



The trinity of COVID-19: immunity, inflammation and intervention

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Abstract | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the ongoing coronavirus disease 2019 (COVID-19) pandemic. Alongside investigations into the virology of SARS-CoV-2, understanding the fundamental physiological and immunological processes underlying the clinical manifestations of COVID-19 is vital for the identification and rational design of effective therapies. Here, we provide an overview of the pathophysiology of SARS-CoV-2 infection. We describe the interaction of SARS-CoV-2 with the immune system and the subsequent contribution of dysfunctional immune responses to disease progression. From nascent reports describing SARS-CoV-2, we make inferences on the basis of the parallel pathophysiological and immunological features of the other human coronaviruses targeting the lower respiratory tract — severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Finally, we highlight the implications of these approaches for potential therapeutic interventions that target viral infection and/or immunoregulation.

The first cases of coronavirus disease 2019 (COVID-19) likely occurred from a zoonotic transmission in China in December 2019, linked to a large seafood market that also traded in live wild animals. The causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is capable of human-to-human transmission and spread rapidly to other parts of China and then to other locations. By 24 March 2020, SARS-CoV-2 had infected more than 381,000 people across 195 countries/regions and killed more than 16,000: a pandemic as declared by the World Health Organization¹. Daily reports of sharp rises in the number of new cases continue to emerge from many countries/regions, but efforts to overcome the virus are hampered by a lack of knowledge of several important aspects of SARS-CoV-2 infection, ranging from pathogen biology to host response and treatment options. Therefore, there is an urgent need to better understand the host–pathogen biology of COVID-19 as this will offer important insights into treatment and management of the disease, including identification of new therapies. Here, we review the literature on SARS-CoV-2 pathophysiology, its interaction with target cells and the immune response to the virus, including the contribution of dysfunctional immune responses to disease progression. Specifically, we highlight the implications of specific features of the infection for promising therapeutic interventions that could target the virus or the dysfunctional immune response. Moreover, we discuss how studies focused

on the adaptive immune response will be crucial in informing the development of vaccines and therapeutic monoclonal antibodies.

Pathogenesis of COVID-19

Coronaviruses are known to cause disease in humans and animals. Among these, four (human coronaviruses 229E, NL63, OC43 and HKU1) typically infect only the upper respiratory tract and cause relatively minor symptoms². However, there are three coronaviruses (severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2) that can replicate in the lower respiratory tract and cause pneumonia, which can be fatal. SARS-CoV-2 belongs to the betacoronavirus genus. Its closest relative among human coronaviruses is SARS-CoV, with 79% genetic similarity³. However, among all known coronavirus sequences, SARS-CoV-2 is most similar to bat coronavirus RaTG13, with 98% similarity⁴, and coronavirus sequences in the pangolin (a scaly anteater) also share high similarity⁵.

Like the other respiratory coronaviruses, SARS-CoV-2 is transmitted primarily via respiratory droplets, with a possible, but unproven, faecal–oral transmission route. On infection, the median incubation period is approximately 4–5 days before symptom onset^{6–9}, with 97.5% of symptomatic patients developing symptoms within 11.5 days⁸. At the point of hospital admission, patients with COVID-19 typically exhibit a fever and dry cough;

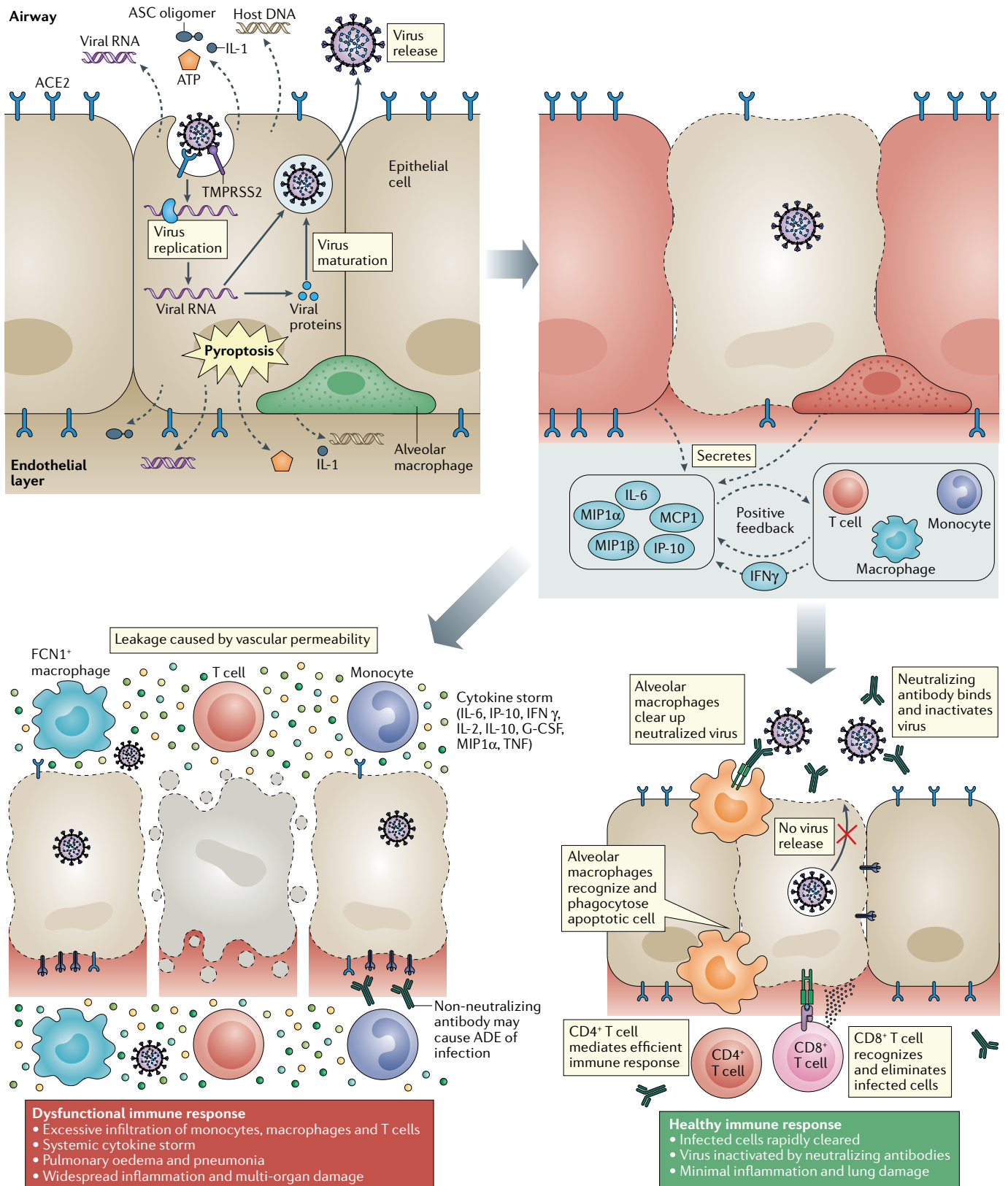
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less commonly, patients also experience difficulty in breathing, muscle and/or joint pain, headache/dizziness, diarrhoea, nausea and the coughing up of blood^{6,10-15}. Within 5-6 days of symptom onset, SARS-CoV-2 viral load reaches its peak — significantly earlier than that of

the related SARS-CoV, where viral load peaks at about 10 days after symptom onset¹⁶⁻¹⁹. Severe COVID-19 cases progress to acute respiratory distress syndrome (ARDS), on average around 8-9 days after symptom onset^{11,20}.

◀ Fig. 1 | **Chronology of events during SARS-CoV-2 infection.** When severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells expressing the surface receptors angiotensin-converting enzyme 2 (ACE2) and TMPRSS2, the active replication and release of the virus cause the host cell to undergo pyroptosis and release damage-associated molecular patterns, including ATP, nucleic acids and ASC oligomers. These are recognized by neighbouring epithelial cells, endothelial cells and alveolar macrophages, triggering the generation of pro-inflammatory cytokines and chemokines (including IL-6, IP-10, macrophage inflammatory protein 1 α (MIP1 α), MIP1 β and MCP1). These proteins attract monocytes, macrophages and T cells to the site of infection, promoting further inflammation (with the addition of IFN γ produced by T cells) and establishing a pro-inflammatory feedback loop. In a defective immune response (left side) this may lead to further accumulation of immune cells in the lungs, causing overproduction of pro-inflammatory cytokines, which eventually damages the lung infrastructure. The resulting cytokine storm circulates to other organs, leading to multi-organ damage. In addition, non-neutralizing antibodies produced by B cells may enhance SARS-CoV-2 infection through antibody-dependent enhancement (ADE), further exacerbating organ damage. Alternatively, in a healthy immune response (right side), the initial inflammation attracts virus-specific T cells to the site of infection, where they can eliminate the infected cells before the virus spreads. Neutralizing antibodies in these individuals can block viral infection, and alveolar macrophages recognize neutralized viruses and apoptotic cells and clear them by phagocytosis. Altogether, these processes lead to clearance of the virus and minimal lung damage, resulting in recovery. G-CSF, granulocyte colony-stimulating factor; TNF, tumour necrosis factor.

The pathophysiology of SARS-CoV-2 infection closely resembles that of SARS-CoV infection, with aggressive inflammatory responses strongly implicated in the resulting damage to the airways²¹. Therefore, disease severity in patients is due to not only the viral infection but also the host response. The pattern of increasing severity with age is also broadly consistent with the epidemiology of SARS-CoV and MERS-CoV^{6,11,14}.

ARDS seen in severe COVID-19 is characterized by difficulty in breathing and low blood oxygen level²². As a result, some patients may succumb to secondary bacterial and fungal infections¹⁴. ARDS may lead directly to respiratory failure, which is the cause of death in 70% of fatal COVID-19 cases²². In addition, the vast release of cytokines by the immune system in response to the viral infection and/or secondary infections can result in a cytokine storm and symptoms of sepsis that are the cause of death in 28% of fatal COVID-19 cases²². In these cases, uncontrolled inflammation inflicts multi-organ damage leading to organ failure, especially of the cardiac, hepatic and renal systems (FIG. 1). Most patients with SARS-CoV infection who progressed to renal failure eventually died²³.

Host cell infection and its prevention

The first step in infection is virus binding to a host cell through its target receptor. Earlier work on SARS-CoV demonstrated that this virus principally targets airway epithelial cells, alveolar epithelial cells, vascular endothelial cells and macrophages in the lung, all of which express the angiotensin-converting enzyme 2 (ACE2) host target receptor used by SARS-CoV^{24–26} (FIG. 2). As SARS-CoV-2 uses the same entry receptor, these cell subsets are likely targeted by this virus^{4,27,28}. SARS-CoV infection reduces ACE2 expression in lung cells. Because loss of pulmonary ACE2 function is associated with acute lung injury, virus-induced ACE2 downregulation may be important for disease pathology^{29–32}. ACE2 has been shown to regulate the renin–angiotensin system (RAS)³².

Therefore, a reduction in ACE2 function after viral infection could result in a dysfunction of the RAS, which influences blood pressure and fluid/electrolyte balance, and enhance inflammation and vascular permeability in the airways.

COVID-19 shows a difference in fatality rate between males (2.8%) and females (1.7%)³³. As ACE2 is located on the X chromosome, there may be alleles that confer resistance to COVID-19, explaining the lower fatality rate in females. Alternatively, the oestrogen and testosterone sex hormones have different immunoregulatory functions, which could influence immune protection or disease severity³⁴.

SARS-CoV-2 shares 79% genome sequence identity with SARS-CoV⁴. The spike (S) protein is expressed on the surface of the virus particles, giving the characteristic ‘crown’ appearance. The S protein comprises two subunits: S1 and S2. The S1 subunit consists of an amino-terminal domain and a receptor-binding domain (RBD), which in SARS-CoV spans from amino acid residue 318 to amino acid residue 510 (REFS^{35–37}). The RBD binds to ACE2 as its host cell target receptor, which starts the infection process⁴. RBD binding to ACE2 triggers endocytosis of the SARS-CoV-2 virion and exposes it to endosomal proteases³⁸. The S2 subunit consists of a fusion peptide (FP) region and two heptad repeat regions: HR1 and HR2 (REFS^{39,40}). Within the endosome, the S1 subunit is cleaved away, exposing the fusion peptide, which inserts into the host membrane. The S2 region then folds in on itself to bring the HR1 and HR2 regions together. This leads to membrane fusion and releases the viral package into the host cytoplasm.

There is 72% similarity in the amino acid sequence of the RBDs of SARS-CoV and SARS-CoV-2, with highly similar tertiary structures. Computational modelling and biophysical measurements indicate that the SARS-CoV-2 RBD binds to ACE2 with higher affinity than that of SARS-CoV^{41,42}. In addition, the SARS-CoV-2 S protein contains a furin-like cleavage site, similarly to MERS-CoV and human coronavirus OC43, which is not found in SARS-CoV⁴³. These characteristics could contribute to the increased infectivity of SARS-CoV-2 relative to SARS-CoV. In addition to furin precleavage, the cellular serine protease TMPRSS2 is also required to properly process the SARS-CoV-2 spike protein and facilitate host cell entry⁴⁴.

One pathway for the development of therapeutics against SARS-CoV-2 is to block the host target ACE2 receptor or TMPRSS2 (FIG. 3). Currently, there are compounds that target these molecules that have been clinically approved for other indications. For example, machine learning algorithms predicted that baricitinib, a Janus kinase (JAK) inhibitor approved for treatment of rheumatoid arthritis, could inhibit ACE2-mediated endocytosis⁴⁵. Another JAK inhibitor, ruxolitinib, will be tested in clinical trials for treatment of COVID-19 later this year⁴⁶. An alternative strategy is to deliver high concentrations of a soluble form of ACE2 that could potentially reduce virus entry into target host cells. This principle is being tested with APN01, a recombinant form of ACE2 developed by APEIRON that is currently in clinical trials⁴⁷. Monoclonal antibodies targeting the

S protein may also inhibit virus entry or fusion and are further discussed in the section entitled B cell immunity. Nafamostat mesylate^{48,49} and camostat mesylate⁴⁴ are known inhibitors of TMPRSS2 and are currently approved in several countries/regions to treat other conditions. While there are no clinical trials specifically testing these drugs against COVID-19 at the time of writing, when camostat mesylate was tested on SARS-CoV-2 isolated from a patient, it prevented entry of the virus into lung cells^{44,50}. If this approach is validated, rapid repurposing of these drugs will be effective and timely in the fight against COVID-19.

Inflammatory immunopathogenesis

SARS-CoV-2 infection and the destruction of lung cells triggers a local immune response, recruiting macrophages and monocytes that respond to the infection, release cytokines and prime adaptive T and B cell immune responses. In most cases, this process is capable of resolving the infection. However, in some cases, a dysfunctional immune response occurs, which can cause severe lung and even systemic pathology.

Cytopathic viruses, including SARS-CoV-2 (REF.⁵¹), induce death and injury of virus-infected cells and tissues as part of the virus replicative cycle. Viral infection and replication in airway epithelial cells⁵² could cause high levels of virus-linked pyroptosis with associated vascular leakage, as seen in patients with SARS-CoV⁵³. Pyroptosis is a highly inflammatory form of programmed cell death that is commonly seen with cytopathic viruses⁵⁴. This is a likely trigger for the subsequent inflammatory response⁵⁵. IL-1 β , an important cytokine released during pyroptosis, is elevated during SARS-CoV-2 infection¹¹. Using a variety of pattern-recognition receptors (PRRs), alveolar epithelial cells and alveolar macrophages detect the released pathogen-associated molecular patterns (PAMPs), such

as viral RNA, and damage-associated molecular patterns (DAMPs), including ATP, DNA and ASC oligomers. A wave of local inflammation ensues, involving increased secretion of the pro-inflammatory cytokines and chemokines IL-6, IFN γ , MCP1 and IP-10 into the blood of afflicted patients^{11,22}. These cytokines are indicators of a T helper 1 (T_H1) cell-polarized response, which parallels observations made for SARS-CoV and MERS-CoV⁵⁶. Secretion of such cytokines and chemokines attracts immune cells, notably monocytes and T lymphocytes, but not neutrophils, from the blood into the infected site^{57,58}. Pulmonary recruitment of immune cells from the blood and the infiltration of lymphocytes into the airways may explain the lymphopenia and increased neutrophil-lymphocyte ratio seen in around 80% of patients with SARS-CoV-2 infection^{5,59}.

In most individuals, recruited cells clear the infection in the lung, the immune response recedes and patients recover. However, in some patients, a dysfunctional immune response occurs, which triggers a cytokine storm that mediates widespread lung inflammation. It was observed that patients with severe COVID-19, requiring intensive care in hospitals, exhibited higher blood plasma levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, MCP1, macrophage inflammatory protein 1 α (MIP1 α) and tumour necrosis factor (TNF)¹¹. IL-6 levels in these patients continue to increase over time and are relatively more elevated in non-survivors than survivors⁶⁰. Notably, there exists a highly inflammatory monocyte-derived FCN1⁺ macrophage population in the bronchoalveolar lavage fluid of patients with severe but not mild COVID-19 (REF.⁶¹). Also, patients with severe disease show a significantly higher percentage of CD14⁺CD16⁺ inflammatory monocytes in peripheral blood than patients with mild disease⁶². These cells secrete inflammatory cytokines that contribute to the cytokine storm, including MCP1, IP-10 and MIP1 α (FIG. 1).

The mechanisms by which SARS-CoV-2 subverts the body's innate antiviral cytokine responses are yet to be studied, but research on SARS-CoV shows that multiple viral structural and non-structural proteins antagonize interferon responses. Antagonism occurs at various stages of the interferon signalling pathway, including by preventing PRR recognition of viral RNA^{63–65}, by preventing PRR signalling through TBK1/inhibitor of nuclear factor- κ B kinase subunit- ϵ (IKK ϵ), TRAF3 and IRF3 (REFS^{63,66}), by preventing downstream interferon signalling through STAT1 (REF.⁶⁷) and by promoting host mRNA degradation and inhibiting host protein translation⁶⁸. It is very likely that at least some of these pathways are conserved in SARS-CoV-2. Antagonism of the interferon response aids viral replication, resulting in increased release of pyroptosis products that can further induce aberrant inflammatory responses.

Unrestrained inflammatory cell infiltration can itself mediate damage in the lung through excessive secretion of proteases and reactive oxygen species, in addition to the direct damage resulting from the virus. Together, these result in diffuse alveolar damage, including desquamation of alveolar cells, hyaline membrane formation and pulmonary oedema^{57,58}. This limits the

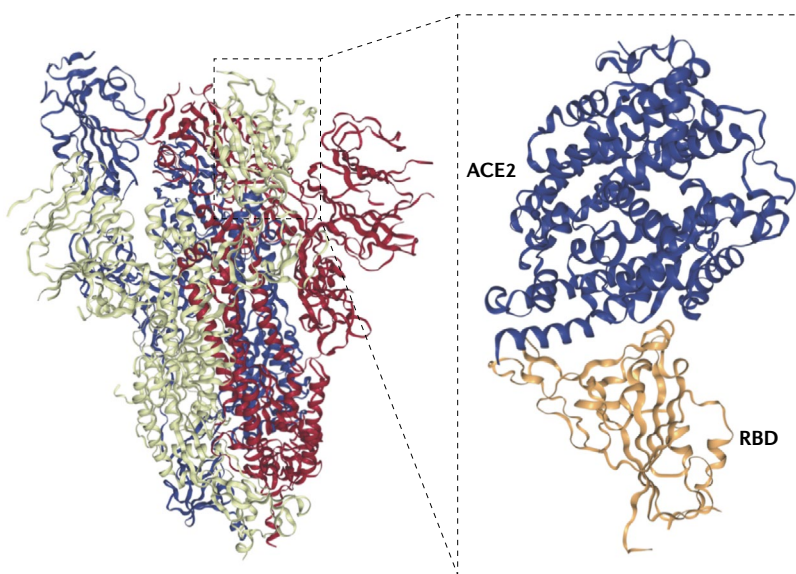


Fig. 2 | The structure of the trimeric spike protein of SARS-CoV-2. The receptor-binding domain (RBD) is shown interacting with its receptor, human angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Adapted from Protein Data Bank IDs 6VSB⁴² and 6VW1 (REF.¹⁵⁰).

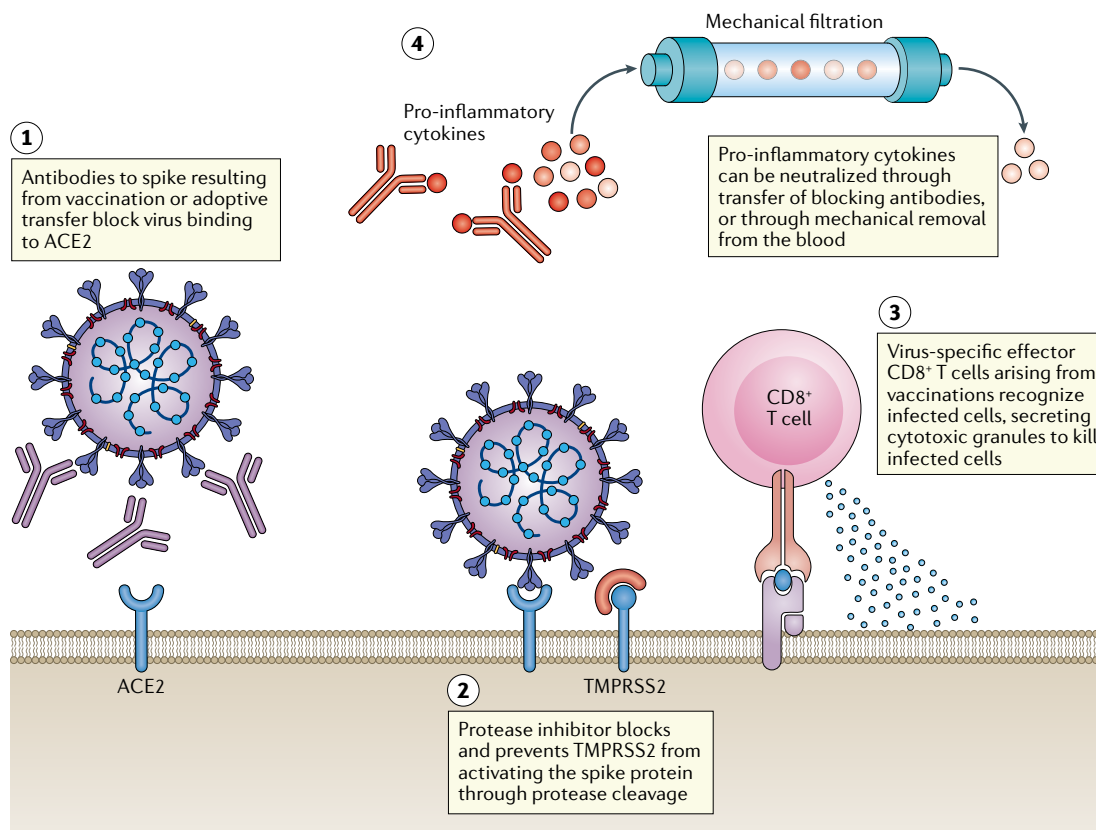


Fig. 3 | Potential therapeutic approaches against SARS-CoV-2. (1) Antibodies against the spike protein (raised through vaccination or by adoptive transfer) could block severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from interacting with the angiotensin-converting enzyme 2 (ACE2) receptor on host cells. (2) Protease inhibitors against the serine protease TMPRSS2 can prevent spike protein cleavage, which is necessary for viral fusion into the host cell. Blocking either ACE2 interaction or viral fusion could prevent the virus from infecting the host cell. (3) Virus-specific memory CD8⁺ T cells from a previous vaccination or infection can differentiate into effector cells during rechallenge. When they identify infected cells presenting virus-specific epitopes, they degranulate and kill infected cells before they can produce mature virions. (4) In a novel treatment method that targets the cytokine storm symptoms, the blood of patients with coronavirus disease 2019 (COVID-19) can be passed through customized columns that are specially designed to trap pro-inflammatory cytokines, before the purified blood is passed back into patients.

efficiency of gas exchange in the lung, causing difficulty in breathing and low blood oxygen levels. The lung also becomes more vulnerable to secondary infections.

In addition to local damage, cytokine storm also has ripple effects across the body. Elevated levels of cytokines such as TNF can cause septic shock and multi-organ failure. These may result in myocardial damage and circulatory failure observed in some patients⁶⁹. Older people (those aged over 60 years) and people with co-morbidities are more likely to develop such a dysfunctional immune response that causes pathology and also fails to successfully eradicate the pathogen. The exact reasons for this are unclear, although one reason may be an ageing lung microenvironment causing altered dendritic cell maturation and migration to the lymphoid organs⁷⁰, and thereby defective T cell activation. In contrast, children tend not to develop severe disease despite being capable of experiencing high viral titres⁷¹. Across all age groups younger than 18 years, more than 50% of children experienced mild symptoms or were asymptomatic, with less than 6% of children developing severe symptoms⁷². Thus, while the aforementioned studies

represent important inroads, a full picture of the critical host immune factors that underlie the development of severer inflammatory responses in some patients remains poorly defined.

It remains controversial whether virus persistence is necessary to drive the ongoing damage. The peak of viral titres in respiratory tract samples might occur even before symptom onset of pneumonia in SARS-CoV and SARS-CoV-2 infections^{17,19}. However, a large retrospective cohort study showed that viral RNA was detectable in non-survivors up until the point of death, suggesting a correlation between virus persistence and poor disease outcome⁶⁰. As viral RNA may linger even after active infection, and is not representative of the infectivity of the virus, whether the poor disease outcome is directly due to large amounts of infectious particles is speculative at this moment. Furthermore, earlier studies of SARS-CoV found that the virus may infect other targets besides lung cells. Notably, virus was found in T lymphocytes⁷³, macrophages^{74–76} and monocyte-derived dendritic cells⁷⁷. Direct virus killing of lymphocytes could contribute to the observed lymphopenia in patients⁷³.

Table 1 | Summary of approved interventional clinical trials for COVID-19 as of March 2020

Clinical trial no.	Location	Title and scope of clinical study
Clinical trials aimed at repairing damage to infected airways		
NCT04273646	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China	Title: Clinical Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19 Scope: use of infused umbilical cord mesenchymal stem cells to repair tissue damage in patients with pneumonia
NCT04288102	Multiple sites in China	Title: Treatment with Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19) Scope: use of infused mesenchymal stem cells to repair tissue damage in patients with pneumonia
NCT04285190	Tasly Pharmaceuticals Inc., China	Title: A Clinical Study to Investigate the Effect of T89 on Improving Oxygen Saturation and Clinical Symptoms in Patients with Coronavirus Disease 2019 (COVID-19) Scope: use of T89 (Dantonic) in patients with COVID-19
NCT04287686	The First Affiliated Hospital of Guangzhou Medical University	Title: Recombinant Human Angiotensin-Converting Enzyme 2 (rhACE2) as a Treatment for Patients with COVID-19 Scope: delivery of rhACE2 to regulate damage mediated by its downregulation by SARS-CoV-2 infection
NCT04275414	Qilu Hospital of Shandong University Jinan, Shandong, China	Title: Bevacizumab in Severe or Critical Patients with COVID-19 Pneumonia Scope: use of bevacizumab (Avastin) in patients with COVID-19
Clinical trials aimed at blocking SARS-CoV-2 infectivity		
NCT04273763	The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China	Title: Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined with Standard Treatment in Patients with Suspected and Mild Novel Coronavirus Pneumonia (COVID-19) Scope: treatment of patients with COVID-19 with bromhexine hydrochloride, umifenovir hydrochloride, recombinant human interferon- α 2b and favipiravir
NCT04280705	USA	Title: Adaptive COVID-19 Treatment Trial Scope: remdesivir treatment of patients with COVID-19
ChiCTR2000030039	Affiliated Hospital of Xuzhou Medical University	Title: Clinical Study for Infusing Convalescent Plasma to Treat Patients with New Coronavirus Pneumonia (COVID-19) Scope: infusion of polyclonal antibodies derived from immune plasma from convalescent patients with COVID-19
NCT04286503	Multiple sites in China	Title: The Efficacy and Safety of Carrimycin Treatment in Patients with Novel Coronavirus Infectious Disease (COVID-19): A Multicenter, Randomized, Open Label Controlled Study Scope: a multicentre, randomized (1:1), open-controlled (one of lopinavir/ritonavir tablets or umifenovir or chloroquine phosphate) study
ChiCTR2000030000	Nanchang Ninth Hospital	Title: An Open, Controlled Clinical Trial for Evaluation of Ganovo Combined with Ritonavir and Integrated Traditional Chinese and Western Medicine in the Treatment of Novel Coronavirus Infection (COVID-19) Scope: use of danoprevir (Ganovo), a macrocyclic peptidomimetic inhibitor of HCV protease, in patients with COVID-19
ChiCTR2000029740	The First Hospital of Peking University	Title: Efficacy of Therapeutic Effects of Hydroxychloroquine in Novel Coronavirus Pneumonia (COVID-19) Patients. Randomized Open-Label Controlled Clinical Trial Scope: use of hydroxychloroquine to test its antiviral and anti-inflammatory effects in patients with COVID-19
ChiCTR2000029559	Renmin Hospital of Wuhan University	Title: Therapeutic Effect of Hydroxychloroquine on Novel Coronavirus Pneumonia (COVID-19) Scope: use of hydroxychloroquine to test its antiviral and anti-inflammatory effects in patients with COVID-19

Table 1 (cont.) | Summary of approved interventional clinical trials for COVID-19 as of March 2020

Clinical trial no.	Location	Title and scope of clinical study
Clinical trials aimed at reducing inflammatory disease		
NCT04273321	Multiple sites in China	Title: Efficacy and Safety of Corticosteroids in COVID-19 Scope: multicentre study analysing the effect of methylprednisolone at a dosage of 1 mg kg ⁻¹ per day for 7 days in patients with COVID-19
NCT04280588	First Affiliated Hospital of Fujian Medical University	Title: Fingolimod in COVID-19 Scope: use of fingolimod, a sphingosine 1-phosphate receptor modulator, in patients with COVID-19
NCT04273581	First Affiliated Hospital of Wenzhou Medical University	Title: The Efficacy and Safety of Thalidomide Combined with Low-Dose Hormones in the Treatment of Severe COVID-19 Scope: testing the anti-inflammatory effects of thalidomide in combination with methylprednisolone in patients with COVID-19-induced pneumonia
NCT04288713	Hudson Medical	Title: Eculizumab (Soliris) in Covid-19 Infected Patients Scope: testing the efficacy of the complement C5 inhibitor eculizumab in patients with COVID-19
NCT04291053	Tongji Hospital	Title: The Efficacy and Safety of Huaier in the Adjuvant Treatment of COVID-19 Scope: testing the anti-inflammatory effects of an extract of <i>Trametes robiniophila</i> Murr (Huaier) in patients with COVID-19
ChiCTR2000030388	Jingzhou First People's Hospital	Title: Efficacy and Safety of Xue-Bi-Jing Injection in the Treatment of Severe Cases of Novel Coronavirus Pneumonia (COVID-19) Scope: analysing the anti-inflammatory effects of an extract from <i>Salvia miltiorrhiza</i> (Chinese red sage) on patients with COVID-19
ChiCTR2000029954	Hubei Hospital of Traditional Chinese Medicine	Title: Efficacy and Safety of Honeysuckle Oral Liquid in the Treatment of Novel Coronavirus Pneumonia (COVID-19) Scope: a multicentre, randomized, controlled, open clinical trial aimed at analysing the impact of honeysuckle oral liquid on boosting immunity against COVID-19
ChiCTR2000029855	The First Affiliated Hospital of Medical College of Zhejiang University	Title: A Randomized, Open and Controlled Clinical Trial for Traditional Chinese Medicine in the Treatment of Novel Coronavirus Pneumonia (COVID-19) Scope: no information available

Data from ClinicalTrials.gov¹⁴⁹. COVID-19, coronavirus disease 2019; HCV, hepatitis C virus; rhACE2, recombinant human angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Viral infection in immune cells such as monocytes and macrophages can result in aberrant cytokine production, even if viral infection is not productive^{74–77}. The degree to which SARS-CoV-2 targets these cells remains poorly defined. Understanding the precise drivers of immune dysfunction is crucial to guide the application of appropriate immunomodulatory treatments.

Several immunosuppressive therapies aimed at limiting immunomediated damage in COVID-19 are at various phases of development and are listed in TABLE 1. Currently, trials of corticosteroids for treatment of COVID-19 are under way⁷⁸, although this class of treatment was not recommended during the 2003 SARS epidemic^{79,80}. A clinical trial of the IL-6 antagonist tocilizumab is also under way to test its efficacy⁸¹, and sarilumab is also being explored⁸². Other clinical trials are also testing the effects of targeting granulocyte-macrophage colony-stimulating factor (GM-CSF), including the use of gimsilumab⁸³, lenzilumab⁸⁴ and namilumab⁸⁵. Another novel adjunctive therapy is

cytosorb⁸⁶, which acts by absorbing a broad spectrum of cytokines, DAMPs and PAMPs in order to reduce their circulating levels and ameliorate immunopathology. Thalidomide, an agent with immunomodulatory properties, has also been successfully administered to a single patient with COVID-19 (REF.⁸⁷). As a result, two clinical trials have now been initiated to test its potential to reduce lung injury^{88,89}. TNF antagonism was suggested but not tested in the context of SARS-CoV infection, and it has not yet been tested in patients with COVID-19 (REF.⁹⁰). A small open-label, non-randomized study suggested that a combination of hydroxychloroquine (a known antimalarial agent) and azithromycin (a common antibiotic) may be beneficial for treating patients with severe COVID-19 (REF.⁹¹). Although hydroxychloroquine's effect on direct inhibition of the virus⁹² and its anti-inflammatory and immunomodulatory activities are known⁹³, whether these mechanisms play a role against COVID-19 remains to be determined⁹⁴.

T cell immunity

Both T and B cell responses against SARS-CoV-2 are detected in the blood around 1 week after the onset of COVID-19 symptoms. CD8⁺ T cells are important for directly attacking and killing virus-infected cells, whereas CD4⁺ T cells are crucial to prime both CD8⁺ T cells and B cells. CD4⁺ T cells are also responsible for cytokine production to drive immune cell recruitment. The first autopsy of a patient with COVID-19 revealed an accumulation of mononuclear cells (likely monocytes and T cells) in the lungs, coupled with low levels of hyperactive T cells in the peripheral blood⁵⁷. Together with reports of lymphopenia and reduced peripheral T cell levels in patients^{6,95–97}, these findings suggest that T cells are attracted away from the blood and into the infected site to control the viral infection. In patients with COVID-19, increased T cell exhaustion and reduced functional diversity predicted severe disease⁹⁸. Despite the impaired response, patients who recovered from SARS-CoV infection developed coronavirus-specific memory T cells, which were found up to 2 years after recovery^{99,100}.

SARS-CoV-specific CD4⁺ T cells express IFN γ , TNF and IL-2, which suggests that patients with SARS-CoV infection exhibit a T_H1 cell response and mainly use cellular immunity to control the infection^{101,102}. Although this pro-inflammatory profile may be an aggravating factor for immunopathogenesis, CD4⁺ T cells have been hypothesized to control SARS, as depletion of these cells in mice resulted in slower clearance of the virus from the host and severer lung inflammation¹⁰³. With the use of a mouse-adapted strain of SARS-CoV, immunization with dendritic cells bearing SARS-CoV peptides resulted in higher numbers of virus-specific CD4⁺ and CD8⁺ T cells that accumulated in the lungs and increased survival^{104,105}. Also, transfer of SARS-CoV-specific CD4⁺ and CD8⁺ T cells into immunodeficient mice resulted in better protection against a mouse-adapted strain of SARS-CoV¹⁰⁵.

Despite evidence for an important role of T cells in controlling infection, several vaccine formulations against SARS-CoV previously tested in animal models showed signs of immunopathology associated with T_H2 cell-mediated eosinophil infiltration^{106,107}. In particular, aged mice that were vaccinated seemed to display increased immunopathology rather than protection¹⁰⁸. Further study of the nature of protective versus detrimental T cell responses is critically needed to determine the optimal T cell engagement strategies for vaccines¹⁰⁹.

Coronavirus-specific T cells are clearly important in eliminating the virus and controlling disease development and should be considered in vaccine strategies. However, whether T cell responses alone are capable of preventing infection in human settings remains to be investigated. This knowledge will be important for vaccine development.

B cell immunity

B cell responses in patients with COVID-19 occur concomitantly with T follicular helper cell responses, from around 1 week after symptom onset¹¹⁰. In patients with SARS-CoV infection, B cell responses typically arise first against the nucleocapsid (N) protein. Within 4–8 days

after symptom onset, antibody responses to S protein are found^{111,112}. Neutralizing antibody responses, likely to the S protein, begin to develop by week 2, and most patients develop neutralizing antibodies by week 3 (REFS^{113,114}). Given that viral titres peak earlier for SARS-CoV-2 than for SARS-CoV^{16–19}, antibody responses may also arise earlier. It seems that a subset of patients may not develop long-lasting antibodies to SARS-CoV-2 (REF¹¹⁵). It remains unknown whether these patients are susceptible to reinfection, of which there are sporadic reports^{116,117}. Antibodies are likely to be effective against SARS-CoV-2: convalescent serum samples have been applied with apparently good clinical results in COVID-19 (REF¹¹⁸) and were also previously used successfully in the treatment of SARS^{119–121}.

While mechanistic correlates of protection have not yet been identified in humans, neutralization of the virus is presumed to be an important mechanism of action for antibodies, although the specific titre and specificity of the antibody repertoire required (for protection) remain undefined. In SARS-CoV, the primary target of neutralizing antibodies is the RBD¹²², comprising a 193 amino acid region (amino acids 318–510) in the S protein, which can independently bind to the host target ACE2 receptor^{35–37}. Although a few previously identified monoclonal antibodies to SARS-CoV also bind to or neutralize SARS-CoV-2 (REF¹²³), the majority do not¹²⁴. This could be due to significant differences in the RBDs of SARS-CoV-2 and SARS-CoV (FIG. 4). In particular, of the 33 amino acids in the region (amino acids 460–492) in the SARS-CoV S protein that contains the critical residues that contact ACE2 (REF¹²⁵), less than half (15/33) are conserved in SARS-CoV-2. Nevertheless, mouse antiserum raised against SARS-CoV protein can cross-neutralize SARS-CoV-2 pseudovirus, indicating overlapping neutralizing epitopes between the two viruses^{28,126}.

In China, hospitals have initiated the use of convalescent plasma as a source of therapeutic polyclonal antibodies for treatment of COVID-19, and early data suggest a positive impact on respiratory viral load and mortality^{127,128}. Efforts are under way to develop therapeutic monoclonal antibodies to SARS-CoV-2, using approaches including phage library display, traditional mouse immunization and hybridoma isolation, and cloning of B cell sequences from convalescent human patients^{129–132}. SARS-CoV does not appear to have strong mechanisms to escape or prevent antibody neutralization, such as glycan shielding of the receptor-binding site against antibody binding¹³³. This is further corroborated by the fact that patients with SARS-CoV infection were generally capable of developing neutralizing antibodies. A recombinant S protein fragment that included the RBD of SARS-CoV showed the highest immunogenicity relative to other recombinant S protein fragments tested, suggesting that the immune system is capable of targeting neutralizing epitopes effectively¹³⁴. Thus, if SARS-CoV-2 behaves like SARS-CoV in this respect, it is likely that these efforts will be successful in developing neutralizing monoclonal antibodies.

It is possible that alterations in the S protein will render SARS-CoV-2 resistant to some monoclonal antibodies, especially as it spreads and mutates. As of now, the entire RBD remains conserved, and there are only four

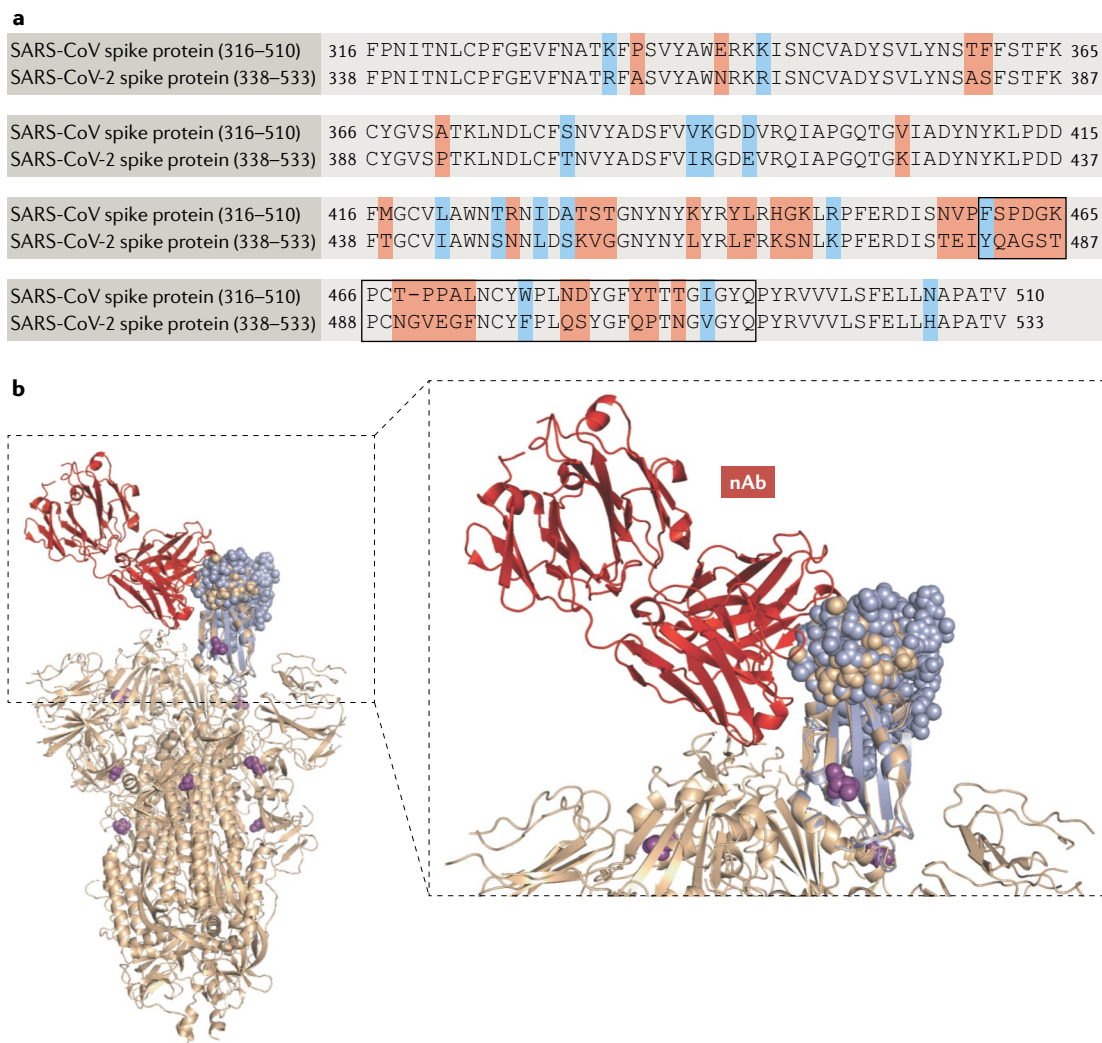


Fig. 4 | Sequence alignment and structural comparison of SARS-CoV and SARS-CoV-2 spike proteins. **a** | Sequence alignment of severe acute respiratory syndrome coronavirus (SARS-CoV) spike protein and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, with conserved amino acid residues shown in black and non-conserved residues shown in colours. **b** | The 3D structure of SARS-CoV-2 (Protein Data Bank ID 6VSB⁴², peach ribbon) is superimposed on the SARS-CoV receptor-binding motif (RBM) complex with the neutralizing antibody (nAb; red ribbon) interfacing with the RBM (Protein Data Bank 2DD8 (REF.¹⁵¹), purple ribbon). Peach and purple spheres denote the RBMs of SARS-CoV-2 and SARS-CoV, respectively. Magenta spheres denote non-synonymous alterations in the SARS-CoV-2 spike protein that have been reported¹³⁵.

known rare non-synonymous alterations in the S protein: V483A, L455I, F456V and G476S¹³⁵. The V483A alteration maps to a similar natural alteration found in MERS-CoV, I529T, where it reduced viral protein binding to the host receptor target and also increased resistance to antibody neutralization from serum samples from patients with MERS¹³⁶. F456V and G476S alterations also map to similar alteration positions in SARS-CoV (L443R and D463G), which were found in a panel of neutralization escape mutants¹³⁷.

However, the selection of therapeutic antibody candidates should include careful consideration of potential unwanted side effects. For example, pre-existing antibodies to other coronaviruses may exacerbate SARS-CoV infections through antibody-dependent enhancement^{138–140}. Also, previous studies in animal models showed that in SARS-CoV infection, neutralizing antibodies

to S protein can potentially augment severe lung injury by exacerbating inflammatory responses¹⁴¹. In addition, a correlation has been observed where development of ARDS coincides with antiviral IgG seroconversion in 80% of patients¹⁹. Patients who developed neutralizing antibodies to S protein earlier in infection had a higher rate of disease; it took an average of only 14.7 days for patients who died of infection to reach their peak levels of neutralizing antibody activity, as opposed to 20 days for patients who went on to recover¹⁴². Similarly, for MERS, patients with severer disease appear to have higher antibody titres than those with mild disease^{143,144}, although one study argues that it is a delay in the development of antibody responses that is associated with disease¹⁴⁵. The binding of antibody–virus immune complexes to activating Fc receptors on alveolar macrophages could induce the expression of pro-inflammatory factors, including

IL-8 and MCP1, which add to the immunostimulatory milieu¹⁴⁶. Such complexes may also activate the complement system and lead to further unwanted inflammation¹⁴¹. As a result, it is important to consider engineering therapeutic antibodies with little or no pro-inflammatory activity but that retain their virus-neutralizing capacity¹⁴⁷. For instance, alterations could be made to the Fc region and/or its glycosylation to change its binding affinity for activating Fc receptors^{146,148}.

Conclusion

This Review has presented the various mechanisms of SARS-CoV-2 infection and COVID-19 immunopathogenesis. Controlling the inflammatory response may be

as important as targeting the virus. Therapies inhibiting viral infection and regulation of dysfunctional immune responses may synergize to block pathologies at multiple steps. At the same time, the association between immune dysfunction and outcome of disease severity in patients with COVID-19 should serve as a note of caution in vaccine development and evaluation. Further studies of the host immune response to SARS-CoV-2 are necessary, including a detailed investigation of the determinants of healthy versus dysfunctional outcomes. These will also help identify biomarkers to define immune correlates of protection and disease severity for effective triage of patients.

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