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Importance of IL-1β in SARS-CoV-2 infection

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) provokes the host immune responses and induces severe respiratory syndrome by overreaction of immune cells. IL-1β is a pro-inflammatory cytokine highly associated with the related inflammation and cytokine storm, and several IL-1β antagonists are being used to treat cytokine release syndrome (CRS). Accordingly, some studies and clinical trials are investigating the effects of IL-1β antagonists for controlling Coronavirus disease 2019 (COVID-19) associated CRS. Here, we will review any interaction and association between IL-1β and SARS-CoV-2 infection.

Key Words: COVID-19, Cytokine storm, IL-1β, Inflammation, SARS-CoV2.

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1- INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been confirmed by a new viral agent that caused a severe acute respiratory syndrome (SARS-CoV-2) outbreak in December 2019. It caused a serious global health crisis (1, 2) which led the World Health Organization (WHO) to identify COVID-19 as a public health priority (3, 4). According to the pandemic situations and lack of approved treatment and prevention strategies along with the high mortality rate, SARS-CoV-2 is the most challenging disorder these days (5, 6). The pathophysiology of SARS-CoV-2 infection is very similar to that of the SARS-CoV, as the host's inflammatory response is involved in damaging the respiratory system during infection (7, 8). Therefore, the severity of the disease in patients depends not only on the viral infection, but also on the host responses (9, 10). Acute respiratory distress syndrome (ARDS) directly causes respiratory failure in COVID-19 patients, as it has been shown that 70% of deaths appeared to be related to the ARDS (11). In addition, the unbalanced production of cytokines and inflammatory mediators such as interleukin (IL)-1β, IL-6 and TNF-α during immune responses to SARS-CoV-2 infection could prime a "cytokine storm" that contributes to many of ARDS related COVID-19 deaths (12, 13). Since several studies have demonstrated immunopathology of SARS-CoV-2, the role of IL-1β in COVID-19 is being highlighted (14-16). IL-1β is considered as one of the main pro-inflammatory factors that contribute to the pathophysiology of several respiratory viral diseases. In this regard, we aimed to review various aspects of IL-1β function in SARS-CoV-2 infection.

2- INFLAMMATION IN COVID-19 PATIENTS

SARS-CoV-2 is considered as a threat to human health and warned people all over the world (17-19). Different clinical symptoms have been observed among COVID-19 patients. Pattern recognition receptors (PRRs) including toll-like receptors (i.e. TLR-3, -7, -8), RIG-I like receptors (RLRs), and NOD-like receptors (NLR) recognize pathogen-associated molecular patterns (PAMPs) (20). All this kind of receptors could get involved in these patients (21, 22) and activate several signaling cascades with down-stream transcription factors, such as NF-κB and IRF3/7, to produce inflammatory cytokines (TNF-α, IL-1β, IL-6) (23). Production of these cytokines are considered as a main feature in immunopathology of COVID-19 which could lead symptoms to the mild, moderate, or severe situations (24, 25). SARS-CoV-2 infection is associated with an invasive inflammatory response by production of various pro-inflammatory cytokines in a large scale and in an incident recognized as "cytokine storm" (26). The patient's immune responses against this virus could be aggressive and lead to an extreme inflammatory reaction. Numerous studies have analyzed COVID-19 related cytokine profiles and suggested that the cytokine storm is linked with an undesirable prognosis of COVID-19, multi-organ failure and lung damage, as ARDS is the most important response (11, 27, 28). Accordingly, low levels of oxygen capacity is the main reason for mortality in COVID-19 patients (29). Although the mechanism of ARDS in COVID-19 is not completely identified, the intensive release of pro-inflammatory cytokines is recognized as the main factor of death in ARDS (3, 30). The key pro-inflammatory cytokines which are mainly included in ARDS related cytokine storms are IL-1, IL-6, and TNF-α which are elevated in the blood of patients (31). Accordingly, cytokine profile related to the pathogenesis of SARS-CoV-2 infection have been evaluated in angiotensin-converting enzyme 2 (ACE-2) expressing cells (32,

33) and IL-1β has been considered as one of the main pro-inflammatory factors that contribute in pathophysiology of SARS-CoV-2 (34).

In a recently published study, it was shown that monocytes/macrophages secreting IL-1β could reduce alveolar epithelial regeneration and so develop pathological progress of fibrosis. It suggested that the higher level of IL-1β production by myeloid cells is a unique consequence of COVID-19 compared to other bacterial or viral pneumonia (35).

3- SIGNALING PATHWAY RELATED IL-1B AND COVID-19

Production of mature IL-1β is dependent on an intracellular proteolytic activity of caspase-1 that converts IL-1β precursor to an active cytokine. Activation of caspase-1, which is also known as IL-1β–converting enzyme (ICE) could be mediated by the inflammasome and related complex (36). All NALP3 (NLR family pyrin domain containing 3), ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) and P2RX7 (purinergic receptor P2X7) could also induce its activation (37).

NALP is one of the members of the intracellular NOD-like receptor (NLRs) family that recognize pathogen-associated molecular patterns (PAMPs), such as viral genome, bacterial peptidoglycans, and toxins (38, 39). NALP3 inflammasome is a key element of IL-1β production (40, 41). NALP3 binds to ATP/dATP from infected cells and provides P2RX7 incorporation to facilitate active IL-1β secretion, in cooperation with caspase-1 (42). Activation of toll-like receptors (TLRs) could also affect IL-1β signaling through the NF-K pathway (43). TLRs could be involved in the primary failure of virus elimination and also in its following progress of the lethal consequences of COVID-19 and severe lung injury (44). In-silico studies have revealed that viral spike protein has a significant interaction with TLR1, TLR6, and especially TLR4 (45). It is noteworthy that downstream signaling cascade of TLR4 is highly associated with the COVID-19 severity through involving IL-6 and TNF-α (45).

Sensing extracellular inflammatory condition and stimulation of cells via IL-1β, activate IkB kinase (IKK) with phosphorylation and degradation of IkB (inhibitor of NF-KB), as consequences. So, NF-KB translocates to the nucleus and stimulates the expression of target genes, such as inflammatory and oncogenic factors (46-52). Protein kinase A (PKA) could also activate NF-kB after IL-1β exposure (53, 54) via PI-3K/AKT enzymes (55).

In the peripheral blood and especially broncho-alveolar lavage fluid (BALF) of COVID-19 patients with pneumonia, high levels of IL-1β have been detected (24, 56-58). IL-1β is induced by some SARS-CoV components, such as Viroporin-A, E-protein and ORF3 proteins, through NALP3 inflammasome (59-61) which are also observed in any other respiratory diseases (62-64). It has a key role in the initiation of inflammatory cascades and its suppression could interrupt inflammatory processes and harmful outcomes (65, 66). Also epithelial damages in SARS-CoV2 infection induce IL-1α release (67, 68) and recruitment of neutrophils and monocytes (68) and so trigger IL-1β production. Stimulation of pro-IL-1β secretion in monocyte/macrophages by positive feedback may lead to an excessive IL-1 production within innate immune cells. This auto-inflammatory loop of IL-1 (IL-1α and IL-1β) could be a target of some inhibitors, (69) such as Anakinra which inhibits the IL-1 receptor (IL-1R) and subsequently will suppress auto-inflammation through the prevention of IL-1α impacts. Its effect can also encompass IL-1β and IL-6 as well (70).

Also in human smooth muscle cells, in response to IL-1β activation, protein kinases get activated and signal transduction is carried out from the cell surface to nucleus (71). In other words, IL-1β is able to induce expression of P38 mitogen activated protein kinase (MAPK) without affecting Erk1/2, Jnk, and Akt factors (72).

As mentioned above, IL-1β is involved in different viral immune responses (73). Its gene is located on chromosome 2q14 (74) with two functional single nucleotide polymorphisms (SNPs) in promoter, (75) that could affect its transcription activity (76). The main sources of IL-1β are sentinel cells as the first line of innate immune responses, including different types of antigen-presenting cells (77-80), epithelial cells, endothelial cells, and fibroblasts (42, 81-83). IL-1β participates in different cellular events including cell proliferation, differentiation and cell death. Moreover, following foreign agents interactions, such as various viral particles, IL-1β production supports nitric oxide synthesis during inflammation (84-86) and has an important role in acute and chronic inflammations (87). On the other hand, its paracrine or systematic (endocrine) effects could prompt more survival through the induction of vascular endothelial growth factor (VEGF) (88, 89).

Hypoxia inducible factor (HIF)-1 is a heterodimeric transcription factor that acts as a key mediator in cell proliferation and tumor progression (90). HIF-1α has been considered as an effective element in SARS-CoV-2 cell entry. HIF-1α could suppress the ACE2 receptor, transmembrane protease serine 2 (TMPRSS2) and also modulate metalloproteinase domain-containing protein 17 (ADAM17) which has an important role in the process of TNFα and IL-6R secretion (91, 92). HIF-1α triggers chemo-attractants including chemical chemokine 2 (CCL-2), MCP-1 and IL-1β to initiate inflammatory responses (93). Activation of HIF-1α in inflammation can robust immune responses through IL-1β by activation of some downstream signaling pathways (94, 95).

The Pyroptosis which mainly occurs in macrophages, dendritic cells, neutrophils, CD4+ T cells, keratinocytes, epithelial cells, endothelial cells and neurons, is another pathway that highlights the importance of IL-1β in inflammation induction (96). Pyroptosis is a kind of lytic programmed cell death that is dependent on caspase-1 and has an exclusive mechanism of action (97) which potentially causes cytoplasmic content leakage, facilitated infiltration of inflammatory cells and enhanced local inflammatory responses (98, 99). TLR related caspase-1 activation triggers IL-1β maturation and the active form of IL-1β induces cleavage of gasdermin D which has a key role in apoptosis induction (100). It has been reported that impaired gasdermin D function could affect both inflammasome formation and cytokine release, showing that gasdermin D has a significant impact on coronavirus-induced cytokine release (101, 102) (**Fig. 1**).

4- THERAPEUTIC APPROACHES

Emerging pandemic of COVID-19 made various attitudes and approaches against SARS-CoV-2 (103, 104). Accordingly, several therapeutic strategies and immune modulators including Corticosteroids, Hydroxychloroquine (HCQ), Janus kinase (JAK) inhibitors, IL-1 and IL-6 and TNF-α inhibitors, NF-κB inhibitors, PD-1 inhibitor, intravenous immunoglobulin (IVIG), and cytokine-adsorption devices have been considered and studied to control cytokine storm (25, 105-107). Inhibitors of IL-1 which previously have been used in influenza and respiratory syncytial virus (RSV) could be effective in degradation of inflammasome complex (108-110) and some of IL-1 inhibitors (such as Anakinra,

Canakinumab and Rilonacept) are under investigation in clinical trials (109, 111, 112).

Today, Ankinara as human IL-1 receptor antagonist, is used in the treatment of several inflammatory disorders containing cytokine storm such as rheumatoid arthritis (RA), cryopyrin-associated periodic syndromes, neonatal-onset multisystem inflammatory disease, cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis (113).

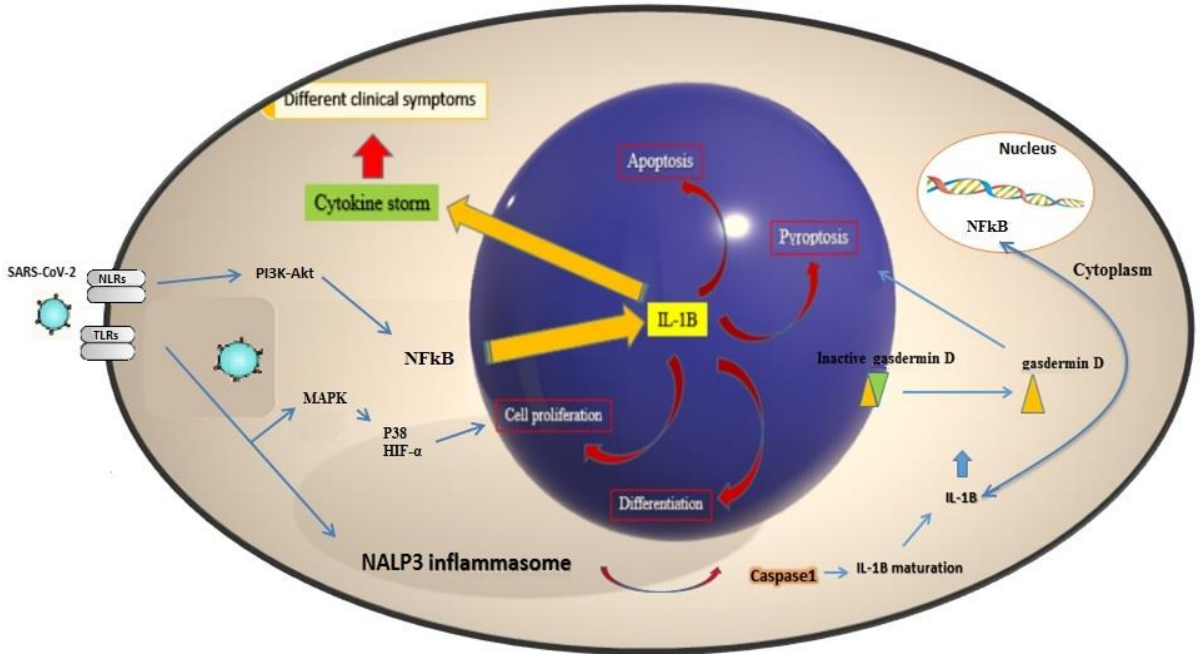

Fig.1: IL-1β interactions with the cytokine storm related COVID-19

It is potentially capable of inhibiting IL-1β and neutrophil extracellular traps (NET) feedback cycle (114). Hence, due to common consequences with COVID-19, it is expected that inhibition of IL-1 or its signaling pathway could be one of the potential targets for the treatment of COVID-19 patients. In this regard, Anakinra could be a safe choice with satisfactory efficacy, as previously observed (115). Its effectiveness for COVID-19 patients is also under assessment in some clinical trials. The leading randomized trial is in phase 3 and the other is in phase 2 with 100 mg daily by intravenous Anakinra administration to block the hyper-inflammatory impacts of IL-1β in these patients (116, 117). Two other studies have also demonstrated improvements in clinical outcomes of COVID-19 patients following Anakinra administration (109, 118) which was not found after IL-6 inhibition (109).

Canakinumab is an anti-IL-1β specific monoclonal antibody which significantly decreases the rate of recurrent cardiovascular disorders in COVID-19 patients with a former myocardial infarction (119). It is also being used in a phase 3 trial in patients with pneumonia and cytokine release syndrome (CRS) (120). In another phase 2 trial study, 80 ambulatory patients with moderate severity of COVID-19 disease and no hospitalized situation, also used Canakinumab for CRS

inhibition (121). Rilonacept, as another IL-1β inhibitor, was also used in a phase 3 clinical trial in COVID-19 patients with acute symptoms of recurrent pericarditis and systemic inflammation. Administration of Rilonacept could significantly improve recurrent pericarditis episodes in these patients (122).

5- CONCLUSION

Obviously, IL-1β plays a key role in immunopathology and cytokine storm related SARS-CoV2 infection. Delineating the exact mechanisms of interaction between the virus and IL-1β could definitely illuminate any potential strategy for controlling CRS related COVID-19. Given the interconnected nature of these pathways, targeting of the IL-1β for the treatment of COVID-19 requires further clinical studies to assess efficacy and safety of drugs within different populations. Immunoregulatory and anti-inflammatory based antiviral treatments for severe COVID-19 are progressively being investigated and need more details to be developed and dedicated. Finally, in the battle against deadly SARS-CoV-2, inhibition of IL-1β might be considered as a potent treatment strategy to save patients' lives.

6- AUTHORS' CONTRIBUTIONS

Conceptualization, writing-original draft, and review were conducted by E.B, H.T and V.H; Supervision, review and editing was performed by A.M.

7- COMPETING INTERESTS

None.

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