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Immunopathogenesis of COVID-19: Looking into the Eye of the Cytokine Storm

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In December 2019, an outbreak of pneumonia occurred in Wuhan, China that rapidly spread globally.[1] In January 2020, it was announced by WHO that a novel Coronavirus was the cause of the outbreak. Later, the International Committee on Taxonomy of Viruses under the auspices of WHO named this novel virus as SARS-CoV-2, and the disease as Corona Virus Disease-2019 (COVID-19).[2] Due to its high pathogenic potential and rapid transmissibility from human to human, it was declared that COVID-19 was a pandemic.[3]

So far as the pathogenesis of the disease is concerned, the host immune system plays a pivotal role. Knowledge on pathogenesis in general, and immuno-pathogenesis, in particular, will help not only in understanding the disease progression but also in designing suitable immunotherapy.[4]

COVID-19 virus is an enveloped positive-sense, single-stranded RNA virus with a genome size of 26,000-32,000 nucleotides encoding 14 open reading frames (ORFs). It has four structural proteins namely spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein.[5] Spike protein allows the entry of the virus into the host cell. M and E proteins regulate virus assembly and N protein facilitates RNA synthesis.[6]

The virus is transmitted from infected individuals to healthy persons either through direct contact or via respiratory droplets.[7] The incubation period on an average is 5.1 days but may vary from 3-14 days. The usual mode of presentation is the signs and symptoms such as dry cough, fever, chest pain, weakness, and dyspnea. Severe cases develop acute respiratory distress syndrome (ARDS). ARDS is characterized by hypoxemia, pulmonary edema that may lead to respiratory failure.[8]

The genome of SARS-CoV-2 shares 79% homology with the SARS-CoV of 2002-2003, which also started from China and Asia Pacific regions and affected peoples across 37 countries.[9] Like SARS-CoV, this novel virus also binds to angiotensin-converting enzyme 2 (ACE-2) receptors via its spike protein. ACE-2 is abundantly expressed on lung epithelial cells, and also to some extent on the epithelial cells of the small intestine, mucosa of the oral cavity, vascular endothelial cells, and arterial smooth muscles of various organs.[10] Such wide distribution of receptors giving rise to enormous scope for the virus to attach to various organs could be the main

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reason behind multi-organ failure in severe cases of COVID-19.

ACE-2 converts Angiotensin I to Angiotensin II which is the major protein of the Renin-Angiotensin System (RAS) and is required for vasoconstriction and other biological functions.[11,12] In a normal physiological state, ACE-2 has a negative signal on RAS, thereby suppressing the angiotensin II level, maintaining homeostasis. SARS-CoV-2 getting attached to the ACE-2 receptor, in a way, hijacks this receptor, leaving no site for the ACE to attach.

Knowledge regarding the above physiological behavior of ACE-2 and its receptor helps understand the subsequent events involving the attachment and entry of the virus to the host cell. The virus, thus, attaches to type 2 alveolar epithelial cells through ACE-2 receptors and is internalized, following which it replicates intra-cellularly and induces a phenomenon called pyroptosis, which is a type of non-programmed cell death. These injured/dead cells as a result of pyroptosis produce the molecules known as damage-associated molecular patterns (DAMPs). These DAMP molecules in conjunction with pathogen-associated molecular patterns (PAMPs) of the virus stimulate adjoining epithelial cells, alveolar macrophages, and endothelial cells to secrete pro-inflammatory cytokines and chemokines such as Interleukin 6 (IL6), IL10, Macrophage Inflammatory Protein 1-alpha (MIP 1-alpha), MIP 1-beta, and macrophage chemotactic protein-1 (MCP-1). The release of these cytokines and chemokines promotes the recruitment of monocytes, macrophages, and neutrophils from the intravascular compartment to the site of infection. These recruited cells get activated further by the PAMPs and secrete more and more cytokines to clear the virus, thereby forming an intense inflammatory feedback loop.

Normally such an inflammatory response should be capable of eliminating the virus, but sometimes the immune system gets dysregulated in such a way that it gives rise to a drastic alteration in the immune homeostasis.[13] In the case of SARS-CoV-2 infection, this altered homeostasis is manifested by persistent recruitment of immune cells, which leads to overproduction of proinflammatory cytokines. Excessive production of these cytokines causes tissue damage giving rise to pulmonary pathology in the form of ARDS and acute lung injury.[13] This dysregulation of the immune system happens solely because of the imbalance between Th1 and Th2 responses, the balance tilting more in favor of Th1 (proinflammatory) rather than Th2(anti-inflammatory) type of response. This kind of switching up of host immune response, giving rise to exaggerated and heightened proinflammatory events is known as a cytokine storm.

Over and above the cytokine storm, the recruited macrophages, monocytes, and neutrophils also produce a profuse amount of reactive oxygen species (ROS) and proteases to cause cell death.[14] Additionally, cytokine storm-induced influx of immune cells like neutrophils and monocytes into the lungs creates an environment in which there is persistent overproduction of cytokines and chemokines as stated above. It has been seen that of all the cytokines enumerated above, IL-1 beta is the one that promotes pyroptosis.[15] It has also been observed that patients who did not survive due to COVID-19 severe infection, had sustained higher levels of IL 1-beta and IL-6 throughout their clinical course as compared to those who survived.[16]

Overall, it is undoubtedly true that cytokine storm violently attacks multiple organs, most importantly the lung, eliciting severe pulmonary pathology in the form of massive alveolar damage, pulmonary edema, hyaline membrane formation, and desquamation of pneumocytes determining the initial features of ARDS.

In conclusion, therefore, ARDS and hypoxemia are primarily the most important pathological consequences featuring severe COVID-19. Besides, there could be acute kidney injury, acute liver injury, and cardiac injury as the receptors for the glycoprotein domain in the S protein of the virus are widely distributed in various organs and tissues of the

host. Clinicians may face a further challenge if the patient acquires secondary infections due to bacteria and fungi during COVID-19, which is not uncommon.

Control of inflammatory response is vital for targeting the viral infection, and thus the mechanism behind the hyper inflammation process which is part of the cytokine storm must be elucidated in further detail so that better management strategies, including therapeutics, could be designed to restrict the propagation of the pathogen.

CONFLICT OF INTEREST

None

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None

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