Role of upper respiratory tract in COVID-19 patient cases
Роля на горните дихателни пътища при COVID-19

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In the month of December 2019 in Wuhan, China for the first time a series of cases of an atypical pneumonia caused by a new type of coronavirus were reported (21). The disease was called COVID-19. COVID-19 is a disease which mainly causes high body temperature, coughing, shortness of breath, myalgia and general malaise. These symptoms are typical for the respiratory system and demonstrate an acute respiratory distress (14). According to the American Academy of Otolaryngology - Head and Neck Surgery anosmia and dysgeusia should be added to the symptoms of COVID-19 (19).

The cause of the disease is a virus - SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) (15).

SARS-CoV-2 is a single-stranded RNA virus, member of the genus Betacoronavirus (16). Its phylogenetic analysis shows that there is a 98,7% similarity with the coronavirus in bats from the Rhinolophus genus. The evolutionary analysis demonstrates that SARS-CoV-2 is a novel coronavirus passed from animals to humans (17). It is believed that the transition is carried out through an intermediate host – pangolin (18). After that, the spread among humans started. Transmission of the infection is accomplished through airborne way, close contact and contaminated surfaces. Virus
It is likely that viral transmission is connected with receptor distribution in the respiratory tracts. Due to the high receptor expression in the nasal cells we can suppose that these cells play an important role during the initial infection and are a possible reservoir for dissemination for the individual and between people. Taking facts into account until this moment, we can confirm, with high probability that nasal mucosa is of extreme importance for the transmission of the virus. Higher levels of the viral

enters human organism through the mucosa of the respiratory tract.

Angiotensin-converting enzyme 2 (ACE2) acts as a receptor for SARS-CoV-2 (7). ACE2 is an enzyme which converts angiotensin II into angiotensin (1-7) (4). ACE2 is a membrane-attached aminopeptidase found in the endothelium of blood vessels, kidneys, heart, small intestine and testicles (1, 2, 3). Significant gene expression of ACE2 is proven in alveolar epithelium cells type II (6). The presence of ACE2 in the nasal and bronchial epithelium secretion is proven as well (5). According to different pieces of research related to all parts of the respiratory tract, ACE2 is mainly expressed in the nasal secretory and ciliary type of cells. It is likely that this expression of the viral receptors in the upper respiratory tract is connected with and corresponding to the viral transmission. At the moment scientists have studied the expression of viral gene receptors in other coronaviruses and influenza viruses. Investigations are done for ANPEP in HCoV-22944, DPP4 – used by MERS-CoV45, enzymes ST6GAL1 and ST3GAL4, important for the influenza viruses (8, 9, 10). Important here is the fact that expression of their receptors coincides with the viral transmission as far as R0 is concerned (basic reproduction number). R0 shows the number of people that get infected by one infected person. It is established that more viral receptors in the upper respiratory tract is observed in viruses with higher R0. For instance, for SARS-CoV/SARS-CoV-2: R0 ~1.4–5.0, for the influenza virus: R0 ~1.347 (11, 12). On the other hand, there is a clear contrast in terms of DPP4 distribution, receptor for MERS-CoV. MERS-CoV is a human coronavirus with a low ability for transmission (R0 ~0.3–0.8). There, receptor distribution is mainly in the lower respiratory tract and the pulmonary parenchyma (13).
load are proven when investigating nasal in comparison with throat samples. As pathologic changes are observed in both halves of the lungs, this suggests viral dissemination after the initial infection (21). It is possible that this dissemination towards the lungs occurs because of the initial infection in the nasal mucosa. Probably, after the replication of the virus in the nasal cells, viral particles could reach pulmonary parenchyma where they cause severe changes. In patients who died from COVID-19, pathohistologically, severe diffuse alveolar changes were observed, which corresponds to the acute respiratory distress syndrome (ARDS) (22). The presence of ACE2 in the cells of the conjunctiva suggests distribution towards the respiratory tract through the nasolacrimal canal (20).

Attaching to and entering into the cells of the coronaviruses is determined by the virus spike(S) protein. Its S1 subunit connects him to the receptor, and the S2 subunit guides the process of priming and cutting of the S-protein which allows the merging of the viral and cell membranes. The priming process is delivered by cell proteases. SARS-CoV utilizes the cell serine protease TMPRSS2 (23). SARS-CoV-2 also could use TMPRSS2 for the S protein priming. Hence, the spread of SARS-CoV-2 also depends on the activity of TMPRSS2. TMPRSS2 is a factor of the host cell which is of great importance for the spread of some clinically important viruses, including Type A Influenza viruses and coronaviruses (23, 24, 25, 26). It is found out that rabbit serums against the S1 subunit lower SARS-S and SARS-2-S entering of the cell with high effectivity as inhibiting the SARS-S entering is more effective. Thus, antibody responses towards SARS-S during infection or vaccination may provide some kind of protection against infection with SARS-CoV-2.

Currently, there are still many unknowns for SARS-CoV-2 and COVID-19. For sure, upper respiratory tracts are of great importance for the epidemiology of the viral infection and the course of the disease. Изключително важно значение за трансмисията на вируса. По-високи нива на вирусния товар са установени при изследването на носни проби в сравнение с гърлени проби. Тъй като патологични промени се наблюдават и в двете половини на белия дроб, това предполага вирусна дисеминация след първоначално инфектиране (21). Възможно е тази дисеминация към белия дроб да настъпва от първоначалната инфекция в надалната мукоза. Вероятно е след репликацията на вируса в носните клетки вирусните частици да достигат до белия дроб, където да предизвикат тежки изменения. При пациенти, починали от COVID-19, патохистологично са установяват тежки, дифузни алвеоларни изменения, които съответстват на acute respiratory distress syndrome (ARDS) (22). Наличието на АСЕ2 в клетките на конюнктивата предполага разпространението към дихателните пътища през назолакрималния канал (20).

Прикрепването и навлизането на коронавирусите в клетките се определя от вирусния (S) spike протеин. Неговата S1 субединица го свързва към рецептора, а S2 субединицата ръководи процеса на праймиране и срязване на S протеина, което позволява сливането на вирусните и клетъчните мембрани. Праймирането се осъществява посредством клетъчни протеази. SARS-CoV използва клетъчната серинова протеаза TMPRSS2 (23). SARS-CoV-2 също може да използва TMPRSS2 за S протеиново праймиране. Следователно разпространението на SARS-CoV-2 също зависи и от активността на TMPRSS2. TMPRSS2 е фактор на клетката гостоприемник, който е изключително важен за разпространението на няколко клинично значими вируса, включително вируси на грип A и коронавируси (23, 24, 25, 26). Установено е, че заещки серуми срещу S1 субединица на SARS-S намаляват както SARS-S-, така и SARS-2-S-предизвиканото навлизане с висока ефективност, като инхибираният на SARS-S-предизвиканото навлизане е по-ефективно. По този начин отговорите на антителата срещу SARS-S по време на инфекция или ваксинация могат да осигурят известна степен на защита срещу инфекция със SARS-CoV-2.

Към настоящия момент съществуват все още много неизвестни за SARS-COV-2 и COVID-19. Със сигурност ГДП са от съществено значение за епидемиологията на вирусната инфекция и за
Nasal mucosa plays an important role for the distribution of the virus for the individual and for the general distribution in the human population. Future investigations in the field are required. They will determine the specific mechanisms of interactions between the mucosa of the upper respiratory tracts and the virus.

References:


