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Targeting the NLRP3 Inflammasome in Severe COVID-19

*Tracey L. Freeman and Talia H. Swartz**

Division of Infectious Diseases, Department of Medicine, Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of the genus *Betacoronavirus* within the family *Coronaviridae*. It is an enveloped single-stranded positive-sense RNA virus. Since December of 2019, a global expansion of the infection has occurred with widespread dissemination of coronavirus disease 2019 (COVID-19). COVID-19 often manifests as only mild cold-like symptomatology, but severe disease with complications occurs in 15% of cases. Respiratory failure occurs in severe disease that can be accompanied by a systemic inflammatory reaction characterized by inflammatory cytokine release. In severe cases, fatality is caused by the rapid development of severe lung injury characteristic of acute respiratory distress syndrome (ARDS). Although ARDS is a complication of SARS-CoV-2 infection, it is not viral replication or infection that causes tissue injury; rather, it is the result of dysregulated hyperinflammation in response to viral infection. This pathology is characterized by intense, rapid stimulation of the innate immune response that triggers activation of the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome pathway and release of its products including the proinflammatory cytokines IL-6 and IL-1β. Here we review the literature that describes the pathogenesis of severe COVID-19 and NLRP3 activation and describe an important role in targeting this pathway for the treatment of severe COVID-19.

Keywords: NLRP3 inflammasome, COVID-19, SARS-CoV-2, IL-1β, cytokine release syndrome (CRS), cytokine storm, coronavirus, acute respiratory distress syndrome (ARDS)

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***Correspondence:**
Talia H. Swartz
talia.swartz@mssm.edu

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of the genus *Betacoronavirus* within the family *Coronaviridae*. It is an enveloped single-stranded positive-sense RNA virus (1). In December of 2019, the first cases of an atypical viral pneumonia were reported in Wuhan, China. Since that time, a global expansion of the infection has occurred with widespread dissemination of coronavirus disease 2019 (COVID-19) (2, 3). For most, the infection is mild with low-grade fever and cough, but 15% are associated with respiratory compromise. Severe cases result in acute respiratory distress syndrome (ARDS) with systemic inflammation in which lung injury is associated with release of inflammatory cytokines IL-6 and IL-1β (2, 4). The systemic inflammatory syndrome is characterized by dysregulated proinflammatory cytokine cascades triggered by an intense, rapid activation of the innate immune response. COVID-19 severity is associated with increased proinflammatory cytokines and chemokines and IL-6, specifically, is predictive of COVID-19 fatality (5). High levels of interleukin IL-1β and IL-6 were detected in autopsy tissues from SARS-CoV patients (6) and single cell RNA-seq analysis of peripheral

blood in COVID-19 patients show increased subsets of $CD14^+$ IL-1β-producing monocytes (7). A clear mechanism is not yet understood. The inflammatory basis underlying COVID-19 fatality renders development of immunoregulatory agents of paramount importance (8). There is significant literature implicating the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome, and cytokine release syndrome or cytokine storm in this pathogenesis (9–12). The NLRP3 inflammasome is an important cause of activation of the innate immune system to recognize pathogens, including viral infections (13, 14). SARS-CoV 3a protein activates the NLRP3 inflammasome in lipopolysaccharide-primed macrophages with 3a-mediated IL-1β secretion associated with K^+ efflux and mitochondrial reactive oxygen species (15).

Individuals at risk for this inflammatory syndrome include those with hypertension, diabetes, cardiovascular disease, respiratory disease, and cancer (16, 17). It is not clear why individuals at risk include those with cardiovascular risk factors but may relate to the virology of SARS-CoV-2 infection. SARS-CoV uses the spike glycoprotein (S protein) on the surface of the virion to mediate viral membrane fusion (18). The S protein is a trimer that is cleaved into S1 and S2 subunits; S1 binds directly to the peptidase domain of angiotensin-converting enzyme 2 (ACE2) (19) to expose S2 to cleavage that enables fusion and entry (20). The physiological function of ACE2 in the cell is the maturation of angiotensin (Ang) which regulates blood pressure through vasoconstriction. Clinical literature based on the 2003 SARS-CoV epidemic suggested that the virus caused ACE2 downregulation and that lung injury may be improved by Angiotensive II Receptor Blocker (ARB) treatment (21, 22). Further literature implicates ACE2 signaling in NLRP3 activation in multiple settings. AngII can induce NLRP3 inflammasome activation in renal tubular epithelial cells (23), AngII induces pulmonary fibrosis which is attenuated by ACE2 (24), and NLRP3 inflammasome activation drives Ang II-induced vascular smooth muscle cell (VSMC) proliferation and vascular remodeling and hypertension (25, 26).

COVID-19 INFECTION CLINICAL SYNDROME

Individuals infected with SARS-CoV-2 can present with an array of clinical severity from asymptomatic through severe disease characterized by pneumonia requiring supplemental oxygen, and progression to acute respiratory distress syndrome (ARDS) with systemic inflammatory response syndrome (SIRS), shock and multiorgan dysfunction, coagulopathy, and death (27). Early symptoms can include shortness of breath, fever, and cough with increasing reports of loss of taste and smell (4, 17, 28–30). Individuals demonstrated to be at high risk of severe outcomes include those with advanced age, hypertension, cardiovascular disease, and diabetes mellitus (4, 29, 31, 32). Severe COVID-19 is associated with increased serum inflammatory cytokine levels including IL-1, IL-6, granulocyte-colony stimulating factor (G-CSF), interferon-γ inducible protein 10 (IP-10), and tumor necrosis factor-α (TNF-α) (5, 17, 33–36).

Overwhelming inflammatory cytokine secretion can result in ARDS through massive recruitment of immune cells leading to vascular leakage, fluid accumulation causing pulmonary edema, and resulting hypoxemia (37–39). Reports of patients with severe COVID-19 indicate that elevated levels of IL-1β and IL-6 are associated with elevated immune exhaustion and reduced T cell functional diversity (40). By contrast, individuals with COVID-19 who experience more mild disease have lower levels of IL-6, together with activated T lymphocytes and IgM SARS-CoV-2-binding antibodies (41). These observations indicate that a robust inflammatory cytokine response mediates severe disease while low inflammatory cytokine responses may be associated with an adaptive response that favors disease resolution. IL-1β is a key regulator of many chronic inflammatory diseases (42–49). Therefore, probing the role of IL-1β and its inhibition might lead to reduced inflammatory signaling, thus reducing lung injury in ARDS associated with severe COVID-19.

NLRP3 INFLAMMASOME BIOLOGY

The NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome consists of a sensor (NLRP3), an adaptor (ASC; also known as PYCARD), and an effector (caspase 1) (50). NLRP3 contains an amino-terminal pyrin domain (PYD), a central NACHT domain (domain present in NAIP, CIITA, HET-E, and TP1) and a carboxy-terminal leucine-rich repeat domain (LRR domain). The NACHT domain mediates ATPase function that is vital for NLRP3 self-association and function (51) and the LRR domains autoregulate through folding back onto the NACHT domain. ASC has two protein binding domains, an amino-terminal PYD and a carboxy-terminal caspase recruitment domain (CARD). NLRP3 can oligomerize between NACHT domains upon stimulation which leads to ASC recruitment through PYD–PYD interactions. The formation of multiple ASC filaments is referred to as an ASC speck (52–54). The assembled ASC complex can recruit caspase 1 to facilitate cleavage and activation.

Activation of the inflammasome is highly regulated and mediated by a two-step process in which first priming occurs and then activation occurs. Priming allows for transcription upregulation of the NLRP3 genes in response to recognition of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides and viral RNA, or damage-associated molecular patterns (DAMPs), such as ATP and reactive oxygen species, through purine sensing receptors including P2RX7 (13, 14, 54–56). Engagement of PAMPS and/or DAMPS can activate pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) or nucleotide-binding oligomerization domain-containing protein 2 (NOD2). This leads to activation of nuclear factor-κB (NF-κB) activation and gene transcription (57). Priming also shifts oxidative phosphorylation to glycolysis in macrophages, resulting in stabilization of hypoxia-inducible factor 1α (HIF1α) and increase in *IL1B* gene transcription (58). Priming additionally induces post-translational modifications of the NLRP3 inflammasome which include ubiquitylation, phosphorylation, and sumoylation that stabilize the NLRP3

inflammasome in an auto-suppressed inactive, signal-competent, state (59).

After priming, NLRP3 inflammasome activation can occur in response to an array of pathogens or endogenous DAMPs. Multiple cellular signaling events can result in NLRP3 activation at the membrane, including efflux of potassium (K^+) or chloride ions (Cl^-), and flux of calcium ions (Ca^{2+}) (60–70) as well as other cellular functions including lysosomal disruption, mitochondrial dysfunction, metabolic changes, and *trans*-Golgi disassembly (50).

NLRP3 activation can lead to pyroptosis, an inflammatory programmed cell death pathway that takes place in T lymphocytes (71). This inflammatory cell death is activated through gasdermin D (GSDMD) cleavage by caspase 1, 4, 5, and/or 11 and results in a series of cellular events including swelling of the cytoplasm, plasma membrane rupture, and consolidation of the nucleus with release of cytoplasmic contents into the extracellular space (72, 73). GSDMD contains an amino-terminal cell death domain ($GSDMD^{Nterm}$) which is exposed through caspase cleavage to bind phosphatidylinositol phosphates and phosphatidylserine in the cell membrane, inserting into the plasma membrane and forming a pore that kills the cell from within (74, 75). Additionally, GSDMD can mediate IL-1β and IL-18 secretion (76, 77) and this occurs both through pathways dependent and independent of NLRP3 signaling.

Cell death is an important cause of pathogenesis in viral infections. HIV-1 infection is associated with programmed cell death through pyroptosis in bystander cells (78–82) and represents an important mechanism of NLRP3 inflammasome-mediated immune cell depletion. Programmed cell death through multiple mechanisms has been reported in coronavirus infections as an important mechanism of viral pathogenesis (83–88).

THE NLRP3 INFLAMMASOME IN CORONAVIRUS PATHOGENESIS

There are numerous studies that implicate the NLRP3 inflammasome and IL-1β in mediating inflammation during lung injury and ARDS (39, 89, 90). Bronchoalveolar fluid and plasma in patients with ARDS have elevated IL-1β levels compared to healthy controls (91–94) and is associated with worse clinical outcomes. In other coronavirus infections including MERS-CoV and SARS-CoV, patients with ARDS had high levels of IL-1β, IL-6, and IL-8 (6, 95–97). In other respiratory viral infections such as influenza, high levels of IL-1β have been detected in bronchoalveolar fluid and plasma from patients with lung injury (91–94, 98–101). Furthermore, animal studies in which mice deficient in components of the inflammasome have reduced lung injury and enhanced survival with influenza infection (45, 102). In pharmacologic studies in which IL-1β or IL-1R was antagonized, influenza associated lung injury was reduced (103, 104). Taken together, IL-1β appears to play a key role in acute lung injury with respiratory viral infections and pharmacologic targeting of this pathway represents an important area of intervention.

Injury of type II alveolar epithelial cells expressing ACE2 leads to NLRP3 inflammasome activation (14, 15, 105). The acute immune response to SARS-CoV-2 infection is largely driven by inflammatory alveolar and monocyte-derived macrophages that are activated by PAMPs and DAMPs released by infected, apoptotic pneumocytes (11, 106–108). TNF-α and IL-1β secreted by alveolar macrophages initiate the acute proinflammatory cascade immediately following infection. The secretion of these cytokines induces cell death and damage, PAMP/DAMP production, immune cell recruitment, and widespread NLRP3 activation, establishing a proinflammatory positive feedback cascade (11, 106, 108–110). More recently, Blanco-Melo et al. demonstrated that SARS-CoV-2 infection of primary human bronchial epithelial cells resulted in expression of multiple cytokines and chemokines including TNF-α, IL-6, and IL-1β (111).

This localized inflammatory cell death extends to the vasculature, inducing the leakage, edema, and pneumonia characteristic of COVID-19 (11, 108, 109). It is important to note that the onset of this pathological immune response is characterized not by systemic inflammation, but by a hyperinflammatory microenvironment localized to the site of tissue injury. As the inflammatory cascade progresses, IL-1β, and TNF-α induce the secretion of additional NLRP3 cytokines such as IL-6 which can subsequently be observed in the peripheral blood due to the loss of vascular integrity (11, 107–110, 112, 113). The kinetics of the inflammatory response are essential to effective clinical practice—circulating biomarkers such as IL-6 may prove useful to predicting outcomes and informing immunomodulatory treatment decisions (31, 33, 114–116).

The rapid decline of COVID-19 patients coincides with an abrupt shift from the NLRP3 cytokine storm to a compensatory immunosuppressive state (5, 107). This repair and recovery-oriented phase is characterized by production of IL-10, polarization of macrophages to the anti-inflammatory M2 state, suppression of NLRP3, and recruitment of fibroblasts and platelets. The accumulation of fibroblasts and M2 macrophages in the lung initiates the deposition of collagen and construction of the extracellular matrices that characterize ARDS fibrosis (11, 108, 117). M2 macrophages and other markers of this pro-fibrotic, anti-inflammatory environment have been detected in the bronchioalveolar fluid of severe COVID-19 patients (117, 118).

Unique to SARS-CoV and SARS-CoV-2 is the downmodulation of the ACE2 receptor. SARS-CoV entry has been reported to be dependent on TNF-α converting enzyme and coupled to the release of TNF-α from the cell membrane (110). TNF-α, specifically, has been shown to act as an alternative toll-like receptor (TLR) agonist that may increase the sensitivity and longevity of NLRP3 activation (113, 119). Downregulation of ACE2 is associated with both SARS-CoV and SARS-CoV-2 disease severity (21, 120, 121); this contrasts with a minimally symptomatic coronavirus strain, HCoV-NL63, that utilizes but does not cleave or downmodulate the ACE2 receptor (122). The overproduction of TNF-α in COVID-19 may preferentially activate the NLRP3 inflammasome relative to other immunological pathways. These observations warrant further

TABLE 1 | NLRP3 inflammasome-targeted therapeutics in development.

Development stage	Drug name	Company	Mechanism of action	Reference(s)
Preclinical	N/A	Ardan ImmunoPharma	Small-molecule activators and inhibitors of the TMEM176B ion channel, which is an inhibitor of the inflammasome	(132, 133)
	N/A	Genentech	NLRP3 inhibitors acquired from Jecure Therapeutics	(134)
	N/A	IFM Therapeutics	Small-molecule inhibitors of the NLRP1, NLRP6, NLRP10, and NLRC4 inflammasomes	(134)
	N/A	NodThera	Small-molecule NLRP3 inhibitors expected to begin clinical studies this year	(134)
	IC 100	ZyVersa Therapeutics	Antibody inhibitors of the inflammasome protein ASC	(135)
Phase I	N/A	Bristol-Myers Squibb	NLRP3 activators for cancer immunotherapy acquired from IFM Therapeutics	(134)
	CRID3 (CP-456, 773, MCC950)	Pfizer	Selective NLRP3 inhibitor	(134, 136–138)
	Inzomelid (also Somalix)	Inflazome	Small-molecule NLRP3 inhibitors	(134, 139)
	IFM-2427	Novartis	Small-molecule NLRP3 inhibitors acquired from IFM Therapeutics and developed in-house	(135)
Phase II	Dapansutrile (OLT1177)	Olatec Therapeutics	Small-molecule NLRP3 inhibitors	(140–143)
	Canakinumab	Novartis	IL-1β-neutralizing antibody	(144, 145)
	Anakinra	Sobi	Recombinant IL-1 receptor antagonist	(146, 147)
	Rilonacept	Regeneron	Decoy receptor that binds IL-1β and IL-1α	(147–149)
	Gevokizumab	XOMA	Decreases the binding affinity of IL-1β for the IL-1 receptor	(150–152)

investigation into the mechanisms by and extent to which TNF-α acts as a significant modulator of severe COVID-19.

The SARS-CoV genome encodes 3 ion channel proteins: E, open reading frame 3a (ORF3a), and ORF8a in which E and ORF3a are required for both replication and virulence (87, 109, 123–126). In addition to the canonical NLRP3 activation pathway by PAMPs and DAMPs, the E, 3a, and 8b proteins of SARS-CoV function as NLRP3 agonists (84, 107, 109, 123, 127); many of these sequences are conserved in SARS-CoV-2 and likely play a role in inflammatory pathogenesis (107, 128). The SARS-CoV E, 3a, and 8b proteins are all reported to induce NLRP3 activation and IL-1β release in LPS-primed macrophage models (15, 127). A wide variety of mechanisms have been proposed for this NLRP3 agonism including E-, 3a-, and 8b-induced viroporin activity, interferon antagonism, membrane-bound organelle stress, reactive oxygen species production, and direct binding to and regulation of inflammasome components such as caspase 1, NLRP3, and NF-κB (15, 86, 107, 109, 112, 123, 127). There are multiple pathways by which SARS-CoV triggers NLRP3 activation which have yet to be characterized and are likely influenced by cell type and the extracellular microenvironment (15, 84, 86, 88, 107).

Notably, the NLRP3-implicated ORFs 3a and 8 are the primary sites driving genetic diversification of SARS-CoV-2. ORF3a, specifically, is the only gene undergoing diversifying mutations that are predicted to exhibit altered phenotypes (84, 113, 127, 129). Ongoing mutations in ORF8 are particularly concerning, as a 29-nt deletion of the SARS-CoV genome is suspected to have increased the pathogenicity of the virus during the SARS-CoV epidemic by antagonizing interferon, increasing viral titers, and agonizing NLRP3 (127, 130). The uniquely low homology between SARS-CoV-2 and SARS-CoV ORFs 3a and 8 may play a role in the differences in virulence and pathogenesis between these two related viral infections (107, 131). Defining the inflammatory activities of these two proteins is therefore critical to predictive monitoring and modeling of novel SARS-CoV-2 strain emergence.

Genetic variations in host inflammasome pathways may also influence disease outcome. Mutations in the LRR domain of bat NLRP3 mediate an overall dampened NLRP3 response to agonists (85). In the context of coronavirus infections, MERS-CoV does not induce clinical disease in bats despite high viral titers; this appears to be mediated by NLRP3 (85). Interestingly, SARS-CoV ORF8b is reported to activate NLRP3 via direct binding to the LRR domain, suggesting a mechanism of coronavirus-induced NLRP3 activation and further indicating therapeutic potential for NLRP3 immunomodulatory agents (127). Defining these mechanisms should be a focus of SARS-CoV-2 research so as to identify targeted therapeutics such as those summarized in **Table 1**.

THE NLRP3 INFLAMMASOME IN CYTOKINE RELEASE SYNDROMES

Cytokine release syndrome (CRS) is a systemic inflammatory response that can be triggered by a number of stimuli including drugs and infections (153, 154). The term was originally coined in response to administration of anti-T-cell antibody muromonab-CD3 (OKT3) to solid organ transplant patients who experienced an idiosyncratic cytokine storm following treatment (155, 156). A number of other drugs have stimulated

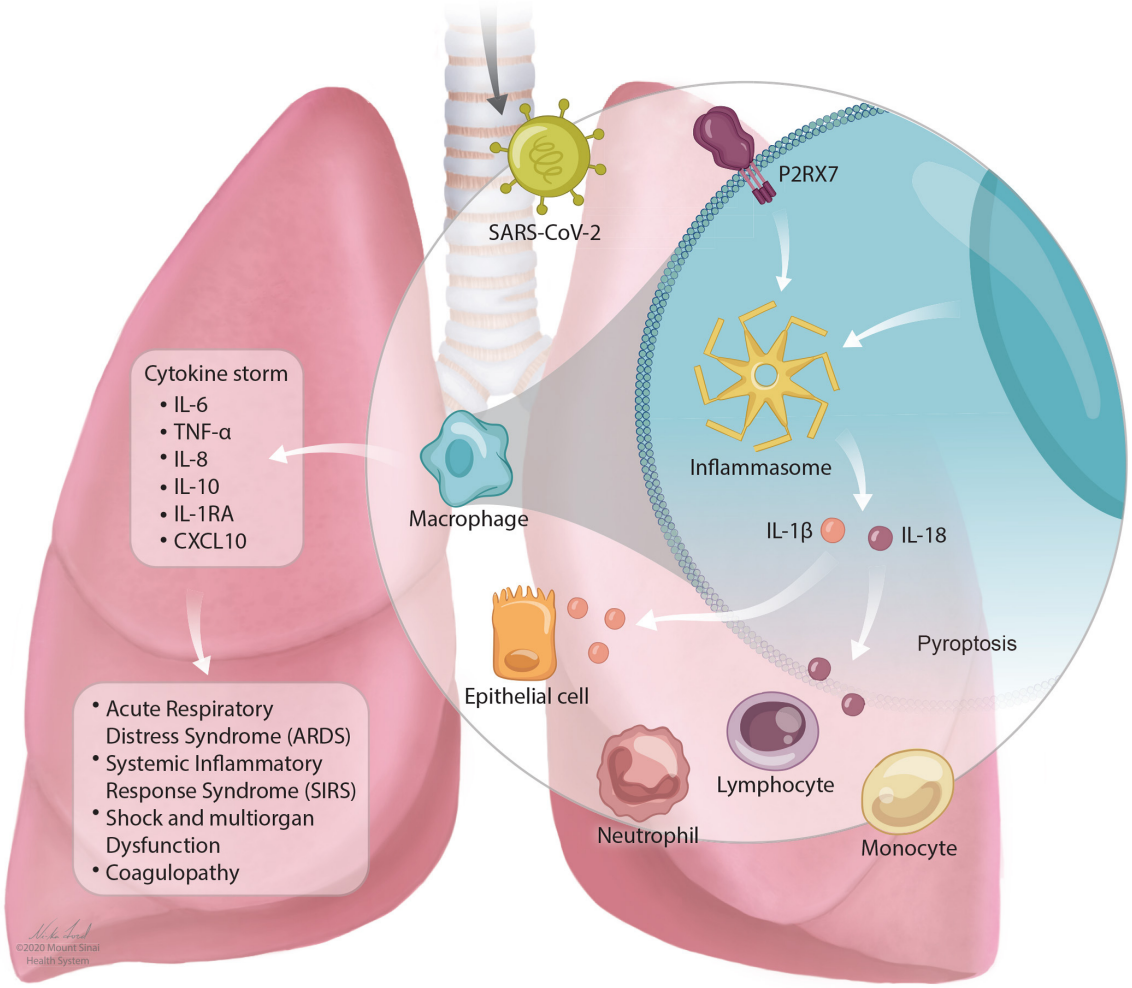

FIGURE 1 | The NLRP3 inflammasome mediates lung inflammation in SARS-CoV-2 infection. SARS-CoV-2 is inhaled into the airway and mediates activation of the P2RX7 receptor by release of extracellular ATP. P2RX7 signaling can lead to NLRP3 activation through direct or indirect activation in activated macrophages. Activation of the NLRP3 inflammasome drives the secretion of IL-1β and IL-18 which can result in pyroptosis (programmed cell death). Activation of immune cell subsets, largely through activated macrophages, results in a cascade of massive inflammatory cytokine activation including IL-6, TNF-α, IL-8, IL-10, IL-1RA, and CXCL10 that lead to acute lung injury with acute respiratory distress syndrome, systemic inflammatory response syndrome (SIRS), shock and multiorgan dysfunction, and coagulopathy.

similar infusion reactions including antibody-based therapies (157–164) and cancer therapeutics (165, 166). Other reported stimuli for the development of CRS include haploidentical donor stem cell transplantation, graft-vs.-host disease (167, 168), and respiratory viral infections including influenza (11, 169). Most recently, new classes of immunotherapeutic agents are used in a variety of hematologic malignancies including bispecific antibody constructs and chimeric antigen receptor (CAR) T cell therapies.

In response to these stimuli, patients experience robust cytokine-mediated response that is associated with fever, hypotension and hypoxemia. The syndrome can be mild and resolve spontaneously or can progress to persistent high-grade fevers, vasodilatory shock with hemodynamic instability, severe hypoxemia requiring mechanical ventilation. This can be associated with end-organ damage including liver injury, cardiac ischemia, clotting dysfunction, kidney dysfunction, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (154). The timing of onset is unpredictable, between 1 day to 2 months after exposure (170).

In SARS-CoV-2 infection, a cytokine storm occurs that has similar features to CRS as described above. Individuals with severe COVID-19 with cytokine storm have elevated systemic inflammatory biomarkers including C-reactive protein, D-dimer, ferritin (3, 115, 171–173). Patients experience a dysfunctional immune response characterized by high levels of plasma cytokines including IL-6, TNF-α, IL-8, IL-10, IL-1RA, and CXCL10 (4, 117). IL-6 levels increase over time higher in those who die of the infection compared to those who survive (27). The stimulation of inflammatory cytokines, largely through activated macrophages, leads to acute lung injury, acute respiratory distress syndrome, systemic inflammatory response syndrome (SIRS), shock and multiorgan dysfunction, and coagulopathy (117). This is described in **Figure 1**.

Individuals with severe COVID-19 have developed a coagulopathy which is associated with reduced platelet count, increased levels of fibrin degradation productions (D-dimer), and increased microthrombi in lungs, brain, kidney, and extremities (174–176). The NLRP3 inflammasome may play a key role in mediating this coagulopathy. Activated macrophages undergoing NLRP3 inflammasome activation release tissue factor which initiates coagulation (177, 178), regulation of platelet integrins (179, 180), and through hypoxia-inducible factor 1-alpha (HIF-1α) (181). Whether NLRP3 inflammasome activation as a mediator of coagulopathy is an area of great interest for future investigation.

NLRP3-TARGETED THERAPEUTICS

Experimental therapeutics assessed *in vitro* and *in vivo* have provided further insight into the role of NLRP3 in mediating SARS-CoV pathogenicity. In bone marrow-derived macrophages, a mitochondrial antioxidant reduced IL-1β secretion induced by SARS-CoV 3a and E proteins (15). In SARS-CoV-infected mice, the NF-κB antagonists CAPE, resveratrol, Bay11-7082, and parthenolide improved survival and reduced proinflammatory cytokine levels in the lungs (182). Depletion of inflammatory macrophages also mitigated SARS-CoV-associated inflammatory lung pathology in mice without impacting viral load (108). These reports elucidate molecular and clinical inflammatory phenotypes that appear to parallel those seen in COVID-19 and should be used to inform novel therapeutic development and pathogenesis studies.

Cross-regulation between type I interferon (IFN-I) and the NLRP3 inflammasome is implicated in the abrupt proinflammatory response to immunosuppressive switch characteristic of SARS and COVID-19 ARDS through an undefined mechanism (5, 107). Early IFN-I administration may therapeutically regulate NLRP3 and has been shown to abrogate clinical symptomatology in SARS-CoV-infected macaques (112) and mice (108). Dual corticosteroid-IFN-I treatment appeared to improve outcomes in a small-cohort SARS-CoV trial (183, 184). The therapeutic impact observed in mice, macaques, and humans in each setting occurred despite unchanged viral loads (108, 112, 183, 184).

Both IL-6R and IL-1 receptor blocking agents have been used for the treatment of CRS (185, 186). Tocilizumab, an IL-6R blocking antibody has been used to treat severe CRS (187, 188) in the setting of CAR-T cell therapy and in the setting of SARS-CoV-2 infection (5). Similarly, the IL-1 receptor antagonist anakinra improves CAR-T cell therapy CRS outcomes and also significantly increases survival of SARS-CoV-infected mice with hyperactive NLRP3 inflammasomes (186, 189, 190). In a retrospective cohort analysis, intravenous administration of high-dose anakinra increased survival and clinical improvement in COVID-19 patients with ARDS (191). Evidence from CAR-T-induced CRS suggests parallels to the COVID-19 inflammatory response that would suggest that targeting IL-1β would reduce the inflammatory signaling that mediates lung injury, ARDS, and mortality. **Table 1** shows a list of agents in various stages of development that target the NLRP3 inflammasome.

Therapeutics targeting IL-1β and the NLRP3 inflammasome pathway have similarly been employed and efficacious in the context of cardiovascular disease. The NLRP3 inhibitors arglabin and MCC950 reduced IL-1β plasma levels and decreased atherosclerotic lesion size (48, 192). IL-1β neutralizing antibodies and anakinra showed reduced cardiac hypertrophy and myocardial dysfunction post-MI (193–195). The CANTOS trial randomized patients with past MI and elevated hsCRP to receive canakinumab, a monoclonal antibody targeting IL-1β and found a 15% reduction in major CV events (144).

CONCLUSIONS

In sum, COVID-19 causes an array of disease manifestations, the most severe of which is mediated by a massive inflammatory response that appears to occur through stimulation of the NLRP3 inflammasome. Direct data linking the NLRP3 inflammasome and SARS-CoV-2 infection are limited given the recent onset of this new pathogen and its global impact. The pathogenesis of this infection and cytokine storm, mirrors many of those features observed in cardiovascular disease, HIV-1 pathogenesis, and SARS-CoV. For this reason, it is of value to contextualize what is already known about the NLRP3 as a mediator of inflammatory signaling to inform future studies of pathogenesis and therapeutic development given the urgent need for drug discovery.

Significant evidence supports the role of IL-1β and NLRP3-dependent inflammasome activation in the pathogenesis of acute lung injury. An abundance of literature supports targeting this pathway in the development of therapeutic strategies. In consideration of direct acting anti-viral agents, viral load appears non- or minimally consequential in determining SARS-CoV and SARS-CoV-2 disease outcomes. When tested in the context of SARS-CoV infection, treatments targeting NLRP3 pathway components including NF-κB, inflammatory macrophages, and IFN-I all demonstrated significant efficacy despite unchanged viral titers their respective human, murine, macaque, and/or *in vitro* models (5, 35, 106, 107, 196). In COVID-19 clinical trials, hydroxychloroquine demonstrated antiviral activity (197, 198), yet without demonstrated clinical benefit (199–201). The known role of NLRP3 in hyperinflammatory ARDS and CRS, documented NLRP3 involvement in MERS-CoV and SARS-CoV severity, and apparent efficacy of anti-NLRP3 therapeutics in SARS-CoV and SARS-CoV-2 clinical trials and animal models strongly indicate that NLRP3 is a central mediator of severe COVID-19. The potential central role of NLRP3 in severe COVID-19 necessitates investigation into the therapeutic targeting of the NLRP3 inflammasome.

Timing of therapy is critical as once individuals develop ARDS, the chances of improved outcomes with therapy are severely reduced. Targeted therapy for individuals with moderate disease before the development of respiratory failure will be critical. There is an urgent need to develop therapeutics that improve patient outcomes in severe COVID-19. Therefore, targeting this pathway through existing available therapeutic options would represent an important and viable approach to reducing SARS-CoV-2-induced inflammatory cytokine signaling and immediately improve patient outcomes.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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