PATHOGENETIC POINTS OF APPLICATION OF THE EFFECTS OF CERTAIN DRUGS FOR THE TREATMENT OF CORONAVIRUS INFECTION

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Coronaviruses are a family of RNA viruses that cause zoonotic infection [1].

The interaction of SARS-CoV-2 with humans begins directly in the mucous membranes of the nose, larynx and bronchial tree. By inhibiting the mobility of the epithelial cilia and the death of epithelial cells, the activity of mucociliary clearance is suppressed and the virus penetrates through the mucous membrane into the peripheral blood and subsequently affects the target organs - the lungs, digestive tract, heart, kidneys, whose cells express angiotensin-converting enzyme 2 (angiotensin-converting enzyme 2). 2 - ACE2) [2].

With the help of the S-spike protein, the SARS-CoV-2 virus binds to human receptors and enters the cell. Spike S-protein is a trimeric peaked glycoprotein, the molecule of which consists of three domains: ectodomain, membrane anchor domain, and short intracellular tail. The ectodomain consists of a receptor-binding S1 subunit and a membrane-bound S2 subunit. The S1 receptor-binding subunit contains two independent domains: N- (N-terminal domain - NTD) and C-terminal domain (C-domain - CD). The SARS-CoV-2 virus CD S protein domain is a receptor-binding domain (RBD) that recognizes the ACE2 protein as its receptor.

Due to the presence of the F486 phenylalanine residue in the RBD flexible loop, the penetration of RBD trimers of the SARSCoV-2 virus S-protein into the hydrophobic pocket of the ACE2 protein is persistent [2].

It follows that to prevent the penetration of the virus into the cell, the main groups of drugs should be aimed at preventing the binding of the S-protein of the SARSCoV-2 virus to membrane-associated ACE2.

As a drug that blocks the interaction of the S-protein of the SARS-CoV-2 virus with the ACE2 protein and prevents the glycosylation of human cell receptors, the American Medical Association is promoting the antimalarial drug chloroquine. Its mechanism of action is based on the presence of a positive charge, which alkalizes the contents of phagolysosomes, which leads to disruption of the fusion of the virus with the cell [2, 3].

The mechanism of action of the drug umifenovir is aimed at preventing the binding of the virus with the cell. The drug interacts with the hemagglutinin of the virus and prevents the fusion of the lipid membrane of the virus and human cell membranes [4].

Another mechanism of action that prevents the penetration of the SARS-CoV-2 virus into the cell is aimed at disrupting the cleavage of the ACE2 molecule, which blocks further communication with the spike S-protein of the virus. The cleavage of the ACE2 protein is carried out by the transmembrane protease serine 2 (TMPRSS2). An example of this group of drugs is camostat mesylate, which is a serine protease inhibitor [2, 3].

When SARS-CoV-2 enters the cell, the viral RNA is released into the cytoplasm and the viral genome begins to replicate. Viral replication within the cell takes place in membrane-surrounded organelles called viroplasm-like vesicles. They protect the virus from being recognized by innate immune receptors (Toll receptors). In addition, the SARS protein NSp16 helps mask viral pathogenic molecular structures, unmethylated 5'-tri / diphosphate dsRNA terminal sequences. This allows the SARS-CoV-2 virus to remain unnoticed when it enters the cell, which subsequently allows it to quickly spread throughout the body [5].

Remdesivir is considered to be a drug that acts on RNA-dependent polymerase. As an analogue of adenosine, remdesivir blocks the synthesis of SARS-CoV-2 viral RNA [2].

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A similar mechanism of action is possessed by the drug ribavirin, which is similar in pharmacodynamics to guanine, as well as drugs of the antiviral group such as triazavirin (a synthetic analogue of the bases of purine nucleosides (guanine)) and halidesivir (an analogue of adenosine nucleoside), which, being metabolized into a nucleotide, blocks the viral RNA polymerase 2, 6].

Virus replication is affected by favipiravir, which, being metabolized in cells to favipiravir ribosyl triphosphate (RTF favipiravir), selectively inhibits RNA-dependent polymerase. The nucleotide of the drug binds to the growing strand of the viral RNA, which leads to its premature termination. Thus, the formation of a new viral particle is disrupted.

The antiretroviral drug lopinavir in combination with ritonavir has been approved by the US Food and Drug Administration to fight coronavirus infection. This drug exerts intracellular activity against coronavirus infection by inhibiting 3-chymotrypsin-like protease [6].

Summarizing the information presented, there are several directions for combating the SARS-CoV-2 virus:

1. Prevention of fusion of membranes of the viral envelope with the human cell. The drugs of choice in this area of action are chloroquine, umifenovir, camostat mesylate.

2. Blocking the synthesis of viral RNA. Nucleoside analogs are carried out: remdesivir, ribavirin, triazavirin, halidesivir, favipiravir.

3. Inhibition of viral protease. The synergism of action was revealed with the combined use of the antiretroviral drug lopinavir and ritonavir.

References

1. Klompas M., Branson R., Eichenwald E.C., Greene L.R., Howell M.D., Lee G. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014; 35(8): 915–36. URL: https://doi.org/10.1086/677144. (дата обращения 10.06.2020).
2. Abaturov A.E., Agafonova E.A., Krivusha E.L., Nikulina A.A. Pathogenesis COVID-19 // Review of Literature. 2020. Vol. 15. № 2. C. 133-144. [Abaturov A.E., Agafonova E.A., Krivusha E.L., Nikulina A.A. Pathogenesis of COVID-19. 2020; 15 (2): 133-144].
3. Evaluation of the effectiveness of various groups of drugs used in the treatment of COVID-19. Medicinskij mir. URL: https://www.medmir.com/tekst-stati/pharmacologic-treatments-for-coronavirus-disease-2019-covid-19-2/ (circulation date 06.10.2020) (In Russ).].
4. Encyclopedia of Medicines and Pharmacy Products // Umifenovir. URL: https://www.rlsnet.ru/mnn_index_id_6264.htm (дата обращения 10.06.2020). [Encyclopedia of medicines and pharmacy products // Umifenovir. URL: https://www.rlsnet.ru/mnn_index_id_6264.htm (circulation date 10.06.2020).].
5. Kostinov M.P. Immunopathogenic properties of SARS-CoV-2 as a basis for the choice of pathogenetic therapy. Immunologija. 2020; 41 (1): 83–91. doi: 10.33029/0206-4952-2020-41-1-83-91. (circulation date 06.10.2020) (In Russ).
6. James M. Sanders, PhD, PharmD; Marguerite L. Monogue, PharmD; Tomasz Z. Jodlowski, PharmD; James B. Cutrell, MD. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19). American Medical Association. URL: https://www.tjod.org/wp-content/uploads/2020/04/Pharmacologic-Treatments-for-Coronavirus-Disease-2019-COVID-19.pdf. (circulation date 06.10.2020).

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