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Pathogensis of Covid-19: An Update

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ABSTRACT

The vital step for life cycle for any kind of virus is an attachment and ensuing entry in the cell of the host. It has been proved the attachment of SARSCoV2 is attained by interlinkage of ACE -2 (angiotensin converting enzyme 2) and spike surface S glycoprotein. the impetus of the viral storm plummets on the distal airways, alveoli of lung, having elevated expression of ACE2, especially in the pneumocytes that is type II pneumocytes. Damage to type pneumocytes causes release inflammatory mediators stimulate macrophages to release cytokines such as IL-1(interleukin-1) , IL-6(Interleukin-6), tumor necrotic factor alpha(TNF- α) causing cytokine storm these cytokines come to blood stream and cause endothelial cells to undergo dilatation increasing capillary permeability leading to leaking of plasma into interstitial spaces and potentially into the alveoli.It can also affects other organs such as brain, heart, kidneys and by causing systemic inflammatory response (SIRS) can cause multiorgan failure.

Keywords: *COVID-19, ACE-2, Cytokines*

INTRODUCTION

COVID-19 caused by coronavirus is a single-stranded RNA virus. Some of the Studies show evident immunological foundation for COVID-19 infection. Coronavirus can affect multiple organs mainly it affects lungs it can also involve heart, kidney, brain, gastrointestinal system and also skin can be affected. Subjects with co-morbid conditions are affected more and can have severe disease. Coronavirus can spread via aerosols, droplets and virus uses respiratory pathways to organize respiratory tract infections locally and can also lead to systemic disease. It can also occur through faeco-oral route. Regarding the pathogenesis of COVID-19 infection there is entangled reciprocity and equity between immunological, inflammatory and hemostatic reactions. Lymphopenia and neutrophiliais seen on haematological examination in cases of COVID-19 which indicates indirectly corroboration of immunological element for this infection. The incubation period varies from 4-14 days. The vital step for life cycle for any kind of virus is an attachment and ensuingentry in the cell of the host. It has been proved the attachment of SARS-CoV-2 is attained by interlinkage of ACE -2 (angiotensin-converting enzyme 2) and spike surface Sglyco protein. (ACE-2) is a carboxy peptidase on membrane that is uniformly present in diverse human tissues. Serine protease TMPRSS2 and protease furin are also thought to be neccessary for the entry of the virus.SARS-Cov-2 through S Spikes attaches to ACE-2 and it is not astonishing that the impetus of the viral storm plummets on the distal airways, alveoli of lung, having elevated expression of ACE-2, especially in the pneumocytes that is type II pneumocytes.[1]

After entering into type 2 pneumocytes virus releases single stranded RNA (ssRNA) in the cytoplasm after releasing of the ssRNA it can utilize the host cell ribosomes and can take mRNA leading to the process of translation and there is conversion of ssRNA into specific polyproteins. ssRNA (positive sense) utilizes RNA dependent RNA polymerase(RdRp) means take RNA and synthesize more RNA. ssRNA will make more ssRNA. Polyproteins get converted into all the component of the virus that is the nucleocapsid, specific enzymes, spike proteins. Specific proteolytic enzymes are required for making this whole viral structure. These enzymes are the proteases which are going to proteolytically cleave these poly proteins to make the structure of the virus. So with the proteolytic cleavage the nucleoscapsid structure formed with synthesis of ssRNA makes tons of viral particles destroying the type II pneumocytesin the process. Damage to type pneumocytes causes release inflammatory mediators stimulate macrophages to release

cytokines such as IL-1(interleukin-1) , IL-6 (Interleukin-6), tumor necrotic factor alpha(TNF-α) causing cytokine storm these cytokines come to blood stream and cause endothelial cells to undergo dilatation increasing capillary permeability leading to leaking of plasma into interstitial spaces and potentially into the alveoli. Fluid accumulates outside the alveoli it will try to compress the alveoli and some of the fluid enter into the alveoli causing alveolar edema drowning out the surfactant increasing the surface tension.[2] Due to increased surface tension , applying laplace's law which states pressure is equal to two times the tension divided by the radius. As surface tension increases it increases the collapsing pressure leading to alveolar collapse. Alveolar collapse leads to decreased gaseous exchange and hypoxemia. Alveolar collapse also increase work of breathing can lead to acute respiratory distress syndrome (ARDS) clinically presenting as difficulty in breathing. Inflammatory mediators brings tons of neutrophils. Neutrophils try to destroy the virus by releasing reactive oxygen species, proteases but some of the virus are destroyed but also damages type 1 and type 2 pneumocytesas the cells are getting destroyed they start to get sloughed off in the centre of the alveoli. Centre of alveoli has fluid , neutrophils , macrophages , type 1 and type 2 pneumocytes cell debris leading to consolidation and hypoxemia. Because of the consolidation clinically they can present with productive cough.IL-1 and IL-6 can travel to the central nervous system via blood. IL-1 and IL-6 affects hypothalamus causing hypothalamus releasing prostaglandins like (PGE2) which causes increased body temperature so most common presentation is fever. Hypoxemia causing decreased partial pressure of oxygen (PO2) stimulating chemoreceptors triggering reflux activating sympathetic nervous system increasing the heart rate of the patient. So the patient can have tachycardia. Severe inflammation of lung leads to systemic inflammatory response syndrome (SIRS). ARDS can also lead to SIRS potentially leading to septic shock.[3] If inflammation is spreading to the entire circulatory system increasing capillary permeability in the systemic circulation leaking fluid into tissue spaces decreasing the blood volume causing vasodilatation of systemic arterioles dropping total peripheral resistance causing hypotension decreasing perfusion to multiple organs leading to multi-organ failure. COVID-19 subjects are also more prone for thrombosis because of the fluid leakage from the capillaries. Kidneys are not getting enough blood leading to increased BUN (Blood urea nitrogen) and increased creatinine. Liver also not getting enough blood flow so, COVID-19 subjects can have increased AST(Aspartate transaminase) , ALT (Alanine transaminase)and can have increased Acute phase reactants such CRP(C-reactive protein) , Fibrinogen and IL-6.It suggests that these parameters should be also be checked in COVID-19 subjects.[4]

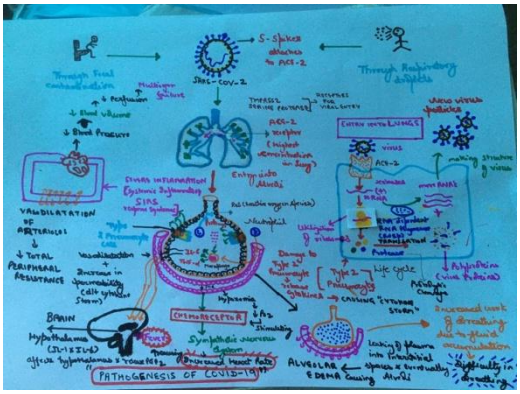

Figure1. *COVID-19 pathogenesis*

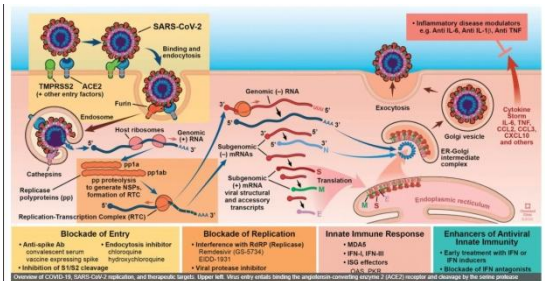

Figure2. *Adapted from Bergmann CC, Silverman RH COVID-19: Coronavirus replication, pathogenesis and therapeutic strategies ClevelClin J Med 2020;87:321-27.4*

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