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 coronavirus 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 proinflammatory 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 these compelling 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 et al., 2007; Meylan et al., 2008; Zhang et al., 2016; Zhang et al., 2017). In the context of SARS-CoV-2 infection, RIG-I is activated by viral RNA, while MDA5 is activated by viral RNAs and dsRNAs. Recognition of viral RNA by RIG-I or MDA5 leads to the activation of the mitochondrial antiviral signaling protein (MAVS), which is essential for activating the IFN pathway. MAVS associates with the mitochondrial outer membrane and recruits the CARD-containing protein, NLR family pyrin domain containing 3 (NLRP3), to form a complex that includes the adaptor protein, ASC, and the pro-caspase, caspase-1. This complex, known as the inflammasome, promotes the maturation and release of the pro-inflammatory cytokines, IL-1β and IL-18, which contribute to the immune response against SARS-CoV-2.


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Regulation of innate immune signaling pathways by SARS-CoV-2

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, mitochondriantonal antivirus signaling protein (MAVS). Activated MAVS interacts with inhibitor of nuclear factor kappa-B kinase subunit epsilon (IKKe) and the serine/threonine-protein kinase 1 (TBK1) to phosphorylate transcription factors, such as nuclear factor kB (NF-kB) 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-28Ra) 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; Majorsor et al., 2017). The ISGs interfere with the virus life cycle by blocking viral entry, uncoating, gene expression, replication, assembly or egress (Schooggins, 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-1, is essential for sensing SARS-CoV-2 and inducing type I and III IFNs in lung epithelial cells (Rebendenne et al., 2021). Interestingly, RIG-1 has also been shown to inhibit SARS-CoV-2 replication in a manner independent of type I and III IFN signaling. Upon infection, RIG-1 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 IFR3 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 IFR3 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 IKKe-induced IFN-β promoter activity and nuclear translocation of IFR3 (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 IKKe-induced IFN-β promoter activation, interacts with TBK1, and inhibits phosphorylation of IFR3 (Xia et al., 2020). NSP12, a RNA-dependent RNA polymerase (RdRP) (Peng et al., 2020), inhibits the nuclear translocation of IFR3 and suppresses RIG-1, MDA5, MAVS and IFR3-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 IFR3 (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 IFR3 and inhibit RIG-1-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-1, 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 (Zhang et al., 2020). The protein inhibits the RIG-I/ MDA5 signaling pathway, but not TRIF- or STING-mediated IFN activation (Zhang 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 IFR3 (Fu et al., 2021). Further reports suggest that the M protein interacts with MDA5, TRAF3, TBK1, and IKKe 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 IFR3, 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 IFR3, thus suppressing phosphorylation and nuclear translocation of IFR3 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 IFR3 and IFR3-induced type I IFN activation (Konno et al., 2020). ORF6 inhibits RIG-I, MDA5-, MAVS-, TBK1-, and IFR3-5D-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 KPNAs, but not the other KPNAs, suppressing nuclear translocation of IFR3 (Lei et al., 2020; Xia et al., 2020; Yuen et al., 2020). Another study by Miorin et al. (2020) reports that ORF6 interacts with KPNAs, KPNAs2 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-
Mechanism of action

Cao
Inhibits RIG-I and MDA5
Inhibits RIG-I- and MDA5-induced IFN-β promoter activation
De-ISGylated MDA5 and IRF3
Inhibits phosphorylation of STAT2 and nuclear translocation of STAT1
Interacts with NEMO and suppresses K63-linked polyubiquitination

Wu
Inhibits RIG-I-induced IFN-β promoter activation
Increases SeV-induced IFN-β promoter activation
Interacts with STING and inhibits degradation of IκB
Inhibits phosphorylation of STAT1 and nuclear translocation of IRF3
Inhibits MAVS-, TBK1- and IKKε-induced IFN-β promoter activation

Xia
Increases SeV-induced IFN-β promoter activation

References
Inhibits nuclear translocation of IRF3

Raw Text: Mechanism of action

Cao
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Inhibits MAVS-, TBK1- and IKKε-induced IFN-β promoter activation

Xia
Increases SeV-induced IFN-β promoter activation

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 nuclear translocation of IRF3 | Kumar et al. (2021)                 |
|       | Inhibits RIG-I- and MDA5-induced IFN-β promoter activation | 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 | Fung et al. (2021)                  |
|       | Interacts with STING and inhibits recruitment of TBK1 and IKKβ | 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 | Wang et al. (2021)                  |
|       | Inhibits nuclear translocation of IRF3                  | Wang et al. (2021)                  |
| NSP13 | Inhibits phosphorylation of TBK1 and IRF3               | Xie et al. (2020)                   |
|       | Inhibits RIG-I-induced IFN-β promoter activation         | Yuen et al. (2020)                  |
|       | Inhibits nuclear translocation of IRF3                  | Yuen et al. (2020)                  |
| NSP14 | Inhibits phosphorylation of STAT1 and nuclear translocation of IRF3 | Yuen et al. (2020)                  |
|       | Inhibits nuclear translocation of IRF3                  | Hsu et al. (2021)                   |
| NSP15 | Inhibits RIG-I-induced IFN-β promoter activation         | Yuen et al. (2020)                  |
|       | Inhibits nuclear translocation of IRF3                  | Yuen et al. (2020)                  |
| S     | Increases SeV-induced IFN-β promoter activation          | Lei et al. (2020)                   |
| M     | Inhibits RIG-I and MDA5                                  | Zheng et al. (2020)                 |
|       | Degradation of TBK1 via K48-linked ubiquitination        | Sui et al. (2021)                   |
| N     | Interacts with RIG-I and inhibits TBK1                   | Chen et al. (2021)                  |
|       | Interacts with STING and inhibits degradation of IκB     | Liu et al. (2021b)                  |
|       | Inhibits nuclear translocation of IRF3                  | Oh and Shin (2021)                  |
| ORF3a | Interacts with TBK1 and inhibits TBK1                    | Rui et al. (2021)                   |
| ORF3b | Inhibits nuclear translocation of IRF3                   | Kono et al. (2020)                  |
| ORF6  | Inhibits RIG-I and MDA5                                  | Lei et al. (2020)                   |
|       | Inhibits nuclear translocation of STAT                   | Xia et al. (2020)                   |
|       | Inhibits nuclear translocation of IRF3                   | Yuen 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)                   |

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.

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.

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 nuclear translocation of IRF3 | Kumar et al. (2021)                 |
|       | Inhibits RIG-I- and MDA5-induced IFN-β promoter activation | 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 | Fung et al. (2021)                  |
|       | Interacts with STING and inhibits recruitment of TBK1 and IKKβ | 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 | Wang et al. (2021)                  |
|       | Inhibits nuclear translocation of IRF3                  | Wang et al. (2021)                  |
| NSP13 | Inhibits phosphorylation of TBK1 and IRF3               | Xie et al. (2020)                   |
|       | Inhibits RIG-I-induced IFN-β promoter activation         | Yuen et al. (2020)                  |
|       | Inhibits nuclear translocation of IRF3                  | Yuen et al. (2020)                  |
| NSP14 | Inhibits phosphorylation of STAT1 and nuclear translocation of IRF3 | Yuen et al. (2020)                  |
|       | Inhibits nuclear translocation of IRF3                  | Hsu et al. (2021)                   |
| NSP15 | Inhibits RIG-I-induced IFN-β promoter activation         | Yuen et al. (2020)                  |
|       | Inhibits nuclear translocation of IRF3                  | Yuen et al. (2020)                  |
| S     | Increases SeV-induced IFN-β promoter activation          | Lei et al. (2020)                   |
| M     | Inhibits RIG-I and MDA5                                  | Zheng et al. (2020)                 |
|       | Degradation of TBK1 via K48-linked ubiquitination        | Sui et al. (2021)                   |
| N     | Interacts with RIG-I and inhibits TBK1                   | Chen et al. (2021)                  |
|       | Interacts with STING and inhibits degradation of IκB     | Liu et al. (2021b)                  |
|       | Inhibits nuclear translocation of IRF3                  | Oh and Shin (2021)                  |
| ORF3a | Interacts with TBK1 and inhibits TBK1                    | Rui et al. (2021)                   |
| ORF3b | Inhibits nuclear translocation of IRF3                   | Kono et al. (2020)                  |
| ORF6  | Inhibits RIG-I and MDA5                                  | Lei et al. (2020)                   |
|       | Inhibits nuclear translocation of STAT                   | Xia et al. (2020)                   |
|       | Inhibits nuclear translocation of IRF3                  | Yuen 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)                   |
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-
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.

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