Review Article

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TANAFFOS

Involvement of NLRP3 Inflammasome in SARS-Cov-2-Induced Multiorgan Dysfunction in Patients with COVID-19: A Review of Molecular Mechanisms

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Nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3) inflammasome is a critical component of the innate immune system. The inflammasome activation is correlated with the COVID-19 severity. Furthermore, the underlying conditions are accompanied by hyperactivation of NLRP3 inflammasome and poor outcomes. Herein, we presented the involvement of NLRP3 inflammasome in the pathogenies of SARS-CoV-2-induced multiorgan dysfunction and potential therapeutics. Overexpression of NLRP3 inflammasome components and subsequently increased levels of cytokines following viral infection leads to the cytokine storm and indirectly affects the organ functions. Besides, invading host cells via SARS-CoV-2 further activates the NLRP3 inflammasome and induces pyroptosis in immune cells, resulting in the secretion of higher levels of proinflammatory cytokines into the extracellular matrix. These events continued by induction of fibrosis and organ dysfunction following infection with SARS-CoV-2 in critically ill patients. This condition can be observed in individuals with comorbidities (e.g., diabetes, obesity, etc.) due to a primed state of immunity, which can cause severe disease or death in this population. Therefore, understanding the mechanisms underlying host-SARS-CoV-2 interaction may help to clarify the pathophysiology of SARS-CoV-2-induced multiorgan dysfunction and introduce potential therapeutic strategies.

Keywords: SARS-CoV-2; COVID-19; Innate immunity; NLRPa3 inflammasome; Therapeutic strategies

INTRODUCTION

The emergence of coronavirus disease (COVID-19) as a result of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has taken a heavy toll on human lives worldwide (1). This virus mainly affects the respiratory systems (bronchioles and alveoli) in humans, leading to fever, shortness of breath, dry cough, fatigue, pain, diarrhea, and other manifestations, and causes severe symptoms and even death in fewer critically ill cases (2, 3). CoVs are enveloped, single-stranded, positive-sense RNA viruses (4). The viral genome encodes structural proteins, including the spike (S), membrane (M), phosphorylated nucleocapsid (N), and envelope (E) protein (5). In addition, structural proteins, and accessory proteins, e.g., open reading frame 3b (ORF3b), ORF6, ORF7a, and ORF8 play an essential role in the pathogenies of disease (6).

Angiotensin-converting enzyme 2 (ACE2) acts as a receptor for SARS-CoV-2, which can invade host cells. The ACE2 expression has been detected among several organs

(7). Studies have demonstrated that dysregulated innate immune responses play a significant role in detecting the fate of COVID-19 patients (8). Autopsy findings of children and adolescents showed that SARS-CoV-2 could harm body organs such as the lungs, brain, kidneys, liver, and heart, leading to death due to multiple organ dysfunction in critically ill patients (9). Besides, detrimental clinical outcomes have been observed in the presence of comorbidities, which increases the risk of mortality (10). Infected cases with at least one pre-existing disorder, e.g., cerebrovascular disease, cardiovascular disease (CVD), diabetes, hypertension, or chronic renal diseases, commonly show severe manifestations (11). The pathologic features of COVID-19 are now well known. However, the mechanisms underlying disease severity and development remain obscure.

In general, a storm of inflammatory mediators, particularly tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 is implicated in the tissue injury observed in severe COVID-19 cases with acute lung injury (ALI) and respiratory distress syndrome (ARDS) (12). Inflammasomes, including AIM2, nucleotide-binding domain and leucine-rich repeat protein-1 (NLRP1), NLRP3, and NLRC4, have an essential role as sensor proteins in the innate immune system by detecting infections and cellular stresses (13, 14). The inflammasome activation is responsible for the secretion of proinflammatory cytokines (15). SARS-CoV-2 induces acute inflammatory responses mediated by inflammasomes in patients with underlying situations with chronic inflammation, resulting in severe responses in this population (16). Among all types of inflammasomes, NLRP3 has attracted more attention; it plays a critical role in restricting the replication of intracellular pathogens (17). Recent investigations have demonstrated that SARS-CoV-2 can activate NLRP3 inflammasome (18).

Despite vaccination, various treatment options are also being explored (19). The immunomodulatory drugs including plitidepsin, dexamethasone, and monoclonal antibody therapies (e.g., eculizumab and tocilizumab), have exhibited promising effects in alleviating the cytokine release syndrome (CRS) caused by cytokine storm, and lowering severe consequences in COVID-19 patients (20-23). Strategies suppressing the inflammasome/pyroptosis-associated cascades involved in the secretion of effector cytokines may be a new approach against COVID-19-triggered immune perturbations (24). Pyroptosis, in turn, raises the levels of pro-inflammatory cytokines and worsens the CRS condition (25).

In this review, we discussed the NLRP3 inflammasome activation in COVID-19 cases and highlighted the role of NLRP3 inflammasome in the pathology of multiorgan dysfunction. In addition, we attempted to highlight the effects of strategies suppressing upstream molecules of the NLRP3 signaling pathway in the production of cytokines.

NLRP3 ROLE IN COVID-19

CRS is a term used to describe the hyper-inflammation condition (26). The release of a high amount of cytokines leads to severe inflammation and acute damage to multiple organs following SARS-CoV-2 infection (27). As a key component of innate immunity, inflammasomes are multiprotein complexes that aggregate in the cytoplasm in response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). As cytosolic sensors, activation of these complexes triggers the processing and production of pro-inflammatory cytokines. In addition, caspase-1 activated in inflammasomes induces pyroptosis, also referred to as gasdermin-mediated programmed necrotic cell death (14, 28). Following activation of these sensors, adaptor apoptosis-associated speck-like proteins containing a C-terminal caspase recruitment domain (ASC) are recruited to form inflammasome specks in myocytes and macrophages. Afterward, the recruitment of inflammatory caspase-1 leads to the production of cytokines (29).

The NLRP3 inflammasome has been under intense investigations which have proved its association with various inflammatory disorders (30). Two signals contribute to the stimulation of the NLRP3 inflammasome

activation: the first signal is the nuclear factor kappa B (NF-κB)-dependent signaling pathways, which is mediated by TNF-α, IL-1β, and Toll-like receptor (TLR) agonists; the second signal is mediated by multiple stimuli, ATP, bacterial pore-forming toxins (PFTs), nigericin, crystalline, or viral RNA, in addition to particulate matters (16, 31). Pyroptosis, a pro-inflammatory lytic cell death, is critical for controlling microbial infections. Several pathological stimuli (i.e., cancer, brain stroke, and CVD) can induce this type of cell death (32-34). It is featured by rapid loss of plasma membrane integrity and the release of pro-inflammatory markers and intracellular contents (35, 36). Recently, SARS-CoV-2 has been reported to activate inflammasomes in immune cells and tissues. The severity of disease and poor outcomes are correlated with the concentrations of inflammasome-related products, including active caspase-1, IL-1β, and IL-18 (37). The SARS-CoV ORF3a protein was revealed to induce NLRP3 inflammasome activity and elevate the secretion of IL-1β (38, 39).

Infection of rhesus macaques by SARS-CoV-2 was reported to increase the activity of caspase-1 and upregulate the pro-inflammatory biomarkers, e.g., TNFα, IL-1, IL-6, IL-8, C-reactive protein, MX dynamin-like GTPase1 (Mx1), and NF-κB in immune cells. The upregulation of these factors is accompanied by endothelial disruption, macrophage infiltration, platelet activation, and thrombosis in histopathologic sections of the lungs within two days after inoculation (40). Activation and modulation of the inflammasome complex and how SARS-CoV-2 infection intersects with this signaling pathway are vital fields of investigation (41). Caspase activity in COVID-19, especially caspase-1, has shown significance in SARS-CoV-2-induced coagulopathies (42, 43).

Given the above data from COVID-19 patients and especially the elevated concentrations of IL-1β and IL-18, it seems highly likely that SARS-CoV-2 activates the NLRP3 inflammasome. This activation and the subsequent pathologic events are likely to induce multiorgan dysfunction.

NLRP3 ROLE IN SARS-COV2-INDUCED MULTIORGAN DYSFUNCTIONS

Multiorgan damage, including the lung, heart, brain, liver, kidney, and spleen, has been detected in patients infected by SARS-CoV-2 (44). Previous studies have provided better knowledge of mechanisms underlying COVID-19-associated pathology. Herein, we mainly discuss the contribution of NLRP3 inflammasome in the pathogenesis of COVID-19 and associated multiorgan damages (Figure 1).

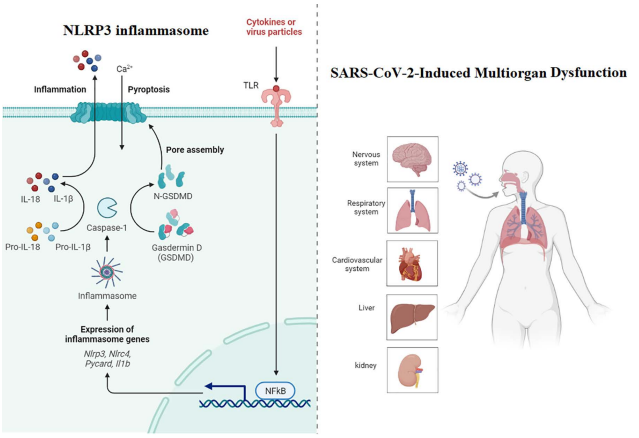

Figure 1. The role of NLRP3 inflammasome in SARS-CoV-2-induced multiorgan dysfunction in patients with COVID-19.

SARS-CoV-2 can activate the NLRP3 inflammasome to produce more inflammatory cytokines, including IL-1β and IL-18, and induce pyroptosis in the macrophages. This increases the level of cytokines and leads to induce cytokine storm and subsequently, increase the risk of multiorgan dysfunction (Created with BioRender.com).

Pulmonary damage

ARDS and respiratory failure are significant causes of mortality in COVID-19 patients. In particular, pulmonary pathologic features such as diffuse alveolar impairments and interstitial fibrosis following the infiltration of immune cells and the disturbance of the blood–air barrier, were recorded in the lung samples of COVID-19 cases (45). Post-mortem lung tissues from cases who died from COVID-19 exhibited several lung pathological alterations, including

an intermediate and early proliferative phase of subsequent alveolar damage, the presence of platelet–fibrin thrombi, and inflammatory characteristics (46-48).

SARS-CoV-2 induces the progression of a highly severe fibrotic response and increases the risk of idiopathic pulmonary fibrosis in severe cases of COVID-19 (49). To date, autopsy findings and animal models have confirmed that the abnormal expression of NLRP3 inflammasome has a key role in the pathophysiology of ARDS, which can predict poor outcomes of ARDS (50, 51). The number of NLRP3 and ASC-positive cells was extremely enhanced in the autopsy lung samples from COVID-19 patients compared to those of control lung samples (52). Notably, leukocytes of post-mortem lung tissues were positive for inflammasome components, including NLRP3, caspase-1, and ASC, in patients who died from COVID-19 (53). Furthermore, ASC speck formation and macrophage infiltration were observed in the lung autopsy findings of cases with COVID-19 (54). In severe patients, NLRP3-associated inflammatory pathways cause severe clinical manifestations, necrosis, the rise of DAMP, and severe inflammation of the lungs (55). Moreover, NLRP3 inflammasome directly contributes to the development of lung fibrosis (56). Exogenous IL-1β was reported to establish pulmonary damage by inducing inflammatory responses, alveolar tissue disturbance, tissue remodeling, and fibrosis (57). An elevated level of IL-18 was observed in the pathogenies of idiopathic pulmonary fibrosis (58). Therefore, targeting NLRP3 inflammasome may reduce the severity of inflammatory responses and prevent the progress of pulmonary fibrosis in COVID-19 cases.

Cardiovascular damage

Cardiovascular abnormalities are common among COVID-19 cases observed at different stages of the disease. Direct infection of cardiac tissue through the ACE2 receptor increases the risk of cardiac injury, thrombotic activity, and stress cardiomyopathy. Also, heart failure is associated with CRS induced by viral infection (59). The autopsy samples from COVID-19 cases showed several pathologic features including the severe deposition of fibrin in the capillaries, capillary dilation in the myocardium, and micro-hemorrhage (60). Moreover, remarkable vascular alterations were detected in autopsy samples of SARS-CoV-2-positive cases. SARS-CoV-2 directly invades endothelial cells in the vascular system due to the expression of ACE2 on their surfaces (61). Severe phenotypes, e.g., deep vein thrombosis, pulmonary arterial thromboembolism, and hypercoagulability, were seen in the blood vessels (61). Interestingly, patients with underlying CVDs might be vulnerable to SARS-CoV-2 infection (62).

According to the RNA sequencing of heart tissues, the immune-associated genes (i.e., chemokine ligands (CCLs) and ILs) and NF-κB-associated genes (i.e., IKBKG and NFKBIA) were dysregulated in COVID-19 patients and patients suffering from ischemic cardiomyopathy non- or ischemic dilated cardiomyopathy (62). The RNA sequencing of peripheral blood mononuclear cells (PBMCs) from cases with COVID-19 displays similar gene expression patterns of immune responses compared to those from cases with coronary artery diseases. Furthermore, dysregulation of inflammasome-associated genes, including NFKBIA and CHUK, was detected in both cases (62). Taken together, inhibition of NLRP3 inflammasome can be suggested as a potential therapeutic option for cardiovascular damage observed in COVID-19 patients.

Nervous system damage

It is well documented that SARS-CoV-2 induces diverse neuropsychological disorders leading to long-term consequences (63). More importantly, the autopsy findings have revealed that cortical neurons were infected by SARS-CoV-2 related to minimal immune cell infiltration in the CNS tissues (64). Recently, the virus was detected in the cerebrospinal fluid (CSF) of severe COVID-19 patients with neurological symptoms. Although SARS-CoV-2 presents some neurological complications such as hypogeusia, headaches, dizziness, impaired consciousness, myalgia,

hyposmia, ataxia, seizures, etc. (65-68), the pathogenic features of COVID-19-mediated CNS damage are still largely unknown.

Among various mechanisms defined for SARS-CoV-2, CRS can cause potentially life-threatening complications (69). On the other hand, SARS-CoV-2 may enter different cells of the CNS, including neurons, microglia, and astrocytes, endothelial cells of the blood–brain–barrier (BBB) through CD147 and ACE2 (70, 71). A post-mortem analysis of samples confirmed the presence of activated microglia and reactive astrogliosis in the cerebellum and medulla oblongata, along with the infiltration of immune cells (e.g., lymphocytes) into the parenchymal and perivascular regions in the brains of cases who died from SARS-CoV-2 infection (72).

Glial cells, notably astrocytes and microglia, are recognized as the main host cells of CNS tissue involved in COVID-19. Pro-inflammatory cytokines are mainly released by microglia and astrocytes, leading to neuroinflammation (71). BV-2 microglia induced by SARS-CoV-2 spike glycoprotein was reported to trigger the secretion of inflammatory mediators, e.g., TNFα, IL-1β, IL-6, and nitric oxide. Notably, NF-κB, NLRP3, and caspase-1 activity were elevated in the BV-2 microglial cell line after stimulation by SARS-CoV-2 spike glycoprotein (73). Moreover, spike protein stimulated the synthesis of NF-κB, interferon-beta, and TNF-α in human microglia (74). A post-mortem report of three COVID-19 cases showed that SARS-CoV-2-induced cerebral pathogenicity was associated with microglial NLRP3 inflammasome. Infiltrated CD68+ macrophages co-localized within the brain were positive for NLRP3 (75).

Generally, activation of caspase-1 mediated by NLRP3 inflammasome increases the cleavage of IL-18 and IL-1β from their pro-forms and leads to pyroptosis. Active caspase-1 also induces BBB disturbance and triggers neuroinflammatory responses (76, 77). In this regard, elevated levels of ILs stimulate the production of other pro-inflammatory mediators by neurons, astrocytes, and microglia, resulting in neuroinflammation (78-80). It has been reported that IL-1β, secreted by activated microglia, plays a crucial role in the BBB disruption and subsequently increased permeability allowing for inflammatory and immune cells to reach the brain parenchyma (81, 82). Likewise, IL-18 can activate microglia via the activation of caspase-1 and the secretion of inflammatory mediators into the CNS (83, 84).

P2X7 receptors and viroporins of SARS-CoV-2 were reported to promote the assembly of inflammasome and lead to pyroptosis in CNS glial cells (85, 86). Pyroptosis is characterized by the formation of pores mediated by gasdermins on the cell membrane following caspase-1 activation, resulting in the rapid release of pro-inflammatory mediators into the extracellular space (87). These pathological events intensify neuroinflammation-triggered CNS damage and induce neuropsychological symptoms following SARS-CoV-2 infection (88). NLRP3 inflammasome contributes to COVID-19-associated CNS damages, confirming its potential role as a therapeutic target.

Hepatic damage

Hepatic symptoms also were detected in COVID-19 patients. According to findings of the post-mortem evaluations, SARS-CoV-2 infection contributes to inducing platelet-fibrin microthrombi, hyperplasia, aberrant hepatic enzymes, lobular inflammation, ischemic hepatic necrosis, and steatosis (89). Binuclear hepatocytes and massive apoptosis were reported in the liver tissues infected by SARS-CoV-2 (90). Furthermore, the elevated levels of lactate dehydrogenase (LDH) and IL-18 in the liver samples and enhanced activity of T lymphocyte caspase-1 were seen in COVID-19 patients who suffered from liver cirrhosis and alcoholic fatty liver disease, suggesting that pyroptosis mechanisms may play an essential role in severe illness (16, 91).

While the virus can be detected in the hepatic cells, CRS exhibits a significant role in the pathogenies of SARS-CoV-2-induced liver injuries (92). Increased activity of Kupffer cells, resident liver macrophages, was observed in post-

mortem biopsies of infected cases (93). The attendance of these cells within the sinusoidal regions was reported. Furthermore, sinusoidal and pericellular fibrosis was detected in COVID-19 autopsy specimens (94). In inflammatory conditions, Kupffer cells were shown to be activated through different mechanisms, and they can induce liver damage and fibrosis via dysregulation of the NLRP3 inflammasome and overproduction of IL-1β (95, 96). There is no evidence to show the involvement of NLRP3 inflammasome in the pathology of COVID-19-associated liver damage. So, further investigations are required to find the related pathways and potential therapies.

Renal damage

Acute renal failure (ARF) has also been documented in individuals hospitalized due to COVID-19 (97). A reduction in the density of kidneys was observed in CT scans of these patients, confirming renal inflammation and edema (98). SARS-CoV-2 may infect renal cells (i.e., proximal straight tubule cells and podocytes) and induce renal injury in patients with COVID-19 (99). Recent evidence has revealed that inflammation-triggered tissue damage is a basic pathological mechanism underlying the establishment of sepsis-induced ARF (100). On the other hand, AKI may occur in response to CRS due to renal inflammation in COVID-19 cases (101). In SARS-CoV-2 infections, infiltration of pro-inflammatory cells (i.e., CD68+ macrophages) into the tubulointerstitium of renal tissues was observed (102). The macrophage infiltration plays a key role in inducing inflammation, fibrosis, and renal injury, which contribute to disease progress (100). Additionally, COVID-19-associated hemophagocytic macrophage activation and microangiopathy can cause ARF (103). Hypoperfusion due to CRS partly leads to renal injury (104). There was no data to support the involvement of NLRP3 inflammasome in the pathogenesis of SARS-CoV-2-induced ARF. However, the abnormal activation of NLRP3 inflammasome is linked to the inflammatory disease associated with ARF (105). Therefore, NLRP3 suppression may be a potential emerging approach for managing the ARF in patients with COVID-19.

AVAILABLE STRATEGIES FOR SUPPRESSION OF NLRP3 INFLAMMASOME

Immunomodulatory failure and organ dysfunction are major leading causes of death in many patients with COVID-19 accompanied by pneumonia, ARDS, or CRS (106-108). Immunomodulatory therapies targeting the NLRP3 inflammasome formation and activity will be required to control SARS-CoV-2-induced inflammation and subsequent multiorgan dysfunction during the COVID-19 pandemic.

NLRP3 inhibition

Dexamethasone is widely used for the management of COVID-19. The treatment of SARS-CoV-2 S1 protein-stimulated human PBMCs with dexamethasone diminished the dysregulation of IL-1β, which can slightly modulate the protein levels of NLRP3 (52). MCC950S, a selective NLRP3 inflammasome inhibitor, can reverse S-protein-triggered NLRP3 inflammasome activation and suppress the release of IL-1β in primary human monocytes (37). Moreover, colchicine, an available, safe, and inexpensive drug with anti-inflammatory effects on NLRP3 inflammasome, could not be effective on the duration of hospitalization, 28-day mortality, oxygen-support requirements, or death (109).

Glyburide, an antidiabetic medicine, was reported to reverse the activation of the NLRP3 inflammasome via inhibition of K+ efflux and reduce the secretion of IL-1β from cells infected by other RNA viruses, such as encephalomyocarditis virus and vesicular stomatitis virus (110, 111). CRID3 (NLRP3 inhibitor) administration could efficiently diminish the expression of caspase-1 NLRP3 and reverse the elevated levels of IL-1β in human PBMCs exposed to the SARS-CoV-2 S1 protein (52). Also, targeting NlRP3 via nanotechnology-based products can be used to treat COVID-19 patients (112). For example, 25-hydroxycholesterol and didodecyldimethylammonium

bromide (25-HC@DDAB) nanovesicles were designed to inhibit lung diseases, effectively. The 25-HC@DDAB was shown to inhibit the CRS in PBMCs isolated from cases infected with SARS-CoV-2. Moreover, the treatment with 25-HC@DDAB could successfully reverse the gene expression of the NLRP3 and inhibit the secretion of IL-1β from peripheral blood mononuclear cells (PBMCs) isolated from severe patients (112). Bay 11-7082, a phenyl vinyl sulfone-related substance, has been proposed to exhibit its beneficial effects via suppressing the NLRP3 inflammasome (5). Besides, pretreatment of SARS-CoV-2 S-exposed human PBMCs with an NF-κB inhibitor, BAY-11-7082, suppressed the NF-κB p65 phosphorylation and prevented the NF-κB p65 translocation to the nucleus in the (52).

Recently, natural products attracted more attention for the management of COVID-19. Some of these components can prevent the NLRP3 inflammasome activation including dihydroquercetin (113), resveratrol (114), quercetin (115), isoliquiritigenin (116), icariin (117), oridonin (118). So, these active agents can be introduced as a good candidate for the regulation of SARS-CoV-2-induced NLRP3 inflammasome activation.

On the other hand, a list of antiviral natural components without considering their role in the suppression of NLRP3 inflammasome has been recommended including resveratrol, baicalin, coumarin, naringenin, and epigallocatechin 3-gallate (119). Among several effective substances, curcumin, also called diferuloylmethane, is a principal curcuminoid of turmeric and has been demonstrated to inhibit the NLRP3 inflammasome observed in COVID-19 patients without any adverse effects (120). Therefore, suppression of the NLRP3 inflammasome through specific inhibitors or with agents with this ability can be used as a potential therapeutic approach for the management of COVID-19.

ASC inhibition

There was no report to show the effects of specific inhibitors of ASC in the regulation of inflammation in COVID-19 patients. Nevertheless, metformin, a diabetes medicine, could prevent SARS-CoV-2-associated pulmonary inflammation via attenuating ASC speck formation and immune cell recruitment in SARS-CoV-2-infected animals (54). More investigations are required to prove the effects of ASC inhibitors in the treatment of COVID-19.

Caspase inhibition

VX-765, known as a caspase-1 inhibitor, could not effectively reverse the SARS-CoV-2-induced IL-1β secretion (121). An elevated level of IL-1β following infection with SARS-CoV-2 was suppressed by the treatment with AC -YVAD-CMK, a caspase-1 inhibitor, or Z-VAD-FMK, a pan-caspase inhibitor (122). In the same way, emricasan (pan-caspase inhibitor) could suppress the activity of caspase-1 in CD4+ T lymphocytes isolated from COVID-19 patients with moderate to severe illness (123). A growing body of evidence has confirmed the effectiveness of some caspase inhibitors. However, more investigations are needed to prove their potential in the treatment of SARS-CoV-2 infection.

IL-1 inhibition

Blockage of IL-1β through canakinumab, a fully human IgG monoclonal antibody, beneficially affected mechanical ventilation requirements in COVID-19 patients with pneumonia (124). Similarly, IL-1RA (the IL-1 receptor antagonist) suppressed the SARS-CoV-2-induced caspase-1 activation and pyroptosis. It could reverse the overproduction of pro-inflammatory mediators, including IL-6 and TNF-α (122). Anakinra is a recombinant IL-1RA, which is known to decrease proinflammatory mediators (e.g., IL-1α and IL-1β). In the same way, Anakinra displayed clinical improvements in COVID-19 patients. A high dose of anakinra could suppress hyperinflammation and CRS and exhibit effectiveness in reversing respiratory dysfunction in patients with COVID-19 (125). Therefore, IL-1 inhibitors are a potential therapeutic approach for the management of COVID-19 patients.

CONCLUSIONS

In summary, CRS leads to detrimental clinical outcomes in some patients infected with SARS-CoV2. NLRP3 inflammasome may be a key regulator of the CRS and subsequent multiorgan dysfunction. Infection by the virus can stimulate the NLRP3 inflammasome activation and induce the production of pro-inflammatory cytokines. The NLRP3 inflammasome modulation exhibits a therapeutic effect against COVID-19. Several agents with anti-inflammatory properties can suppress the gene expression of the NLRP3 inflammasome components and reduce the levels of inflammatory cytokines. In addition, they can reduce caspase-1-mediated cell death. On the other hand, the inhibition of the NLRP3 inflammasome complex formation and activation may help to determine the pathogenic mechanisms underlying COVID-19 and establish novel promising therapeutic strategies. While there are limited observations or clinical trials to confirm the beneficial effects of therapeutic candidates, they can be examined and applied in clinical practice.

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