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Innate Immunity in Protection and Pathogenesis During Coronavirus Infections and COVID-19

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Abstract

The COVID-19 pandemic was caused by the recently emerged β-coronavirus SARS-CoV-2. SARS-CoV-2 has had a catastrophic impact, resulting in nearly 7 million fatalities worldwide to date. The innate immune system is the first line of defense against infections, including the detection and response to SARS-CoV-2. Here, we discuss the innate immune mechanisms that sense coronaviruses, with a focus on SARS-CoV-2 infection and how these protective responses can become detrimental in severe cases of COVID-19, contributing to cytokine storm, inflammation, long-COVID, and other complications. We also highlight the complex cross talk among cytokines and the cellular components of the innate immune system, which can aid in viral clearance but also contribute to inflammatory cell death, cytokine storm, and organ damage in severe COVID-19 pathogenesis. Furthermore, we discuss how SARS-CoV-2 evades key protective innate immune mechanisms to enhance its virulence and pathogenicity, as well as how innate immunity can be therapeutically targeted as part of the vaccination and treatment strategy. Overall, we highlight how a comprehensive understanding of innate immune mechanisms has been crucial in the fight against SARS-CoV-2 infections and the development of novel host-directed immunotherapeutic strategies for various diseases.

INTRODUCTION

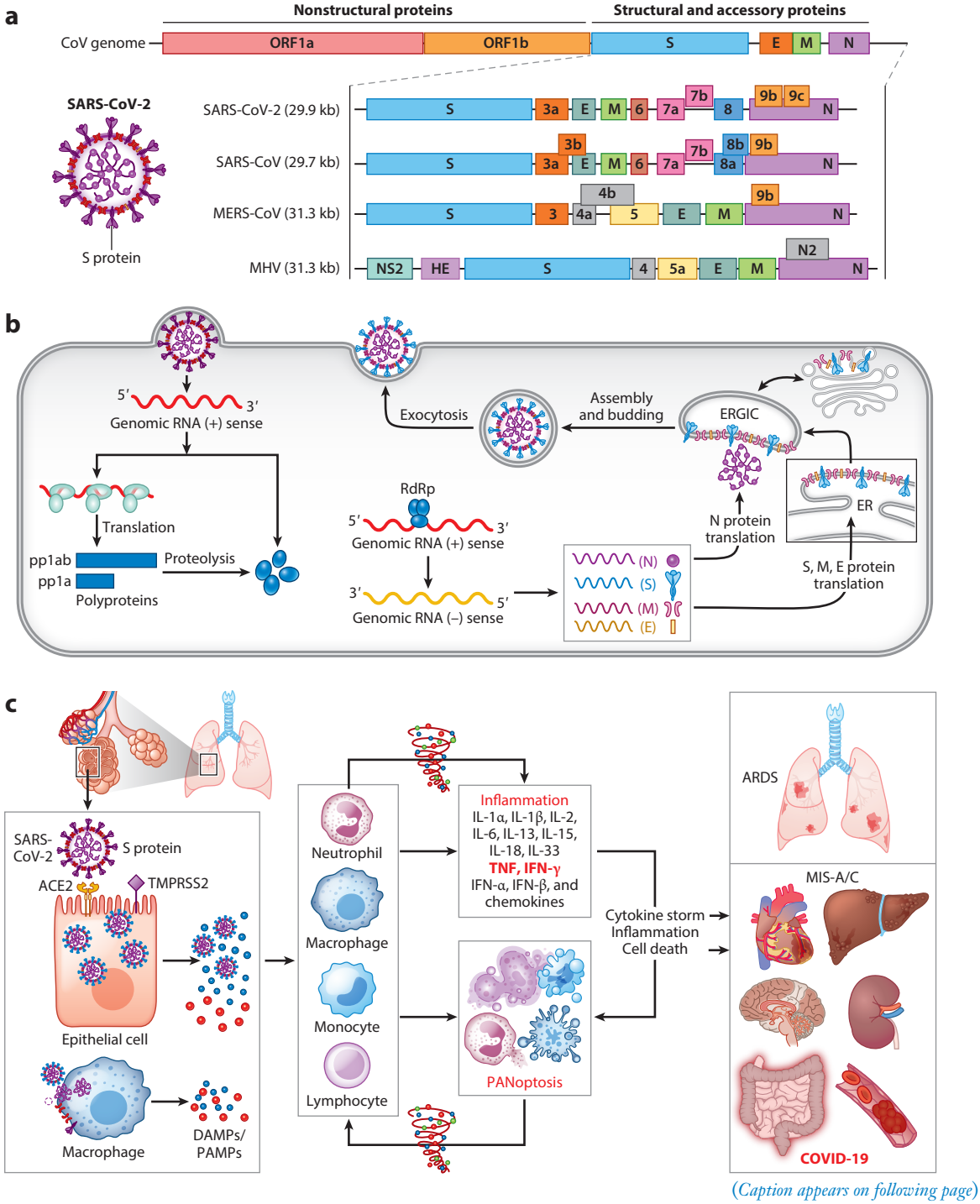
Coronaviruses have long been identified as human pathogens that cause frequent respiratory illnesses (1). The *Coronaviridae* family is divided into four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. While the alphacoronaviruses and betacoronaviruses are believed to be of bat origin and infect humans, the gammacoronaviruses and deltacoronaviruses infect primarily birds and swine species. Among the seven human coronaviruses (HCoVs) identified to date, SARS-CoV, Middle East respiratory syndrome (MERS)-CoV, and SARS-CoV-2 are the most highly pathogenic, whereas HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are less pathogenic. These betacoronaviruses are prototypical examples of human communicable zoonotic viruses. SARS-CoV triggered the SARS outbreak (2002–2004), causing a range of disease manifestations, from mild flu-like symptoms to life-threatening acute respiratory distress syndrome (ARDS), with a case mortality rate of approximately 9.6% (2). Similar symptoms were observed in response to MERS-CoV-2, which caused the first MERS epidemic in 2012 and led to multiple subsequent outbreaks and sporadic cases, with a very high mortality rate of approximately 34.3% (3). Several lethal and nonlethal coronaviruses from all four genera (*Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*) have been identified in domesticated species (e.g., cats, rats, dogs, horses, and chickens), raising the possibility that a new variant could emerge and cause future zoonotic infections (4).

The emergence of SARS-CoV-2 in December 2019 (5–7) initiated the COVID-19 pandemic (8), which has caused significant global mortality (9). SARS-CoV-2 infects primarily pulmonary cells and triggers a wide spectrum of clinical manifestations, from asymptomatic, mild, and moderate to severe and critical symptoms in COVID-19 illness (5). While most SARS-CoV-2 infections are nonlethal, some patients develop uncontrolled inflammatory cell death, systemic inflammation with severe cytokine storm, ARDS, thromboembolism, pneumonia, and multiorgan failure with fatal outcomes (5, 10, 11) (**Figure 1**).

Here, we review the current understanding of the innate immune cells and pattern-recognition receptors (PRRs) in detecting and responding to coronaviruses, with a focus on SARS-CoV-2. We discuss the innate immune pathways activated by PRRs and the resulting expression of inflammatory cytokines and interferons, as well as cell death during COVID-19, with brief examples from other coronaviruses. We also highlight how pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and cytokines trigger inflammatory, lytic cell death, PANoptosis, and the role of cell death in COVID-19 pathogenesis. Furthermore, we highlight how a greater understanding of innate immune sensing mechanisms contributed to the development of mRNA-based COVID-19 vaccines and immunomodulatory treatment strategies. Finally, we outline the knowledge gaps in the field and the importance of rapid and robust activation of the innate immune response as a key paradigm central to host defense against COVID-19 pathogenesis, which provides potential therapeutic opportunities to target innate immune mechanisms.

SARS-COV-2: THE VIRAL PATHOGEN OF COVID-19

While zoonotic spillovers of other betacoronaviruses, including SARS-CoV and MERS-CoV, have resulted in localized outbreaks in the past, the novel betacoronavirus SARS-CoV-2, identified in 2019, caused the largest global pandemic of the current century (5, 7). Like SARS-CoV and MERS-CoV, SARS-CoV-2 belongs to the *Betacoronavirus* genus, where members have largely conserved genome structures (7) (**Figure 1*a***). Like other betacoronaviruses, SARS-CoV-2 is a zoonotic, enveloped, positive-sense single-stranded RNA (ssRNA) virus with a genome length of approximately 30,000 nucleotides (12–14). Its viral genome displays the typical organization



(Caption appears on following page)

Figure 1 (*Figure appears on preceding page*)

Betacoronavirus genomic structures and SARS-CoV-2 viral life cycle and innate immune detection in COVID-19 pathology. (*a*) The generic genome structure is presented in the 5′ to 3′ direction. ORF1a encodes a polyprotein, pp1a, and a ribosomal frameshift produces pp1ab polyprotein from ORF1b, which then undergoes proteolysis by PLpro and Mpro to produce 16 nonstructural proteins. The annotated and protein-coding regions of the genomes from related betacoronaviruses are compared, while excluding ORF1a and ORF1b, and the length of the RNA genomes along with the names of the representative viruses are indicated on the left. The RNA lengths are not drawn to scale. (*b*) Schematic depicting the replication cycle of SARS-CoV-2. SARS-CoV-2 S protein binds to ACE2 receptors on the target cells and is further proteolytically activated by TMPRSS2, which then leads to membrane fusion and release of the viral genome into the host cell. The viral genome (positive-sense single-stranded RNA) is immediately translated by host cells to release pp1a and pp1ab polyproteins. Upon proteolysis, pp1a and pp1ab release several nonstructural proteins, which serve multiple functions, including assembly of the replication–transcription complex by inducing double membrane vesicles to evade immune recognition, modulation of host cellular compartments such as the ER and Golgi (ERGIC) for generation of new virions, and the extracellular release of virions via exocytosis. (*c*) An overview of the innate immune response and immunopathogenesis in COVID-19. SARS-CoV-2 first infects the epithelial cells in the respiratory tract and then replicates, and new virions are released. Along with virions, PAMPs, DAMPs, and immune modulators are also released. These released virions, PAMPs, DAMPs, and immune modulators can all be sensed by cells of the innate immune system to initiate a robust multilayered inflammatory immune response and activate adaptive immune responses to clear the infection. However, if the virus persists due to a delay or defect in the primary immune response, it can result in overt activation of different immune cells, followed by inflammatory cell death and a cytokine storm that leads to the development of ARDS and MIS, thus damaging vital organs and resulting in fatal outcomes. Abbreviations: ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; DAMP, damage-associated molecular pattern; E, envelope; ER, endoplasmic reticulum; ERGIC, endoplasmic reticulum–Golgi intermediate compartment; IFN, interferon; M, membrane; MERS, Middle East respiratory syndrome; MHV, mouse hepatitis virus; MIS-A/C, multisystem inflammatory syndrome in adults/children; Mpro, main protease; N, nucleocapsid; ORF, open reading frame; PAMP, pathogen-associated molecular pattern; PLpro, papain-like protease; pp, polyprotein; RdRp, RNA-dependent RNA polymerase; S, spike; TMPRSS2, transmembrane protease, serine 2.

of betacoronaviruses and encodes 29 proteins with diverse functional roles in the virus life cycle, promoting replication, packaging, and infection. Among the 29 proteins, four are structural proteins: nucleocapsid (N), envelope (E), membrane (M), and spike (S). Like SARS-CoV, the S protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) for entry, but the SARS-CoV-2 S protein has evolved to have better affinity and immune evasion efficiencies. The SARS-CoV-2 S protein uses both ubiquitously expressed furin and TMPRSS2 proteases for proteolysis at the S1/S2 and S2′ cleavage sites for its activation and cell fusion, which substantially expands the SARS-CoV-2 tropism to multiple cell types; this increased tropism may be responsible for its ability to cause multiorgan systemic infection (15, 16). In addition, the genome encodes nine accessory proteins that promote viral fitness (**Figure 1*a*,*b***). It also encodes two large polyproteins (pp1a and pp1ab) that are proteolytically cleaved by virus-encoded proteases nsp3 [papain-like protease (PLpro)] and nsp5 [3C-like cysteine protease (3CLpro) or Mpro] into 16 nonstructural proteins (12) (**Figure 1*a*,*b***).

INNATE IMMUNE PATTERN-RECOGNITION RECEPTORS AND SENSING OF SARS-COV-2

The innate immune system provides the first line of defense against SARS-CoV-2 invasion and infection. Innate immune cells are equipped with different classes of genetically encoded PRRs that sense PAMPs and DAMPs during SARS-CoV-2 infection. Activated PRRs drive the expression of inflammatory cytokines, chemokines, and interferons, which recruit and activate other immune cells, further amplifying the immune response and cell death to protect against SARS-CoV-2 infection (17, 18) (**Figure 1*c***). Betacoronaviruses, including SARS-CoV-2, MERS-CoV, SARS-CoV, and mouse hepatitis virus (MHV), a well-studied animal model for researching betacoronaviruses (19), infect both immune and nonimmune cells in the respiratory tract. Upon infection, they are sensed by PRRs to induce inflammatory cytokine and interferon production, as well as cell death, which can drive viral clearance and the activation of antiviral functions (20) (**Figure 2**).

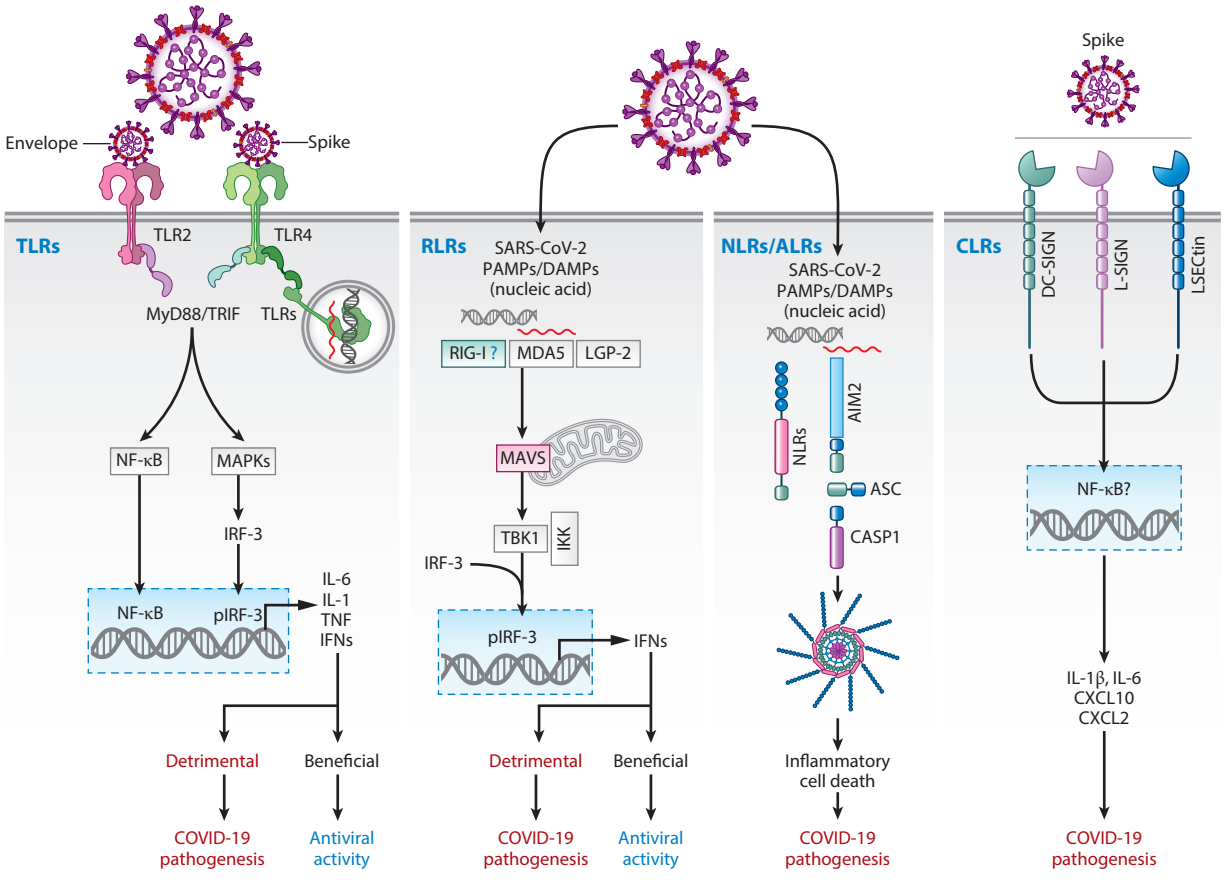


Figure 2

PRR signaling during SARS-CoV-2 infection. Intracellular and cell surface TLRs recognize different components of SARS-CoV-2. While the cell surface receptors TLR2 and TLR4 recognize envelope protein and spike protein, respectively, the intracellular, endosomal receptors TLR3, TLR7, and TLR8 sense viral RNA and antiphospholipid antibodies. This leads to the activation of innate immune signaling and the production of inflammatory cytokines, which can be beneficial while clearing the virus but can also be detrimental and lead to COVID-19 pathogenesis. RLRs, such as RIG-I and MDA5, sense PAMPs and DAMPs from SARS-CoV-2 infection, leading to the production of IFNs, which are beneficial early in infection but detrimental at later time points. Inflammasome sensors, such as different NLRs and AIM2, sense SARS-CoV-2-induced DAMPs and PAMPs, including viral RNA and spike and nucleocapsid proteins, leading to the formation of an inflammasome, the induction of inflammatory cell death, and the release of inflammatory cytokines that drive COVID-19 pathology. CLRs, such as DC-SIGN, L-SIGN, and LSECtin, recognize spike proteins from SARS-CoV-2 upon virus entry into the cell, which leads to the production of inflammatory cytokines and COVID-19 pathogenesis. Abbreviations: AIM2, absent in melanoma 2; CASP, caspase; CLR, C-type lectin receptor; DAMP, damage-associated molecular pattern; DC-SIGN, dendritic cell–specific intercellular adhesion molecule 3-grabbing non-integrin; IFN, interferon; LSECtin, liver sinusoidal endothelial cell lectin; L-SIGN, liver/lymph node–specific intercellular adhesion molecule-3-grabbing integrin; MDA5, melanoma differentiation-associated protein 5; NLR, nucleotide-binding oligomerization domain-like receptor; PAMP, pathogen-associated molecular pattern; PRR, pattern-recognition receptor; RIG-I, retinoic acid–inducible gene-I; RLR, RIG-I-like receptor; TLR, Toll-like receptor.

However, a delayed and deregulated innate immune response due to viral evasion strategies or genetic mutations may result in failure to clear the infection, triggering uncontrolled production of inflammatory cytokines such as TNF and interferons, which in turn promote PANoptosis and cytokine storm that can drive ARDS and severe COVID-19 (21, 22) (**Figure 1*c***).

TLRs and SARS-CoV-2 Infection

Toll-like receptors (TLRs) are evolutionarily conserved PRRs expressed predominantly in innate immune cells, such as macrophages, that show heterogeneous expression in other cells. Upon sensing their cognate PAMPs and DAMPs, TLRs use MyD88 and TRIF as key adaptors for their signaling (23). While both MyD88 and TRIF can activate NF-κB and MAPK pathways, TRIF is primarily involved in TBK1-dependent interferon production. Hence, TLR activation results in the transcriptional upregulation of NF-κB-dependent proinflammatory cytokines and TBK-dependent interferons; it also primes the expression of other innate sensors such as NLRP3, AIM2, and ZBP1 (17, 24). Previous studies have shown that several TLRs, including TLR2, TLR3, TLR4, TLR7, and TLR8, can sense diverse coronaviruses and play critical roles in inducing innate immune responses (4, 20) (**Figure 2**). The role of cell surface TLRs in SARS-CoV-2 infection has been extensively studied in both in vitro and in vivo systems. TLR2 senses the E protein from SARS-CoV-2 and is required for inflammatory signaling and cytokine production during viral infection in human peripheral blood mononuclear cells (25, 26). Additionally, E protein induces cell death and inflammatory cytokine production in the lungs in a mouse model (26). Viral E protein, but not S protein, interacts directly with TLR2 (25). Additionally, blocking TLR2 reduces the production of inflammatory cytokines and improves survival in the K18-hACE2 mouse model of SARS-CoV-2 infection (26). In addition, TLR2 triggers SARS-CoV-2-induced neutrophil extracellular trap (NET) formation in neutrophils and promotes lung inflammation in mice (27). Furthermore, blocking TLR2 alleviates E protein–induced depression-like behaviors and dyssomnia in mice (28), suggesting that TLR2 can also regulate the neuro-immune axis during SARS-CoV-2 infection. However, another study found that TLR2 sensing of SARS-CoV-2 S protein induced inflammation via the NF-κB pathway (29), which could be attributed to the differences in the cell lines and viral protein sources used in these studies.

In addition to the role for TLR2, TLR4 is also critically involved in sensing SARS-CoV-2. S protein–induced cytokine production is reduced in TLR4-deficient macrophages (30), which is further supported by in silico studies that showed strong binding of the S protein to TLR4 (31). Moreover, TLR4-mediated sensing of the SARS-CoV-2 S protein drives cognitive dysfunction, recapitulating post-COVID-19 syndrome in mice (32). Together, these data suggest that it is likely that TLR2 and TLR4 can recognize SARS-CoV-2 E and S proteins, respectively, to induce inflammatory cytokines in patients with COVID-19 and that their inhibition can be beneficial (**Figure 2**).

In addition to these cell surface TLRs, the endosomal TLRs are also associated with COVID-19. TLR3 signaling in mice is protective in the context of other coronavirus infections (33), and the TLR3 ligand poly(I:C) prevents cytokine storm in the K18-hACE2 mouse model of SARS-CoV-2 infection (34). Likewise, reduced expression of TLR3 and inborn errors in the gene have been associated with unfavorable outcomes in patients with COVID-19 (35, 36). However, a recent study reported a detrimental effect for endothelial TLR3 signaling during SARS-CoV-2 infection (37). Treatment with TLR3 inhibitors or small interfering RNAs targeting the mRNA decreased the production of type I interferon (IFN-I), type III interferon (IFN-III), and proinflammatory cytokines after SARS-CoV-2 infection (38), suggesting that TLR3 drives interferon production in this context. Together, these results suggest conflicting roles for TLR3 in both protective and detrimental signaling, which may depend on the timing and cell type involved. Beyond TLR3, the ssRNA sensor TLR7 is reported to be important for interferon production in human plasmacytoid dendritic cells (DCs) following SARS-CoV-2 infection (39), which is consistent with the release of ssRNA fragments during infection (40). In addition, antiphospholipid antibodies are upregulated in patients with severe COVID-19 and can be sensed by TLR7 and TLR8 to augment their expression and activation (41). Furthermore, mutations and deficiencies in *TLR7* have

emerged as an X-linked factor associated with increased incidences of severe pneumonia in male patients with COVID-19 (36, 42–46). Overall, TLR sensing is a critical first step in the innate immune response to SARS-CoV-2, and the signaling it initiates can have both protective and detrimental effects in COVID-19 (**Figure 2**).

RLRs and SARS-CoV-2 Infections

The retinoic acid–inducible gene (RIG)-I-like receptors (RLRs) are a family of RNA-binding helicases that include RIG-I (DDX58), melanoma differentiation-associated protein 5 (MDA5; encoded by the gene *IFIH1*), and laboratory of genetics and physiology 2 (LGP-2). Activated RLRs bind to the adaptor protein MAVS and activate TBK1/IKK-IRF-3 signaling and interferon production for antiviral host defense (47, 48) in response to mouse and human coronaviruses such as MHV, SARS-CoV, and MERS-CoV (20). Screening putative sensors of RNA viruses and CRISPR-based deletion strategies in lung epithelial cells identified MDA5, LGP-2, and MAVS as primary regulators of interferon production during SARS-CoV-2 infection (49, 50) (**Figure 2**), and their depletion reduces cell death (51). While the critical roles for these sensors and adaptors have been consistently observed, the role of RIG-I requires further study. Although some studies have shown that loss of RIG-I in Calu-3 and HEK-293 cells abolishes the production of IFN-β and other proinflammatory cytokines during SARS-CoV-2 infection (51, 52), a similar investigation failed to demonstrate a role for RIG-I in IFN-β production (49). The helicase domain of RIG-I recognizes the 3′-untranslated region of SARS-CoV-2 genomic RNA to limit replication, irrespective of its role in MAVS–interferon signaling (53). Nevertheless, higher basal expression of innate immune sensors such as RIG-I and MDA5 can drive a strong early innate antiviral response in children, thus offering better protection against infection (54). Innate antiviral responses can also be driven by exposure to *Bacillus* Calmette-Guérin vaccination or inflammatory mediators, which promote epigenetic reprogramming and immune memory in innate immune cells, a phenomenon known as trained immunity. This strategy broadly activates RLRs and other innate immune sensors to create an antiviral environment in the host, which holds potential to provide nonspecific beneficial protection against COVID-19 (55). However, robust activation of RIG-I and MDA5 may also produce NF-κB-dependent inflammatory cytokines and drive immunopathology in COVID-19 (51). Therefore, future studies are warranted to fully understand the tissue-specific and time-sensitive functions of RLRs and resolve the uncertainty surrounding the role of RIG-I in sensing SARS-CoV-2 RNA and extending protection against COVID-19.

NLRs, Inflammasomes, and SARS-CoV-2 Infection

Nucleotide-binding oligomerization domain-like receptors (NLRs) are cytosolic innate immune sensors of PAMPs and DAMPs that induce the production of inflammatory cytokines and interferons, and some NLRs assemble regulated cell death–inducing protein complexes. NLRP3 is the most well-studied NLR and represents a typical example of a sensor that induces formation of the inflammasome, a multiprotein complex that assembles in response to innate immune stimuli and contains a sensor, the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase activation and recruitment domain), and caspase-1. Formation of the inflammasome leads to the proteolytic autoactivation of caspase-1, which in turn cleaves IL-1β, IL-18, and gasdermin D (GSDMD), promoting their activation and induction of inflammatory cell death, pyroptosis (56). NLRP3 is upregulated and activated by multiple SARS-CoV-2 PAMPs, including GU-rich RNAs and E, N, S, and open reading frame 3a (ORF3a) proteins, and NLRP3 is associated with COVID-19 pathogenesis (17, 26, 57) (**Figure 2**). Expression of the noncanonical NLRP3 inflammasome signaling molecules caspase-11 in mice and caspase-4 in humans is also upregulated in response to

SARS-CoV-2 (58). The formation of NLRP3 and ASC complexes in monocytes and lung tissues from patients with COVID-19 was reported, suggesting that NLRP3 inflammasome activation occurs in these patients (59). In addition, SARS-CoV-2-infected human primary monocytes show NLRP3-dependent caspase-1 cleavage, GSDMD activation, and IL-1β maturation (59, 60), with similar observations in MHV infection models (61). In addition to NLRP3, SARS-CoV-2 also activates the NLRP1 inflammasome in human lung epithelial cells (62) and the AIM2 inflammasome in circulating monocytes (63) (**Figure 2**), and inflammasome activation has been visualized in lung samples from patient autopsies (64).

The pathophysiological relevance of NLRP3 has been demonstrated in several studies of betacoronaviruses. For example, the pathology and mortality induced by SARS-CoV-2 proteins are reduced by treatment with the NLRP3 inflammasome inhibitor MCC950 or by genetic deletion of *Nlrp3* in mice (57, 65). Additionally, viral spread to the brain in the K18-hACE2 mouse model of SARS-CoV-2 infection leads to upregulation of NLRP3 in microglia, and inhibition of the NLRP3 inflammasome improves survival in these mice (66). Moreover, mice deficient in the noncanonical NLRP3 inflammasome (caspase-11-deficient mice) show reduced pathology and better survival in response to mouse-adapted SARS-CoV-2 (strain MA10) infection (58), and levels of OxPAPC, which can bind caspase-4 to drive noncanonical inflammasome activation in human cells, are high in patients with COVID-19 (67). Together, these data suggest that caspase-11 (caspase-4 in humans) may promote disease severity in COVID-19 infection.

Inflammasome activation is often viewed as a general innate immune mechanism that induces pyroptosis in mice and humans in response to diverse coronavirus infections (4, 20). In contrast, bats express ASC2, a truncated PYD-only mutant of the ASC protein, which cannot assemble the inflammasome and limits virus-induced inflammation; the presence of this unique protein may explain the ability of bats to act as coronavirus reservoirs without developing inflammation and illness (4, 20, 68).

Other NLRs, such as NLRP6, are associated with the regulation of SARS-CoV-2-induced cellular immunity via modulating IL-18 production in intestinal epithelial cells (69), and NLRC3 is downregulated in patients with severe COVID-19 (70). Additionally, NLRC1 plays a role in NF-κB activation and IFN-β production during the infection (49). Overall, NLRs often contribute to enhanced inflammatory pathology during COVID-19, but it is unclear whether there is any functional dichotomy comparable to that observed with interferons, where early effects are protective but later activation is pathogenic; these questions warrant additional investigation.

cGAS-STING Signaling and SARS-CoV-2 Infection

The cytosolic cGAS–STING pathway is a vital component of the innate immune system, which detects both self- and nonself-DNA during infectious or inflammatory conditions, including SARS-CoV-2 infection, and induces production of interferons and inflammatory cytokines (71). In fact, expression of SARS-CoV-2 S protein and ACE2 in host cells triggers the generation of syncytia and micronuclei (72), and cGAS is reported to sense DNA from extranuclear micronuclei and induce IFN-β expression. Furthermore, stimulation of the cGAS–STING–IFN pathway has been suggested to increase the inflammatory response, as seen in the lungs of patients with severe COVID-19 (73) (**Figure 3**).

In accordance with their canonical functions, STING agonists block SARS-CoV-2 replication by upregulating IFN-I responses (74, 75). STING agonists, such as cyclic GAMP or diamidobenzimidazole, limit SARS-CoV-2 infection in mouse models when administered prophylactically or during early infection (74, 75). However, overactivation of the cGAS–STING pathway in endothelial cells may lead to vascular damage and coagulopathy in patients with severe COVID-19 (76). Consequently, the macrophages adjacent to the damaged endothelial cells may sense the

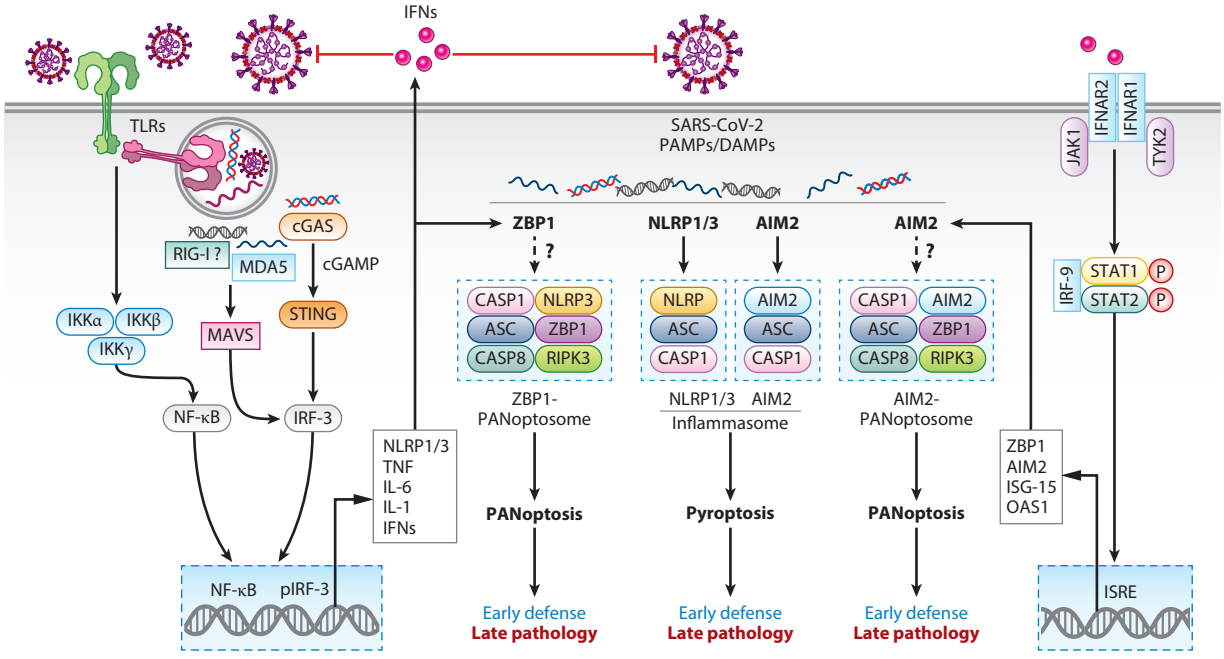


Figure 3

Inflammatory cell death in SARS-CoV-2 infection. PRRs located on the cell surface and in the cytosol lead to the upregulation of NLRs, inflammatory cytokines, and IFNs in response to SARS-CoV-2 infection. NLRP1, NLRP3, and AIM2 sense cytosolic DAMPs and PAMPs, which are released during SARS-CoV-2 infection, and form the inflammasome, leading to pyroptosis. IFNs signal in both paracrine and autocrine manners to upregulate hundreds of ISGs, including ZBP1, AIM2, and ISG-15, among others. Upregulated ZBP1 may sense viral RNA from SARS-CoV-2 and form a multiprotein complex known as the ZBP1-PANoptosome, leading to PANoptosis. In addition, AIM2 may sense mitochondrial DNA, cell-free DNA, or endogenous DNA released during SARS-CoV-2 infection and form a multiprotein complex known as the AIM2-PANoptosome. These cytosolic multimeric cell death complexes activated downstream of PRR sensing in response to DAMPs and PAMPs lead to PANoptosis, an inflammatory form of cell death, and may contribute to host defense against SARS-CoV-2 infection. Abbreviations: AIM2, absent in melanoma 2; DAMP, damage-associated molecular pattern; IFN, interferon; ISG, interferon-stimulated gene; JAK, Janus kinase; NLR, nucleotide-binding oligomerization domain-like receptor; NLRP1/3, NLR pyrin domain–containing 1/3; PAMP, pathogen-associated molecular pattern; PRR, pattern-recognition receptor; RIPK3, receptor-interacting protein kinase 3; STAT, signal transducer and activator of transcription; TLR, Toll-like receptor; ZBP1, Z-DNA-binding protein 1.

mitochondrial DNA released by the dying cells to drive STING-dependent IFN-I production (77). Administration of H-151 (a STING inhibitor) 6 days postinfection can diminish lung inflammation in mice, counteracting this process (78). Furthermore, the cGAS–STING pathway has been reported to promote NF-κB-dependent production of proinflammatory cytokines but not interferons in SARS-CoV-2-infected epithelial cells (78), which may potentially enhance immunopathology. Overall, these data suggest that early activation of the STING–interferon axis is largely beneficial and blocks viral replication, but that delayed activation of the cGAS–STING pathway exacerbates immunopathology. Therefore, future studies should focus on determining the appropriate route, timing, and dose of STING agonists to mitigate COVID-19 outcomes.

CLR Signaling in SARS-CoV-2 Infection

C-type lectin receptors (CLRs) alert the immune system by recognizing the carbohydrate moieties of DAMPs and PAMPs (79). CLRs are expressed in the innate immune cells of patients with severe COVID-19 and are genetic risk factors for COVID-19 infection (80, 81). The SARS-CoV-2

S protein is highly glycosylated and interacts with the CLRs DC-SIGN (dendritic cell–specific intercellular adhesion molecule 3-grabbing non-integrin), L-SIGN (liver/lymph node–specific intercellular adhesion molecule-3-grabbing integrin), LSECtin (liver sinusoidal endothelial cell lectin), ASGR1, and CLEC10A on host cells to facilitate attachment (80). Moreover, PM26, a glycomimetic antagonist of DC-SIGN, inhibits S protein interactions and blocks DC-SIGN-mediated SARS-CoV-2 transinfection of Vero E6 cells (82). However, the ectopic expression of DC-SIGN, L-SIGN, and SIGLEC-1 does not support infection of ACE2-negative cells, suggesting that these lectin receptors may not be the primary viral infection entry points (83). SYK, a tyrosine kinase that functions downstream of CLRs, has been linked to COVID-19 pathogenesis, and inhibiting it with fostamatinib restores near-normal myeloid cell phenotypes and production of inflammatory mediators in patients with COVID-19 while also improving secondary clinical end points in patients (84–86). Overall, these studies suggest that lectin signaling partly facilitates viral replication but also plays a major role in disease pathogenesis by boosting the inflammatory response in myeloid cells (**Figure 2**), which requires substantiation by future studies.

INNATE IMMUNE CELLS AND COVID-19

Cell types that mediate innate immunity, including macrophages and neutrophils, are the primary first responders to coronavirus infections (87–90). However, the cellular innate immune arm is rather extensive and contains multiple cell types beyond macrophages and neutrophils, including DCs, natural killer (NK) cells, eosinophils, basophils, and innate lymphoid cells (ILCs). The cells of the innate immune system recognize and restrict infectious agents such as SARS-CoV-2 to serve as the first line of defense. Additionally, many of these cells also process microbial PAMPs intracellularly and present them to T cells via MHC molecules to activate adaptive immunity to assist in clearing the infection (87–90). Therefore, the role of the innate immune cells is twofold: to provide the initial management of the infection and to direct the adaptive immune responses for coronavirus infection clearance and sterile immunity (87–90). Moreover, this process is vital for the development of antigen-specific adaptive immunological memory, which is essential for vaccine efficacy. The role and function of these innate immune cell types that sense PAMPs and DAMPs during coronavirus infections, specifically in the context of SARS-CoV-2 and COVID-19, are discussed below.

Myeloid Cells and COVID-19

Myeloid cells, which are phagocytic in nature, represent a pivotal cellular component of innate immunity, and they are rapidly recruited to the site of infection to eliminate pathogens and promote healing. Despite the fact that myeloid cells are the initial responders that recognize and initiate immune responses to SARS-CoV-2 infection, profound alterations in the myeloid cell compartment have been linked with severe instances of COVID-19 late in the disease (91, 92). Moreover, COVID-19 is characterized by excessive inflammation resulting from cytokine storm, with a high risk of respiratory failure (93–95). This inflammation results from a failure to clear the initial infection that leads to altered differentiation of myeloid cells toward a more inflammatory phenotype, which can amplify cytokine storm and the development of ARDS in patients with COVID-19. The roles of several subtypes of myeloid cells, as well as other innate immune cells, in COVID-19 are discussed below.

Macrophages and COVID-19. The resident alveolar macrophages and monocyte-derived macrophages together constitute most of the myeloid cells in the lungs of patients with COVID-19 (96). A transcriptome-wide association study identified monocyte-macrophage activation as a

potentially druggable target of COVID-19 for better therapeutic outcomes (97). A functional dichotomy between these macrophages has been observed, where COVID-19 severity is associated with a reduction in the number of protective alveolar macrophages, whereas monocyte-derived macrophages are correlated with severe disease (98, 99). However, SARS-CoV-2 can evade immune detection and interferon production in alveolar macrophages (100). Moreover, monocytes contribute to inflammasome activation in COVID-19-associated fibrosis and worsen disease severity (99). Single-cell profiling studies also show that specific monocyte and macrophage subsets with pronounced expression of inflammatory cytokines and chemokines are present (101), and they are associated with the development of severe COVID-19 and other inflammatory conditions (102). The inflammatory macrophage activation phenotype observed in COVID-19 is similar to macrophage hyperactivation in hemophagocytic lymphohistiocytosis and macrophage activation syndrome (11, 96).

Similar to macrophages, other monocyte subsets also show a high degree of variability and correlate with the severity of COVID-19 illness. For instance, HLA-DR^{hi}CD11c^{hi} inflammatory monocytes with an interferon-stimulated gene signature are elevated in mild COVID-19 (103) but depleted in severe COVID-19 (103–106). However, the classical HLA-DR^{lo} monocytes produce large amounts of alarmins such as calprotectin (S100A8/S100A9) in severe COVID-19 (103, 105). Overall, deregulation of innate immune cell composition has been identified as a strong prognostic factor for COVID-19. These findings indicate that macrophages can enhance the cytokine storm during SARS-CoV-2 infection, which may result in rapid pathogenesis and an increase in the incidence of COVID-19 fatalities. Furthermore, additional research on the involvement of innate immune monocytes and macrophages is much needed to address their potential impact on long-COVID and COVID-19-associated health issues.

Neutrophils and COVID-19. Neutrophils are generally the first cells to respond to an infection or insult, and they are recruited in large numbers to the site of infection or damage, including respiratory viral infections (107). Accumulating evidence suggests that neutrophils, the neutrophil attractant chemokine IL-8, and the related cytokines IL-1 and IL-6 play critical roles in the pathophysiology of COVID-19 (108, 109). Indeed, greater neutrophil activation and neutrophil-to-lymphocyte ratios are predictive of poor clinical outcomes (93, 108, 110). Patients with COVID-19 also present with markers for neutrophil NETosis, a unique form of cell death characterized by extracellular release of decondensed chromatin, potentially contributing to detrimental pathophysiology (111, 112). Moreover, neutrophil NETs promote epithelial cell death and immunothrombosis, which may contribute to thromboembolism in patients with COVID-19 (111, 113). Additionally, in patients with severe COVID-19, emergency myelopoiesis drives the accumulation of CD10^{lo}CD101^{-}CXCR4$^{+/-}$ immature neutrophils, which release high levels of DAMPs such as calprotectin (S100A8/ S100A9), contributing to the pathophysiology (105). While it is generally hypothesized that neutrophils are deregulated and may be detrimental during COVID-19 (103, 114), a recent study demonstrated that there are two neutrophil subpopulations (A1 and A2) in the airway compartment and that a reduction in the A2 subset abrogates viral clearance and reduces the 30-day survival in patients with COVID-19 (115). This study also demonstrated that the A2 subset induces robust interferon signaling, and mechanistically, IFIT3 is required for IRF-3 phosphorylation and IFN-I production in neutrophils of patients with COVID-19 (115). Overall, the role of neutrophils is relatively understudied, and it is unclear whether the early activation of neutrophils, such as macrophages, protects against the development of severe COVID-19.

Basophils and eosinophils in COVID-19. Basophils and eosinophils are associated primarily with parasitic infections and asthmatic lung pathologies. However, these cells also produce

antiviral molecules and may be associated with lung pathology in respiratory viral infections (116, 117). The role of basophils and eosinophils in COVID-19 is less understood when compared with that of the other myeloid subsets. Eosinophil and basophil counts are decreased in patients with COVID-19, indicating that basopenia and eosinopenia are occurring (93, 118–120). IFN-γ-induced $CD62L^+$ eosinophils expand during the development of severe COVID-19, potentially contributing to hyperinflammation and lung pathology (120). A similar study reported that SARS-CoV-2 may drive eosinophil-mediated Th2-biased inflammation and subsequent pulmonary pathogenesis via overt complement activation in myeloid cells (118). Overall, it is hypothesized that an optimal early activation of basophils and eosinophils is required for protective immunity and that their overactivation or depletion later in the infection reflects a failed immune response. Future studies are needed to establish whether their activation is a result of deregulated inflammation or a causative factor in COVID-19 pathological inflammation.

Lymphocytes and Other Innate Immune Cells in COVID-19

Recent research suggests that ILCs play a role in many illnesses, including COVID-19. Several studies have shown that a decrease in ILC count is a consistent feature of severe inflammation in COVID-19 (121). A recent single-cell RNA-sequencing study found that lymphoid cells also express the alarmins S100A8 and S100A9, which are hallmarks of severe COVID-19 (122). The role of lymphoid cell types, including T cells, B cells, and ILCs, in COVID-19 has been extensively studied, and the consensus in the field suggests that lymphopenia is a common clinical feature associated with severe COVID-19 (89, 90, 123).

In addition to lymphocytes, DCs have also been implicated in COVID-19. DCs represent the professional antigen-presenting cells of the innate immune system. While DCs are primarily responsible for bridging the innate and adaptive immune responses, the DC counts and their ability to produce large amounts of IFN-I also play critical roles in the antiviral response against SARS-CoV-2 and in preventing the development of severe COVID-19 (87–90). Understanding these cell types in greater depth offers considerable potential for developing improved vaccines and immunotherapies against coronavirus infections.

INNATE IMMUNITY AND INFLAMMATORY MEDIATORS

As discussed above, the PRRs of the innate immune system engage with PAMPs and DAMPs during coronavirus infections and activate transcriptional programs to drive the expression of inflammatory cytokines, chemokines, and interferons (124) (**Figure 2**). Among the inflammatory mediators, interferons are best known for their antiviral functions and for shaping effective immune responses via autocrine and paracrine signaling (125). In the context of SARS-CoV-2 infection, interferons have both protective and pathogenic roles. Additionally, SARS-CoV-2 infection is associated with the production of many other cytokines, which can contribute to cytokine storm, inflammatory cell death, and disease pathology.

Innate Immunity and Interferons

Interferons are the most effective multifaceted antiviral immune molecules, and their deregulation often results in a cascade of inflammation and cell death contributing to pathogenesis and organ damage (125, 126). Interferons are generally classified into three families on the basis of the type of cellular receptor they engage, namely IFN-I (IFNAR1 and IFNAR2 receptors), IFN-II (IFNGR1 and IFNGR2 receptors), and IFN-III (IFNLR1 and IL-10Rβ receptors) (125, 126). These receptors activate the tyrosine kinases Janus kinase 1/2 (JAK1/2) and TYK2 to phosphorylate signal transducer and activator of transcription (STAT) family members, which assemble

transcriptional complexes and regulate the expression of hundreds of interferon-stimulated genes (ISGs) to induce potent antiviral immunity (125, 126). While interferons are classically known for their antiviral immune responses, they also regulate cell death, including the activation of the lytic inflammatory cell death called PANoptosis (21, 22) (**Figure 3**).

Coronaviruses in general (20), and SARS-CoV-2 specifically, are sensitive to exogenously added interferons (127–129). Despite being less potent than IFN-I, IFN-III can control virus replication in human intestinal epithelial cells, colon organoids, and Vero E6 cells (127, 128, 130). The importance of interferons in counteracting coronaviruses is further highlighted by the strong selection for and evolution of coronaviruses capable of evading interferon signaling (131, 132). Moreover, genetic defects and neutralizing autoantibodies affecting IFN-I and IFN-III production or function have emerged as risk factors for developing life-threatening COVID-19 pneumonia (age independent), accounting for 20% of critical COVID-19 cases in people over the age of 80 (36, 133–135). SARS-CoV-2-infected intestinal and lung epithelial cells produce the type III interferons, IFN-λ, and these control SARS-CoV-2 infection when added to human intestinal epithelial cells both before and after infection (136). Furthermore, IFN-III diminishes SARS-CoV-2 burden at the liquid interface in lung organoid models, and IFN-λ is efficient at limiting SARS-CoV-2 (129, 137).

In contrast to these protective antiviral functions, a large body of COVID-19 literature demonstrates that interferons can promote COVID-19 pathogenesis (138–140). To explain the paradoxical roles of interferons in protective versus destructive responses in COVID-19, a two-phase pathophysiologic model was proposed (141), in which insufficient interferons produced early in the infection may be the primary factor responsible for uncontrolled viral replication. This uncontrolled replication then leads to hyperactivation of the immune cells in later phases of infection, which drives excessive inflammation and cytokine storm in COVID-19 (142). Indeed, unlike other non-coronavirus viruses, SARS-CoV, MERS-CoV, MHV, and SARS-CoV-2 antagonize and delay interferon responses (20, 100, 132, 139, 142), providing further support for this two-phase model. However, clinical data suggest that the interferon response cannot fully explain SARS-CoV-2 pathology. For example, in multisystem inflammatory syndrome in children (MIS-C), a delayed and rare clinical manifestation occurring approximately 6 weeks after clearance of benign SARS-CoV-2 infections in children, inborn errors in innate immune checkpoints such as the anti-inflammatory *SOCS1* gene have often been identified (143–145). Thus, MIS-C presents a contrasting paradigm in which loss of innate immune checkpoints may result in successful and nonsymptomatic clearance of the pathogen but may instigate multisystem inflammatory disease postinfection. Interferon may still play a key role in MIS-C, as overactivation of the RLR–MAVS–interferon axis to drive the inflammatory syndrome has also been reported (143–145). Nevertheless, MIS-C is a highly complex inflammatory phenomenon similar to that seen in long-COVID (146), and targeting a single arm, such as interferons, may not be the optimal approach for treating this group of patients.

Overall, these studies indicate that the precise activation and deactivation of innate immune responses, particularly interferons, is of paramount importance for viral clearance and the resolution of severe inflammatory effects. As a result, therapeutic administration of interferons has produced varying outcomes, from improved clinical outcomes to pathological effects when administered later in the course of infection. This is covered in detail below in the section titled Therapeutic Targeting and Innate Immunity. Future research is warranted to further understand the mechanism by which IFN-I and IFN-III interact with other inflammatory cytokines to limit SARS-CoV-2 infection and whether there are better therapeutic options than interferons for treating these infections.

Innate Immunity, Cytokine Storm, and PANoptosis

The innate immune PRR activation during SARS-CoV-2 infection induces the expression of non-interferon cytokines and chemokines in COVID-19, including IL-1, IL-33, IL-6, TNF, IL-12, and IL-17, among others (5, 124, 140, 142). Several studies have concluded that many COVID-19 fatalities occur as a result of ARDS, which is often a consequence of cytokine storm induced by overproduction of proinflammatory cytokines that can damage vital organs, including the lungs and heart (5, 10, 140, 147, 148). Indeed, the US Food and Drug Administration (FDA) has approved several anti-inflammatory modalities that target cytokines to mitigate COVID-19 morbidity and mortality, emphasizing their role in inflammatory damage during COVID-19 (as detailed in the section titled Therapeutic Targeting and Innate Immunity). Moreover, several studies have reported that cytokines, PAMPs, and DAMPs promote lytic forms of inflammatory cell death, contributing to fatal outcomes in COVID-19 illness (18, 21, 22, 60, 63, 149–152). For example, the combination of TNF and IFN-γ produced during COVID-19 triggers PANoptosis (22), a unique innate immune, inflammatory, lytic cell death pathway driven by caspases and receptor-interacting protein kinases (RIPKs) and regulated by PANoptosome complexes. COVID-19-induced PANoptosis can kill both immune and nonimmune cells (64), thereby releasing DAMPs and alarmins to drive pathogenesis (22). Mechanistically, the key components of interferon signaling, STAT1 and IRF-1, as well as NOS2, promote priming and activation of caspase-8-dependent PANoptosis (22, 152). Moreover, genetic deletion of *Nos2* protects mice from developing severe disease in a mouse model of SARS-CoV-2 infection (152). Although COVID-19 is a complex inflammatory disease with multiple mechanisms, combination treatment with TNF and IFN-γ is sufficient to drive COVID-19-like disease in mice, and the neutralization of both TNF and IFN-γ reduces mortality in SARS-CoV-2-infected mice (22), suggesting that cytokine-induced PANoptosis is a key component of the disease pathology (11, 22) (**Figures 1*c*** and **3**). Moreover, single-cell profiles from patients with COVID-19, along with five other inflammatory diseases, showed that COVID-19 macrophage profiles closely align with the macrophage phenotype induced by TNF and IFN-γ cotreatment (102), further suggesting that these cytokines are key drivers of disease phenotypes. Together, these data suggest that targeting these PANoptosis modulators holds promise for the development of immunomodulatory therapies to mitigate a range of cytokine storm–mediated conditions.

To produce these pathological cytokines, PAMPs from the virus and DAMPs from the host can complement each other to amplify cytokine production and induce inflammatory cell death, PANoptosis (22, 61, 153–161). For example, ZBP1, an ISG induced by interferon signaling that acts as a cytosolic Z-form nucleic acid sensor, is highly expressed in patients who succumbed to COVID-19 (21), and it also promotes PANoptosis, inflammatory responses, and lung damage in mice and humans (21, 162). Additionally, alveolar type II pneumocytes undergo lytic forms of cell death, including PANoptosis, during SARS-CoV-2 infection, which promotes hyperinflammation and pathology (64). Similarly, endothelial cell death and organ damage in adults with severe COVID-19 and children with MIS-C have been reported (163). Additionally, the hyperinflammatory state of severe COVID-19 also shapes the prothrombotic state associated with endothelial damage and coagulopathy, both of which trigger abnormal blood clots (thromboembolism), leading to severe lung damage, myocardial infarction, and stroke (164). The TNF-associated hyperinflammatory state can also result in lymphopenia in severe COVID-19 (165–169). TRAIL, another death receptor ligand, has also been linked to COVID-19-associated lymphopenia (170). However, it is unclear whether TRAIL, in combination with interferons, can cause PANoptosis-induced lymphopenia. Overall, these studies suggest that cell death contributes to COVID-19 pathology. From a therapeutic standpoint, inhibiting inflammatory cell death alone may be

beneficial, or it may also improve the efficacy of interferon therapy during coronavirus infection by selectively alleviating immunopathology while maintaining the antiviral properties of interferons.

SARS-CoV-2 and Evasion of Innate Immunity

While innate immunity employs a multitude of antimicrobial mechanisms, the interferon response is primarily responsible for driving a state of antiviral resistance. However, SARS-CoV-2 is adept at evading interferon responses, as its genome encodes multiple proteins that act to avoid detection and antagonize immune defenses (**Figure 4**).

Several SARS-CoV-2 nonstructural proteins antagonize the RLR–MAVS–IRF-3-mediated induction of interferon production (132) (**Figure 4**). For example, SARS-CoV-2 limits the nuclear import of IRF-3 and nuclear export of interferon transcripts; additionally, nsp1 and nsp14 can selectively affect host transcripts to inhibit antiviral gene expression while simultaneously repurposing the host machinery for viral replication (171–177). The viral protein nsp1 has unique functions; it binds to a precise region at the mRNA entry channel on the ribosome to selectively block host mRNA translation at the global level while enabling efficient translation of viral mRNAs, resulting in inhibition of interferon production and robust replication of viral progeny (173–177). In addition to nsp1, nsp3 (PLpro) of SARS-CoV-2 removes the ISG-15 modifications of MDA5 and blocks its activation (178, 179). Moreover, nsp16 binds to the U1 and U2 spliceosome components, suppressing the host splicing machinery (173). Early in the course of infection, the structural N protein of SARS-CoV-2 blocks IFN-β production by inhibiting RIG-I recognition of viral RNAs (180), while the M protein can directly interact with both MDA5 and RIG-I and their downstream targets to promote their degradation via K48-linked ubiquitination (181). The N protein also destabilizes double-stranded RNA, masking its recognition by RLRs (182) and promoting phase separation to suppress the G3BP1-dependent host immune response (183, 184). It can also prevent aggregation of viral RNA with MAVS to block induction of the interferon pathway (185). Moreover, the N protein interacts with the helicase domain of RIG-I and prevents its binding to TRIM25 to suppress interferon production (180, 186). The viral accessory protein ORF9b is highly versatile and can interact with multiple innate immune components, including RLR, TLR, and cGAS–STING pathways and their downstream effectors. Moreover, ORF9b blocks the polyubiquitination of IKKγ and phosphorylation of IRF-3 to abrogate NF-κB signaling and interferon induction (187, 188). Furthermore, ORF6, ORF8, and N proteins interfere with the interferon-stimulated response element and NF-κB-responsive promoters to block antiviral responses (189). A premature stop codon in ORF3b distinguishes SARS-CoV-2 from its more pathogenic counterpart, SARS-CoV, and the truncated ORF3b is better at inhibiting interferon expression, making SARS-CoV-2 less pathogenic in infected individuals, which may paradoxically promote its fitness to cause a global pandemic (190). In all, it has become clear that cytosolic PRRs act as the first line of defense to detect coronavirus RNA and induce protective antiviral responses, but SARS-CoV-2 has evolved multiple mechanisms to counteract these responses to enable its replication and spread. For example, while both influenza A virus and SARS-CoV-2 are respiratory viral infections, influenza A virus is characterized by early interferon production that can help clear the virus. In contrast, interferon production is delayed in response to SARS-CoV-2 infection, and patients generally manifest a more severe course of disease owing to systemic viral replication that leads to severe innate immune-mediated cytokine production (cytokine storm), uncontrolled inflammatory cell death, PANoptosis, and organ damage in the later stages of the infection (18, 21). These observations further support the theory that a failure or deregulation of innate immune activation results in uncontrolled viral replication and the development of fatal COVID-19. Moreover, while initial innate immune-mediated inflammatory responses are

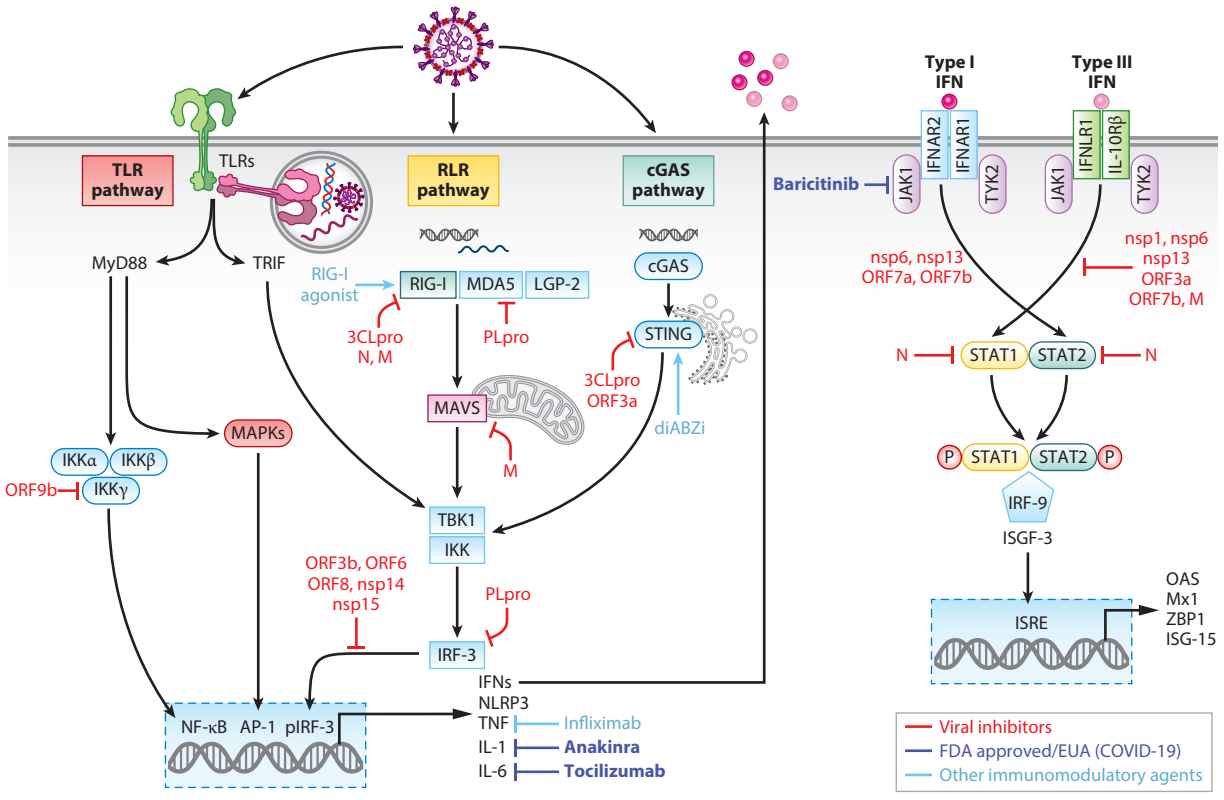


Figure 4

SARS-CoV-2 immune evasion mechanisms and therapeutic targeting. SARS-CoV-2 evades multiple steps of innate immune signaling (indicated by *red blocking arrows*), beginning from the initial sensing of the virus to the downstream signaling and upregulation of ISGs. For example, the viral protease 3CLpro and the structural proteins M and N directly inhibit RIG-I. Similarly, nsp3 (also known as PLpro) of SARS-CoV-2 inhibits MDA5. The viral protein ORF9b has far-reaching effects that are not fully illustrated here due to space constraints, and it interacts with multiple innate immune components such as RLR, TLR, and cGAS–STING pathways and their downstream effectors. Additionally, ORF9b blocks the polyubiquitination of IKKγ and phosphorylation of IRF-3 to abrogate NF-κB signaling and IFN induction. The cGAS pathway is also blocked by viral proteins, including 3CLpro and ORF3a, at the level of STING activation. Moreover, many SARS-CoV-2 proteins, including nsp1, nsp6, nsp13, ORF3a, ORF7a, ORF7b, and N and M proteins, inhibit STAT signaling, which is required for ISGF-3 complex formation and ISG expression. Several therapeutics have been repurposed to treat COVID-19 pathogenesis, and their points of action are indicated by blue activating or blocking arrows. RIG-I and STING agonists promote the production of IFNs and maintain the level of ISGs, which are crucial to restrict viral replication. JAK inhibitors such as baricitinib block signals from cytokine receptors, and baricitinib specifically is FDA approved for adult patients and has received EUA for pediatric patients with COVID-19. In addition, several inflammatory cytokine antagonists, such as infliximab (against TNF), anakinra (against IL-1R), and tocilizumab (against IL-6), have been used therapeutically. Abbreviations: 3CLpro, 3-chymotrypsin-like protease; cGAS, cyclic GMP-AMP synthase; EUA, emergency use authorization; FDA, US Food and Drug Administration; IFN, interferon; IKK, inhibitor of NF-κB kinase; IRF, interferon regulatory factor; ISG, interferon-stimulated gene; ISGF-3, interferon-stimulated gene factor 3; JAK, Janus kinase; LGP-2, laboratory of genetics and physiology 2; M, membrane protein; MDA5, melanoma differentiation-associated protein 5; N, nucleocapsid protein; NLR, nucleotide oligomerization domain-like receptor; NLRP3, NLR pyrin domain–containing 3; nsp, nonstructural protein; ORF, open reading frame; PLpro, papain-like protease; RIG-I, retinoic acid-inducible gene-I; RLR, RIG-I-like receptor; STAT, signal transducer and activator of transcription; STING, stimulator of interferon genes; TNF, tumor necrosis factor; TLR, Toll-like receptor; ZBP1, Z-DNA-binding protein 1.

necessary for host defense against viral infections, unregulated late inflammatory responses can result in organ failure and mortality.

THERAPEUTIC TARGETING AND INNATE IMMUNITY

Innate Immune System and the Success of the COVID-19 mRNA Vaccines

The long-term public health response to the COVID-19 pandemic has greatly relied on the development and implementation of vaccines. As a result of the pandemic, several safe and effective vaccine platforms were developed. The two mRNA vaccines, mRNA-1273 (191) and BNT162b2 (192, 193), were the first to receive emergency use authorization (EUA) and FDA approval, and a viral vector-based vaccine Ad26.COV2.S (194) and the protein-based adjuvanted NVX-CoV2373 vaccine (195, 196) soon followed. While viral vector-based and protein-based adjuvanted vaccines had been used successfully in the past, the mRNA strategy was new (197). The mRNA-based vaccines against SARS-CoV-2 were developed rapidly and efficiently, but this approach faced some obstacles. In addition to the limitations in designing an mRNA capable of stable antigen expression and delivery (198), adverse reactions to these vaccines can be caused by innate immune sensing of the therapeutic RNA products through the cytoplasmic RNA sensors RIG-I, MDA5, and protein kinase R and the membrane-bound TLR3, TLR7, and TLR8. However, advancements in understanding distinct RNA modifications that allow recognition as "self" molecules to avoid innate immune sensing and activation have been critical for the efficacy of the mRNA vaccines. For example, it was found that the innate immune system selectively detects RNAs that lack nucleoside modifications, and that incorporation of modified nucleosides such as 5-methylcytidine (m5C), m6A, m5U, s2U, or pseudouridine (Ψ) blocks sensing by human TLR3, TLR7, and TLR8 (199). Additionally, mRNAs containing the N1-methylpseudouridine (m1Ψ) modification in combination with m5C outperform other mRNA platforms and increase the protein expression by 44-fold when compared to the pseudouridine-based platforms, as they are protected from sensing by TLR3 (200). These studies laid the foundation for vaccine developers to incorporate the m1Ψ modification into synthetic SARS-CoV-2 S protein–coding mRNAs, along with other modifications mimicking natural host RNAs (201, 202), ultimately leading to the development of COVID-19 mRNA vaccines. These mRNA vaccines induce superior humoral responses and provide better protection against severe forms of COVID-19 when compared with inactivated whole-virus vaccines such as Sinovac-CoronaVac and BBIBP-CorV, despite moderate $CD4^+$ and $CD8^+$ T cell responses. However, the inactivated vaccine formulations offer improved distribution logistics owing to their stability at 2–8°C (203–207). The success of mRNA vaccines against COVID-19 has generated tremendous interest in developing a range of mRNA-based therapeutics in academia and industry and provides a promising strategy to target a wide spectrum of illnesses, including infections, inflammatory diseases, and cancer.

Host-Directed Therapies and Innate Immunity

The unprecedented scientific and medicinal effort put forth during the COVID-19 pandemic has resulted in historic successes in developing treatment strategies, with over 9,500 investigative studies targeting COVID-19 registered through ClinicalTrials.gov (**https://clinicaltrials.gov/**) as of February 5, 2024. The rapid development of highly efficacious vaccines saved millions of lives during the pandemic (191–196), although there was a lag in the development of specialized treatment options.

In principle, SARS-CoV-2 treatment strategies can be broadly categorized as either antiviral or host-directed immunomodulatory strategies (17, 18) (**Figure 4**). Among the antivirals, several SARS-CoV-2-neutralizing antibodies were granted EUA by the FDA, but emerging variants

of concern resulted in reduced efficacy, and the FDA has revoked several initial authorizations. However, some chemical antivirals have proven to be extremely beneficial in reducing viral loads and providing measurable clinical benefits. For example, remdesivir, which targets the viral RNA-dependent RNA polymerase (RdRp), was the first antiviral compound approved by the FDA. In addition, molnupiravir, which also targets RdRp, is currently in clinical use on the basis of its EUA (17). On May 25, 2023, the FDA approved the first oral antiviral pill, a copackage of nirmatrelvir and ritonavir, which target 3CLpro (Paxlovid), for adults at risk of severe COVID-19, including hospitalization and death, on the basis of the significant treatment benefits in the EPIC-HR and EPIC-SR clinical trials (208, 209). The EUA for Paxlovid has also been recently expanded to treat pediatric patients 12 years of age and older who meet eligibility criteria.

Despite some success with antivirals, the understanding that COVID-19 is a disease of excessive and deregulated immune activation also led to the development of a wide range of immunomodulators. These host-directed therapies range from antiviral biologics to immunomodulators that help activate, enhance, or suppress immune function. The hyperactivated immune system was considered a causal factor for clinical manifestations during the early COVID-19 pandemic, prompting clinical trials with anti-inflammatory corticosteroids (including dexamethasone and hydrocortisone). This strategy met with initial skepticism, but quickly established benefits, with low-dose dexamethasone significantly reducing COVID-19-related symptoms and mortality (210); these results led to the recommendation by the World Health Organization for dexamethasone use as first-line therapy in hospitalized cases of severe COVID-19 (211). Some studies suggest that methylprednisolone may be a better agent than dexamethasone, but the findings are inconsistent (212–214); therefore, further studies may help identify glucocorticoids with better efficacy and safety profiles to benefit patients with COVID-19.

While corticosteroids provide general immunosuppressive effects, more targeted immunomodulatory strategies have also been tested to block the pathogenic effects of cytokine storm. The cytokine storm is defined as an acute overproduction and uncontrolled release of proinflammatory mediators that trigger local and systemic inflammatory pathologies (11). Cytokine storm was reported as a major cause of morbidity in MERS-CoV, SARS-CoV, and SARS-CoV-2 infections (215–217). Additionally, ARDS, which is exacerbated by elevated levels of proinflammatory cytokines such as IL-1, IL-6, IL-17, interferons, and TNF (cytokine storm), is one of the primary causes of mortality in patients with COVID-19 (11, 218). On the basis of the findings from four clinical trials, the FDA approved tocilizumab, an anti-IL-6R antibody (Actemra), for the treatment of hospitalized patients with COVID-19 (17), which is consistent with the therapeutic benefits of blocking IL-6 signaling to manage cytokine release syndrome in CAR T cell therapy (219). However, some trials found limited benefits for IL-6-blocking therapies, suggesting that these may be most effective in certain patient populations or at specific times during the infection process. Similarly, anakinra, an IL-1 receptor antagonist, was granted EUA for the treatment of patients with COVID-19 with elevated serum levels of soluble urokinase plasminogen activator receptor on the basis of the findings from the SAVE-MORE clinical trial (220). Anakinra has also been reported to restore inflammatory homeostasis and support the long-term management of COVID-19 (221, 222). However, a later randomized study reported that anakinra failed to prevent the need for mechanical ventilation or reduce the mortality risk when compared with standard of care alone (223), but patients in the anakinra group did have reduced lung fibrosis, indicating that anakinra may still be beneficial if given before the development of severe hyperinflammation in COVID-19 (223). Similarly, baricitinib, a JAK1/2 inhibitor that blocks signals from cytokine receptors and immune cell function, is FDA approved for use in pediatric and adult patients with COVID-19 on the basis of the data from the ACTT-2 and RECOVERY clinical trials (224, 225). COVID-19 is also

associated with extensive endothelial damage and thrombosis (the occurrence of blood clots), as well as strong complement activation as part of the innate immune response. Moreover, the multicenter phase III PANAMO trial demonstrated that neutralization of the complement factor C5a significantly reduced all-cause mortality by 23.9% (226), leading the FDA to issue an EUA for vilobelimab (Gohibic), a first-in-class monoclonal antihuman complement factor C5a antibody, for the treatment of critically ill patients with COVID-19.

Immunophenotyping and genetic studies of patients with COVID-19 have strongly established that interferons are critical for protection against the disease, particularly in the early stage of infection. However, interferons can be pathological at later stages. In line with these observations, the efficacies of different interferons have been evaluated in clinical trials with varied outcomes. IFN-α2b treatment reduces the duration of viral shedding and promotes the resolution of inflammation in patients with COVID-19, especially when administered early (227, 228). Treatment with inhaled nebulized IFN-β (SNG001) is both safe and efficacious against SARS-CoV-2 infections (229). Similarly, treatment with intranasal IFN-I reduces viral load and inflammation in the SARS-CoV-2 hamster model (230). Moreover, the association between low levels of interferons and undesirable inflammatory conditions in patients with COVID-19 (138) suggests that supplementing interferon levels while also providing other antiviral or anti-inflammatory drugs would be more beneficial. In vitro and in vivo, IFN-α in combination with remdesivir or nafamostat improves cell viability and reduces viral replication (231, 232). Additionally, combining IFN-β with lopinavir and ribavirin reduces COVID-19 mortality (233). In line with this, a clinical trial found that early triple antiviral therapy with IFN-β plus the combination of lopinavir-ritonavir and ribavirin was safe and superior to lopinavir-ritonavir alone in patients with mild to moderate COVID-19 (234). Moreover, the combination of IFN-β with nirmatrelvir, or with EIDD-1931 and aprotinin, showed a strong antiviral response (235), suggesting these combinations could be potential candidates for clinical testing against different SARS-CoV-2 variants. Despite these successes, several other studies using interferon treatment for COVID-19 have yielded mixed results and poor outcomes (17). This discrepancy suggests that although host-directed therapies involving interferons or interferon inducers can be safe and promising when administered in specific patient populations at the right time, extreme caution is warranted, and additional research is needed to better understand the protective and pathological mechanisms of interferons in various scenarios of SARS-CoV-2 infection (236).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In this review, we discussed several important aspects of innate immunity, emphasizing its role as the first line of defense in coronavirus detection and elimination, with a focus on SARS-CoV-2 infection, and how failure of the innate immune response results in the development of fatal COVID-19. We covered the important components of innate immunity, including PRR-sensing mechanisms and distinct innate immune cell types and their protective and detrimental roles in sensing SARS-CoV-2 and triggering critical COVID-19. In addition, we provided a detailed overview of the expression of inflammatory mediators (such as cytokines and interferons) and their connections to inducing cell death, highlighting the cross talk between inflammatory cytokines and interferons, and how this interaction initiates a positive-feedback mechanism of uncontrolled inflammation resulting in a cytokine storm that drives pathological manifestations in severe COVID-19. We further extended the premise that early interferon responses are crucial in limiting SARS-CoV-2 infection and must be tightly regulated to reduce excessive inflammation while retaining antiviral functions. However, SARS-CoV-2 has evolved efficient mechanisms to evade innate immune responses, such as IFN-I production, establishing COVID-19 as a disease of failed innate immunity.

The critical role of innate immunity extends beyond the initial infection to the long-term clinical manifestations of COVID-19. For example, one of the major public health consequences of the COVID-19 pandemic has been the emergence of long-COVID, a multisystemic inflammatory condition that affects many organs and can develop post-SARS-CoV-2 infection and persist for several months (146, 237). Long-COVID, also known as postacute sequelae of COVID-19, is often associated with a loss of innate immune checkpoints and highly activated innate immune cells with elevated interferon expression (238). Like acute COVID-19, long-COVID presents with inflammatory manifestations in the cardiovascular, thrombotic, and cerebrovascular systems (239, 240). Likewise, animal models of long-COVID demonstrate persistent inflammation with proinflammatory cytokine production and cell death involving innate and adaptive immune cells (241–243). Additionally, mast cell activation is prevalent in long-COVID, and histamine receptor antagonists provide significant clinical improvement in 72% of patients (244). Furthermore, MIS-C is associated with several long-COVID manifestations, including multisystemic inflammation, innate immune activation, inflammatory cytokine production, and cell death (143–146). It is likely that both conditions represent diseases of innate immune deregulation in which the innate immune sensor checkpoints are affected. Also, genetic errors in the RNA-sensing RIG-I–MAVS–interferon axis or *SOCS1* were found to be responsible for the development of MIS-C (144, 145), providing an insight into the potential mechanisms of the postacute COVID-19 spectrum of inflammatory conditions. However, the specific etiology of long-COVID remains unclear. Due to the delayed onset of long-COVID following SARS-CoV-2 infection and its presentation with many nonrespiratory symptoms, there was a significant failure to detect or report long-COVID during the early days of the COVID-19 pandemic, but the condition has grown into a global concern, with over 65 million people estimated to be affected (245). A rigorous research agenda is urgently required to understand the biological mechanisms driving long-COVID and to develop treatment options for assessment in evidence-based clinical trials.

Beyond the innate immune system itself, there is a constant interplay between the virus and its host. Since viruses are intracellular obligate parasites, immune evasion is a primordial requirement for escape from host recognition and subsequent elimination. Therefore, a central requirement for a virus to become a pathogen and induce illness is its ability to circumvent the immune system. Understanding host mechanisms of innate immunity in conjunction with the evasion strategies of SARS-CoV-2 is essential for identifying the pathophysiological mechanisms of disease and developing effective vaccines and treatment modalities. Future research should focus on gaining a better understanding of the molecular mechanisms of innate immune pathways in the context of inflammation, inflammatory cell death, and the immune checkpoints that reinforce effective antiviral responses while maintaining immune homeostasis and healing. This will be critical for identifying new therapeutic strategies not only against COVID-19 but also for future coronavirus outbreaks and other infections and inflammatory conditions.

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