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COVID-19: CURRENT CONCEPTS OF PATHOGENESIS AND PATHOPHYSIOLOGY (LITERATURE REVIEW)

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Abstract: Infection caused by the SARS-CoV-2 coronavirus is a multisystem disease with a wide spectrum of manifestations, ranging from asymptomatic carriage to critical illness with multiple organ failure. Pathogenesis is based on the direct cytopathic effect of the virus, mediated by binding to angiotensin -converting enzyme 2 (ACE2) , and subsequent hyperactivation of the immune system with the development of a " cytokine storm" and coagulopathy . This review systematizes current data on the key stages of COVID-19 pathogenesis, from viral entry to the pathophysiological basis of long-term complications.
Key words : SARS-CoV-2, COVID-19, pathogenesis, pathophysiology, ACE 2 , cytokine storm, immune response, coagulopathy , post-COVID syndrome.

1. Introduction

SARS-CoV-2 is a single-stranded , positive-sense RNA virus belonging to the genus Betacoronavirus . Its pathogenicity is determined by the high affinity of the spike (S) protein for the angiotensin -converting enzyme 2 (ACE2) receptor, which is expressed on the surface of cells in the respiratory epithelium, vascular endothelium, heart, kidneys, intestines, and other organs [1, 2]. This affinity predetermines the systemic nature of the infection.

2. Mechanism of virus penetration and initial replication

The infection process begins with the binding of the viral S protein to the ACE2 receptor domain. Cellular transmembrane serine protease 2 (TMPRSS2) priming of the S protein cleaves it into S1 and S2 subunits, which is necessary for the fusion of the viral envelope with the cellular membrane or endosome membrane [3]. After penetration, the virus releases its RNA, which is translated into polyproteins and then, under the action of viral proteases (Mpro , PLpro), is cleaved into functional proteins. New virions are assembled in the endoplasmic reticulum reticulum - the Golgi apparatus and exocytosis leave the cell, leading to its death.

3. Pathogenesis of lung damage

The lungs are the primary target for SARS-CoV-2.

Virus-induced injury: Infection of type II pneumocytes (rich in ACE2) disrupts surfactant synthesis , leading to loss of alveolar epithelial integrity and the development of alveolar injury.

Endotheliitis : The virus directly infects endothelial cells of the pulmonary capillaries, leading to their activation, apoptosis , barrier dysfunction, and increased vascular permeability. This causes edema and fibrin exudation into the alveoli [4].

Immunopathogenesis : Infected cells and alveolar macrophages secrete proinflammatory cytokines (IL-1, IL-6, TNF-α) and chemokines (CCL2, CXCL10), which attract neutrophils, monocytes, and lymphocytes to the site. Uncontrolled activation of the immune system forms the phenomenon of a " cytokine storm" – a key link in the progression to acute respiratory distress syndrome (ARDS) [5]. High levels of interleukin-6 (IL-6) correlate with the severity of the disease.

Ventilation- perfusion imbalance : Vasculitis , microthrombosis , and edema lead to impaired perfusion of the ventilated alveoli, contributing to the development of severe hypoxemia, often without a pronounced feeling of dyspnea (“happy hypoxia”) – probably due to direct damage to juxtacapillary (J-receptors) by the virus.

4. Systemic manifestations and multiple organ damage

Coagulopathy : COVID-19-associated coagulopathy is characterized by a marked increase in D-dimer and fibrinogen with a relatively moderate prolongation of APTT. Endothelial dysfunction,

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hyperactive inflammation (IL-6 induces tissue factor synthesis), and platelet activation lead to a prothrombotic state with a high risk of venous thromboembolism and the formation of microthrombi in the vessels of the lungs, kidneys, heart, and brain [6].

Cardiovascular complications: Include myocarditis (direct viral infection of ACE2 - expressing cardiomyocytes), stress-induced cardiomyopathy (Takotsubo syndrome), acute myocardial injury due to hypoxia, and imbalance in the renin- angiotensin -aldosterone system (RAAS) [7]. Viral binding to ACE2 leads to its internalization and decreased activity, which disrupts the cardioprotective and vasodilatory effects of this enzyme.

Neurological manifestations (Neuro -COVID): Mechanisms include: 1) direct invasion through the olfactory epithelium and penetration into the olfactory bulb; 2) hematogenous spread; 3) immune-mediated damage (cross- antibody response). Encephalopathy, acute cerebrovascular disease, and Guillain-Barré syndrome have been described . Long-term anosmia is associated with damage to the supporting cells of the olfactory epithelium, rather than neurons [8].

Gastrointestinal and liver damage: Enterocytes They express ACE2 , which explains the diarrhea and the possibility of fecal-oral transmission. Liver damage (increased transaminases) most often occurs as secondary reactive hepatitis due to systemic inflammation, hypoxia, and drug toxicity .

5. Immune response and factors determining the severity of the disease

Innate immunity: Delay in the production of type I interferons (IFN-α/β) in the early stages is a critical factor allowing the virus to replicate unimpeded. Subsequently, compensatory hyperactivation of macrophages and neutrophils with the development of inflammation [9].

Acquired immunity: Adequate humoral (neutralizing antibodies to the S protein) and cellular (cytotoxic CD8+ T lymphocytes) responses are associated with clinical recovery. However, some patients experience lymphopenia (a decrease in CD4+ and CD8+ T cells), which is a prognostic marker for severe disease, likely due to their apoptosis , depletion, or sequestration in lymphoid organs.

The role of autoantibodies : Autoantibodies against type I interferons have been detected (especially in elderly men), which explains the severity of the disease. Autoantibodies to phospholipids, coagulation factors, and cellular components have also been identified, contributing to thrombosis and immunopathology [10].

6. Post-COVID syndrome (Long COVID)

The pathogenesis remains poorly understood. Key hypotheses include:

Persistence of viral antigen in reservoirs (intestines, central nervous system) with maintenance of chronic inflammation.

Autoimmune reactions initiated by molecular mimicry of viral and human proteins.

Endothelial dysfunction and persistent microangiopathy.

Dysregulation of the autonomic nervous system (postural orthostatic tachycardia – POTS).

7. Conclusion

The pathogenesis and pathophysiology of COVID-19 represent a complex cascade of events, beginning with the interaction of the virus with the ACE2 receptor and culminating in a systemic inflammatory response, coagulopathy , and multiorgan damage. Key factors determining the transition from a local infection to a critical systemic disease are the characteristics of the host immune response, particularly dysregulation of innate immunity and the development of a cytokine storm. Understanding these mechanisms is the basis for the development of targeted therapies aimed not only at the virus but also at correcting abnormal immune and coagulation responses. Further research should focus on the pathogenesis of post-COVID syndrome and the identification of biomarkers for risk stratification.

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