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THE ROLE OF CYTOKIN STORM AND OXIDATIVE STRESS IN THE SPREAD OF SARS-COV INFECTION

Summary

SARS CoV infection is one of the most common and economically damaging and life-threatening infections of the last 100 years. To combat it, first of all, it is necessary to study the mechanisms that stimulate its development. For this purpose, the role of genomic changes and oxidative stress in the spread of SARS-CoV virus is investigated. During the spread of this disease, lung damage has been found to occur under a "cytokine storm" caused by active forms of oxygen. SARS virus binds to target cells via angiotensin converting enzyme-2 (ACE2). In the early stages of the disease, SARS viruses cause accumulation and activation of NLRP3-inflammation, which plays a leading role in the formation of the inflammatory response to the virus. During the cytokine storm phase, interleukins, monocytic hematopoietic protein MCP-1, macrophage inflammatory protein MIP-1a, TGF, CCL2, CXCL10, CNXL9, TNF-a continue to increase. SARS-CoV-3b protein and nonstructural protein 10 (nsp10) of COVID virus in mitochondria

It promotes the formation of OAF. 3CLpro protease is also known to cause apoptosis in human promonocytes by increasing OAF formation. Activation of the NF-κB transcription factor through oxidative stress can lead to severe lung damage. Naturally, in response to oxidative stress, the antioxidant system is activated, resulting in the depletion of the enzymatic and non-enzymatic branches of the system. After acquaintance with this mechanism, the reason for the spread of SARS COV infection in patients with hypertension treated with ACE-2 blockers is known. The therapeutic effect of antioxidants in this disease is also accepted as an undeniable fact.

***Key words**: SARS-CoV, cytokine storm, oxidative stress*

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SARS-COV infeksiyasının yayılmasında Sitokin Fırtınasının və Oksidativ Stressin rolu

Xülasə

SARS CoV infeksiyası son 100 ilin ən çox yayılmış və iqtisadi cəhətdən zərərli və həyati təhlükəsi olan infeksiyalardan biridir. Bununla mübarizə aparmaq üçün ilk növbədə onun inkişafını stimullaşdıran mexanizmləri öyrənmək lazımdır. Bu məqsədlə SARS-CoV virusunun yayılmasında genomik dəyişikliklərin və oksidləşdirici stressin rolu araşdırılır. Bu xəstəliyin yayılması zamanı oksigenin aktiv formalarının yaratdığı "sitokin fırtınası" altında ağciyər zədələnməsinin baş verdiyi aşkar edilmişdir. SARS virusu angiotenzin çevirən ferment-2 (ACE2) vasitəsilə hədəf hüceyrələrə bağlanır. Xəstəliyin erkən mərhələlərində SARS virusları NLRP3-iltihabın yığılmasına və aktivləşməsinə səbəb olur, virusa qarşı iltihablı reaksiyanın formalaşmasında aparıcı rol oynayır. Sitokin fırtınası mərhələsində interleykinlər, monositik hematopoetik protein MCP-1, makrofaq iltihablı protein MIP-1a, TGF, CCL2, CXCL10, CNXL9, TNF-a artmağa davam edir. Mitoxondriyadakı SARS-CoV-3b zülalı və qeyri-struktur protein 10 (nsp10) COVID virusu OAF-nin əmələ gəlməsini təşviq edir. 3CLpro proteazının OAF əmələ gəlməsini artıraraq insan promonositlərində apoptoza səbəb olduğu da məlumdur. NF-κB transkripsiya faktorunun oksidləşdirici stress vasitəsilə aktivləşdirilməsi ağciyərin ciddi zədələnməsinə səbəb ola bilər. Təbii ki, oksidləşdirici stressə cavab olaraq antioksidant sistem aktivləşir, nəticədə sistemin fermentativ və qeyri-fermentik şaxələri tükənir. Bu mexanizmlə tanışlıqdan sonra ACE-2 blokerləri ilə müalicə olunan hipertansiyonlu xəstələrdə SARS COV infeksiyasının yayılmasının səbəbi məlumdur. Bu xəstəlikdə antioksidantların müalicəvi təsiri də danılmaz fakt kimi qəbul edilir.

Açar sözlər: *SARS-CoV, sitokin fırtınası, oksidləşdirici stress*

History has witnessed many epidemics affecting human health and the economies of nations. Recent outbreaks of coronavirus infections occurred in 2002 and 2012, but these were characterized by relatively low prevalence and prevalence. The following strains of coronavirus are known: HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1, SARS-CoV-1, MERS-CoV, SARS-CoV-2. The current SARS-CoV-2 strain is characterized by the highest virulence and susceptibility (Liu D. X. Et al., 2021). The high mortality rate and the creation of serious economic and social disadvantages have made the investigation of the mechanisms and treatment methods of this disease the most urgent problem in medicine. But the exact pathogenesis of this infection has not yet been determined, but the collected data show that the virus is a factor that causes polyorganic pathology and damages not only the lungs, but also the vessel wall, its hemostasis. The virus also makes a significant contribution to comorbid pathology characterized by an increase in active forms of oxygen (OAF) and a compromised immune system. Virus-induced OAF and redox imbalance exacerbate the inflammatory response to SARS-CoV infection, and mitochondria, the source of OAF, are closely monitored. However, little is known about SARS-CoV-2, the interaction of viral activity with oxidative stress, the effects of these relationships on cells and tissues, and the role of antioxidant deficiencies in the occurrence of infection have not been fully elucidated. Although the pathogenesis of coronavirus has been studied closely for nearly 20 years, effective prophylaxis and treatment methods have not yet been developed. There are several reasons for this, some of which are the ability of the virus to mutate intensively, high virulence of strains, features of the pathogenetic course, rapid spread.

Activation of antimicrobial cells, including neutrophils and macrophages, and generation of inflammatory cytokines are mainly dependent on OAF. Optimal levels of OAF in the body are maintained by the enzymatic and non-enzymatic antioxidant system. When antioxidant defenses are weakened, a condition called oxidative stress occurs. Numerous studies have shown that an increase in OAF accompanies all infectious respiratory viral infections, as well as HIV and hepatitis. Activation of a number of pathological processes in the body that cause complications occurs with an increase in OAF, and the development of coronavirus infection does not go beyond this rule. Coronaviruses (Latin: Coronaviridae) are a class of about 40 zoonotic RNA-containing viruses common in the human

population and among animals. There are 5 main types of coronavirus, two of which (α- and β-viruses) infect humans (Yücel B. and d., 2019). The first human coronavirus (HCoV-B814) was first detected in 1965 in a patient with acute respiratory viral infection. XXI. At the turn of the century, coronaviruses were known as veterinary pathogens and posed no threat to humans. The SARS-CoV coronavirus, which caused severe acute respiratory syndrome in China in 2002-2003 and the Middle East coronavirus (MERS-CoV) in 2012, killed more than 10,000 people; The mortality rate was 10% in SARS-CoV and 37% in MERS-CoV (Challen R. et al., 2020.) In late 2019, a new severe acute respiratory syndrome (A new type of coronavirus that causes COVID-19 has been detected. Recent genetic studies have shown that the virus originally arose in bats, but whether bats can infect themselves is still under investigation. The virus is a circular pleomorphic pathogen with a lipid coating of 80-229 nm (Tai L. et al., 2021); Three pathogenic structural proteins are found on its surface. Outside the virus are crown-shaped glycoprotein protrusions (spike S-protein) designed to attach to the surface of the target cell. The spike protein of the SARS-CoV-2 virus binds to target cells via active angiotensin-forming angiotensin converting enzyme-2 (ACE2) (Jia, H. P. et al., 2005). Cells susceptible to SARS-CoV-2 interact with ACE2 and CD147 receptors that bind to the virus, these cells are considered entry routes of infection; they are located on the surface of the epithelial cells of the upper respiratory tract and gastrointestinal tract. The products of interaction of the virus with the target cell are recognized by specific NOD-receptors involved in the formation of the polyprotein complex called the inflammasome (Li, G. et al., 2020). In the early stages of the disease, RNA viruses induce the accumulation and activation of NLRP3-inflammasome, which plays a leading role in the formation of the inflammatory reaction against the virus (Yalcinkaya, M. et al, 2021). Metabolites of the virus produce OAF, which damages mitochondria and stimulates DNA release. While heat shock protein A1L (Heat Shock Protein A1L, HSPA1L - Heat Shock Protein AIL) increases viral replication in the host cell (Lippi, A. et al.,2020), DNA methylation rate decreases in SARS-CoV infection because DNA in epithelial cells of COVID lung tissue reduces the activity of methyl transferases (Shirvaliloo M., 2021).

Unlike low virulence strains, SARS-CoV-2 has the ability to penetrate the lower respiratory tract and damage endothelial cells as well as type I and II alveocytes. This process results in the expression and secretion of anti-inflammatory cytokines. During the cytokine secretion phase, the alveolar epithelium undergoes pyroptosis and the resulting products are absorbed by granulocytes and tissue macrophages. In this case, neutrophils and cytotoxic T cells, together with the cyto- and chemokines formed, participate in the virus protection process of lung tissue (Wong, C. K. et al., 2004).

Unlike host strains, SARS-CoV-2, if infected, has the ability to penetrate the lower respiratory tract and damage endothelial cells as well as type I and II alveocytes. This process results in the expression and secretion of anti-inflammatory cytokines. During the cytokine secretion phase, the alveolar epithelium undergoes pyroptosis and the resulting products are absorbed by granulocytes and tissue macrophages.

Thus, due to the stimulation of the synthesis of endogenous immunomodulators (COVID-19), severe forms of cytokine "storm syndrome" occur, resulting in loss of control of the inflammatory process and a significant lack of organs and systems [Song, P., et al., 2020]. In the early stages of the disease, the virus nsp1 and rp6 proteins inhibit the formation of interferon. Macrophages that enter the site of inflammation continue to produce chemoattractants for mononuclear cells (mononuclear cells), thereby increasing their density rapidly, which promotes the inflammatory process to the next stage, the "cytokine storm".

Viral respiratory infections stimulate the inflammatory process and contribute to the development of pathophysiological processes against the background of overactive forms of cytokines and oxygen and / or nitrogen.

The main producer of OAF is mitochondria, the SARS-CoV-3b protein of the COVID virus and nonstructural protein 10 (nsp10) can change the course of processes in the mitochondria.

While SARS-CoV 3b can enter mitochondria, nsp10 can interact specifically with the NADH 4L subunit and cytochromoxidase II. In peripheral blood mononuclear cells, oxidative stress sensitive genes such as peroxiredoxin 1, as well as genes encoding mitochondrial DNA, have also been shown to activate the ferritin heavy chain polypeptide gene. Oxidative stress increases anti-inflammatory phospholipase A2 type 2D expression, which reduces antiviral immunity. Interestingly, in humans, phospholipase A2 is naturally activated as 2D age (Vijay, R. Et al., 2015).

The aggressive reaction of neutrophils, as we have noted, is primarily directed at the infected cell, so the cytotoxic effect of neutrophils weakens as the number of virus-infected cells decreases. However, when the process gets out of control and the virus spreads in the body, acute respiratory distress syndrome occurs (Laforge, M. et al., 2020). Nitric oxide is added to the process of cleansing the body of the virus, accompanied by an increase in nitroquinosine. The deficiency of the antioxidant system leads to the fatal outcome of SARS-CoV infection. Thus, heavy ferrite chain (FTH1) expression is increased in SARS-CoV infection. It indicates the need to strengthen the antioxidant system, as it inhibits the formation of OAF by entering the Fenton reactions by storing iron ferritin, thus forming a very important antioxidant system of the body.

In SARS-CoV infection, there is also an increase in other antioxidant iron-binding proteins that limit the rate of OAF formation. Of course, in the progressive stage of SARS-CoV-2 infection, when the virus spreads rapidly throughout the body, the need for pro-oxidants rather than antioxidants increases. This is because OAF removes damaged cells along with the virus and prevents the infection from spreading. Therefore, at this stage, the concentration of proteins that play an antioxidant role in the body and regulate iron metabolism - haptoglobin, ferrin, transferrin and ceruloplasmin - decreases in the blood. Naturally, the deficiency of the above-mentioned proteins, which prevent the chain reactions of OAF formation at the healing stage and are actively involved in maintaining innate immunity, can cause undesirable complications for the body.

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