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REVIEW on SARS-CoV-2 VIRUS TRANSMISSION MECHANISM in HUMAN

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Abstract

Coronavirus infection has been the most common form of pandemic with high mortality in recent decades, and the recent form of coronavirus mainly results in severe acute respiratory syndrome (SARS-CoV). Prophylaxis & treatment of SARS-CoV remains the big problem of our century. However, this is impossible without knowledge of the subtle mechanisms of the virus entry into the body, stimulating organ damage and the spread of the disease. It is revealed, that the spike protein of the SARS-CoV-2 virus binds to target cells through the angiotensin-converting enzyme-2 (ACE2), which forms active angiotensin II; the SARS virus can also bind to the CD147 cell receptor. They are mainly located on the surface of respiratory and gastrointestinal epithelial cells and play role of the entry routes of infection. After the attachment of the virus to the cell, the spike protein is cleaved into subunits S1 and S2 as result of proteolysis through a transmembrane serine protease type 2. The virus then activates endocytosis. SARS-CoV-2 is capable of damaging alveocytes type I and II, as well as endothelial cells. This process leads to the expression and secretion of anti-inflammatory cytokines, detailed in this paper. Preventing the development of these mechanisms of SARS virulence forms the basis of today's official protocols.

Key words: SARS-CoV, cytokine storm, reactive oxygen forms, receptors.

Introduction

İt is acknown that last outbreaks of coronavirus infections occurred in 2002 and 2012, but they were characterized by relatively low prevalence. The following types of coronaviruses are known: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV-1, MERS-Cov, and SARS-CoV-2. The recent type of SARS-CoV-2 has the highest virulence and susceptibility [1]. The high mortality rate, as well as serious economic and social

disadvantages, have made the study of the mechanisms of this disease and therapeutic approaches the most pressing problem in medicine. Reactive oxygen forms (ROF) formed during metabolism are of great importance, as they act as messengers in the cell. It is acknown that ROF kinases can stimulate inflammatory signals in the cell by increasing the expression of transcription and inflammatory genes.

The coronavirus SARS-CoV, which caused China's severe acute respiratory syndrome in 2002-2003, and the Middle East coronavirus (MERS-CoV) in 2012, killed more than 10,000 people; Mortality was 10% in SARS-CoV and 37% in MERS-CoV [2]. In late 2019 was identified a new strain of coronavirus, identified by the WHO as SARS-CoV-2 and causing a new severe acute respiratory syndrome (COVID-19). As for its structure, on the outside of the virus are crown-shaped glycoprotein protrusions known as spike S-protein, which is designed to bind to the surface of the target cell. It has been found, that spike proteins have the ability to hide from innate immunity by undergoing conformational changes. The spike protein of the SARS-CoV-2 virus binds to target cells through angiotensin converting enzyme-2 (ACE2), which forms active angiotensin II [3]. ACE2 is mainly expressed in cells of the gastrointestinal tract, kidneys, blood vessels, heart and lungs. The SARS virus can also bind to the CD147 cell receptor, also known as BASIGIN [4]. As a result of the virus attaching to the cell, the spike protein is broken down into S1 and S2 subunits by proteolysis of the cell via trans-membrane serine protease type 2 (trans-membrane serine 2 protease, TMPRSS2). Then S1 subunit binds to ACE2, after which the S1-RBD PD-ACE2 complex dissociates, while the hydrophobic S2-FP (fusion peptide) peptide is released from S2, and the virus enters to the target cell by activating endocytosis [5]. Then the permanent mechanism of virus developement is activated: target cell organelles perform translation on template viral RNA, resulting in the formation of structural proteins necessary for the virus development, which start a new generation of SARS -CoV-2 virions, and continue to damage new target cells. ACE2 CD147 and TMPRSS2 are the receptors sensitive to SARS-CoV-2, the upper branches of which are located on the surface of respiratory and gastrointestinal epithelial cells are the entry routes of infection [6, 7]. The products of the virus interaction with the target cell are recognized by specific Nod-receptors involved in the formation of the polyprotein complex, the inflammasome [8].

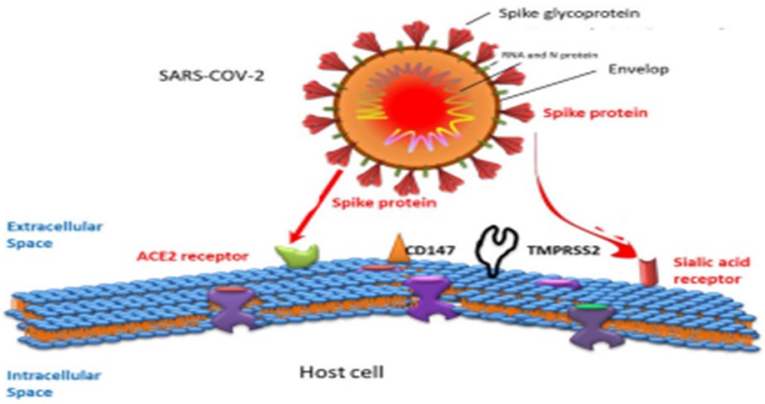

Fig 1. Interaction of SARS-CoV spike protein with cell CD147, ACE2, TMPRSS2 receptors. Is re-published with kind permission Tripathy S., 2020 [9]

Unlike strains with low virulence, SARS-CoV-2 passing into the lower respiratory tract gains the ability to damage alveocytes type I and II, as well as endothelial cells [10]. This process results in the expression and secretion of anti-inflammatory cytokines. During the secretion of cytokines, the epithelium of alveocytes undergoes pyroptosis, and the resulting products are phagocytosed by granulocytes and tissue macrophages [11]. In this condition, neutrophils and cytotoxic T cells, along with the formed cyto- and chemokines, cause severe pulmonary pneumonia, which causes damage to lung tissue, promotes the development of edema at the site of injury, causes acute respiratory distress syndrome, and results in fibrosis [12]. The age factor aggravates the pathological process, i.e. the changes listed in the elderly are more pronounced [13, 14, 15]. By infecting the membranes of alveolar-capillary cells, SARS-CoV-2 enters the bloodstream and can damage other organs and cells that have receptors on its surface: intestines, kidneys, esophagus, heart, blood vessels, brain, bladder, etc [16]. In the early stages of the disease, the nsp1 and rp6 proteins of the virus inhibit the formation of interferon. Vazquez C. et al. also state that NSP1 and NSP13 proteins of SARS-CoV-2 block activation of interferon via different mechanisms [17]. Macrophages entering the site of inflammation continue to produce chemo-attractants for mononuclear cells, and thus their concentration increases rapidly, which triggers the inflammatory process to move to the next stage, the cytokine "storm" [18, 19, 20]. At this stage, the level of inflammatory cytokines and chemo-attractants continues to increase dramatically, so interleukins, monocyte chemo-attractant protein MCP-1 [21], macrophages inflammatory protein MIP-1a, TGF, CCL2, CXCL10, CXCL9, TNF (CXCL9), tumor (CXCL9) increase sharply, even the cytokines HGF and CXCL13 levels in the blood predict the severity and the mortality in SARS-CoV patients [22].

In severe cases of SARS-CoV-2 infection, there are significant changes in the acute phase proteins of the blood, and at this stage markers such as C-reactive protein, ferritin, ceruloplasmin[23], blood clotting factors [24, 25], serum enzymes indicate a failure of numerous organs. In about 82% of cases leukopenia, thrombocytopenia and loss of eosinophils along with lymphopenia are observed in peripheral blood, sometimes leucocytes, neutrophils are increased [26]. Viral respiratory infections stimulate the inflammatory process and contribute to the development of pathophysiological processes against the background of an excess of cytokines, oxygen and/or nitrogen active forms. Mitochondria is the main generator of reactive oxygen forms (ROF), and along with SARS-CoV 3b protein and non-structural protein 10 (nsp10) they can change the course of processes in mitochondria [27]. SARS -CoV 3b may enter mitochondria [28, 29], while nsp10 may interact specifically with the NADH 4L subunit and cytochromoxidase II [28, 27]. It has also been shown, that after these interations the genes encoding mitochondrial DNA in peripheral blood mononuclear cells, as well as genes sensitive to oxidative stress such as peroxiredoxin 1 [30], the

ferritin heavy chain polypeptide gene are activated. Oxidative stress increases the expression of 2D type of anti-inflammatory phospholipase A2 [31], which lowers antiviral immunity. Interestingly, in humans, phospholipase A2 is naturally activated as 2D ages [32]. In humans, there is also protein kinase, which is activated by mitogens from the damaging effects of the external environment, such as oxidative stress, accumulation of DNA damage, carcinogens and viruses. Thus, those who have a deletion of the ncf1 gene that stimulates the formation of ROF and do not have Toll-like receptor-4 (TLR4), which activates innate immunity, have a natural resistance to respiratory viruses, including SARS COVID virus. Imai Y. et al observed that the oxidized phospholipid was inducing lung injury and cytokine production by lung macrophages via TLR4-TRIF [33]. This is explained by the fact that living organisms with such deletions do not produce oxidized 1-palmitoyl -2-arachidoinyl-phosphatidyl choline, which stimulates the formation of cytokines by macrophages and activates damaging mechanisms. It is also known that SARS-CoV 3CLpro protease induces apoptosis in human promonocytes [34] by increasing the formation of ROF [35]. Occurrence of oxidative stress can lead to severe lung damage. *In vivo* oxidative stress activates 3CLpro NF-kB-factor [36, 37], but inhibits protein-1-dependent transcription [38], so ROF-induced transmission of the 3CLpro-stimulated NF-kB signal may have played a leading role in the pathophysiology of SARSCoV infection. This is because the activation of the phosphatidylinositol-3-kinase/protein kinase pathway by various viruses during latent or chronic infections [39, 40] allows infected cells to avoid apoptosis [41], which in turn contributes to the spread of the virus in the body.

All the data accumulated to date make it possible to correctly guide the process of treatment for SARS-CoV infection and reduce mortality among patients, prevent complications, and choose the right drugs to preserve the viability of organs and tissues. The further investigations will make even more accurately guide the processes of therapy and prevention of SARS-CoV infection seemingly incurable.

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