



INVITED REVIEW

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): pathogenesis and virus-host interactions

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Ağır akut solunum yolu yetersizliği sendromu coronavirus 2 (SARS-CoV-2): patogenez ve virus-konak etkileşimleri

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Öz

Coronavirüsler son yirmi yıl içerisinde üç farklı dönemde salgına neden olarak küresel bir tehdit oluşturmuştur. İlk olarak 2003'te Ağır Akut Solunum Yolu Yetersizliği Sendromu (SARS-CoV) ortaya çıktı. Sonra 2012'de Ortadoğu Ağır Akut Solunum Yolu Yetersizliği Sendromu (MERS-CoV) tespit edildi. 2019 yılının sonlarında ise Ağır Akut Solunum Yolu Yetersizliği Sendromu Coronavirus 2 (SARS-CoV-2)'nin izole edildiği bildirildi. SARS-CoV ve MERS-CoV'a kıyasla çok daha şiddetli ve yaygın bir enfeksiyona neden olan SARS-CoV-2, aşı geliştirilinceye kadar küresel bir tehdit olmaya devam edecektir. SARS-CoV-2 salgınının hala devam etmesi nedeniyle, virus-konak etkileşimleri ve hastalığın patogenezi ile ilgili birçok konunun daha detaylı ele alınması gerekmektedir.

Anahtar kelimeler: Coronavirus, patogenez, etkileşim, konak, ace2

Abstract

Coronaviruses have posed a global threat in three different periods over the past two decades. Severe Acute Respiratory Failure Syndrome (SARS-CoV) was first revealed in 2003. Then, in 2012, Middle East Severe Acute Respiratory Failure Syndrome (MERS-CoV) was detected. In late 2019, it was reported that Coronavirus 2 (SARS-Cov-2) was isolated from Severe Acute Respiratory Failure Syndrome. SARS-Cov-2, which causes a much more severe and common infection compared to SARS-Cov and MERS-Cov, remains a global threat until the vaccine is developed. Owing to the ongoing outbreak of SARS-Cov-2, many facts regarding virus-host interactions and pathogenesis of disease, still needed to be addressed in more detail.

Keywords: Coronavirus, pathogenesis, interaction, host, ace2





Introduction

Coronaviruses have caused a global threat by causing epidemics in three separate periods in the last 20 years. Firstly, in Southeast Asia, North America, Europe and South America, severe acute respiratory syndrome (SARS-CoV) progressing with pneumonia, cough and dyspnea appeared (Leo et al 2003). Then in Middle East, severe acute respiratory syndrome (MERS-CoV) was detected connected with people traveling to Arabian Peninsula mainly (Zaki et al 2012). Finally, during late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing fever, dry cough, dyspnea and pneumonia was reported in China (Zhu et al 2020). The agent of coronavirus disease (COVID-19) causing a global epidemic is named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (CSG of the International 2020). Based on different views in studies carried out towards the origin of the agent, uncertainties about the reasons of COVID-19 still remain a mystery. Depending on many people exposed to the infection in a livestock market in Wuhan, China, COVID-19 is regarded as a zoonotic disease. Although there are studies stating that some bat and snake species are the reservoir for SARS-CoV-2, more studies are needed to make it clear (Cheng et al 2007, Ji et al 2020). On the other hand, SARS-CoV-2 infection is reported to be pangolin-based by 99% (Lam et al 2020). Patients with COVID-19 infection are the main source of the infection. In addition, the infected individuals without any symptoms could cause viral spreading (Hoehl et al 2020). This condition makes it difficult to control the infection. The main factor in transmission of the infection is the droplets spreading in the environment from the respiratory tracts (sneezing, coughing etc.) of individuals. COVID-19 still causes the death of hundreds in many countries from the day it was first detected. Virus reproduction number (R_0) is a value showing how many people could be infected in an environment where the agent is not present. This value used in calculating how contagious the virus is, reveals the size of the epidemic. When R_0 is calculated, numerous criteria is considered such as incubation period, ways of transmission, number of cases and loss of lives. Mortality and morbidity of COVID-19 should vary from country to country depending on many factors such as the age of population, population density, environmental conditions, travel and temperature. Around the world, R_0 value for COVID-19 is known to proceed between 1.4 and 3.9 at 95% confidence interval (Li et al 2020).

Virus-host interactions

Transmission of SARS-CoV-2 primarily happens by direct contact or droplets spreading with sneezing/coughing by an infected person. The first stage of the infection is fusion with cell membrane and then receptor binding expressed by cell hosts. Person to person transmission is believed to occur by connecting of the virus receptor binding areas known

as 'spike' onto host cell angiotensin converting enzyme 2 (ACE2) receptors. Spike proteins of SARS-CoV-2 have also been reported to be similar to SARS-CoV (Wan et al 2020). This data intensifies the fact that COVID-19 agent performs its entrance into host cells by ACE2 receptors. In a study, binding of ACE2 by spike proteins of COVID-19 has been reported as 10-20 times more compared to SARS-CoV (Wrapp et al 2020). Organs such as lungs, heart, liver, spleen, kidneys, brain and testicles express ACE2 (Baig et al 2020). These organs are among the potential targets of SARS-CoV-2. The agent has also been reported to penetrate through transmembrane protease serin 2 pathway (TMPRSS2) (Mahmoud et al 2020). Although more studies are needed, integrin has been regarded to have a potential role for SARS-CoV-2 to enter into host cells (Sigrist et al 2020). Besides, the agent has been regarded to have a binding function on spike proteins host cell sialic acid glycans and to be an alternative receptor to ACE2 (Robson 2020). In a study, SARS-CoV-2 RNA has been reported to localize within host mitochondria and nucleolus and that could play a role in viral replication and host-virus interaction (Wu et al 2020). According to this hypothesis, three important proteins of SARS-CoV-2 which can interact with fibrinogen and prothrombin, which have a role on blood coagulation and immune response regulation and which is released in *S.aureus* have been discussed. As a result, these proteins that might be homologous with N protein are believed to be effective in concealment of the virus from immune response (Sangith 2020). Cellular ways most affected by SARS-CoV-2 viral proteins in sensitive hosts have been revealed in a study by Li et al (2020). In this study, especially IL-8 induction of non-structural protein (nsp)10 has been reported to cause uncontrolled neutrophil infiltration and activation. In the same study, nsp10 has also been stated as a potential virulence factor. Chemical signals such as IL-8 and IL-6 cause the oscillation of inflammation mediators together with neutrophil chemotaxis induction. As numerous macrophage and neutrophil are found in alveolar cavity, the host might cause failure in vital organs of the individual (Kolaczowska and Kubes 2013, Wang et al 2020).

SARS-CoV-2 with a positive sense RNA, has a length of 29.9kb while it is 27.9kb for SARS-CoV and 30.1kb for MERS-CoV (De Wit et al 2016, Wu et al 2020). Within coronavirus genome, two polyproteins and 16 nsps as pp1a and pp1b are coded in the first ORF (ORF1a/b) including two third of RNA. Within the remaining part of ORF, structural and accessory proteins are coded. Rest of the genome happens to code critical structural proteins such as spike (S), membrane (M) and nucleocapsid (N) including several accessory proteins (Cui et al 2019). Some of the interactions caused by some of the important gene areas of the virus on the host cell are as follows:

ORF1a/b nsp1 in host cell and CCL5 in NF- κ B activation and



lung epitheliums might induce CXCL10 (IP10) and CCL3 expression. Also, they can make virus replication easier by deteriorating cellular RNA and block immunity responses (Connor et al 2007, Law et al 2007). ORF1a/b nsp3 plays a role in proteolytic function of viral polyproteins and synthesis of subgenomic RNA parts. On this area, papain-like protease2 could turn host cell ubiquitination process into advantage and provide the virus with new strategies (Baretto et al 2005).

ORF1a/b nsp5 is reported to cause apoptosis and growth interruption in human pneumocytes expressing 3CLpro by caspase3 and caspase9 activities (Lin et al 2006).

ORF1a/b nsp10 is regarded to be connected with depolarization of human embryo lung fibroblast mitochondria membrane infected by NADH 4L sub-unit and cytochrome oxidase II and common cytopathic effect (Li et al 2005).

ORF2 is the glycoproteins also known as peplomer whose spike proteins are located on viral membrane. It plays a crucial role in adsorption and penetration stages. These proteins have been reported to be effective in tropism, host range and virulence and to cause formation of multi-nucleated syncytia cells, IL-8 oscillation and severe acute lung failure by blocking renin-angiotensin way (Cheng et al 2007).

ORF3a is said to trigger apoptosis in lung epithelial cell lines, to be influential in regulating the fibrinogen released intracellularly and mRNA on Vero cell line, to induce neutralized antibody production, to have high immunogenic feature and to increase production of IL-8 promotor activity and inflammatory chemokines on A549 cell line (Kanzawa et al 2006, Law et al 2005, Tan et al 2005).

ORF3b might cause apoptosis and necrosis focal formations especially on Vero E6 cell line and inhibition of IFN- β expression (Khan et al 2006, Kopecky-Bromberg et al 2007).

ORF4 is a membrane protein. It participates in viral budding and releasing. In absence of growth factors, it is associated with induction apoptosis of Jurkat T cells and lymphopenia in SARS-CoV patients (Yang et al 2005).

ORF5 in M gene that is responsible for surface proteins. These proteins play crucial role in viral aggression and budding. It is believed to cause apoptosis in HEK293T cells with pressure of caspase inhibitors (Chan et al 2007).

ORF6 blocks the expression of genes activated by STAT1 while it inhibits IFN synthesis and signalization (Cheng et al 2007, Kopecky-Bromberg et al 2007).

ORF7a causes apoptosis by a caspase 3 dependent way on cell lines originated in lungs, kidneys and liver (Tan et al 2004).

ORF9 inhibits IFN- β synthesis and causes inflammation in lungs (Cheng et al 2007).

It would be worthwhile to mention coronaviruses' S protein in a little more detail. S protein, which has two subunits: S1 and S2, is associated with tropism, host spectrum, virus-cell membrane fusion (Soufi et al 2020). The accessory encoded by ORF8, and spike (S) protein which includes receptor binding-domain (RBD) encoded by the S gene, are components where recombination can be seen quite often (Cui et al 2019). This condition, which increases the importance of spike glycoproteins, shows that the virus has the potential to be effective in cross-species transmissions. (Ji et al 2020). In the S protein, it has also been reported that the furin-like cleavage region has an important function in viral replication and pathogenesis (Mahmoud et al 2020).

Pathogenesis

Coronaviruses generally cause respiratory and digestive system problems. For individuals with COVID-19, respiratory, hepatic, enteric and neurological findings are remarkable. In addition, severe pneumonia, acute heart failure, multiple organ failure and an increase in chemokine/leucocyte/cytokine values progressing together with abnormal respiratory symptoms have been reported (Rothan et al 2020). In contrast to SARS and MERS infections, COVID-19 patients have been regarded as asymptomatic despite high biochemical values in terms of viral load (Holsue et al 2020). The estimated incubation period of the illness is 1-14 days (Huang et al 2020). COVID-19 threats especially older individuals (over 65 years of age) while it can be deadly for patients with masked/chronic hypertension, diabetes and heart and lung disorders. In fatal cases, findings such as cytokine storm, coagulation dysfunction and metabolic acidosis might be seen (Guo et al 2020). In lungs, histopathological symptoms are interstitial lymphocyte infiltration, multi-nucleated giant cell formation related with pneumocytes, alveolar fibrin accumulation, viral particle formation in pneumocytes, cytoplasmic vacuolization in pulmonary arteries, alveolar hemorrhage and capillary congestion (Tabary et al 2020). In lungs and cardiovascular system, heart disorders such as acute myocardial damage triggered by SARS-CoV-2 infection related with commonly expressed ACE2 might be seen. Since ACE2 is commonly found in enterocytes and glandular epithelium cells, stomach, duodenum and rectum is also affected by COVID-19. Patients mostly display intestinal ischemia due to thrombosis in small veins (Bhayana et al 2020). Also in COVID-19 in liver, similar pathological findings have been detected as in SARS and MERS (Xiao et al 2020, Xu et al 2020). In kidneys, it causes proximal acute tubule failure, vacuole degeneration, tubular necrosis, lymphocyte infiltration, interstitial fibrosis in cortical parenchyma and hyperplasic epithelium cell formations (Diao et al 2020, Peleg et al 2020). It has also been reported to cause viral exanthema like lesions and skin changes oc-





curing due to vascular defects (Suchonwanit et al 2020). In these cases, perivascular dermatitis, mucin accumulation in dermis/hypodermis and necrosis in keratinocytes stand out histopathologically. Decreasing of cell composition in spleen, atrophic white pulps, neutrophils and plasma cells infiltration, decrease or absence of lymphoid follicles can be seen (Feng et al 2020, Xu et al 2020). In glial cells and neurons, expressing ACE2 receptors puts the central nervous system into target position against SARS-CoV-2. Symptoms such as dull anosmia, ageusia, twitching, seizures and especially white matter hemorrhage, axonal damages, leucocyte infiltration and common acute perivascular encephalitis have been found (Das et al 2020, Reichard et al 2020, Varatharaj et al 2020).

Conclusion

More studies need to be carried out for individuals who recovered from COVID-19 infection. Studies on potential animal hosts that could play a role in preventing and controlling this disease should be increased. Compared to SARS and MERS, unless a specific treatment and vaccine against COVID-19 that causes a much more severe and common infection is found, the illness will continue to be a global threat. This new viral pathogen has directly or indirectly challenged the economy and public health of all states around the world. In the future, the potential for such outbreaks is very high. Therefore, while fighting the current epidemic, it is necessary to be more prepared for new viral epidemics that may occur in the future.

Conflict of Interest

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During this study, any pharmaceutical company which has a direct connection with the research subject, a company that provides and / or manufactures medical instruments, equipment and materials or any commercial company may have a negative impact on the decision to be made during the evaluation process of the study. or no moral support.

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