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Journey of SARS-CoV-19 from Mucosa Towards Angiotensin-Converting Enzyme2 Pathway: A Review

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ABSTRACT

The disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or simply corona virus disease-2019 (COVID-19), has rapidly spread throughout the world. World Health Organization declared a global health emergency on January 30, 2020 announcing it as a Pandemic. The outbreak of the disease has posed serious health threat. A search was conducted for review which included various articles from 2019 to 2021 in PubMed/MEDLINE with keywords ACE2, 2019 NCOV, pandemic, physiopathology, SARS, Transmission. Both humoral and acquired immunity are targeted by the virus during progression of diseases. A cellular biology perceptive of pathogenesis is useful for framing clinical course of the diseases and its related complication. Knowledge of underlying pathophysiology regarding release of innate immune modulators such as CXCL10, beta and alpha interferons will facilitate the development of therapeutic modalities in future. Despite implementing all the preventive efforts SARS-CoV-2, exponential mode of infection rate is still existing with epidemic doubling time less than a week. In this review, an update on pathophysiology, cell biology of virus and immune modulation related to diseases are considered and has been described. Any of the mechanisms and assumptions discussed in the article and in our understanding of SARS-CoV-2 may be revised as further evidence emerges.

Keywords: ACE2; 2019 NCOV; pandemic; physiopathology; SARS; transmission.

INTRODUCTION

SARS-CoV-2 is responsible for atypical respiratory illness. It causes gastrointestinal and respiratory symptoms along with involvement of other organs.[1] In January 2020, WHO declared Cov-2 outbreak as sixth health emergency of global concern. SARS CoV-2 is positive-stranded RNA virus which is inherently categorized into four types depending upon genomic configuration; Gamma, Delta, Beta and Alpha. Initially, infection was considered to be zoonotic spread which eventually lead to human to human transmission,[2,3] although exact mechanism of transmission is still unknown. It is believed that there are direct and indirect ways of transmission. First mode of transmission is via direct contact with patient and their secretion whereas secondly through viral infected surfaces and objects.[4] Epidemiological studies have shown that mortality is higher in elderly patient and incidence of disease is much lower among children.[5,6] The reason for this difference remains elusive. Few hypothesis discuss this difference concerning pathophysiology of disease. Recent reports suggest that expression level of Angiotensin converting enzyme 2 (ACE2) is high in well differentiated ciliated epithelium, which are less developed in children than in adults. Presence of other viruses in epithelium, competes with SARS-CoV-2 in children that might limit growth of virus, making children less susceptible for the diseases.[7,8]

SARS CoV-2 STRUCTURE, LIFE CYCLE AND RELATED VIRULENCE

It is an enveloped β-coronavirus, with a genetic sequence very similar to SARS-CoV-1 (80%). SARS CoV-2 undergoes several stages of infection during its life cycle. The life cycle of the virus with host consists of following five steps; attachment, penetration, biosynthesis, maturation and release. Once virus binds to host receptor (attachment), they enter host cell either through membrane fusion or endocytosis (penetration). Once virus enter into host cell they release their content and viral RNA starts replicating into host nucleus. The viral mRNA are used for synthesis of viral protein (biosynthesis) and gets mature and released. [9] The virion has four structural protein namely S (spike), E (envelope), M (membrane), and N (nucleocapsid).[10] The S, E and M protein constitutes for viral envelope. Envelope (E) of virus

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is coated by spike(S) glycoprotein, and membrane (M) proteins. S protein mediates viral entry and binding to the host cell. S protein is composed of two functional subunits (S_1 and S_2).[11] When virus binds to a host cell through its target receptor the first step of infection occurs. Receptor binding domain of sub-unit (S1) is present on S protein which binds to the peptidase domain of ACE2. For S protein priming the virus uses serine proteases TMPRSS2 (transmembrane protease serine 2) thus, infecting the target cells[12] The spike protein needs to be cleaved by cellular proteases from the S1/S2 cleavage site to facilitate virion attachment and fusion to the cell membrane. Unfortunately, the molecular analysis of S proteins identified an insertion of extra genetic content at S1/S2 site. However, this insertion was not present in other variant of SARS-CoV.[13] It is believed, this unique insertion is helping virus for an easy cell infection and rapid spread in human host. Higher viral loads were reported with virus containing G614 variant of S protein thus postulating increased infectivity and transmissibility of the virus. When compared with SARS-CoV-1, SARS-CoV-2 has a higher reproductive number, resulting much more efficient spread.[14, 15] However, because of difference in surface protein structure of SARS-CoV-2 enables stronger binding to the ACE2 receptor and has greater efficiency at invading host cells.[16] Peak viral (SARS-CoV-2) load is noted at the time of symptom onset or in the first week of illness thereafter subsequent decline is observed. This fact favors the highest infectiousness potential just before or within the first five days of symptom onset. Study by Wolfel et al. suggests that viral culture from PCR positive upper respiratory tract samples rarely shows positive beyond nine days of illness. Even detection of virus from RNA by quantitative reverse transcription polymerase chain reaction (qRT-PCR) does not necessarily equate to infectiousness.[16] Whereas, in case of SARS-CoV-1 onset of symptoms occur in the second week of illness resulting in minimal contagiousness in the first week after symptom onset thus enabling early detection of viral infection.[17] Severity of illness depends upon duration of viral RNA shedding, prolonged virus shedding is seen in severely ill or immune-compromised patients. Relatively, intermittent RNA shedding is evident in patient with mild illness. While in asymptomatic individuals infectiousness seems to be limited but are vulnerable for the transmission of infection.[18-20]

A CELL BIOLOGY PERCEPTIVE OF SARS CoV-2 PATHOGENESIS

Understanding of viral pathology from the cellular perceptive is important in framing the clinical course of diseases and focusing on areas of respiratory tract involvement. Depending upon the cell that are infected, SARS CoV-2 can be divided into 3 stages which correlates with clinical courses.[21] Initial stage (asymptomatic phase) inhalation of virus, attachment to the host respiratory epithelium (nasal mucosa) and starts replicating. ACE2 in the ciliated epithelium functions as a receptor and local propagation of the virus is possible but with limited initiate immunity response. However, being a single stranded RNA virus the expression of ACE2 do not correlate with viral load.[22,23] Symptomatic phase (upper respiratory involvement) robust innate immunity is triggered once the virus propagates and migrates down to the respiratory tract along with conducting airways. Presence of SARS CoV-2 infected cells with expression of cytokines such as beta, lambda interferon and CXCL10 warrants the useful marker of diseases. Hence determining the innate immune markers might predict the diseases and can be utilized for more aggressive monitoring.[24,25,26] Progression towards acute respiratory distress syndrome(stage 3) virus reaches lungs and starts infecting type II alveolar cells.[27,28] Release of large amount of viral particles causes the cells to undergo apoptosis thus enabling ground glass opacity in chest Xray. Type II alveolar cell is considered as precursor cell for type I, end result is likely a self-replicating pulmonary toxin damaging adjacent cells.[29,30] Diffuse alveolar damage, formation of hyaline membrane and secondary epithelial regeneration are main consequences of involved pathogenesis in this stage of infection.[31,32] Significant knowledge gap regarding the cellular biology of SARS CoV-2 still exists, which needs to be addressed in future with evidence based research.

TRANSMISSION PORTALS AND MECHANISM

Target host receptors are resided in human respiratory tract epithelium, (oropharynx and upper airway) and acts as transmission portals. Similarly, conjunctiva and gastro intestinal tracts are also viable for infection and transmission. Primary mechanism of transmission of SARS-CoV-2 via viral infected respiratory droplets like other corona viruses. Inhalation, direct or indirect contact on related surfaces, causes entry of virus through mucosa.[33] Close contact ranging (15 minutes face to face and within 2m), spread of virus through households, gathering are some of the major cause for the virus transmission. However, sleeping in the same room as with infected individual, poorly ventilated indoor settings increases the risk of infection.[34] According to a systematic review, super spreading events occurred indoors.[35-39] Both SARS-CoV-2 and SARS-CoV-1 remain viable for many days on smooth surfaces (stainless steel, plastic,

glass) and at lower temperature and humidity.[40,41] Combination of preventive measures such as physical distancing, tracing, and self-isolation, emphasizing on use of disinfectants, hand washing are regarded as preventive tools which need to be continued to reduce the contamination of virus.

PATHOGENESIS

Cytokine storm Cytokines normally mediate and regulate immunity, inflammation, and haematopoiesis; however, further exacerbation of immune reaction and accumulation of cytokines in other organs in some patients may cause extensive tissue damage, or a cytokine release syndrome (cytokinestorm), resulting in capillary leak, thrombus formation, and organ dysfunction.[42, 43]

SARS-CoV-2 binds to ACE2, the host target cell receptor. Active replication and release of the virus in the lung cells lead to non-specific symptoms such as fever, myalgia, headache, and respiratory symptoms.[44] Transient damage to olfactory epithelium leading to olfactory dysfunction causing loss of taste and smell. Presence of ACE2 receptors on different organs determines the site of infection and related clinical manifestations.[45] Postmortem of the patient who died of Covid 19,upon examination of lungs, liver, heart, and kidney revealed Lymphocytic endotheliitis as well as myocardial infarction and liver cell necrosis.[46] Whether these pathological changes in respiratory epithelium, endothelium is due to direct consequence of viral infection, cytokine storm, coagulopathy or are multifactorial is still unknown. Further research is needed to conclude the exact mechanism for these changes.

IMMUNE RESPONSE AND DISEASES PROGRESSION

Entry of virus produces initial inflammatory mediators which attracts virus specific T cell at the site of infection causing elimination of infected cells thereby withholding the virus spread, leading to recovery in most of the patient.[47] Post mortem evidence confirms the inflammatory nature of injury by presence of bilateral alveolar damage, hyaline-membrane formation, interstitial mononuclear inflammatory infiltrates, and desquamation in accordance with ARDS (acute respiratory distress syndrome). Following the study using post mortem detail, they found that presence of mucus plugs with fibrinous exudate in the respiratory tract, even in young adult approves the severity of SARS Cov2 infection. Overproduction and accumulation of pro inflammatory cytokines into lung parenchyma results in damage of lungs. Release of highly sensitive troponin and natriuretic peptide causes cardiovascular complications.[48,47] Evidence of focal intra-alveolar hemorrhage and presence of platelet-fibrin thrombi in small arterial vessels were also observed in post mortem examination which might lead to stroke in some patient.[49,50] Multi organ involvement and related complication regarding the infection is associated with presence of ACE2 or is due to consequences of immune response have to be discussed further with recent updates.

FUTURE DIRECTION

Implication of additional knowledge, research and evidence are needed for better understanding of underlying pathophysiology of diseases and cellular biology of virus. Efforts are underway to know better about immune modulation of the host towards the infection and related severity. A handful of literature focusing on determinants of diseases severity needs further evaluation.

Conflict of Interest: None.

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