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Review Article

Patho mechanism in SARS-CoV-2 infection in neurological, renal and respiratory systems: insights from the ground

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Abstract

SARS-CoV-2, a viral infection from the family of corona viruses, is in the news from the fourth quarter of 2019 because of its infectivity. It is probably the biggest pandemic in terms of affected population in the history of humankind, infecting 25 million already and killing close to 1 million people worldwide till writing this review. It is well known that this virus spreads and infects predominantly the Bronchopulmonary system. But, what is less well known is that a for a significant portion of the population the infection spreads to the central nervous system, renal system and respiratory system with significant symptoms. This review explores the pathomechanism of infection in SARS-CoV-2 in these systems. Herein recent information from researchers as well as clinical practitioners has been correlated to establish the symptomatic trend and likely mechanism of infection in the three organ systems.

Keyword: Pathomechanism, Neurological, Humankind, Coronavirus, Mechanism.

1. Introduction

COVID-19, officially designated as severe acute respiratory syndrome 2 (SARS-CoV-2), is a beta coronavirus. It shares the same family with the previously reported coronaviruses of human significance, namely; severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) and very similar pathogenesis [1-4]. SARS-CoV-2 and SARS-CoV share 76% sequence homology [1]. All the related coronaviruses share the basic structure of their spike proteins (S) These proteins expressed on the surfaces are responsible for their attachment to the angiotensin converting enzyme 2 (ACE2) ubiquitously present on the surface of human cells for the viral entry [5]. Related coronaviruses like MERSCoV enters into the host human cells through binding to the surface protein, dipeptidyl peptidase 4 (DPP4) [6]. Animal experiments have suggested that the entry of SARS-CoV-2 entry into cells is dependent on the receptor ACE2) as well as a compatible protease like surface protein transmembrane serine protease 2 (TMPRSS2) [7-15]. SARS-CoV-2 is known to use ACE2 followed by priming of the spike protein of the virus by TMPRSS2 [12]. Both the proteins ACE2 and TMPRSS2 are co-expressed in bronchial transient secretary cells and sustentacular cells in the human olfactory neuro-epithelium [8, 13, 14]. Similarities between spike protein of SARS-CoV-2 and that of HIV-1 namely gp120 and Gag have also been reported [7-10]. All though spike proteins role in the infective process is not clear, it plays important role in entry of Sars-Cov-2 in cells. We are summarizing below the path mechanisms of Sars-CoV-2 in three major organ systems.

Patho mechanism in nervous system

Current body of evidence shows that neurotropism is a common trend among all beta coronaviruses including SARS-CoV, MERS-CoV as well as human coronavirus 229E (HCoV-229E) [11]. SARS-CoV2-RNA has been detected in cerebellum from the right hemisphere in brain through real time-polymerase chain reaction (RT-PCR). This is accompanied by massive bleeding detected by imaging techniques [16-24]. It is to be noted the ACE-2 receptors are present in the cerebral vascular epithelium and regulated the cerebral blood pressure through local vasodilation. It is entirely possible that the

ACE-2 receptors are taken out/inactivated by SARS-CoV-2 spike protein in the cerebral vessel epithelium, causing elevation of blood pressure and as a consequence vessel rupture [24]. SARS-CoV-2 has been detected in brainstem an area that contains the nuclei regulating the respiratory rhythm. The CNS received CO2 and O2 related information from chemoreceptors and increase or decrease respiratory effort [25, 26]. The brainstem has connection with the respiratory system. Invasion and disruption of this area can contribute to decrease in involuntary breathing. Indeed, anecdotal evidence from a 24-year-old graduate student from Wuhan University supports this view point. The student, who was infected and subsequently recovered, reported to have temporarily lost her natural ability to breath. She had to stay awake and breath consciously and actively during the intensive care at the hospital [5]. It is quite possible that the neuro-invasion rather than or in combination with direct lung invasion is at least partially responsible for the respiratory failure commonly seen COVID19 patients.

ACE-2 messenger RNA (mRNA) is present virtually everywhere including oral and nasal mucosa, nasopharynx, lymphoid tissue, renal and urinary tracts well as brain [16]. In the initial period of infection, the SARS-CoV-2 can enter the nervous system through the cranial nerves of the olfactory system (cranial nerve I), eye (cranial nerve II), and tongue (cranial nerve VIII and IX) simply because these nerve endings are exposed to the viral mist which is the primary route of transmission. Indeed, early report from the isolation unit for SARS-CoV-2 at Tell Aviv Medical Center indicate about 35.7% of the patients experience loss of smell (anosmia), and 33.3% of the patients reported distortion of taste (dysgeusia). These symptoms happened in the early stages of infection with a median of 3.3 days of onset of illness in contrast with the common cold influenza, in which case the symptoms appear post infection [8]. The reported anosmia and dysgeusia are short-lived, disappearing within 7 days, while the recovery takes several weeks to months. Some researchers believe that the anosmia and dysgeusia are results of infection of local non-neuronal cell types though this view is being seriously disputed by the confirmation of SARS-CoV-2 in cerebrospinal fluid through genome sequencing [19, 20]. Regardless of the route of nervous invasion of the SARS-CoV-2, the most commonly sensations affected to be anosmia and dysgeusia and these symptoms are being suggested as a possible pre-screening tool [21, 22]. SARS-CoV-2 infection to the eye is also reported and proven through reverse transcriptase-polymerase chain reaction of the conjunctival swab [27, 31]. The manifestations include epiphora (overflow of tear on face), conjunctival congestion, chemiosmosis etc. The SARS-CoV-2 mRNA has been detected from conjunctival swab albeit only in a very small number of patients with the disease. Though the conjunctival tissue is exposed to the viral mist (from cough etc.) and the virus might transmit through the conjunctival route, evidence suggests that conjunctiva is neither common route of transmission, nor the preferred tissue for it [23]. The probability of hematogenous and lymphatic route of neuro-invasion looks rather remote given that no viral particle in similar corona virus infections could be detected historically in non-neuronal cells in the infected brain areas [27, 28].

Patho mechanisms in renal system

Kidney damage or renal infection is relatively rare among SARS-CoV-2 patients, but renal failure is closely related to fatality [29]. In-vitro evidence from DNA sequencing indicates that ACE-2 inhibiters are expressed in proximal tubule and glomerular parietal cells. Just like the case of other organs, SARS-CoV2 invasion of kidney takes place through attachment to ACE-2 receptors on cell surface followed by priming by TMPRSS2. Single cell transcriptome analysis clearly identifies that podocytes and proximal straight tubule cells serves as the host cells for kidney infection for SARS-CoV-2 [32-34]. These are the cells, in which ACE-2 and TMPRSS-2 co-expression occurs in kidney. Imbalance in ACE-2 expression, renin-angiotensin system (RAS) activation and neutrophil related process are involved in SARS-CoV-2 path mechanisms of kidney injury [29]. The renal tubular epithelium, once infected and injured, upregulates interleukin-6 (IL6) [30]. Elevated levels of IL-6 can be detected in serum of humans and animals and harms human body in many ways including through inflammatory and autoimmune mode and the condition is known as cytokine release syndrome (CRS or cytokine storm) [30, 31]. CRS occurrence is widely reported in SARSCoV-2 cases from the early stages [31, 32]. Acute kidney injury (AKI) can happen in CRS through direct kidney lesion, cardio-renal syndrome, renal medullary hypoxia, tubular toxicity, renal hypoperfusion and endotoxin mediated septic AKI [30]. AKI and CRS each can be the cause of the other, but CRS is a systemic condition that cause a much broader damage in the body including lung. AKI has been correlated with higher alveolar capillary permeability and pulmonary haemorrhage [29-31]. The entry of SARS-CoV-2 in systemic circulation is a key process that precedes AKI by 7 days [33, 34].

Patho mechanisms in respiratory system

SARS-CoV-2, caused a series of acute atypical respiratory diseases in Wuhan, Hubei Province, China. The novel corona virus caused by this virus was termed COVID-19. Corona virus is transmittable between humans and has caused pandemic worldwide. The count of death tolls has been continuing to rise and many countries have been forced to do social distancing and lockdown. Shortage of targeted therapy continues to be a problem. Novel corona virus epidemiological studies showed that elder patients were more susceptible to severe diseases, while children tend to have milder symptoms. The current knowledge about corona disease and considered the potential explanation of the different symptomatology between children adults and old age [35]. Corona viruses are responsible for infections of the respiratory tract, such as influenza, bird flu, swine flu, but also coronavirus is not primarily cytopathogenic. Novel corona virus-infected epithelial cells have to be eliminated by the body's own defence mechanisms e.g. macrophages, killer lymphocytes etc. Study requires an increase of permeability of the capil-

lary bed in which - mediated by proinflammatory cytokines (LOX, COX, PGE2, LTB4, Il2). An excessive production of these proinflammatory cytokines (cytokine storm) leads to an increased permeability of the capillary bed in many organs – resulting in multiorgan failure and death. Successful therapy requires a mitigation of the over expression of cytokines in the entire body. Disease can be prevented by corticosteroids with known side effects. However various herbal extracts (cineol, triterpenes) have been found to block the production of these proinflammatory cytokines effectively [36].

Corona viruses have been known for a long time to induce airway obstruction in asthmatic patients, but not in healthy subjects. Adenosine-monophosphate (AMP) mechanism is indirectly occurs via its decay product, adenosine, which attaches to mast cells through its low-affinity receptor A2B to release histamine, ultimately causing smooth muscle contraction. This mechanism of adenosine action reveals its proinflammatory function, which may play important role in asthma. Adenosine deaminase (ADA) an enzyme decomposing adenosine causes asthma-like disorder with elevated IgE, eosinophilia and airway hyperresponsiveness [36]. Human clinical studies showing elevated adenosine levels in bronchoalveolar lavage and exhaled breath condensate of asthmatics as compared to healthy people. Certain human ADA phenotypes are associated with prevalence of asthma. Present data suggest a protective role for ADA and a pro-inflammatory function for adenosine in asthma. The function and importance of adenosine in inflammatory processes, however, is not unequivocal. In vitro studies have shown adenosine binding to its high-affinity receptor A2A, which results in inhibition of leukotriene synthesis or function of adhesion molecules. It is very much possible that the concentration of adenosine in lung tissues determines whether it promotes or reduces inflammation. The role of adenosine and adenosine receptors in asthma and other pulmonary disorders is well established [35]. Adenosine is associated with other respiratory diseases such as fibrosis, sarcoidosis, cystic fibrosis or tuberculosis. Recognition of adenosine receptor subtypes and their role in the patho mechanisms of respiratory diseases can provide new targets [37].

In summary, the patho mechanisms of Sars-Cov-2 are being elucidated in various human organ system. This understanding can greatly help in identification of new therapeutic targets for development of effective therapies for COVID-19 infections.

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