Role of inflammatory markers in coronavirus disease (COVID-19) patients: A review

A novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the causative agent of coronavirus pandemic 2019. Investigating the role of inflammatory markers helps in designing a rational and effective therapy for this infection.

Acute inflammation in the lungs is a complex pathophysiological mechanism involving inflammatory mediators such as cytokines and chemokines, which stimulate the macrophages in the alveoli, leading to poor immune system regulation.

Cytokine regulation of inflammation in nCOVID-19 infection

Cytokines are proteins, peptides, or glycoproteins secreted by hematopoietic and non-hematopoietic cells in response to various stimuli. They are soluble in nature. Cytokines function in the regulation of growth by activating JAK, activates transcription, and regulates gene expression. It also activates other inflammatory mediators.

Cytokine storm syndrome was analyzed in critically ill nCOVID-19 patients. It manifested high inflammatory mediators, systemic inflammation, and multiple organ failure. It has been observed in the case of coronaviruses infection like SARS-CoV and MERS-CoV, where inflammatory cell infiltration occurs because of rapid viral replication and cytokine storm, resulting in acute lung injury, ARDS, and death.

Most studies have concluded and reported elevated levels of IL-6 in critically ill patients with nCOVID-19. The elevated level of IL-6 is important for the production of Th-17 cells in the interaction of T cells with dendritic cells. During this process, the autoreactive T cells are stimulated by autoantigens presented by the dendritic cells resulting in ARDS.

A persistently elevated level of ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), and TNF-α has also been reported in severe cases of corona-infected patients. They are found to be associated with an increased risk of ARDS, disseminated intravascular coagulation (DIC), hypercoagulation manifested as thrombocytopenia, and systemic stimulation of blood coagulation resulting in generation and accumulation of fibrin causing microvascular thrombi in the organ system. This inflammation causes airflow obstruction, which has a profound effect on gas exchange processes and cardiac functions.

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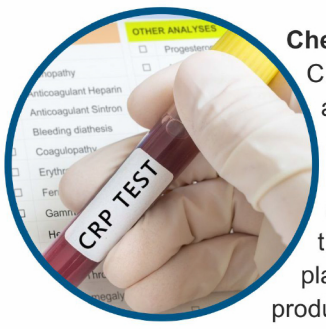

Chemokines regulation of inflammation in nCOVID-19 infection

Chemokines are proteins that play a major role in cell signalling in the immune system and act through transmembrane G-protein receptors, and deliver the molecular code responsible for the precise organization of leukocytes migration under homeostatic as well as proinflammatory conditions. During a viral infection, changes occur in both homeostatic and inflammatory chemokine receptors, guiding dendritic cells to the lymph nodes where they facilitate the changes from innate to adaptive immunity. Initially, the virus stimulates the plasmacytoid subsets present on the dendritic cells to generate IFN-α, which induces the production of CCL3, an inflammatory chemokine. CCL3 helps in part of the recruitment of NK cells that tries to kill the viral-infected cells directly and helps in producing a large quantity of IFN-γ, which in turn plays a major role in the enrolment of CD8+ T and Th1-polarized CD4+ cells. The general cascade of immunoregulation in the occurrence of viral infection has the concept of a cytokine to chemokines and then again to cytokines.

Inflammation and hyperferritinemia

Some studies suggest that ferritin helps in protecting the host body system against active infection by restricting the availability of iron to the pathogen, along with significant activation of macrophages. Patients manifesting hyperferritinemia phenotype show an abnormal pattern of activation of the reticuloendothelial system and multiple organ damage where excess macrophage activation caused by IFN-γ results from its failure to eliminate pathogens subsequently to inherited disorder in NK cell and CTL-mediated cytolysis.

Fibrinogen regulation of inflammation in nCOVID-19 infection

Major mediators of the coagulation reaction such as fibrinogen, tissue factor, and thrombin are found to be associated with diseases as an inflammatory component. Fibrinogen has been identified as a risk factor as well as a modulator of inflammatory pathways in several infectious diseases. It is an acute-phase mediator that gets broken down into fibrinopeptides during activation of coagulation reaction, thus exposing several sites for polymerization and allowing fibrin fibrils formation. Fibrinogen and its derivative peptides play a major role in activating immune cells by ligand-receptor interactions. This pro-inflammatory response is caused by non-overlapping fibrinogen signals expressed by leukocytes of the innate immune system. SARS coronavirus 3a protein upregulates fibrinogen expression in epithelial cells in the lungs of patients by upregulating the mRNA levels of three polypeptide chains of fibrinogen. As a result, the secretion, as well as the intracellular level of fibrinogen, have been found to be elevated in the nCOVID-19 patient presenting with highly elevated levels of D-dimer and degraded products of fibrinogen.

Dysregulation of the immune system in nCOVID-19 patient

The nCOVID-19 infection leads to impairment in inflammatory adaptive and innate immune responses.
Lymphocytopenia is the prominent clinical and diagnostic feature observed in nCOVID-19 patients. T cells, as well as NK cells, are reduced, and this point of reduction was found even lower and undetectable in critically ill patients.
Cellular damage occurs to secondary lymphoid tissue, and there is a reduction in the number of lymphocytes, macrophage activation, proliferation, and phagocytosis with focal hemorrhage and necrosis. In the lungs, diffuse alveolar damage along with infiltration of macrophages, monocytes, moderate multinucleated giant cells, and few lymphocytes (CD4+ T cells) are observed. In some cases, virus inclusion bodies can be detected in the epithelium of type II alveoli and macrophages consistent with the features of the “primary cytokine.”

Conclusion To conclude, the role of inflammatory mediators in nCOVID-19-infected patients is diverse and multifunctional. In the majority of the cases, the immunopathogenesis of nCOVID-19 infection involves disturbances of inflammatory mediators that do not cause the disease but helps in the progression of the disease. The specific set of cytokines and chemokines are to be therapeutically targeted, and a synergistic action may be obtained with the drugs that are used for the treatment of nCOVID-19 infection. Thorough knowledge of pattern recognition receptors, inflammatory mediators like cytokines, chemokines, ferritin, fibrinogen, and clinical immunology are required to find out the best therapeutic interventions. Therapies involving the regulation of immune responses help in inhibiting the various steps in pathologies of infection.