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Innate immunity: the first line of defense against SARS-CoV-2

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The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus (SARS-CoV)-2, continues to cause substantial morbidity and mortality. While most infections are mild, some patients experience severe and potentially fatal systemic inflammation, tissue damage, cytokine storm and acute respiratory distress syndrome. The innate immune system acts as the first line of defense, sensing the virus through pattern recognition receptors and activating inflammatory pathways that promote viral clearance. Here, we discuss innate immune processes involved in SARS-CoV-2 recognition and the resultant inflammation. Improved understanding of how the innate immune system detects and responds to SARS-CoV-2 will help identify targeted therapeutic modalities that mitigate severe disease and improve patient outcomes.

In 2019, SARS-CoV-2 emerged as a new pathogen that resulted in the COVID-19 pandemic. Initially identified in Wuhan, China in December 2019 (refs. [1,2]), SARS-CoV-2 rapidly spread throughout the world, leading to an ongoing public health crisis, and, as of 2 December 2021, there have been over 263 million infections and 5.2 million deaths[3]. SARS-CoV-2 causes upper and lower respiratory tract infections that are often associated with fever, cough and loss of smell and taste. Most infections remain mild, and up to 20–40% of patients are asymptomatic. However, some patients experience more severe disease and develop systemic inflammation, tissue damage, acute respiratory distress syndrome, thromboembolic complications, cardiac injury and/or cytokine storm, which can be fatal[1,4] (Fig. 1). The risk of COVID-19 disease severity depends on comorbidities (for example, diabetes, hypertension and obesity), age, ethnicity, genetic factors, vaccination status and other conditions[5], making understanding the underlying disease mechanisms important for risk stratification and clinical triage.

The extensive morbidity and mortality associated with the COVID-19 pandemic made the development of SARS-CoV-2 vaccines a global health priority. In less than 1 year, several effective vaccines targeting the SARS-CoV-2 spike protein from multiple platforms (lipid nanoparticle-encapsulated mRNA, inactivated virion or viral-vectored vaccine platforms[6]) gained emergency use authorization (EUA) or approval and were deployed to billions of people worldwide. In countries with high rates of vaccination, markedly reduced numbers of infections, hospitalizations and deaths have been observed, although the success of vaccination has been jeopardized by the emergence of variants including B.1.351 (Beta), B.1.1.28 (Gamma), B.1.617.2 (Delta) and the latest B.1.1.529 (Omicron) and vaccine hesitancy[7]. Compared to vaccine countermeasures, specific treatment options have remained more limited. Remdesivir, a viral polymerase inhibitor, has been approved by the Food and Drug Administration (FDA) for hospitalized patients, and EUA has been granted to the antivirals molnupiravir and paxlovid (combination of nirmatrelvir and ritonavir) as well as baricitinib, a Janus kinase (JAK) inhibitor (in combination with remdesivir); tocilizumab, an anti-interleukin (IL)-6 receptor monoclonal antibody; and sotrovimab and monoclonal antibody cocktails (casirivimab and imdevimab as well as bamlanivimab and etesevimab), which are all neutralizing monoclonal antibodies that bind the viral spike protein. Among these, baricitinib and tocilizumab represent immunomodulatory strategies and have been used along with systemic administration of steroids to control SARS-CoV-2-induced inflammation[8]. Notwithstanding these EUA and approvals, many of these drugs have limited therapeutic indications, and most cases of severe disease worldwide remain untreated with specific drugs.

The innate immune system functions as the first line of host defense against pathogens, including SARS-CoV-2. Innate immune responses limit viral entry, translation, replication and assembly, help identify and remove infected cells and coordinate and accelerate the development of adaptive immunity. Cell surface, endosomal and cytosolic pattern recognition receptors (PRRs) respond to pathogen-associated molecular patterns (PAMPs) to trigger inflammatory responses and programmed cell death that limit viral infection and promote clearance[9]. However, excessive immune activation can lead to systemic inflammation and severe disease. In response to innate immune-dependent viral clearance mechanisms, coronaviruses (CoVs) have evolved evasion strategies to limit host control and enhance replication and transmission[10–13]. Here, we review the innate immune detection and signaling pathways that the host uses against SARS-CoV-2, highlighting the role of viral entry, critical PRRs and signaling pathways, cytokine production and cell death as well as viral immune evasion strategies. An improved understanding of these processes may increase our ability to treat and prevent CoV infections in this pandemic and beyond.

SARS-CoV-2 viral entry and PRR sensing

SARS-CoV-2 is a member of the *Betacoronavirus* genus in the *Coronaviridae* family and is related closely to SARS-CoV and Middle East respiratory syndrome CoV[14,15]. The CoV virion contains spike (S), envelope (E) and membrane (M) proteins in the viral membrane, with genomic RNA complexed with nucleocapsid (N) protein to create a helical capsid. The S protein is a type I glycoprotein that forms peplomers on the virion surface. The E protein is hydrophobic, and the M protein contains a short N-terminal ectodomain with a cytoplasmic tail[14]. The virus also produces several open reading frames (ORFs) that encode accessory proteins with diverse roles in viral pathogenesis[10,11].

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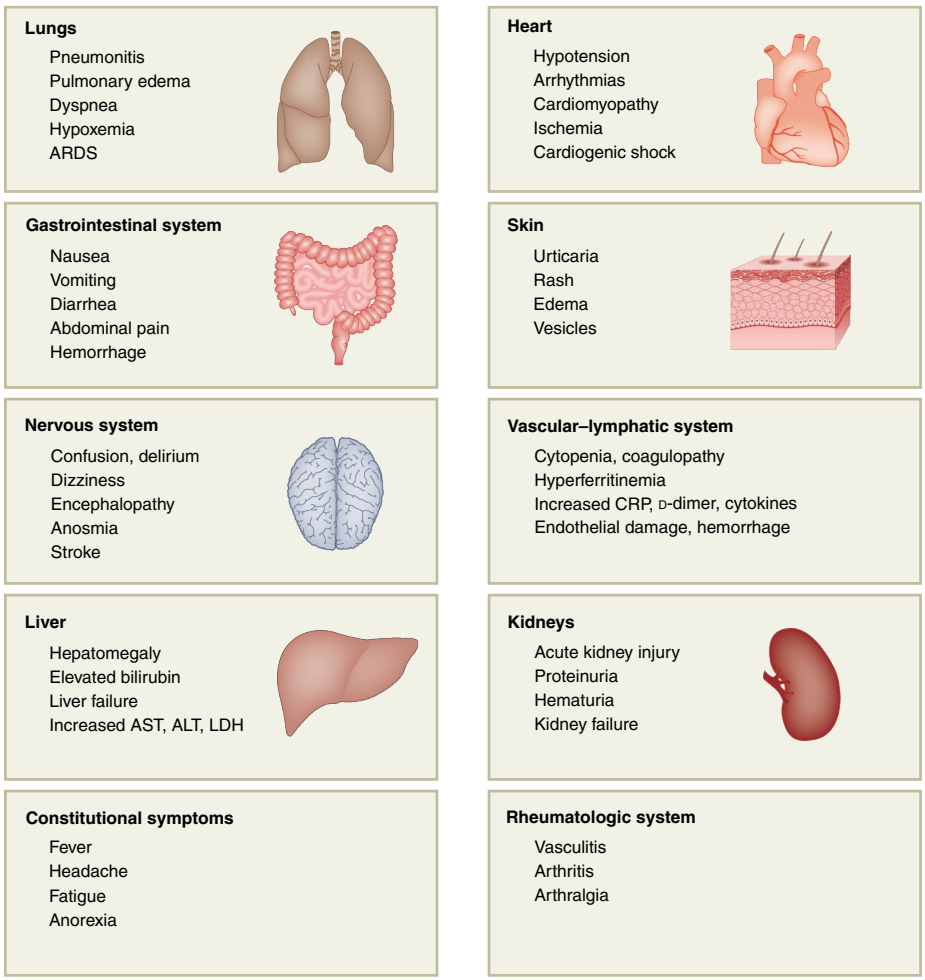

Fig. 1 | Clinical manifestations of COVID-19. SARS-CoV-2 infection affects several body systems, including the cardiovascular, gastrointestinal, nervous, vascular–lymphatic and rheumatological systems and others. ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase.

For infection of most host cells, the SARS-CoV-2 S protein binds to its principal cellular receptor, angiotensin-converting enzyme 2 (ACE2)[2] (Fig. 2). Additionally, the host serine protease TMPRSS2 is important for proteolytic priming of the S protein for receptor interactions and entry[16]. Other host proteins, such as neuropilin-1, heparin sulfate proteoglycans, C-type lectins or furin, can also act as cofactors for viral entry[17–20]. Upon S protein binding to cells, viral and host membranes can fuse[16], releasing viral genomic RNA directly into the cytoplasm. Alternatively, in some cells, SARS-CoV-2 is internalized into endosomes, and, after low pH-triggered cathepsin-mediated cleavage, viral membranes fuse with the endosomal membrane to facilitate nucleocapsid entry into the cytoplasm[21] (Fig. 2). Once in the cytoplasm, SARS-CoV-2 is believed to follow the same route as other CoVs; CoV genomic RNA is translated into two large polyproteins, pp1a and pp1ab, that encode 16 nonstructural proteins (NSPs). These proteins facilitate formation of the viral replication-transcription complex[22,23], which generates an antisense negative-strand template from viral RNA. The NSPs then reorganize membranes derived from the endoplasmic reticulum (ER) and Golgi to form double-membrane vesicles to compartmentalize viral replication and transcription away from host sensor detection[24]. When new viral structural proteins are synthesized, they traffic to the ER or Golgi membranes and combine with genomic RNA and N proteins to create nascent viral particles. Assembly at the ER–Golgi intermediate compartment leads to the creation of virion-containing vesicles that can fuse with the plasma membrane during exocytosis and release virus into the extracellular space[25,26] (Fig. 2). The steps in viral entry and replication present several opportunities for the innate immune system to sense viral components. For example, the virion's S, E and M proteins are exposed to host cell surface sensors during the binding step and host cytoplasmic sensors could detect viral proteins and nucleic acids before their compartmentalization by NSPs. These detection steps facilitate activation of inflammatory signaling pathways, cytokine production and cell death.

Innate immune cells, including macrophages, monocytes, dendritic cells, neutrophils and innate lymphoid cells (ILCs) such as natural killer (NK) cells, are armed with an arsenal of PRRs that recognize PAMPs or damage-associated molecular patterns (DAMPs) to induce inflammatory signaling pathways and immune responses. The five primary PRR families include Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), C-type lectin receptors and absent in melanoma 2 (AIM2)-like receptors[9]. Signaling through these receptors in innate immune cells in response to pathogens, PAMPs or DAMPs leads to production of inflammatory cytokines and chemokines as well as induction of cell death to clear infected cells. To date, several PRRs, in particular, TLRs, RLRs and NLRs and inflammasomes, have been shown to activate their signaling pathways in response to SARS-CoV-2.

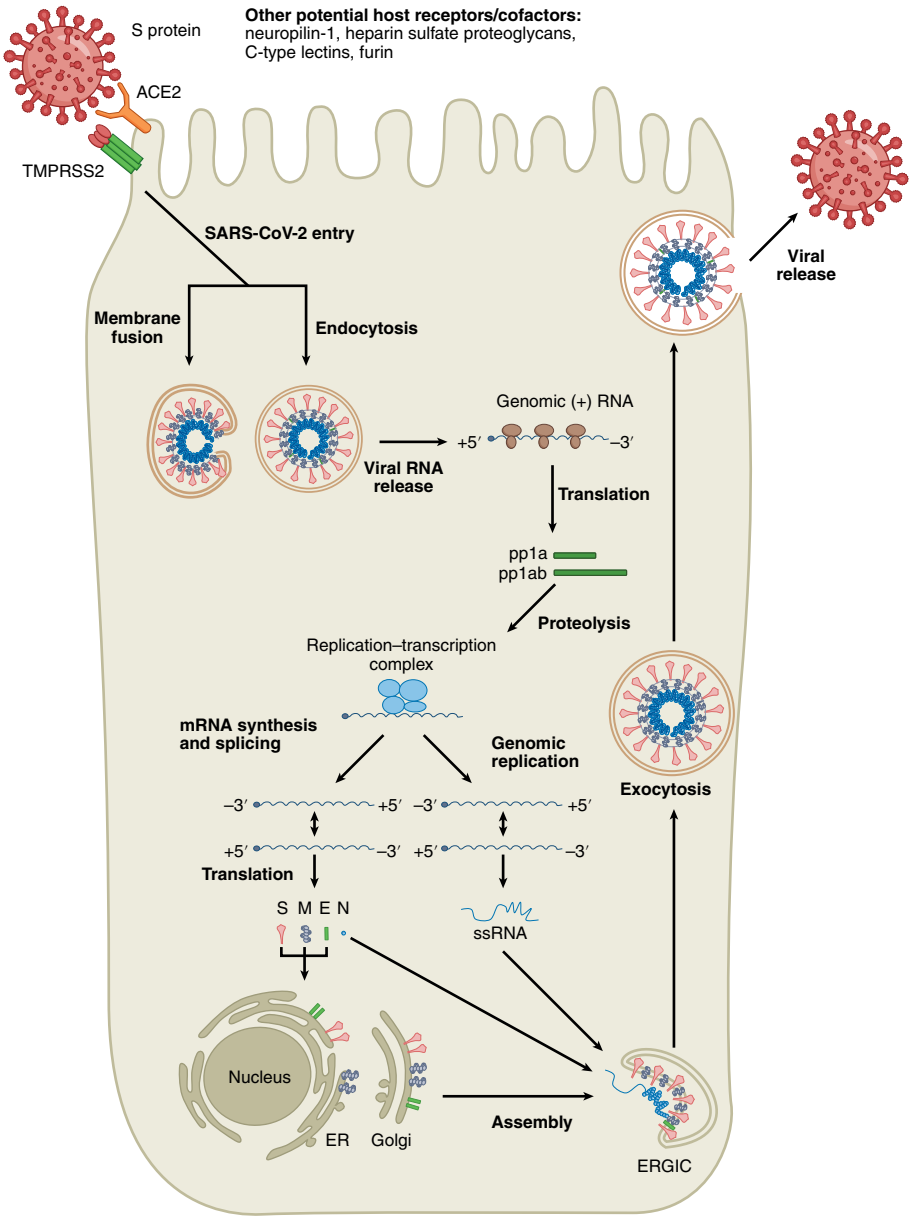

Fig. 2 | SARS-CoV-2 viral entry and replication cycle. On most cells, the SARS-CoV-2 S protein binds to the cell surface and its cognate receptor ACE2. The host serine protease TMPRSS2 helps mediate entry by cleaving S protein. Other potential host receptors and cofactors have been implicated in this process, including neuropilin-1, heparin sulfate proteoglycans, C-type lectins and/or furin. The virion enters through membrane fusion or endocytosis. After entry, viral RNA is released and translated into viral polyproteins pp1a and pp1ab. These polyproteins are processed by virus-encoded proteases to facilitate replication and produce full-length negative-strand RNA and subgenomic RNA. Subgenomic RNA is translated into structural and accessory proteins, including S, M, E and N proteins. Structural proteins are inserted into ER and Golgi membranes and transverse to the ER–Golgi intermediate compartment (ERGIC), where virions can assemble. Fully formed virions are exocytosed. ssRNA, single-stranded RNA.

TLRs and SARS-CoV-2

Many viruses activate the innate immune system through TLR signaling (Fig. 3). TLRs are expressed throughout the human respiratory tract but show heterogeneous expression across innate immune cell populations; for example, TLR3 is more abundant in NK cells, whereas TLR4 is more common in macrophages[27]. TLRs generally transduce signals via two key adaptor molecules, MyD88 and TRIF. Most TLRs use MyD88 to trigger inflammatory cytokine production; TLR3 is the exception and signals exclusively through TRIF. TLR4 is unique in that it can bind and signal through either MyD88 or TRIF[28]. Downstream of MyD88, nuclear factor (NF)-κB, mitogen-activated protein kinases (MAPKs) and interferon (IFN) regulatory factors (IRFs) are activated. Nuclear translocation of these molecules results in transcriptional activation of several pro-inflammatory cytokines including tumor necrosis factor (TNF), IL-6 and IL-1 along with transcription of genes encoding other innate immune sensors, such as NLRP3, and production of IFNs and IFN-stimulated genes (ISGs) (Fig. 3). Signaling through TRIF also activates IFN production and several TLR4- and TLR3-dependent transcription factors, some of which have direct antiviral activity[28].

SARS-CoV-2-mediated induction of pro-inflammatory signaling pathways and cytokine production are attenuated in TLR2-deficient murine macrophages and in human macrophages treated with a

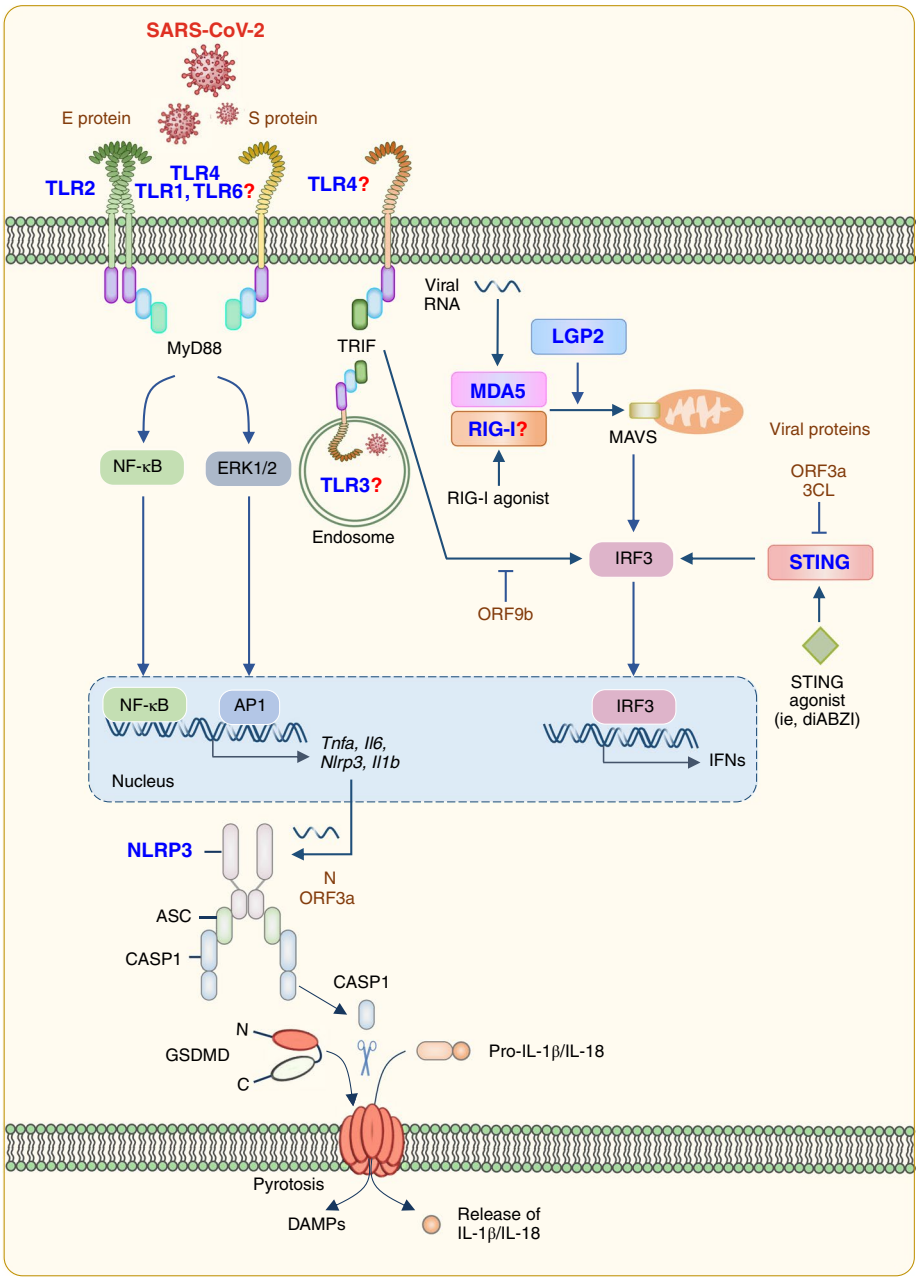

Fig. 3 | Putative activation of PRR signaling during SARS-CoV-2 infection based on current data. PRRs on the cell surface and endosomal membranes and in the cytosol may respond to SARS-CoV-2 PAMPs to activate innate immune signaling pathways. TLR1, TLR2, TLR4 and TLR6 can signal through MyD88 to activate NF-κB and MAPK signaling pathways to induce transcription of genes encoding pro-inflammatory cytokines and other sensors. TLR3 and TLR4 can signal through TRIF to activate IRF3 and induce expression of type I and type III IFNs. Strong experimental evidence supports SARS-CoV-2-mediated activation of TLR2, while activation of TLR1, TLR3, TLR4 and TLR6 has been suggested bioinformatically and through associative studies. Signaling through RIG-I, MDA5 and STING also activates IRF3 and type I and type III IFN production. Data regarding the activation of RIG-I during SARS-CoV-2 infection remain mixed. NLRP3 inflammasome formation also can occur in response to SARS-CoV-2 infection, leading to cleavage of GSDMD to form membrane pores and release IL-1β and IL-18 and induce pyroptosis. Question marks indicate sensors that are expected to be involved in SARS-CoV-2 sensing but that have not been experimentally validated to date. CASP, caspase.

TLR2 inhibitor following stimulation with the SARS-CoV-2 E protein, suggesting that TLR2 senses the E protein to mount inflammatory responses[29,30]. Furthermore, the SARS-CoV-2 E protein induces TLR2-dependent inflammation in vivo, as serum levels of IL-6 are reduced in *Tlr2*$^{-/-}$ mice upon administration of the E protein[29]. An independent single-cell computational analysis aimed at predicting targets that could be modulated to reduce the dysregulated innate immune response during SARS-CoV-2 infection also suggests that TLR2 is involved in innate immune activation[31]. Consistent with these findings, treatment of K18-hACE2 transgenic mice with a TLR2 inhibitor reduces levels of inflammatory cytokines in the blood and improves survival following SARS-CoV-2 infection[29]. However, additional work is required to determine whether TLR2 directly binds the E protein or other SARS-CoV-2 ligands.

Beyond TLR2, the role of other TLRs in SARS-CoV-2 infection has not been as conclusively studied in vitro and in vivo. In the context of SARS-CoV, the TLR3 signaling pathway has a protective role in vivo[26,32–34]; *Tlr3*$^{-/-}$ mice have increased viral burden and impaired

pulmonary function compared to control mice during infection with mouse-adapted SARS-CoV (MA15)[34]. Additionally, stimulation with a TLR3 agonist reduces SARS-CoV burden in human alveolar epithelial cells[32]. However, no studies to date have linked TLR3 with SARS-CoV-2 sensing specifically. While one genomic analysis of patients with severe COVID-19 found an association between inborn errors in TLR3 and disease severity[35], a follow-up study failed to validate these associations[36]. Therefore, the role of TLR3 in SARS-CoV-2 infection remains unclear.

In silico studies suggest that the SARS-CoV-2 S protein may bind to TLR1, TLR4 and TLR6, with TLR4 having the highest affinity[37]. TLR4 activation in response to the S protein is supported by reduced gene expression of *Il1b* in S protein-stimulated *Tlr4*$^{-/-}$ murine macrophages compared with expression in wild-type cells in vitro[38]. However, computational modeling and in vitro analyses show that the S protein has high binding affinity to lipopolysaccharide[39], raising concerns that lipopolysaccharide may contaminate purified S protein preparations and contribute to the release of cytokines in a TLR4-dependent manner. Therefore, whether TLR1, TLR4 or TLR6 can directly sense the S protein requires further confirmation.

Additionally, TLR7 and TLR8 recognize antiphospholipid antibodies[40,41], which are upregulated in patients with severe COVID-19 (refs. [42,43]). X chromosomal *TLR7* genetic anomalies have been linked to severe COVID-19 disease in young individuals[44,45], suggesting that TLR7 has a protective role during SARS-CoV-2 infection. More investigations are needed to corroborate the roles of these and other TLRs in response to SARS-CoV-2 infection.

SARS-CoV-2, RLRs and IFN signaling

Single-stranded RNA derived from genomic, subgenomic or replicative intermediates of SARS-CoV-2 can also be sensed by RLRs intracellularly, which include MDA5, RIG-I and LGP2 (refs. [46–49]) (Fig. 3). RIG-I and MDA5 are the most well-studied RLRs and provide key regulation of IFN pathways. Following post-translational modifications and activation, RIG-I and MDA5 translocate to the mitochondria, where they interact with the adaptor protein mitochondrial antiviral signaling (MAVS) to form a MAVS signalosome. This complex formation activates TNF receptor-associated factor (TRAF)3, TANK-binding kinase (TBK)1 and IκB kinase (IKK) to induce phosphorylation of IRF3 (refs. [50,51]), which facilitates its nuclear translocation and the transcription of genes encoding type I and III IFNs (Fig. 3). Production and subsequent release of IFNs stimulate downstream signaling through IFN receptors (IFNAR1 and/or IFNAR2 for type I IFNs, IFNLR1 and/or IL10Rβ for type III IFNs) in an autocrine and paracrine manner to produce hundreds of ISGs with various antiviral functions[52,53]. For example, the ISG Ly6E can prevent SARS-CoV-2 entry[54], and members of the IFIT family, IFIT1, IFIT3 and IFIT5, inhibit viral replication, and bone marrow stromal cell antigen (BST)2 can block viral egress[55] in cell lines that ectopically or stably express these ISGs. Circulating autoantibodies that target type I IFN have also been identified; patients with these have reduced IFN responses after SARS-CoV-2 infection[56] and are at increased risk of severe COVID-19 and death[57–59]. However, fine tuning of a type I IFN response is critical because both overactivation and underactivation of IFN signaling can be deleterious to the host[60].

A screen for RNA sensors involved in restriction of SARS-CoV-2 infection identified MDA5 and LGP2 as key regulators of antiviral type I IFN induction[46]. Silencing or deleting genes encoding MDA5, LGP2 or the adaptor MAVS in human primary lung airway epithelial or Calu-3 cells results in reduced type I IFN expression during SARS-CoV-2 infection[46–48]. By contrast, there are conflicting results with RIG-I. One study found that small interfering RNA silencing of the gene encoding RIG-I failed to reduce IFN-β production in response to SARS-CoV-2 infection in Calu-3 cells[46], and its genetic deletion by CRISPR–Cas9 targeting in Calu-3 cells provided similar results[48]. However, another study reported that small interfering RNA silencing of the gene encoding RIG-I in Calu-3 cells significantly reduced IFN-β expression during SARS-CoV-2 infection[49]. Instead of engaging the C-terminal domain of RIG-I that normally senses viral RNA, the SARS-CoV-2 genomic RNA 3′ untranslated region is recognized by the helicase domain, resulting in impaired ATPase activation of RIG-I[61]. This unconventional RIG-I engagement may limit its ability to activate the downstream MAVS signaling pathway for type I IFN production[61], although additional confirmatory studies are required.

SARS-CoV-2, NLRs and inflammasome sensors

NLRs also are reported to respond to SARS-CoV-2 infection and induce production of type I IFNs and pro-inflammatory cytokines. NLRP3, one of the best characterized inflammasome sensors, is triggered in response to PAMPs and DAMPs, leading to activation of caspase-1, production and release of bioactive IL-1β and IL-18 and cleavage of gasdermin (GSDM) D, which forms pores in the plasma membrane to drive membrane rupture, mediated by ninjurin 1, and pyroptotic cell death[62,63]. Increased levels of IL-1β and IL-18 in plasma correlate with disease severity and mortality in patients with COVID-19 (refs. [64,65]), and several reports have suggested that NLRP3 senses CoV infection[26,66–70].

NLRP3 deficiency abolishes murine hepatitis virus-induced caspase-1 and GSDMD activation in murine macrophages[66], indicating that CoVs may induce NLRP3 inflammasome assembly. Several PAMPs from SARS-CoV, including those derived from ORF3a[67], ORF8b[68], the E protein[69] and viral RNA[70], can activate the NLRP3 inflammasome. In the case of SARS-CoV-2 infection, monocytes and lung tissues from patients with COVID-19 contain NLRP3 and apoptosis-associated speck-like protein containing a caspase-activating and recruitment domain (CARD) (ASC) puncta[71], suggesting that the NLRP3 inflammasome forms in these patients. Additionally, human primary monocytes infected with SARS-CoV-2 show NLRP3-dependent caspase-1 and GSDMD cleavage and IL-1β maturation[71,72].

Several PAMPs from SARS-CoV-2 are implicated in NLRP3 inflammasome assembly and subsequent cytokine release (Fig. 3). GU-rich single-stranded RNA derived from the SARS-CoV-2 genome activates the NLRP3 inflammasome and cytokine release in macrophages[70]. SARS-CoV-2 ORF3a, also known as viroporin, and the N protein also trigger NLRP3 inflammasome activation in human cell lines (HEK293 cells with or without inflammasome machinery transfected and A549 cells) (refs. [73,74]). Despite its ability to induce NLRP3 inflammasome activation, the N protein has also been associated with inhibition of GSDMD to block pyroptosis and IL-1β release[75], and the direct role of the N protein in IL-1β release remains to be clarified. Upstream, the SARS-CoV-2 E protein triggers TLR2 signaling, which upregulates expression of *Nlrp3* and *Il1b* mRNA in macrophages[29]. Additionally, the S protein upregulates NLRP3 protein expression and induces release of IL-1β in macrophages obtained from patients with COVID-19 but not in those from healthy volunteers[76]. Mechanistically, it has been proposed that SARS-CoV-2 infection causes an imbalance in intracellular potassium efflux to drive NLRP3 inflammasome activation and IL-1β and IL-18 release[72]. Nonetheless, the role of specific SARS-CoV-2 proteins in triggering this imbalance remains to be characterized.

Beyond NLRP3, microscopy studies also have shown colocalization of the AIM2 inflammasome sensor with ASC specks in monocytes from patients with COVID-19 (refs. [77]), although the functional role of AIM2, a DNA sensor, remains unclear in this context. The intracellular sensor of bacterial peptidoglycan, NOD1 (NLRC1), also contributes to SARS-CoV-2 responses and cytokine production. Silencing the gene encoding NLRC1 in lung epithelial cells reduces IFN-β expression during SARS-CoV-2 infection[46]. Additional studies are needed to establish the importance of other

NLRs and inflammasome sensors in sensing SARS-CoV-2 and producing cytokines.

cGAS, STING and SARS-CoV-2 infection

Beyond TLRs, RLRs and NLRs, there are additional cytosolic sensors that can detect viruses and activate pro-inflammatory signaling pathways. The cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) signaling pathway, which is activated upon detection of cytoplasmic DNA, is critical for limiting the replication of both DNA and RNA viruses following infection[78–83]. SARS-CoV-2 infection induces mitochondrial damage[84], which may release mitochondrial DNA into the cytoplasm to activate cGAS, contributing to innate immune responses. However, SARS-CoV-2 accessory proteins ORF3a and 3CL can antagonize cGAS–STING signaling, thereby suppressing antiviral immune responses[85] (Fig. 3). Indeed, restoration of cGAS–STING activation and signaling by administering the exogenous STING agonist diABZI inhibits SARS-CoV-2 replication and improves survival rates in infected human ACE2-expressing transgenic mice[86,87], emphasizing the importance of a robust signaling response to prevent viral spread.

Cytokine signaling, cell death and cytokine storm

PRR signaling engaged by SARS-CoV-2 induces concurrent release of both IFNs and other pro-inflammatory cytokines[88]. Expression of numerous pro-inflammatory cytokines and IFNs is elevated in patients with COVID-19, including that of IL-1β, IL-6, TNF, IL-12, IFN-β, IFN-γ, IL-17 and others[1,89,90]. These cytokines aid in clearing infections but also maintain cellular homeostasis. For instance, transient activation of inflammatory cytokine receptors and, in particular, IL-1 signaling stimulates insulin secretion from pancreatic beta cells, allowing the beta cell to adapt to increased insulin demand during stress[91]. However, dysregulated release of pro-inflammatory cytokines contributes to cytokine storm, defined as a life-threatening condition caused by excessive production of cytokines mediated by inflammatory cell death (PANoptosis)[4]. In the context of COVID-19, the combination of TNF and IFN-γ contributes to disease pathogenesis by signaling cooperatively and inducing inflammatory cell death (PANoptosis)[92] (Fig. 4). PANoptosis is an innate immune inflammatory programmed cell death pathway dependent on PANoptosomes, caspase(s)-containing complexes with or without inflammasome components and RHIM-containing proteins. This cell death pathway cannot be accounted for by pyroptosis, apoptosis, or necroptosis [66,92–109]. PANoptosis induced by the synergism of TNF and IFN-γ depends on signal transducer and activator of transcription (STAT)1 and IRF1 signaling and leads to activation of caspase-8 to drive cell death[92,93] (Fig. 4). The combination of TNF and IFN-γ signaling induces a lethal shock syndrome in mice[92,110], which mirrors the cytokine storm observed in some patients with severe COVID-19 (ref. [92]). Mice treated with blocking antibodies specific to TNF and IFN-γ have reduced mortality during SARS-CoV-2 infection as well as in other models of cytokine storm[92]. A computational analysis of more than 300,000 single-cell transcriptomes concluded that transcriptional programs of macrophages from patients with COVID-19 share many features with macrophages stimulated ex vivo with TNF and IFN-γ, including high levels of *STAT1*, *IFNGR1*, *IFNGR2*, *NFKB1* and *IL1B*[111]. The abundance of these inflammatory macrophages is associated with disease severity in patients with COVID-19 as well as in patients with autoimmune disease (rheumatoid arthritis) and inflammatory disease (Crohn's disease and ulcerative colitis)[111]. Overall, these studies suggest that a positive feedback loop exists, in which cytokine secretion causes PANoptosis that results in more cytokine release, culminating in a cytokine storm that causes life-threatening damage to host tissues and organs[4,92] (Fig. 4). Pathogens, PAMPs, DAMPs and homeostatic perterbations can all trigger PANoptosis[66,92,94–98,100,105,109], which could initiate this feedback loop and promote inflammation and disease progression.

The link between the excessive cytokine signaling and inflammatory cell death could explain the multiorgan damage observed in some patients with COVID-19. For example, lung damage and acute respiratory distress syndrome occur in many patients with severe COVID-19. Mounting evidence suggests that structural damage to endothelial cell membranes and ensuing vascular leakage contribute to the initiation and propagation of acute respiratory distress syndrome during SARS-CoV-2 infection[112]. Additionally, vascular damage, including damage to heart vessels, is a key feature of an unprecedented cluster of hyperinflammatory shock syndromes in children with COVID-19 that is similar to Kawasaki disease and is termed multisystem inflammatory syndrome in children (MIS-C)[113,114]. MIS-C could be a result of endothelial cell damage and death triggered by cytokines, possibly due to the effects of TNF and IFN-γ. Moreover, endothelial cell-associated anticoagulant pathways can be impaired by pro-inflammatory cytokines[115], which could explain some of the thromboembolic complications reported during severe COVID-19 (refs. [116,117]), providing yet another pathogenic mechanism for cytokines in tissue damage.

Another feature of COVID-19 is a depletion of germinal centers in the spleen and lymph nodes[118], which may be due to lymphocyte cell death promoted by TNF and IFN-γ signaling. TNF and IFN-γ shock can drive lymphopenia and immunosuppression[92,119], and high amounts of TNF are found in the remaining germinal centers of patients with severe COVID-19, which could limit B cell affinity maturation, isotype switching and production of mature antibodies[118], leading to detrimental effects on patient outcomes[120].

While accumulating evidence suggests that high levels of cytokines are associated with COVID-19 morbidity and mortality, some studies have questioned whether cytokine storm occurs in COVID-19 (ref. [121]). For example, one group reported lower levels of IL-6 in patients with COVID-19 than in those with sepsis or chimeric antigen receptor T cell-induced cytokine storm syndromes[122]. RNA-seq analysis has revealed reduced cytokine expression in peripheral blood mononuclear cells of patients with COVID-19 compared to that in those infected with influenza virus[123], whereas another group found increased expression of TNF and IL-1 in COVID-19 (ref. [124]). However, the conclusions of these studies are based on comparisons among patients with cytokine storm-associated diseases and not comparisons with healthy individuals[122,123]. Given that SARS-CoV-2 is a respiratory virus, the cytokine profile in the local tissue environment may be more informative than interrogation of peripheral blood samples, which has been used in most studies to date. Indeed, markedly increased levels of pro-inflammatory cytokines and chemokines were observed in lung homogenates from human ACE2-expressing transgenic mice after SARS-CoV-2 infection[125]. Additionally, a study examining the local immune response in nasal wash samples from ferrets infected with SARS-CoV-2 found increased levels of IL-6, IL-1 and other chemokines in cells infected with SARS-CoV-2 compared to cells infected with influenza virus on day 7 after infection[12]. Overall, while cytokines are critical for the innate immune response and successful clearance of viral infections, their release must be controlled to prevent systemic cytokine storm and pathogenic inflammation during SARS-CoV-2 infection.

Viral innate immune evasion strategies

One primary function of the innate immune system during viral infection is to induce an inflammatory response that limits viral replication. However, CoVs have evolved several evasion strategies to counteract this host defense. SARS-CoV-2 can specifically evade antiviral innate immune responses by reducing IFN levels; patients with mild and moderate COVID-19 have low levels of type I and III IFNs in their serum[12]. Indeed, SARS-CoV-2 infection limits type I and III IFN production at post-transcriptional levels by preventing the release of mRNA from sites of transcription and/or triggering transcript degradation in the nucleus[13].

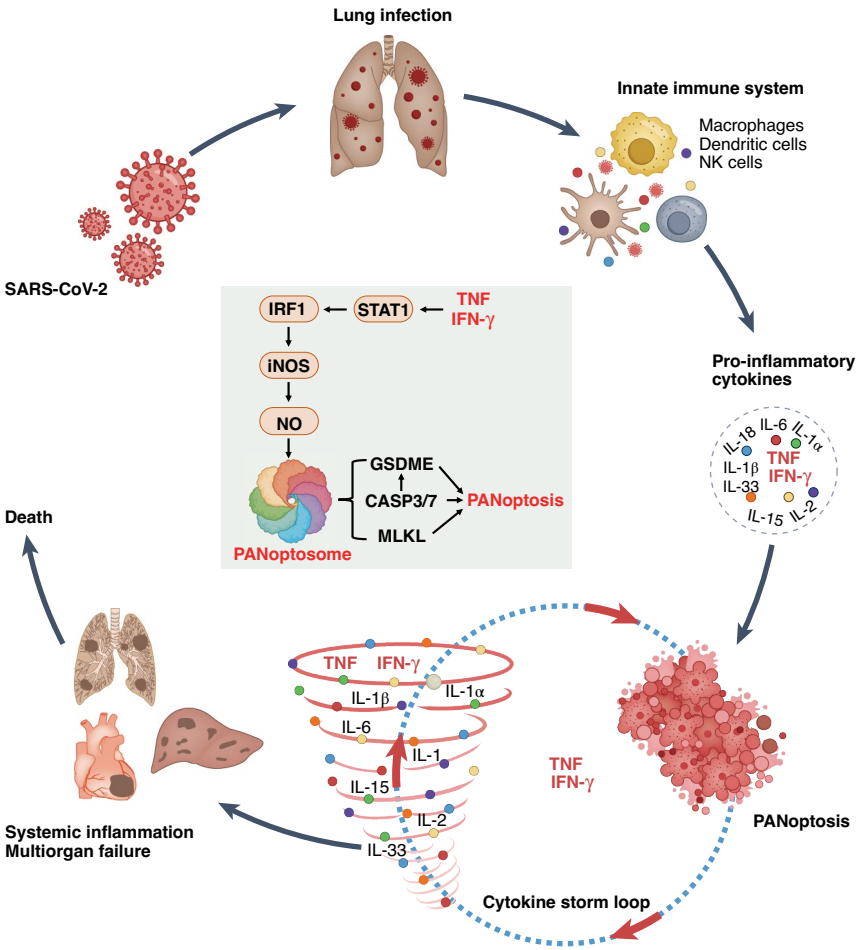

Fig. 4 | PANoptosis and cytokine storm during SARS-CoV-2 infection. Induction of innate immune signaling during SARS-CoV-2 infection leads to the production of pro-inflammatory cytokines. TNF and IFN-γ induce a form of inflammatory cell death called PANoptosis, which is mediated through formation of a multiprotein complex called the PANoptosome. TNF and IFN-γ-mediated PANoptosis can lead to a cytokine storm (CS) loop, featuring further pathogenic cytokine release that can perpetuate PANoptosis as well as systemic inflammation, multiorgan failure and lethality. iNOS, inducible nitric oxide synthase; MLKL, mixed lineage kinase domain-like pseudokinase.

SARS-CoV-2 also encodes several proteins that disrupt RLR sensing pathways and IFN induction, signaling or effector functions. For example, SARS-CoV-2 papain-like protease (PLpro) inhibits MDA5 activation by de-ISGylating MDA5, as ISG15 conjugation, or ISGylation, of the MDA5 CARD domain is essential for its activation following infection with RNA viruses[126]. Additionally, SARS-CoV-2 ORF9b and N and M proteins can inhibit expression of IFN-β and pro-inflammatory cytokines by interfering with RIG-I and MDA5 pathways[11,127–130]. ORF9b also can block the TLR3–TRIF pathway[129]. ORF3b suppresses induction of type I IFN more efficiently than its SARS-CoV ortholog[10]. SARS-CoV-2 ORF6 and ORF8 inhibit expression of IFN-β and activation of ISGs[11]. SARS-CoV-2 NSP1 and NSP14 and potentially other viral proteins can inhibit translation and prevent expression of components of the IFN signaling pathway[131–133]. Finally, the SARS-CoV-2 N protein appears to prevent aggregation of viral RNA with MAVS to block induction of the IFN pathway[134]. Gaining further insights into SARS-CoV-2 immune evasion strategies and the PRRs and IFN and cytokine-production pathways that can counteract them could provide further mechanistic targets for therapeutic development.

Innate immunity and therapeutic development

During the COVID-19 pandemic, many treatment strategies have been investigated. The rate of clinical trials for COVID-19 has been staggering, with over 7,000 registered through https://clinicaltrials.gov/ as of 2 December 2021. In addition to vaccine strategies, which have been extensively covered elsewhere[135], therapeutic strategies can be divided into antiviral or immunomodulatory therapies (Table 1). Clinical trials of these treatments have led to FDA approval of remdesivir and EUA for the antivirals molnupiravir, paxlovid (combination of nirmatrelvir and ritonavir), sotrovimab and monoclonal antibody cocktails[8]. These compounds target the virus by blocking or disrupting viral replication, preventing viral entry by binding the S protein or promoting viral clearance through antibody Fc effector functions[136–138]. In addition, antiviral strategies that modulate immune cell activation and inflammation have also been investigated. In particular, treatment with type I IFNs has been tested in several clinical trials. IFN-α2b treatment reduced the time to viral clearance in the upper respiratory tract and the time to resolution of systemic inflammatory markers in an exploratory study[139]. A retrospective study found that administration of IFN-α2b within 5 d of hospitalization was associated with a decrease in mortality[140]. However, this study also found that later administration was associated with increased mortality[140]. Similarly, preclinical studies showed that exogenous type I IFN therapy reduces viral load when administered before SARS-CoV-2 infection, but this effect is limited once infection is established[141]. These results highlight the importance of understanding disease pathogenesis to identify

Table 1 | Approved and experimental treatment strategies for COVID-19

Category	FDA approved or EUA	Under investigation
Antivirals	Remdesivir; molnupiravir; paxlovid (combination of nirmatrelvir and ritonavir); sotrovimab; anti-spike monoclonal antibody cocktails (REGEN-COV [casirivimab–imdevimab]; bamlanivimab–etesevimab[a])	Chloroquine and/or hydroxychloroquine; IFN-α, IFN-β, IFN-λ therapy; STING agonists; RIG-I agonists
Cytokine inhibition	Anti-IL-6 antibody (tocilizumab)	Anti-IL-6 antibody (sarilumab; siltuximab; levilimab)
		Anti-IL-1 therapy (canakinumab; anakinra; rilonacept)
		Anti-TNF antibody (infliximab; adalimumab; certolizumab; etanercept; golimumab)
		Anti-IFN-γ antibody (emapalumab)
Inflammatory signaling inhibition	Baricitinib	Dexamethasone

[a]On 25 June 2021, the FDA issued a pause on the distribution of bamlanivimab–etesevimab due to lack of efficacy against the Beta and Gamma viral variants.

therapeutic windows for treatments. Type I IFN has also been given in combination with other antivirals and shown to improve patient outcomes[142]. Additional evidence suggests that treatments that upregulate endogenous type I IFN production may also be beneficial. For instance, preclinical studies found that IFN signaling triggered by treatment with the STING agonist limited SARS-CoV-2 infection[86,87,143]; similar results were observed with a RIG-I agonist[144]. In theory, STING or RIG-I agonists could be repurposed as prophylactic agents for vulnerable patient populations.

Treatment with type III IFN also might be advantageous during SARS-CoV-2 infection. While IFN-λ was found to induce lung epithelial barrier damage in response to viral infection in murine models[145], increased IFN-λ1 and IFN-λ2 levels in serum are associated with better prognosis for patients with COVID-19 in observational studies[146,147]. On a cellular level, pretreatment of human primary airway epithelial cells, Calu-3 cells, intestinal epithelial cells and colon organoids with IFN-λ reduces levels of SARS-CoV-2 infection[148–150], and loss of the type III IFN receptor increases cellular susceptibility to infection[149]. In a murine model of SARS-CoV-2 infection, treatment with Peginterferon Lambda-1a, a pegylated, recombinant IFN-λ1a, reduced SARS-CoV-2 replication in mice[150]. Based on these preclinical data, clinical trials have begun investigating Peginterferon Lambda-1a treatment in patients with COVID-19. Among patients with mild disease in a phase 2 trial, there were no significant differences in time to resolution of symptoms or other clinical metrics between Peginterferon Lambda-1a and placebo groups[151]. However, a second phase 2 trial found that treatment with Peginterferon Lambda-1a improved the odds of achieving viral clearance by day 7 (ref. [152]). Further studies are needed to determine whether IFN-λ treatment is advantageous for particular patient populations.

In addition to the antiviral therapies discussed above, immunomodulatory therapies have been extensively evaluated in clinical trials for COVID-19 due to the pathogenicity associated with excess cytokine production, cell death and cytokine storm. Corticosteroids, such as dexamethasone, can inhibit the production of pro-inflammatory cytokines and prevent systemic inflammation. However, the large randomized open-label phase 2–3 RECOVERY trial evaluating treatment strategies in hospitalized patients showed that dexamethasone was effective only in patients requiring mechanical ventilation or supplemental oxygen[153]. Moreover, prolonged use or overuse of corticosteroids can generally increase the risk of secondary infections, although studies in patients with COVID-19 have reported conflicting results to date[154,155]. A more targeted approach of modulating immune responses may be preferable. To this end, many anti-cytokine therapies have been evaluated, leading to EUA for the anti-IL-6 receptor-blocking antibody tocilizumab in hospitalized patients receiving systemic corticosteroids and requiring supplemental oxygen, ventilation or extracorporeal membrane oxygenation[8]. Elevated IL-6 levels are associated with disease severity[1,89,90], as are increases in the downstream marker of inflammation, C-reactive protein (CRP)[156]. CRP is functionally linked to complement activation and inflammatory processes[157], and IL-6 is known to play both protective and pathological roles in the immune response to viral infection through its control of gene expression and signaling pathways[158]. However, clinical trial results with anti-IL-6 therapies in COVID-19 have been mixed, with phase 3 COVACTA and REMDACTA (tocilizumab) and Kevzara and SARTRE (sarilumab) trials failing to improve clinical status or reduce mortality[159–162] and the phase 3 EMPACTA trial of tocilizumab reducing the number of patients requiring ventilation but not improving mortality[163]. The phase 3 REMAP-CAP trial did find tocilizumab and sarilumab to be superior to the control in increasing the number of organ support-free days for patients in the intensive care unit as well as showing an improvement in their 90-d survival[164]. Due to these conflicting findings, more studies are likely needed to identify the particular patient population or disease stage that would benefit the most from anti-IL-6 treatment.

Growing evidence suggests the importance of inflammasome-dependent cytokines in COVID-19 pathogenesis[64,65,67–72], and anti-IL-1 therapies also have been evaluated. An observational study found that canakinumab, an anti-IL-1β antibody, can lead to clinical improvement for hospitalized patients with COVID-19 (ref. [165]), but a more recent randomized phase 3 study found no difference between canakinumab and control groups for survival without ventilation[166]. The phase 3 study only used a single canakinumab infusion, whereas the observational study used two infusions, which may have impacted the findings. Anakinra, an IL-1 receptor antagonist, has also been evaluated. While earlier studies failed to show an effect[167], an open-label trial reported a reduction in inflammatory markers in patients who received anakinra[168], and a retrospective analysis found that early treatment with anakinra with or without glucocorticoids reduced mortality compared to standard-of-care treatment[169].

Given the possible contribution of TNF to COVID-19 pathogenesis[1,89,90,92], several anti-TNF antibodies are under evaluation in clinical trials. Case studies have suggested that anti-TNF therapies may confer protection as prophylaxis, as patients on anti-TNF treatment for rheumatic diseases who became infected with SARS-CoV-2 tended to have lower rates of hospitalization[170]. IFN-γ is another critical cytokine in COVID-19 pathogenesis[1,89,90,92], and the anti-IFN-γ antibody emapalumab, which is FDA-approved for hemophagocytic lymphohistiocytosis, is also being evaluated as a COVID-19-treatment strategy. This therapeutic approach may be linked mechanistically to preclinical data showing that combination of anti-TNF and anti-IFN-γ treatment can decrease clinical features of cytokine storm driven by PANoptosis and reduce

SARS-CoV-2-associated death in mice[92]. Additionally, targeting the pro-inflammatory JAK–STAT signaling pathway in PANoptosis is a potential strategy to mitigate disease[92]. Indeed, baricitinib, a JAK1–JAK2 inhibitor, was granted EUA for treatment of COVID-19 based on results of the phase 3 ACTT-2 trial in hospitalized patients[171]. Baricitinib treatment combined with remdesivir was better than remdesivir alone in reducing recovery time in these patients[171], highlighting the utility of blocking inflammatory signaling as a therapeutic strategy.

Beyond targeting specific cytokines, other strategies have focused on harnessing the power of 'trained immunity', which describes the long-term functional reprogramming of innate immune cells following activation that results in enhanced responses to subsequent infections[172]. This is seen most clearly in the *Bacillus* Calmette–Guérin (BCG) vaccination strategy, in which patients are immunized with an anti-tuberculosis vaccine, and nonspecific protective effects can carry over to reduce the risk of respiratory infections[173]. In the context of COVID-19, correlative studies have suggested that countries with childhood BCG vaccination programs may have reduced rates of disease[174,175], and a study of healthcare workers revealed decreased rates of SARS-CoV-2 infection in those who had previously received the BCG vaccine[176]. However, some results have been contradictory[177], and randomized controlled trials are ongoing to confirm whether this type of trained immunity strategy should be pursued.

Overall, targeting innate immunity has been a focus of COVID-19 disease interventions, although treatments to date have had limited success. Due to various aspects of disease associated with SARS-CoV-2 infection and the ensuing host response, some therapeutics may be more beneficial in certain stages of disease. Identifying which therapies to use and when to implement them will likely be critical for successful treatment. Additionally, combination therapies (including with antiviral antibodies) or targeting multiple cytokines concurrently may have added benefits, and these strategies should continue to be evaluated.

Summary and future directions

In spite of rapid advances in basic and translational science in the past 2 years, SARS-CoV-2 and COVID-19 continue to pose an important global health threat. Innate immune cells, including ILCs that reside in the mucosal epithelia, are an essential first line of defense against SARS-CoV-2 infection. Preliminary clinical studies have shown that worsened disease severity and increased risk of hospitalization are associated with reductions in ILC abundance[178] and that expansion of the ILC2 population is linked to recovery from COVID-19 (ref. [179]), highlighting the importance of innate immune cells to counteract infection[180]. The innate immune system uses an array of sensors and effector molecules, including TLRs, RLRs, NLRs and inflammasome sensors as well as cGAS and STING, to directly and indirectly sense the virus or viral components. Downstream of sensing, IFN signaling, cytokine production and cell death are key features of the innate immune response that can reduce viral replication and eliminate infected cells to prevent viral spread. However, SARS-CoV-2 encodes proteins and mechanisms that counteract innate immune defenses. As a complicating factor, hyperactivation of the host innate immune response is often associated with cell death, cytokine storm, severe disease and mortality. For these reasons, host immunomodulatory drugs that temper inflammatory responses, including baricitinib and tocilizumab, have been evaluated and granted EUA for treatment of severe COVID-19, and many others are under investigation. A more detailed understanding of the host innate immune response to SARS-CoV-2 might help pharmacokinetics achieve the balance of inflammation and immunomodulation that optimizes antiviral responses without causing excessive pathological inflammation. One advantage of targeting innate immunity and host molecules is that this approach should be less vulnerable to viral evolution, variant emergence and resistance, which have jeopardized the efficacy of current COVID-19 vaccines and antiviral antibody-based therapies. As new strains emerge, it will be critical to continue to evaluate the efficacy of current therapeutic strategies and optimize treatment options.

Beyond enhancing our understanding of the underlying mechanisms of disease in COVID-19, it will also be important to consider differences in innate immune activation that occur based on comorbidities, age, sex and other underlying factors. These likely contribute to varying disease severities observed across patient groups[5]. Additionally, most studies to date have considered innate immune responses in adults. Given the growing number of pediatric infections[181], some of which are severe and associated with inflammatory syndromes and MIS-C, there is a need to study immune responses in this population. A deeper understanding of innate immunity to SARS-CoV-2 and associated evasion strategies may help to generate new therapeutic approaches that mitigate severe disease, provide treatments for the ongoing pandemic and identify countermeasures to prevent complications of future ones.

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Competing interests

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