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Proteolytic enzyme and adiponectin receptors as potential targets for COVID-19 therapy

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The coronavirus disease 2019 (COVID-19) pandemic requires not only the creation of vaccines to prevent the spread of the disease, but also the development of novel drugs aimed at reducing viral load, suppressing an excessive immune response and preventing the severe complications such as lung fibrosis and acute respiratory distress syndrome. One of the promising targets for studying the development of pneumonia, systemic inflammation and disseminated intravascular coagulation in COVID-19 is the plasminogen activator system. In patients with a severe disease course, impaired activity or expression of plasminogen activators significantly increases the blood level of D-dimer and fibrinogen, as well as correlates with intravascular coagulation and thrombus formation. The second promising target for studying the pathogenesis of COVID-19 is the adiponectin/T-cadherin system: adiponectin is able to reduce the content of pro-inflammatory cytokines, the increase of which is characteristic of COVID-19, and stimulate the production of an anti-inflammatory cytokine interleukin-10. The review describes the role of plasminogen and T-cadherin activators in their possible participation in the development of pulmonary fibrosis in COVID-19 and hemostasis regulation, as well as cardio- and vasculoprotective function of adiponectin and its receptor, T-cadherin.

Keywords: COVID-19, SARS-CoV-2, plasminogen activator system, urokinase-type plasminogen activator, urokinase-type plasminogen activator receptor, T-cadherin, adiponectin, pulmonary fibrosis.

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Introduction

Acute respiratory distress syndrome (ARDS) is one of the most serious symptoms in Coronavirus disease 2019 (COVID-19). There is a high death risk in patients with ARDS. It is known that one of the main ways of virus entry into lung cells is the high expression of a membrane protein by alveolar type II cells — angiotensin-converting enzyme (ACE2). Massive damage to alveolar type II cells provokes the pulmonary fibrosis, and a rampant immune response, followed by lymphocytopenia and a subsequent cytokine storm, leads to multiple organ failure, involving almost all tissues and organs [1].

In addition to alveolar type II cells, endothelium, pericytes and cardiomyocytes, a relatively high level of ACE2 expression is found in the epithelium of the gastrointestinal tract, gallbladder, kidneys, testes, seminiferous tubules, and adrenal glands at both the level of messenger ribonucleic acid (RNA) and ACE2 protein [2]. The use of the ACE2 by virus to enter cells specifies organs and tissues that are potentially susceptible to infection and damage. A high level of ACE2 expression on the endothelium and pericytes can lead to microvascular dysfunction and acute coronary syndrome, which also determines a negative prognosis in hypertensive patients [2]. In patients with heart failure, the level of ACE2 expression on cardiomyocytes, as a rule, is increased, which is a possible explanation for the increase in viral load and high mortality [2].

Treatment of critically ill patients and rehabilitation after an acute disease phase remains one of the most difficult and urgent tasks. Therefore, studies on the pathogenesis of coronavirus infection pathological conditions, including pulmonary fibrosis, lymphocytopenia, thrombotic and cytokine storm, are relevant and promising for the search for novel diagnostic and therapeutic targets.

The review summarizes the literature data, including clinical, research and review articles, indexed in the PubMed, WoS, Scopus and Russian Science

Citation Index (RSCI) databases. We analyzed more than 70 articles, of which 40 publications were included in the literature list. These papers are devoted to pathogenesis of COVID-19, molecular and cellular targets of coronaviruses, the results of studies on the role of plasminogen and T-cadherin activators in fibrosis development, hemostasis system regulation, cardiac and vascular protective function.

COVID-19 pathogenesis

Representatives of the *Coronaviridae* family are single-stranded positive-sense RNA with a length of 26 and 32 kb [2]. There are four genera in the *Orthocoronavirinae* subfamily, namely alpha-, beta-, gamma- and deltacoronavirus; of these, alpha- and betacoronaviruses infect mammals, and gamma- and deltacoronaviruses — birds. Of the seven coronaviruses that infect humans, alphacoronaviruses (HCoV-NL63 and 229E) are usually mild in adults. Betacoronaviruses MERS (Middle East Respiratory Syndrome) and SARS (Severe Acute Respiratory Syndrome) cause severe acute respiratory syndrome, while coronaviruses OC43 and HKU1 are associated with mild disease. COVID-19 is caused by a novel betacoronavirus and is probably derived from bats after mutations in the receptor-binding domain and the acquisition of a furin protease cleavage site [2]. Coronavirus-cell fusion occurs due to the spike (S) protein in the viral capsid [3], which on the host cell membrane binds to ACE2 or CD209L (C-type lectin L-SIGN protein) for SARS coronaviruses or DPP4 protein (dipeptidyl-peptidase 4) for MERS [4].

For envelope (virus)-membrane (cell) fusion and RNA entry together with the surrounding envelope containing the N protein, S-protein proteolytic cleavage by serine proteases (plasmin and transmembrane serine protease TMPRSS2) is required [5] (in more detail, the role of proteases in COVID-19 pathogenesis is discussed below). In the case of TMPRSS2, effective SARS-CoV-2 infection requires co-expression of ACE2 and TMPRSS2 on the same cells (Figure 1).

To date, an alternative pathway for SARS-CoV-2 entry is known, which bypasses the ACE2-related mechanism. Indeed, several studies have shown the ability of coronavirus to infect cells by binding to the GRP78 receptor and to the transmembrane glycoprotein CD147 (basigin). The importance of this pathway is evidenced by the wide pattern of CD147expression in different organs and tissues and multiple organ failure that occurs in severe COVID-19 course. In addition, the use of monoclonal antibodies meplazumab, blocking CD147, leads to a significant decrease in the severity of clinical course and accelerates the virus elimination [6].

Due to the activity of RNA-dependent RNA polymerase in cells infected with SARS-CoV, 12 subgenomic RNAs are transcribed, which encode 4 structural S-proteins, envelope proteins (E-proteins), membrane proteins (M-proteins), nucleocapsid proteins (N-proteins) and a number of other accessory proteins that are not directly involved in viral replication, but affect the innate immunity of the host [3]. After the fusion of viral membrane with either the plasma membrane or the membrane endosomes of host cell, the viral RNA genome enters the cytoplasm and is released from the envelope. In the cytoplasm, translation with the formation of two polyproteins (pp1a and pp1ab), transcription of subgenomic RNA, and replication of the viral genome occur [3]. Newly synthesized glycoproteins of the viral envelope are translocated into the rough endoplasmic reticulum and/or transported into the Golgi apparatus. As a result of the combination of viral genomic RNA and the capsid proteins, a nucleocapsid is formed, the viral particles bud off from the ER-Golgi intermediate compartment, already covered with a lipid membrane, and fuse with the plasma membrane, providing the release of new viral particles from infected cells [3].

Antigen presentation in coronavirus infection, development of humoral and cellular immunity

When a virus enters the body, its antigens are antigen-presenting cells, which play a central role in the body's antiviral immunity. Antigenic peptides are the major histocompatibility complex (MHC) and are further recognized by virus-specific cytotoxic T-lymphocytes. Similar mechanisms of etiology and pathogenesis in diseases caused by SARS-CoV and MERS-CoV (Middle East Respiratory Syndrome CoronaVirus) suggest common mechanisms that mediate the development of immune responses in COVID-19. It has been shown that antigen presentation in SARS-CoV mainly depends on MHC class I molecules, and to a lesser extent on MHC class II molecules. Subsequently, antigen presentation triggers humoral and cellular immunity mediated by virus-specific B- and T-lymphocytes. Similar to other viral infections, anti-SARS-CoV antibodies are IgM and IgG; the latter has specificity for two types of coronavirus proteins — S and N [7].

In addition to humoral immunity, there is also data on cellular immunity during coronavirus infection. Against the background of COVID-19, significant lymphocytopenia is shown, accompanied by a sharp peripheral blood decrease in the number of CD4+ and CD8+ T-lymphocytes; at the same time, these lymphocytes is activated due to an increase in the cytotoxic T-lymphocyte subpopulation, double positive for HLA-DR+ (CD4 3,47%) and CD8+ (CD8 39,4%) markers [7]. Similarly, there is an acute phase of response in patients with SARS-CoV, which is associated with a pronounced decrease in CD4+ and CD8+ T-lymphocytes.

Studies of patients who have recovered from SARS-CoV show the long-term presence (4 years) of CD4+ and CD8+ memory T cells, a delayed-type

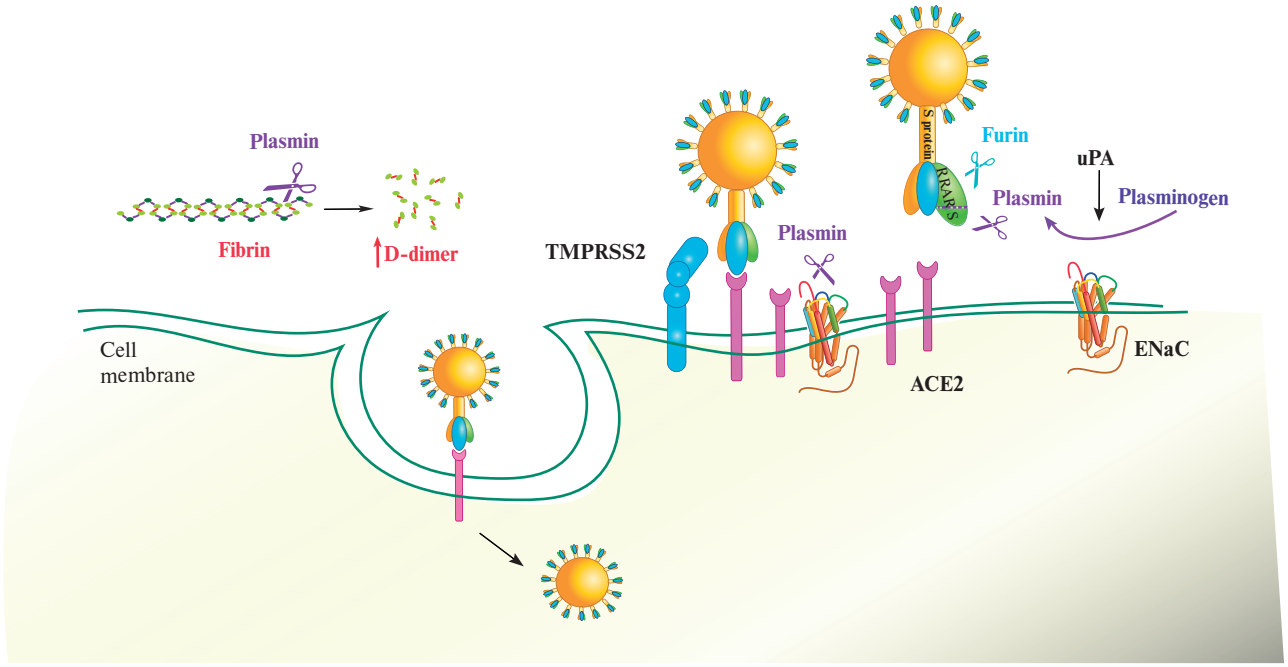

Figure 1 Role of proteases in COVID-19 pathogenesis (Rubina K. A., Semina E. V., 2021).
Note: Plasmin, furin and transmembrane serine protease 2 (TMPRSS2) cleave the S protein of SARS-CoV-2, increasing its ability to bind to the receptor on host cell membrane (ACE2), thus providing the fusion of viral and cellular membranes. Serine protease urokinase (uPA) is one of the main plasminogen activators. Plasmin cleaves excess fibrin with the formation of high D-dimer concentrations both directly in the epithelial lining fluid and in plasma, which leads to a change in blood fibrinolytic properties. In addition, plasmin also proteolyses the epithelial sodium channel (ENaC) subunit located on the apical surface of pulmonary and renal epithelial cell membranes. This increases the sodium ions' entry into epithelial cells and disrupts electrolyte metabolism in tissues.

hypersensitivity reaction and the production of interferon (IFN)-γ by these cells. Using a S-peptide library of the SARS-CoV, a specific T-cell response was detected in recovered patients even after 6 years [8]. Moreover, mice infected with MERS-CoV showed similar effects on CD8+ T lymphocytes.

Cytokine storm in COVID-19

The leading cause of death in COVID-19 is ARDS. ARDS is a common immunopathologic event for all coronavirus infections, including SARS-CoV and MERS-CoV [7]. One of the main mechanisms for severe ARDS is a cytokine storm, which is an uncontrolled systemic inflammatory response caused by the release of a large number of pro-inflammatory cytokines by immunocompetent cells (INF-α and γ, interleukins (IL)-1b, -6, -12, -18, -33, tumor necrosis factor (TNF-α), transforming growth factor (TGF-β-1b), etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc). Then, the concentration of immunosuppressive cytokine IL-10 increases. Similarly, in patients with severe MERS-CoV and SARS-CoV infections, increased serum levels of IL-6, IFN-α and chemokines CCL5, CXCL8, CXCL10 are found compared to patients with mild and moderate clinical course. IL-6 is involved in signaling cascades, the main components of which are kinases such as mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K/AKT) and transcription factor (STAT3), and is an important regulator of inflammation and proliferation. IL-6-mediated activation of STAT3 leads to the activation of the expression of various proteins, including the antiapoptotic protein Mcl-1 [9, 10]. Ultimately, an uncontrolled cytokine storm causes ARDS and multiple organ failure, which is the cause of death [7]. The full causes of the initiation of cytokine storm and its further development are still unknown.

Role of proteases and plasminogen activator system in the pathogenesis of coronavirus infection

SARS-CoV-2 S-protein contains two functional domains: a domain binding ACE on the cell, and a domain containing sequences that ensure the envelope-membrane fusion; for the exposure of these sequences and entry of nucleocapsid into the cell, the S-protein cleavage under the action of cellular proteases is necessary [11]. At the same time, thanks to the receptor-binding domain, the proteolyzed SARS-CoV-2 S-protein binds to ACE2 on the cell membrane (Figure 1). Study of the S-protein polypeptide sequence of SARS-CoV-2 shows the presence of a furin protease recognition site (682RRAR/S686). Since there is a high concentration of furin in respiratory tract cells, the S-protein can undergo furin-dependent proteolysis when synthesized viral particles are released from

the affected epithelial cells, and locally with high efficiency infect other types of lung cells (endothelium, macrophages, smooth muscle cells, etc.), worsening the clinical course [12].

It is known that, in addition to furin, S-protein is cleaved by other proteases (trypsin, plasmin, and transmembrane serine protease 11a (TMPRSS11a)), which are also expressed in respiratory tract tissues. Similar to furin, S-protein proteolysis by these proteases increases the interaction of the virus with epithelial cells of the bronchi and alveoli through ACE2. Analysis of the protease expression profile in human lung tissues using the LGE Web Portal (https://research.cchmc.org/pbge/lunggens/mainportal.html) shows that furin is predominantly expressed in alveolar type II cells, while plasminogen/plasmin, kallikrein and trypsin are expressed both in bronchial epithelial cells and in alveolar cells, both types I and II. Plasminogen is also expressed in vascular endothelial cells, but its greatest synthesis occurs in the liver [13].

The meta-analysis showed that the mean age of patients with SARS-CoV-2 is 46,62 years with a relatively even distribution by sex (men, 55,6%). More than a third (35,6%) had comorbidities as follows: hypertension (18,3%), cardiovascular diseases (CVD) (11,2%), diabetes (10,3%), chronic obstructive pulmonary disease (COPD) (3,9%) or cancer (1,1%) [14]. It should be noted that the severe course of the disease is observed not only in patients with comorbidities, but also in healthy young people. Moreover, recently there have been data on a possible hereditary predisposition to a certain clinical course of COVID-19 [15]. These data make it especially urgent to search for new targets and mechanisms of pathological conditions and complications in coronavirus infection.

Plasminogen and its activators are one of the promising targets for studying the mechanisms of pneumonia and subsequent fibrosis, hemostasis system disorders and systemic inflammation. Plasminogen activators are a group of proteins, including serine proteases (urokinase type plasminogen activator or uPA, and tissue plasminogen activator tPA), urokinase receptor (uPAR), and plasminogen activator inhibitors (PAI-I and PAI- II). Plasmin activated by urokinase, in turn, activates urokinase itself, and this process, according to positive feedback pattern, is constantly maintained activated until it is depleted or uPA and/or plasmin concentration decreases. Proteases catalyze the plasminogen cleavage with plasmin formation, which is an important activator of blood fibrinolysis. In a healthy lung, the fibrin level in the extracellular matrix is controlled by plasmin and urokinase activity [16].

Disturbances in the expression or activity of plasminogen activator system are associated with bleeding and fibrin accumulation in the vessels. Since with COVID-19 there is an increased clotting in small vessels of vital organs and microcirculation block, which is often irreversible, there is reason to believe that the plasminogen activator system can play a decisive role in the unfavorable disease course. Despite the fact that plasmin-mediated extracellular matrix remodeling is an extremely important stage in lung regeneration, disruption of this process can shift the balance towards fibrosis activation. This is especially due to the pathogenesis of respiratory coronavirus infection, because plasmin-dependent proteolysis of the viral S-protein plays a key role in virus-cell entry [17].

In vessels, high concentrations of urokinase can cause negative remodeling and neointima enlargement [18], thereby reducing the vascular lumen. This process is based on the interaction of urokinase with uPAR, which is a glycosylphosphatidylinositol (GPI)-anchored protein. It has been shown that the uPA-to-uPAR binding triggers intracellular signaling with the participation of mitogen-activated protein kinases and the induction of NADPH-oxidase expression (Nox1/4), which increases the production of reactive oxygen species and stimulates cell proliferation, chemotaxis of neutrophils as well as fibroblast transdifferentiation into myofibroblasts [19]. The accumulated data on the role of uPA and uPAR in the vessels indicate that the functions of the urokinase system go beyond fibrinolysis. In tissues, active urokinase and its receptor have a number of effects aimed at their regeneration and restoration. However, the prolonged presence of uPA in the system or excessive uPAR activation can have a number of opposite effects. Published data [20] considers that uPAR is a urokinase trap on the membrane, preventing its translocation into the nucleus and activation of NF-kB, which regulates the epithelial-mesenchymal transition — one of the fibrosis markers. In addition, uPAR can regulate the production of IL-6 by cells, and when converted to a soluble form due to partial proteolysis, uPAR can function as a chemoattractant for immune system cells by binding to the chemokine receptor of fMLP (N-formyl-methionyl-leucyl-phenylalanine) [21]. The absence of uPAR in mice leads to a significant decrease in the number of T-reg lymphocytes, which suppress the immune system activation [22]. At the same time, the content of cytotoxic (CD8+) T-lymphocytes and activated (CD25+/FOXP3+) T-lymphocytes in such mice increases, which specifies the uPAR role in maintaining the balance of various T-lymphocyte types [22] and shifts the balance towards proinflammatory reactions.

Urokinase can mediate fibrosis by another mechanism unrelated to uPAR: in *PLAUR* (Plasminogen Activator Urokinase Receptor) knockout mice, urokinase binds to the muscle-type nicotinic acetylcholine receptor (nAChR-1), which is expressed on fibroblasts, macrophages, endothelial and epithelial cells and mediates its metabotropic effects — stimulates the proliferation of fibroblasts and provokes the severe renal fibrosis.

It is known that acute and chronic lung diseases are characterized by dysfunction of plasminogen activators. In a mice model of bleomycin-induced fibrosis, it was shown that the absence of the plasminogen and tPA genes causes an increase in collagen content and an increase in interstitial lung fibrosis compared to wild-type carriers of these genes. Moreover, in mice knockout for genes encoding uPA and uPAR, pulmonary hemorrhage damage is reduced [23]. The results of this single study indicate the involvement of plasminogen activators in the pulmonary fibrosis, but do not disclose in detail the mechanism.

In favor of the fact that uPA and uPAR play an important role in COVID-19 pathogenesis, the data published in Critical Care indicate that high serum concentrations of soluble uPAR (suPAR) are an early marker of severe respiratory failure in COVID-19 [24]. Despite the fact that the authors showed a strong relationship between high suPAR content and ARDS, the role of suPAR in COVID-19 pathogenesis remains unknown. High concentrations of suPAR can be cause of not only the lung fibrosis, but also the renal one, which together indicates the possible role of urokinase system in the development of multiple organ failure in COVID-19.

Endothelial cell infection in COVID-19 patients

The endothelium plays the role of main vascular homeostasis regulator, since it performs a barrier function in the vessels and is able to respond to various physical and chemical stimuli by developing factors regulating intercellular interactions, proliferation, adhesion and migration of cells, vascular tone, vascular wall inflammation and clotting. Endothelial dysfunction characterizes many diseases such as atherosclerosis, hypertension and diabetes. At the physiological level, a change in endothelial cells' phenotype in endothelial dysfunction is described, which violates intercellular contacts and increases endothelial permeability.

Postmortem analysis in COVID-19 patients revealed viral particles in the vascular endothelium, which was accompanied by infiltration of the vascular wall by immune cells, disruption of endothelial monolayer and its adhesive properties, increased clotting, apoptosis and pyroptosis of endothelial cells. COVID-19-induced endotheliitis (vasculitis) may be the cause of the observed systemic microcirculatory disorders in various organs and serve as an explanation for the observed clinical consequences in patients with COVID-19 [25]. SARS-CoV-2 was originally described as a virus that infects the lower respiratory tract followed by viral pneumonia, as well as the gastrointestinal tract, heart, kidneys, liver and central nervous system. However, it is now clear that vascular damage also plays a huge role in COVID-19 pathogenesis. These data provides a rationale for therapies to stabilize the endothelium using anti-inflammatory anticytokine drugs, ACE inhibitors, anticoagulants and statins lowering blood cholesterol levels, and explain the severe course of infection in patients with endothelial dysfunction (hypertension, diabetes, obesity, CVD).

It is known that an increase in low-density lipoprotein cholesterol (LDL-C) levels is a risk factor, which leads to cholesterol accumulation in the vascular wall and correlates with atherosclerosis development. LDL endocytosis is carried out due to the binding of LDL to classical apoB/E receptor. However, for LDL, a number of effects have been described that mediate changes in the phenotype and functional activity of some cells that are not associated with LDL endocytosis [26]. Thus, LDL can activate macrophages, initiate a change in platelet shape and cause their aggregation, stimulate the surfactant secretion by alveolar cells, regulate vascular tone, proliferation, adhesion and migration of cells [27]. These changes are based on the rapid, reversible "hormone-like" effects of LDL, namely, the activation of phosphoinositide metabolism, an increase in calcium ion concentration in the cytoplasm, and the activation of protein kinase C. In particular, T-cadherin serves as a receptor that causes the rapid LDL effects [28]. T-cadherin belongs to cadherin superfamily, but there is no cytoplasmic and transmembrane domains in its structure; it attached to the extracellular cell membrane surface through a GPI-anchor [29]. It is generally accepted that T-cadherin is a signaling molecule. The introduction of LDL into the culture medium increases intracellular calcium ions, migration ability and proliferative activity of cells [28].

According to laboratory data, T-cadherin is normally expressed in aortic intima, media and adventitia in all layers: in the endothelium, in smooth muscle cells and pericytes. In CVDs, such as atherosclerosis and restenosis, T-cadherin expression in vascular cells is increased [30]. However, the T-cadherin function in these pathologies remains undetected. It is not known whether an increase in T-cadherin expression in atherosclerosis is a compensatory defense response to an increased plasma LDL-C level. It was shown that blood T-cadherin content in patients with atherosclerosis is increased compared to the norm [31], which may indicate endothelial activation/dysfunction and T-cadherin participation in these processes. *In vitro* endothelial monolayer models showed that an increase in T-cadherin expression decreases endothelial barrier function due to impaired intercellular adhesion, which occurs due to clathrin-mediated endocytosis of VE-cadherin and its degradation in lysosomes. Internalization of VE-cadherin is mediated by signaling from T-cadherin, which results in activation of Rho GTPases and their downstream mediators (ROCK-II, LIMK, and PAK1 kinases), phosphorylation of T731 of VE-cadherin cytoplasmic domain, assembly of actin stress fibers and microtubule depolimation [32].

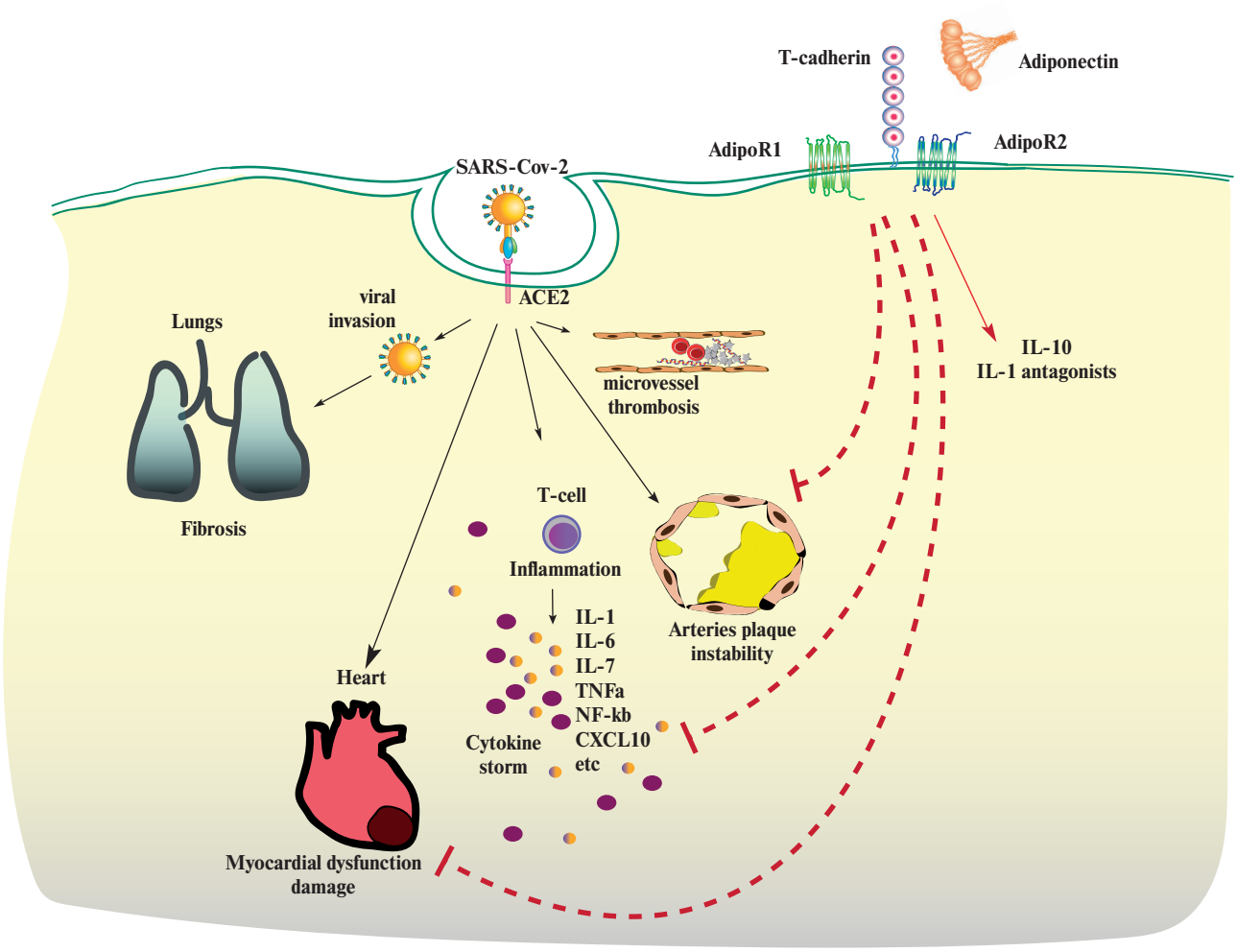

Figure 2 Cardiovascular damage in COVID-19 — key pathogenesis participants and mechanisms of development (Rubina K.A., Semina E.V., 2021). Note: Using the transmembrane ACE2 receptor, SARS-Cov-2 entries into a various host cells, including alveolar type II cells, macrophages, endothelial cells, pericytes and cardiomyocytes, leading to inflammation and multiple organ failure. In particular, endothelial cell damage causes endothelial dysfunction, destabilizes atherosclerotic plaques and leads to acute coronary syndrome. Respiratory tract damage manifests itself in the progression of systemic inflammation and immune hyperactivation, which results in a cytokine storm. The adiponectin receptors (AdipoR1/2 and T-cadherin), realizing signaling effects in the endothelium, can protect the heart and blood vessels due to the release of anti-inflammatory cytokines IL-10, IL-1 antagonists, as well as suppress the hyperproduction of pro-inflammatory cytokines, reducing toxic cardiac and vascular effects.

Understanding the physiological role of T-cadherin is complicated by the fact that T-cadherin serves as a receptor for two ligands at once — LDL and high-molecular-weight adiponectin [26]. Adiponectin, a hormone secreted by adipose tissue, has a protective effect on the cardiovascular system [33]. There is data suggestive of signaling competition between LDL and adiponectin: adiponectin inhibits the LDL-induced release of intracellular Ca^{2+}-stores [34]. It was hypothesized that, being a receptor for two ligands, T-cadherin, depending on the blood plasma concentration of ligands, can mediate both the protective properties of adiponectin and the damaging effects of LDL in the cardiovascular system. Expressing on vascular cells, T-cadherin can be occupied by LDL or adiponectin, depending on the ratio of these ligands in plasma, which differs in healthy people and those with atherosclerosis, obesity, or cancer.

Adiponectin is secreted from adipose tissue. It has a pronounced antiatherogenic, cardioprotective and anti-inflammatory systemic effect, performs a protective function against hyperglycemia and insulin resistance [33]. In addition, a decrease in blood adiponectin concentration (normal range, 5-30 μg/ml) [35] is associated with inflammatory lung diseases and correlates with the condition severity in patients with COPD. A number of studies have shown that adiponectin is able to reduce the content of proinflammatory cytokines (TNF-α, IL-6, and NF-kB) [36] and stimulate the production of anti-inflammatory cytokines (IL-10, etc.). Changes in the serum adiponectin content are associated with impaired expression of adiponectin receptors (AdipoR1, AdipoR2) and, above all, with T-cadherin. Since a change in blood adiponectin level is associated with various cardiovascular and pulmonary pathologies,

as well as with inflammatory diseases, impaired adiponectin production or the expression/functioning of its receptors may contribute to the negative clinical course of coronavirus infection.

In addition to the fact that T-cadherin is an LDL and adiponectin receptor, it is able to mediate weak Ca^{2+}-dependent homophilic cell adhesion in suspension. T-cadherin is expressed on vascular cells (endothelium, pericytes, and smooth muscle cells) and is a molecule that regulates vascular growth during physiological angiogenesis [26], tissue revascularization after injury, and tumor angiogenesis [37]. The T-cadherin function in blood vessels is due to the interaction and homophilic recognition between T-cadherin molecules on the membranes of contacting cells [29]. T-cadherin functions as a vascular growth regulator *in vivo* and *in vitro*. T-cadherin effects are based on inhibition of the initial angiogenesis stages due to suppression of endothelial cell migration, initiation of growth and branching of capillary-like structures [26].

T-cadherin — an adiponectin receptor that mediates the protective role of adiponectin in pulmonary and cardiovascular diseases

In the vascular wall, adiponectin has a protective antiatherogenic effect. It is T-cadherin, and not two other adiponectin receptors (AdipoR1 and AdipoR2), that is required for the binding of adiponectin on the surface of cardiomyocytes and endothelial cells and ensuring the protective function of adiponectin [33]. Adiponectin prevents atherosclerotic lesions in apolipoprotein E-deficient mice. T-cadherin knockout mice models showed that T-cadherin absence leads to the development of cardiac hypertrophy and an increase myocardial infarction area [38], and also inhibits revascularization of the ischemic limb in these mice.

T-cadherin plays an important role not only in CVD pathogenesis, but also in various pulmonary pathologies. T-cadherin mediate the protective anti-inflammatory effect of adiponectin, which is described in COPD, asthma, systemic inflammatory response, sepsis, and severe ARDS [39]. In most studies, the protective function of adiponectin is associated with the suppression of pro-inflammatory cytokines (TNF-α, IL-6, endothelial adhesion molecules ICAM-1 and VCAM-1, NF-kB), and the induction of antiinflammatory cytokines (IL-10) and IL-1 antagonists. In acute respiratory failure, the blood level of adiponectin directly correlates with the systemic level of anti-inflammatory cytokines (IL-10) and inversely correlates with proinflammatory cytokines.

The protective effect of adiponectin is associated with T-cadherin expression and its ability to recruit adiponectin from plasma, thereby fixing it on the cell membrane of various organs and tissues [33]. The meta-analysis showed an association between *CDH13* gene (T-cadherin) polymorphisms and changes in plasma level of circulating adiponectin in patients with COPD [40]. It is known that T-cadherin gene polymorphisms can change the ability of T-cadherin to recruit adiponectin from plasma to organs and tissues, thereby affecting the blood concentration of adiponectin, which may affect the clinical course of COPD [33].

The listed data indicate the participation of T-cadherin in the regulation of physiological vascular cell response; disturbances in the expression or functioning of T-cadherin or the binding of adiponectin to T-cadherin correlate with endothelial dysfunction, pulmonary and cardiovascular pathologies. In this regard, adiponectin and its T-cadherin receptor are the second promising target for studying the mechanisms of pneumonia development, hemostasis system disorders, systemic inflammation and complications associated with impaired cardiovascular system functioning in COVID-19 (Figure 2).

Conclusion

The study of development of pathological conditions in coronavirus infection, such as pulmonary fibrosis, lymphocytopenia, cytokine storm, hemostasis system disorders, are relevant and promising due to the epidemiological situation and disease severity. Fundamental research on plasminogen and T-cadherin/adiponectin activator system and is necessary in terms of finding new diagnostic and therapeutic targets for COVID-19. It is known that T-cadherin expression is necessary to ensure the protective function of the endothelium, while changes in T-cadherin/adiponectin expression correlate with endothelial dysfunction and various pulmonary pathologies. On the other hand, plasminogen activators, urokinase and its receptor uPAR, as well as plasmin itself, can contribute to virus infection of cells through S-protein proteolysis and its binding to ACE2. This provokes the development of pulmonary vascular thrombosis as a result of plasmin decrease and accumulation of fibrin D-dimers. Early diagnosis using data on the expression of T-cadherin, adiponectin, the concentration of LDL-C and plasminogen activator proteins in blood plasma may be important for predicting a severe course and possible complications in the form of ARDS and cytokine storm in COVID-19.

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References

1. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529-39. doi:10.1007/s00281-017-0629-x.
2. Guzik TG, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020;116(10):1666-87. doi:10.1093/cvr/cvaa106.
3. De Wit E, van Doremalen N, Falzarano, D, Munster V. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523-34. doi:10.1038/nrmicro.2016.81.
4. Medina-Enríquez M, Lopez-León S, Carlos-Escalante J, et al. ACE2: the molecular doorway to SARS-CoV-2. Cell Biosci. 2020;10(148). doi:10.1186/s13578-020-00519-8.
5. Hoffmann M, Kleine-Weber Y, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80.e8. doi:10.1016/j.cell.2020.02.052.
6. Bian H, Zheng ZH, We D, et al. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. Medrxiv [Preprint] 2020. Available from: doi:10.1101 /2020.03.21.20040691.
7. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-2. doi:10.1016/S2213-2600(20)30076-X.
8. Tang F, Quan Y, Xin ZT, et al. Lack of Peripheral Memory B Cell Responses in Recovered Patients with Severe Acute Respiratory Syndrome: A Six-Year Follow-Up Study. J Immunol. 2011;186(12):7264-8. doi:10.4049/jimmunol.0903490.
9. Zhou J, Jin J, Patel E, et al. Interleukin-6 inhibits apoptosis of exocrine gland tissues under inflammatory conditions. Cytokine. 2015;76(2):244-52. doi:10.1016/j.cyto.2015.07.027.
10. Nakajima W, Sharma K, Lee JY, et al. DNA damaging agent-induced apoptosis is regulated by MCL-1 phosphorylation and degradation mediated by the Noxa/MCL-1/CDK2 complex. Oncotarget. 2016;7(24):36353-65. doi:10.18632/oncotarget.9217.
11. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3. doi:10.1038/s41586-020-2012-7.
12. Hoffmann M, Kleine-Weber H, Pöhlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell. 2020;78(4):779-84.e5. doi:10.1016/j.molcel.2020.04.022.
13. Raum D, Marcus D, Alpe CA, et al. Synthesis of human plasminogen by the liver. Science. 1980;208(4447):1036-7. doi:10.1126/science.6990488.
14. Cao Y, Liu X, Xiong L, Cai K. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. J Med Virol. 2020;92(9):1449-59. doi:10.1002/jmv.25822.
15. Williams FMK, Freydin M, Mangino M, et al. Clinical and molecular characterization of COVID-19 hospitalized patients. medRxiv [Preprint] 2020. doi:10.1101/2020.05.22.20108845.
16. Schuliga M, Grainge C, Westall G, et al. The fibrogenic actions of the coagulant and plasminogen activation systems in pulmonary fibrosis. Int J Biochem Cell Biol. 2018;97:108-17. doi:10.1016/j.biocel.2018.02.016.
17. Ji HL, Zhao R, Matalon S, Matthay MA. Elevated Plasmin(ogen) as a Common Risk Factor for COVID-19 Susceptibility. Physiol Rev. 2020;100(3):1065-75. doi:10.1152/physrev.00013.2020.
18. Tkachuk V, Plekhanova O, Beloglazova I, Parfenova E. Role of multidomain structure of urokinase in regulation of growth and remodeling of vessels. Ukr Biochem. J. 2013;85(6):18-45. doi:10.15407/ubj85.06.018.
19. Tkachuk VA, Parfyonova YeV, Plekhanova OS, et al. Fibrinolytics: from the thrombolysis to the processes of blood vessels growth and remodeling, neurogenesis, carcinogenesis and fibrosis. Terapevticheskii arkhiv. 2019;91(9):4-9. (In Russ.) doi:10.26442/00403660.2019.09.000411.
20. Semina EV, Rubina KA, Shmakova AA, et al. Downregulation of uPAR promotes urokinase translocation into the nucleus and epithelial to mesenchymal transition in neuroblastoma. J Cell Physiol. 2020;235(9):6268-86. doi:10.1002/jcp.29555.
21. Klimovich PS, Semina EV. Mechanisms of Participation of the Urokinase Receptor in Directed Axonal Growth. Molecular Biology. 2020;54(1):103-13. (In Russ.) doi:10.31857/S0026898420010097.
22. Kulebyakina MA, Dyikanov DT, Rubtsov YP, et al. The components of the urokinase system have a reciprocal effect on the accumulation of anti-inflammatory regulatory and pro-inflammatory cytotoxic T-lymphocytes in the spleen. Immunology. 2018;329(1):38-43. (In Russ.) doi:10.18821/0206-4952-2018-39-1-38-43.
23. Swaisgood CM, French EL, Noga C, et al. The development of bleomycin-induced pulmonary fibrosis in mice deficient for components of the fibrinolytic system. Am J Pathol. 2000;157(1):177-87. doi:10.1016/S0002-9440(10)64529-4.
24. Rovina N, Akinosoglou K, Eugen-Olsen J, et al. Soluble urokinase plasminogen activator receptor (suPAR) as an early predictor of severe respiratory failure in patients with COVID-19 pneumonia. Crit Care. 2020;24(1):187. doi:10.1186/s13054-020-02897-4.
25. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417-8. doi:10.1016/S0140-6736(20)30937-5.
26. Rubina KA, Kalinina NI, Parfenova EV, Tkachuk VA. T-cadherin as a receptor involved in the regulation of angiogenesis and remodeling of blood vessels. Biologicheskie Membrany. 2007;24(1):65-72. (In Russ.)
27. Liu J, Ren Y, Kang L, et al. Oxidized low-density lipoprotein increases the proliferation and migration of human coronary artery smooth muscle cells through the upregulation of osteopontin. Int J Mol Med. 2014;33:1341-7. doi:10.3892/ijmm.2014.1681.
28. Rubina K, Talovskaya E, Cherenkov V, et al. LDL induces intracellular signalling and cell migration via atypical LDL-binding protein T-cadherin. Mol Cell Biochem. 2005;273(1-2):33-41. doi:10.1007/s11010-005-0250-5.
29. Rubina KA, Tkachuk VA. Molecular and cellular mechanisms of physiological and tumor growth of blood vessels. Russian Journal of Physiology im. I. M. Sechenova. 2017;2017(2):121-37. (In Russ.)
30. Frismantiene A, Pfaff D, Frachet A, et al. Regulation of contractile signaling and matrix remodeling by T-cadherin in vascular smooth muscle cells: constitutive and insulin-dependent effects. Cell Signal. 2014;26(9):1897-908. doi:10.1016/j.cellsig.2014.05.001.
31. Philippova M, Suter Y, Toggweiler S, et al. T-cadherin is present on endothelial microparticles and is elevated in plasma in early atherosclerosis. Eur Heart J. 2011;32(6):760-71. doi:10.1093/eurheartj/ehq206.
32. Semina EV, Rubina KA, Sysoeva VY, et al. Novel mechanism regulating endothelial permeability via T-cadherin-dependent

VE-cadherin phosphorylation and clathrin-mediated endocytosis. Mol Cell Biochem. 2014;387(1-2):39-53. doi:10.1007/s11010-013-1867-4.

33. Rubina KA, Semina EV, Balatskaya MN, et al. Mechanisms of regulation of directed growth of nerves and blood vessels by components of the fibrinolytic system and GPI-anchored navigation receptors. Russian Journal of Physiology im. I. M. Sechenova. 2018;104(9):1001-26. (In Russ.) doi:10.7868/S0869813918090010.
34. Balatskaya M, Sharonov G, Baglay A, et al. One receptor, two ligands, different responses: T-cadherin as a receptor for low density lipoprotein and adiponectin. FEBS J. 2017;284:153. doi:10.1111/febs.14174.
35. Min X, Lemon B, Tang J, et al. Crystal structure of a single-chain trimer of human adiponectin globular domain. FEBS Lett. 2012;586(6):912-7. doi:10.1016/j.febslet.2012.02.024.
36. Choi H, Doss H, Kim K. Multifaceted Physiological Roles of Adiponectin in Inflammation and Diseases. Int J Mol Sci. 2020;21(4):1219. doi:10.3390/ijms21041219.
37. Rubina KA, Sysoeva VYu, Semina EV, et al. Features of T-cadherin expression in keratinocytes and vessels of epithelial skin tumors. Russian Journal of Skin and Venereal Diseases. 2013;2013(1):9-14. (In Russ.)
38. Clark L, Taylor C, Zahradka P. Exploring the Cardio-metabolic Relevance of T-cadherin: A Pleiotropic Adiponectin Receptor. Endocr. Metab. Immune Disord. Drug Targets. 2017;17(3):200-6. doi:10.2174/1871530317666170818120224.
39. Nigro E, Matteis M, Roviezzo F, et al. Role of adiponectin in sphingosine-1-phosphate induced airway hyperresponsiveness and inflammation. Pharmacol Res. 2016;103:114-22. doi:10.1016/j.phrs.2015.10.004.
40. Zhong YH, Peng H, Cheng HZ, Wang P. Quantitative assessment of the diagnostic role of CDH13 promoter methylation in lung cancer. Asian Pac J Cancer Prev. 2015;16(3):1139-43. doi:10.7314/apjcp.2015.16.3.1139.