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Pathophysiology of COVID-19: literature of Review

A report

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Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus. Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease,

and cancer are more likely to develop serious illness. (***World Health Organization ,2019)***.

Pathophysiology

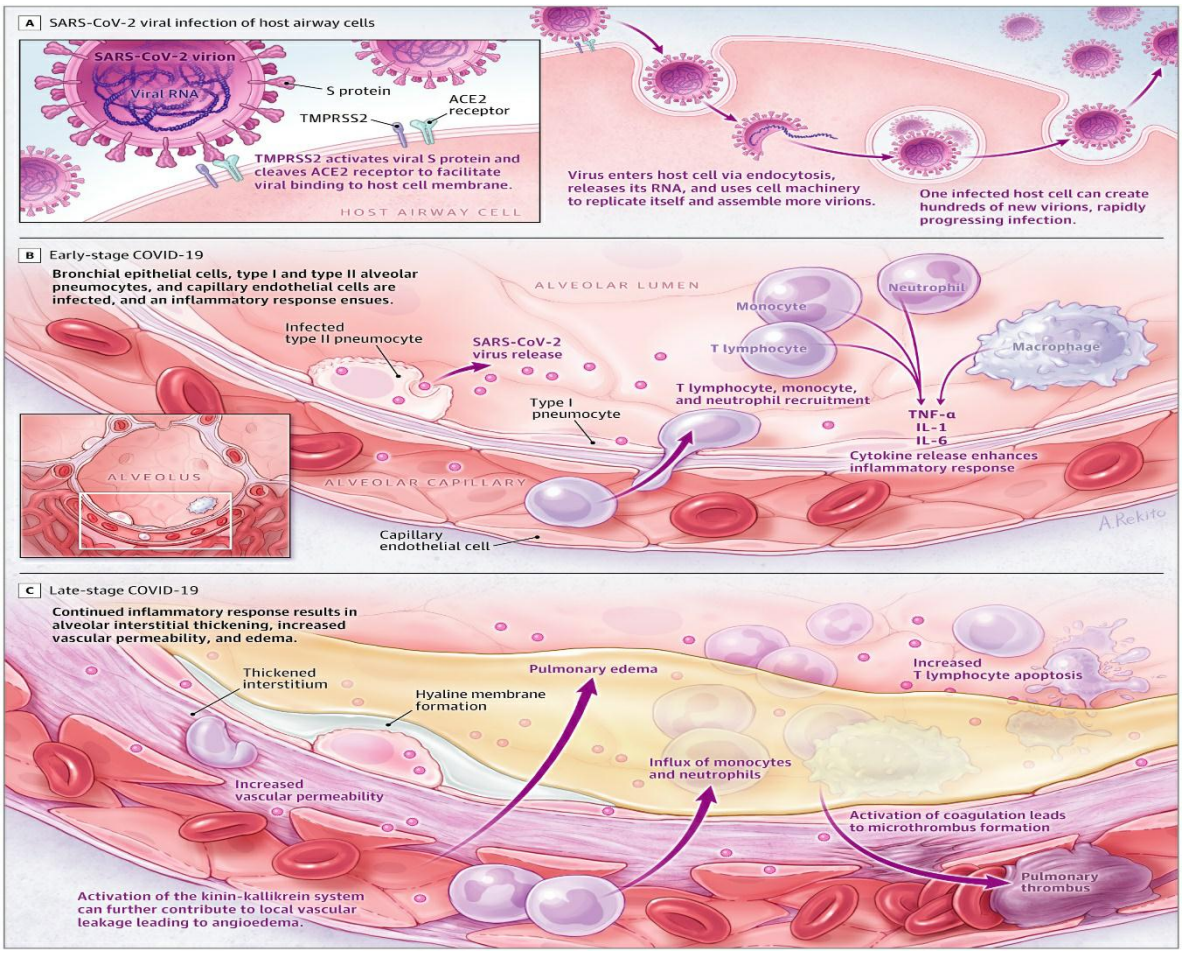
Coronaviruses are large, enveloped, single-stranded RNA viruses found in humans and other mammals, such as dogs, cats, chicken, cattle, pigs, and birds. Coronaviruses cause respiratory, gastrointestinal, and neurological disease. The most common coronaviruses in clinical practice are 229E, OC43, NL63, and HKU1, which typically cause common cold symptoms in immunocompetent individuals. SARS-CoV-2 is the third coronavirus that has caused severe disease in humans to spread globally in the past 2 decades. ***(Zhu N, Zhang D, Wang W, et al; China Novel Coronavirus Investigating and Research Team).***

The first coronavirus that caused severe disease was severe acute respiratory syndrome (SARS), which was thought to originate in Foshan, China, and resulted in the 2002-2003 SARS-CoV pandemic. (***Zhong NS, Zheng BJ, Li YM, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003).***

The second was the coronavirus-caused Middle East respiratory syndrome (MERS), which originated from the Arabian peninsula in 2012***. (Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia).***

SARS-CoV-2 has a diameter of 60 nm to 140 nm and distinctive spikes, ranging from 9 nm to 12 nm, giving the virions the appearance of a solar corona (Figure 2***). (Goldsmith CS, Tatti KM, Ksiazek TG, et al. Ultrastructural characterization of SARS coronavirus) .***

Through genetic recombination and variation, coronaviruses can adapt to and infect new hosts. Bats are thought to be a natural reservoir for SARS-CoV-2, but it has been suggested that humans became infected with SARS-CoV-2 via an intermediate host, such as the pangolin. ***(Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet.)***



Immunopathogenesis of Coronavirus Disease 2019 (COVID-19) Current understanding of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–induced host immune response. SARS-CoV-2 targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. The serine protease type 2 transmembrane serine proteas (TMPRSS2) in the host cell further promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein. In the early stage, viral copy numbers can be high in the lower respiratory tract. Inflammatory signaling molecules are released by infected cells and alveolar macrophages in addition to recruited T lymphocytes, monocytes, and neutrophils. In the late stage, pulmonary edema can fill the alveolar spaces with hyaline membrane formation, compatible with early-phase acute respiratory distress syndrome.

When 2019-nCoV enters the human body, it interacts with ACE2 receptors and releases its RNA inside the epithelial cells (ECs), where it replicates and is released for further infection to neighboring cells and spread from nasal passage to alveolar area of lung . (***Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective***)

The gaseous exchange is mediated by alveoli but due to 2019-nCoV infection, there is a vascular integrity defect (increased permeability and leakage), which causes pulmonary edema, activation of disseminated intravascular coagulation (DIC), pulmonary ischemia, hypoxic respiratory failure, and progressive lung damage.(***Teuwen LA, Geldhof V, Pasut A, Carmeliet P. Author correction: COVID-19: the vasculature unleashed).***

Furthermore, it enters the blood from the respiratory tract through infecting ECs and travels throughout the different parts of the body including the brain, gastrointestinal tract, heart, kidney, and liver that may lead to cerebral hemorrhage, neural disorder, ischemic stroke, coma, paralysis, and eventually death.(***Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response***).

Moreover, the vulnerability and severity of 2019-nCoV infection in individuals is highly impacted by comorbidities including hypertension, diabetes, and lung diseases, and also linked with age and dysregulated innate immune response. This may be due to enhanced expression of ACE2 receptor (an integral membrane protein) on the surface of several organs, including the lung, heart, kidney, intestine as well as ECs of the host***(Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19***).

The 2019-nCoV infects ECs through binding with ACE-2 and initiates localized inflammation, endothelial activation, tissue damage, and disordered cytokine release. The severe aggravation of the “cytokine storm” through secretion of vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), and reduced E-cadherin expression on ECs contribute to vascular permeability and leakage, which participate in the pathophysiology of hypotension and pulmonary dysfunction in acute respiratory distress syndrome (ARDS). The majority of the COVID-19 patients die due to ARDS, where pulmonary ECs contribute to the start and broadcast of ARDS by changing vessel barrier integrity, supporting a procoagulative condition, inducing vascular

inflammation and reconciling inflammatory cell infiltration.(***Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation***).

In brief, (a) the 2019-nCoV can directly affect ECs that exhibit widespread endotheliitis characterized by EC dysfunction, lysis, and death, (b) Furthermore, to enter the host cells, 2019-nCoV binds to the ACE2 receptor, which reduces the activity of ACE2, which indirectly turns on the kallikrein-bradykinin pathway with increased vascular permeability, (c) activated neutrophils, recruited to pulmonary ECs, produce histotoxic mediators including reactive oxygen species, (d) immune cells, inflammatory cytokines, and vasoactive molecules lead to increased ECs contractility and loosening/gap of interendothelial junctions, (e) the cytokines IL-1β and tumor necrosis factor (TNF) activate glucuronidases that degrade the glycocalyx but also upregulate hyaluronic acid synthase 2, leading to increased deposition of hyaluronic acid in the extracellular matrix and promoting fluid retention.(***Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation***)

Moreover, the high levels of cytokines intensify the destructive progression that leads to additional ECs dysfunction, DIC, inflammation, and vasodilation of the pulmonary capillary bed. Altogether, these disorders

ultimately lead to multiorgan failure and death due to alveolar dysfunction and ARDS with hypoxic respiratory failure. Moreover, it has been proposed that denudation of the pulmonary vasculature could lead to activation of the complement system, promoting the accumulation of neutrophils and proinflammatory monocytes that enhance the cytokine storm, which was also observed during influenza virus infection where pulmonary ECs induce an amplification loop, involving interferon-producing cells and virus-infected pulmonary ECs**(** ***Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet.)***

Normalization of the vascular wall through metabolic interventions could be considered as an added route of intervention and paves the way for future therapeutic opportunities along with anti-inflammatory, anti-cytokine drugs, and ACE inhibitors etc.[67] However, some additional indirect evidence also suggests a link between ECs, pericytes, and COVID-19. Therefore, the consequences of 2019-nCoV on the entire vasculature require more study.*(* ***Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective).***

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