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

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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.

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). 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. 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, COVID-19 is instead characterised by circulating T cells that show an activated Th17 membrane phenotype (CD38+HLA-DR+CD4+CCR6+) and express granulocyte–macrophage colony-stimulating factor (GM-CSF) in part along with IFNγ. Concentrations of both IL-17 and IFNγ are increased in serum from patients with COVID-19 in proportion with viral load and lung injury. Similarly, Middle East respiratory syndrome has been associated with a combined Th1–Th17 inflammatory response. 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). 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. 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. Among its functions, IL-33 enhances TGFβ-mediated differentiation of Foxp3 regulatory T (Treg) cells and stimulates CD11c+ myeloid dendritic cells to secrete IL-2, which drives Treg cell expansion, thus ultimately promoting resolution of inflammation. Individuals infected with SARS-CoV-2 who develop milder symptoms tend to have large numbers of Treg cells and alveolar macrophages showing a scavenger resolving (FABP4+) phenotype. 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-IRL1) on Treg cells, resulting in increased expression of the canonical

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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. In patients with COVID-19, expression of T-cell chemokine receptors (eg, CXCL9, CXCL10) and their receptors (eg, CCR3) precedes expression of monocyte and neutrophil chemokine receptors (eg, CCL2, CCL3, CCL4, CCL7, CXCL8) and their corresponding receptors (eg, CCR1, CCR2). 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(C)) and chemoattractant (FCN1(SPP-1)) macrophages, which show highly inflammatory M1-like profiles (eg, nuclear factor-kappa B [NF-kB]), CCL2, CCL3), dominate tissue specimens from patients with severe forms of COVID-19 and who are critically ill.

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.

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. 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. 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). 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. Interferons are more highly suppressed by SARS-CoV-2 than by SARS-CoV infection, and this most likely accounts for the impaired antiviral responses and spontaneous apoptosis of dysfunctional lymphocytes.

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, and in patients who are predisposed to MAS, in whom IL-6 overexpression can reduce perforin and granzyme B concentrations inside granules.

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. 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.

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 lymphoctic choriomeningitis virus. Surprisingly, mice lacking both IFNγ and perforin (IFNγ−/−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 IFNγ−/−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. 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. However, IL-2 and IL-7 might amplify ILC2 survival and differentiation induced by IL-33, expand γδ T cells, which produce IL-17 through the signal transducer and activator of transcription (STAT)3, and enhance IL-33-induced pathologic expansion of T cells expressing GM-CSF through STAT5. 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.

IL-7 enables γδ T cells to fully differentiate into γδT17 cells 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. As shown for murine γδT17 cells, human Vδ2 T cells that co-express CCR2 and CCR5 also express the IL-7 receptor and show a Th17-like phenotype (CCR6+CD161+IL-23R+). 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, and global upregulation of IL-17 and IL-17F-related pathways, including the CCR6 ligand CCL20 and IL-23.

IL-23 and IL-1β are required for GM-CSF production by γδT17 cells and conventional αβ Th17 cells. 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. 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. As for γδT17, recruitment of IL-23-driven, GM-CSF-producing Th17 cells requires CCR2.

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, thus also having a potential role in vascular manifestations and pulmonary thromboses associated with COVID-19 pneumonia.

Cytotoxicity against virus-infected alveolar epithelial cells by γδ T cells has been shown for influenza virus 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.

Specifically, γδ T cells might
exert cytotoxic effects through the TNF-related apoptosis-inducing ligand, Fas ligand, and granzyme K, which are all overexpressed in the lungs of patients with COVID-19, 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). 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) inflamasome. 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-1β+ monocytes in the circulation of patients with COVID-19 in the early stages of recovery. 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.49,50 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.49 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-12p70.51,52

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-19.53,54,55 Such an altered cytokine environment would polarise the immune response towards detrimental (Th17-sustained and GM-CSF-induced) hyperinflammation, 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.56,57 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, 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 historical hallmarks of COVID-19 with acute respiratory distress syndrome.4

Feedforward loops might also engage mast cells, macrophages, endothelial cells, T cells, and neutrophils.54 Although whether mast cells and macrophages produce IL-33 is still up for debate, 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.55 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.14,15,26 Conversely, by inhibiting type 1 interferons and IL-12p35, IL-33 might contribute to impaired antiviral cytokotic responses.50 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.15 These features are the same as key characteristics seen in patients with critical COVID-19.13,14

IL-33 has also been implicated in the formation of neutrophil extracellular traps during virus-induced asthma exacerbation.5 Similarly, neutrophil priming with GM-CSF might promote the production of neutrophil extracellular traps.58 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.48
IL-33 has also been shown to stimulate expression of IL-1β, IL-6, CCL2, CXCL2, and G-CSF by adipocytes. 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. 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. 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.

Neutrophil extracellular traps might propagate inflammation and microvascular thrombosis in patients with COVID-19 and severe acute respiratory distress syndrome. 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.

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-3 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 through 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. DG=extracellular fibroblast growth factor. CCL=C-C motif chemokine ligand. CTGF=connective tissue growth factor. CXCL=C-X-C motif chemokine ligand. GM-CSF=granulocyte-macrophage colony-stimulating factor. IFN=interferon. IL=interleukin. IL-33=interleukin 33. IL-8=interleukin 8. IL-6=interleukin 6. LN=lymph node. NK=natural killer. PGE2=prostaglandin E2. PDGF=platelet-derived growth factor. P/F ratio=arterial oxygen partial pressure to fractional inspired oxygen ratio. sST2=soluble ST2. ST2=ST2 receptor. TF=transferrin. TGF=transforming growth factor. VEGF=vascular endothelial growth factor.
**Figure 3: Inflammatory patterns in COVID-19 at various disease stages**

| 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+ alveolar macrophages, Mast cells | Anti-ST2, anti-IL-33, Anti-IL-10, Anti-IL-4, Anti-IL-4Ra, Mast cell stabilisers, Vitamin D |
|                 | IL-33    |            |                      |                   |                   |
| Moderate        | IL-33/ST2 | IL-9, IFNγ, IL-17A | CXCL9-10-11 (CXCR3), CXCL16 (CXCR6) | ILC2+ γδ T cells (Th8-like, Th17-like), FABP4+ alveolar macrophages | Anti-ST2, anti-IL-33, Anti-IL-9, Pentoxifylline, Apremilast, Vitamin D |
|                 | IL-33    |            |                      |                   |                   |
| Severe          | IL-33/ST2 | GM-CSF, IL-2, IL-7 | CXCL9-10 (CXCR3), CCL2-8 (CCR5-2) | CD4+ T cells (Th1-like, Th17-like), Dendritic cells, FCN1+ SPP1+ macrophages | Anti-ST2, Anti-IL-33, Anti-GM-CSF, Anti-IL-17A/IL-17F, Anti-CC18, Anti-CCR5, or CCR2/CCR5 |
|                 | IL-33    |            |                      |                   |                   |
| Critical        | IL-1α, IL-1β, GM-CSF | IL-23, TNF, IL-6, IL-10 | CCL20 (CCR6), CCL2-3-4-7 (CCR1), CXCL1-1-2-6-8 (CXCR2) | CD4+ and CD8+ T cells (Th17-like), Monocyte-derived FCD1+ macrophages, Neutrophils, Endothelial cells | Anti-ST2, Anti-IL-33, Anti-GM-CSF, rIL-3RA, Anti-IL-1β, Anti-IL-12, Anti-CCL2, Anti-CCR5, Anti-CCL2, Anti-CCR5 |
|                 | IL-33    |            |                      |                   |                   |
| Chronic         | IL-33/ST2 | IL-4, IL-10, FGF, VEGF, PDGF | CXCL2-8 (CXCR2), CXCL16-16-17 | ILC2 (Th2-like), FCN1+ macrophages, Myeloid/Myeloblasts | Anti-ST2, Anti-IL-33, Anti-pan TGB, Anti-IL-12, Anti-IL-4Ra, FGF1/VEGF/PDGF-Ri, Anti-IL-23, Anti-IL-17, Anti-CC12, Pifithrinα |
|                 | IL-33    |            |                      |                   |                   |

**Production of soluble ST2 might be reduced by anti-ST2 treatment, and such reduction would modulate T-cell polarization by decreasing pathogenic Th1 and Th17 cells, and increasing IL-10-producing Treg cells.** 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**

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.49 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.49–51 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.52–54 Some patients with either Behçet’s disease55 or COVID-1956 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.57 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.58 IL-33-activated mast cells might also play a role in organ fibrosis.59 Most remarkably, IL-33 has been shown to induce epithelial-to-mesenchymal transition of type 2 pneumocytes through TGFβ signalling.60

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.61 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-2,62–64,67,26 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-19,65 and γδ T cells exposed to TGFβ might produce connective tissue growth factor (figure 2).66

**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)69,70 and by blocking GM-CSF using monoclonal antibodies (mavrilimumab, lenzilumab).69,71 Although some studies
| Molecular targets | Cell targets | Advantages | Disadvantages |
|-------------------|-------------|------------|--------------|
| Anti-ST2 (eg, astegolimab), anti-IL-33 (eg, MEDI-3505), 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 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 haemaphagocytic lymphohistocytosis 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, mavelinumab, giminilumab, lenimulator, 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 homeostasis and alveolar surfactant production |
| Recombinant IL-3RA (eg, anakinra), anti-IL-1β (eg, canakinumab), recombinant IL-37 | IL-1α and IL-1β, or IL-1β | Type 2 pneumocytes, GM-CSF-producing 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 |
| Anti-IL-6 receptor (eg, tocilizumab, sarilumab), anti-IL-6 (eg, clazakizumab, silmitasertib) | 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 homeostatic roles and induce SOCS3, IL-4Ra 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 haemaphagocytic lymphohistocytosis and MAS-like models with IFNγ deficiency; and anti-IFNγ might d俺 prevent antiviral cytokotic 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 d俺 en endosomal toll-like receptor-induced, TRIF-mediated, protective, type 1 interferon signalling; possible cardiotoxicity |
| Type 3 interferon (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 IFNα 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-4Ra (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, myeloid-like cells | 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 |
| Molecular targets | Cell targets | Advantages | Disadvantages |
|-------------------|--------------|------------|---------------|
| (Continued from previous page) | | | |

### Selective JAK2 inhibitors (eg, fedotabinib)

| 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 inhibitors (eg, prozalumab), anti-CCR5 (eg, leonilinab), 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 leonilinab 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-CCR1 (eg, AZD4818), anti-CXCR2 (eg, AZD5069)

| 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 |

### Non-selective phosphodiesterase inhibitors (eg, pentoxifyline)

| 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 anti-thrombotic properties; broad-spectrum antiviral activity | Risk of bleeding |

### Phosphodiesterase-4 inhibitors (eg, apremilast)

| 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)

| Mast cells | 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 inhibitors (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 inhibitors (eg, palivizumab)

| 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 |

NOTE: A2A=adenosine A2A, 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=histamine receptor; IL=interleukin; IFN=interferon; IL-12=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; TRAIL=T 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. Other studies have reported conflicting data on IL-6 and IL-6 receptor expression in patients, and the results with anti-IL-6 receptor antibodies (eg, tocilizumab, sarilumab) have been controversial. 

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, administration of an anti-ST2 antibody significantly reduced airway hyper-responsiveness 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 IFNγ, IL-12p35, and IL-12p70, and reduced viral load. There are several ongoing phase 2 trials using anti-ST2 therapy for inflammatory lung diseases such as chronic obstructive pulmonary disease and asthma. In the IFNy-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. 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, such as COVID-19. A study evaluating the safety and efficacy of astegolimab (MSTT041A) 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.

Additional important cell targets to focus on include ILC2, IL-17-producing and GM-CSF-producing γδT 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), IL-17A, IL-17F, and IL-17E (bimekizumab, brodalumab), and cytokine balance (using colchicine, NLRP3 inhibitors, TLR2 inhibitors, JAK2 inhibitors, apremilast, mast cell stabilisers, and vitamin D).

Acting more directly on the T-cell homing by using anti-CCR5 (leronilimab), anti-CCR2 (prozalizumab), CCR2 and CCR5 inhibitors (BSM-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 (fresolimub, pirfenidone), IL-13 (lebrikizumab, dupilumab), connective tissue growth factor (pamrevlumab), fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor signalling (nite-danib), might all represent viable therapeutic options (figure 3, table).

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 γδT Cells, 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.
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\(^1\) 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 that 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

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References

1. Crayne CB, Albiteunai S, Nichols KE, Cron RQ. The immunology of macrophage activation syndrome. *Front Immunol* 2019; 10: 119.
2. McGonagle D, Shari'\i, O’Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020; 19: 102537.
3. Behrens EM, Canna SW, Slade K, et al. Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. *J Clin Invest* 2011; 121: 2264–77.
4. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; 8: 420–22.
5. Zhou Y, Fu B, Zheng X, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Nat Sci Rev* 2020; 7: 998–1002.
6. Liu Y, Zhang C, Huang F, et al. 2019 novel coronavirus (2019-nCoV) infections trigger an exaggerated cytokine response aggravating lung injury. *ChinaXiv* 2020; published online Feb 12. https://doi.org/10.10274/202002.00018 (preprint).
7. Mahalawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman RA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. *Cytokine* 2018; 104: 8–11.
8. Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* 2004; 136: 95–103.
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
10. Tan M, Liu Y, Zhou R, et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. *Immunology* 2020; 160: 261–68.
11. Xiong Y, Liu Y, Cao L, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emer Microbes Infect* 2020; 9: 763–70.
12. Gabryelasia A, Kuna P, Antczak A, Biadasiewicz P, Panek M. IL-33 mediated inflammation in chronic respiratory diseases: understanding the role of IL-1\(\alpha\) superfamily. *Front Immunol* 2019; 10: 692.
13. Schiering C, Krausgruber T, Chomka A, et al. The alarmin IL-33 promotes regulatory T-cell function in the intestine. *Nature* 2014; 513: 564–68.
14. Matta MM, Lott JM, Mathews LR, et al. IL-33 is an unconventional Alarmin that stimulates IL-2 secretion by dendritic cells to selectively expand IL-33R/ST2\(^+\) regulatory T cells. *J Immunol* 2014; 193: 4010–20.
15. Liao M, Liu Y, Yuan J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med* 2020; 26: 842–44.
16. Chen CC, Kobayashi T, Iijima K, Hsu FC, Kita H. IL-33 dysregulates regulatory T cells and impairs established immunologic tolerance in the lung. *J Allergy Clin Immunol* 2017; 140: 1351–63.e7.
17. Wang L, Tang J, Yang X, et al. TGF-\(\beta\) induces ST2 and programs ILC2 development. *Nat Commun* 2020; 11: 55.
18. Mohapatra A, Van Dyken SJ, Schneider C, Nussbaum JC, Liang HE, Locksley RM. Group 2 innate lymphoid cells utilize the IRF4-IL-9 module to coordinate epithelial cell maintenance of lung homeostasis. *Mucosal Immunol* 2016; 9: 275–86.
19. Guggino G, Ciocca F, Di Liberto D, et al. Interleukin (IL)-9/IL-9R axis drives \(\gamma\)\(\delta\) T cells activation in psoriatic arthritis patients. *Clin Exp Immunol* 2016; 186: 277–83.
20. Peters C, Häslor R, Wesch D, Kabelitz D. Human \(\gamma\)\(\delta\) T cells are a major source of interleukin-9. *Proc Natl Acad Sci USA* 2016; 113: 12520–25.
21. Cheng M, Hu S. Lung-resident \(\gamma\)\(\delta\) T cells and their roles in lung diseases. *Immunology* 2017; 151: 375–84.
22. Lei L, Qian H, Yang X, et al. The phenotypic changes of \(\gamma\)\(\delta\) T cells in COVID-19 patients. *medRxiv* 2020; published online April 7. https://doi.org/10.1016/j.lanea.2020.04.05.20046433 (preprint).
23. Rijkers G, Vervenne T, van der Pol P. More bricks in the wall against SARS-CoV-2 infection: involvement of \(\gamma\)\(\delta\) T cells. *Cell Mol Immunol* 2020; 17: 771–72.
24. Glatzé A, Wesch D, Schiernmann F, Brandt E, Janssen O, Kabelitz D. Patterns of chemokine receptor expression on peripheral blood gamma delta T lymphocytes: strong expression of CCR5 is a selective feature of V delta 2 gamma 9 gamma delta T cells. *J Immunol* 2002; 168: 4920–29.
25. Yang Y, Shen C, Li J, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. *J Allergy Clin Immunol* 2020; 146: 119–27.e4.
26. Zhou Z, Ren L, Zhang L, et al. Heightened innate immune responses in the respiratory tract of COVID-19 patients. *Cell Host Microbe* 2020; 27: 883–90.e2.
27. Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced host response to SARS-CoV2 Drives development of COVID-19. *Cell* 2020; 181: 1036–45.e9.
28. Chu H, Chan JF, Wang Y, Yuan TT, Chai Y, Hou Y, et al. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19. *Clin Infect Dis* 2020; published online April 9. https://doi.org/10.1017/cid.2020.3151–63.e7.
29. Babale N, Britton GJ, Gruber C, et al. Immunology of COVID-19: current state of the science. *Immunology* 2020; 52: 910–41.
30. Hadjadji J, Yatim N, Barnabé I, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020; 369: 718–24.
31. Cifaldi I, Prence G, Caiello I, et al. Inhibition of natural killer cell cytotoxicity by interleukin-6: implications for the pathogenesis of macrophage activation syndrome. *Arthritis Rheumatol* 2015; 67: 3637–46.
32. Burn TN, Weaver L, Rood JE, et al. Genetic deficiency of interferon-\(\gamma\) reveals interferon-\(\gamma\)-independent manifestations of murine hemophagocytic lymphohistiocytosis. *Arthritis Rheumatol* 2020; 72: 335–47.
33. Halim TY, Krauss RH, Sun AC, Takes F. Lung natural helper cells are a critical source of Th1 cell-type cytokines in protease allergen-induced airway inflammation. *Immunology* 2012; 36: 451–63.
34. Michel ML, Pang DJ, Haque SF, Potocnik AJ, Pennington DJ, Hayday AC. Interleukin 7 (IL-7) selectively promotes mouse and human IL-17-producing \(\gamma\)\(\delta\) cells. *Proc Natl Acad Sci USA* 2012; 109: 17549–54.
35. Sherg W, Yang F, Zhou Y, et al. STAT5 programs a distinct subset of GM-CSF-producing T helper cells that is essential for autoimmune neuroninflammation. *Cell Res* 2014; 24: 1387–402.
36. Alvarez F, Fritz JH, Piccirillo CA. Pleiotropic effects of IL-17 in CD4\(^+\) T cell differentiation and effector functions. *Front Immunol* 2019; 10: 522.
37. McKenzie DR, Kara EE, Bastow CR, et al. IL-17-producing \(\gamma\)\(\delta\) T cells switch migratory patterns between resting and activated states. *Nat Commun* 2017; 8: 15632.
38 Severa M, Islam SA, Waggoner SN, et al. The transcriptional repressor Blimp1 furca host defenses by suppressing expression of the chemokine CCL4. J Immunol 2016; 187: 12291–104.

39 Ryan PL, Sumamaria N, Holland Cj, et al. Heterogeneous yet stable Vδ2(+/−) T cell profiles define distinct cytocidal effector potentials in healthy human individuals. Proc Natl Acad Sci USA 2016; 113: 14078–81.

40 Lukens J, Barr MJ, Chaplin DD, Chi H, Kanneganti TD. Inflamasome-activated IL-1β regulates the production of GM-CSF by CD4(+) T cells and γδ T cells. J Immunol 2012; 188: 3107–15.

41 El-Beili M, Cinc C, Dai H, et al. The exchapeitogenicity of T(H)17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF. Nat Immunol 2011; 12: 568–75.

42 Papotto PH, Reinhardt A, Prinz I, Silva-Santos B. Innately versatile: γδ T cells in inflammatory and autoimmune diseases. J Autoimmun 2018; 87: 26–37.

43 Kara EE, McKenzie DR, Bastow CR, et al. CCR2 defines in vivo development and homing of IL-23-driven GM-CSF-producing Th17 cells. Nat Commun 2015; 6: 8646.

44 Marco-Malina V, Balkir-Gurman A, Dardik R, Braun-Moscovici Y, Segel MJ, Bank I. A novel prothrombotic pathway in systemic sclerosis patients: possible role of bisphosphonate-activated γδ T cells. Front Immunol 2014; 5: 414.

45 Li H, Xiang Z, Feng T, et al. Human γγδVδ2 T cells efficiently kill influenza virus-infected lung alveolar epithelial cells. Cold Mol Immol 2013; 10: 159–64.

46 Wen W, Su W, Tang H, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. Cell Discov 2020; 6:31.

47 Farag NS, Breitinger U, Breitinger HG, El Aziz MA. Viroceptors and inflammasomes: a key to understand virus-induced inflammation. Int J Biochem Cell Biol 2020; 122: 105738.

48 Rodriguez AE, Bogart C, Gilbert CM, et al. Enhanced IL-1β production is mediated by a TLR2-MYD88-NFκB signaling axis during coinfection with influenza A virus and Streptococcus pneumoniae. PLoS One 2019; 14:e0212236.

49 Totura AL, Whitmore A, Agnihotram S, et al. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. MBio 2015; 6:e00638–15.

50 Jacques A, Bleau C, Turbide K, Beauchemin N, Lamontagne L. Macrophage interleukin-6 and tumour necrosis factor-alpha are induced by coronavirus fixation to Toll-like receptor 2/parainfluenzae receptors but not carciinobenynocylin cell adhesion antigen la. Immunology 2009; 128(suppl); e81–92.

51 Caylor C, Girard JP. Interleukin-33 (IL-33): a nuclear cytokine from the IL-1 family. Immunol Rev 2018; 281: 154–68.

52 Willart MA, Deswarte K, Pouliot P, et al. Interleukin-1α controls allergic sensitization to inhaled house dust mite via the epithelial release of GM-CSF and IL-33. J Exp Med 2012; 209: 1505–17.

53 Llop-Guevara A, Chu DK, Walker TD, et al. A GM-CSF/IL-33 pathway facilitates allergic airway responses to subthreshold house dust mite exposure. PLoS One 2014; 9:e88714.

54 Altara R, Ghali R, Mallet Z, Cattoli A, Booz GW, Zouein FA. Activating T lymphocytes. Clin Exp Immunol 2017; 188: 189–93.

55 Kass DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. Lancet 2020; 395: 1445–45.

56 Varga Z, Flannmer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet 2020; 395: 1417–18.

57 Kaas DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. Lancet 2020; 395: 1445–45.

58 Zlat S, Sougandakis K, Zoumas B, Kotsiou S, Duckworth K, et al. Viable neutrophil extracellular traps induce endothelial cell activation and tissue factor production through interleukin-1β and cathespin g. Arterioscler Thromb Vasc Biol 2018; 38: 1901–12.

59 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18: 1094–99.

60 Yokota S, Kiyohara Y, Tomita T, et al. Endothelial cell damage due to SARS-CoV-2 mediates severe COVID-19 manifestations. J Thromb Haemost 2020; 18: 1701–17.

61 Workalemahu G, Foerster M, Kroegel C, Braun RK. Human IL-33 induces Th17 cells and promotes Th17-mediated cell recruitment and tissue damage in Behçet’s disease: a systematic review and meta-analysis. PLoS One 2014; 9:e88714.

62 Ravanetti L, Dijkhuis A, Dekker T, et al. IL-33 drives influenza-induced asthma exacerbations by halting innate and adaptive antiviral immunity. J Allergy Clin Immunol 2019; 143: 1355–70.e16.

63 Youssouf S, Mihalache C, Kozlowski E, Schindl I, Simon FH. Viable neutrophil extracellular trap DNA to form neutrophil extracellular traps. Cell Death Differ 2009; 16: 1438–44.

64 Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. JCI Insight 2020; 5: e138099.
84 Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020; 2: e325–31.

85 Dimopoulos G, de Mast Q, Markou N, et al. Favorable anakinra responses in severe COVID-19 patients with secondary hemophagocytic lymphohistiocytosis. *Cell Host Microbe* 2020; 28: 117–23.e1.

86 De Luca G, Cavalli G, Campochiaro C, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol* 2020; 2: e465–73.

87 Temesgen Z, Assi M, Vergidis P, et al. First clinical use of lenzilumab to neutralize GM-CSF in patients with severe COVID-19 pneumonia. *medRxiv* 2020; published online June 14. https://doi.org/10.1101/2020.06.08.20125369 (preprint).

88 Capra R, De Rossi N, Mattioli F, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *Eur J Intern Med* 2020; 76: 31–35.

89 Colaneri M, Bogliolo L, Valsecchi P, et al. Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COVID19 REgistry (SMACORE). *Microorganisms* 2020; 8: 695.

90 Della-Torre E, Campochiaro C, Cavalli G, et al. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. *Ann Rheum Dis* 2020; published online July 3. https://doi.org/10.1136/annrheumdis-2020–218122.

91 Wilkinson T, Dixon R, Page C, et al. ACCORD: a multicentre, seamless, phase 2 adaptive randomisation platform study to assess the efficacy and safety of multiple candidate agents for the treatment of COVID-19 in hospitalised patients: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020; 21: 691.

92 Pacha O, Sallman MA, Evans SE. COVID-19: a case for inhibiting IL-17? *Nat Rev Immunol* 2020; 20: 345–46.

93 Perricone C, Triggianese P, Bartoloni E, et al. The anti-viral facet of anti-rheumatic drugs: lessons from COVID-19. *J Autoimmun* 2020; 111: 102468.