



Immunity, endothelial injury and complement-induced coagulopathy in COVID-19

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Abstract | In December 2019, a novel coronavirus was isolated from the respiratory epithelium of patients with unexplained pneumonia in Wuhan, China. This pathogen, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a pathogenic condition that has been termed coronavirus disease 2019 (COVID-19) and has reached pandemic proportions. As of 17 September 2020, more than 30 million confirmed SARS-CoV-2 infections have been reported in 204 different countries, claiming more than 1 million lives worldwide. Accumulating evidence suggests that SARS-CoV-2 infection can lead to a variety of clinical conditions, ranging from asymptomatic to life-threatening cases. In the early stages of the disease, most patients experience mild clinical symptoms, including a high fever and dry cough. However, 20% of patients rapidly progress to severe illness characterized by atypical interstitial bilateral pneumonia, acute respiratory distress syndrome and multiorgan dysfunction. Almost 10% of these critically ill patients subsequently die. Insights into the pathogenic mechanisms underlying SARS-CoV-2 infection and COVID-19 progression are emerging and highlight the critical role of the immunological hyper-response — characterized by widespread endothelial damage, complement-induced blood clotting and systemic microangiopathy — in disease exacerbation. These insights may aid the identification of new or existing therapeutic interventions to limit the progression of early disease and treat severe cases.

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Coronaviruses are enveloped, single-stranded RNA viruses (FIG. 1a). The *Orthocoronavirinae* family encompasses several coronaviruses that can infect mammals and birds. Although such infections usually cause mild respiratory disease, in the past two decades, coronaviruses have caused two epidemic diseases in humans: severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in 2003 and 2012, respectively. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that was isolated from the respiratory epithelium of patients with unexplained pneumonia in Wuhan, China, in December 2019. As of 17 September 2020, the disease caused by SARS-CoV-2, named coronavirus disease 2019 (COVID-19), has reached pandemic proportions, affecting more than 30 million individuals and claiming more than 1 million lives worldwide.

Bats are considered to be the most likely natural SARS-CoV-2 reservoir¹, although phylogenetic studies have suggested that intermediate animal hosts may have mediated zoonotic transmission to humans^{2–5}.

The genome of SARS-CoV-2 is similar to that of a typical betacoronavirus and contains at least ten open reading frames (ORFs; FIG. 1b). The ORF1a and ORF1b encode non-structural proteins (NSPs) that are generated by proteolytic processing^{1,6}. The NSP12 catalytic subunit, along with its cofactors NSP7 and NSP8, constitutes the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) complex, which is essential for viral replication⁷. The near-atomic resolution of the NSP12-NSP7-NSP8 complex revealed a molecular assembly similar to the equivalent complex in SARS-CoV, the virus responsible for SARS⁸, although biochemical analyses showed that the polymerase activity and thermostability of the SARS-CoV-2 RdRp complex was lower than that of the SARS-CoV RdRp complex, suggesting adaptation of SARS-CoV-2 towards humans, which have lower body temperatures than bats⁷. The other ORFs encode the four main structural proteins: the spike, envelope, nucleocapsid and membrane proteins, as well as several accessory proteins with unknown functions^{1,6}.

Key points

- Although most patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience mild to moderate symptoms that resolve after 6–10 days, almost 20% of patients develop severe illness characterized by atypical interstitial bilateral pneumonia and acute respiratory distress syndrome, with a high fatality rate.
- Accumulating evidence suggests that an unbalanced and unrestrained innate immune response, which comes at the expense of effective adaptive immunity, underpins the progression of coronavirus disease 2019 (COVID-19).
- In severe cases of COVID-19, massive endothelial dysfunction, widespread coagulopathy and complement-induced thrombosis can lead to the development of systemic microangiopathy and thromboembolism; these complications can be life-threatening and ultimately lead to multi-organ failure.
- The kidney is one of the main targets of COVID-19 complications, and abnormal kidney function is associated with a significantly increased risk of death in severely ill patients.
- Most repurposed anti-viral drugs have failed to improve clinical outcomes in COVID-19; by contrast, therapeutic interventions that target the host response, including the hyper-immune response, complement activation and systemic thrombosis, seem to be more promising approaches to the treatment of severe COVID-19.

Betacoronavirus

One of four genera (α , β , γ and δ) of enveloped, positive-strand RNA viruses that infects humans and mammals, causing respiratory diseases that can be mild or severe.

RNA-dependent RNA polymerase

(RdRp). An enzyme encoded by viral RNA that catalyses the synthesis of new RNA strands complementary to the initial RNA template included in the viral capsid.

Incubation period

The number of days between the initial exposure to a pathogen and the day in which the infected individual experiences the first symptoms of the disease.

Anosmia

Complete loss of the ability to detect one or more smells; anosmia can be temporary, as in the case of COVID-19, or permanent such as occurs in certain neurological conditions.

Ageusia

Complete loss of taste on the tongue, particularly the inability to perceive sweetness, sourness, bitterness and saltiness; ageusia can be temporary, as in the case of COVID-19, or permanent such as occurs in certain neurological conditions.

blood clotting and systemic microangiopathy, and describe how these consequences may contribute to the development of kidney complications in severely ill patients with COVID-19. Finally, we discuss the therapeutic interventions that currently hold most promise to limit progression of disease during the early phases and discuss currently available drugs that may be repurposed to treat severe cases of COVID-19.

SARS-CoV-2 infection and COVID-19

The human-to-human transmission of SARS-CoV-2 is primarily mediated by respiratory droplets or aerosols generated during coughing and sneezing. In the early phase of the infection, SARS-CoV-2 entry by inhalation is facilitated by the high expression of ACE2 in the mouth and on the tongue^{16,17}. In the nasal mucosa, secretory goblet cells express high levels of ACE2 and TMPRSS2, suggesting a potential tropism of SARS-CoV-2 for these cells^{17,18}. Virus replication can also occur in the throat¹⁹. SARS-CoV-2 generally has an incubation period of 5 to 6 days²⁰. Once symptoms appear, peak viraemia occurs within 2–5 days of symptom onset²⁰. For about 80% of infected patients, COVID-19 is a mild disease that is mostly restricted to the upper and conducting airways. These individuals normally exhibit modest symptoms, similar to the common flu, including fever and a dry cough, which resolve spontaneously within 6–10 days. However, in almost 20% of patients viral infection progresses down the trachea to the lungs²¹. Within the alveoli, the epithelial cells lining the lower airways are the main viral targets^{17,18}, owing to their substantial expression of ACE2 and TMPRSS2. SARS-CoV-2 infection induces these epithelial cells to undergo apoptotic cell death as part of the viral replication cycle. This apoptotic response is associated with vascular leakage within alveoli that induces a first wave of local inflammation and recruits immune cells from the blood into the lungs to eliminate extra-cellular virus and destroy virus-infected cells^{22,23}. The increase in pro-inflammatory cytokines within the lung leads to the recruitment of leukocytes, further propagating the local inflammatory response that underlies the pathology of atypical interstitial bilateral pneumonia observed in patients with COVID-19. Histology studies have revealed that the central part of the lung is the most affected region, with pneumocyte injury and diffuse alveolar damage, oedema and alveolar haemorrhage, and the presence of interstitial inflammatory infiltrates^{24–26}. During this inflammatory phase in the lungs, the disease can rapidly progress to severe illness characterized by acute respiratory distress syndrome (ARDS), a hyperinflammatory state and multi-organ dysfunction with a fatality rate of nearly 10% among the most severe cases^{27,28}. In this setting, lung-protective mechanical ventilation is the most effective strategy to reduce multiorgan failure and mortality^{29,30}.

Although the lung is the primary site of pathology, an accumulating body of evidence shows that the virus can disseminate to other organs and induce additional pathological conditions. Kidneys, brain, heart, eye and gut can be affected by SARS-CoV-2 infection, potentially leading to specific disease manifestations such as anosmia and ageusia^{31,32}, ocular conjunctivitis³³, abdominal pain

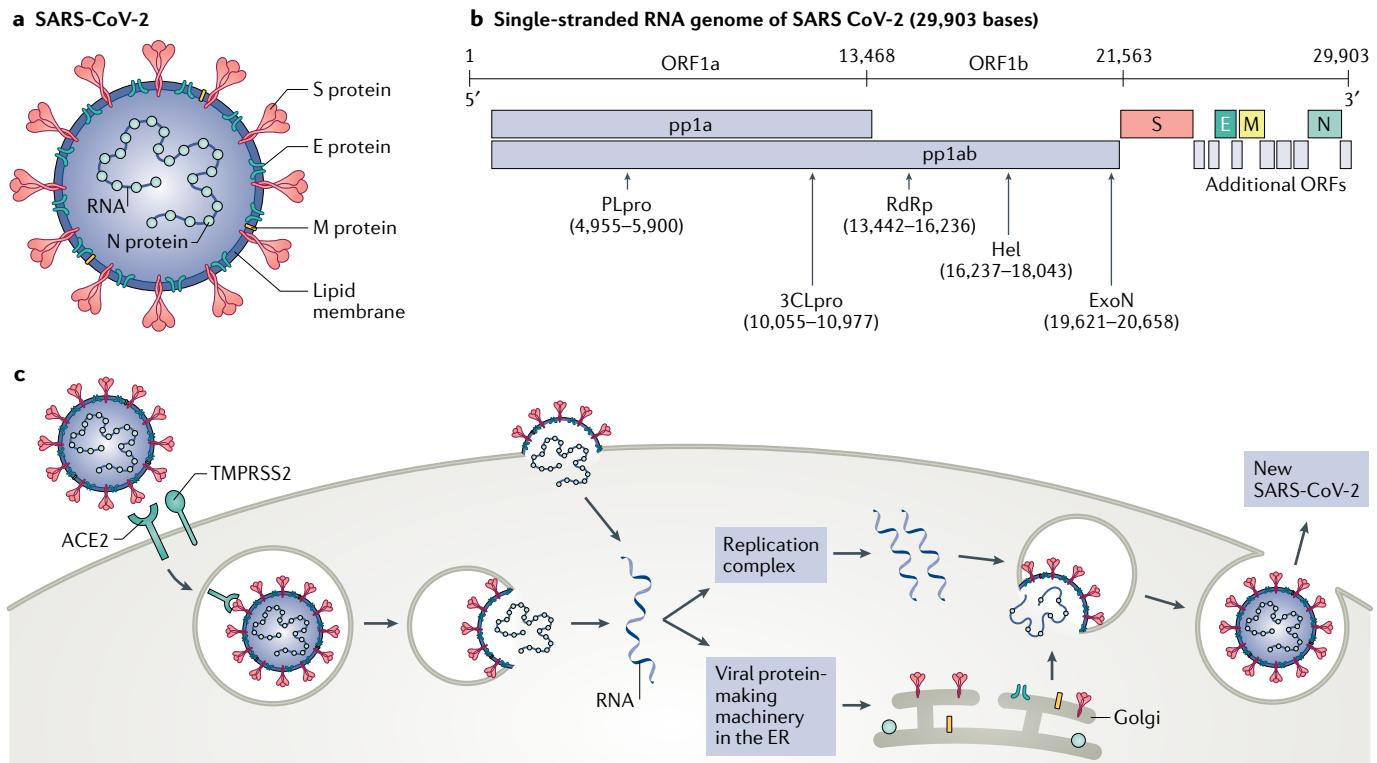


Fig. 1 | SARS-CoV-2 structure, genome composition and life cycle.
a | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a typical betacoronavirus belonging to the Orthocoronavirinae family. Each SARS-CoV-2 virion has a diameter of approximately 100–200 nm. Like other coronaviruses, the SARS-CoV-2 envelope comprises a lipid membrane and three structural components: the spike (S) glycoprotein, the envelope (E) protein and the membrane (M) protein. Within the viral envelope, the nucleocapsid (N) protein holds the positive-sense single-stranded RNA, which is 29,903 bases in length. **b** | The SARS-CoV-2 genome is composed of ten open reading frames (ORFs). At least two-thirds of the viral genome are contained in ORF1a and ORF1b, which together encode a polyprotein, pp1ab, which is further cleaved into 16 non-structural proteins that are involved in genome transcription and replication. Of these proteins, papain-like protease (PLpro) and 3C-like protease (3CLpro) are encoded by ORF1a, whereas RNA-dependent RNA polymerase (RdRp), helicase (Hel) and exonuclease (ExoN) are encoded by ORF1b. The remaining ORFs

encode the structural S glycoproteins, and the E protein, M protein and N protein, as well as several accessory proteins with unknown functions. **c** | SARS-CoV-2 enters the host cell using the endosomal pathway and the cell surface non-endosomal pathway. In the setting of endosomal entry, the SARS-CoV-2 virion attaches to its target cells by direct binding of the S glycoprotein to the host receptor angiotensin-converting enzyme 2 (ACE2). Upon binding, the transmembrane protease serine 2 (TMPRSS2) cleaves and primes S glycoprotein, leading to the fusion of the viral and cell membranes. In addition to canonical viral entry via the endosomal pathway, non-endosomal entry at the plasma membrane may be an additional infection route for SARS-CoV-2. Within the target cells, SARS-CoV-2 is disassembled to release nucleocapsid and viral RNA into the cytoplasm for translation and replication. Translated viral proteins are then assembled in the endoplasmic reticulum (ER) to form the new virions, which are then released from the Golgi membrane system by exocytosis into the extracellular compartment.

and diarrhoea^{34,35}, or cardiac injury³⁶. Many cell types present in these organs express ACE2 and proteases such as TMPRSS2 and have been shown to be infected by SARS-CoV-2 in *in vitro* and *in vivo* studies^{37–39}. Greater insight into the molecular mechanisms underlying disease progression may aid the identification of therapeutic approaches to target different stages of COVID-19.

The SARS-CoV-2 immune response

Both the innate and the adaptive immune response have an essential role in recognizing and eliminating foreign pathogens. Accumulating evidence suggests that a suboptimal or unrestrained immune response during SARS-CoV-2 infection drives the clinical patterns, disease severity and progression of COVID-19. Identification of specific immune signatures may provide novel insights into the divergent disease trajectories observed in individual patients and aid the design of more targeted therapeutic approaches^{40–42}.

Pattern recognition receptors (PRRs). Host sensors that detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) generated during infections or injury.

Innate immune response. The innate immune system is the first line of defence against viral infections⁴³. When viruses colonize their target cells, viral single-stranded RNA, like that of SARS-CoV-2, activates innate immune cells by engaging any one of a number of intracellular pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors and melanoma differentiation-associated gene 5 (MDA5), which sense aberrant RNA structures that often form during viral replication⁴⁴. Following PRR activation, molecular signalling cascades culminate in the activation of downstream transcription factors, such as interferon regulatory factors (IRFs) and nuclear factor- κ B (NF- κ B)⁴⁵. These transcription factors trigger the initial cellular antiviral defences by inducing the transcriptional activation of type I and III interferons (IFN-I and IFN-III) and interferon-stimulated genes (ISGs), as well as cytokines and chemokines (FIG. 2a).

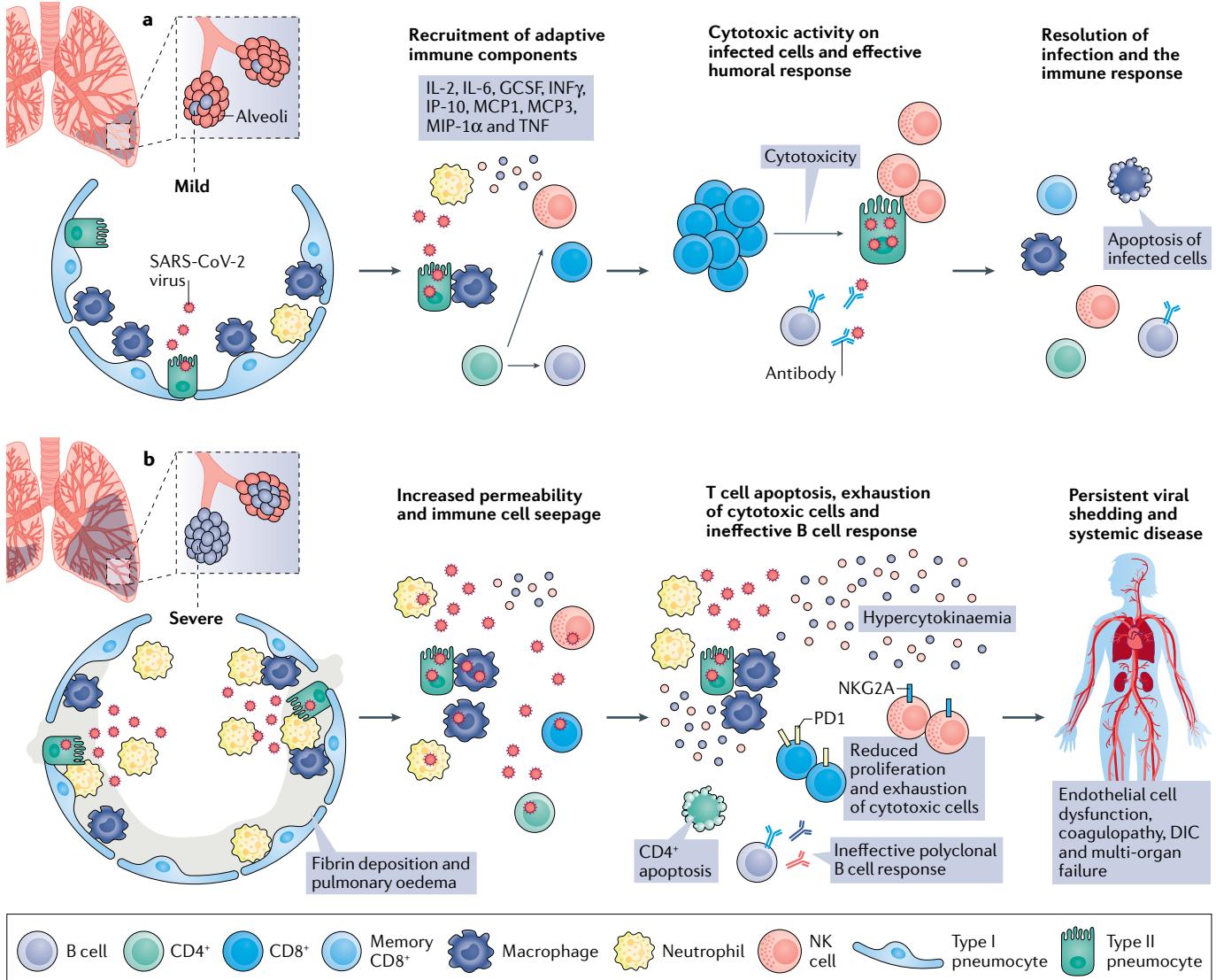


Fig. 2 | Pathogenesis and outcomes of COVID-19. **a** | Following infection of the lungs, (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) induces the death of epithelial cells, in particular, type II pneumocytes, as part of the viral replication cycle. Macrophages and neutrophils elicit a specific innate immune response to eradicate the pathogen and kill virus-infected cells. The increase in pro-inflammatory cytokines within the lung leads to the recruitment of leukocytes, further propagating the local inflammatory response. Among these cytokines, interleukin-2 (IL-2), IL-6, granulocyte-colony-stimulating factor (GCSF), interferon- γ (IFN γ), IFN γ inducible protein 10 (IP-10), monocyte chemoattractant protein 1 and 3 (MCP1 and 3), macrophage inflammatory protein 1 α (MIP-1 α) and tumour necrosis factor (TNF) stimulate the adaptive immune response. At this stage, infiltration of lymphocytes (CD4 $^{+}$ and CD8 $^{+}$ T cells) and natural killer (NK) cells is required to ensure an optimal defence response against SARS-CoV-2. CD4 $^{+}$ T cells mediate antibody production by B cells and also enhance effector CD8 $^{+}$ T cell and NK responses during viral infections. This orchestrated immune response leads to viral eradication and resolution of the disease. In these patients, coronavirus disease 2019 (COVID-19) seems to manifest as a mild disease with symptoms similar to the common flu that

resolve spontaneously. **b** | For unknown reasons, but possibly individual predisposition or differences in viral loads during primary SARS-CoV-2 infection, some patients experience more severe disease. A maladaptive immune response, characterized by lymphopenia and suppression of CD4 $^{+}$ T cells, is likely accountable for the poor prognosis of these patients. In the absence of robust CD4 $^{+}$ T cell activation, B cells generate a polyclonal antibody response that may be ineffective in neutralizing SARS-CoV-2. Increased numbers of exhausted T cells that express high levels of programmed cell death protein 1 (PD1), suggest decreased proliferation and activity of CD8 $^{+}$ T cells. Similarly, NK cells exhibit increased levels of the inhibitory CD94-NKG2 group 2 member A (NKG2A). Impaired cytotoxic activity results in persistent viral shedding that amplifies macrophage and neutrophil activation, leading to the massive production of cytokines (a process referred to as hypercytokinaemia). In these patients, COVID-19 manifests as a severe disease, consisting of advanced pneumonia and acute respiratory distress syndrome. The generation of excess cytokines and persistent viral infection leads to systemic vascular damage, disseminated intravascular coagulation (DIC) and the failure of vital organs, including the kidney and the heart.

This broad antiviral response has placed selective pressure on viruses to develop countless countermeasures to avoid host immune responses, most of which are poorly understood¹⁶. Mechanistically, NSP1

of SARS-CoV-2 suppresses RIG-I-dependent innate immune responses by binding to the 40S ribosomal subunit, resulting in shutdown of host mRNA translation⁴⁷. SARS-CoV-2 may also evade immunological defence

mechanisms through the indirect binding of ORF9b to the mitochondrial antiviral-signalling protein (MAVS) via the translocase of the outer mitochondrial membrane 70 (TOM70)⁴⁸. The localization of MAVS on the outer mitochondrial membrane is essential for the activation of IFN-I after infection of RNA viruses⁴⁹, and it is possible that SARS-CoV-2 binding to MAVS might prevent its translocation and IFN-I activation⁵⁰. In support of this hypothesis, SARS-CoV-2 infection is associated with lower IFN-I and IFN-III levels and a moderate ISG response compared with other respiratory viruses, despite being characterized by vigorous production of inflammatory cytokines^{45,51}.

In line with the above-described findings, the most frequent laboratory abnormalities in patients with unfavourable COVID-19 progression include a cytokine profile characterized by increased levels of IL-2, IL-6, granulocyte colony-stimulating factor (G-CSF), IFNγ inducible protein 10 (IP-10, also known as CXCL10), monocyte chemoattractant protein 1 and 3 (MCP1 and MCP3, also known as CCL2 and CCL7, respectively), macrophage inflammatory protein 1α (MIP-1α, also known as CCL3) and tumour necrosis factor (TNF)^{52–54}. Of these dysregulated cytokines and chemokines, the combined evaluation of IP-10 and MCP3 had the highest predictive value of poor outcomes among patients with COVID-19 (REF.⁵⁴). These findings are reminiscent of the hyper-inflammatory syndrome, secondary haemophagocytic lymphohistiocytosis, and consequently, the immune response to SARS-CoV-2 infection was initially considered to involve a form of cytokine storm, similar to that found in patients with other viral infections or sepsis, as well as in patients with autoimmune conditions such as arthritis^{55,56}. However, this concept has since been revisited and the contribution of cytokines to COVID-19 questioned⁵⁷. In COVID-19, macrophage activation seems to be integral to the initiation and propagation of this hyper-inflammatory reaction⁵⁸ (FIG. 2b). One preliminary study detected ACE2 on the surface of macrophages and showed that SARS-CoV-2 spike proteins interact with CD68⁺ macrophages, suggesting direct viral infection of these cells⁵⁹. Single-cell RNA sequencing of immune cells from bronchoalveolar lavage fluid from patients with COVID-19 suggested the expansion of pro-inflammatory monocytes and Ficolin-positive monocyte-derived macrophages, paralleled by a decrease in tissue-resident reparative alveolar macrophages in patients with severe disease compared with that seen in moderate cases⁶⁰. A further elegant single-cell RNA sequencing study confirmed an enrichment of SARS-CoV-2 RNA in the lung macrophage population of infected patients, and differential gene expression analysis revealed that infected macrophages had higher chemokine expression than non-infected macrophages⁶¹. Moreover, use of untargeted metabolomics has shown that SARS-CoV-2 infection triggers profound alterations in macrophage phenotype and function by downregulating the expression of apolipoproteins that are important for proper macrophage polarization towards anti-inflammatory phenotype^{62,63}. Mechanistically, virus–host interactome and proteomic analysis of peripheral blood cells from patients with

varying symptoms of COVID-19 suggests that NSP9 and NSP10 of SARS-CoV-2 interact with the NF-κB repressor NKRF, which induces an over-exuberant innate immune response to SARS-CoV-2 infection⁶⁴.

A transcriptome analysis of bronchoalveolar lavage fluid cells from eight patients with COVID-19 suggested that SARS-CoV-2 infection elicits more pronounced neutrophil infiltration than other forms of pneumonia⁶⁵. In line with these findings, neutrophilia is predictive of poor outcomes in patients with COVID-19 (REF.⁶⁶; moreover, studies published in preprint form identified a high neutrophil-to-lymphocyte ratio as an independent risk factor for severe disease^{67,68}. A new study has also indicated that neutrophil activation and the formation of neutrophil extracellular traps (NETs) may have a prominent role in propagating the severe cytokine release observed in severe cases of COVID-19, representing a previously unrecognized, but powerful innate defence response that may exacerbate lung damage in affected patients⁶⁹. These findings suggest that unbalanced innate immunity may exacerbate the hyper-inflammatory response in severe cases of the disease (FIG. 2b).

Adaptive immune response. Lymphopenia is a common feature of severe COVID-19, characterized by drastically reduced absolute numbers of CD4⁺ and particularly CD8⁺ T cells^{27,70,71}; this depletion correlates with COVID-19 severity and associated mortality^{72,73}. A proteomic analysis of peripheral blood cells from patients with COVID-19 reported decreased T cell counts, associated with reduced indices of T cell activation and function, including lower expression of T cell receptor (TCR) subunits (CD3e, CD3g, CD247, TRAC and TRBC1) in patients with severe disease than in patients with mild disease⁶⁴. Levels of T cell surface molecules (CD4, CD8a, CD8b and CD2), T cell migration stimulators (DDP4), TCR signalling kinases (ZAP70, LCK and FYN) and MHC class II molecules (HLA-DRA, HLA-DRB1, HLA-DRB4 and HLA-DRB5) were also significantly lower in patients with severe disease, indicating a global impairment in the adaptive immune response⁶⁴. Decreased numbers of peripheral T cells might result from increased migration to the lungs or other infected tissues. However, although CD4⁺ T cells can be detected in lung tissue of deceased patients with COVID-19, CD8⁺ T cell are infrequently observed³¹. Peripheral CD8⁺ T cells from patients with COVID-19 express high levels of exhaustion markers, including programmed cell death protein 1 (PD1) and T cell immunoglobulin mucin-3 (TIM3); of note, this expression pattern was more pronounced among patients who required intensive care than in patients with mild disease⁷⁴. In addition to confirming the exhausted phenotype of CD8⁺ T cells in patients with COVID-19, another study demonstrated that natural killer (NK) cells were also exhausted with increased expression of inhibitory CD94–NK group 2 member A (NKG2A) receptor heterodimer. Of interest, numbers of CD8⁺ T cells and NK cells were restored in convalescent patients, with reduced expression of CD94–NKG2A⁷⁵. These findings suggest that the rise in inflammatory cytokine levels induced by SARS-CoV-2

Cytokine storm

Also called hypercytokinaemia. An excessive and uncontrolled release of pro-inflammatory molecules by the cellular components of the innate immune system in response to a number of infectious and non-infectious aetiologies that can lead to multi-organ damage and failure.

infection might drive the depletion of T and NK cells, which subsequently fail to destroy infected cells.

However, T cell lymphopenia may also result from SARS-CoV-2-induced cell death. Findings from a post-mortem examination of the spleen and lymph nodes of patients with COVID-19, published in pre-print form, identified high levels of T cell apoptosis and increased expression of the death receptor FAS⁷⁵, possibly suggesting that activation-induced cell death (AICD) is likely accountable for T cell depletion in patients with severe COVID-19. Flow cytometry analysis also revealed significantly higher FAS expression in circulating T cells from patients with COVID-19 than in controls⁷⁶. Of note, an earlier report indicated that ACE2 is not expressed by T cells, ruling out the possibility that SARS-CoV-2 has a direct toxic effect on these cells⁵⁹ and further supporting the notion that T cell depletion in COVID-19 results from AICD. Regardless of the underlying cause, however, the absence of an effective anti-viral T cell and NK cell response could play a critical part in the maintenance of a high viral load and hyperactivation of the innate response⁷⁷ (FIG. 2b). Severe infection caused by SARS-CoV-2 has been likened to lymphopenic community-acquired pneumonia⁷⁸ — a specific immunological phenotype associated with a high risk of mortality⁷⁹. Thus, T cell defects in the T cell response might contribute to sustained viral shedding and pathogenesis of multi-organ dysfunction in patients with COVID-19 with clinically severe disease⁸⁰.

Despite the impaired T cell response associated with severe COVID-19, a study from the USA documented the presence of circulating SARS-CoV-2-specific CD4⁺ and CD8⁺ T cells in 100% and 70%, respectively, of patients who had recovered from the disease⁸¹. The functional CD4⁺ T cell response against SARS-CoV-2 was identified as a classical T helper (T_H) type 1 response, which was robust against the spike protein, the membrane protein and the nucleocapsid protein. Additional CD4⁺ T cell responses were found to target NSP3, NSP4, ORF3a and ORF8 in convalescent patients with COVID-19 (REF.⁸¹). The SARS-CoV-2-specific CD8⁺ cells were IFN γ ⁺ and recognized the spike and membrane proteins, and at least eight different SARS-CoV-2 ORFs^{81,82}. Ex vivo stimulation with viral peptides induced SARS-CoV-2-specific CD4⁺ and CD8⁺ T cells; in the blood of patients with severe COVID-19, these SARS-CoV-2-specific lymphocytes were already detectable at ICU admission^{82,83}. Notably, these studies have consistently identified the presence of SARS-CoV-2-specific T cells in a large subset of seronegative convalescent individuals, suggesting that T cells could represent a more sensitive indicator of SARS-CoV-2 exposure than antibodies^{81,84}. An analysis of samples collected from 2015 to 2018 before the emergence of the COVID-19 pandemic detected SARS-CoV-2-specific T cells, including T cells that recognize NSP7 and NSP13, in uninfected individuals, suggesting possible cross-reactivity with common cold coronaviruses^{81,83,85}.

Typically, a robust T cell response is directed towards only a small subset of potentially immunogenic peptides in a foreign protein, and the major constraint that determines this immunodominance is dictated by antigen

processing⁸⁶. In SARS, the spike protein of SARS-CoV accounted for nearly two-thirds of CD4⁺ T cell reactivity whereas no reactivity was found against nucleocapsid and membrane proteins⁸¹. By contrast, the spike, nucleocapsid and membrane proteins of SARS-CoV-2 seem to be co-dominant immunogenic proteins, and marked CD4⁺ T cell responses directed against NSP and ORF proteins have also been reported^{81,87}. The lack of a clear immunodominant CD4⁺ T cell response to SARS-CoV-2 could indicate aberrant antigen processing and consequent dysregulation of the T cell immune response⁸¹. In support of this hypothesis, the frequency of virus-specific memory T cells and the number of immunodominant virus epitopes they responded to were significantly higher in patients with severe disease than in patients with mild disease^{82,84}, raising the question of why these virus-specific T cells are not able to control the disease.

In contrast to T cells, very few studies have demonstrated an effect of SARS-CoV-2 on B cell biology. To date, studies regarding B cell function in COVID-19 have mainly focused on the generation of specific antibodies against SARS-CoV-2. In a study of 285 patients with COVID-19, seroconversion for IgG and IgM against the nucleocapsid and the spike protein occurred simultaneously or sequentially and their titres plateaued within 6 days of seroconversion⁸⁸. Within 19 days of symptom onset, 100% of patients were IgG-positive⁸⁸. Based on the humoral response to SARS and MERS, the development of neutralizing antibodies against the SARS-CoV-2 spike protein is likely to be the most promising approach to ensure COVID-19 protective immunity^{89–91}. Non-human primates reinfected with SARS-CoV-2 <1 month after their first infection displayed a reduced viral load and prevented disease recurrence relative to responses in primo-infected animals^{92,93}; these beneficial effects were associated with potent neutralizing antibody responses. Moreover, treatment with two potent human monoclonal antibodies that recognize the spike protein protected rhesus macaques against a challenge with SARS-CoV-2 as reported by a preprint study⁹⁴ — a finding that strongly suggests that a protective humoral response can be induced by vaccination.

However, the extent to which naturally induced antibodies against disease relapse may provide long-lasting protection is still unknown. The longevity of the humoral response against SARS-CoV-2 in humans may be transient, as demonstrated by the finding that 40% of asymptomatic patients and 13% of symptomatic patients became negative for anti-spike IgG in the early convalescent phase⁹⁵. As shown in a preprint study, longitudinal evaluation of patients with SARS-CoV-2 infection reported a rapid decline in levels of neutralizing antibody during a 4-month follow-up period, with titres approaching the lower threshold of positivity in several individuals⁹⁶. The decay of anti-SARS-CoV-2 antibodies was particularly rapid in patients with COVID-19 with mild disease⁹⁷. However, these findings were challenged by a study in the Icelandic population showing that antibodies against SARS-CoV-2 remained stable for over 4 months⁹⁸. More importantly, neutralizing antibodies from patients with COVID-19 are minimally mutated,

VH gene

The heavy-chain-variable region (VH) gene gene is located along with diversity (D), joining (J) and constant (C) genes at three primary loci in the human genome and undergoes somatic rearrangements for the biosynthesis of the heavy (H) or light (L) chain of IgG.

suggesting that they bind SARS-CoV-2 with low affinity owing to limited affinity maturation⁹⁹; indeed, these antibodies have modest neutralizing activity^{100,101}, targeting epitopes outside the receptor binding domain¹⁰⁰. This disparate antibody response may indicate failure to develop a robust, long-lasting protective humoral response against SARS-CoV-2.

In support of a dysregulated B cell response to SARS-CoV-2 infection, analyses of circulating B cells showed expansion of oligoclonal plasmablasts and reduced memory B cell frequencies in patients with severe COVID-19 compared with responses in patients with mild disease or healthy individuals^{42,102,103}. The antibody sequences of the largest B cell clones detected in patients with severe COVID-19 were variable in terms of somatic hypermutation levels and VH gene usage, suggesting a polyclonal B cell response¹⁰², possibly arising via an extra-follicular pathway, as reported in a preprint study¹⁰⁴. Plasmablast levels in patients with COVID-19 did not correlate with antibody levels against the spike protein, suggesting that these cells generated antibodies against antigens other than the spike protein or generated antibodies with low specificity and affinity.

Surprisingly, anti-SARS-CoV-2 antibodies are elevated in severely-ill patients with COVID-19 (REFS^{95,105}), whereas they are reportedly low in most recovered patients⁸². In a preprint study of individuals with mild COVID-19, titres of neutralizing antibodies correlated positively with age, and blood C-reactive protein levels, but correlated negatively with lymphocyte counts of patients at the time of admission¹⁰⁶. Unfortunately, this study did not assess the potential correlation between viral load and disease symptoms with neutralizing antibody titres in individual patients to evaluate the actual pathogenic role of these antibodies¹⁰⁶. In this context, a study that suggested that the humoral response against the SARS-CoV-2 spike protein may increase the severity of lung injury by skewing macrophage responses, abrogating wound-healing responses and promoting macrophage recruitment and accumulation in the lung parenchyma, is of particular interest¹⁰⁷. Relative levels of IgA and IgG have also been demonstrated to be markedly higher in severely ill patients with COVID-19 than in patients with milder disease, suggesting that IgA may have synergistic effects with IgG in promoting antibody-dependent cellular cytotoxicity and COVID-19 exacerbation¹⁰⁸.

Together, the available evidence indicates that a variety of dysregulated processes occur in innate and adaptive immunity, including the cellular and humoral response to SARS-CoV-2 infection (FIG. 2). These findings indicate the need for further studies to better understand COVID-19 immunopathology and to aid the design of the optimal vaccine and effective therapeutic interventions¹⁰⁹.

Effects of SARS-CoV-2 on the endothelium

Endothelial cells contribute to the preservation of normal haemostasis by maintaining vessel wall integrity and balancing fibrinolysis through the expression of coagulation inhibitors and blood clot-lytic enzymes, and through maintenance of the glycocalyx^{110–112}. Mounting evidence

suggests that loss of vessel barrier integrity and the development of a pro-coagulative endothelium contributes to the initiation and propagation of ARDS in COVID-19, by inducing endotheliitis and mediating inflammatory cell infiltration in the lungs^{24,113,114}. A substantial proportion of patients with severe COVID-19, including young individuals and children, develop venous and arterial complications. In New York City, over a 2-week period from 23 March to 7 April, 2020, researchers observed a sevenfold increase in large-vessel stroke among patients younger than 50 years of age compared with a 2-week time frame over the previous 12 months^{115,116}. Although early evidence suggested that children may be at a lower risk of SARS-CoV-2 infection than adults owing to the lower expression of ACE2 in nasal epithelia¹¹⁷, an unprecedented cluster of hyper-inflammatory shock syndrome was observed in South East England, UK over a 10-day period in mid-April 2020 in eight children with likely family COVID-19 exposure¹¹⁸. This syndrome has been described as a pathological condition with features similar to Kawasaki disease — a rare condition that affects blood vessels, including those in the heart. All children tested negative for SARS-CoV-2 on bronchoalveolar lavage or nasopharyngeal aspirates, but laboratory tests were indicative of infection and inflammation, including high levels of C-reactive protein, ferritin and D-dimers¹¹⁸. More recent evidence suggested that this syndrome, now termed multisystem inflammatory syndrome in children (MIS-C), has unique haematological and immunological characteristics that are distinct from those of both typical COVID-19 in adults and Kawasaki disease¹¹⁹. Similar cases of MIS-C have been observed in 17 patients under 18 years of age in New York City¹²⁰ and in Bergamo¹²¹, one of the hardest hit areas of northern Italy. A retrospective study of 35 children with MIS-C in France described acute heart failure as a result of the severe inflammatory state caused by SARS-CoV-2 infection; none of these children had underlying cardiovascular disease¹²².

SARS-CoV-2 may alter vascular homeostasis by directly infecting endothelial cells via ACE2 (FIG. 3a). In support of this proposal, SARS-CoV-2 can successfully infect engineered human blood vessel organoids, confirming SARS-CoV-2 tropism for endothelial cells¹²³. This finding is further corroborated by electron microscopy analyses of post-mortem tissue, which have shown that SARS-CoV-2 can infect pulmonary endothelial cells and induce endotheliitis, at least in a subset of critically ill patients¹¹⁴. After binding by SARS-CoV-2, ACE2 is internalized and downregulated on endothelial cells, which favour the progression of inflammatory and pro-fibrotic processes in the lung triggered by local angiotensin II (Ang II) hyperactivity¹²⁴. Given that ACE2 converts Ang II into Ang (1–7), which acts on the MAS receptor, it is conceivable that a reduction of ACE2 expression by endothelial cells in response to SARS-CoV-2 infection leads to reduced generation of Ang 1–7 and consequently, reduced activation of MAS, promoting a local pro-thrombotic endothelial cell phenotype (FIG. 3a). Furthermore, reduced expression of ACE2 might in turn indirectly activate the kallikrein–kinin system (KKS), which ultimately leads to increases in vascular permeability^{113,125}. Indeed, several

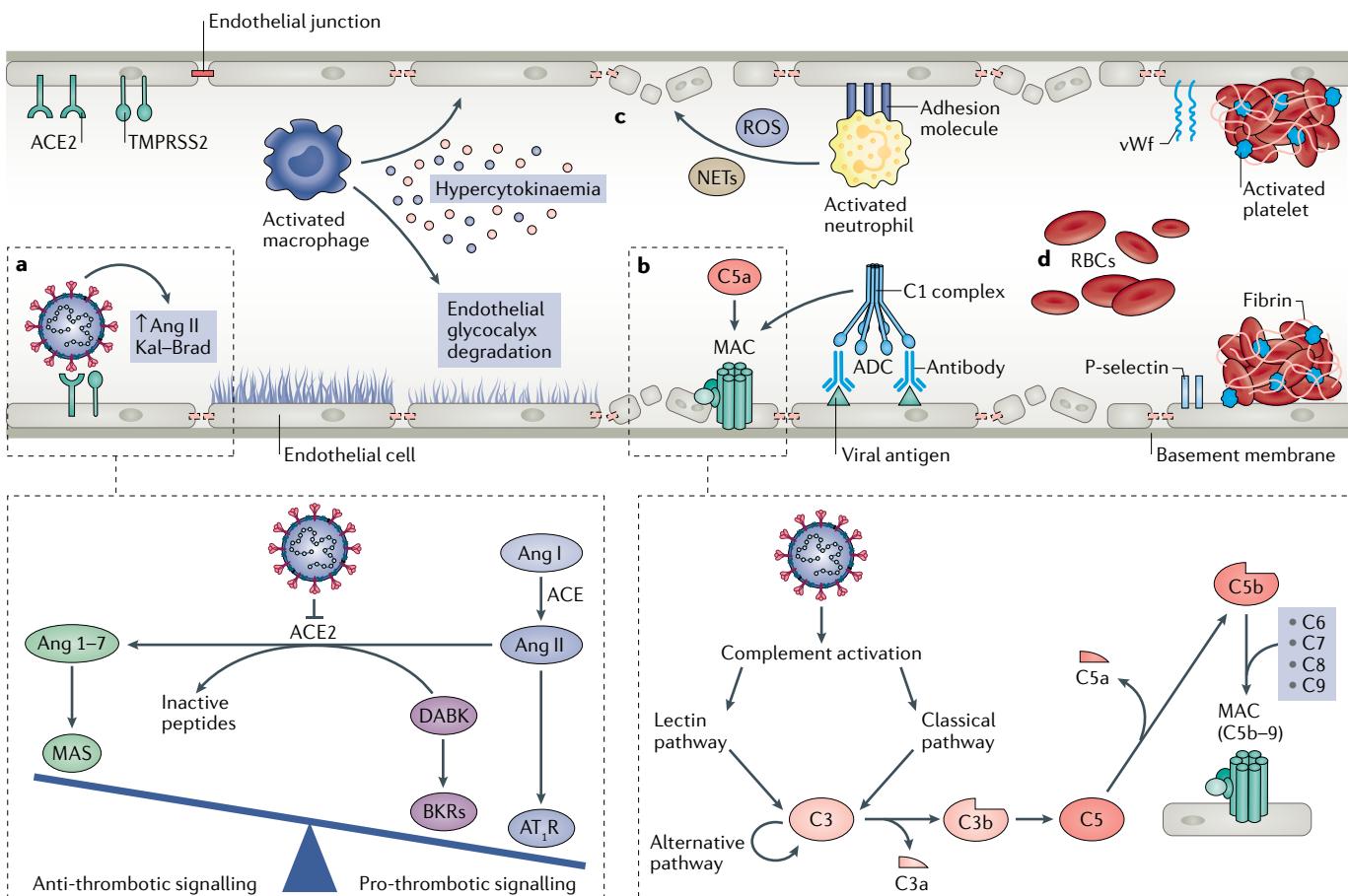


Fig. 3 | Effect of SARS-CoV-2 infection on endothelial cell function, systemic coagulation and thrombosis. **a** | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly infects endothelial cells owing to their high expression levels of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). After binding by SARS-CoV-2, ACE2 is internalized, and the lack of ACE2 on endothelial cells favours the progression of inflammatory and thrombotic processes triggered by local angiotensin II (Ang II) hyperactivity. Inhibition of ACE2 by binding of SARS-CoV-2 reduces the ACE2-mediated conversion of Ang II to Ang 1–7, the vasoactive ligand of the MAS receptor. The reduction of MAS receptor activation induces a pro-inflammatory phenotype through increased activation of type 1 angiotensin receptors (AT₁R). Additionally, the reduction in levels of ACE2 limits the degradation of des-Arg⁹ bradykinin (DABK) into inactive peptides, ultimately leading to increased pro-thrombotic signalling via the activation of bradykinin receptors (BKR). **b** | SARS-CoV-2 also activates the complement system — an integral component of the innate immune response. The complement cascade can be activated by three different pathways, the classical, the lectin and the alternative pathway, that resolve around the formation of the C3 convertases that cleave C3, generating the pro-inflammatory peptide C3a and large amount of C3b that opsonizes pathogens. C3b also forms the

C5 convertase, which leads to release of the potent anaphylatoxin C5a, as well as the fragment C5b, responsible for the formation of the membrane attack complex (MAC) C5b–9 on target cells, which is considered to be the terminal event of complement activation. In addition, complexes of SARS-CoV-2-specific antibodies and viral antigens might induce endothelial cell injury through activation of the C1 complex of the classical pathway and induction of antibody-dependent cytotoxicity (ADC). **c** | Pro-inflammatory cytokines and chemokines released by activated macrophages amplify the vicious cycle of vascular integrity disruption, vessel coagulation and thrombosis by degrading the endothelial glycocalyx, activating the coagulation system and dampening anticoagulant mechanisms. The adhesive phenotype of endothelial cells induced by inflammatory cytokines and chemokines promotes infiltration of neutrophils, which produce large amounts of histotoxic mediators, including reactive oxygen species (ROS) and neutrophil extracellular traps (NETs), ultimately leading to injury of endothelial cells. **d** | Activated endothelial cells initiate coagulation by expressing P-selectin, von Willebrand factor (vWF) and fibrinogen, leading to massive platelet binding, fibrin formation and clotting of red blood cells (RBCs), ultimately resulting in systemic thrombosis and disseminated intravascular coagulation.

studies have documented that a tight balance between the KKS and renin–angiotensin systems is required to regulate the thromboresistance of endothelial cells^{126–128}. The reduction in pulmonary ACE2 impairs the inactivation of des-Arg⁹ bradykinin (DABK), leaving it free to bind its cognate receptors^{129–131} (FIG. 3a). Moreover, high levels of bradykinin in patients with COVID-19 might explain the majority of severe symptoms, spanning from blood vessel injury to neurological complications¹³², suggesting that inhibition of the KKS, for example, with the

bradykinin B2 receptor antagonist icatibant¹³², could be a possible therapeutic strategy^{133,134}. Mechanistically, disruption of the endothelial barrier by SARS-CoV-2 spike protein is mediated by changes in the surface expression of intracellular adhesion molecule-1 (ICAM1), vascular cell adhesion protein-1 (VCAM1) and the tight junction scaffold protein zonula occludens-1 (ZO-1), as reported by a preprint study¹³⁵.

However, the finding that viral RNA is rarely detectable in blood¹³⁶ indicates that additional host-dependent

Glucuronidases

A class of enzyme that includes beta-glucuronidases — a glycosidases that catalyse the breakdown of complex carbohydrates by hydrolysing β -D-glucuronic acid residues from the non-reducing end of glycosaminoglycans, such as heparan sulfate.

factors might contribute to systemic endothelial dysfunction and vasculopathy in COVID-19, rather than direct viral-dependent effects on endothelial cells. As reviewed elsewhere, the hypercytokinaemia and the massive pro-inflammatory response of the host may contribute to endothelial dysfunction in COVID-19, particularly via the actions of IL-6 and TNF — levels of which are strongly increased in critically ill patients¹¹³. Cytokines exert their pathogenic effects through various mechanisms. For example, IL-6 can increase vascular permeability and promote the secretion of pro-inflammatory cytokines by endothelial cells themselves, thereby amplifying the cytokine release¹¹³. TNF can activate glucuronidases that might degrade the endothelial glycocalyx but might also upregulate hyaluronic acid synthase 2, leading to increased deposition of hyaluronic acid in the extracellular matrix and promoting fluid retention¹¹³. Additional mechanisms, such as a reduction of endothelial nitric oxide synthase activity and nitric oxide levels, as well as the release of vascular endothelial growth factor (VEGF) as a consequence of the systemic hypoxia induced by ARDS, have also been proposed as key pathogenic processes underlying endothelial dysfunction following SARS-CoV-2 infection¹³⁶. Below, we focus on the possible role of the complement system in inducing systemic endothelial dysfunction in COVID-19.

Excessive complement activation. The complement system is an integral component of the innate immune response and comprises over 30 different proteins¹³⁷. This system can be activated by three different pathways: the classical, the lectin and the alternative pathway¹³⁷. All of these pathways converge on the formation of C3 convertases that cleave C3 to generate the pro-inflammatory peptide C3a and a large amount of C3b, which opsonizes pathogens¹³⁷. C3b also forms C5 convertase, which induces release of the potent anaphylatoxin C5a, as well as the fragment C5b that is responsible for the formation of the membrane attack complex C5b–9 on target cells — the terminal event of complement activation. Although complement, like other innate immune system components, helps to control bacterial and viral infections, its unrestrained activation — for example, in the context of prolonged SARS-CoV-2 infection — can be detrimental by causing direct damage of host tissues¹³⁸ (FIG. 3b).

Most available data on complement activation in the context of coronavirus infection are derived from the SARS and MERS epidemics. A 2018 study of SARS-CoV demonstrated that C3-deficient mice experienced a less severe form of disease than wild-type mice, associated with reduced lung infiltration of inflammatory cells and lower hypercytokinaemia in both the lungs and sera¹³⁹. SARS-CoV activates the lectin pathway by interacting with the complement component mannose-binding lectin (MBL) — a C-type lectin that activates mannose-binding protein-associated serine protease 2 (MASP-2) — enhancing the deposition of C4 activation fragments on virus-infected cells¹⁴⁰. In mice infected with MERS-CoV, levels of circulating C5a increased post-infection and the expression of the C5a receptor (C5aR) was upregulated in pneumocytes

and inflammatory leukocytes, associated with strong C5b–9 deposition on bronchiolar epithelial cells, pneumocytes and infiltrating leukocytes¹⁴¹. In line with these findings, immunohistochemistry analyses in post-mortem lung tissue from SARS-CoV-2-infected patients revealed high expression of the complement components MBL, C4, C3 and C5b–9, in alveolar epithelial cells and pneumocytes, as well as in inflammatory cells, as reported by a preprint study¹⁴². As mentioned above, the nucleocapsid protein of SARS-CoV-2 can interact indirectly with MASP-2 and initiate the lectin pathway of complement, resulting in aberrant complement activation and aggravated inflammatory lung injury¹⁴². Circulating levels of C5a were higher in patients with severe COVID-19 than in patients with mild disease who had levels of C5a similar to those of healthy controls¹⁴². Use of an untargeted metabolomic approach also demonstrated upregulation of complement activation proteins, including membrane attack complex proteins such as C5, C6 and C8, in sera from 46 patients with severe disease⁶².

In addition to the lectin pathway, the classical pathway may also contribute to tissue injury induced by coronavirus infection. Indeed, immune complexes formed by viral antigens and antibodies can activate C1 and initiate complement activation. In patients with SARS-CoV infection, the development of autoantibodies against human pulmonary epithelial cells and endothelial cells mediated complement-dependent cytotoxicity¹⁴³; however, whether this process is also activated following SARS-CoV-2 infection is unknown. Use of an ultra-high-throughput clinical proteomic approach identified consistent activation of the classical complement pathway (specifically, complement components C1R, C1S and C8A) in the sera of patients with clinically severe COVID-19, along with increased activation of the alternative pathway component, complement factor B (CFB) and its modulators CFI and CFH¹⁴⁴. Findings from another study suggest that enhanced IgA levels during SARS-CoV-2 infection might act synergistically with IgG to promote antibody-dependent cytotoxicity¹⁰⁸. These researchers also proposed that COVID-19 might be at least in part an IgA-mediated disease¹⁰⁸, possibly inducing a vasculitis phenotype via classical pathway-mediated cytotoxicity.

Although clinical insights into complement activation following SARS-CoV-2 infection are limited¹⁴⁵, the above findings indicate that unrestrained complement activation — mainly at the downstream terminal phases of the complement cascades — may contribute to endothelial cell injury, thrombosis and intravascular coagulation, ultimately leading to multi-systemic organ failure in patients with COVID-19 (REF.¹³⁷).

Microangiopathy and vessel thrombosis. Activation of the complement system leads to endothelial cell injury and death with subsequent vascular denudation and exposure of the thrombogenic basement membrane, which drives activation of clotting cascades. These events result in inflammation, microvascular thrombosis, vessel oedema and haemorrhagic sequelae — all of which are prominent features of the lung pathology of patients with COVID-19-associated pneumonia¹⁴⁶. In an

autopsy study of ten patients with COVID-19, small vessel thrombus formation in the lung periphery was associated with foci of alveolar haemorrhage¹⁴⁷. In a larger series of post-mortem pulmonary analyses in Northern Italy, a predominant finding was the presence of platelet — fibrin thrombi in small arterial vessels, further suggesting that coagulopathy has an important role in outcomes following SARS-CoV-2 infection¹⁴⁸. Indeed, patients with SARS-CoV-2 infection are at an increased risk of widespread coagulation of small and large vessels¹⁴⁹, and venous thromboembolic complications — in particular acute pulmonary embolisms^{150–153} — are recognized as life-threatening complications in patients with COVID-19.

Pro-inflammatory cells, cytokines and chemokines amplify the vicious cycle of vessel coagulation and thrombosis, by acting to simultaneously activate the coagulation system and dampen anticoagulant mechanisms¹⁵⁴. Infiltrating, activated neutrophils (FIG. 3c) produce large amounts of histotoxic mediators, including reactive oxygen species¹¹³, as well as NETs, which have been found in arterial microthrombi in the post-mortem lung specimens from four deceased patients with COVID-19 (REF.¹⁵⁵). The expression of tissue factor (TF) by activated monocytes stimulates the coagulation cascade and the subsequent generation of thrombin; these processes are ineffectually counterbalanced by tissue factor pathway inhibitor (TFPI), which is present in plasma and platelets, and produced mainly by endothelial cells¹⁵⁴. Concurrently, endothelial cell-associated anticoagulant pathways, in particular the protein C system, are impaired by pro-inflammatory cytokines¹⁵⁴. In response to activation by IL-1β and TNF, endothelial cells promote coagulation by expressing P-selectin, von Willebrand factor and fibrinogen, leading to massive platelet binding¹¹³ (FIG. 3d). This process is further supported by the release of trophic cytokines by endothelial cells, which augment platelet production¹¹³. The recruited platelets release VEGF, which amplifies the expression of TF by endothelial cells, further stimulating the coagulation cascade¹¹³. Together, these events contribute to the increase in fibrin generation, inducing the deposition of blood clots in the microvasculature¹⁵⁴ (FIG. 3).

Kidney involvement in COVID-19

The lungs are the main site for SARS-CoV-2 infection and the first affected organ in COVID-19. However, sustained viral shedding and hyperactivation of the immune response in severe cases greatly increases the risk of systemic multi-organ failure. Of the organs affected by COVID-19, the kidney is one of the main sites of COVID-19 complications (FIG. 4), and abnormal renal function is a significant risk factor for death in severely ill patients with COVID-19 in the ICU setting. In a prospective cohort study of 701 patients with COVID-19 in Wuhan, China, almost 17% (113) died in hospital¹⁵⁶. On admission, 43.9% of patients had proteinuria and 26.7% haematuria, whereas 5.1% of patients experienced acute kidney injury (AKI) during the study¹⁵⁶. Reports published later in the pandemic described a higher incidence of AKI (8–17%), with the highest ranges in the critically ill (14–35%)^{157,158}. In most patients with COVID-19,

abnormal kidney function in the presence of low-level proteinuria possibly reflects tubular injury. In some cases, however, proteinuria is abundant or contains albumin, suggesting glomerular impairment¹⁵⁸. Patients with kidney disease are at a significantly higher risk of death than those without kidney disease, and elevated levels of baseline serum creatinine or blood urea nitrogen, AKI stage, proteinuria or haematuria were independent risk factors for in-hospital mortality¹⁵⁶. A systematic review and meta-analysis suggested that, in patients with COVID-19, severe AKI is an ominous clinical predictor and is associated with high mortality^{159,160}. As a result, dialysis is an important tool for the management of severely ill patients with AKI^{161,162}.

In autopsy specimens, the spectrum of renal pathological abnormalities includes loss of the brush border and vacuolar degeneration in tubular epithelial cells, with debris composed of necrotic epithelium in tubular lumens¹⁶³. As seen in the lung¹⁶⁴, post-mortem examination of kidney specimens in a preprint study also identified deposition of C5b–9 on tubule cells and massive interstitial infiltration of macrophages as hallmarks of kidney complications in patients with severe disease¹⁶⁵. The relevance of microvascular thrombosis in the kidney is still a matter of investigation. One autopsy study identified limited fibrin thrombi in glomerular capillaries of kidney specimens from patients with COVID-19 with severe disease¹⁶³. However, renal vasculopathy has not been consistently found in the kidney and no significant glomerular disease has been described, with the exception of collapsing focal segmental glomerulosclerosis, which has been reported in a few patients and seems to be associated with the presence of genetic ‘risk’ variants of *APOL1*^{166,167}. Together, these findings suggest that the kidney is severely affected in some patients with COVID-19 and imply that further insight into disease pathogenesis may aid the identification of novel therapeutic targets to prevent kidney dysfunction and/or hasten renal recovery during SARS-CoV-2 infection.

Several non-specific mechanisms may contribute to the development of AKI in the setting of COVID-19, including haemodynamic alterations, cardiac dysfunction, hypovolaemia due to poor oral intake or high-grade fever, use of nephrotoxic drugs and nosocomial sepsis¹³⁸. Additionally, high levels of mechanical ventilation can potentially induce AKI by inducing neuro-humoral-mediated alterations in intra-renal blood flow and other haemodynamic changes that impair renal perfusion, and through the induction of systemic inflammatory mediators as a consequence of ventilator-induced lung injury¹⁶⁸.

However, emerging evidence suggests that SARS-CoV-2 may have a direct effect on kidney cells^{169–172}. Tubule epithelial cells and podocytes exhibit high levels of ACE2 and TMPRSS2, suggesting that they are potential SARS-CoV-2 targets^{173,174}. ACE2 internalization following SARS-CoV-2 infection could induce an imbalance in the renin–angiotensin–aldosterone system, with increased Ang II signalling leading to pro-inflammatory and profibrotic processes in the kidney^{14,175}. The critical role of ACE2 in SARS-CoV-2 kidney infection is emphasized by findings from in vitro studies that show

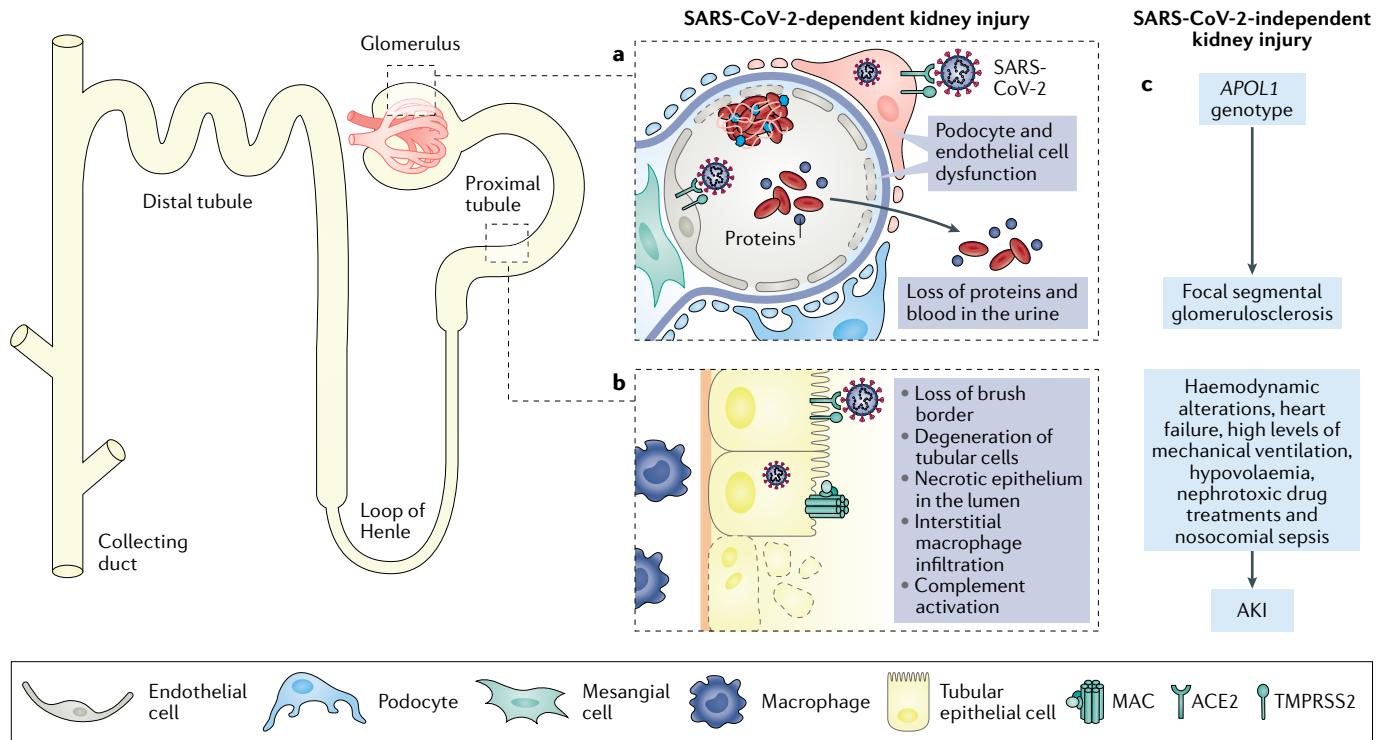


Fig. 4 | The effects of COVID-19 on the kidney. The kidney expresses high levels of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) and has been identified as a target organ for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by several studies. **a** | Within the glomerulus, podocytes and endothelial cells have been identified as specific sites for viral infection. SARS-CoV-2-induced podocyte dysfunction is likely to induce impairment of glomerular filtration, leading to proteinuria and haematuria, which are often observed in patients with coronavirus disease 2019 (COVID-19). Infection of endothelial cells alters glomerular capillary haemostasis and induces the formation of fibrin thrombi. **b** | SARS-CoV-2 has also been found in proximal tubular cells, which exhibit high levels of ACE2 in the apical brush border.

SARS-CoV-2 infection leads to loss of the brush border and vacuolar degeneration in tubular epithelial cells, with luminal debris composed of necrotic epithelium with evidence of complement activation and membrane attack complex (MAC) (C5b–9) deposition on tubular cells and massive macrophage infiltration in the kidney interstitium. **c** | In addition, a non-viral-dependent mechanism might also be accountable for kidney dysfunction in the context of COVID-19, including a possible contribution of the APOL1 'risk' genotype in inducing focal segmental glomerulosclerosis following SARS-CoV-2 infection, as well as the role of haemodynamic factors, cardiac dysfunction, high levels of mechanical ventilation, hypovolaemia, nephrotoxic drug treatments and nosocomial sepsis resulting in COVID-19-associated acute kidney injury (AKI).

that SARS-CoV-2 can infect human kidney organoids and that this infection can be limited by expression of human recombinant soluble ACE2 — a decoy receptor that is undergoing evaluation in clinical trials¹²³. Also, in support of the hypothesis that SARS-CoV-2 exerts tropism in the kidney, electron microscopy examination of autopsy samples from 26 patients who had died with COVID-19 demonstrated clusters of viral particles in the tubular epithelium and podocytes¹⁶³. Another study that involved microdissection of autopic tissue demonstrated detectable SARS-CoV-2 viral load in three of six deceased patients; within the three SARS-CoV-2-positive samples, virus was detected in all kidney compartments examined, with preferential targeting of glomerular cells¹⁷⁶. However, most analyses of kidney tissue have used electron microscopy, light microscopy and/or immunohistochemistry, which cannot conclusively ascertain whether the identified particles are actually SARS-CoV-2 or merely viral-like structures. In particular, the identification of viral particles in kidney tissue by electron microscopy has been questioned given the resemblance of these particles to other cellular structures, such as clathrin-coated vesicles¹⁷⁷, and the

fact that several studies have been unable to confirm the presence of virus in the kidney^{178–181}. Moreover, studies of SARS-CoV-2 in biological fluids have rarely shown viral shedding in the urine¹⁵⁸, raising the possibility that a reservoir of SARS-CoV-2 might not exist in the kidney. Despite these discrepancies and unknowns, one elegant study has documented enrichment of SARS-CoV-2 RNA in glomerular epithelial and endothelial cells by *in situ* hybridization¹⁷⁶. In line with this finding, active viral replication in different tissues, including kidney tissue, was found in a subset of patients with COVID-19 (REF.¹⁸²), although it is still not clear whether this renal active replication contributes to the viral burden in the body.

As described earlier, innate and adaptive immune responses contribute to the pathogenesis of COVID-19. Some evidence exists to suggest that modulation of these processes in patients with kidney failure may have consequences for disease outcomes. Despite some early small, uncontrolled studies showing the opposite^{183,184}, a report from Japan showed substantially higher mortality among patients on maintenance haemodialysis with COVID-19 than among non-dialysis patients, although

this difference in mortality could be due to the older age of patients on haemodialysis¹⁸⁵. Two further studies from the UK and Italy also reported significantly higher mortality among patients on haemodialysis than among the non-dialysis population^{162,186}. In the Italian study, ARDS was probably the cause of death among hospitalized patients on haemodialysis¹⁶².

Therapeutic considerations

Huge effort has gone into developing an effective vaccine against SARS-CoV-2. However, despite the existence of more than 130 vaccine candidates currently under investigation¹⁸⁷, our current understanding of SARS-CoV-2 biology and knowledge gained during the SARS and MERS epidemics suggests that the successful development of a vaccine will be challenging¹⁸⁸. Until a safe and effective vaccine is available, it is imperative that alternative therapeutic strategies are identified that can be used during the current phase of the pandemic. From this point of view, understanding of the pathogenic mechanisms of COVID-19 offers important opportunities to identify and repurpose therapeutics that are already available to attenuate viral attachment and replication, hyperinflammation and the mechanisms underlying endothelial damage, blood clotting and systemic microangiopathy.

Antiviral therapies

The first week following SARS-CoV-2 infection — during which the virus enters alveolar cells and starts replicating in the lungs — represents a critical time for blocking the infection using antiviral agents. Of the repurposed antivirals investigated to date, the adenine analogue remdesivir was initially identified as a promising therapy to induce premature termination of SARS-CoV-2 RNA replication by competing with endogenous nucleotides for the viral RdRp¹⁸⁹. Despite initial, encouraging results¹⁹⁰, the first placebo-controlled trial in COVID-19 failed to demonstrate a beneficial effect of remdesivir¹⁹¹. However, the US FDA granted emergency use authorization for remdesivir when review of the topline data from an ongoing randomized, double-blind, placebo-controlled trial¹⁹² showed that patients with COVID-19 who received remdesivir recovered 30% more quickly than those who had received placebo, although no statistical difference in mortality was found between the two study arms¹⁹³. One major obstacle to the development of effective nucleotide-based drugs is our lack of understanding of the molecular mechanisms underlying substrate recognition during SARS-CoV-2 replication. New studies that have provided insights into the structural basis of RNA replication by the RdRp complex¹⁹⁴ and the residues that are critical for nucleotide recognition and excision¹⁸⁹ may aid the identification of more effective and targeted nucleotide-based therapies. The combination of HIV protease inhibitors lopinavir–ritonavir has also been investigated for their ability to treat COVID-19. However, these drugs specifically inhibit the HIV aspartyl protease (retropepsin), an enzyme that is essential HIV virion maturation¹⁹⁵. Consistent with this high selectivity, a randomized, controlled, open-label trial reported no differences between

treatment with lopinavir–ritonavir and standard care in time to clinical improvement¹⁹⁶. Given the lack of specific SARS-CoV-2 protease inhibitors, preclinical studies are underway to develop more effective antiviral treatments for COVID-19, including a specific inhibitor of the SARS-CoV-2 protease M^{pro} (also called 3CL^{pro})¹⁹⁷, although it may be some time before these novel targeted drugs are available for use in humans.

The finding that most repurposed antivirals are ineffective in COVID-19 is of utmost importance for clinical practice. Owing to their strong drug interactions, most antivirals cannot be administered in combination with life-saving drugs for other medical conditions. For example, lopinavir–ritonavir cannot be given in combination with immunosuppressive drugs^{198,199}, which has consequences for specific patient groups such as kidney transplant recipients.

The anti-malaria drug hydroxychloroquine has also been investigated for its ability to inhibit viral infections²⁰⁰. However, available evidence does not support a beneficial effect of hydroxychloroquine over standard therapy in treating mild-to-moderate disease²⁰¹, nor as a post-exposure prophylaxis strategy²⁰². Moreover, two clinical trials have shown that hydroxychloroquine treatment poses serious safety concerns, increasing the risk of cardiovascular death by more than twofold^{203,204}. Given the lack of definitive proof of efficacy for any of these drugs in patients with COVID-19, caution is warranted, particularly when the use of these compounds prevents the use of other, life-saving treatments for concurrent conditions.

Targeting hyperinflammation

In patients with adult-onset secondary haemophagocytic lymphohistiocytosis, early intervention with corticosteroids is of utmost importance for patient survival²⁰⁵. Corticosteroids exert anti-inflammatory effects by repressing a plethora of pro-inflammatory factors²⁰⁶, and prompt intervention with these drugs could be crucial for controlling the early stages of immune-mediated lung injury in COVID-19. Based on experience gained with previous coronavirus outbreaks, the use of high-dose corticosteroids in COVID-19 was initially discouraged because of the potential risk of secondary infections, long-term complications and prolonged virus shedding²⁰⁷. However, early reports from China indicated that treatment with methylprednisolone decreased the risk of death of patients with COVID-19 (REF.²⁰⁸) — a finding that is supported by other reports, indicating that a low to moderate dose of corticosteroids for a short period could be effective during the early stages of the disease^{209,210}. In randomized case-control studies in adult patients with severe community-acquired pneumonia, early and short-term (from 5 to 7 days) corticosteroid therapy and intravenous administration of immunoglobulin after hospital admission reduced morbidity and rates of treatment failure^{211–213}. A preliminary study found that an early, short course of methylprednisolone therapy improved outcomes of adult patients with COVID-19 with moderate or severe disease²¹⁴. In a prospective meta-analysis of clinical trials of critically ill patients with COVID-19, use of systemic corticosteroids

was associated with lower 28-day all-cause mortality compared with usual care or placebo²¹⁵. A further study also documented an association between use of adjunctive steroid therapy plus intravenous immunoglobulin and recovery of cardiac function in children with MIS-C associated with SARS-CoV-2 infection¹²². A large randomized controlled trial showed that dexamethasone reduced 28-day mortality in severely ill patients who were receiving either invasive mechanical ventilation or oxygen alone at randomization, but not among those receiving no respiratory support²¹⁶. These findings are encouraging since dexamethasone treatment is also highly beneficial in patients with pre-existing chronic kidney disease^{217,218}.

Given the role of immune system hyperactivation and cytokines in the pathogenesis of COVID-19, the potential benefits of more targeted therapies should also be considered. For example, the observed suppression of interferon responses following SARS-CoV-2 infection suggests that interferon supplementation may be a potential therapeutic approach for COVID-19, as it is for other infectious diseases such as hepatitis. However, caution must be taken with this approach given the important immunomodulatory properties of interferon therapy, since interferon supplementation could induce or aggravate pre-existing autoimmune diseases or induce life-threatening complications, such as kidney and/or cardiac impairment or pulmonary interstitial fibrosis²¹⁹. In addition, the finding that interferon stimulates expression of ACE2 in epithelial tissues indicates that interferon therapy could potentially promote virus entry into host cells^{17,18}.

The first drug used to target specific components of the hyperactivated immune response in COVID-19 was the IL-6 inhibitor tocilizumab. Two retrospective reviews found that tocilizumab treatment was associated with a significant reduction in markers of inflammation and in the need for ventilatory support, and with improvements in radiological findings in patients with severe disease^{220,221}. However, phase III trials of IL-6 inhibitors^{192,222}, including tocilizumab and sarilumab, were inconclusive and their use is currently not recommended²²³. A small case series reported the beneficial effects of another targeted therapy — the IL-1 receptor antagonist anakinra — in severe patients with COVID-19 (REF²²⁴). However, adequately powered, randomized controlled trials are still needed, and at least 16 different clinical trials are currently underway to assess the effects of other anti-interleukin drugs. Importantly, anti-interleukin agents will only limit propagation of the hypercytokinaemia but are unlikely to resolve the underlying cause of immune system dysregulation in COVID-19.

The clinical characteristics of lymphocytopenia and exhausted circulating T cells indicate that immunotherapies could represent another potential therapeutic option for COVID-19. As in cancer, PD1-mediated inhibitory signals contribute to T cell exhaustion and inhibit T cell effector functions in the early stages of viral infection^{225,226}. Thus, PD1 blockade with the use of immune checkpoint inhibitors may enhance the effector function of T cells and stimulate viral clearance^{225,226}.

In patients with lung cancer, PD1-targeted immunotherapy increased proliferation of PD1⁺ CD8⁺ T cells and was associated with positive clinical outcomes²²⁷. Whether such PD1-targeted immunotherapies will also be effective in redirecting the cytotoxic activity of CD8⁺ T cells in COVID-19 is unknown, but will be assessed in three ongoing clinical trials underway to assess the efficacy of anti-PD1 antibodies in severely ill patients with COVID-19 (REFS^{228–230}). A more intriguing possibility is whether combining anti-PD1 antibodies with anti-cytotoxic T lymphocyte antigen 4 (CTLA4) blockade might increase the efficacy of the respective monotherapies. Indeed, combination therapy can promote switching of phenotypically exhausted CD8⁺ T cells towards an activated effector CD8⁺ T cell phenotype²³¹, suggesting that this approach may have the potential to promote recovery of the antiviral activity of T cells against SARS-CoV-2. In line with this hypothesis, treatment of COVID-19 patients with a synthetic biological immune response modifier, thymosin alpha 1 (REF²³²), effectively restored CD8⁺ and CD4⁺ T cell counts, as well as reversed T cell exhaustion by reducing expression of the T cell exhaustion markers PD1 and TIM-3 on CD8⁺ T cells²³³. Compared with untreated patients, supplementation of thymosin alpha 1 in COVID-19 patients with severe lymphocytopenia was associated with a significantly lower death rate and reduced need for invasive mechanical ventilation²³³.

Targeting endothelial dysfunction

In light of the major contribution of widespread coagulopathy and thrombosis to poor outcomes in COVID-19, the use of prophylactic doses of low-molecular-weight heparin (LMWH) has emerged as a valuable strategy for preventing the development of venous thromboembolisms. In a report from China published in preprint form, administration of LMWH to patients with COVID-19 improved indices of coagulation dysfunction and reduced levels of IL-6 (REF²³⁴). As recommended by the International Society on Thrombosis and Haemostasis, the management of COVID-19-associated coagulopathy with LMWH should be accompanied by close monitoring of platelet counts, fibrinogen and the prothrombin time for the early diagnosis of bleeding²³⁵, although bleeding seems to be rare in patients with COVID-19 (REF²³⁶). A more promising approach than LMWH may be the serine protease inhibitor nafamostat mesylate, which is under investigation in four different clinical trials^{237–240}. This agent has short-acting anticoagulant effects and can limit viral infection and replication by inhibiting TMPRSS2 (REF²⁴¹). That fact TMPRSS2 is a valuable therapeutic target in COVID-19 has been shown by an open-label randomized clinical trial documenting that early administration of oral bromhexine, a TMPRSS2 inhibitor, reduces ICU admission, intubation and mortality²⁴². Alternatively, inhibition of platelet aggregation may represent another therapeutic avenue for patients with COVID-19. In support of this proposal, a small clinical trial conducted in China and published in preprint form showed that prophylactic anti-coagulation therapy supplemented by the anti-platelet drug dipyridamole prevented the progression of COVID-19 to

severe stages of the disease by significantly increasing platelet and lymphocyte counts and decreasing D-dimer levels²⁴³. Notably, through virtual screening of an approved drug library, dipyridamole was also found to suppress SARS-CoV-2 replication *in vitro*²⁴³. Despite these promising findings, available clinical data suggest that anti-coagulation therapies might have only a partial effect on coagulopathy and thromboembolism in severe forms of the disease²⁴⁴. For this reason, additional therapeutic interventions are needed to attenuate endothelial cell dysfunction and thromboembolic complications¹⁴⁵.

Of the available drugs, inhibitors of the complement system may have the most potential to preserve endothelial cell function and limit thromboembolic complications. A case report of a patient with COVID-19-associated ARDS and pneumonia showed that treatment with a C3 inhibitor was safe and associated with a favourable course²⁴⁵, suggesting that C3 blockade may have broad anti-inflammatory potential owing to the upstream positioning of C3 in innate immune cascade signalling. However, C3 inhibition prevents activation of the entire complement cascade, halting the opsonization of viral particles by C3b. Indeed, studies in knockout mice have demonstrated that C3 is required for protection from the highly pathogenic H5N1 influenza infection and proper viral clearance²⁴⁶, suggesting that C3 inhibition may have undesirable consequences.

Among other available inhibitors of the complement cascade²⁴⁷, the anti-C5 monoclonal antibody eculizumab could be the most valuable tool for preventing complement activation in COVID-19. C5 inhibitors block the formation of the terminal products that are common to the three complement pathways, while still allowing C3 activation and viral opsonization¹³⁷. A 2015 study in an experimental model of sepsis found that eculizumab significantly lowered consumptive coagulopathy by inhibiting the formation of C5b–9, and by preventing inflammation and widespread intravascular coagulation²⁴⁸. Notably, C5 inhibition did not interfere with phagocytosis or the intracellular digestion of pathogens, ensuring the efficient removal of bacteria²⁴⁸. A clinical trial has now been initiated to evaluate the therapeutic effect of eculizumab in patients with COVID-19 (REF²⁴⁹). C5a may represent an alternative therapeutic target. C5a stimulates cytokine release, increases vascular permeability and induces the upregulation of adhesion molecules that favour leukocyte extravasation and transmigration into lung parenchyma²⁵⁰ — pathological events that are all observed in severe cases of COVID-19. Interestingly, a preliminary study published in preprint form reported a promising immunosuppressive effect of the anti-C5a antibody BDB-001 in two severely ill patients with COVID-19 (REF¹⁴²). Of note, C5 blockade has demonstrated benefit in various kidney diseases, including C3 glomerulopathy and atypical haemolytic uraemic syndrome^{251,252}, suggesting that targeting complement might protect both the lung and kidney in COVID-19.

Cautious oxygen support

Oxygen therapy has been used as first-line supportive treatment for breathing dysfunction and dyspnoea in patients with COVID-19 with pneumonia and ARDS.

However, despite fulfilling most of the criteria of classic ARDS, COVID-19-associated pneumonia may be a discrete disease characterized by two distinct phenotypes^{253,254}. In the early phase of the disease, the severe hypoxaemia induced by ARDS is often associated with near normal respiratory system compliance^{253,254}. In these patients, gentle oxygen therapy — such as high flow nasal cannula, continuous positive airway pressure or non-invasive ventilation — is recommended^{253,254}. During this phase, a patient's condition may remain unchanged for a period of time and then either improve or suddenly deteriorate to a more severe disease stage. In the latter situation, the resulting ARDS phenotype is similar to that of acute fibrinous and organizing pneumonia — a rare form of acute lung injury that differs from the diffuse alveolar damage found in classic forms of ARDS²⁵⁵. The obliterative pattern of lung injury in these severe cases of COVID-19 raises concerns about the potential deleterious effect of invasive mechanical ventilation at a high level of positive end-expiratory pressure (PEEP)^{253,256}. Indeed, if vascular alterations, such as pulmonary vasoconstriction, pulmonary emboli or thrombi, are the major driver of hypoxaemia in COVID-19, then increasing PEEP levels might not improve oxygenation but, conversely, might contribute to lung damage^{29,30,257}. For this reason, oxygen therapy should be personalized in each patient because the response to PEEP differs on the basis of individual respiratory mechanics^{29,30,257}. This issue is of particular relevance for nephrologists, given that mechanical ventilation is also associated with a threefold increase in the risk of AKI, and that patients with combined respiratory failure and AKI have a mortality of 60–80% in the ICU setting¹⁶⁸. On the other hand, acute fibrinous and organizing pneumonia is a cortico-sensitive pathology and, as described above, appropriate corticosteroid therapy should be established for the clinical management of severely ill patients to avoid unnecessary ventilation.

Convalescent plasma

One virus-targeted approach under investigation is passive antibody therapy. This approach involves the infusion of sera from convalescent patients into infected patients with the aim of transferring neutralizing SARS-CoV-2 antibodies to patients with active disease²⁵⁸. To date, little is known about the efficacy of this treatment as most data are derived from uncontrolled case studies of patients with COVID-19. All case reports of patients with severe COVID-19 have described a rapid improvement in clinical symptoms over the course of 3 days, with resorption of lung lesions within a week, as revealed by radiological examination^{259–261}. A small clinical trial of six critically ill patients with COVID-19 treated with convalescent plasma reported elimination of SARS-CoV-2 RNA within 3 days of therapeutic plasma infusion, although the mortality of these patients did not differ from that of 15 patients who received placebo²⁶². Moreover, a larger randomized clinical trial of 103 patients with COVID-19 (REF²⁶³), as well as a preprint report from India²⁶⁴, showed no significant clinical improvements after convalescent plasma therapy. Future studies should focus on developing approaches

to isolating SARS-CoV-2 neutralizing antibodies from convalescent plasma, which may increase the efficacy of this treatment. In addition, two important factors mentioned earlier need to be taken into consideration when performing plasma collection. First, if protective neutralizing antibodies are short-lived, plasma should be collected early after recovery from COVID-19. Second, patients with more severe disease have higher antibody levels than patients with asymptomatic or mild disease; however, the extent of protection provided by antibodies in patients with severe disease is unclear, and it might therefore be counterproductive to select plasma donors based only on antibody levels. As an alternative approach, a number of neutralizing human monoclonal antibodies have been developed, some of which are entering phase I clinical trials^{94,265–270}. If successful, such an approach would avoid the limitations and the time-consuming procedures required to obtain plasma or to purify polyclonal antibodies from convalescent patients.

Conclusions

Available evidence demonstrates that SARS-CoV-2 infection induces immune dysfunction, widespread endothelial injury, complement-associated coagulopathy and systemic microangiopathy. The clinical outcome of COVID-19 seems to be profoundly dependent on the individual response of the host. Although the contribution of differences in viral loads to clinical outcome cannot be excluded²⁷¹, it is possible that predisposing genetic or biological factors may modulate the degree of disease severity. Additionally, socioeconomic conditions and structural racism may contribute to poor disease outcomes in some regions, as demonstrated by disproportionately poor outcomes among minority ethnic groups, including Black, Asian and Pakistani populations²⁷².

Improved insights into the mechanisms underlying

predisposition to adverse disease outcomes might aid the identification of new strategies and targets for therapy, as well as identify ways to improve outcomes for susceptible individuals and those from minority ethnic backgrounds. However, the development of new drugs is a long process and may not be useful for dealing with the immediate challenge posed by the current COVID-19 pandemic.

Currently, no vaccines or effective antiviral drugs are available for COVID-19, although many are in development and some may become available soon. The paucity of available specific therapies has stimulated the search for existing drugs that can be repurposed for COVID-19. So far, these drugs have included steroids, several anti-interleukin drugs, complement inhibitors and agents that target coagulation and endothelial dysfunction. However, some of these next-generation targeted therapies are not devoid of adverse effects, which can be serious and sometimes life-threatening. The identification of inexpensive and effective drugs — including low-dose steroids and LWMH — is of utmost importance to prevent exacerbation of inflammatory and thrombotic processes and halt disease progression. Given the spectrum of pathogenic mechanisms involved in the development of severe COVID-19, ranging from immune hyperactivation to thromboembolic complications, it is unlikely that a single individual treatment will be effective. Although corticosteroids may be able to target most of these pathogenic pathways, the multifactorial pathogenic nature of the disease indicates that multiple avenues of treatment might be required and major effort should therefore be invested to determine the optimal timing and combinations in which these drugs should be administered to maximize their efficacy in severely ill patients with COVID-19.

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