DOI: https://doi.org/10.36233/0372-9311-2020-97-4-6

REVIEWS

Angiotensin-converting enzyme 2. Approaches to pathogenetic therapy of COVID-19

Polina O. Shatunova✉, Anatoly S. Bykov, Oksana A. Svitich, Vitaly V. Zverev

I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991, Moscow, Russia

The SARS-CoV-2 virus is a pathogen causing the coronavirus infection that culminated in a worldwide pandemic in 2020. It belongs to β-coronaviruses and has high genetic similarity to the SARS-CoV virus that is responsible for an outbreak of severe acute respiratory syndrome in 2002–2003. The analysis of molecular interactions shows that SARS-CoV-2 has higher virulence due to lower binding free energy in interaction with the angiotensin-converting enzyme 2 (ACE2), which is used by the virus to enter the host cell. At the time of the global coronavirus pandemic, the thorough study of ACE2 as a key component of the disease pathogenesis comes to the fore. The detailed study of the enzyme, which is a receptor located on the surface of different tissues and which normally catalyzes the conversion of angiotensin II to angiotensin (1–7), led to diverging conclusions. Being non-tissue specific, the receptor is abundantly present in the heart, kidneys, small intestine, testes, thyroid, and adipose tissue. Besides regulating blood pressure, it suppresses inflammation, mainly in the lung tissue, participates in amino acid transport and maintains the activity of the gut microbiome. With all its essential positive functions, the role of ACE2 is highly ambiguous, specifically in coronavirus infection. The influence on the renin-angiotensin system can be seen as a promising therapeutic route in treatment of coronavirus infection. The preliminary data on using of ACE2 inhibitors, soluble forms of ACE2, and angiotensin II receptor blockers demonstrate their effectiveness and, consequently, improvement in symptoms and prognoses for patients with coronavirus infection. The review presents information about ACE2 distribution in human tissues, explores its interaction with SARS-CoV-2, provides a theoretical basis for medications involving ACE2 metabolic pathways and for using them in treatment of coronavirus infection and its prevention.

Keywords: *ACE2; angiotensin-converting enzyme 2; SARS-CoV-2; coronavirus infection; angiotensin-converting enzyme; COVID-19; angiotensin II receptor blockers.*

Acknowledgments. The study had no sponsorship.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For citation: Shatunova P.O., Bykov A.S., Svitich O.A., Zverev V.V. Angiotensin-converting enzyme 2. Approaches to pathogenetic therapy of COVID-19. *Journal of microbiology, epidemiology and immunobiology = Zhurnal mikrobiologii, èpidemiologii i immunobiologii.* 2020; 97(4): 339–344.
DOI: https://doi.org/10.36233/0372-9311-2020-97-4-6

Received 4 June 2020
Accepted 16 June 2020

Ангиотензинпревращающий фермент 2. Подходы к патогенетической терапии COVID-19

Шатунова П.О.✉, Быков А.С., Свитич О.А., Зверев В.В.

ФГАОУ ВО Первый МГМУ им. И.М. Сеченова Минздрава России (Сеченовский Университет), 119991, Москва, Россия

Возбудителем коронавирусной инфекции, которая привела к пандемии в 2020 г., является вирус SARS-CoV-2. Он относится к β-коронавирусам и имеет высокое генетическое сходство с вирусом SARS-CoV, вызвавшим вспышку тяжелого острого респираторного синдрома в 2002–2003 гг. Анализ межмолекулярных взаимодействий показывает, что SARS-CoV-2 более вирулентен вследствие снижения свободной энергии при связывании с ангиотензинпревращающим ферментом 2 (ACE2), который является транспортером для вируса в клетку-хозяина. В связи с широким распространением коронавирусной инфекции по всему миру остро встает вопрос о подробном изучении ключевого звена патогенеза заболевания — ACE2. Детальное

изучение фермента, который является рецептором на поверхности различных тканей и в норме осуществляет превращение ангиотензина II в ангиотензин (1–7), привело к неоднозначным выводам. Будучи нетканеспецифичным, рецептор широко распространен в сердце, почках, тонкой кишке, яичках, щитовидной железе, жировой ткани. Помимо прямой барорегулирующей функции он подавляет воспаление, главным образом в легочной ткани, участвует в транспорте аминокислот и поддерживает жизнедеятельность микробиома кишечника. Ввиду существенных положительных функций становится очевидной неоднозначность ACE2, в том числе при коронавирусной инфекции. Перспективным терапевтическим направлением при коронавирусной инфекции может оказаться влияние на ренин-ангиотензиновую систему. Предварительные данные о применении ингибиторов ACE2, препаратов, содержащих данный рецептор в циркуляторной форме, и блокаторов ангиотензинового рецептора II свидетельствуют об их эффективности и, как следствие, улучшении состояния и прогнозов для пациентов с коронавирусной инфекцией.
В обзоре представлена информация о распространении ACE2 в различных тканях человека, его взаимодействии с SARS-CoV-2, дано теоретическое обоснование практического применения препаратов, связанных с метаболическим путем ACE2, для лечения и ограничения распространения коронавирусной инфекции.

Ключевые слова: *ACE2; ангиотензин-превращающий фермент 2; SARS-CoV-2; коронавирусная инфекция; COVID-19; блокаторы ангиотензинового рецептора II.*

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Для цитирования: Шатунова П.О., Быков А.С., Свитич О.А., Зверев В.В. Ангиотензинпревращающий фермент 2. Подходы к патогенетической терапии COVID-19. *Журнал микробиологии, эпидемиологии и иммунобиологии.* 2020; 97(4): 339–344.
DOI: https://doi.org/10.36233/0372-9311-2020-97-4-6

Поступила 04.06.2020
Принята в печать 16.06.2020

Introduction

In December 2019, China reported an outbreak of acute respiratory infection accompanied by such symptoms as fever, dry cough, shortness of breath and pneumonia [1]. The infection was caused by the novel coronavirus belonging to β-coronaviruses and having common features with the virus causing severe acute respiratory syndrome (SARS), which was a pandemic strain in 2002–2003. The novel virus was named coronavirus-2 (SARS-CoV-2) and the disease was referred to as coronavirus infection 2019 (COVID-19). The COVID-19 death rate tends to increase in groups of elderly people (over 70 years) and people with chronic health conditions (hypertension, diabetes, cardiovascular diseases). Two of the above listed diseases are closely associated with administered medications acting as inhibitors of the receptor of the angiotensin-converting enzyme (ACE). They are used to block the angiotensin receptor and, consequently, to lower blood pressure.

Scientists thoroughly study pathophysiologic mechanisms of COVID-19, the interaction of the virus with the human lungs and heart. According to different sources, ACE2 located on alveolar epithelial cells serves as a co-transporter for SARS-CoV-2, helping it enter human lungs. Therefore, ACE2 is the key to understanding the COVID-19 pathogenesis.

The review presents information about ACE2 distribution in human tissues, explores its interaction with SARS-CoV-2, provides a theoretical basis for medications involving ACE2 metabolic pathways and for using them in treatment of COVID-19 and its prevention.

Role of ACE2 in COVID-19 pathogenesis

SARS-CoV-2

SARS-CoV-2 is a single-stranded RNA virus with a crown-like appearance of spike glycoproteins (S proteins). The whole-genome sequence of the SARS-CoV-2 virus revealed that it is 96% identical to the SARS-like coronavirus found in bats. Besides, this virus is 79.5% identical to SARS-CoV [2], while some encoded proteins like coronavirus main proteinase, papain-like protease and RNA-dependent RNA polymerase [3] show 96% identity to SARS-CoV. Their close relationship suggests that pathogenic mechanisms of infection progression both in SARS-CoV and SARS-CoV-2 are based on the same principle.

The SARS-CoV-2 virus uses the surface spike (S) glycoprotein to enter the host cell and to mediate the host cell and viral membrane fusion during infection. The S-glycoprotein is a trimeric protein. It is essential for survival of coronaviruses, as it not only acts as an important component of the virion, but also is responsible for attachment and fusion with host cell membranes. In addition, the S-protein is the major surface protein of coronaviruses; it determines the solubility of virus particles and, consequently, contagiousness of SARS-CoV-2.

The S-protein is composed of two subunits, S1 and S2; the S1 subunit binds to host receptors and the S2 subunit facilitates membrane fusion [4]. The S1 subunit contains an N-terminal (NTD) and C-terminal domains (CTD1, CTD2 and CTD3). The receptor-binding domain (RBD) is located in CTD1 of the SARS-CoV virus.

The SARS-CoV-2 coronavirus is highly homologous to the SARS-CoV virus [5]. It penetrates the host cell through interaction between the S-protein of the virus and ACE2 of a human. However, the underlying molecular mechanism of this relationship as well as the evolution of SARS-CoV-2 need further study.

It was proved that the S-glycoprotein of SARS-CoV-2 has a significantly lower free energy than SARS-CoV [5]. This observation implies that SARS-CoV-2 is more stable and is not as easily destroyed at warmer temperatures, which means that SARS-CoV-2 has stronger persistence than SARS-CoV at the same temperature.

S-protein has RBD domain that is important for activity of the coronavirus, as it is critical for infection. Interestingly, the RBD free energy and solvation energy in SARS-CoV-2 are lower than in SARS-CoV. The fact is that RBD must move away from the S-glycoprotein and get dissolved in water in order to bind to ACE2. In other words, SARS-CoV-2 becomes more soluble so that it can bind to ACE2 more easily.

The lower free energy of the S-glycoprotein and lower RBD solvation energy in SARS-CoV-2 can result from the evolution of the virus or its adaptation to the host organism; normally bats serve as natural reservoirs for SARS-like coronaviruses, as their body temperature is consistently higher than the temperature in humans [6].

RBD of SARS-CoV-2 has another distinctive feature: It exhibits significantly higher flexibility than RBD of SARS-CoV. In other words, it must overcome a higher entropy penalty in order to bind to ACE2 and, therefore, the RBD–ACE2 complex loses its stability at higher temperatures. The latter gives hope that the pandemic rates will go down when the weather gets warmer.

It was found that SARS-CoV-2 can bind to the human enzyme with a higher binding affinity than SARS-CoV. Adaptive mutations in SARS-CoV-2 as compared to SARS-CoV can provide explanation of the higher infection ability of SARS-CoV-2 and wide spread of COVID-19.

ACE2: Structure and function

The human carboxypeptidase ACE2 is encoded by the *ACE2* gene located on chromosome 22 [7]. ACE2 is a type I transmembrane protein comprised of an extracellular N-glycosylated N-terminal domain containing a carboxypeptidase site and a short intracellular C-terminal cytoplasmic tail [8]. The N-terminal peptidase domain is also an ACE2 and SARS-CoV binding site. There are two forms of ACE2 protein: cellular (membrane-bound) and circulating (soluble). The cellular form is a full-length protein, which is expressed abundantly in pneumocytes and enterocytes of the small intestine.

The circulating form (with the N-terminal peptidase domain) is cleaved from the cellular ACE2 form by the ADAM17 metalloprotease and then released into the extracellular environment [8]. On the other hand, the interaction of ACE2 with the type II transmembrane serine protease, TMPRSS2, helps SARS-CoV-2 enter target cells of lung tissue and small intestine. The TMPRSS2-cleavage path can inhibit the ADAM17-cleavage path. TMPRSS2 binds to ADAM17 to dissociate the ADAM17–ACE2 complex. Both ADAM17 and TMPRSS2 cleave a short C-terminal fragment from ACE2, thus facilitating the entry of the SARS-CoV virus into the cell.

Despite the similarity between *ACE* and *ACE2* genes, ACE and ACE2 proteins function differently in the human body. For example, ACE cleaves a single amino acid from the substrate, acting as carboxypeptidase, while ACE2 hydrolyzes the bond between the protein backbone and the C-terminal dipeptide. ACE and ACE2 are key components of the renin-angiotensin system (RAS) playing a critical role in maintaining the homeostasis of the cardiovascular system and functions of different organs as well as in regulating the systolic blood pressure, fluid and electrolyte balance.

The angiotensinogen is synthesized in the liver and then is cleaved by renin to form angiotensin I (AngI), which is further converted to angiotensin II (AngII) by ACE. AngII is a key player of RAS; it binds to the angiotensin type I receptor (AT1R), thus inducing contraction of bronchial smooth muscles, proliferation of lung fibroblasts, alveolar epithelial cell apoptosis, increased pulmonary vascular permeability, and acute respiratory distress syndrome [9]. In the meantime, ACE2 acts as a counter-regulator of the activities of the ACE–AngII–AT1R axis; it hydrolyzes AngII into Ang(1–7), which, mediating through the Mas-receptor, causes vasodilation, a decrease in the arterial pressure and induction of apoptosis. The similar protective function can be observed when AngII binds to the AngII receptor. Besides, ACE2 can interact with AngI and convert it to Ang(1–9), which can be converted to Ang(1–7) with the help of ACE. Acting as a partner for the B0AT1 amino acid transporter, ACE2 participates in the intestinal absorption of neutral amino acids [9].

ACE2 is highly expressed in type I and II alveolar epithelial cells, in vascular endothelial cells, and in pulmonary smooth muscle cells [10]. The coronavirus can enter the human body in different ways, the most common of which is the aerogenic mechanism of transmission, when the infected person develops symptoms of severe pneumonia. On the other hand, high ACE levels were found in the small intestine, testes, kidneys, heart, thyroid, and adipose tissue. ACE is present in lower concentrations in the liver, colon, bladder and adrenal glands.

The structural modelling has demonstrated that the ACE2–B0AT1 complex can bind to the S-protein of the SARS-CoV-2 virus. Thus, SARS-CoV 2 can enter

the human body through other tissues and organs, bypassing the respiratory tract [11]. This fact is supported by recent studies that revealed the presence of SARS-CoV-2 in feces of infected patients and by the disease development without pneumonia or with other symptoms unrelated to the respiratory tract. Then, patients develop gastrointestinal symptoms: diarrhea, nausea, vomiting as well as confusion, headache and cardiac involvement [12–14].

The ACE2 presence in testes and testicular vessels suggests that males may be more susceptible to COVID-19. Although no gender, age or race-related differences have been found in ACE2 concentration levels in the human body, males and older adults face a higher risk of death than females and younger adults, respectively. It can be explained by age and functional characteristics of innate and adaptive immune mechanisms and by the ability of SARS-CoV-2 to cause a cytokine storm, which leads to immunopathological events in patients with coronavirus infection. Different numbers of lung-tissue-resident immune cells fight off infection and auto-damage differently. It was found that in females (gender groups) and in younger adults (two age groups of under and over 49 years), the lung-tissue cells that expressed high levels of ACE2 were infected by SARS-CoV more easily, and there were fewer immune cells than in the similar tissues with medium expression of ACE2. Older people and males demonstrate the opposite relationship – the higher expression of ACE2 and an increasing number of immune cells in the lung tissue. It means that if infected with SARS-CoV and SARS-CoV-2, these people are most likely to have auto-aggression and a cytokine storm, which can aggravate the disease progression.

ACE2 and coronavirus infection

COVID-19 is a disease, which affects the lower respiratory tract [15]. The anatomic pathology reports indicated that people who died from COVID-19 had seriously injured lungs with fibrosis and exudative lesions. Phlegm and exudates filled up the lower respiratory tract and alveoli. Compared to SARS-CoV, exudative lesions were significantly more sever, but fibrosis was much milder in SARS-CoV-2. The segmental dilatation and stenosis of the small intestine in the cadavers suggest the development of an infection process in this organ. Lesions of other organs and tissues were not found. The pathological findings obtained from other COVID-19 victims [12] showed bilateral diffuse alveolar damage with fibromyxoid exudates, desquamation of pneumocytes and hyaline membrane formation in the lungs.

If the immune system is not able to defeat SARS-CoV-2, the virus will be massively replicated, will occupy cellular ACE2 and then will destroy the host cells when released to the extracellular space. As a consequence, the metabolic pathway of the angiotensin is not inhibited. It results in aggravation of the infection process and development of inflammation. The cytokine storm disrupts functioning of the respiratory tract, cardiovascular system as well as other systems and organs. Patients with such underlying diseases as hypertension, coronary heart disease and diabetes are at high risk when infected with SARS-CoV-2: With these diseases, the metabolic pathway of angiotensin becomes redundant and the coronavirus infection aggravates severely concurrent conditions and, therefore, can induce critical conditions and even death.

ACE2 is a major player in many pathological and physiological conditions. It is found that mice infected with SARS-CoV experience a shortage of ACE2; they have an elevated level of AngII and they develop severe conditions of the respiratory system [16]. The absence of ACE2, which maintains the protective function, results in RAS dysfunction and acute pathological respiratory conditions. Interestingly, the protective function of ACE2 in severe lung involvement can be observed not only during coronavirus infection. Restoration of the lung tissue was observed in laboratory mice, which had massive pulmonary edema, the severest form of hypoxia, hyaline degeneration and inflammable cellular infiltrates, when recombinant ACE2 was injected. ACE2 also protects against excessive inflammation when infected with the avian flu. The severity of the disease, its progression and lethality depend directly on the AngII level in blood plasma.

The presence of ACE2 in non-respiratory organs has a positive impact on functioning of the related tissues. Laboratory mice with endogenous deficiency of ACE2 develop severe cardiac involvement — decreased contractility caused by insufficient ventricular dilation and thinning of the left ventricular wall [9].

The concentration levels of ACE2 can increase after an ischemic stroke. It is a compensatory response aimed at removing excessive amounts of Ang (1–7) and at providing protective effects by balancing AngII.

ACE2 participates in pathological processes in renal tissue, though the exact mechanism is not obvious. Mice with ACE2 deficiency develop glomerulosclerosis and albuminuria [17]. Decreased concentration levels of ACE2 cause imbalance of AngII, which participates in inflammation of kidneys and fibrosis, thus explaining, though partially, the reasons for progressing renal disease.

An important non-peptidase function of ACE2 is its participation in transportation of amino acids through the wall of the small intestine. One of such amino acids is tryptophan regulating secretion of antimicrobial peptides, which have an impact on the intestinal microbiome composition. The latter can offer explanation to development of colitis in mice with ACE2 deficiency; the mice have disruption in the tryptophan transport; the disruption causes its deficiency, which leads to dysbiosis and inflammation.

Despite intensive therapy, the death rates from COVID-19 remain high. Creation of a vaccine is a time and labor-consuming process. Besides, SARS-CoV-2 tends to mutate in every replication cycle. It substantially complicates the development of a vaccine and even may make it useless. Theoretically, medications regulating the RAS imbalance can be used for other purposes. For example, they can be used to block the SARS-CoV-2 and ACE2 binding site; ACE2 can be used in a soluble form to inhibit the viral entry into the cell by binding to the RBD of the virus. Furthermore, ACE2 can subdue development of pathological changes by participating in different protective metabolic pathways.

The type II transmembrane serine protease, TMPRSS2, plays a key role in the cellular entry of SARS-CoV-2 and dysfunction of ACE2; therefore, if this enzyme is blocked, it may help prevent severe critical complications of COVID-19. It is found that the inhibitor camostat mesylate TMPRSS2 can partially block the TMPRSS2-ACE2-mediated entry of SARS-CoV-2 into the cell [18]. At the same time, the nafamostat mesylate, which inhibits the membrane fusion of the host cell and SARS-CoV-2, demonstrates ten times higher efficiency than camostat mesylate. Both camostat mesylate and nafamostat mesylate are clinically safe and, therefore, can be used for COVID-19 treatment in clinical practices. Nafamostat mesylate has another property — it can block the proteolysis of fibrinogen into fibrin. Coronavirus infection can cause increased D-dimer levels in bold serum. D-dimer is a fibrin degradation product and its concentration exceeding 1 mg/ml is associated with high risk of death for COVID-19 patients. Thus, nafamostat mesylate is potentially a product of dual action: It not only blocks the entry of SARS-CoV-2 into the cell, but also prevents thrombosis and disseminated intravascular coagulation. Clinical trials of this product intended for coronavirus infection treatment started in Japan in March 2020.

ACE inhibitors, AngII receptor blockers, agonists of AngII or Mas receptors may help fix impairments in RAS. AngII receptor blockers gain trust due to their proven symptomatic relief in case of pulmonary tissue injury caused by SARS and the avian influenza virus. It is expected that blocking of AngI receptors with the help of AngII receptor blocker will be more reliable than using ACE inhibitors, as AngII can be synthetized by different enzymes. It should be noted that the above products are clinically safe and commonly used. Paradoxically, based on clinical data [19], the increased ACE expression during treatment with the above medications does not cause any increase in the SARS-CoV-2 virulence. Studies of the human immunodeficiency virus (HIV) showed that the increased expression of HIV-binding CCR5 and CD4 sites protects patients against the virus virulence. HIV avoids superinfection during its entry into the cell by reducing the amounts of CCR5. Such reduction facilitates efficient replication of the virus and, consequently, affects the pathological mechanisms of the acquired immune deficiency syndrome. It remains unclear whether this concept can be applied to SARS-CoV-2; however, if the coronavirus uses the similar mechanism, application of AngII receptor blockers and ACEI is well-reasoned.

Conclusion

Significant mutation changes in the SARS-CoV virus genome resulted in emergence of a stronger type, SARS-CoV-2, and caused a global pandemic in 2020. On the one hand, ACE2 plays a key role in the viral entry into the host cell; on the other hand, it protects the human body from severe damage that may me caused to internal organs by coronavirus infection. The development of a vaccine against the virus that undergoes numerous mutations is a labor-intensive and time-consuming process. Being aware of the ACE2 role in RAS, it is possible to use medications that can affect this metabolic pathway during treatment of COVID-19.

ЛИТЕРАТУРА/REFERENCES

1. Wu F., Zhao S., Yu B., Chen Y.M., Wang W., Song Z.G., et al. A new coronavirus associated with human respiratory disease in China. *Nature.* 2020; 579(7798): 265-9. DOI: http://doi.org/10.1038/s41586-020-2008-3
2. Zhou P., Yang X.L., Wang X.G., Hu B., Zhang L., Zhang W., et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020; 579(7798): 270-3. DOI: http://doi.org/10.1038/s41586-020-2012-7
3. Morse J.S., Lalonde T., Xu S., Liu W.R. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. *Chembiochem.* 2020; 21(5): 730-8. DOI: http://doi.org/10.1002/cbic.202000047
4. Song W., Gui M., Wang X., Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. *PLoS Pathog.* 2018; 14(8): e1007236. DOI: http://doi.org/10.1371/journal.ppat.1007236
5. He J., Tao H., Yan Y., Huang S.Y., Xiao Y. Molecular Mechanism of Evolution and Human Infection with SARS-CoV-2. *Viruses.* 2020; 12(4): 428. DOI: http://doi.org/10.3390/v12040428
6. Banerjee A., Kulcsar K., Misra V., Frieman M., Mossman K. Bats and coronaviruses. *Viruses.* 2019; 11(1): 41. DOI: http://doi.org/10.3390/v11010041
7. Tipnis S.R., Hooper N.M., Hyde R., Karran E., Christie G., Turner A.J. A human homolog of angiotensinconverting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. *J. Biol. Chem.* 2000; 275(43): 33238-43. DOI: http://doi.org/10.1074/jbc.M002615200
8. Lambert D.W., Yarski M., Warner F.J., Thornhill P., Parkin E.T., Smith A.I., et al. Tumor necrosis factor-alpha convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). *J. Biol. Chem.* 2005; 280(34): 30113-9. DOI: http://doi.org/10.1074/jbc.M505111200
9. Hamming I., Cooper M.E., Haagmans B.L., Hooper N.M., Korstanje R., Osterhaus A.D., et al. The emerging role of ACE2 in physiology and disease. *J. Pathol.* 2007; 212(1): 1-11. DOI: http://doi.org/10.1002/path.2162

10. Li M.Y., Li L., Zhang Y., Wang X.S. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect. Dis. Poverty.* 2020; 9(1): 45. DOI: http://doi.org/10.1186/s40249-020-00662-x
11. Li W., Moore M.J., Vasilieva N., Sui J., Wong S.K., Berne M.A., et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature.* 2003; 426(6965): 450-4. DOI: http://doi.org/10.1007/s00018-004-4242-5
12. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020; 395(10223): 497-506. DOI: http://doi.org/10.1016/S0140-6736(20)30183-5
13. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020; 395(10223): 507-13. DOI: http://doi.org/10.1016/S0140-6736(20)30211-7
14. Holshue M.L., DeBolt C., Lindquist S., Lofy K.H., Wiesman J., Bruce H., et al. First case of 2019 novel coronavirus in the United States. *N. Engl. J. Med.* 2020; 382(10): 929-36. DOI: http://doi.org/10.1056/NEJMoa2001191
15. Yan T., Xiao R., Lin G. Angiotensin-converting enzyme 2 in severe acute respiratory syndrome coronavirus and SARS-CoV-2: A double-edged sword? *FASEB J.* 2020; 34(5): 6017-26. DOI: http://doi.org/10.1096/fj.202000782
16. Kuba K., Imai Y., Rao S., Gao H., Guo F., Guan B., et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat. Med.* 2005; 11(8): 875-9. DOI: http://doi.org/10.1038/nm1267
17. Ye M., Wysocki J., William J., Soler M.J., Cokic I., Batlle D. Glomerular localization and expression of Angiotensin-converting enzyme 2 and Angiotensin-converting enzyme: implications for albuminuria in diabetes. *J. Am. Soc. Nephrol.* 2006; 17(11): 3067-75. DOI: http://doi.org/10.1681/ASN.2006050423
18. Xiao L., Sakagami H., Miwa N. ACE2: The key molecule for understanding the pathophysiology of severe and critical conditions of COVID-19: demon or angel? *Viruses.* 2020; 12(5): 491. DOI: http://doi.org/10.3390/v12050491
19. Rico-Mesa J.S., White A., Anderson A.S. Outcomes in patients with COVID-19 infection taking ACEI/ARB. *Curr. Cardiol. Rep.* 2020; 22(5): 31. DOI: http://doi.org/10.1007/s11886-020-01291-4

Information about the authors:

Polina O. Shatunova✉ — student, I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991, Moscow, Russia.
ORCID ID: https://orcid.org/0000-0001-7478-8783.
E-mail: ppolite@mail.ru

Anatoly S. Bykov — D. Sci. (Med.), Prof., Department of Microbiology, Virology and Immunology, I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991, Moscow, Russia.
ORCID ID: https://orcid.org/0000-0002-8099-6201.

Oksana A. Svitich — D. Sci. (Med.), Corresponding Member of RAS, Prof., Department of Microbiology, Virology and Immunology, I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991, Moscow, Russia.
ORCID ID: https://orcid.org/0000-0003-1757-8389.

Vitaly V. Zverev — D. Sci. (Biol.), Full Member of RAS, Head, Department of Microbiology, Virology and Immunology, I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991, Moscow, Russia.
ORCID ID: https://orcid.org/0000-0001-5808-2246.

Contribution: the authors contributed equally to this article.

Информация об авторах:

Шатунова Полина Олеговна✉ — студент ФГАОУ ВО Первый МГМУ им. И.М. Сеченова Минздрава России (Сеченовский Университет), 119991, Москва, Россия.
ORCID ID: https://orcid.org/0000-0001-7478-8783.
E-mail: ppolite@mail.ru

Быков Анатолий Сергеевич — д.м.н., проф. каф. микробиологии, вирусологии и иммунологии ФГАОУ ВО Первый МГМУ им. И.М. Сеченова Минздрава России (Сеченовский Университет), 119991, Москва, Россия.
ORCID ID: https://orcid.org/0000-0002-8099-6201.

Свитич Оксана Анатольевна — д.м.н., член-корреспондент РАН, проф. каф. микробиологии, вирусологии и иммунологии ФГАОУ ВО Первый МГМУ им. И.М. Сеченова Минздрава России (Сеченовский Университет), 119991, Москва, Россия.
ORCID ID: https://orcid.org/0000-0003-1757-8389.

Зверев Виталий Васильевич — д.б.н., академик РАН, зав. каф. микробиологии, вирусологии и иммунологии ФГАОУ ВО Первый МГМУ им. И.М. Сеченова Минздрава России (Сеченовский Университет), 119991, Москва, Россия.
ORCID ID: https://orcid.org/0000-0001-5808-2246.

Участие авторов: все авторы сделали эквивалентный вклад в подготовку публикации.