



# Genes affecting in cytokine storm as therapeutic targets in COVID-19 infection

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## Abstract

**Background:** A cytokine storm is an abnormal host immune system response and a principal responsibility for the incidence of acute respiratory distress syndrome. The existence of the virus-induced cytokine has been linked to mortality in patients with COVID-19. This study aimed to review the gene's role in cytokine storm as a therapeutic target in patients with COVID-19.

We demonstrated the role of pro-inflammatory cytokines in conditions that are often associated with COVID-19. Hyperproduction of mostly pro-inflammatory cytokines such as IFN- $\gamma$ , IL-6, IL-1, TNF- $\alpha$ , and Chemokines, which target lung tissue preferentially, can significantly worsen the prognosis in almost all cases. The cytokines' data in this disease will support the development of more useful COVID-19 patient management strategies. In managing COVID-19 patients, targeting cytokines can decrease mortality and increase survival rates.

**Key words:** COVID-19, Cytokine storm, Therapy, Genes

## Background

The outbreak of the SARS-CoV-2 virus from Wuhan, China, and owing to its rapid spread to most parts of the world and the increasing threat caused by COVID-19 to global health, prompted the World Health Organization to declare an epidemic (1, 2). COVID-19 syndrome manifests itself in a wide range of clinical manifestations. While most cases resolve with just minor symptoms such as fever, dry cough, myalgia, and pain, several patients show fatal complications such as diffuse alveolar injury with heparin membrane formation (106), acute respiratory distress syndrome (ARDS), pulmonary edema, and septic shock (3-5). SARS-CoV-2 enters the cell by binding spike proteins to the angiotensin-converting enzyme receptor 2 (ACE-2) receptor binding domain (RBD) (6). One of the most common causes of ARDS and multiple organ failure is cytokine storm (7). As a result, controlling the cytokine storm adequately is crucial for preventing COVID-19 infection and saving patients' lives (5, 8). Cytokines are a large collection of tiny proteins released by cells to regulate cell extensive functionalities (9). In most people with severe COVID-19 infections, it has been seen that cytokine profiles support the enhanced levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$ , IL-2, IL-6, IL-8, and several chemokines (3, 10). In acute patients, the host response to infection can result

in clinical and biochemical symptoms of the cytokine storm. According to the cytokine storm mechanisms in SARS-CoV-2, the Covid19 infection also triggers the activation of both STAT3 and NF- $\kappa$ B in the respiratory system (11). The molecular mechanism was examined, however, the evidence for the regulation of cytokine expression is currently insufficient (12).

Furthermore, because there is a cross-over between the host pathways for viral-induced cytokine regulation for distinct viral infections, host immunomodulatory therapy could be used to manage disease (9). Therefore, finding genes that affected cytokine storm, may be essential and potentially will be used as the target in treating respiratory virus outbreaks in the future. This review aims to present the mechanism of hyper-inflammatory response, which causes cytokine storm in COVID-19 patients, with an emphasis on the related cytokines to COVID-19 severity.

## Cytokines

Cytokines are a collection of tiny proteins released by cells for signaling and intercellular communication. They are also complex interconnected networks, each with its level of redundancy and alternative pathways. They play an important role in differentiation, proliferation, cell control, and

regulation of immune, inflammatory responses, and angiogenesis. Most of the cytokines have a variety of roles that are dependent on the target cell or the absence or presence of some other cytokines. Several cytokines have low sequence identity and involve separate target receptors, but signals are transmitted throughout usual intracellular pathways, a clear example of which are type I/III interferons [IFNs] (13, 14). The findings confirm the association of covid19 cytokines with inflammatory cell death induced by "interferon-gamma" (INF), "tumor necrosis factor-alpha" (TNF) proteins, and other cytokine-associated cytokines and treatments based on cytokine targeting could be candidates for rapid clinical trials to treat COVID-19 and other often fatal disorders associated with cytokine storms.

### Interferon

In innate immunity against pathogens of viruses and other microbes, interferons are members of the cytokine family, which play an important function (15, 16). Based on the characteristics of the receptor, it is classified into three major types (types I, II, and III). Type I IFNs, which contain two subtypes of alpha and beta (17), are signaled through a heterodimeric receptor complex, IFNAR1/IFNAR2 (17). Interferon 1 (IFN- I) is the virus's most efficient innate immune defense and increasing its leads to virus replication inhibition and its elimination in the early stages (18-20). By altering interferon production or messaging, SARS-CoV-2 suppresses and lowers this response. This strategy is closely related to the severity of the disease (20). Along with this suppression, to compensate for the suppression, immune cells existing at the site of virus entry release more amounts of IFN-I, causing more macrophages and neutrophils to invade the site of inflammation (19). Finally, we see the cytokine storm. Type II IFN (IFN-gamma) signals through FN-AR1/IFN-AR2 (17). CD4 T cells are a common source of IFN- $\gamma$ , which promotes CD8 T cell differentiation and activates their cytotoxic abilities. IFN- $\gamma$  is a granulocyte and monocyte colony-stimulating factor that also promotes CD8 T cell development and activation (21). A new class of interferons is lambda IFNs with antiviral properties. This interferon has three classes: interleukin-29 [IL-29], IL-28a, and IL-28b, respectively, which functionally transmit signals through the Jak-STAT signaling pathway like type I IFNs (18, 22-24). Downstream signaling cascades are triggered by receptor engagement, hundreds of IFN-stimulated genes were induced, and transcription factors were activated as a result. These genes produce proteins that have antiviral, anti-replication, or immune-modulating characteristics. To confirm the viral load, it has been observed that IFN- $\gamma$  quantities in people with COVID-19 have raised (25). Subsequently, as the number of lymphocytes decreases, the penetration of neutrophils into the lungs' alveoli increases, with the decline of the patient's condition (25-27). Along with IFN- $\gamma$ , IL-6 is a reliable indication of COVID-19 patient worsening (19, 27). Types of interferon are listed in table 1.

**Table 1.** Types of interferon and SARS-CoV-2

Types of interferon		Response to SARS-CoV-2
IFN-I	IFN-a	SARS-CoV-2 disrupting interferon production or messaging. Increased amounts of IFN-I to compensate, more macrophages and neutrophils invade the site of inflammation.
	IFN-B	
IFN-II	IFN- $\gamma$	Encourages CD8 T cell development and turns on their cytotoxic capabilities, fewer lymphocytes are present, and the penetration of neutrophils into the alveoli in the lungs increases.
IFN-III (IFN- $\lambda$ )	IL-29	The Jak-STAT signalling pathway is used by Interleukin-29 (IL-29), IL-28a, and IL-28b to transmit signals, which activate transcription factors and induce hundreds of IFN-stimulated genes.
	IL-28a	
	IL-28b	

### Interleukins

A broad group of immune system work as regulators is Interleukins, the primary function is to differentiate and activate immune cells. They can be pro- or anti-inflammatory, and they can produce a variety of immune responses. The name interleukin used to be derived from cytokines generated by leukocytes that function in intercellular communication, but today it is known that they are produced by a broad variety of cells (28). IL-1 which is encoded by 11 genes, is a member of the cytokine family (29). T-cell-derived immunity relied on IL-1, which promotes IL-2 production and expression, as well as the main Interleukin in T-cell homeostasis (30, 31). Alpha and beta-type of IL-1 are pro-inflammatory cytokines that are produced by direct and indirect mechanisms due to the host's response to infection (32). Increase acute-phase signaling, immune cells trafficking to the position of original infection, epithelial cell activation, and secondary cytokine generation are some of their biological functions. IL-1 $\alpha$  can express stimulant function on TH2 cells without having any effect on TH1 cells (30). Acute pulmonary immunopathology is caused by IL-1 receptor signaling, which improves the existence of mice with influenza by increasing IgM immune reaction and attracting CD4 T cells to the infection site. Because the IL-1 family of pro-inflammatory cytokines is one of the regulators of IL-6 output, therefore great levels of IL-1 cytokines are another sign of the cytokine storm. COVID-19 patients have also been shown to have high amounts of these cytokines. In COVID-19, the lungs of patients with multilateral lobular pneumonia are associated with increased levels of IL-1 $\beta$ , IL-7, IL-8, and IL-9 at initial plasma concentrations secreted by injured tissue, and they are early immune drivers of the immune response in COVID-19 (30). In this regard, IL-10 seems to be a strong modulator of the immune system and is considered an indicator of immunological delinquency in COVID-19 (27). It should be noted that IL-10 levels rise in the second week after the incidence of symptoms (27). IL-4 is a suppressor of inflammation and a TH2 cytokine. While ILs are not anti-viral cytokines like IFNs, they are undoubtedly linked to

cytokine storms (25).

We can name IL6 the storm's eye. Human IL-6 is included of 212 amino acids, apart from a 28-amino acid signal peptide, and is located in chromosome 7p21. IL-6 is a major component of antiviral immunity in the immune system. IL-6 is a pleiotropic cytokine, meaning it may operate as both a pro-inflammatory cytokine and an anti-inflammatory cytokine. IL-6 links to its soluble receptor, which is found on a variety of immune cells and tissues and forms the IL6/IL6R complex, after its production. Two transmembrane-IL-6 binding chains, two soluble IL6 receptors, and two cytoplasmic signaling molecules (gp130), the latter of which is apportioned by other members of the IL-6 family, such as an inhibiting factor of leukemia, IL-22, IL-27, and IL-25. IL-6 upregulates the gp130 by binding soluble IL-6 to its ligand. Allowing the creation of the IL-6/IL-6R complex, which starts the IL-6-related intracellular cascade's downstream signaling. The Janus kinase (JAK)-STAT3 pathway and the JAK-SHP-2-MAP kinase pathway are both activated in the intracellular cascade. By completing suppressor cytokine signaling-1 (SOCS1) and SOCS3, STAT3 modulates IL-6 responses (21).

IL-6 promotes TH7 differentiation as well as the activation and variation of cytotoxic CD8 T lymphocytes (33, 34) as well as the differentiation of naive CD4 T cells into effector and helper cells (35). In addition, IL-6 creates a long list of autoimmune diseases by inhibiting the production of T CD4 + CD25 + FOXP3 regulatory T cells (36).

Some studies dedicate that some viruses like HIV-1 can influence the intracellular cascade of events that ascribe to an inflammatory state and the release of IL-6. Through direct binding of NFkB regulatory site on IL-6 promoter, SARS-Cov-family structural protein N activated IL-6 promoter in human airway epithelial cell cultures (36). However, further studies are needed to assess the impacts of COVID-19 long-term mechanisms, particularly concerning environmental factors and transient disorders of autoimmune resulting from viral infections (21).

One of the major interleukins in the COVID-19 pandemic is IL-6 (37). IL-6 levels were among the reliable indicators for disease severity and predictors for breathing assistance (34, 38). Increased levels of IL-6 with TNF- $\alpha$  and IL10 were directly related to decreasing the chance of recovery according to Pedersen and colleagues' research (27).

Studies have shown that in the early stages of COVID-19 infection, poor type-1 IFNs response played a crucial role in the formation of cytokine storm and that numerous cytokines such as IL-6 and IL-1 were engaged in severe COVID-19 infection (39).

### Chemokines

Chemokines are one of the largest families of cytokines, with 44 members that link to one or more than 21 G-protein-coupled receptors (40), and most of them are considered pro-inflammatory, which leads to immune system cells (neutrophils, monocytes/macrophages, and lymphocytes) to be absorbed in the site of infection (41). Chemokines are small secretory proteins that are divided into 4 types (CXC, CC, C, and CX3C) according to the distance between the two primary cysteine residues. Chemokines act as chemo-attractants to control and regulate cell migration, especially immune system cells, and help in a range of functions, including the growth,

embryogenesis, and function of the innate and adaptive immune system, and cancer metastasis (42). Like, regulation of CXCR3, CXCL9, CXCL10, and CXCL11 ligands by differential expression of IFN gamma to influence T cell function and peripheral penetration during inflammation (43).

Chemokine production is a crucial anti-viral response, especially in the immune response to coronaviruses. According that chemokines work to absorb immune cells to eliminate the virus, inflammation increases as their expression increases. As a result, ARDS occurs, which is a common complication of COVID-19 (44-46). In this regard, studying the characteristics of chemokines and manipulating chemokines and their inflammatory effects might help us better understand the immunological pathogenic process of SARS-CoV-2 infection and be used as a useful marker.

Chemokines play a role in disease pathogenesis and are implicated in all phases of SARS-CoV-2 infection. The increase in chemokines indicated a chemokine signature of asymptomatic, mildly infected, and severely infected patients, as established by transcriptome analysis and kinetic studies.

CCL3, CCL4 and CCL5 were detected (47). Furthermore, SARS-CoV-2 serum analysis in generalized patients revealed and significant rise in CXCL2, CXCL8, CXCL9, and CXCL16 levels (48). Collectively, T and NK cells, monocytes, macrophages, and neutrophils were the most common immune cells found in COVID-19 patients' lungs (49). CXCL10 and CCL3 levels were raised in advanced disease stages (50) CXCL10, on the other hand, is not present in healthy people, so we can use CXCL10 for early diagnosis and potential predictive marker (47). Those dying from SARS-CoV-2 P have considerably greater plasma levels of CXCL8, CXCL9, CXCL10, CCL2, CCL3, CCL7, CCL20, and CX3CL1 than patients with severe or mild COVID-19. In this regard, the use of CXCL10 and CCL7 due to their relationship with ARDS can be considered independent predictors of COVID-19 progression (51). CCL2, CXCL8, and CXCL10 which are upregulated in highly infected patients could be used as acceptable biomarkers for disease. Therefore, all of these studies confirm that the chemokine profile is a valuable diagnostic tool for SARS-CoV-2 infection intervention and therapy (52).

### Colony-stimulating factors (CSFs)

CSFs, such as Granulocyte-macrophage colony-stimulating factor (GM-CSF) which is made up of a unique alpha chain of GM-CSF and a signal transduction component shared with the IL-3 and IL-5 receptors (53-55). Endotoxins can also cause an increase in serum GM-CSF levels. Therefore, GM-CSF stimulates the proliferation and activation of macrophages, neutrophils, monocytes, dendritic cells, and so on (56) involved in the inflammatory process (57-59). During the acute phase of SARS-CoV-2 infection, high levels of serum GM-CSF have been found (5).

The hematopoietic cells' monoblasts, promonocytes, monocytes, macrophages, and osteoclasts can develop, proliferate, and differentiate under the influence of a protein called macrophage colony-stimulating factor (M-CSF) (34, 60). It seeks the synergic effects of IL-1 and IL-3 during the early stages of myeloid line cell differentiation (60). Significantly patients with COVID-19 have high levels of this factor. Hyperexpression

of this and other cytokines has been linked to lung damage, which could help predict disease severity (61).

Granulocyte colony-stimulating factor (G-CSF), which is necessary for polymorphonuclear granulocyte cells (PMNs) maturation and proliferation. As a result, G-CSF is hematopoietic growth factor properties (62, 63). Wu D and Yang XO demonstrated that IL-17 generated by Th17 lymphocytes can increase the production of G-CSF, indicating that Th17 contributes to the SARS-CoV-2-induced cytokine storm (25).

They promote the proliferation and development of hematopoietic progenitor cells and are linked to inflammation. It could be a pro-inflammatory cytokine-like IL-1 or tumor necrosis factor (TNF) (64). Colony-stimulating substances may be part of the cascade that operates on persistent inflammatory reactions by causing macrophages to produce cytokines at the site of inflammation (13).

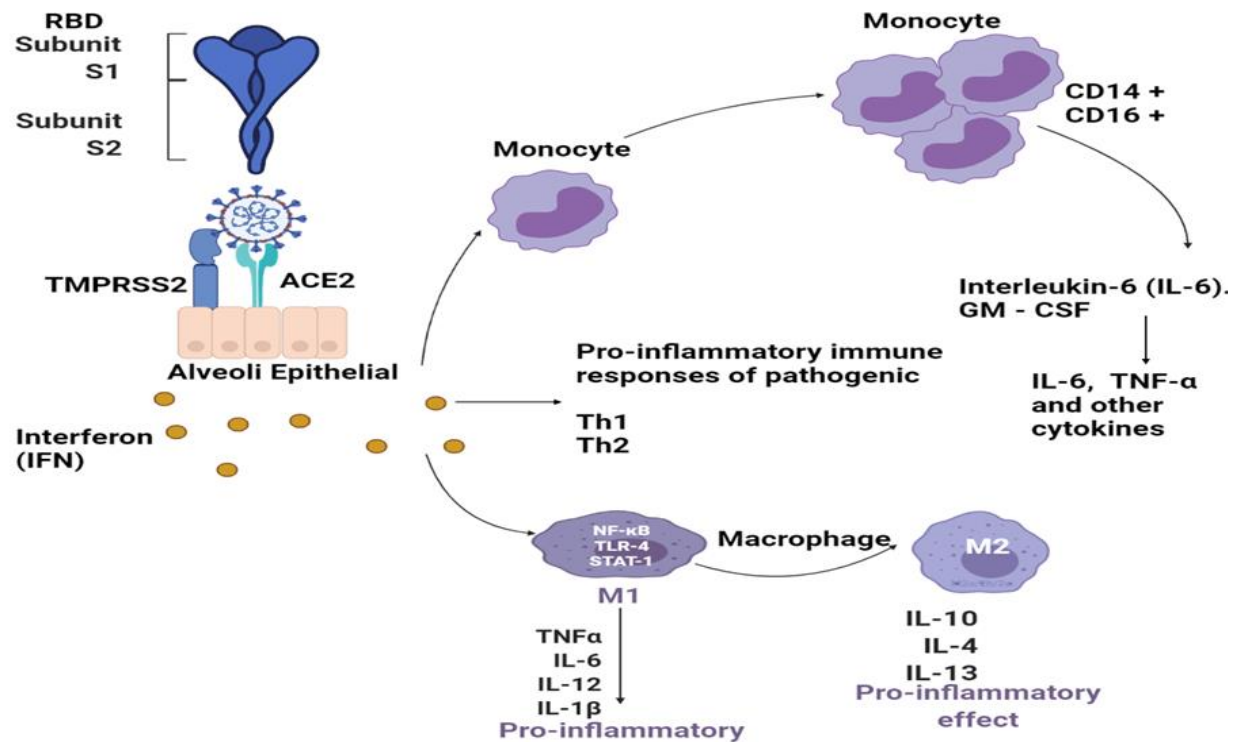
### TNFs

Tumor necrosis factor (TNF) operates a distinguished role in the cytokine storm. It has been related to proinflammatory (65). TNF expression is by a variety of immune cells and TNFR1 is the primary receptor for it. Further, it includes 19 members that are signaled with 29 receptors [66] and operate like cytokines when they depart the cell membrane mostly through the cleavage of extracellular proteolytic (21). Also, TNF- $\alpha$  levels like those of IL-6 and the soluble IL-2 receptor, raise early in the infection and stay high throughout (25, 27). TNF- $\alpha$  causes inflammation of HA-synthase-2 (HAS2) in the COVID-19 patient's lungs, which is the main cause of fluid invasion in the lung alveoli and lack of oxygen, and ultimately the use of a ventilator (22, 66). Presumably, an inadequate prognosis in patients with SARS-CoV could be related to the overproduction of TNF- $\alpha$ .

### The mechanisms of cytokine storm in COVID-19 infection

The binding of S proteins on the virion's surface to the cellular receptor ACE2 and TMPRSS2 (67, 68), a host membrane serine protease (68), is required for SARS-CoV-2 cell entrance. Specifically, this interaction (ACE2) is mediated by the receptor-binding domain (RBD) within the spike protein of the virus (6, 69). In vitro investigations have specifically dedicated that RBD of SARS-CoV-2 prefers to extend contact with the ACE2's N-terminal helix, which could explain the virus's increased affinity for binding ACE2 (70, 71). Some human proteases must cleave the spike protein, dissociating the S1 and S2 subunits, the latter of which must undergo significant structural changes required to fuse with the host cell membrane (71). In this procedure, transmembrane serine protease 2 (TMPRSS2), together with lysosomal cathepsins, is the other unique and most significant enzyme [73]. Furin, a subtilisin-like proprotein convertase that cleaves the region between both S1 and S2 subunits of the SARS-CoV-2 spike protein, is a type 1 membrane-bound protease (105). Significantly, furin is expressed in many organs, like the lungs. After binding, furin catalyzes the cleavage of the spike protein (S1/S2) (72). This alternative mechanism, which includes furin-mediate activation, might allow SARS-CoV-2 to infect cells with less reliance on TMPRSS2 co-expressions at the cell surface. So, SARS-CoV-2 could infect a wide spectrum of cells with low TMPRSS2 expression (73). SARS-CoV-2 elicits an immunological response by generating inflammatory cytokines and a modest interferon (IFN) response when it enters respiratory epithelial cells. Membrane immune receptors and downstream signal transduction pathways mediate pathogenic Th1 cells' and CD14 + CD16 + monocytes' pro-inflammatory immune responses. By the penetration of macrophages and neutrophils into the alveoli epithelial, a cytokine storm occurs (74). Cell experiments done in vitro show that in the early stages of SARS-CoV infection, respiratory epithelial cells, dendritic cells (DCs), and macrophages delay the release of cytokines and chemokines. Later, the cells emit low levels of the antiviral factors interferons (IFNs) as well as significant levels of pro-inflammatory cytokines (interleukin (IL)-1  $\beta$ , IL-6, and tumor necrosis factor (TNF)) and chemokines (66, 75-77).

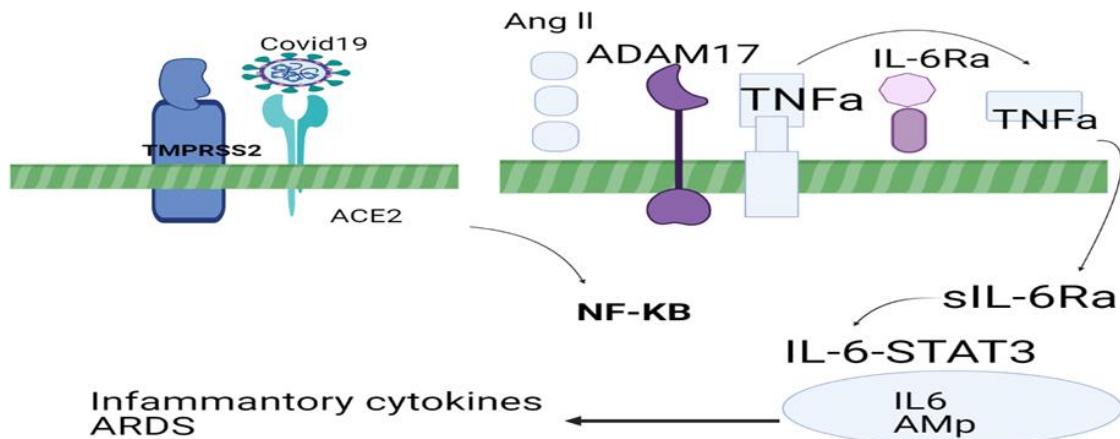
SARS-CoV-2, in particular, can activate pathogenic Th1 cells rapidly and release pro-inflammatory cytokines, like granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6). In addition, GM-CSF stimulates inflammatory monocytes of CD14 + CD16 + and produces significant amounts of IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and other cytokines (6). Membrane-bound immune receptors (such as Fc and Toll-like receptors) may chip into an unbalanced inflammatory response, and faint induction of IFN- $\gamma$  could be a crucial cytokine booster (74). Extracellular Traps in Neutrophils: the neutrophils' extracellular networks may have a role in the extrication of cytokines (78). IL-6, TNF- $\alpha$  are very important because a high level of production of these cytokines defines the cytokine storm in COVID-19 (11) (Figure1).



**Figure 1.** The cytokine storm mechanism in COVID-19. Initially, coronaviruses enter to host alveoli epithelial. The virus attacks host defenses via binding with ACE2 and TMPRSS2 on the cell surface by S-protein RBD and tethers the virus to the outside of the human cell. The immune response is evoked by SARS-CoV-2 by producing inflammatory cytokines with an interferon (IFN) response. A Cytokine storm is caused by pro-inflammatory immune responses of pathogenic Th1 cells and CD14+ CD16+ monocytes, neutrophils, and macrophages in the lung tissue. Specifically, granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6) are activated by SARS-CoV-2. Image source: Created with BioRender.com

### Role of angiotensin 2 (AngII) pathway in the mechanism of cytokine storm

SARS activates CoV-2 nuclear factor- $\kappa$ B (NF- $\kappa$ B) through receptors of pattern recognition. It binds ACE2 on the cell membrane, thereby reducing ACE2 expression and subsequently increasing AngII. The AngII angiotensin receptor type 2 axis, in addition to activating NF- $\kappa$ B, also be able to stimulate TNF- $\alpha$  and the dissolved form of IL-6Ra (sIL-6Ra) by degradation and metalloprotease 17 (ADAM17) (79). The disintegrating and metalloproteinase domain 17 (ADAM17) catalyzes the release of ectodomains from a variety of transmembrane proteins, like ACE2, in addition to cleavage of the tumor necrosis factor- $\alpha$  (pro-TNF- $\alpha$ ) (80). ACE2 splashing is decreased when ADAM17 expression is reduced, while overexpression of ADAM17 increases its cellular release (81) and ACE2 shedding. In this viewpoint, SARS-CoV-2's ability to discover an accessible host receptor for cellular entry is reduced (82). The complex of IL-6 sIL-6R is formed when IL-6 binds sIL-6R via gp130 to activate the signal transducer and transcription activator 3 (STAT3) in non-immune cells. Both NF- $\kappa$ B and STAT3 can amplify IL-6 amplifiers to produce cytokines and proinflammatory cytokines, according to vascular endothelial growth factor, monocyte chemoattractant protein 1 (MCP-1), IL-8, and IL-6 (83). IL-6 acts on cis signaling via binding to sIL-6R, and it can also affect signal transduction by binding to the IL-6 membrane receptor (mIL-6R) by gp130. So influences of pleiotropic occur on acquisitive and innate immune cells, then it leads to cytokine storms (84). Figure 2 shows the graphic pathogenesis of SARS-CoV-2.



**Figure 2.** The proposed angiotensin 2 (AngII) pathway leads to cytokine storm in COVID-19 patients. By cleaving with transmembrane serine protease 2 (TMPRSS2) and furin, SARS-CoV-2 attaches to the host ACE2. The virus then enters the host cell via fusion or endocytosis after this attachment. Hyperactivation of the transcription factor NF- $\kappa$ B causes a cytokine-related syndrome, ARDS. COVID-19 occupies ACE2 on the cell surface. Though disintegrin and A disintegrin and metalloprotease 17 (ADAM17), AngII accumulates and produces inflammatory cytokines containing TNF $\alpha$  and IL-6-soluble (s)IL-6R. ADAM17 stimulates the shedding of proinflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), etc, in addition to ACE2 release from the cell surface. TNF- $\alpha$  and sIL-6R $\alpha$  are produced as a result, and the IL-6R-STAT3 pathway is activated. Inflammatory cascades of NF- $\kappa$ B- and STAT3-mediated signaling further augment NF- $\kappa$ B activity and enhance the IL-6 amplifier (IL-6 AMP). Thus, in COVID-19 patients, the cytokine storm generated by the hyper-activation of NF- $\kappa$ B in IL-6 AMP could result in catastrophic symptoms such as ARDS. Image source: Created with BioRender.com

### The signaling pathway JAK/signal transducers and activators of transcription (STAT)

JAK is a tyrosine kinase that participates in the signaling caused by roughly 40 different cytokines and growth hormones (107,108). Cytokines and growth factors attach to cell surface receptors, activating the JAKs that phosphorylate the receptor's intracellular domain and link to the transcription factor STAT (108). By translocating STAT to the nucleus and mediates the transcription of many genes involved in infection and immunity. JAK/STATs have attracted considerable attention for therapeutic purposes, especially in immune diseases. (JAK1, JAK2, JAK3, and TYK2) four JAK isoforms form heterodimers or homodimers to relay intracellular signals and trigger transcription of genes encoding diverse cytokines, and cell function-mediating molecules in collaboration with seven types of STATs (109).

Low-molecular kinase inhibitors and biologics targeting cytokines have been introduced for the treatment of autoimmune disorders, transforming the therapeutic landscape. JAK3 is activated by IL-2, 4, 7, 9, 15, and 21 of the c family and plays an important function in the immune system. Tofacitinib binds competitively to the ATP binding site of JAK3 and specifically suppresses cytokine signaling (110). Tofacitinib has pharmacological characteristics and is rapidly metabolized in the body.

### Clinical symptoms are associated with changes in the activity of cytokines and ACE2.

In patients with severe/critical COVID-19, SARS-CoV-2-induced cellular perturbations, cytokine storm, and IFNs-I suppression result in catastrophic clinical consequences such as ARDS, thrombo-inflammation, MODS, and mortality (111). The reduction of ACE2 after virus entry, as well as ADAM17 activity, may explain the rise in blood pressure, increased permeability of pulmonary arteries, acute lung injury (ALI), and fibrotic and thrombotic reactions. Furthermore, reduced/delayed IFNs-I responses contribute to excessive monocyte/macrophage tissue infiltration and downregulation of their pro-repair actions in the airways (112). The reduction of these cytokines has also been linked to the progression of pulmonary failure. Furthermore, each of the inflammatory mediators has the potential to cause severe clinical consequences. Previous research indicated that ACE2 is related to the severity of SARS-CoV-induced acute respiratory syndrome and mediates the generation of cytokines associated with acute respiratory distress syndrome. Furthermore, ACE2 is linked to adaptive immune responses (112,113). ACE2 expression was associated with innate immune responses, adaptive immunological responses, B cell regulation, and cytokine release, as well as an accelerated inflammatory response generated by IL-1, IL-10, IL-6, and IL-8 (113). We hypothesize that the immune system dysfunction associated with increased ACE2 expression is connected to cytokine storm symptoms.



### Controlling the Cytokine storm is a determinative key to COVID-19 fate

The positive relevance between cytokine storm and disease severity was investigated by Huang et al. In this observation, patients admitted to the intensive care unit showed high levels of plasma inflammatory cytokines, such as IL-2, IL-7, IL-10, G-CSF (granulocyte colony-stimulating factor), IFN- $\gamma$ , and MCP and TNF- $\alpha$ . These cytokines not only caused responses of Th 1 but also Th 2 in COVID-19 (85). One of the key links in the cytokine storm in COVID-19 could be the activated mononuclear cells by GM-CSF to boost the further release of IL-6 and other proinflammatory cytokines (86). One of the key links in the cytokine storm in COVID-19 could be the activated mononuclear cells by GM-CSF to boost the further release of IL-6 and other proinflammatory cytokines (86). GM-CSF is secreted after CD4+ T cells were activated by infection with SARS-CoV-2 and differentiation of them into Th 1 cells (85, 87).

Recent studies have shown that in very severe cases, both IL-6 and Th-17 cell levels increase significantly, suggesting that cytokine storms may exacerbate tissue damage. Levels of CD4+ T cells, CD8+ T cells, and NK cells were reduced, denoting immunosuppression in severe COVID-19 patients (88).

Activation of monocytes and over-activation of T lymphocytes during the cytokine storm may cause severe damage and immunosuppression. Cytokine storms directly penetrate the capillary mucosa of the lungs, increasing alveolar edema and releasing inflammatory cytokines, leading to alveolar damage and structural disruption (87, 89). Accordingly, the initial and mild stage of infection is a key period for control and treatment. Therefore, finding targeted treatments to prevent cytokine storms is essential.

### Using Cytokine Storm Targeting to Reduce COVID-19 Mortality

Choosing the right targets, time, and complementary therapies is essential to preventing COVID-19 death (90). Antiviral drugs that inhibit virus transmission and replication can directly reduce COVID-19 cell damage (91, 92). It is also possible to resist the virus-induced cytokine storm by treating immune regulators that inhibit hyperactive inflammatory reactions (93).

IL-6 is a good index for poor prognosis in COVID-19 (94). Tocilizumab (an IL-6 receptor blocker, IL-6R) (95) in a clinical trial in China (ChiCTR2000029765) showed a rapid improvement in fever control and respiratory function in patients with severe COVID-19 (14). A study was also published in Italy (Toniati's group) on 100 COVID-19 patients, which showed that the response to Tocilizumab was rapid, stable, and with considerable clinical improvements (96). A meta-analysis of observational studies and a systematic review showed a reduction in mortality in tocilizumab-treated COVID-19 patients (97). Another type of IL-6R blocker that is being tested for SARS-CoV-2 infection is Sarilumab. Because mortality and hyperinflammation due to cytokines are reduced (98, 99). Respectively, Anakinra (100) and Canakinumab block the activity of both IL-1 $\alpha$  and IL-1 $\beta$  and selectively target IL-1 $\beta$ . Anakinra has a short half-life, so it is safer and more convenient for severely ill patients (101, 102). Canakinumab is safe and well-tolerated. Canakinumab is related to a rapid decline in the systemic inflammatory response and improved cardiorespiratory function (103, 104). Both can be used to treat cytokine storms caused by infection and significantly improve survival (86). However, more and stronger evidence-based randomized controlled trials are required for the use of Anakinra and Canakinumab in COVID-19.

### Conclusions

As the coronavirus spreads around the world, it is necessary to study various factors to prevent and treat it to minimize the number of deaths due to the disease. Studies have shown that cytokine storms affect the severity and progression of COVID-19 and cause complications such as multiple organ failure and ARDS. It seems that the Cytokine storm is one of the generic causes of mortality in the recently promulgated pandemic of COVID-19. This event mentions a group of clinical disorders brought on by overactive immunological responses, and it has been identified as a major contributor to severe COVID-19. So, the investigation into how these early molecular processes can impress later phases of disease phenotypes linked to the cytokine storm is important. In this regard, we reviewed several articles; we introduced several important cytokines in the cytokine storm and the mechanism of action of the cytokine storm in COVID-19. Therapeutic approaches used to operate the COVID-19 cytokine storm might prepare a procedure to reduce COVID-19-related morbidity and mortality and be one of the most centralizations of future research.

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