragment of Fc antibodies to the S protein, blocks the coronavirus [26]. It has also been demonstrated that the antimalarial drug chloroquine inhibits the glycosylation of cellular receptors and blocks the interaction of the SARS-CoV-2 S-protein with the ACE2 protein [9]. Of interest are some SARSCoV-specific neutralizing antibodies (m396, CR3014) that target the ACE2 binding site

Figure 3. Domain structure of the ACE2 [2]molecule Note: The ACE2 molecule consists of two domains: a single active site peptidase domain (HEMGH) at the N-terminus and a transmembrane domain (TM) homologous to the virus collectrin SARS-CoV, don't link S-virus protein SARS-CoV-2 [35]. However, the presence of ACE2 is not sufficient for internalization of the virus to occur. For example, some human endothelial cells and intestinal cell lines expressing ACE2 are not infected with SARS-CoV, while cells without a detectable level of ACE2 expression, such as hepatocytes, may be infected with the SARS-CoV virus [31]. These facts suggest that the adhesion of the SARS-CoV-2 virus to the macroorganism cell may occur using other receptors that have not yet been identified [28]. Internalization of the SARS-CoV-2 virus and Viral RNA release Binding of the SARS-CoV-2 virus to the ACE2 protein stimulates clathrin-dependent and clathrin-independent endocytosis. For effective infection with the SARS-CoV-2 virus, both the ACE2 protein and the S protein must be cleaved. The ACE2 molecule is cleaved by transmembrane protease serine 2 (TMPRSS2) in the region of amino acid residues 697-716 of the C-terminal segment [21, 38, 43]. A TMPRSS2 inhibitor approved for clinical use blocks internalization of the coronavirus/ACE2 complex and may pose a risk of infection. It is a treatment option for COVID-19 [21]. Camostatmesylate (FOY 305), originally developed for the treatment of chronic pancreatitis, suppresses the activity of TMPRSS2 protease and prevents the entry of SARS-CoV-2 virus into the cell [47]. Also, the presence of the sodium-dependent neutral amino acid transporter B (0) AT1 may block access of TMPRSS2 to the site of ACE2 cleavage. The B(0)AT1 transporter has also been shown to interact with another coronavirus receptor, aminopeptidase N (APN or CD13) [73]. Considering the critical role of low pH in endosomes in the internalization process It has been suggested that the antimalarial drugs chloroquine and its derivative hydroxychloroquine may have a strong antiviral effect due to their ability to increase the pH level in endosomes. The positive charge of chloroquine alkalizes the contents of phagolysosomes and inhibits both virus fusion and replication [13, 35, 58]. Endosomal pH-dependent cysteine protease cathepsin L cleaves the S protein at 2 sites, promoting the fusion of viral and cell membranes, which leads to the formation of a pore in the endosome wall and the release of coronavirus RNA into the cytoplasm cells [78]. Viral replication After the virus enters the cell, viral RNA is released into the cytoplasm, from which two polyproteins and structural proteins are translated and replication of the viral genome begins. The newly formed glycoproteins of the coronavirus envelope are embedded in the membrane of the endoplasmic reticulum or Golgi complex. The viral particles are then transported to the endoplasmic reticulum — Golgi intermediate compartment (ERGIC), and finally the vesicles containing the viral particles fuse with the cell's plasma membrane and are released from an infected cell [30]. Drug-induced blocking of SARS-CoV-2 viral RNA synthesis can be performed by the adenosine analog remdesivir, which acts on RNA-dependent RNA polymerase. Viral

replication is also sensitive to the effects of the viral RNA-dependent RNA polymerase inhibitor favipiravir, the non-nucleoside antiviral drug triazavirin, antiretroviral drugs (lopinavir in combination with ritonavir), nelfinavir, ribavirin, halidesivir, umifenovir, chymotrypsin-like protease inhibitors (cinanserin, flavonoids) and papain-like protease. Papain-like protease is a virus-encoded deubiquitinase and is a type I IFN antagonist [65]. Immune response Innate immune system response Currently, the innate immune system response in SARSCoV-2-infected patients is extremely poorly understood. It is believed that the key manifestation of activation of innate immunity in COVID-19 is an increase in the total number of neutrophils, an increase in the concentration of IL-6 and C-reactive protein in blood serum [37]. A characteristic feature of the severe form of COVID-19 is lymphocytopenia [51].

Activation of image recognition receptors The human innate immune system detects viral pathogen-associated molecular patterns (PAMP) using image recognition receptors (PRR). The PRR families are represented by Toll-like receptor (TLR), RIG-I — like receptor (RLR), NOD-like receptor (NLR), C-type lectin-like receptors (CLmin), and cytoplasmic receptors (cGAS, IFI16, STING, and DAI) [1, 29]. In speech recognition PAMP of the SARS-CoV-2 virus involves TLR2, TLR3, and TLR4. It has been demonstrated that TLR-4, recognizing the SARS-CoV-2 S-protein, activates the production of numerous proinflammatory cytokines via the MyD88-dependent signaling pathway. Activation of TLR2, TLR4 induces the production of pro-IL-1β, IL-6, IL-8, IL-21, TNF-β, and CCL2 by epithelial cells and macrophages, and subsequent activation of inflammasomes leads to the release of active mature IL-1β, which recruits neutrophils into lung tissue and causes fever. Suppression of IL-1b and IL-6 activity has been shown to promote recovery in patients with COVID-19. It is suggested that IL-37 and IL-38, which suppress the IL-1b-associated inflammatory response, can be used in the treatment of patients with severe COVID-19 [10]. Blocking the IL-6 receptor with tocilizumab, which is a recombinant humanized monoclonal antibody, has a positive therapeutic effect in many inflammatory diseases, including COVID-19 [36]. TLR3 excitation by viral RNAs activates the cascade of transcription factor IRF signaling pathways, which leads to the production of IFN type I and proinflammatory cytokines [29]. The involvement of RLR, NLR, CLmin and other PRRS in the development of COVID-19 has not yet been studied. However, coronaviruses can induce the formation of two-membrane vesicles in which PRRS are absent, and by replicating in these vesicles, they avoid the macroorganism's recognition of their RNA, which prevents the activation of the innate immune system [30].

Epithelial cells Airway epithelial cells secrete a variety of cytokines, chemokines, antimicrobial peptides, and other factors in response to viral infection. In particular, epithelial cells produce IL-6, TNF-α, CXCL8 (IL-8), granulocyte colony-stimulating factor (G — CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). These colony-stimulating factors induce the differentiation of cells of myeloid origin: G-CSF activates the differentiation and proliferation of neutrophils, and GM-CSF stimulates the proliferation and differentiation of various types of immune progenitor cells. In lung tissue, GM-CSF causes proliferation and activation of pulmonary dendritic cells and macrophages. GM-CSF-deficient mice are highly susceptible to respiratory viruses. The chemokine CXCL8 purposefully recruits neutrophils to the focus of lung damage [15, 40].

Neutrophils Overproduction of the cytokine IL-1b and the chemokine CXCL8 causes both proliferation and recruitment of neutrophils in the affected tissues. Many mediators released by neutrophils themselves are neutrophilicchemoattractants, so neutrophils can recruit other neutrophils. In turn, neutrophils, producing pro-inflammatory cytokines and chemokines, recruit monocytes. A high level of neutrophils in peripheral blood is associated with an unfavorable prognosis of COVID-19 [37]. Neutrophils are characterized by a fast rate of phagocytosis, a higher rate of phagocytosis.

the intensity of generation of activated oxygen-containing metabolites. Neutrophil granules contain a fairly wide range of enzymes that are secreted into the extracellular space and can cause tissue destruction [14]. Despite the presence of neutrophils in coronavirus-infected tissues, their role in the clearance of coronaviruses remains unknown.

Mast cells Coronaviruses (regardless of the types) primarily affect immune cells, including mast cells that are located in the submucosa of the respiratory tract. Mast cells activated by coronavirus release proinflammatory substances such as histamine and proteases (tryptase and chymase) in the early period of the disease, and IL — 1b, IL-6, and IL-33 in the later period [25]. Thus, mast cells support inflammation of the affected tissues during the late stage of COVID-19 development.

Cytokine response COVID-19 disease is accompanied by an extremely high level of pro-inflammatory cytokine production (IFN-α, IFN-γ, IL-1β, IL-6, IL-12,

At the same time, in mice deficient in Type I IFN production, the course of SARS-CoV infection practically does not differ from the course of this infection in wild-type mice, but mice with knockout of Stat1 and Myd88 genes have a higher mortality rate [57]. Like many viruses, SARS-CoV encodes proteins that counteract the innate immune defense, including by suppressing the activity of Type I IFN production [67]. The SARS-CoV-2 virus generates a short protein, orf8, which is encoded by the orf3b sequence.

The SARS-CoV-2 virus Orf3b protein, although it does not contain any known functional domain or motif, inhibits the expression of the IFN-β gene [5]. Response adaptive immune system Antigenpresentation in coronavirus infection, the adaptive immune system response begins when the antigen-presenting cells present the SARS-CoV-2 CD4+virus antigen

Th1 cells, inducing the production of IL-12, which, in turn, increases the activation of these immunocytes. CD4+ Th1 cells are involved in the activation of antigen-specific cytotoxic CD8+ T cells that cause lysis of SARS-CoV-2-infected cells. Presentation of the SARS-CoV antigen is mainly associated with Class I HLA molecules, and therefore some polymorphisms of the HLA system antigens (HLA-B∗4601, HLA-B∗0703, HLA-DRB1∗1202 and HLA-Cw∗0801) are highly associated with susceptibility to coronaviruses, while the HLA-DR0301, HLA-Cw1502 and HLA-A alleles∗0201s are associated with a low risk of developing a coronavirus infection. Activated CD4+ Th1 cells also stimulate B cells, causing the generation of antigen-specific antibodies [30, 17].

Cellular immunity response The development of an infection associated with the SARS-CoV-2 virus is accompanied by excessive activation of cellular immunity, as evidenced by a sharp increase in the level of representation of cells expressing HLA-DR and CD38 [30], against the background of a significant decrease in the population of CD4+ and NK cells in the peripheral blood of patients. It is believed that a decrease in the content of CD4+ T cells is a characteristic feature of COVID-19 [11, 26]. The level of representation of cytotoxic CD38+HLA-DR+CD8+ T cells increases rapidly starting from the 7th day of the disease. Data Pool the number of cells decreases only after three weeks of the disease. Cytotoxic CD8+ T cells in COVID-19 produce a large amount (34-54% more than in healthy people) of granzymesA and B and perforin. It is believed that a fairly rapid increase in the population of cytotoxic CD38+HLA-DR+CD8+ T cells by day 7-9 of the disease contributes to the sanogenesis of COVID-19 [23]. Patients with COVID-19 have a high content of pro-inflammatory CCR6+ Th17 cells. It is believed that excessive activation of Th17 cells and extremely high levels of CD8+ T cell cytotoxicity underlie the severity of immune damage to the lung tissue of patients. Also, in patients with COVID-19, there is a depletion of the pool of Tged cells, which determines the unlimited activation of inflammatory mechanisms and delays the resolution of the inflammatory process [22].

Humoral immune response Activation of virus-specific B cells leads to their differentiation into plasma cells that consistently produce specific IgM and IgG class antibodies. It was demonstrated that antibody-producing CD3-CD19+ CD27HICD38HI cells in the peripheral bloodstream of COVID-19 appear on the 7th day, their number reaches its maximum value on the 8th day of the disease. Changes in the representation of antibody-producing cells are synchronized with fluctuations in the size of the pool of follicular CD4+CXCR5+ICOS+PDOS-1+ TFH cells. During the development of COVID-19, there is a gradual increase in the concentration of SARS-CoV-2 binding IgM and IgG class antibodies in the blood serum from the 7th to the 20th day of the disease [23]. It has been demonstrated that SARS-CoV-2-specific IgM-class antibodies disappear at the end of the 12th week from the moment of disease onset, and IgG-class antibodies persist for a long period of time, determining the level of protection against re-infection. Detection of specific antibodies in an individual's blood serum is the basis for rapid diagnosis of COVID-19 [32]. It is established that the use in patients with acute and severe SARS-CoV-2 infection with recombinant human monoclonal antibodies (CR3022) in the plasma of people who have had COVID-19 is accompanied by a significant positive clinical effect [56]. Damage to organs and systems There are two phases of SARS-CoV-2 infection: early and late. In the early phase of the disease, which is usually manifested by a mild degree of severity of COVID-19, the main role is played by non-specific defense mechanisms and a specific adaptive immune response that allows you to eliminate the coronavirus from the macroorganism. In this regard, at this stage, it is recommended to conduct medical measures aimed at strengthening the immune response (use serum from people who have had COVID-19, or pegylated IFN-αpreparations). However, if the immune response is ineffective, the second or late phase of COVID-19 develops, which is based on the superreplication of the SARS-CoV-2 virus and a "cytokine storm". Large-scale viral replication is accompanied by the generation of a large number of virions, which leads to massive damage to targeted body tissues, including lung tissue. Damaged ACE2-expressing cells produce pro-inflammatory cytokines that recruit effector cells (macrophages, neutrophils) and release alarms that induce the activity of inflammasomes. The functioning of inflammasomes is accompanied by the release of a large volume of pro-inflammatory cytokines and the development of a" cytokine storm", which increases the recruitment of macrophages and neutrophils, providing an extraordinary level of inflammation in the lungs.

Thus, the late phase of COVID-19 requires prescribing drugs that have a pronounced anti-inflammatory effect (corticosteroids, IL-1b, IL-6 and TNF blockers), and reparative measures (prescribing mesenchymal stromal / stem cells — MSC). It should be noted that the use of vitamin B3 (niacin or nicotinamide) in preventing lung tissue damage has been shown to be highly effective in animal models with bleomycin-induced lung damage [26]. It is believed that in the treatment of severe forms of COVID-19, MSC should be activated with IFN-γ to enhance the anti-inflammatory effect of MSC, since in SARS-CoV-2 infection, T cells have sufficient resistance to activating triggers [11].

Lung damage Lung damage is the main cause of both severe course and fatal outcomes of COVID-19 [72]. After the SARS-CoV-2 virus enters the human body, ACE2 protein production is inhibited, which leads to a decrease in the level of ACE2 protein representativeness, especially in lung tissues. The imbalance of ACE2 and ACE leads to an increase in the concentration of Ang II, which over-activates AT1a receptors in the lungs, which leads to an increase in capillary permeability and the development of pulmonary edema, activation of AEC apoptosis and the development of an inflammatory response of lung tissue. Decline ACE2 concentration leads to activation of signaling pathways associated with the inducible B1-receptor Des-Arg9 bradykinin, which further increases inflammation and promotes damage to lung tissue [28, 26]. At the first stage of the development of lung damage, alveolar macrophages, recognizing the SARS-CoV-2 virus, begin to produce pro-inflammatory interleukins and chemokines that recruit effector T lymphocytes. Subsequently, in the

late period of the disease development, an extremely high level of production of proinflammatory cytokines (IL-6, IL-1b, TNF-α, etc.) by these cells provides the influx of a large number of monocytes and neutrophils, which increase the phenomena of inflammation and contribute to the development of edema of lung tissue in patients with COVID-19. Cytokines IL-1β, TNF-α induce the activity of hyaluronan synthase 2 (hyaluronan synthase 2 — HAS2) in endothelial CD31+cells, alveolar epithelial EpCAM+cells of the lungs, and fibroblasts, which leads to an excess of hyaluronic acid production and fluid accumulation in the alveolar space [4]. Overexpression of hyaluronan plays a key role in the development of inflammation and edema [20]. It is believed that reducing the amount of hyaluronan or suppressing its production will contribute to an increase in the gas exchange surface in the alveoli and the recovery of patients with COVID-19 [51]. In particular, a drug approved for the treatment of gallbladder dysfunction, hymecromone (4-Methylumbelliferone, 4-MU) is a HAS2 inhibitor [8].

Effect of the virus on the cardiovascular system Infection with the SARS-CoV-2 virus can inhibit the activity of ACE2 expression, which leads to toxic excessive accumulation of angiotensin II, which causes ARDS and the development of lightning myocarditis [6, 18]. Arterial hypertension and cardiovascular diseases are associated with a high risk of death from COVID-19, but the mechanisms underlying this thanatogenesis remain unknown. More than two-thirds of patients who died from COVID-19 had a history of hypertension, cardiovascular disease, or diabetes. diabetes [12, 18]. It is assumed that the course of COVID-19 against the background of cardiovascular diseases is predetermined by the state of the renin-angiotensin system. Two competing hypotheses are put forward, which postulate that: 1) blockade of the renin-angiotensin system reduces the pro-inflammatory activity of Ang II, reducing the risk of ARDS, myocarditis, or mortality in COVID-19, or 2) blockade of the renin-angiotensin system increases ACE2 expression, promoting internalization of SARS-CoV-2 virus into lung and heart cells, leading to ARDS, myocarditis, and death [18]. Shown, It is shown that in COVID-19, an increased representation of ACE2 in the lungs can play a protective role, since ACE2-dependent generation of the Ang 1-7 peptide from Ang II creates a cytoprotective environment in the lung tissue, contributes to the suppression of vasoconstriction mechanisms and the activity of profibrotic processes. Some authors believe that the administration of angiotensin receptor 1 (AT1R) blockers, such as losartan, may have a beneficial effect on the course of COVID-19, as it is accompanied by a 2-to 5-fold increase in ACE2 expression in kidney and heart tissues [17]. Discontinuation of blocker therapy AT1R leads to deterioration of cardiac function and heart failure within a few days or weeks, with a possible increase in mortality [28]. Myocardial damage associated with SARS-CoV-2 infection occurred in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan and was accompanied by a sharp increase in the concentration of troponin I (hs-cTnI) (> 28 pg / ml) [22]. The mechanism of acute myocardial injury caused by the SARS-CoV-2 virus may be associated with increased expression of the ACE2 protein. Other hypothesized mechanisms of myocardial damage include a "cytokine storm" caused by an imbalance in the Th1 and Thed cell response, and hypoxemia caused by COVID-19 [17].

Kidney damage The kidneys are a specific target for the SARS-CoV-2 virus [12, 19], since ACE2 is highly expressed in epithelial cells located at the border of the proximal tubules, and, to a lesser extent, in podocytes [30]. Proteinuria and hematuria are detected in almost 40 % of inpatient patients with COVID-19 [12]. In SARS-CoV-2 viral infection, proinflammatory CD68+macrophages are recruited to tubulointerstition and C5b-9 complement is strongly deposited in the renal tubules. These pathological processes and accumulation of SARS-CoV-2 virus antigens in the renal tubules can cause the development of acute renal failure [13].

Damage to the central nervous system Ling Mao et al. [18] showed that 78-88% of patients with severe forms of COVID-19 have signs of damage to the central nervous system (CNS) in the form

of impaired consciousness and cerebrovascular disorders (dizziness, headache), reduced taste (hypogeusia) and olfactory sensitivity (hyposmia). Loss of consciousness is mainly observed in cases where the course of COVID-19 was accompanied by the development of ischemic or hemorrhagic stroke. However, the potential for CNS damage by the SARS-CoV-2 virus remains insufficiently studied. For the first time, the presence of the SARS-CoV-2 virus gene in the cerebrospinal fluid of a patient with COVID-19 and neurological disorders was identified on March 4, 2020 by researchers from Beijing Ditan Hospital (China) [55]. Experimental studies using transgenic mice have shown that when administered intranasally, coronaviruses can enter the brain. It is assumed that the SARS-CoV-2 virus, like other coronaviruses, initially infects peripheral nerve endings, and then, using the trans-synaptic transfer mechanism, penetrates the central nervous system tissue, mainly affecting the cells of the thalamus and brain stem [31]. Conclusion The results of further study of the molecular mechanisms of SARS-CoV-2 virus vital activity and its interaction with various human cells will probably allow us to create new antiviral drugs, both therapeutic and preventive, while understanding the development of the response of the innate and adaptive immune system of a macroorganism to infection with the SARS-CoV-2 virus — therapeutic strategies that will be aimed at preventing the development and treatment of both acute respiratory as well as conditions caused by damage to other targeted organs in COVID-19.

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