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Imperfect storm: is interleukin-33 the Achilles heel of COVID-19?

Gaetano Zizzo, Philip L Cohen

The unique cytokine signature of COVID-19 might provide clues to disease mechanisms and possible future therapies. Here, we propose a pathogenic model in which the alarmin cytokine, interleukin (IL)-33, is a key player in driving all stages of COVID-19 disease (ie, asymptomatic, mild–moderate, severe–critical, and chronic–fibrotic). In susceptible individuals, IL-33 release by damaged lower respiratory cells might induce dysregulated GATA-binding factor 3-expressing regulatory T cells, thereby breaking immune tolerance and eliciting severe acute respiratory syndrome coronavirus 2-induced autoinflammatory lung disease. Such disease might be initially sustained by IL-33-differentiated type-2 innate lymphoid cells and locally expanded γδ T cells. In severe COVID-19 cases, the IL-33–ST2 axis might act to expand the number of pathogenic granulocyte–macrophage colony-stimulating factor-expressing T cells, dampen antiviral interferon responses, elicit hyperinflammation, and favour thromboses. In patients who survive severe COVID-19, IL-33 might drive pulmonary fibrosis by inducing myofibroblasts and epithelial–mesenchymal transition. We discuss the therapeutic implications of these hypothetical pathways, including use of therapies that target IL-33 (eg, anti-ST2), T helper 17-like γδ T cells, immune cell homing, and cytokine balance.

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Temple Autoimmunity Center (G Zizzo MD, Prof P L Cohen MD) **and Section of Rheumatology, Department of Medicine** (Prof P L Cohen), **Lewis Katz School of Medicine at Temple University, Philadelphia, PA 19140, USA; and Unit of Rheumatology, Department of Internal Medicine, ASST Ovest Milanese, Milan, Italy** (G Zizzo)

Correspondence to: Prof Philip L Cohen, Temple Autoimmunity Center, Lewis Katz School of Medicine at Temple University, Philadelphia, PA 19140, USA **philco@temple.edu**

Introduction

Intensive efforts are underway to unravel the immunopathology of COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and to control the pandemic. Given the public health emergency, scarcity of effective antiviral therapies, and rapid evolution of lung disease associated with COVID-19, patients who are critically ill with COVID-19 and have exuberant inflammation, life-threatening acute respiratory distress syndrome, and coagulopathy, are basically treated as if they had secondary haemophagocytic lymphohistiocytosis or virus-associated macrophage activation syndrome (MAS). These treatments are focused on therapies that neutralise key cytokines driving classical MAS, such as interleukin-6 ([IL]-6; eg, tocilizumab) or interferon gamma (IFNγ; eg, emapalumab).[1,2] In fact, some fatal cases of COVID-19 are accompanied not only by severe respiratory disease, but also by increased systemic inflammation as shown by higher ferritin concentrations.[2] However, in many aspects, COVID-19 does not resemble typical MAS. We propose that the cytokine storm syndrome seen in COVID-19 is dissimilar to that seen in canonical MAS and should be regarded as a distinct entity and approached in a novel way reflecting its unique qualities.

Cellular immunity and T-cell polarisation in COVID-19

Whereas virus-induced MAS shows the classic hallmarks of a T-helper (Th)-1 profile, with high production of IFNγ,[1,3] COVID-19 is instead characterised by circulating T cells that show an activated Th17 membrane phenotype ($CD38^+HLA\text{-}DR^+CD4^+CCR6^+$)[4] and express granulocyte–macrophage colony-stimulating factor (GM-CSF) in part along with IFNγ.[5] Concentrations of both IL-17 and IFNγ are increased in serum from patients with COVID-19 in proportion with viral load and lung injury.[6] Similarly, Middle East respiratory syndrome has been associated with a combined Th1–Th17 inflammatory response.[7] Notably, the cytokine storm composition induced by SARS-CoV-2 differs from that induced by severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus, with lower production of type 1 cytokines (eg, IL-12p70, IL-15), and high concentrations of type 2 cytokines (eg, IL-4, IL-9, IL-10, transforming growth factor β [TGFβ], IL-13).[6–11] These findings might provide important clues to the specific immunopathology of COVID-19.

Transcriptomic analyses of bronchoalveolar lavage fluid from patients with COVID-19 have revealed a strong upregulation of IL-33.[11] IL-33 is a cytokine of the IL-1 family that is expressed in barrier tissues and exerts pleiotropic functions. In the lungs, IL-33 is promptly released, mainly by injured epithelial alveolar cells, following infection and cellular damage.[12] Among its functions, IL-33 enhances TGFβ-mediated differentiation of $Foxp3^+$ regulatory T (Treg) cells[13] and stimulates $CD11c^+$ myeloid dendritic cells to secrete IL-2, which drives Treg cell expansion, thus ultimately promoting resolution of inflammation.[14] Individuals infected with SARS-CoV-2 who develop milder symptoms tend to have large numbers of Treg cells[10] and alveolar macrophages showing a scavenger resolving ($FABP4^+$) phenotype.[15] In the presence of an adequate immune response and virus clearance, IL-33 might drive rapid Treg cell-dependent restoration of respiratory tissue homoeostasis, which probably accounts for the mild or asymptomatic forms of COVID-19 seen in most individuals.

IL-33 and cellular drivers of mild–moderate COVID-19

In susceptible individuals who develop symptomatic SARS-CoV-2 infection and COVID-19 pneumonia (eg, in the presence of individual cytokine or receptor polymorphisms), IL-33 might abnormally upregulate expression of its own receptor ST2 (also known as IL-1RL1) on Treg cells, resulting in increased expression of the canonical

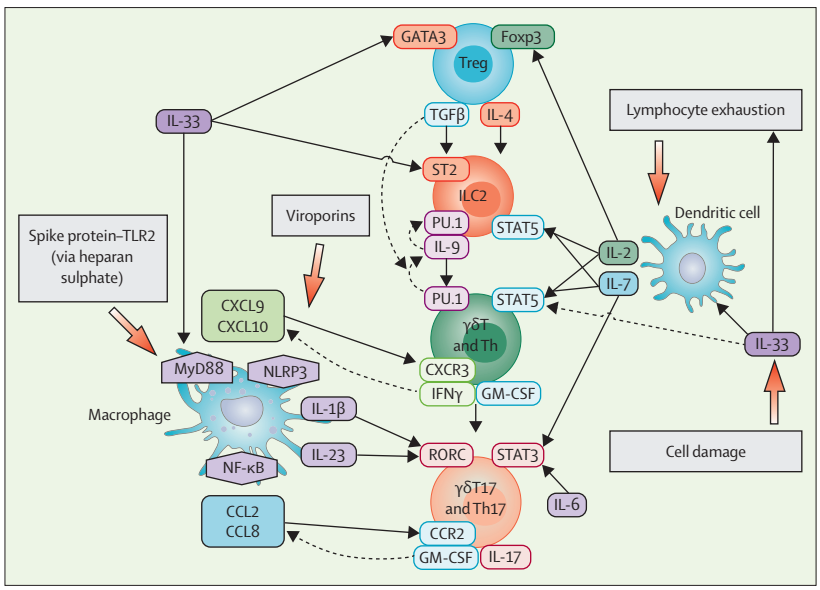


Figure 1: **T-cell polarisation in COVID-19**
IL-33 released from virus-damaged cells might induce dysregulated GATA3$^+$Foxp3$^+$ Tregs and promote IL-2 production by dendritic cells, resulting in further expansion of Tregs. IL-33 might also elicit differentiation of ILC2, with TGFβ enhancing ST2 expression on these cells and facilitating production of IL-9. IL-9 in turn stimulates expansion of effector memory Vγ9Vδ2$^+$ T cells with mixed Th1 and Th17 profiles that express CXCR3 and are recruited to the lungs by CXCL9 and CXCL10. IL-9 possibly induces its own transcription factor PU.1 and thus act in an autocrine and paracrine manner (along with TGFβ) to drive proliferation and survival of ILC2 and γδ T cells. Additional positive loops might be fed by IFNγ, which triggers production of CXCL9 and CXCL10 by macrophages. In severe forms of COVID-19, IL-33, along with IL-2 and IL-7 released by dendritic cells, might further stimulate T-cell expansion through STAT5 and induce production of large amounts of GM-CSF by γδ and T helper cells. At advanced stages of disease, aberrant activation of the MyD88-related NF-κB pathway and activation of the NLRP3 inflammasome might induce virus-exposed cells and infiltrating monocytes–macrophages to overproduce IL-1β, IL-23, and IL-6. IL-1β, IL-23, IL-6, and IL-7 act on STAT3 and RORC, thus promoting differentiation of CCR2$^+$ T cells that are recruited to the lungs by CCL2 and CCL8 into γδT17 and Th17 cells producing IL-17 and GM-CSF. In turn, GM-CSF might further recruit and activate proinflammatory monocytes–macrophages. CCR=C-C motif chemokine receptor. CCL=C-C motif chemokine ligand. CXCL=C-X-C motif chemokine ligand. CXCR=C-X-C chemokine receptor. Foxp=forkhead box protein. GATA=GATA-binding factor. GM-CSF=granulocyte-macrophage colony-stimulating factor. IL=interleukin. ILC2=type 2 innate lymphoid cell. MyD88=myeloid differentiation primary response protein. NF-κB=nuclear factor-kappa B. NLRP=NACHT, LRR, and PYD domains-containing protein. PU.1=transcription factor PU.1. RORC=nuclear receptor ROR-gamma. ST2=ST2 receptor. STAT=signal transducer and transcription activator. TGF=transforming growth factor. Th=T-helper. TLR=toll-like receptors. Treg=regulatory T cell.

Th2 transcription factor GATA-binding factor 3 (GATA3), which impairs the suppressive function of Treg cells. The dysregulation of GATA3$^+$ Foxp3$^+$ Treg cells might result in impaired immunological tolerance and increased secretion of type 2 cytokines, thus promoting autoinflammatory lung disease.[16] *TGFβ2*, which is also increased in the bronchoalveolar lavage fluid of patients with COVID-19,[11] might further enhance ST2 expression in innate lymphoid cells, and IL-33 is the key cytokine that drives these cells to differentiate into type 2 innate lymphoid cells (ILC2).[17] ILC2 subsequently elicit lung inflammation by releasing large amounts of IL-9, which promotes their own survival and expands γδ T cells.[18,19] IL-9 is known to stimulate proliferation and expansion of Vγ9Vδ2$^+$ T cells that have a predominantly effector memory phenotype and a combined Th1–Th17 cytokine response profile.[19] When exposed to TGFβ, γδ T cells can also become an important source of IL-9.[20] By acting in both autocrine and paracrine manners, IL-33-induced IL-9 might sustain a proinflammatory ILC2–γδT cell axis in the lungs of patients with COVID-19, thus initiating mild–moderate forms of pneumonia.

Both ILC2 and γδ T cells are centrally involved in lung homoeostasis and are rapidly activated in response to pathogens including viruses;[19,21] in COVID-19, IL-4 is upregulated at early stages and in milder forms of the disease,[10] whereas IL-9 and activated γδ T cells are observed more frequently in mild-to-moderate disease,[9,22] and IFNγ and IL-17 progressively increase with disease severity.[6] Vγ9Vδ2$^+$ T cells from patients with COVID-19 have been found to express an effector memory phenotype three times more frequently than do conventional αβ T cells,[23] thus suggesting that this T cell subset is selectively stimulated in COVID-19. Because of significantly higher expression of the chemokine receptor CXCR3 compared with their αβ counterparts,[24] γδ T cells might be rapidly recruited into inflamed lungs of patients with COVID-19 in response to the observed strong upregulation of the CXCR3 ligands CXCL9 and CXCL10 (figure 1).[6,9,11,15,25–28]

IL-33 induction of GM-CSF-expressing T cells in severe COVID-19

The cellular composition of lung infiltrates in patients with COVID-19 pneumonia changes with the progression of disease. Infiltrates in patients with moderate pneumonia include mainly lymphoid and dendritic cells; whereas, severe forms of disease are characterised by massive infiltration of macrophages and neutrophils.[15] In patients with COVID-19, expression of T-cell chemoattractants (eg, CXCL9, CXCL10) and their receptors (eg, CXCR3) precedes expression of monocyte and neutrophil chemoattractants (eg, CCL2, CCL3, CCL4, CCL7, CXCL8) and their corresponding receptors (eg, CCR1, CXCR2).[15] The composition and phenotypes of lung macrophages also change with disease severity. Resident alveolar (A-FABP4$^+$) macrophages, which show scavenger and lipid metabolic functions typical of anti-inflammatory or resolving M2-like cells (eg, macrophage receptor MARCO, PPAR-γ, Apo-CI), predominate in mild and moderate forms, whereas CD14$^+$ monocyte-derived macrophages (FCN1^{high}) and chemoattractant (FCN1^{low}SPP-1$^+$) macrophages, which show highly inflammatory M1-like profiles (eg, nuclear factor-kappa B [NF-κB], CCL2, CCL3), dominate tissue specimens from patients with severe forms of COVID-19 and who are critically ill.[15]

In the circulation of patients with COVID-19, amounts of proinflammatory CD14$^+$CD16$^+$ intermediate monocytes increase with disease severity, and upregulation of GM-CSF in CD4$^+$ and CD8$^+$ T cells might account for tissue recruitment and activation of neutrophils and monocyte-derived macrophages in most severe forms of the disease.[5]

Although described as Th1 cells, at least half of the GM-CSF-producing T cells observed in the circulation of patients with severe COVID-19 do not coexpress the

canonical Th1 cytokine IFNγ.[5] Lymphocytes from patients with COVID-19 appear to be functionally exhausted, producing lower amounts of IFNγ, IL-2, and tumour necrosis factor (TNF), and having decreased cytotoxic function.[29] Many factors could possibly explain this lymphocyte dysfunction, in particular the upregulation of multiple coinhibitory receptors such as CD94, CD152 (cytotoxic T-lymphocyte-associated antigen 4), programmed cell death protein 1 (PD-1), and T-cell immunoglobulin mucin receptor 3 (TIM-3).[29] However, suboptimal production of IFNγ, poor cytotoxic capabilities, a shorter lymphocyte lifespan, and lymphopenia might also be attributable to a scarcity in type I and III interferons (IFNα, IFNβ, and IFNλ), in the blood as well as in the lungs of patients with COVID-19.[27] Interferons are more highly suppressed by SARS-CoV-2 than by SARS-CoV infection,[27,28] and this most likely accounts for the impaired antiviral responses and spontaneous apoptosis of dysfunctional lymphocytes.[11,30]

Lymphocyte impairment in COVID-19 resembles the cytotoxic dysfunction of $CD8^+$ cytotoxic T lymphocytes and natural killer cells observed in familial haemophagocytic lymphohistiocytosis, in which T cell dysfunction is the result of heterozygous mutations in genes affecting the expression of perforin or other proteins involved in the trafficking and docking of cytolytic granules,[1] and in patients who are predisposed to MAS, in whom IL-6 overexpression can reduce perforin and granzyme B concentration inside granules.[31]

The inability to kill infected or activated antigen-presenting cells in patients with either MAS or COVID-19 could result in persistent interactions between T cells and antigen presenting cells, culminating in hyperproduction of cytokines as a result of overstimulation of both cell types.[1] However, by contrast with COVID-19, IFNγ is not impaired in MAS, and is a major driver of disease. In MAS, IFNγ-producing $CD8^+$ T-cell populations are elevated in primary and secondary lymphoid organs, leading to IFNγ-driven macrophage hyperactivation and haemophagocytosis.[1,3]

The effects of IFNγ deficiency have been investigated in an experimental model of haemophagocytic lymphohistiocytosis, which develops when perforin deficient ($Prf1^{-/-}$) mice are infected with the lymphocytic choriomeningitis virus. Surprisingly, mice lacking both IFNγ and perforin ($IFN\gamma^{-/-}Prf1^{-/-}$) still develop a severe MAS-like disease that requires the IL-33–ST2 axis and is downstream mediated by GM-CSF-producing $CD8^+$ T cells. The inflammatory burden in infected $IFN\gamma^{-/-}Prf1^{-/-}$ mice is even higher than in $Prf1^{-/-}$ mice, being characterised by a 10–15 times increase in neutrophils and stronger upregulation of IL-1β and IL-6.[32] The same interplay between IL-33 and GM-CSF might occur in patients with COVID-19, which would initiate the cytokine storm syndrome. Thus, severe forms of COVID-19 might represent atypical MAS or MAS-like reactions with incorporated interferon deficiencies.

Cellular expansion in severe–critical COVID-19

Failure of lymphocytes to adequately respond to viral antigens and proapoptotic signals might induce dendritic cells to produce large amounts of the lymphocyte growth factors IL-7 and IL-2, thereby stimulating T-cell survival and expansion. High concentrations of IL-2 and IL-7 in serum are characteristic of severe COVID-19 cases.[6,9] However, IL-2 and IL-7 might amplify ILC2 survival and differentiation induced by IL-33,[33] expand γδ T cells, which produce IL-17 through the signal transducer and activator of transcription (STAT)3,[34] and enhance IL-33-induced pathologic expansion of T cells expressing GM-CSF through STAT5.[35,36] Patients infected with SARS-CoV-2 show an increase in circulating $CD4^+$ γδ T cells that overexpress the IL-2 receptor CD25 but not PD-1, suggesting that these cells are not exhausted, but are specifically activated in response to IL-2.[22]

IL-7 enables γδ T cells to fully differentiate into γδT17 cells[34] that coproduce IL-17F along with IL-17A, and rapidly migrate into inflamed tissues in response to CCR2 and CCR5 ligands such as CCL2 and CCL8.[37,38] As shown for murine γδT17 cells, human $V\delta2^+$ T cells that co-express CCR2 and CCR5 also express the IL-7 receptor and show a Th17-like phenotype ($CCR6^+CD161^+IL\text{-}23R^+$).[39] Transcriptional analyses of respiratory cell populations in response to SARS-CoV-2 infection reveal strong upregulation of CCL8, CCL2, CXCL9, CXCL10 and their respective receptors,[11,15,27] and global upregulation of IL-17 and IL-17F-related pathways,[26] including the CCR6 ligand CCL20 and IL-23.[27]

IL-23 and IL-1β are required for GM-CSF production by γδT17 cells and conventional αβ Th17 cells.[40,41] In models of autoimmunity in which GM-CSF is a key pathogenic molecule, such as experimental autoimmune encephalomyelitis, γδ T cells have been identified as the major source of GM-CSF.[42] Whereas conventional αβ Th17 cells evolve to produce IFNγ during the development of the disease, γδT17 cells are less likely to produce IFNγ and will more likely evolve to produce GM-CSF.[42] As for γδT17, recruitment of IL-23-driven, GM-CSF-producing Th17 cells requires CCR2.[43]

By promptly releasing multiple cytokines such as IL-9, IL-17, IL-17F, TNF, IFNγ, and GM-CSF, γδT17 might be instrumental in recruiting neutrophils and proinflammatory monocytes into the capillaries and alveoli of patients with COVID-19. Moreover, activation of γδ T cells might be important in the cytokine-driven induction of procoagulant tissue factor in endothelial cells,[44] thus also having a potential role in vascular manifestations and pulmonary thromboses associated with COVID-19 pneumonia.[2,29]

Cytotoxicity against virus-infected alveolar epithelial cells by γδ T cells has been shown for influenza virus[45] and might involve atypical pathways alternative to granzyme B and perforin, which are more commonly used by $CD8^+$ T cells and natural killer cells and could be impaired in COVID-19 and MAS.[1,29,31] Specifically, γδ T cells might

exert cytotoxic effects through the TNF-related apoptosis-inducing ligand, Fas ligand, and granzyme K,[39,45] which are all overexpressed in the lungs of patients with COVID-19,[11,15] and might therefore explain how γδ T cells cause diffuse damage to the alveolar epithelium (figure 1).

Suppression of antiviral responses and hyperinflammation

Advanced stages of COVID-19 are characterised by high circulating and pulmonary concentrations of IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1RA).[6,15,25] The increased production of these molecules probably relates to high viral loads resulting in increased viroporins and subsequent activation of the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome. The strong expression of IL-1α, IL-1β, and IL-1RA is also due to monocyte activation and intense lung infiltration of monocyte-derived macrophages at later stages, as suggested by an abundance of $CD14^{+}IL\text{-}1\beta^{+}$ monocytes in the circulation of patients with COVID-19 in the early stages of recovery.[46] Active IL-1β is produced following NLRP3 assembly and consequent caspase-1 activation. By modulating ion fluxes across host cell membranes, viroporins (in particular the ORF3a protein) have been shown to activate NLRP3 during SARS-CoV infection, and a similar mechanism might be at play during SARS-CoV-2 infection.[47]

An imbalance in signalling from toll-like receptor (TLR) pathways, with the myeloid differentiation primary response protein (MyD88) pathway predominating over the TIR domain-containing adapter molecule 1 (TICAM-1, also known as TRIF) pathways, might further increase NLRP3 activation.[48] Signalling downstream of IL-1 family receptors, including the IL-33 receptor ST2, and downstream of membrane TLRs, can activate MyD88 and elicit inflammation; whereas TRIF-mediated pathways downstream of endosomal TLRs would be expected to mount antiviral interferon responses and protect against coronaviruses.[48,49] Although coronaviruses are single-stranded RNA viruses that are predicted to bind directly to endosomal TLR7 and TLR8, and indirectly to TLR3 (using double-stranded RNA replication intermediates), aberrant inflammation induced by coronaviruses might instead involve membrane-expressed TLR2, as suggested by virus spike protein interactions with heparan sulphate-enriched regions of TLR2 in studies of the mouse hepatitis coronavirus.[50] A predominance of MyD88 signalling over TRIF signalling would lead virus-exposed cells to produce high amounts of IL-1β, and NF-κB-induced cytokines and chemokines (eg, TNF, IL-8, IL-6, IL-12p40, IL-23, CCL2) rather than interferons, IL-12p35 and IL-12p70.[30,49,50]

High concentrations of MyD88-related cytokines and reduced expression of TRIF-related cytokines characterise the cytokine milieu observed in the lungs of patients with severe and life-threatening COVID-19.[15,27,28] Such an altered cytokine environment would polarise the immune response towards detrimental (Th17-sustained and GM-CSF-induced) hyperinflammation[40,41] caused by monocyte-derived macrophages and neutrophils, in place of protective (Th1-sustained and IFN-induced) antiviral responses exerted by cytotoxic T lymphocytes, natural killer cells, and B cells.[29,30] Altogether, coronaviruses seem to deceive and escape the immune system by eliciting a response that is generally more appropriate for extracellular rather than intracellular pathogens.

IL-33 and pathway synergisms in critical systemic COVID-19

In addition to NLRP3 stimulation and IL-1 release,[47] substantial amounts of viroporins in patients with life-threatening COVID-19 might also account for extensive injury of alveolar epithelial cells and overproduction of IL-33.[51] IL-33, IL-1α, and GM-CSF also stimulate each other's release by alveolar type 2 pneumocytes.[52,53] Accordingly, diffuse alveolar damage with alveolar denudation and reactive type 2 pneumocyte hyperplasia are histological hallmarks of COVID-19 with acute respiratory distress syndrome.[4]

Feedforward loops might also engage mast cells, macrophages, endothelial cells, T cells, and neutrophils.[40,54] Although whether mast cells and macrophages produce IL-33 is still up for debate,[51] it is well established that mast cells, infiltrating neutrophils, and cytotoxic T lymphocytes secrete serine proteases (eg, tryptase, cathepsin G, elastase, granzymes) that cleave IL-33 released from damaged epithelial and endothelial barriers into a mature form of IL-33 that is 10–30 times more active.[51] IL-33 amplifies lung inflammation by inducing various proinflammatory cytokines (eg, GM-CSF, IL-1β, IL-6, TNF, granulocyte colony-stimulating factor [G-CSF]), chemokines (eg, CXCL1, CXCL2, CXCL6, CXCL8, CCL2, CCL20), and adhesion molecules (eg, E-selectin, ICAM1, VCAM1) in several target cells.[32,54–57] Conversely, by inhibiting type 1 interferons and IL-12p35, IL-33 might contribute to impaired antiviral cytotoxic responses.[58] In models of MAS-like disease, IL-33 is a crucial contributor to the weight loss and hyperferritinaemia related to systemic hyperinflammation, and to the expansion of GM-CSF-producing $CD8^{+}$ T cells, upregulation of IL-1β and IL-6, and tissue neutrophilia.[32] These features are the same as key characteristics seen in patients with critical COVID-19.[5,15,26]

IL-33 has also been implicated in the formation of neutrophil extracellular traps during virus-induced asthma exacerbation.[58] Similarly, neutrophil priming with GM-CSF might promote the production of neutrophil extracellular traps.[59] By releasing neutrophil elastase and other proteinases, neutrophil extracellular traps could in turn cleave and further activate IL-33. These pathways might be relevant in patients with critical COVID-19, since neutrophilia and the neutrophil-to-lymphocyte ratio are associated with poor prognosis, and high concentrations of neutrophil extracellular traps have been detected in patients with COVID-19 admitted to hospital and receiving mechanical ventilation.[60]

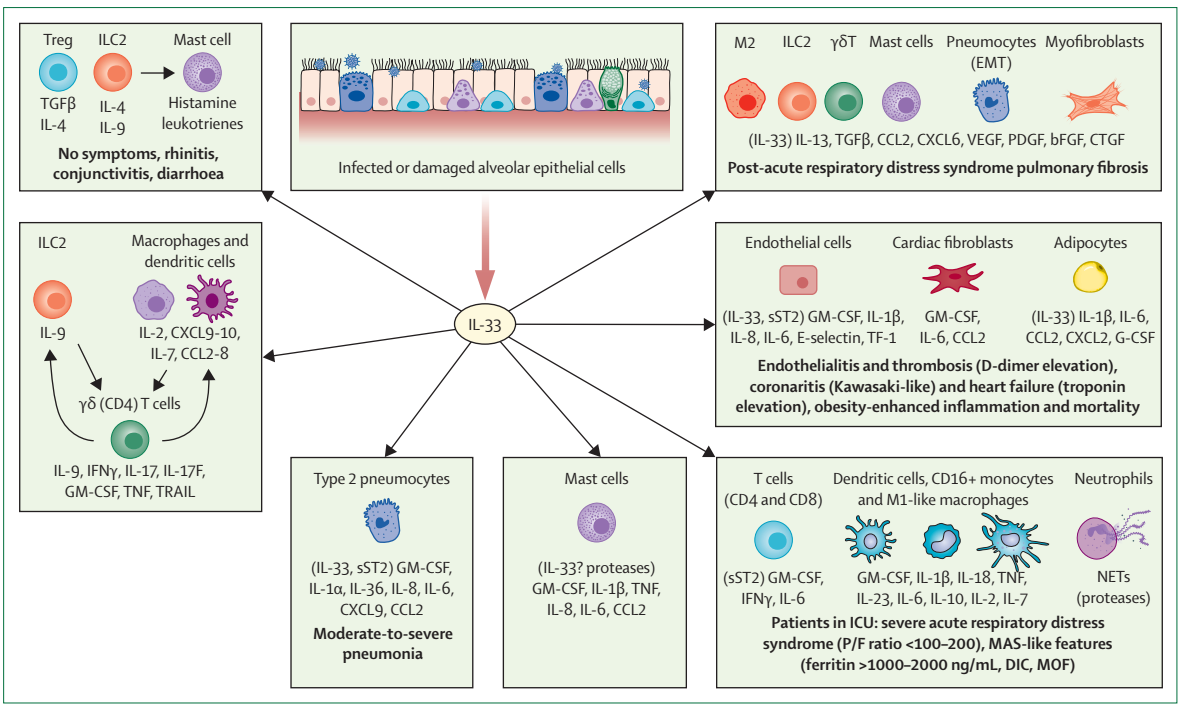


Figure 2: **IL-33 might orchestrate all pathogenic phases of COVID-19**
IL-33 might induce numerous cytokines and chemokines as well as its own receptor, ST2, in various cell types. In asymptomatic or paucisymptomatic patients, IL-33 might expand anti-inflammatory Foxp3⁺ Treg cells or induce IL-4 production by GATA3⁺Foxp3⁺ Tregs and ILC2, thus stimulating mast cells, which might account for minor, allergy-like symptoms. In individuals with mild-to-moderate disease, IL-33 (along with TGFβ) might induce ILC2 to release large amounts of IL-9, driving local expansion of effector memory Vγ9Vδ2⁺ T cells in the lungs. In moderate–to-severe pneumonia, IL-33 combined with IL-2 and IL-7 from dendritic cells might further expand ILC2, γδT cells, and GM-CSF-producing T cells. In severe–critical COVID-19, IL-33, GM-CSF, and IL-1 might stimulate each other's release by acting on multiple cell types. IL-33 induction of cytokines, chemokines, adhesion molecules, tissue factor, and neutrophil extracellular traps might contribute to endothelialitis, thrombosis, and extrapulmonary involvement in patients with MAS-like disease. Neutrophil extracellular traps and mast cell degranulation could provoke protease-mediated cleavage of IL-33 into a 10–30 times more potent form, and IL-33-induced release of its soluble receptor ST2 might further polarise T cells and contribute to cardiovascular manifestations. In patients who survive, IL-33 might drive the post-acute fibrotic phase thorugh induction of IL-13 and TGFβ in M2-differentiated macrophages and ILC2, thereby stimulating myofibroblasts and eliciting the epithelial–to–mesenchymal transition of type 2 pneumocytes. Molecules inside brackets are part of self-amplifying proinflammatory loops fed by IL-33 and outside brackets indicate different factors possibly induced by IL-33. Question mark indicates the uncertainty of whether mast cells produce IL-33. bFGF=fibroblast growth factor. CCL=C-C motif chemokine ligand. CTGF=connective tissue growth factor. CXCL=C-X-C motif chemokine ligand. DIC=(systemic vascular thromboses mimicking) diffuse intravascular coagulation. EMT=epithelial-mesenchymal transition. Foxp=forkhead box protein. GATA=GATA-binding factor. G-CSF=granulocyte colony-stimulating factor. GM-CSF=granulocyte-macrophage colony-stimulating factor. ICU=intensive care unit. IFN=interferon. IL=interleukin. ILC2=type 2 innate lymphoid cell. MAS=macrophage activation syndrome. MOF=multiple organ failure. NET=neutrophil extracellular trap. PDGF=platelet-derived growth factor. P/F ratio=arterial oxygen partial pressure to fractional inspired oxygen ratio. sST2=soluble ST2. ST2=ST2 receptor. TGF=transforming growth factor. TF-1=tissue factor-1. TNF=tumour necrosis factor. TRAIL=TNF-related apoptosis-inducing ligand. Treg=regulatory T cell.

Neutrophil extracellular traps might propagate inflammation and microvascular thrombosis in patients with COVID-19 and severe acute respiratory distress syndrome.[60] Along with IL-33, IL-1, TNF, and other cytokines, neutrophil extracellular traps might increase endothelial permeability and induce a procoagulant phenotype in endothelial tissues by inducing expression of tissue factor,[61–63] thus representing a possible link between hyperinflammation and hypercoagulability that could account for D-dimer elevation, pulmonary thrombosis, and microvascular manifestations affecting the heart, kidneys, and small bowel seen in patients with critical COVID-19.[64,65] Endothelialitis and endothelial dysfunction would also account for predominant exudative-phase diffuse alveolar damage characterised by hyaline membranes and fibrin deposits typically observed in patients with COVID-19 and severe acute respiratory distress syndrome.[4]

IL-33 has also been shown to stimulate expression of IL-1β, IL-6, CCL2, CXCL2, and G-CSF by adipocytes.[57] Elevated circulating concentrations of soluble ST2 (measured more often than IL-33 because of its higher concentration and stability) are associated with obesity, diabetes, hypertension, and acute cardiovascular diseases. High soluble ST2 concentrations also predict worse outcomes and are associated with extension of heart damage, heart failure, increased cardiovascular death, and all-cause mortality.[54] Notably, diabetes, hypertension, and cardiovascular diseases are common comorbidities in patients with COVID-19, and obesity has been independently associated with increased severity and mortality among younger patients with COVID-19.[66] Circulating concentrations of soluble ST2 correlate with the extent of tissue damage, and might represent an indicator in plasma of IL-33 release and bioactivity in tissues.

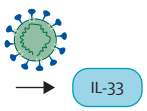
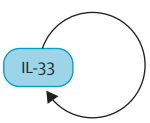
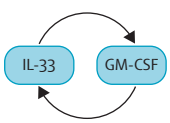
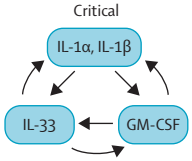
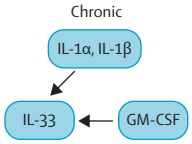
COVID-19 stages	Cytokines	Chemokines	Cells and phenotypes	Possible treatments
Mild 	IL-33/ST2 IL-4 IL-10 TGFβ	Tissue resident (low CCL2)	GATA3^{+} Treg ILC2 FABP4^{+} alveolar macrophages Mast cells	Anti-ST2, anti-IL-33 Anti-IL-4R α Mast cell stabilisers Vitamin D
Moderate 	IL-33/ST2 TGFβ IL-9 IFNγ IL-17A	CXCL9-10-11 (CXCR3) CXCL16 (CXCR6)	ILC2 γδ T cells (Th9-like, Th17-like) FABP4^{+} alveolar macrophages	Anti-ST2, anti-IL-33 Anti-IL-9 Pentoxifylline Apremilast Vitamin D
Severe 	IL-33/ST2 GM-CSF IL-2 IL-7 IL-17A, IL-17F	CXCL9-10 (CXCR3) CCL2-8 (CCR2-5)	CD4 T cells (Th1-like, Th17-like) Dendritic cells FCN1^{lo} SPP1^{+} macrophages	Anti-ST2, anti-IL-33 Anti-GM-CSF Anti-IL-17A/IL-17F Anti-CCL8, anti-CCR5, or CCR2/CCR5i
Critical 	IL-33/sST2 GM-CSF IL-1α, IL-1β IL-23 TNF IL-6 IL-10	CCL20 (CCR6) CCL2-3-4-7 (CCR1) CXCL1-2-6-8 (CXCR2)	CD4 and CD8 T cells (Th17-like) Monocyte-derived FCN1^{hi} macrophages Neutrophils Endothelial cells	Anti-ST2, anti-IL-33 Anti-GM-CSF rIL-1RA, anti-IL-1β, rIL-37 Colchicine, NLRP3i Anti-IL6R, heparin, TLR2i JAK2i (IL-6/IL-23i)
Chronic 	IL-33/ST2 TGFβ IL-13 FGF VEGF PDGF	CCL2-8 CXCL6-16-17	ILC2 (Th2-like) SPP1^{+} macrophages Myofibroblasts	Anti-ST2, anti-IL-33 Anti-(pan) TGFβ Anti-IL-13, Anti-IL-4Rα FGF/VEGF/PDGF-Ri Anti-CCL2 Pirfenidone

Figure 3: **Inflammatory patterns in COVID-19 at various disease stages**
Cytokine interplay between IL-33, GM-CSF, IL-1α, and IL-1β, and key cytokines, chemokines, and receptors, the composition of lung inflammatory infiltrates, cell phenotypes involved, and possible therapeutic options according to different stages of disease. CCR=C-C motif chemokine receptor. CCL=C-C motif chemokine ligand. CXCL=C-X-C motif chemokine. CXCR=C-X-C motif chemokine receptor. FABP=fatty acid-binding protein. FCN=ficolin. FGF=fibroblast growth factors. GATA=GATA-binding factor. GM-CSF=granulocyte-macrophage colony-stimulating factor. i=inhibitor. IFN=interferon. IL=interleukin. ILC2=type 2 innate lymphoid cell. JAK=Janus kinase. NLRP=NACHT, LRR, and PYD domains-containing protein. PDGF=platelet-derived growth factor. PDGF-Ri=platelet-derived growth factor receptor inhibitor. rIL=recombinant interleukin. SPP=secreted phosphoprotein. sST2= soluble ST2. ST2=ST2 receptor. TGF=transforming growth factor. Th=T-helper. TLR=toll-like receptor. Treg=regulatory T cell. VEGF=vascular endothelial growth factor.

Production of soluble ST2 might be reduced by anti-ST2 treatment, and such reduction would modulate T-cell polarisation by decreasing pathogenic Th1 and Th17 cells, and increasing IL-10-producing Treg cells.[67] Future research should focus on whether soluble ST2 concentrations in plasma have prognostic value in patients with COVID-19 (figure 2).

Similarities between COVID-19, Kawasaki disease, and Behçet's disease

For the **WHO clinical trial registry** see https://clinicaltrials.gov/ct2/who_table

Parallels between COVID-19 and rheumatic disorders can be made by referring to discrete autoinflammatory syndromes that share symptoms with COVID-19 such as fever, frequent conjunctivitis, and—most remarkably—vasculitic manifestations with neutrophilia, thrombosis, and aneurysmal dilations, involving coronary vessels (eg, Kawasaki disease in infants) or pulmonary vessels (eg, Behçet's disease in adults).

Case series of children infected with SARS-CoV-2 who develop Kawasaki-like disease with MAS features have been described.[68] GM-CSF produced by cardiac fibroblasts is key in disease progression in mouse models of Kawasaki disease, and significantly increased soluble ST2, E-selectin, CXCL10, IL-17F, and in some cases IL-9, have been reported in the circulation of patients with acute Kawasaki disease compared with other children who are febrile.[69–71] Similarly, Behçet's disease has been associated with high concentrations of both soluble ST2 and IL-33, as well as increased CXCL10 and CCL2, Vγ9Vδ2 T-cell expansion, IL-17F gene polymorphisms, and intense recruitment of T cells producing IL-9 and IL-17 to the lungs.[72–76] Some patients with either Behçet's disease[77] or COVID-19[78] also show positivity for antiphospholipid antibodies, which might further contribute to the coagulopathy seen in both conditions.

IL-33 induction of pulmonary fibrosis in chronic COVID-19

Lung alveolar inflammation in COVID-19 is accompanied by loose interstitial fibrosis and can result in widespread fibrotic changes.[79] IL-33 could also be important at these later stages of the disease. In a bleomycin-induced pulmonary fibrosis mouse model, the IL-33–ST2 axis is required to induce alternatively activated M2 macrophages and ILC2 to release key profibrotic cytokines.[80] IL-33-activated mast cells might also play a role in organ fibrosis.[81] Most remarkably, IL-33 has been shown to induce epithelial-to-mesechymal transition of type 2 pneumocytes through TGFβ signalling.[82]

IL-33 concentrations are elevated in patients with systemic sclerosis and correlate with the severity of pulmonary fibrosis, and patients with idiopathic pulmonary fibrosis show increased serum concentrations of soluble ST2 when the disease is exacerbated.[82] IL-33 can induce cytokines (eg, TGFβ, IL-13) and chemokines (eg, CCL2, CXCL6) involved in pulmonary fibrosis, which are also increased in patients infected with SARS-CoV-2,[6,9,11,15,26] thus suggesting additional roles for IL-33 in driving the post-acute fibrotic phase of COVID-19. Growth factors such as vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor are all involved in fibrotic processes and are overexpressed in patients with COVID-19,[9] and γδ T cells exposed to TGFβ might produce connective tissue growth factor (figure 2).[83]

Implications for therapy

Although more conclusive results are awaited from randomised controlled trials, encouraging preliminary results have been reported for the successful management of severe and critical COVID-19 by therapeutic modulation of IL-1α and IL-1β with recombinant IL-1RA (anakinra)[84,85] and by blocking GM-CSF using monoclonal antibodies (mavrilimumab, lenzilumab).[86,87] Although some studies

	Molecular targets	Cell targets	Advantages	Disadvantages
Anti-ST2 (eg, astegolimab), anti-IL-33 (eg, MEDI-3506), small-molecule ST2 inhibitors	IL-33-ST2 axis, soluble ST2	GATA3$^+$ regulatory T cells, ILC2, type 2 pneumocytes, IL-2 and IL-7-producing dendritic cells, IL-9 and IL-7-driven γδT17 cells, GM-CSF-producing T cells, neutrophils, endothelial cells, mast cells, and M2 macrophages	Effective against virus-induced exacerbations of asthma, might restore antiviral interferon responses; effective in haemophagocytic lymphohistiocytosis and MAS-like models incorporating interferon deficiencies (resembling severe–critical COVID-19); might be effective at all stages of COVID-19; and has potential against obesity-related severe COVID-19	Complexity of IL-33 biology—eg, nuclear versus extracellular cytokine, full-length versus cleaved form, membrane versus soluble receptor (targeting ST2 over IL-33 seems safer); atheroprotective and cardioprotective roles hypothesised for IL-33; unclear whether suppression of proinflammatory Th1 and Th17 cells by anti-ST2 favours Th2 responses along with regulatory T cell expansion; however, inhibition of ILC2, M2 and type 2 pneumocytes should overall result in antifibrotic effects
Anti-GM-CSF (eg, mavrilimumab, gimsilumab, lenzilumab, otilimab)	GM-CSF	Type 2 pneumocytes, monocytes, macrophages, neutrophils, endothelial cells	Encouraging preliminary data in severe-to-critical COVID-19 and good safety	Might be less effective at earlier stages; possibly interferes with alveolar macrophage homoeostasis and alveolar surfactant production
Recombinant IL-1RA (eg, anakinra), anti-IL-1β (eg, canakinumab), recombinant IL-37	IL-1α and IL-1β, or IL-1β	Type-2 pneumocytes, GM-CSF-producing γδT and Th17 cells, monocytes, macrophages, neutrophils, endothelial cells, adipocytes	Encouraging preliminary data in severe–critical COVID-19; potential against obesity-related severe forms of COVID-19; good safety (short half-life of anakinra)	Might be less effective at earlier stages
Recombinant IL-36RA or IL-38	IL-36 cytokines	T cells, mast cells, neutrophils, monocytes, macrophages, endothelial cells, fibroblasts	IL-36α promotes influenza virus-induced lung injury and mortality	IL-36β supports antiviral interferon responses; IL-36γ supports alveolar macrophage survival during viral infection
Anti-IL-6 receptor (eg, tocilizumab, sarilumab), anti-IL-6 (eg, clazakizumab, siltuximab)	IL-6	Natural killer cells, T cells, B cells, endothelial cells	Might help restore suppressed natural killer cell functions and oppose acute respiratory distress syndrome development	IL-6 might have homoeostatic roles and induce SOCS3, IL-4Rα and CD163; conflicting preliminary results in severe–critical COVID-19; might favour bacterial, viral, and opportunistic infections (long half-life of IL-6 inhibitors)
Anti-IFNγ (eg, emapalumab)	IFNγ	Macrophages, dendritic cells, B cells, T cells, endothelial cells	Might inhibit macrophage hyperactivation and induction of CXCL9 and CXCL10; might partly inhibit pathogenicity of effector T cells coexpressing GM-CSF and IFNγ	Exogenous IFNγ inhibited the expression of GM-CSF by CD8$^+$T cells in haemophagocytic lymphohistiocytosis and MAS-like models with IFNγ deficiency; and anti-IFNγ might dampen protective antiviral cytotoxic T lymphocytes and B-cell responses orchestrated by interferons and Th1 cells
Antimalarials (eg, chloroquine, hydroxychloroquine)	Endosomal toll-like receptors	Dendritic cells, monocytes, macrophages, neutrophils, B cells, pneumocytes	Might inhibit virus entry in vitro	Possibly dampen endosomal toll-like receptor-induced, TRIF-mediated, protective, type 1 interferon signalling; possible cardiotoxicity
Type 3 interferons (eg, peg-interferon lambda-1, or recombinant IL-29)	Anti-viral immune responses	Pneumocytes (tissue-barrier epithelial cells), dendritic cells, macrophages, neutrophils	IFNλ might overcome suppression of interferons and stimulate antiviral immune responses without detrimental hyperinflammation (restricted expression pattern of IFNλ receptor 1); less inflammatory side-effects than IFNα in patients with hepatitis C virus and in influenza-infected mice	Knowledge of interferon lambda biology in humans is incomplete
Heparins (and small molecule toll-like receptor 2 inhibitors)	Virus interaction with heparan sulphate on cell membranes	Virus-susceptible host cells	Possibly block coronavirus-induced, toll-like receptor 2-mediated, TNF and IL-6 production; might inhibit virus entry; and have antithrombotic effects	Effective dose and best route of administration are unclear; risk of bleeding
Anti-IL-4Rα (eg, dupilumab), anti-IL-13 (eg, lebrikizumab)	IL-4 and IL-13, or IL-13	M2 macrophages, ILC2, Th2 cells, mast cells, eosinophils, B cells, myofibroblasts	Might inhibit virus-induced asthma exacerbations; and have a potential benefit in pulmonary fibrosis	Possible exacerbation of Th17 responses and neutrophilia in severe–critical COVID-19
Anti-IL-9 (eg, MEDI-528)	IL-9	ILC2, γδT17 cells, effector memory T cells, neutrophils, mast cells, M2 macrophages	Might inhibit expansion of lymphoid cells, mast cell activation, and neutrophil recruitment in COVID-19 pneumonia; and might inhibit production of TGFβ and pulmonary fibrosis	Might favour proinflammatory activation of monocytes and macrophages
Anti-IL-17A and anti-IL-17F (eg, bimekizumab), anti-IL-17RA (eg, brodalumab)	IL-17A, IL-17F, IL-17E (or IL-25)	Neutrophils, monocytes, macrophages, mast cells, endothelial cells, fibroblasts, ILC2	Might inhibit neutrophil recruitment and detrimental inflammation in severe COVID-19; and by acting on IL-25, brodalumab could also inhibit ILC2 differentiation	Might favour fungal and bacterial infections

(Table continues on next page)

	Molecular targets	Cell targets	Advantages	Disadvantages
(Continued from previous page)				
Selective JAK2 inhibitors (eg, fedratinib)	IL-23, IL-6	γδT17 cells, Th17, GM-CSF-producing T cells, mast cells, neutrophils	Possibly inhibit inflammation in severe COVID-19 and do not interfere with JAK1-dependent interferon signalling	Do not interfere with IL-9, IL-2, and IL-7-mediated expansion of effector T cells; might favour bacterial, viral, and opportunistic infections
Anti-CCR2 (eg, prozalizumab), anti-CCR5 (eg, leronlimab), dual CCR2 and CCR5-inhibitors (eg, BMS-813160)	CCR2 or CCR5, or both	γδT17 cells, GM-CSF-producing T cells, monocytes, macrophages	Might inhibit homing of mononuclear cells; encouraging data have been shown for leronlimab on restoration of immune functions in COVID-19 and clinical improvement; good safety	Redundancy and complexity of the chemokine receptor system; several compounds targeting CCR2 or CCR5 did not show clinical efficacy as presumed from preclinical models
Anti-CCL2 (eg, carlumab), anti-CCL8	CCL2 or CCL8	γδT17 cells, T cells, monocytes, macrophages, neutrophils, fibroblasts	Possibly act on different stages of COVID-19	Use of carlumab was unsuccessful in idiopathic pulmonary fibrosis
Anti-CCR1 (eg, AZD4818), anti-CXCR2 (eg, AZD5069)	CCR1 or CXCR2	Monocytes, macrophages, neutrophils	Possibly inhibit tissue recruitment of monocytes and neutrophils	Use of these drugs was unsuccessful in chronic obstructive pulmonary disease and asthma
Colchicine	Tubulin (cytoskeleton)	Monocytes, macrophages, pneumocytes, neutrophils, endothelial cells, platelets	Might inhibit NLRP3 assembly, neutrophil recruitment, and platelet aggregation; has antiviral properties	Use of colchicine was unsuccessful in idiopathic pulmonary fibrosis; frequent diarrhoea
NLRP3 inflammasome inhibitors (eg, dapansutrile, CP-456773)	NLRP3	Macrophages and other cells	Shown to inhibit caspase-1, thereby preventing activation of IL-1β and IL-18; effective in murine models of pulmonary inflammation; and have a potential benefit in heart failure	Might be less effective at earlier stages
Non-selective phosphodiesterase inhibitors (eg, pentoxifylline)	Phosphodiesterases (adenosine receptor A2A-dependent mechanisms)	γδ T cells, alveolar macrophages, mast cells, neutrophils, endothelial cells, platelets	Might inhibit proinflammatory Vγ9Vδ2 T cells and TNF release; anti-inflammatory effects in experimental acute lung injury; haemorheological and antithrombotic properties; broad-spectrum antiviral activity	Risk of bleeding
Phosphodiesterase-4 inhibitors (eg, apremilast)	Phosphodiesterase-4 (enhanced by adenosine receptor A2A agonists)	Monocytes, macrophages, dendritic cells, T cells, fibroblasts	Possibly inhibit production of CXCL10, interferon gamma, IL-23, TNF, and leucocyte infiltration; ameliorate pulmonary inflammation in experimental models	Frequent diarrhoea
Mast cell stabilisers (eg, sodium cromoglycate, ketotifen)	Ion (calcium) channels, histamine receptor H1	Mast cells	Might act on several symptomatic and pathogenic aspects of COVID-19	Might cause sedation, possibly favouring respiratory depression
Vitamin D	Vitamin D response elements	Regulatory T cells, effector T cells, dendritic cells, adipocytes, mast cells	Possibly shifts the T cell balance in favour of regulatory T cells rather than Th9 and Th17; might inhibit Vγ9Vδ2 T cells and adipocyte release of CCL2, and stabilise mast cells	Appropriate dosage for use as an immunomodulant is not defined; potential toxicity linked to hypercalcaemia
Anti-(pan)TGFβ (eg, fresolimumab)	TGFβ(2)	ILC2, IL-9, and IL-17- producing T cells, M2 macrophages, fibroblasts, pneumocytes	Might act on different stages of COVID-19; might inhibit ST2 upregulation and IL-9 production; and has a potential benefit in pulmonary fibrosis	Might inhibit regulatory T cell activity
Anti-connective tissue growth factor (eg, pamrevlumab)	CTGF, TGFβ pathway	Fibroblasts, pericytes, endothelial cells, cardiomyocytes	Potential benefit in pulmonary fibrosis	Might be effective only at later stages
Receptor tyrosine kinase inhibitors (eg, nintedanib)	Vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor receptors	Fibroblasts, pericytes, endothelial cells, cardiomyocytes	Approved for treating pulmonary fibrosis	Might be effective only at later stages and correct timing is unclear; frequent diarrhoea; risk of bleeding
Pirfenidone	TGFβ pathway	M2 macrophages, fibroblasts	Approved for treating pulmonary fibrosis	Might be effective only at later stages

A2A=adenosine 2A. CCR=C-C motif chemokine receptor. CCL=C-C motif chemokine ligand. CTGF=connective tissue growth factor. CXCL=C-X-C motif chemokine. CXCR=C-X-C motif chemokine receptor. GATA=GATA-binding factor. GM-CSF=granulocyte-macrophage colony-stimulating factor. H1 receptor=histamine receptor. IFN=interferon. IL=interleukin. ILC2=type 2 innate lymphoid cells. JAK=Janus kinase. MAS=macrophage activation syndrome. NLRP=NACHT, LRR, and PYD domains-containing protein. SOCS=suppressor of cytokine signalling. ST2=ST2 receptor. TGF=transforming growth factor. Th=T-helper. TNF=tumour necrosis factor. TRIF=TIR domain-containing adapter molecule 1.

Table: **Advantages and disadvantages of various drugs for COVID-19**

have shown that IL-6 peaks at advanced stages of COVID-19 and is associated with disease severity,[2,10,15] other studies have reported conflicting data on IL-6 and IL-6 receptor expression in patients,[9,11] and the results with anti-IL-6 receptor antibodies (eg, tocilizumab, sarilumab) have been controversial.[88–90]

Targeting IL-33 (eg, by using anti-ST2 antibodies such as astegolimab), could be the key for controlling excessive lung inflammation. In a mouse model of influenza virus-induced asthma exacerbation,[58] administration of an anti-ST2 antibody significantly reduced airway hyperresponsiveness and bodyweight loss, lowered inflammatory cell numbers in the lungs, and eliminated neutrophil extracellular traps in the airway lumen; moreover, anti-ST2 treatment restored lung expression of IFNβ, IL-12p35, and IL-12p70, and reduced viral load.[58] There are several ongoing phase 2 trials using anti-ST2 therapy for inflammatory lung diseases such as chronic obstructive pulmonary disease and asthma.[12] In the IFNγ-deficient mouse model of atypical MAS, blocking ST2 provided significant protection against weight loss, increased survival, reduced serum ferritin and soluble CD25 concentrations, and lowered CD8+ T-cell frequencies and neutrophilia.[32] By contrast, individually blocking IL-6, IL-1β, or GM-CSF did not provide major protection against disease, suggesting that dampening IL-33–ST2 signalling, rather than individual downstream effector cytokines, might be more effective in treating either canonical MAS or atypical MAS-like diseases,[32] such as COVID-19.[2] A study evaluating the safety and efficacy of astegolimab (MSTT1041A) in severe COVID-19 pneumonia is recruiting participants (NCT04386616; EudraCT 2020-002713-17). The anti-IL-33 monoclonal antibody, MEDI3506, has also been included among possible therapies for the treatment of hospitalised patients with COVID-19 and is currently being tested in a phase 2 adaptive platform study.[91]

Additional important cell targets to focus on include ILC2, IL-17-producing and GM-CSF-producing γδT17 cells, proinflammatory monocytes–macrophages, extracellular trap-producing neutrophils, and mast cells. Different strategies could be set up to control aberrant activation of these cells, for instance by targeting IL-9 (MEDI-528), Vγ9Vδ2 T-cell activation (pentoxifylline),[74] IL-17A, IL-17F, and IL-17E (bimekizumab, brodalumab),[92] and cytokine balance (using colchicine,[93] NLRP3 inhibitors,[94] TLR2 inhibitors,[95] JAK2 inhibitors,[96] apremilast,[97] mast cells stabilisers,[55] and vitamin D).[98]

Acting more directly on the T-cell homing by using anti-CCR5 (leronlimab),[99] anti-CCR2 (prozalizumab), CCR2 and CCR5 inhibitors (BMS-813160), anti-CCL2 (carlumab), or anti-CCL8 antibodies, might be another crucial strategy in the management of patients with COVID-19. Additionally, anti-CCR1 (AZD4818) and anti-CXCR2 (AZD5069) antibodies, which selectively act on recruitment of monocytes and neutrophils, might be considered for patients at advanced stages of disease. In patients with post-acute respiratory distress syndrome, diverse antifibrotic agents acting on TGFβ (fresolimumab, pirfenidone), IL-13 (lebrikizumab, dupilumab),[100] connective tissue growth factor (pamrevlumab), fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor signalling (nintedanib),[79] might all represent viable therapeutic options (figure 3, table).

Search strategy and selection criteria

We searched PubMed and Google Scholar for articles published in English from Jan 1, 2020, to July 31, 2020, using the search terms "COVID-19", "coronavirus", "IL-33", "ST2", "type-2 innate lymphoid cells (ILC-2)", "gamma delta T cells", "T cells", "macrophages", "mast cells", "neutrophils", "endothelial cells", "adipocytes", "IL-17", "IL-7 ", "IL-9", "GM-CSF", "cytokines", "chemokines", "bronchoalveolar lavage fluid (BALF)", "lung", "heart", "hyperinflammation", "vasculitis", "thrombosis", "adult respiratory distress syndrome (ARDS)", "hemophagocytic lymphohistiocytosis (HLH)", "macrophage activation syndrome (MAS)", "obesity", and "treatment".

Conclusion

Upon increasing release of alarmin IL-33 from injured respiratory cells, in the lack of interferon expression, and alongside efforts of the immune system to overcome inefficient natural killer cells, cytotoxic T lymphocytes, and Th1 antiviral responses, sequential compensatory secretion of IL-2 family cytokines (ie. IL-4, IL-9, IL-2, IL-7) from dysregulated GATA3$^+$ Treg cells, differentiated ILC2, and overstimulated antigen-presenting cells might account for the early expansion of polyfunctional (CXCR3$^+$) Vγ9Vδ2 T cells and the later expansion of (CCR2$^+$CCR5$^+$) GM-CSF-producing lymphocytes, both recruited to the lungs by specific chemoattractants. These cells amplify alveolar damage and establish autoinflammatory lung disease. At advanced stages of COVID-19, intense activation of the NLRP3 inflammasome and TLR2–MyD88–NF-κB mediated pathways most likely create a cytokine environment enriched in IL-1β, IL-23, IL-6, and TNF, which would further elicit Th17 differentiation and GM-CSF production by γδT17, Th17, and CD8 T cells (figure 1). Ultimately, the resulting cytokine and chemokine milieu could account for the hyperinflammatory state of tissues and vessels mediated by dysfunctional endothelial cells, mast cells, monocyte-derived macrophages, and extracellular trap-producing neutrophils. Endothelial release of tissue factor induced by IL-33, activated γδT cells, and neutrophil extracellular traps might act to promote thrombotic manifestations. In patients who survive acute COVID-19, IL-33 might finally drive pulmonary fibrosis by activating M2 macrophages, ILC2, and mast cells to release TGFβ and IL-13, which act in turn on fibroblasts and type 2 pneumocytes to elicit an epithelial-to-mesenchymal

transition (figure 2). As a result, different stages of COVID-19 disease can be distinguished (ie, mild-to-moderate, severe-to-critical, chronic-to-fibrotic), and we suggest that IL-33 plays a central role in all of these pathogenic phases (figure 3). A preprint[101] that recently appeared online supports our model, revealing that SARS-CoV-2 peptide exposure elicits IL-33 expression from patients who are virus seropositive, and IL-33 production is correlated with T-cell activation and lung disease severity. Targeting the IL-33–ST2 axis using monoclonal antibodies (or, alternatively, small-molecule inhibitors) could prove to be an effective strategy for controlling the COVID-19 pandemic.

Contributors
GZ searched the literature, wrote the manuscript, and designed the figures and table. PLC organised the manuscript.

Declaration of interests
We declare no competing interests.

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