Cytokine and COVID19: A Literature Review

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ABSTRACT

The outbreak of Covid 19 was initially identified in Wuhan city of China in December 2019 and led to a global pandemic. Clinical evidence indicates that covid-19 infection can range from asymptomatic or mild symptoms in the majority of cases to serious complication such as ARDS, multi-organ failure and death in severe cases. It has been also indicated that there is uncontrolled and excessive production of cytokine in critically ill-patients of covid-19 which give rise to "cytokine storm". Which are responsible for the exacerbation of symptoms and development of the disease? There are many unresolved questions regarding the pathological features, pathophysiological mechanisms and treatment of the cytokine storm induced by covid-19. This review will be aimed at suggesting therapeutic strategies such as the use of immunomodulators to confront the cytokine storm and an overview of the current understanding of the covid-19 infection.

KEYWORDS: Covid-19, cytokine, Cytokine storm, Inflammation, Immunomodulation

INTRODUCTION

In December 2019, a group of patients were infected with pneumonia of unknown aetiology in Wuhan city of China. The disease was named as Covid-19 having novel coronavirus(nCoV) as the causative agent. Sars-CoV-2 belongs to a large family of Coronavirus which are known to cause human disease. Diseases ranging from the common cold to more severe diseases like SAR-CoV and MERS-CoV. The novel coronavirus is a new strain of coronavirus which was not recognized earlier in humans. Covid-19 is Zoonotic in origin similar to SARS coronavirus and MERS coronavirus revealed by the phylogenetic analysis means it transmit between animals and people [1].

Cytokines are a broad class of proteins, peptides or glycoproteins which are secreted majorly by certain cells of the immune system. Cytokines have a role in mediating and regulating immunity, inflammation and haematopoiesis in the human body. However, their rapid release in large quantities can cause multisystem organ failure and death It has been reported that cytokine plays a significant role in Covid-19 patients. In the critical cases of covid-19, the decline of health and even death is reported in association with cytokine storm [2].

CYTOKINE STORM

Cytokine level boosts when a pathogen attacks the respiratory epithelial cells and results in infection [3]. The cells including alveolar macrophages are can be infected by the further surge of the pathogens after primary exposure.

which ultimately leads to cell death this generate the inflammatory response. Because of this inflammatory response, there is increased blood flow resulting in elevated local temperature and pain sensation. It also leads to the activation of pro-inflammatory cytokines on the induction of inflammatory cells. These cytokines trigger several genes which are responsible for their up regulation or down regulation and can either lead to the formation of other cytokines & new cell surface receptors, or through negative feedback may suppress the cytokine effect. However, sever inflammation associated with cytokine storm there is several pathological changes observed like specific change in lungs structure, hyaline membrane formation along alveoli wall which makes gas exchange difficult, fibrin exudates and fibrosis. Systemic cytokine storms and thus multi-organ system failure also can be caused in the case severe inflammatory cytokines irrupt over major body circulation. Pathogens are recognised by receptors of innate immune cells and thus the inflammatory response is generated [4,5]. It has been reported that in sever cytokine storm there is increased level of pro-inflammatory cytokines such as interferons (IFNs), tumour necrosis factors (TNFs), interleukins (ILs), and chemokines [6].

The following are the signalling pathways activated by these proinflammatory cytokines and producing the immune response:

Interferon play important role in producing an innate immune response to the pathogen. By interacting with their specific receptors IFNs activate STAT (signal transducer & activator of transcription) complexes. STAT activation initiates the Janus-Kinase-STAT signalling pathway and produces an immunomodulatory effect. Interferon signal the neighbouring uninfected cells to destroy mRNA and inhibit protein synthesis of the pathogen and interfere with its replication. However, their overproduction can lead to severe lung damage [7].

Tumour necrosis factor (TNF) it regulates the immune cells. TNF binds with its specific receptors TNFR1 and TNFR2 and activates the MAPK (Mitogen-activated protein kinase) pathway. TNF also induces activation of JNK pathways which is one of the major MAPK cascades. The JNK pathway involved in cell differentiation, proliferation and promotes apoptosis.

Interleukins (ILs) especially IL-1 and IL-6 are the two main pro-inflammatory cytokines released during pathogenic infection.IL-1α and IL-1β bind type 1 IL-1 receptor and induce activation of intercellular myeloid differentiation primary response gene 88(MYD88) which is responsible for transmitting the inflammatory signal by enrolling IL-1 receptor-associated kinase 1 (IRAK1) and IRAK4 together with TNF receptor-associated factor 6(TRAF6). This complex activates TAK (transforming growth factor β-activated kinase and TAB (TAK -binding protein). Both TAK and TAB activates MAPK signalling cascade and NF-κB pathway [8]. While the IL-6 interacts with its receptors and triggers the gp130 and IL-6R proteins. Complex associated with gp130 triggers the activation of associated JAKs and STAT pathways.

Chemokines receptors activate G-proteins, which subsequently activates phospholipase C(PLC). PLC cleaves PIP2 (Phosphatidylinositol(4,5)-bisphosphate) into two secondary messengers- IP3 and DAG which together triggers intracellular signalling events. These events promote MAPK signalling cascade pathway.

CYTOKINE STORM AND COVID-19

Accumulating evidence shows that sever covid-19 patients may have cytokine storm syndrome (CSS) meaning the uncontrolled and excessive release of cytokines. It was reported that in comparison to non-ICU patients, ICU patients had higher plasma concentration of cytokines such as interleukins IL2, IL6, IL7, IL10, interferon-gamma (IFN-γ),

tumour necrosis factor alpha (TNF-α) and granulocyte-colony stimulating factor(G-CSF). Which was found to be similar to the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) pathogenesis [9,10].

There is a significant role of RAAS in the promotion and maintenance of inflammation. Renin, an aspartic protease enzyme cleaves angiotensinogen to Angiotensin-1(Ang-1). Ang 1 is converted into angiotensin-2 by the enzyme Angiotensin converting enzyme (ACE).Ang-2 is thus the major ACE product and the most active hormone in the system, acting in a pro-inflammatory manner, involving especially AT1 receptors [11,12].

There is an abundance of ACE-2 receptors in the lungs epithelium, protecting the alveolar epithelial type 2 cells. Once the host gets infected by the SARS CoV-2, the body initiates an immune response by activating different immune cells such as T helper cells, macrophages, dendritic cells, Th1, Th2, Th17 and neutrophils [13]. Activation of these immune cells results in abnormally high levels cytokines and pro-inflammatory chemokines [14]. Cytokine storm phenomena results from the accumulated cytokines that further permit invasion of SAR-CoV-2 by sending signals which attract different immune cells. The outcome is a more sustained release of cytokines, commencing an aggressive inflammatory response and severe respiratory complications like Acute respiratory distress syndrome (ARDS) [15]. Cytokine regulates the immune response and haematopoiesis by activation of JAK-STAT-SOCS signal transduction pathway. Cytokine signalling both positively and negatively regulates all cell types through a restricted number of JAK-STAT pathways. SOCS (suppressor of cytokine signalling) family of proteins is a primary negative regulator of JAKs. whose action is persuaded by JAK-STAT activation and then it inhibits the signalling cascade, which generates a negative feedback loop. SOCS proteins contain a central SH2 domain and C-terminal SOCS box domain [16]. SOCS1 and SOCS3 are the most potent suppressors of signalling as they contain kinase inhibitory region which allows them to suppress the signalling by direct inhibition of JAK catalytic activity [17,18]. Activation of JAK-STAT pathway by cytokine stimulation leads to the production of CIS, SOCS1, SOCS2 and/or SOCS3. These SOCS proteins then inhibit the signalling pathways which initially led to their production. SOCS proteins act in part of a negative feedback loop [19].
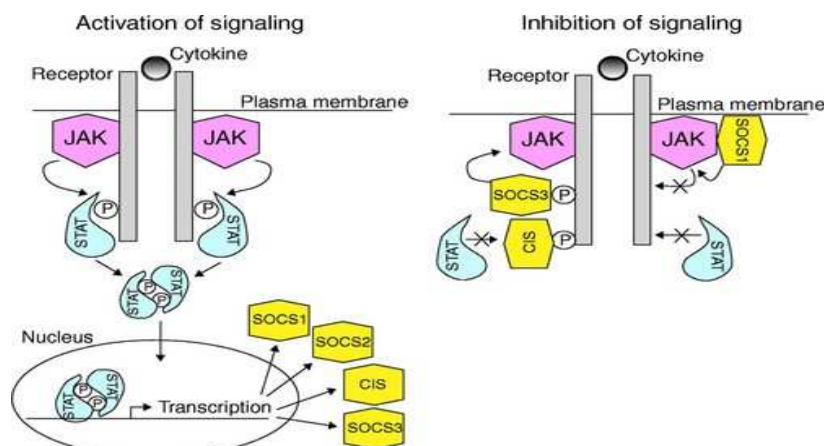

Figure.1 Cytokine Signalling Mechanism [21]

SOCS1 directly binds to activated JAK, thereby inhibits its catalytic activity. On the other hand, SOCS3 binds to JAK-proximal sites on cytokine receptors and diminish JAK activity [20]. CIS prevents the binding of STATs to cytokine receptors. SOC2 mechanism of action remains undetermined [21].

Hence, targeting the aggravate cytokines and inhibiting the pathways would be therapeutically beneficial for the management of COVID-19. There is a potential role of JAK-inhibitors in treating COVID-19 patients and is an active area of investigation along with the multiple ongoing Clinical trials.

THERAPY FOR CYTOKINE STORM IN COVID-19 PATIENTS
For the treatment of patients with covid-19, Immunomodulators can prove to be effective for controlling inflammatory responses and to improve the prognosis of infection. There is no specific drug or vaccine available for COVID-19. However, we suggest that patients with COVID-19 can be given immunotherapy treatment in order to block the possibility of a subsequent cytokine storm. Early use of these treatments may reduce mortality in most of the severe cases.

Interleukins
IL-1 and IL-6 are the two pro-inflammatory cytokines which plays important role in cytokine storm and consequences caused.

Anakinra is the recombinant IL-1 receptor antagonist that blocks the binding of both IL-1α and IL-1β to IL-1R, thereby inhibits the proinflammatory effects of IL-1. Anakinra can be used to treat the cytokine storm caused by infection. It was found that Anakinra is effective in patients with severe sepsis and thereby improves the survival rate without significant adverse effects [22].

Also, it was found that IL-6 blockade therapy using a humanized anti-IL-6 receptor antibody, tocilizumab is remarkably beneficial in severely ill patients. There is the pivotal role of IL-6 in the cytokine storm. IL-6 inhibitor Tocilizumab is currently used to treat rheumatoid arthritis an autoimmune disease [23].

Hence use of Interleukin antagonist may significantly improve survival in patients with sepsis. This therapeutic strategy can be beneficial to counteract the elevated interleukins level in cytokine storm and management of Covid-19.

Interferons
IFN-γ stimulates antiviral genes in epithelial cells, without over stimulating the immune system. It also suppresses the recruitment and function of mononuclear macrophages and other innate immune cells responsible for the inflammation-γ could be a good strategy for treating the Covid-19 infection. According to some studies, the pegylated and non-pegylated interferons have shown varied efficacy following a different period. Early administration of Interferon is beneficial to reduce the pathogenic load compared to the delayed administration of interferon having no benefit and mortality rate remaining unchanged. Therefore, the timing of IFN treatment is crucial to the outcome of diseases to avoid an uncontrolled inflammatory reaction, IFN-αβ receptor inhibitors could be used in severe patient of covid-19 infection and improve the clinical symptoms of patients to a certain extent.

TNF Blockers
TNF is involved in autoimmune disorders such as rheumatoid arthritis. TNFs plays a key role in producing an inflammatory response by triggering a cytokine storm. TNF inhibitors suppress the physiologic response of TNF. Therefore, can be used for the treatment of TNF induced disorders. It has been observed that patients with covid-19 infection have a higher serum level of TNF -α. However, the potential role of anti-TNF in treating patients with covid-19 needs further investigation [24,25].

JAK Inhibitors.
JAK-inhibitors have a potential role in treating COVID-19 patients. Baricitinib, fedratinib, and ruxolitinib are an inhibitor of the JAK-STAT pathway, which are used for suppressing proinflammatory cytokine production and systemic inflammation indicated in RA.JAK-inhibitors are likely to be effective against the consequences of the elevated levels of cytokines (including interferon-γ) typically observed in people with COVID-19 and are an active area of investigation along with the multiple ongoing Clinical trials.

CONCLUSION
Inflammation is an immune response to harmful pathogens. On the onset of the inflammation, the innate immune cell surface receptors are known as pattern recognition receptors (PRRs) recognize the pathogen-associated molecular pattern (PAMP) and undergoes activation. Activation of these cells leads to release of inflammatory mediators that contribute to host defence through the stimulation of acute-phase response, haematopoiesis and immune reactions. However, Covid-19 infection induces the uncontrolled and excessive release of these inflammation mediators to give rise to cytokine storm in some individuals and can cause multiorgan failure and death. Early recognition and appropriate treatment of cytokine storm are required through immunomodulators, cytokine inhibitors and other targeted interventions. Thereby, reducing the morbidity and mortality rate of Covid-19 patient and improving the survival rate. Since the data and reports about covid-19 are changing with great speed further investigation and experimentations are required to better understand the immune response of covid-19 patients and the mechanism involved.

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