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COVID-19: Inflammatory Profile

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Abstract

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has resulted in a pandemic that has had widespread effects on human activities. The clinical presentation of severe COVID-19 includes a broad spectrum of clinical disease, most notably acute respiratory distress syndrome, cytokine release syndrome (CRS), multiorgan failure, and death. Direct viral damage and uncontrolled inflammation have been suggested as contributory factors in COVID-19 disease severity. The COVID-19 pandemic has emphasized the critical role of an effective host immune response in controlling a virus infection and demonstrated the devastating effect of immune dysregulation. Understanding the nature of the immune response to SARS-CoV-2 pathogenesis is key to developing effective treatments for COVID-19. Here, we describe the nature of the dysregulated host immune response in COVID-19, identify potential mechanisms involved in CRS, and discuss potential strategies that can be used to manage immune dysregulation in COVID-19.

ANTIVIRAL IMMUNITY AND IMMUNE HOMEOSTASIS

Coronavirus disease 2019 (COVID-19) is characterized by a sex- and age-dependent bias in mortality (1, 2). Much of this variability is related to the host immune response; thus, it is critical that we understand how antiviral immune responses are orchestrated differently in COVID-19 patients under different circumstances and how immune hemostasis is regulated during both the acute and convalescent stages of the infection (3). The optimal antiviral immune response is tightly regulated and well organized with an appropriate balance of factors important for virus clearance and for minimizing damage to host tissue (4). For optimal outcomes upon virus infection, the innate immune response is activated to detect, recognize, and respond to the virus, triggering interferon (IFN) production and expression of proinflammatory cytokines and chemokines. Dendritic cells either are infected by viruses or ingest viral debris of infected cells and are then transported into lymphoid organs, where they elicit adaptive immune responses to specifically clear virus-infected cells and generate protective immune memory. CD4 T cells elicit cytokine-producing effector cells, such as T helper 1 (Th1) cells, which limit viral replication and facilitate optimal CD8 T cell and B cell function and differentiation. CD4 T cells also differentiate into T follicular helper cells that are crucial for isotype switching and the development of plasma cells and memory B cells that produce high-affinity antibodies. CD8 T cells produce cytokines to inhibit viral replication and directly lyse infected cells. Thus, immune homeostasis results from the coordinated actions of the innate and adaptive responses, with amplification of a protective response that is proportionate to pathogen burden with limited immune hyperactivity (5). Immune cell priming, migration to sites of infection, and pathogen clearance—with optimal regulation—lead to a successful antiviral immune response, which generally occurs within 1–2 weeks post infection (4).

CYTOKINE RELEASE SYNDROME

Cytokine release syndrome (CRS) is a life-threatening systemic inflammatory syndrome. Also known as a cytokine storm, CRS is characterized by elevated levels of circulating cytokines and immune cell hyperactivation. CRS can be triggered by various pathogens, cancers, autoimmune conditions, and T cell–based therapies (6), but proinflammatory mediators in COVID-19 are not as highly expressed as in some of these other settings. In the case of COVID-19, an apparently dysregulated, rather than greatly elevated, immune response is the most notable predictor of severe disease and poor outcomes. No single definition of CRS is widely accepted, as certain cytokines may be both helpful in controlling an infection and harmful to the host under specific circumstances. Further understanding and definition of cytokines and chemokines involved in COVID-19-associated CRS have both prognostic and therapeutic implications. Here, we discuss the key cytokines and chemokines involved in COVID-19 pathogenesis.

INFLAMMATORY PROFILE

CRS is common to severe human coronavirus (CoV) infections (7), notably SARS (severe acute respiratory syndrome)–CoV, MERS (Middle East respiratory syndrome)–CoV, and SARS-CoV-2 (5). Compared with other common respiratory viruses, such as influenza A virus (IAV), infection with these CoVs in general results in upregulation of a different set of cytokines and chemokines in experimentally infected animals and patients. All CoVs are adept at blocking type I IFN (IFN-I) induction or signaling. Specifically, several CoV proteins inhibit either IFN expression or signaling (8, 9), although many of these reports used cells transfected with viral proteins. In some cases, results were confirmed using infectious virus, which is critical because the elevated levels of these proteins observed in transfected cells may not duplicate the natural infection. Confirmation

is most robust when nonessential proteins, such as ORF6 or ORF8, which are present in both SARS-CoV and SARS-CoV-2, are studied (10). Both ORF6 and ORF8 are accessory proteins and therefore can be deleted without affecting virus replication (11). In both cases, deletion of the protein diminishes the extent of immune evasion, but not completely, since multiple viral proteins have similar functions (12).

SARS-CoV-2 infection of primary human bronchial epithelial cells results in upregulation of several proinflammatory cytokines and chemokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF), CCL20 [chemokine (C-C motif) ligand 20], CXCL1 [chemokine (CXC motif) ligand 1], CXCL3, CXCL5, CXCL6, CXCL2, and CXCL16, mirroring the inflammatory molecule expression observed in patients (13, 14). In another study of cytokine expression in COVID-19 patients, IL-6, IL-10, and CXCL10 were elevated in patients with severe disease and correlated with COVID-19 progression (15). Similar results were observed in SARS-CoV-2-infected mice, hamsters, and nonhuman primates, in which robust cytokine secretion was observed (16). Parallel results were observed in COVID-19 patients. Increased levels of proinflammatory chemokines were detected in bronchoalveolar lavage fluid (BALF), including CCL2, CCL2, CCL4, and CXCL10 (17). Other studies showed elevated blood levels of proinflammatory mediators such as IL-1, IFN-γ, IL-17, TNF, IP-10, MCP (monocyte chemoattractant protein)-1, MCP-3, G-CSF (granulocyte colony-stimulating factor), GM-CSF (granulocyte-macrophage colony-stimulating factor), IL-1RA (IL-1 receptor antagonist), CCL2, CCL3, CCL5, CCL8, CXCL2, CXCL8, CXCL9, and CXCL16 (13, 18–21).

A comparison of immune responses in COVID-19 and in severe influenza performed using single-cell RNA sequencing of peripheral blood mononuclear cells (PBMCs) showed that COVID-19 was characterized by a more robust TNF/IL-1β-driven inflammatory response with less substantial expression of IFN-stimulated genes (ISGs) compared to IAV infection (22). Further, inflammatory molecules were upregulated to a greater extent in the context of IAV compared to SARS-CoV-2 infection, suggesting that cytokine dysregulation rather than very elevated expression contributed to CRS in COVID-19 (22).

THE ROLE OF INTERFERON

As discussed above, the induction of the IFN-I response is critical for the initiation of an appropriate immune response to most viruses, including SARS-CoV-2. IFN-I is expressed by cells after recognition of viral RNA or other molecules by Toll-like receptors or intracellular helical sensors, including RIG-I (retinoic acid–inducible gene I) and MDA5 (melanoma differentiation-associated protein 5). After release from an infected or neighboring cell, IFN-I binds to the IFN-α/β receptor (IFNAR) to induce multiple ISGs via JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling, which initiates an antiviral state in the downstream cell. IFN-I has been intensively studied in COVID-19, with results that are not always consistent. In several reports, IFN-I expression is low or delayed in patients with severe disease (23, 24), resulting in the subsequent development of high levels of proinflammatory cytokines as described below. However, some studies described a robust IFN-I response in patients with severe disease (22, 25). Similar disparities in the IFN-I response were observed in patients with SARS. Most studies found that the IFN-I response was minimal in SARS patients with severe disease (26, 27), while at least one showed that a prolonged IFN-I response correlated with poor outcomes (28).

Many of the features of the IFN-I response are duplicated in experimentally infected animals. In mice with severe SARS, the IFN-I response lagged behind virus replication, resulting in uncontrolled virus replication (29). In this instance, administration of IFN-I at early stages after the infection prevented severe disease. Further, disease severity was ameliorated if IFN-I was blocked

with neutralizing antibody or by infection of mice with genetic deletion of the IFNAR, demonstrating how delayed IFN signaling can contribute to disease severity. In addition, exogenous administration of IFN-I to mice sublethally infected with SARS-CoV or MERS-CoV at the peak of virus replication changed a sublethal infection to a lethal one. In this instance, exogenous IFN-I administered when the innate immune response was undergoing resolution appeared to duplicate some of the inflammatory molecule changes observed in the lethal infection (29, 30). Consistent with these results, treatment of MERS patients with IFN-I was efficacious only if delivered at early times after infection and was not useful if delivered later in the disease course (31). Together, these results indicate that the timing of IFN priming is critical for IFN-I efficacy.

A highly impaired IFN-I response (characterized by no IFN-β and low IFN-α production and activity) was strongly associated with persistent viral RNA in the blood and an exacerbated inflammatory response (prominent increases in TNF-α and IL-6 production and signaling) in severe COVID-19 patients (18). Patients with inherited deficiencies in proteins involved in the IFN-I production or signaling pathways, including IRF3 (interferon regulatory factor 3) and IRF7, are more vulnerable to severe COVID-19 (23). Up to 10% of patients with severe disease have autoantibodies against IFN-I in their blood, again emphasizing the key role of IFN-I in orchestrating a protective immune response against SARS-CoV-2 (32). While these studies are not all consistent, a common feature is that an impaired and delayed IFN response and elevated and prolonged expression of proinflammatory molecules are associated with worse COVID-19 outcomes.

The role of IFN-II (IFN-γ) is less clear. IFN-γ expression by natural killer and virus-specific T cells is important for an optimal immune response (33). Treatment with IFN-γ and TNF activated the JAK/STAT1 pathway, induced nitric oxide production, and resulted in enhanced cell death via caspase8/FADD (Fas associated via death domain)-mediated PANoptosis (PANoptosis has features of apoptosis, pyroptosis, and necrosis) in bone marrow–derived macrophages (34). Type III interferon (IFN-III) was elevated in bronchial aspirates in COVID-19 patients and correlated with lower virus loads (35). A high ratio of IFN-III/IFN-I in the BALF of patients correlated with diminished disease severity (36) and better outcomes (35), demonstrating the importance of an optimal balance between IFN-III and IFN-I in the pathogenesis of COVID-19.

Since the data together indicate that IFN-I and IFN-III are protective in COVID-19 if present at appropriate levels and expressed at the appropriate time during infection, recombinant IFN-I and IFN-III have been proposed as possible therapeutic options for COVID-19 patients. Recombinant forms of IFN-I, including IFN-α (IFNα-1a, IFNα-1b, and IFNα-2b) and IFN-β (IFNβ-1a) as well as IFN-III (Peg-IFNλ-1a), have been used for this purpose (see **Table 1** for some of the therapeutic targets being evaluated in ongoing clinical trials).

THE ROLE OF INTERLEUKIN-6

IL-6 is considered a key component of the immune response to SARS-CoV-2 (37). IL-6 has pleiotropic functions involved in acute infections due to its role in regulating the acute phase response (38). It is produced by macrophages, monocytes, dendritic cells, mast cells, lymphocytes, and other nonlymphocytic cells, such as fibroblasts, endothelial cells, and keratinocytes. IL-6 expression is enhanced by IL-1β and TNF. Patients with severe COVID-19 have high serum levels of IL-6, which are associated with pulmonary inflammation and extensive lung damage (39–42). Circulating levels of IL-6 are positively correlated with disease severity, and IL-6 is a potential biomarker for development of fatal SARS-CoV-2 pneumonia (40–42). As such, IL-6 has been recognized as a possible therapeutic target for diminishing CRS-associated organ damage in patients with severe COVID-19. Tocilizumab, an anti-IL-6 receptor monoclonal antibody,

Table 1 Potential targets, therapeutics, and clinical trials in COVID-19

Target or signaling pathway	Role of target in COVID-19	Drug type	Drug name	Drug usage/mode of action	Clinical trial(s)
IL-6 signaling	Proinflammatory	Anti-IL-6 receptor	Tocilizumab	Approved by FDA for treatment of inflammatory diseases such as rheumatoid arthritis	NCT04317092
		Anti-IL-6 receptor	Sarilumab	Approved for treatment of rheumatoid arthritis	**https://clinicaltrials.gov/ct2/results?term=Sarilumab&cond=COVID-19**
		Anti-IL-6	Siltuximab	Anti-IL-6 chimeric antibody	**https://clinicaltrials.gov/ct2/results?term=Siltuximab&cond=COVID-19**
		Anti-IL-6	Clazakizumab	Anti-IL-6 monoclonal antibody	**https://clinicaltrials.gov/ct2/results?term=Clazakizumab&cond=COVID-19**
TNF signaling	Proinflammatory	Anti-TNF	Infliximab	Chimeric monoclonal antibody that binds to TNF and is used to treat autoimmune diseases	**https://clinicaltrials.gov/ct2/results?term=Infliximab&cond=COVID-19**
			Adalimumab	Monoclonal antibody that inactivates TNF and is used to treat autoimmune diseases	**https://clinicaltrials.gov/ct2/results?term=adalimumab&cond=COVID-19**
			Golimumab	Human monoclonal antibody to TNF	None
			Certolizumab	Fab′-pegol specific to TNF	None
			Etanercept	Fusion TNFR2–IgG1–Fc that functions as a decoy receptor, inhibiting TNF	None
NLRP3 inflammasome/ IL-1b signaling	Proinflammatory	Anti-IL-1 receptor	Anakinra	Human IL-1 receptor antagonist used to treat rheumatoid arthritis	**https://clinicaltrials.gov/ct2/results?term=anakinra&cond=COVID-19**
		Anti-IL-1β	Canakinumab	Human anti-IL-1β monoclonal antibody	**https://clinicaltrials.gov/ct2/results?term=Canakinumab&cond=COVID-19**
		NLRP3 inflammasome	Melatonin	Anti-inflammatory and antioxidative hormone	**https://clinicaltrials.gov/ct2/results?term=melatonin&cond=COVID-19**

(*Continued*)

Table 1 (*Continued*)

Target or signaling pathway	Role of target in COVID-19	Drug type	Drug name	Drug usage/mode of action	Clinical trial(s)
GM-CSF signaling	Proinflammatory; drives tissue repair in lungs	Anti-GM-CSF	Otilimab	Human monoclonal antibody that inhibits GM-CSF	**https://clinicaltrials.gov/ct2/results?term=otilimab&cond=COVID-19**
		Anti-GM-CSF	Gimsilumab	Human monoclonal antibody targeting GM-CSF	**https://clinicaltrials.gov/ct2/results?term=Gimsilumab&cond=COVID-19**
		Anti-GM-CSF	Lenzilumab	Human monoclonal antibody targeting GM-CSF	**https://clinicaltrials.gov/ct2/results?term=Lenzilumab&cond=COVID-19**
		Anti-GM-CSF	TJ003234	Human monoclonal antibody targeting GM-CSF	**https://clinicaltrials.gov/ct2/results?term=TJ003234&cond=COVID-19**
		Anti-GM-CSFR	Mavrilimumab	Human monoclonal antibody targeting GM-CSF receptor	**https://clinicaltrials.gov/ct2/results?term=Mavrilimumab&cond=COVID-19**
		Anti-GM-CSF	Namilumab	Human monoclonal antibody targeting GM-CSF	None
		RhuGM-CSF	Sargramostim	Recombinant human GM-CSF	**https://clinicaltrials.gov/ct2/results?term=Sargramostim&cond=COVID-19**
IFN-I	Stimulates ISGs to confer antiviral activities to host cells	IFN-α	IFN-α1a IFN-α1b IFN-α2b	Recombinant human IFN-α	**https://clinicaltrials.gov/ct2/results?term=interferon+alpha&cond=COVID-19**
		IFN-β	IFN-β1a Peginterferon β1a	Recombinant human IFN-β	**https://clinicaltrials.gov/ct2/results?term=interferon+beta&cond=COVID-19**
IFN-III	Confers antiviral response without triggering systemic inflammation	IFN-λ	Peginterferon λ1a	Recombinant IFNλ-1a	**https://clinicaltrials.gov/ct2/results?term=interferon+lambda&cond=COVID-19**
JAK/STAT signaling	Mediates cytokine signaling	Inhibitors of JAK/STAT signaling	Tofacitinib	Inhibitor of JAK1 and JAK3	**https://clinicaltrials.gov/ct2/results?term=tofacitinib&cond=COVID-19**
			Ruxolitinib	Inhibitor of JAK1 and JAK2	**https://clinicaltrials.gov/ct2/results?term=ruxolitinib&cond=COVID-19**
			Baricitinib	Inhibitor of JAK1, JAK2, and Tyr2	**https://clinicaltrials.gov/ct2/results?term=baricitinib&cond=COVID-19**
			Upadacitinib	Inhibitor that mainly targets JAK1	None
			Fedratinib	Inhibitor of JAK2 and JAK3	None

(*Continued*)

Table 1 (*Continued*)

Target or signaling pathway	Role of target in COVID-19	Drug type	Drug name	Drug usage/mode of action	Clinical trial(s)
p38 MAPK	A proinflammatory pathway implicated in lung and heart injury in COVID-19	P38 inhibitor	Silymarin	Has antiviral, anti-inflammatory, and antioxidant effects	**https://clinicaltrials.gov/ct2/results?term=Silymarin&cond=COVID-19**
		P38 inhibitor	Losmapimod	Selectively inhibits enzymes p38α/β mitogen-activated protein kinases	**https://clinicaltrials.gov/ct2/results?term=Losmapimod&cond=COVID-19**
NF-κB	Activates proinflammatory cytokine production	Indirectly inhibit NF-κB activity	Glucocorticoids	Inhibit NF-κB function (among other effects)	**https://clinicaltrials.gov/ct2/results/details?term=Corticosteroids&cond=COVID-19 https://clinicaltrials.gov/ct2/results?term=dexamethasone&cond=COVID-19**
PGD_2	Impairs immune response in lungs of aged people	PGD_2 receptor DP1 inhibitor	Asapiprant (Bioage-175)	Orally administered inhibitor of DP1 signaling pathway	**https://clinicaltrials.gov/ct2/results?term=BGE-175&cond=COVID-19**
Complement	Implicated in thrombosis and endothelialitis in COVID-19	Complement inhibitor	Ravulizumab Zilucoplan®	Humanized monoclonal antibody complement inhibitor to prevent the activation of complement C5	NCT04570397
		Complement inhibitor	AMY-101	Complement C3 inhibitor	NCT04395456
NETosis	NET formation in COVID-19 mediated inflammatory and thrombotic tissue damage	NETosis inhibitor	R406	A potent spleen tyrosine kinase inhibitor can abrogate the release of NETs	None
VEGF	VEGF contributes to vascular damage by enhancing vascular permeability	VEGF inhibitor	Bevacizumab	Monoclonal antibody target VEGF-A	NCT04275414

Abbreviations: COVID-19, coronavirus disease 2019; DP1, prostaglandin D2 receptor 1; FDA, US Food and Drug Administration; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; ISG, interferon-stimulated gene; JAK/STAT, Janus kinase/signal transducer and activator of transcription; NET, neutrophil extracellular trap; NF-κB, nuclear factor κ light chain enhancer of activated B cells; pegol, polyethylene glycol attachment; PGD_2, prostaglandin D2; TNF, tumor necrosis factor; TNFR2–IgG1–Fc, TNF receptor 2–IgG1–fragment crystallizable; VEGF, vascular endothelial growth factor.

which has been approved for use in treating the chimeric antigen receptor T–associated cytokine syndrome, has been used in the treatment of severe COVID-19 patients in clinical trials. As has been true with many therapies used in COVID-19, timing of administration of tocilizumab relative to disease onset has been critical in demonstrating efficacy. Some studies suggested that IL-6 blockade diminished mortality in patients with severe COVID-19 requiring intensive care unit (ICU) support or mechanical ventilation (43–45), while no benefit was shown in three other randomized trials that enrolled COVID-19 patients with pneumonia requiring oxygen support but not ICU care (46–49). In one study of critically ill patients with COVID-19 in ICUs, treatment with tocilizumab or sarilumab, IL-6 receptor antagonists, improved outcomes and increased survival (50). The RECOVERY study evaluating IL-6 therapy enrolled 4,116 patients in an open-label trial. All patients received corticosteroids. Tocilizumab treatment was shown to reduce mortality and time to hospital discharge (51).

Although these studies did not consistently show the utility of IL-6 blockade, meta-analysis supported the conclusion that tocilizumab treatment improved clinical outcomes and reduced mortality of patients with severe to critical COVID-19 (52, 53). Protective effects appear to depend on coadministration of glucocorticoids. Together, these data indicate that targeting IL-6 may be useful in a subset of patients with severe COVID-19. Some of the clinical trials studying the effects of anti-IL-6 therapies are listed in **Table 1**.

THE ROLE OF TUMOR NECROSIS FACTOR

TNF is an important proinflammatory cytokine that is induced in nearly all acute inflammatory settings and acts as an amplifier of inflammation. Like IL-6, TNF is increased in the blood of patients with COVID-19, and elevated levels are a strong predictor of disease severity and mortality in these patients (39). TNF and IFN-γ in the absence of infection triggered a CRS in mice similar to that observed in human COVID-19 (34). Mice that express the human ACE2 (angiotensin converter enzyme 2) receptor under the control of the epithelial cell cytokeratin-18 promoter (K18-hACE2) develop a lethal disease after infection with SARS-CoV-2. Treatment of these mice with anti-TNF and anti-IFN-γ antibodies enhanced survival (34). A study of 50 COVID-19 patients with varying disease severity demonstrated a correlation between disease severity and TNF levels (18). Another study showed a positive correlation of SARS-CoV-2 viral loads with TNF production in COVID-19 patients (25). Since TNF has been associated with several chronic inflammatory and autoimmune diseases and anti-TNF antibodies have been used for more than 20 years to treat autoimmune inflammatory disease, TNF inhibitors are predicted to be useful in dampening COVID-19 severity (54). Multiple clinical trials are ongoing to evaluate the efficacy of anti-TNF therapies, but results from these trials are not yet available (55) (**Table 1**).

THE ROLE OF INFLAMMASOME ACTIVATION

IL-1β and IL-18, the products of inflammasome activation, are pleiotropic proinflammatory cytokines. The expression of IL-1β and IL-18 requires inflammasome activation, with the NLRP3 (nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 3) inflammasome considered most important in SARS-CoV-2 infections. Inflammasome assembly and activation result in cleavage of procaspase-1 to active caspase-1, which in turn cleaves pro-IL-1β/pro-IL-18 to IL-1β/IL-18 and also initiates pyroptosis, generally by cleavage and subsequent activation of gasdermin D (56). High levels of IL-1β were detected in BALF and plasma of patients with ARDS and lung injury. Further, viral infection of, or other physiological insults to, type II alveolar epithelial cells also stimulated NLRP3 inflammasome formation and IL-1β production (57). Dysregulated NLRP3 inflammasome activation and increased levels of

IL-1β in the plasma are associated with increased disease severity and mortality in COVID-19 patients (18, 25, 58). IL-1β may be a risk factor for damage to hematopoietic stem cells in patients with severe disease (59). Several studies showed that CoV and specific CoV proteins can activate the NLRP3 inflammasome, although many of these studies relied on overexpression assays (58, 60, 61). In one instance, SARS-CoV 3a protein, a transmembrane pore-forming viral protein, was shown to activate the NLRP3 inflammasome, with its ion channel activity being essential for IL-1β secretion (60). SARS-CoV ORF8b activates the NLRP3 inflammasome by direct interaction with the NLRP3-LRR domain (61). In primary human monocytes, infection with SARS-CoV-2 activates the NLRP3 inflammasome and triggers pyroptosis (62). In COVID-19 patients, the NLRP3 inflammasome was found to be activated in PBMCs, and NLRP3-ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) inflammasome puncta were detected by immunostaining in tissues of patients upon autopsy (58). Levels of inflammasome-derived products Casp1p20, IL-18, and IL-6 were shown to be associated with COVID-19 severity (58). Based on these observations, the IL-1 receptor antagonist anakinra is being evaluated as a therapeutic intervention in severe COVID-19 (**Table 1**).

THE ROLES OF GM-CSF AND VEGF

GM-CSF has been postulated to contribute to the thrombosis and endothelial damage characteristic of severe COVID-19. Consequently, GM-CSF has been targeted in several clinical trials (**Table 1**). It should be noted that GM-CSF may also enhance alveolar macrophage survival and diminish apoptosis of alveolar cells, contributing to improved outcomes. Thus, some clinical trials use GM-CSF therapeutically. These results, which appear contradictory, indicate that GM-CSF has both protective and pathogenic effects in SARS-CoV-2, suggesting that it has different effects at different stages of the disease process (63).

Another factor, vascular endothelial growth factor (VEGF), may contribute to vascular damage by enhancing vascular permeability (64). The effect of VEGF blockade is also being examined in clinical trials (**Table 1**).

SIGNALING PATHWAYS INVOLVED IN CYTOKINE RELEASE SYNDROME AND SARS-COV-2-SPECIFIC IMMUNE RESPONSES

JAK/STAT Pathway

The JAK/STAT pathway is critical in IFN-I/III signaling and is implicated in SARS-CoV-2-induced CRS (65, 66). SARS-CoV-2 infection results in an immune response involving activation of macrophages, lymphocytes, natural killer cells, and dendritic cells with a major role for JAK/STAT signaling. The JAK/STAT signaling pathway is required for the activation and function of at least 50 cytokines. The JAK/STAT signaling cascade requires cytokine binding to its cognate receptor at the cell surface, activation of four JAKs (JAK1, JAK2, JAK3, and TYK2), and activation of transcription factors [seven STATs and eight SOCS (suppressor of cytokine signaling)] to elicit a response. After cytokine receptor activation, JAKs undergo transphosphorylation and gain the ability to phosphorylate the receptor. This results in STAT phosphorylation with subsequent translocation into the cell nucleus. STATs are transcription factors that mediate the expression of downstream genes, which are often inflammatory mediators. The expression of several of the cytokines involved in the COVID-19 CRS (e.g., IL-6, IL-2, IL-7, IL-10, GM-CSF, G-CSF, and IFN-γ) is mediated by JAK/STAT signaling.

In addition, the JAK/STAT pathway has a role in complement activation (67), which has been implicated in the thrombosis and endothelialitis observed in COVID-19 patients (68).

Complement C3a is activated in respiratory epithelial cells infected with SARS-CoV-2 (67). In COVID-19 patients, complement is also activated in myeloid, lymphoid, and epithelial cells from the BALF, and this activation tracks with disease severity (67). For all of these reasons, inhibition of JAK/STAT signaling has been evaluated as a therapeutic target in severe COVID-19.

Inhibition of JAK/STAT signaling with ruxolitinib reversed complement activation in lung epithelial cells (67). In another study, using primary human liver cells as well as infected patients, JAK inhibitors were shown to target virus entry, replication, and cytokine expression and also diminish disease severity (69). Other studies showed that use of a JAK inhibitor significantly reduced the likelihood of ICU admission and death while enhancing that of hospital discharge (70). The US Food and Drug Administration has authorized the use of a JAK inhibitor (baricitinib) in combination with remdesivir for treatment of COVID-19, since the cotreatment is superior, albeit modestly, to remdesivir alone in improving clinical outcomes (71).

Another downstream effect of JAK/STAT signaling is neutrophil extracellular trap (NET) formation (NETosis). Neutrophilia is a well-described complication of COVID-19, and NETs are detected in the lungs of COVID-19 patients at autopsy, contributing to microvascular thrombosis (72). Clinical trials evaluating drugs with anti-NETosis properties are being considered for COVID-19 treatment (**Table 1**).

P38 MAPK Signaling

The p38 mitogen-activated protein kinase (MAPK) family acts as a regulator of proinflammatory cytokine production (IL-6, TNF-α, and IL-1β) and has been involved in acute lung injury and myocardial dysfunction. Unrestrained p38 MAPK activation is believed to contribute to inflammation, thrombosis, and vasoconstriction, which are hallmarks of severe cardiac and pulmonary injury in COVID-19 patients (73). P38 MAPK activation may be facilitated by SARS-CoV-2 entry, which results in downregulation of ACE2 on the cell surface and, potentially, increased activity of angiotensin II (73). Angiotensin II activity is regulated by ACE2. Viral proteins may directly activate p38 MAPK signaling. In specific, one study showed that SARS-CoV 7a protein could activate p38 MAPK (74), which, based on studies of IAV infections, was postulated to be proviral (74, 75). Previous studies showed that p38 MAPK inhibitors suppressed proinflammatory cytokine production and so are predicted to be useful in severe COVID-19 (76). In mice infected with SARS-CoV, p38 MAPK inhibitors decreased the expression of inflammatory cytokines, diminished levels of virus replication, and increased survival, confirming the relevance of the p38 MAPK pathway to SARS-CoV virulence (77). A study of global phosphorylation in SARS-CoV-2-infected cells identified activation of the p38 MAPK cascade, among other kinase pathways (78). In addition, treatment of these cells with the p38 inhibitor SB203580 resulted in decreased expression of IL-6, TNF-α, IFN-β, CCL2, CXCL8, and CXCL20 as well as decreased production of subgenomic RNA (78). Based on these results, clinical trials of drugs that target p38 MAPK signaling in COVID-19 have been initiated, using the p38 inhibitors silymarin and losmapimod (73) (**Table 1**).

NF-κB Pathway

Nuclear factor κ light chain enhancer of activated B cells (NF-κB) is a central mediator of proinflammatory gene induction and function in both innate and adaptive immune cells. NF-κB induces the expression of various proinflammatory genes, including those encoding cytokines and chemokines, and also participates in inflammasome regulation. Previous studies showed that the MERS-CoV 4b protein prevented excessive NF-κB-mediated immune responses by binding to karyopherin-α4, which is involved in NF-κB nucleus translocation and activation (79). SARS-CoV nucleocapsid protein has been shown to activate NF-κB in Vero E6 cells, although this was found

under conditions of transient expression (80). Another study showed that purified recombinant SARS-CoV spike protein served as a TLR2 ligand and could induce the activation of NF-κB in blood monocytes, thereby inducing the expression of cytokines such as IL-8, IL-6, IL-1β, and MIP (macrophage inflammatory protein)-1β. Infection with recombinant SARS-CoV in which the E protein, a protein with ion channel activity, was deleted resulted in diminished NF-κB activity, reduced inflammation and lung pathology, and increased survival of infected mice. Treatment of mice infected with wild-type SARS-CoV with NF-κB inhibitors CAPE (caffeic acid phenethyl ester) and parthenolide resulted in increased survival and reduced lung pathology (81). These results indicate that NF-κB activation is a major contributor to inflammation and virus virulence in the context of SARS (81). Hyperactivation of NF-κB is also involved in the pathogenesis of severe COVID-19 (18). SARS-CoV-2 activates NF-κB in various cells such as macrophages in the lung, liver, kidney, and central nervous system, leading to the production of proinflammatory cytokines such as IL-1, IL-2, IL-6, IL-12, TNF, GM-CSF, and various chemokines, which in turn augments the inflammatory process (82). Thus, targeting the NF-κB pathway in severe COVID-19 may help control CRS and alleviate COVID-19 severity (82). So far, no drugs that directly target the NF-κB pathway are being used for COVID-19 treatment.

The most widely used intervention in patients with severe COVID-19 is treatment with glucocorticoids (dexamethasone). Glucocorticoids improve outcomes in ICU patients but may have deleterious effects if administered to patients with mild disease. Steroid treatment reduces mortality from 41.4% to 29.3% in mechanically ventilated patients in the ICU (83). Glucocorticoids function in part by inhibiting NF-κB activation (84).

IMBALANCED CELLULAR IMMUNE RESPONSE AND IMMUNOSENESCENCE

The cellular immune system has innate and adaptive components that play linked and important roles. Each consists of several cell types with different functions (85). An imbalanced cellular immune response was associated with enhanced COVID-19 severity and worse outcomes (25, 86, 87). Immune profiling of SARS-CoV-2-infected patients demonstrated an overall increase in innate cell lineages including monocytes, neutrophils, and eosinophils, as well as pronounced T cell activation (25, 88). Extensive T cell activation during COVID-19 likely contributes to lymphopenia and functional exhaustion (86, 89), alteration of subset composition, and loss of function, which further limits viral clearance and increases morbidity and mortality (90). An increased level of IL-17 secretion by circulating CD4 T cells and elevated plasma IL-17A and IL-22 levels are hallmarks of severe COVID-19 (25). CD8 T cell lymphopenia is observed in patients with severe disease (91), while moderate disease is characterized by an increased number of highly activated CD8 T cells (90, 92). SARS-CoV-2-specific CD4 and CD8 T cells can be detected in both acutely infected and recovered patients, and their detection at early times in the disease course may be predictive of a protective cell-mediated immune response (88, 90). In contrast, the virus-specific antibody response may be elevated but differs in specificity in patients with varying disease severity. A spike protein antibody response is more common in patients who survived COVID-19, while a nucleocapsid-specific antibody response is more prominent in individuals who ultimately died (93).

COVID-19 has high morbidity and mortality in aged individuals. Aging is characterized by immunosenescence with reduced B and T cell production in the bone marrow and thymus and diminished function of mature lymphocytes in secondary lymphoid tissues. As a consequence, elderly individuals do not respond to immune challenge as robustly as the young (94). Other reports speculate that activation of memory T cells, which are more abundant in older adults than

in children, contribute to more severe disease in aged individuals (86). Age-dependent changes in the lung milieu may contribute to severe disease. In one study, expression of several eicosanoids was shown to increase with aging. Specifically, phospholipase A_2 (PLA_2) group IID (PLA_2G2D) and its downstream product, prostaglandin D2 (PGD_2), are two factors found to increase with aging and to contribute to worse outcomes in SARS-CoV-infected mice. Augmented expression of PGD_2 results in impaired migration of respiratory dendritic cells to draining lymph nodes and subsequent dampened T cell responses upon SARS-CoV infection in mice (95, 96). Infection of $PLA_2G2D^{-/-}$ mice increased survival after SARS-CoV infection from 0% observed in wild-type mice to >80%. PGD_2 and PLA_2G2D are likely to have similar roles in SARS-CoV-2 infection, at least in mice.

CONCLUSION AND PERSPECTIVE

As described in this review, an individual's immune response to SARS-CoV-2 varies widely, and a dysregulated inflammatory cytokine/chemokine response contributes to greater disease severity in patients. While substantial progress has been made in our understanding of the basis of this abnormal immune response, there is still clearly much to learn. This information will allow for the development of specific therapies to diminish the dysregulated immune response that is seen in patients with severe disease.

The variability in COVID-19 presentation indicates that therapy must be tailored for individual patients. No single cytokine or other factor has been shown to be a useful biomarker for identifying patients who will develop mild versus severe disease. Identification of such a biomarker will be very useful in guiding therapy. The rapid development of vaccines has helped to mitigate the global spread of the virus, but with the advent of variants that exhibit diminished susceptibility to the natural infection–induced or vaccine-induced antibody response, the development of additional interventions that target the host immune response is critical.

Sun Tzu's *The Art of War* advises, "If you know the enemy and know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. If you know neither the enemy nor yourself, you will succumb in every battle." To defeat SARS-CoV-2, we need to understand both the virus and the host immune response.

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