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REVIEW

Coordinated regulation of interferon and inflammasome signaling pathways by SARS-CoV-2 proteins

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Type I and III interferons (IFNs) and the nucleotide-binding domain (NBD) leucine-rich repeat (LRR)-containing receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome play pivotal roles in the pathogenesis of SARS-CoV-2. While optimal IFN and inflammasome responses are essential for limiting SARS-CoV-2 infection, aberrant activation of these innate immune responses is associated with COVID-19 pathogenesis. In this review, we focus our discussion on recent findings on SARS-CoV-2-induced type I and III IFNs and NLRP3 inflammasome responses and the viral proteins regulating these mechanisms.

Keywords: inflammasome, interferon, severe acute respiratory syndrome corona virus 2

Introduction

The innate immune system acts as an advance guard that recognizes viral infection and activates a host defense response. Cells of the innate immune system recognize viral pathogen-associated molecular patterns (PAMPs) via germ line-encoded pattern recognition receptors (PRRs). Viral nucleic acids serve as major PAMPs to initiate innate immune responses. Cytosolic PRRs, including retinoic acid-inducible gene-I (RIG-I) like receptors (RLRs), play pivotal roles in sensing viral nucleic acids. Upon recognition of viral nucleic acids, cytosolic PRRs trigger intracellular signaling pathways to stimulate the expression of type I and III interferons (IFNs) as well as pro-inflammatory cytokines which recruit macrophages and monocytes from the blood to the site of infection and prime adaptive immune responses. Type I (IFN-α/β) and III (IFN-λ) IFNs act in an autocrine/paracrine manner and activate the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway to promote the expression of interferon-stimulated genes (ISGs) for establishing an antiviral state. Recognition of viral PAMPs by PRRs as well as cellular stress signals induced by viral infection additionally triggers inflammasome assembly. The inflammasome promotes activation of canonical and non-canonical caspases, in turn, leading to secretion of the proinflammatory cytokines, IL-1β and IL-18, and pyroptosis of infected cells.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent for the coronavirus disease 2019 (COVID-19) outbreak. Similar to other RNA viruses, SARS-CoV-2 infection induces type I and III IFNs and activates the inflammasome. While optimal innate immune responses are essential for eliminating infection, aberrant IFN and inflammasome activation are associated with COVID-19 pathogenesis. Suppression of type I and III IFN responses and exacerbation of NLRP3 inflammasome activation are reported to be associated with severe COVID-19 (Arunachalam *et al.*, 2020; Hadjadj *et al.*, 2020; Ferreira *et al.*, 2021; Galani *et al.*, 2021; Junqueira *et al.*, 2021; Rodrigues *et al.*, 2021; Zheng *et al.*, 2021). In support of these findings, mutations in genes associated with type I IFN signaling pathway and neutralizing auto-antibodies against type I IFNs have been identified in 3.5% and 10% severe COVID-19 cases, respectively (Bastard *et al.*, 2020; Zhang *et al.*, 2020; Pairo-Castineira *et al.*, 2021). In contrast, other studies have reported robust type I IFN responses in patients with severe COVID-19 (Wilk *et al.*, 2020; Zhou *et al.*, 2020). At the cellular level, efficient SARS-CoV-2 infection of lung epithelial cells induces delayed hyper-induction of type I and III IFNs without affecting virus replication (Rebendenne *et al.*, 2021). In association with theses complicating phenomena, SARS-CoV-2 employs various viral proteins to promote and/or impede type I and III and inflammasome responses (Fig. 1). Orchestrated regulation of IFN and inflammasome responses by SARS-CoV-2 at the cellular and systemic host levels may contribute to viral replication, transmission and pathogenesis. Here, we focus our review on providing an overview of recent findings on SARS-CoV-2-mediated IFN and inflammasome activation mechanisms and associated regulatory viral proteins.

SARS-CoV-2 and Type I and III IFN Signaling Pathways

RLRs, including RIG-I and melanoma differentiation-associated protein 5 (MDA5), function as important sensors of RNA viruses, including hepatitis C virus (HCV), Sendai virus (SeV), influenza virus, flaviviruses and picornaviruses (Meylan

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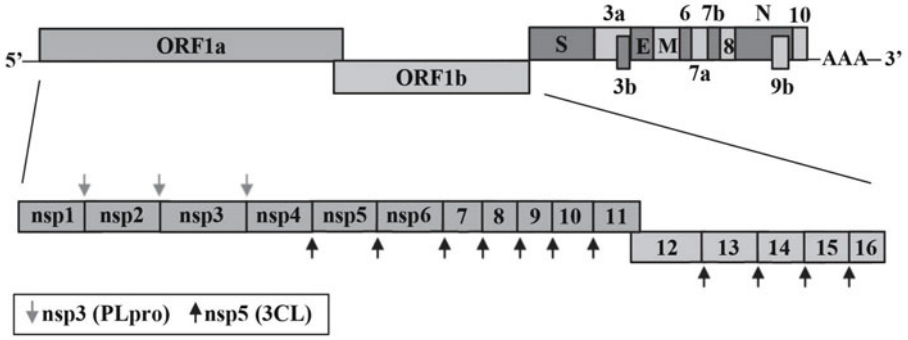

Fig. 1. SARS-CoV-2 genome and proteins. SARS-CoV-2 contains a single-stranded positive-sense RNA genome of ~30 kb. The polyproteins, pp1a and pp1ab, are directly translated from two overlapping ORFs, ORF1a, and ORF1b, respectively, and processed into 16 NSPs by two viral protease, NSP3 (PLpro) and NSP5 (3CL). The structural proteins including spike (S), envelope (E), membrane (M) and nucleocapsid (N), and accessory proteins are translated from subgenomic RNAs produced by the discontinuous translation of negative-strand RNAs (Fernandes *et al.*, 2020; Huston *et al.*, 2021; V'kovski *et al.*, 2021; Yan *et al.*, 2021).

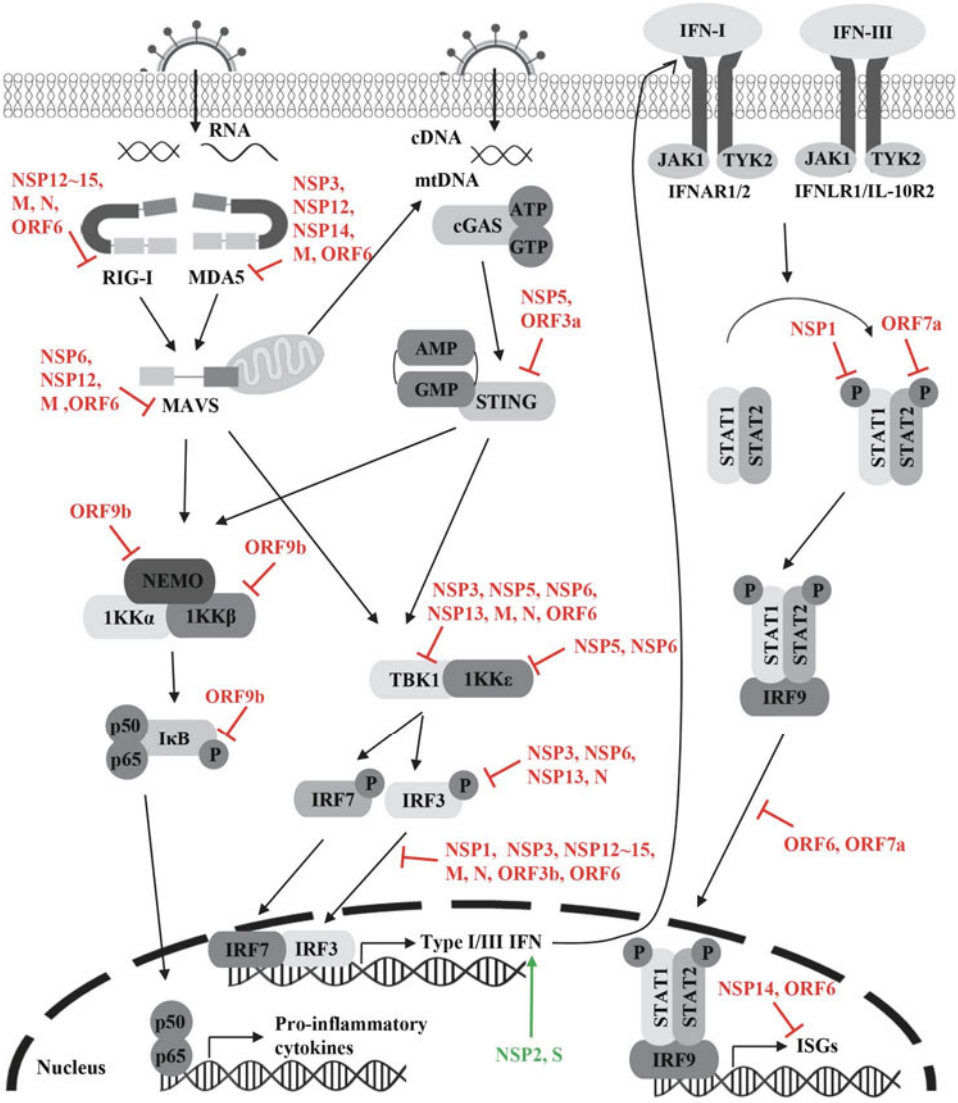

Fig. 2. Regulation of type I and III IFN signaling pathways by SARS-CoV-2 proteins. Cellular proteins involved in type I and III IFN signaling pathways are represented in gray. SARS-CoV-2 proteins which activate and inhibit the pathways are represented in green and red, respectively.

and Tschopp, 2006; Chiu *et al.*, 2009; Nakhaei *et al.*, 2009; Stone *et al.*, 2019). RLRs sense viral RNAs in the cytoplasm and activate the adaptor protein, mitochondrial antiviral signaling protein (MAVS). Activated MAVS interacts with inhibitor of nuclear factor kappa-B kinase subunit epsilon (IKKε) and the serine/threonine-protein kinase 1 (TBK1) to phosphorylate transcription factors, such as nuclear factor κB (NF-κB) and interferon (IFN) regulatory factor 3 and 7 (IRF3 and IRF7). Phosphorylated transcription factors translocate to the nucleus and induce the expression of pro-inflammatory cytokines and type I and III IFNs (Dutta *et al.*, 2017; Brisse and Ly, 2019; Zhang *et al.*, 2019). Upon binding of type I and III IFNs to the heterodimeric receptors composed of the IFN-α receptor 1 (IFNAR1) and the IFN-α receptor 2 (IFNAR2) and the IFN-λ receptor (IFNLR1 or IL-28Rα) and the interleukin 10 receptor 2 (IL-10R2), respectively, the Janus kinase (JAK) family of protein tyrosine kinases is activated and phosphorylates signal transducer and activator of transcription (STAT) 1 and 2. Phosphorylated STAT1 and 2 bind to the IRF9 and form interferon-stimulated gene factor 3 (ISGF3) transcription factor complex which translocates to the nucleus and induces the expression of the ISGs (Chmiest *et al.*, 2016; Majoros *et al.*, 2017). The ISGs interfere with the virus life cycle by blocking viral entry, uncoating, gene expression, replication, assembly or egress (Schoggins, 2019). Indeed, ISGs inhibit the different stages of the SARS-CoV-2 life cycle. For example, SARS-CoV-2 replication and egress are suppressed by LY6E and BST2, respectively (Martin-Sancho *et al.*, 2021). Furthermore, LY6E, CLEC4D, UBC, ELF1, FAM46C, and REC8 block SARS-CoV-2 entry (Martin-Sancho *et al.*, 2021).

RLRs are reported to play a critical role in suppressing SARS-CoV-2 replication (Rebendenne *et al.*, 2021; Yamada *et al.*, 2021). MDA5, but not RIG-I, is essential for sensing SARS-CoV-2 and inducing type I and III IFNs in lung epithelial cells (Rebendenne *et al.*, 2021). Interestingly, RIG-I has also been shown to inhibit SARS-CoV-2 replication in a manner independent of type I and III IFN signaling. Upon infection, RIG-I senses the 3' untranslated region of the RNA genome of SARS-CoV-2 and interferes with viral RNA-dependent RNA polymerase (RdRP)-mediated replication (Yamada *et al.*, 2021).

To evade host innate immune responses, SARS-CoV-2 employs a number of viral proteins that block RLR-mediated IFN signaling pathways (Fig. 2). Nonstructural protein 1 (NSP1) suppresses translocation of IRF3 to the nucleus and reduces the IFN-β level in addition to inhibiting phosphorylation of STAT1 and degrading STAT2 via proteasome (Xia *et al.*, 2020; Kumar *et al.*, 2021). The papain-like protease (PLpro) domain of NSP3, which cleaves the viral polyproteins to generate NSP1, NSP2, and NSP3 (Klemm *et al.*, 2020), interacts with and de-ISGylates MDA5 to block ISG15 conjugation and activation of MDA5 (Liu *et al.*, 2021a). Furthermore, PLpro suppresses phosphorylation of TBK1 and promotes de-ISGylation of IRF3 to inhibit its phosphorylation and nuclear translocation (Shin *et al.*, 2020). NSP5 protease (3CLpro or Mpro), which cleaves the viral polyproteins to generate 13 NSPs (NSP4 to NSP16) (Klemm *et al.*, 2020), blocks TBK1- and IKKε-induced IFN-β promoter activity and nuclear translocation of IRF3 (Fung *et al.*, 2021). NSP6, a membrane protein which forms a replication-transcription complex with NSP3 and NSP4 (Pandey *et al.*, 2020), suppresses MAVS-, TBK1- and IKKε-induced IFN-β promoter activation, interacts with TBK1, and inhibits phosphorylation of IRF3 (Xia *et al.*, 2020). NSP12, a RNA-dependent RNA polymerase (RdRp) (Peng *et al.*, 2020), inhibits the nuclear translocation of IRF3 and suppresses RIG-I, MDA5, MAVS and IRF3-induced IFN-β promoter activation (Wang *et al.*, 2021). Mutational studies further indicate that the enzymatic activity of NSP12 is not required for this inhibition (Wang *et al.*, 2021). NSP13 helicase interacts with TBK1, consequently inhibiting phosphorylation of TBK1 and IRF3 (Xia *et al.*, 2020). NSP13 as well as NSP14, which contains 3' to 5' exoribonuclease and methyltransferase guanine-N7 methyltransferase activity, and NSP15 a uridine specific endoribonuclease, individually block nuclear translocation of IRF3 and inhibit RIG-I-induced IFN-β promoter activation (Yuen *et al.*, 2020). Furthermore, NSP14 inhibits IFN-dependent ISG induction through suppressing synthesis of proteins such as ISGs, RIG-I, MDA5, and STING (Hsu *et al.*, 2021). Membrane (M) protein interacts with RIG-I, MDA5, MAVS, and TBK1 and blocks the formation of complexes with downstream proteins of the signaling pathway (Zheng *et al.*, 2020). The protein inhibits the RIG-I/MDA5 signaling pathway, but not TRIF- or STING-mediated IFN activation (Zheng *et al.*, 2020). In another study, the M protein is reported to interact with MAVS, but not RIG-I, MDA5 or TBK1, and block recruitment of downstream proteins including TRAF3, TBK1, and IRF3 (Fu *et al.*, 2021). Further reports suggest that the M protein interacts with MDA5, TRAF3, TBK1, and IKKε and degrades TBK1 via K48-linked ubiquitination to suppress type I IFN production (Sui *et al.*, 2021). The M protein is additionally reported to inhibit nuclear translocation of IRF3, but not phosphorylation (Sui *et al.*, 2021). Although it is well established that the M protein inhibits RIG-I/MDA5 signaling pathway, the detailed mechanisms remain unclear. The nucleocapsid (N) protein interacts with RIG-I and blocks TBK1 interactions with IRF3, thus suppressing phosphorylation and nuclear translocation of IRF3 and inhibiting IFNβ promoter activation (Chen *et al.*, 2021; Liu *et al.*, 2021b; Oh and Shin, 2021). The open-reading frame (ORF) 3b (ORF3b) of SARS-CoV-2 includes four stop codons that produce four derivatives, specifically, 57a.a, 79a.a, 119a.a, and 155a.a. Except for 155a.a, ORF3b derivatives suppress IFN-β promoter activity to a greater extent. For instance, Ecuador variant ORF3b lacking the first stop codon inhibits type I IFN activation more significantly than original SARS-CoV-2 ORF3b. In addition, ORF3b inhibits nuclear translocation of IRF3 and IRF3-induced type I IFN activation (Konno *et al.*, 2020). ORF6 inhibits RIG-I-, MDA5-, MAVS-, TBK1-, and IRF3-5D-induced IFN-β promoter activation and IFN-β-induced ISRE promoter activation with amino acids (aa) at position 53 to 61 identified as the key region involved in suppression of both IFN-β promoter activation and type I and III IFN secretion. In addition, ORF6 binds KPNA2, but not the other KPNAs, suppressing nuclear translocation of IRF3 (Lei *et al.*, 2020; Xia *et al.*, 2020; Yuen *et al.*, 2020). Another study by Miorin *et al.* (2020) reports that ORF6 interacts with KPNA1, KPNA2 and Nup98-Rae1 complex and blocks nuclear translocation of STAT. ORF7a inhibits IFNα-induced mRNA expression of ISGs, such as ISG56, IFITM and OAS1, through K63-linked ubiquitina-

Table 1. Summary of SARS-CoV-2 proteins regulating type I and III IFN pathways

ORF	Mechanism of action	References
NSP1	Inhibits phosphorylation of STAT1 and nucleus translocation of IRF3	Kumar *et al.* (2021) Xia *et al.* (2020)
NSP2	Increases SeV-induced IFN-β promoter activation	Lei *et al.* (2020)
NSP3 (PLpro)	De-ISGylated MDA5 and IRF3	Liu *et al.* (2021a)
NSP5 (3CL)	Inhibits TBK1- or IKKε-induced IFN-β promoter activation Interacts with STING and inhibits recruitment of TBK1 and IKKβ	Fung *et al.* (2021) Rui *et al.* (2021)
NSP6	Inhibits MAVS-, TBK1- and IKKε-induced IFN-β promoter activation	Xia *et al.* (2020)
NSP12	Inhibits RIG-I- and MDA5-induced IFN-β promoter activation Inhibits nuclear translocation of IRF3	Wang *et al.* (2021) Wang *et al.* (2021)
NSP13	Inhibits phosphorylation of TBK1 and IRF3 Inhibits RIG-I-induced IFN-β promoter activation Inhibits nuclear translocation of IRF3	Xia *et al.* (2020) Yuen *et al.* (2020) Yuen *et al.* (2020)
NSP14	Inhibits RIG-I-induced IFN-β promoter activation Inhibits nuclear translocation of IRF3 Inhibits IFN-dependent ISG induction	Yuen *et al.* (2020) Yuen *et al.* (2020) Hsu *et al.* (2021)
NSP15	Inhibits RIG-I-induced IFN-β promoter activation Inhibits nuclear translocation of IRF3	Yuen *et al.* (2020) Yuen *et al.* (2020)
S	Increases SeV-induced IFN-β promoter activation	Lei *et al.* (2020)
M	Inhibits RIG-I and MDA5 Degradation of TBK1 via K48-linked ubiquitination	Zheng *et al.* (2020) Sui *et al.* (2021)
N	Interacts with RIG-I and inhibits TBK1	Chen *et al.* (2021) Liu *et al.* (2021b) Oh and Shin (2021)
ORF3a	Interacts with STING and inhibits degradation of IκB	Rui *et al.* (2021)
ORF3b	Inhibits nuclear translocation of IRF3	Konno *et al.* (2020)
ORF6	Inhibits RIG-I and MDA5 Inhibits nuclear translocation of STAT	Lei *et al.* (2020) Xia *et al.* (2020) Yuen *et al.* (2020) Miorin *et al.* (2020)
ORF7a	Inhibits phosphorylation of STAT2 and nuclear translocation of STAT1	Cao *et al.* (2021)
ORF9b	Interacts with NEMO and suppresses K63-linked polyubiquitination	Wu *et al.* (2021)

tion (Cao *et al.*, 2021). Ubiqutinated ORF7a suppresses STAT2 phosphorylation and nuclear translocation of STAT1 (Cao *et al.*, 2021). ORF9b interacts with TOM70, an adapter protein of the RIG-I/MDA5-triggered signaling complex, localizes to the mitochondrial membrane through interactions with the C-terminal domain of TOM70, and inhibits MAVS-induced IFN-β promoter activation (Jiang *et al.*, 2020). ORF9b has additionally been shown to inhibit SARS-CoV-2-, SeV-, VSV-, and poly(I:C)-induced IFNβ promoter activity and VSV-mediated expression of pro-inflammatory cytokine and chemokine genes, such as IL-6, TNF, CCL2, CXCL10 and ISG15 (Wu *et al.*, 2021). Upon confirming a more specific mechanism, ORF9b suppresses IFNβ and NF-κB promoter activation induced by constitutively active form of RIG-I and MAVS, but not TBK1 and IKKβ. Moreover, ORF9b interacts with NF-κB essential modulator (NEMO) through the N terminus, suppressing its K63-linked polyubiquitination and inhibits phosphorylation of IKKβ and inbibitor of κB (IκB) as well as translocation of NF-κB into the nucleus (Wu *et al.*, 2021).

Interestingly, SARS-CoV-2 also employs viral proteins that activate type I and III IFN signaling pathways. For example, NSP2 and S proteins are reported to enhance SeV-induced IFN-β promoter activation (Lei *et al.*, 2020). However, the specific involvement of IFN-β promoter activation by NSP2 and S proteins in the life-cycle and pathogenesis of SARS-CoV-2 require further investigation.

Although cyclic GMP-AMP (cGAMP) synthase (cGAS) is a cytosolic DNA sensor that recognizes viral DNA for activation of type I and III IFN signaling pathways, activation of stimulator interferon genes (STING) also inhibits SARS-CoV-2 infection (Liu *et al.*, 2021c). Upon DNA binding, cGAS synthesizes cGAMP that activates STING on the endoplasmic reticulum (Dai *et al.*, 2019). STING activates TBK1 and IKK activity, thereby stimulating IRF3 and NF-κB to induce expression of type I and III IFNs (Carroll *et al.*, 2016; Prabakaran *et al.*, 2018; Zierhut *et al.*, 2019). RNA viruses, such as human immunodeficiency virus (HIV) and Dengue virus, activate cGAS by producing reverse-transcribed cDNA (Sun *et al.*, 2017) and inducing mitochondrial damage leading to release of mitochondrial DNA (mtDNA) (Sun *et al.*, 2017; Gatti *et al.*, 2020). To counteract the cGAS-STING pathway, SARS-CoV-2 3CL pro (NSP5) and ORF3a interact with STING and inhibit nuclear translocation of NF-κB p65. Furthermore, recruitment of downstream factors, such as TBK1 and IKKβ, is suppressed by 3CL pro but not ORF3a (Rui *et al.*, 2021) (Fig. 2). Further research is required to establish the role of the cGAS-STING pathway in SARS-CoV-2-induced type I and III IFN signaling pathways and identify the viral proteins counteracting the pathway. The mechanisms used by SARS-CoV-2 proteins to regulate type I and III IFN pathways are summarized in Table 1.

SARS-CoV-2 and the NLRP3 Inflammasome

The inflammasome is an intracellular multi-protein complex consisting of a sensor protein, the adaptor apoptosis-associated speck-like protein containing a CARD (ASC) protein and caspase-1 (Guo *et al.*, 2015; Próchnicki and Latz, 2017; Yang *et al.*, 2019). Upon virus infection, NLRP3 and the pyrin and hematopoietic interferon-inducible nuclear (PYHIN) domain proteins, including absent in melanoma 2 (AIM2) and interferon-γ (IFN-γ) inducible protein 16 (IFI16), recruit the adaptor ASC proteins and promote ASC oligomerization to activate caspase-1. Subsequently, activated caspase-1 proteolytically cleaves and activates the pro-inflammatory cytokines, IL-β and pro-IL-18. Caspase-1 also cleaves gasdermin D (GSDMD) to induce pyroptosis of infected cells.

SARS-CoV-2 infection clearly activates the NLRP3 inflammasome (Rodrigues *et al.*, 2021). Levels of inflammasome products, such as caspase-1, IL-1β and IL-18, are significantly increased in SARS-CoV-2 infection and COVID-19 patients (Ferreira *et al.*, 2021; Rodrigues *et al.*, 2021). Dysregulated IL-1β induces IL-6 secretion and subsequent production of vascular endothelial growth factor, which damages the pulmonary endothelium associated with immune cell infiltration (Vora *et al.*, 2021). NLRP3 inhibitors, such as glyburide and MCC950, have been shown to inhibit SARS-CoV-2-triggered caspase-1 activation and IL-1β production (Ferreira *et al.*, 2021; Rodrigues *et al.*, 2021).

According to a recent study, potassium (K^+) efflux induced by GU-rich RNA of SARS-CoV-2 is one of the mechanisms underlying NLRP3 inflammasome activation (Campbell *et al.*, 2021) (Fig. 3). Furthermore, N protein of SARS-CoV-2 activates the NLRP3 inflammasome by interacting with NLRP3 and promoting its interactions with ASC, resulting in ASC oligomerization. In addition, N protein promotes mRNA expression of IL-1β, CXCL10, IL-11,TNF and IL-13 and IL-1β secretion (Pan *et al.*, 2021).

Interestingly, SARS-CoV-2 also employs NSP1 and NSP13 to inhibit NLRP3-inflammasome-induced caspase-1 activity and IL-1β secretion (Kim *et al.*, 2021) (Fig. 3). NSP1 of SARS-CoV-1 binds the 40S ribosome subunit and inhibits host mRNA translation (Kamitani *et al.*, 2006; Wathelet *et al.*, 2007; Narayanan *et al.*, 2008; Huang *et al.*, 2011). SARS-CoV-2 NSP1 may utilize a similar mechanism to inhibit the NLRP3 inflammasome since NLRP3, ASC and caspase-1 levels are significantly reduced in NSP1-expressing human monocytic THP-1 cells (Kim *et al.*, 2021). On the other hand, NSP13 inhibits NLRP3 inflammasome-induced caspase-1 cleavage without affecting NLRP3, ASC and caspase-1 protein levels (Kim *et al.*, 2021). NSP13 helicase is proposed to be associated with inhibition of caspase-1 enzymatic activity (Kim *et al.*, 2021). Another study by Ma *et al.* (2021) reports that the N protein inhibits pyroptosis by blocking GSDMD clea-

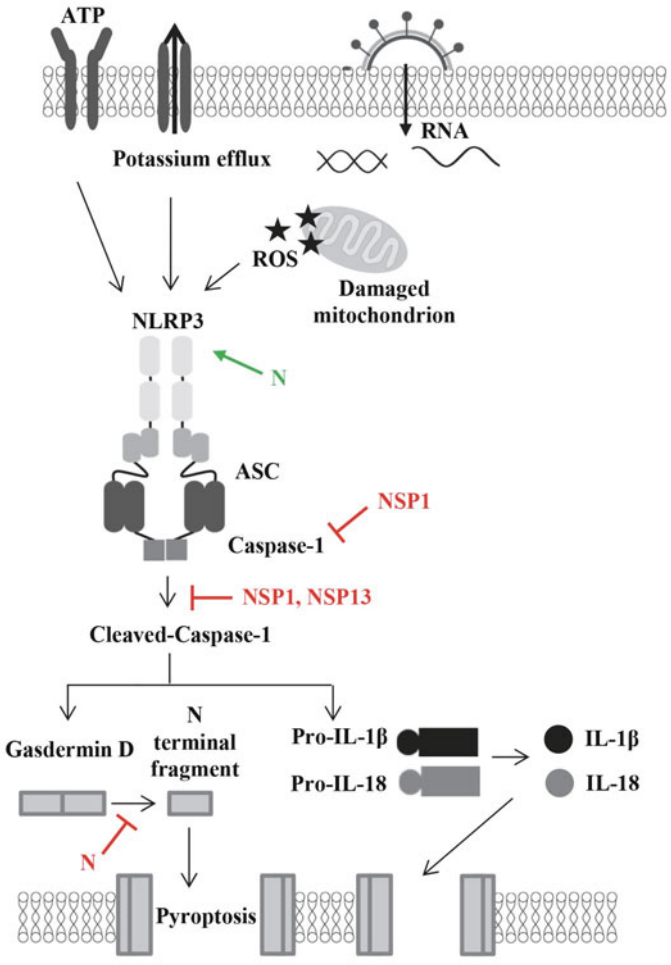

Fig. 3. Regulation of the NLRP3 inflammasome by SARS-CoV-2 proteins. Cellular proteins involved in the NLRP3 inflammasome pathway are represented in gray. SARS-CoV-2 proteins which activate and inhibit the pathway are represented in green and red, respectively.

Table 2. Summary of SARS-CoV-2 proteins regulating the NLRP3 inflammasome

ORF	Mechanism of action	References
NSP1	Inhibits caspase-1 activity	Kim *et al.* (2021)
NSP13	Inhibits caspase-1 activity	Kim *et al.* (2021)
N	Interacts with NLRP3 and activates the NLRP3 inflammasome Interacts with GSDMD and inhibits GSDMD cleavage	Pan *et al.* (2021) Ma *et al.* (2021)

vage via interaction with GSDMD C terminus and the linker region. The potential mechanisms by which SARS-CoV-2 proteins regulate the NLRP3 inflammasome are summarized in Table 2.

Conclusion

Type I and III IFNs and the inflammasome play pivotal roles in pathogenesis of SARS-CoV-2. Properly regulated type I and III IFN and inflammasome responses are essential for the host to eliminate the virus. Notably, aberrant IFN and inflammasome activation are signatures of SARS-CoV-2 infection and COVID-19 severity is highly associated with suppressed type I and III IFN responses and exaggerated inflammasome activation (Arunachalam *et al.*, 2020; Hadjadj *et al.*, 2020; Ferreira *et al.*, 2021; Galani *et al.*, 2021; Junqueira *et al.*, 2021; Rodrigues *et al.*, 2021; Zheng *et al.*, 2021). In keeping with these characteristics, pre-treatment with type I IFN is reported to significantly suppress SARS-CoV-2 replication and blockade of the IL-1 receptor is an effective strategy for COVID-19 patients with severe respiratory conditions (Cauchois *et al.*, 2020; Felgenhauer *et al.*, 2020; Lokugamage *et al.*, 2020; Mantlo *et al.*, 2020; Rebendenne *et al.*, 2021). However, type I and III and inflammasome responses to SARS-CoV-2 infection are more complex than initially anticipated. SARS-CoV-2 utilizes viral proteins to evade the above immune mechanisms while simultaneously activating these responses to promote viral dissemination and immunopathogenesis. As other pathogens, SARS-CoV-2 pathogenesis is affected by a triad of factors: virus, host and environment. Type I and III and inflammasome responses to SARS-CoV-2 may differ depending on various factors including the infectious dose and differences in the genetic background of virus and host cells and at cellular and systemic host levels. Further studies considering these multiple factors are necessary to understand the mechanisms underlying viral-pathogenesis and develop effective therapeutic interventions for COVID-19.

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Conflict of Interest

The authors have no conflict of interest to report.

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