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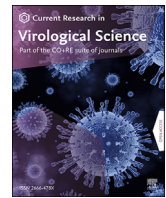
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## Devil's tools: SARS-CoV-2 antagonists against innate immunity

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### ABSTRACT

The unprecedented Coronavirus pandemic of 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Like other coronaviruses, to establish its infection, SARS-CoV-2 is required to overcome the innate interferon (IFN) response, which is the first line of host defense. SARS-CoV-2 has also developed complex antagonism approaches involving almost all its encoding viral proteins. Here, we summarize our current understanding of these different viral factors and their roles in suppressing IFN responses. Some of them are conserved IFN evasion strategies used by SARS-CoV; others are novel countermeasures only employed by SARS-CoV-2. The filling of gaps in understanding these underlying mechanisms will provide rationale guidance for applying IFN treatment against SARS-CoV-2 infection.

### 1. Introduction

The World Health Organization declared the 2019 Coronavirus disease (COVID-19) outbreak as a pandemic on March 11<sup>th</sup>, 2020. There are more than 248 million recorded cases, resulting in over 5 million deaths globally as of the end of October 2021. This ongoing pandemic poses an unprecedented threat to global public health. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to Betacoronavirus, which is one of the four genera (Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus) of the Orthocoronavirinae subfamily of the Coronaviridae family (Fung and Liu, 2019). As of now, there are a total of seven strains of alpha- and betacoronaviruses known to cause human illnesses. Among them, HCoV-229E, HCoVOC43, HCoV-NL63, and HCoV-HKU1 cause only mild upper respiratory symptoms, resulting in the so-called seasonal common cold (Fung and Liu, 2019). However, infection with the other three betacoronaviruses, SARS-CoV, MERS-CoV, and SARS-CoV-2, can cause severe respiratory symptoms with unique disease outcomes, such as severe lymphopenia and acute respiratory distress syndrome (ARDS) (Tse et al., 2020).

Like other coronaviruses, SARS-CoV-2 is an enveloped virus with a ~30 kb single-stranded positive-sense RNA genome wrapped with viral nucleocapsid (N) protein (Fung and Liu, 2019). It encodes 16 nonstructural proteins (NSP1–16), 4 structural proteins [spike (S), envelop (E), membrane (M), and nucleocapsid (N) protein], and 8 accessory proteins (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, and ORF10)

(Biswal et al., 2021; Finkel et al., 2021; Jungreis et al., 2021; Yaara Finkel et al., 2020). SARS-CoV-2 virus enters cells through the binding of its surface glycoprotein (S protein) to its cell surface receptor, human angiotensin I-converting enzyme-2 (hACE2) (Wan et al., 2020). After entry, its genomic RNA is released from N proteins and first translated into two open reading frames (ORFs), ORF1a and ORF1b, resulting in two polyproteins, pp1a and pp1ab. These two large polyproteins are further processed to generate 16 nonstructural proteins (NSP1–NSP16) through the cleavage by two viral proteases, NSP3 (papain-like protease) and NSP5 (3C-like protease) (Thiel et al., 2003). Subsequently, newly generated NSP2–NSP16 will form the viral replication and transcription complex (RTC) to start viral genomic RNA replication and subgenomic mRNA transcription. Among these viral proteins, NSP12 is the core component of the RNA-dependent RNA polymerase (RdRp), NSP7 and NSP8 serve as cofactors, and NSP13–NSP16 are RNA-modifying enzymes. Together, they complete viral RNA synthesis. This happens in the protective microenvironment of double membrane vesicles (DMV). Viral structural proteins (S, E, M, and N) are translated from subgenomic mRNAs. They subsequently migrate from the endoplasmic reticulum (ER) to the ER-to-Golgi intermediate compartment (ERGIC). In here, together with newly synthesized genomic RNA coated by the N protein, they form virions. Mature virions are released through the host exocytosis pathway for the next round of infection (Thiel et al., 2003).

The innate interferon (IFN) response is a critical component of the host's first line of defense, which is required to limit viral infection. There are three types of IFNs. Specifically, type I IFN (IFN-I) is a key factor in

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IFN responses that combat the virus through autocrine and paracrine type I IFN receptor (IFNAR)-mediated signaling responses (Acharya et al., 2020; Meylan et al., 2006; Park and Iwasaki, 2020). COVID-19 cases among people with compromised IFN conditions often correlate to prolonged and severe symptoms (Peyneau et al., 2021). Further study revealed that enhanced disease outcomes are associated with mutations in genes such as TLR3 and UNC93B, which are known regulators of IFN production or factors involved in IFN-I signaling pathways (Zhang et al., 2020).

Therefore, to establish infection successfully, SARS-CoV-2 needs to inhibit IFN-I responses. It is no surprise that SARS-CoV-2 has developed complex strategies to inhibit the induction of IFN-I (Hayn et al., 2021). In the following short review, we will focus on summarizing the current understanding of SARS-CoV-2 proteins involved in antagonizing host IFN-I production and/or signaling. This information will help to promote our understanding of COVID-19 outcomes, since they are determined by the combination of SARS-CoV-2 infection and host immune responses induced by the infection (Xia and Shi, 2020).

## 2. Viral-encoded IFN-I antagonists

### 2.1. Nonstructural proteins

SARS-CoV-2 utilizes several of its 16 NSPs (NSP1-16) to suppress host IFN-I response by targeting various biological factors/pathways.

#### 2.2. NSP1

NSP1 (PDB: 7K7P) is a known potent IFN suppressor in other coronaviruses (Clark et al., 2021). In SARS-CoV, NSP1 has been shown to inhibit IFN-I production through inhibiting expression of host genes (likely due to mRNA degradation and/or direct translation inhibition) and reducing the phosphorylation of STAT1 (Huang et al., 2011; Kamitani et al., 2009; Narayanan et al., 2008). Since SARS-CoV-2 NSP1 is over 80% amino acid sequence identical to its SARS-CoV counterpart, it is not surprising to see that SARS-CoV-2 NSP1 can also inhibit IFN-I induction and signaling (Mantlo et al., 2020). It can inhibit host gene expression through blocking the mRNA export machinery (Zhang et al., 2021a; Jin et al., 2021) or by directly binding to the 40S ribosomal subunit (Thoms et al., 2020). Nsp1-bound 40S ribosomal complexes have been revealed by cryo-electron microscopy (cryo-EM) (Thoms et al., 2020). Intriguingly, SARS-CoV-2 NSP1 uses additional approaches to antagonize host IFN-I responses. It can prevent IFN induction through blocking IRF3 phosphorylation, and lessen interferon-stimulated gene (ISG) induction by triggering the depletion of TYK2 and STAT2, components of the IFN-I signaling pathway (Kumar et al., 2021).

#### 2.3. NSP3

NSP3 is the largest coronaviral protein (Alhammad et al., 2021; Brosey et al., 2021) with 3 three tandem MacroD-like macrodomains (Mac1, Mac2, and Mac3). NSP3 binds to and removes ADP-ribose from proteins in a dynamic posttranslational process (Alhammad et al., 2021). This putative ADP-ribosylation function was further supported by the crystal structure of the Mac1 domain (PDB: 6WOJ) (Alhammad et al., 2021). Additionally, NSP3 was shown to be involved with the disruption of innate host immunity through multiple functions, such as its papain-like protease (PLpro) being required for the separation of NSP1-4 (Alhammad et al., 2021). It also contains a potential deubiquitinase (DUB) domain based on sequence analysis, which suggests its role in deubiquitinating host polyubiquitinated proteins (Clementz et al., 2010; Klemm et al., 2020). Experimental evidence has been obtained to show that SARS-CoV-2 NSP3 inhibits IFN-I production through 1) cleaving the ubiquitin-like protein, ISG15, 2) decreasing IRF3 phosphorylation, or 3) directly cleaving IRF3 (Shin et al., 2020; Moustaqil et al., 2021; Liu et al., 2021).

#### 2.4. NSP6

Together with NSP3 and NSP4, NSP6a transmembrane protein plays a critical role in DMV formation. The DMV microenvironment was shown to suppress host autophagy responses, resulting in restricted a IFN-I response (Xia et al., 2020; Cottam et al., 2011). Unlike SARS NSP6—which blocks the nuclear translocation of STAT1 to achieve downstream interferon signaling (Frieman et al., 2007)—SARS-CoV-2 NSP6 was shown to inhibit the IRF3 activation through interacting with TBK1 in an *in vitro* IFN- $\beta$  promoter-driven reporter assay (Xia et al., 2020).

#### 2.5. NSP7 and NSP8

Besides their accessory roles in facilitating RdRp activity, these two small proteins, NSP7 and NSP8 (PDB: 7DCD), have been shown to moderately suppress IFN-I responses (Biswal et al., 2021; Zhang et al., 2021b; Yuen et al., 2020). The molecular mechanism is better understood for NSP8, which suppresses the MDA5-derived IFN signaling pathway by physically binding to MDA5 CARD and blocking K63-linked polyubiquitination (Yang et al., 2020). However, NSP8 does not significantly suppress IFN-I signaling when compared with other nonstructural proteins, like NSP1, NSP6, NSP7 and NSP14 (Xia et al., 2020).

#### 2.6. NSP13, NSP14, and NSP15

These three proteins are RNA-modifying enzymes serving as accessory factors for the core RdRp. NSP13 (PDB: 6XEZ) is a helicase (Chen et al., 2020), which is highly conserved among coronaviruses (Finkel et al., 2021; Jungreis et al., 2021; Yaara Finkel et al., 2020; Wu et al., 2020). It is likely the driving factor enabling RdRp backtracking, improving proofreading and leading to template switching. When over-expressed, NSP13 has been shown to suppress IFN- $\beta$ -driven luciferase activity (Xia et al., 2020; Yuen et al., 2020; Lei et al., 2020). NSP13 can also decrease phosphorylation of TBK1 through their direct interaction, resulting in the inactivation of IRF3 (Jin et al., 2021; Xia et al., 2020; Gordon et al., 2020; Hoffmann et al., 2021). NSP13 was also shown to block STAT1 and STAT2 activation by hindering STAT1 from entering the nucleus, resulting in the suppression of IFN-I signaling (Xia et al., 2020; Yuen et al., 2020; Lei et al., 2020).

Both SARS-CoV-2 NSP14 and NSP15 significantly suppress the IFN- $\beta$  promoter driven luciferase expression and IFN-I signaling (Yuen et al., 2020; Lei et al., 2020). NSP14 contains two domains, 3'-to-5' exoribonuclease (ExoN) and guanine-N7-methyltransferase (N7-MTase). ExoN is required to maintain a certain degree of fidelity, and N7-MTase is involved in mRNA capping (Ogando et al., 2020). Further evidence was provided in a recent crystal structure of the ExoN region (Lin et al., 2021). The conformation reveals that its ExoN (PDB: 7DIY) maintains a complete exoribonuclease fold and an active configuration in the catalytic center. NSP14 was also shown to suppress host protein synthesis (Hsu et al., 2021). NSP15 is a uridine-specific endoribonuclease with a C-terminal EndoU like catalytic domain, conserved among coronaviruses. Its nucleotide-bound crystal structure (PDB: 6X4I) suggests a second base binding site, which can accommodate any other base (Kim et al., 2021). Even though endoribonuclease activity seems to be responsible for the interference with the innate immune response, current evidence suggests that NSP15 is likely to suppress IFN-I induction through binding to RNF41, which is an E3 ligase involved in activation of IRF3 (Gordon et al., 2020). Further studies are still required to understand the molecular mechanisms underlying their suppression of IFN.

#### 2.7. Accessory proteins

Some of the eight SARS-CoV-2 accessory proteins have also been shown to be involved in modulating IFN responses.

## 2.8. ORF3a

Along with two other viral proteins, E and ORF8a, ORF3a is a SARS-CoV-2 putative ion channel, which is located at the plasma membrane of the ER and Golgi (Kern et al., 2021; Castaño-Rodríguez et al., 2018). The 3a cryo-EM structure (ORF: 6XDC) demonstrated that 3a forms an ion channel in reconstituted liposomes (Kern et al., 2021). Experimental evidence has implied that 3a is involved in viral budding (Ghosh et al., 2020), suppressing autophagy (Miao et al., 2021), inflammasome activation (Siu et al., 2019), and promoting cell death (Freundt et al., 2010; Ren et al., 2020). Even though both SARS-CoV and SARS-CoV-2 ORF3a proteins have been shown to induce host cell apoptosis, they use different mechanisms. SARS-CoV ORF3a was shown to trigger Golgi fragmentation (Freundt et al., 2010). On the other hand, SARS-CoV-2 ORF3a was shown to activate the caspase signaling pathway (Freundt et al., 2010; Ren et al., 2020).

## 2.9. ORF3b

ORF3b is a viral protein, that travels between nucleus and cytoplasm during infection (Konno et al., 2020). Specifically, it constantly translocates between the nucleus and the outer membrane of mitochondria (Konno et al., 2020). It is a potent interferon suppressor for both SARS-CoV and SARS-CoV-2 viruses. Even though SARS-CoV-2 is more sensitive to IFN-I treatment compared to SARS-CoV (Lokugamage et al., 2020), SARS-CoV-2 ORF3b exhibited more efficient inhibition of IFN-I induction than its SARS-CoV counterpart (Konno et al., 2020). This enhancement of suppression by SARS-CoV-2 ORF3b was achieved through inhibiting the nuclear localization of IRF3 (Konno et al., 2020). Its virulence role is further supported by two natural variants, which encoded a similar elongated form of ORF3b due to the loss of its original first stop codon (Konno et al., 2020). The variants were isolated from patients with particularly severe COVID-19 symptoms from a family cluster in Quito, Ecuador (Konno et al., 2020). They exhibited even more potent inhibition on type I interferon responses compared to the wild type form (Konno et al., 2020). Interestingly, when fully restoring the SARS-CoV ORF3b-like protein in SARS-CoV-2 virus through reverting those stop codons, there was a decrease in anti-IFN activity (Konno et al., 2020). This suggests that the C-terminal region of ORF3b has a negative impact on its immune suppression activity. To better understand the underlying mechanism, structural information is needed.

## 2.10. ORF6

SARS-CoV-2 ORF6 is located at the nuclear pore through binding to Nup98-Rae1 complex (Addetia et al., 2021; Miorin et al., 2020). This results in blocking nuclear translocation of STAT1 and STAT2 causing compromised induction of ISGs (Miorin et al., 2020). This conclusion was further supported by the observation that there is no ISG inhibition when ORF6 was mutated to prevent its binding to the nuclear pore complex (Miorin et al., 2020). Through blocking of the nuclear pore, ORF6 can also cause nuclear retention of host mRNAs, resulting in a reduction in expression of host genes (Addetia et al., 2021).

## 2.11. ORF7a/7b

SARS-CoV ORF7a is a type I transmembrane protein. Its N-terminal ectodomain (PDB: 1XAK) contains a compact Ig-like domain (Nelson et al., 2005). It is mainly located in the Golgi network (Nelson et al., 2005). It has been shown to trigger cell cycle arrest (Nelson et al., 2005). Both SARS-CoV-2 ORF7a and ORF7b inhibit IFN-I signaling by blocking phosphorylation of STAT proteins. Specifically, ORF7a only inhibits STAT2 phosphorylation while ORF7b suppresses both STAT1 and STAT2 phosphorylation (Xia et al., 2020; Cao et al., 2021). In another report, SARS-CoV-2 ORF7a was shown to be an immunomodulating factor for immune cell binding that upregulates inflammatory responses (Zhou

et al., 2021).

## 2.12. ORF8

SARS-CoV-2 ORF8 is a secreted protein, containing an N-terminal signal sequence followed by an Ig-like structure revealed in its crystal structure (PDB: 7JTL) (Flower et al., 2021; Hassan et al., 2021). Its N-terminal signal sequence guides its entry into the lumen of the ER. There, SARS-CoV-2 ORF8 interacts with several host proteins, some of which have been shown to be involved in ER-associated degradation. Besides its inhibitory role in suppressing IFN- $\beta$  production and signaling (Li et al., 2020a, 2020b), SARS-CoV-2 ORF8 was shown to down-regulate MHC-I and protect virus-infected cells against Cytotoxic T lymphocytes (CTLs) (Zhang et al., 2021c), even though the underlying mechanism remains elusive.

## 2.13. ORF9b

Among the current known coronaviruses, ORF9b is only present in both SARS-CoV-2 and SARS-CoV, sized at about 98-amino acid long, and encoded by an alternative reading frame within the N gene (Xu et al., 2009). It suppresses IFN-I responses through targeting mitochondria adapter TOM70 (Gao et al., 2021; Jiang et al., 2020), which is further supported by the crystal structure of ORF9b in complex with the cytosolic domain of TOM70 (PDB: 7DHG) (Gao et al., 2021). Additionally, it can target TRIF or STING to block the activation of types I and III IFNs (Han et al., 2021). In the same study, ORF9b was shown to further compromise nuclear translocation of IRF3 by blocking IRF3 phosphorylation. Additionally, more ORF9b-associated factors were revealed, such as RIG-I, MDA-5, MAVS, TRIF, STING, and TBK1 (Han et al., 2021). It is intriguing that such a small protein has so many binding partners.

## 2.14. Structural proteins

Among the four structure proteins encoded by SARS-CoV-2, two of them, M and N proteins, have also been reported to suppress IFN-I production and signaling, just like their SARS-CoV counterparts. However, their specific targets can differ. In SARS-CoV, M protein crippled downstream IRF3/IRF7 activation and IFN production by inhibiting the formation of the TRAF3-TRAF family member associated NF- $\kappa$ B activator (TANK)-TBK1/IKK $\epsilon$  complex (Siu et al., 2009). However, in SARS-CoV-2, M protein suppresses type I and III IFN production by blocking the sensing pathways through desensitizing cytosolic viral RNA sensors, including RIG-I, MDA5, MAVS, and TBK1 via direct binding (Zheng et al., 2020). It is not clear whether these associations are mediated by mainly one transmembrane domain or the collaborative efforts of two or three transmembrane domains.

N protein comprises an N-terminal (NTD) and a C-terminal (CTD) domain. Both of them can bind to RNA. It wraps the viral RNA genome and mediates its attachment to the viral envelope as shown in the crystal structure for the complex of N protein and RNA components (PDB: 7ACT) (Ye et al., 2020; Dinesh et al., 2020). Besides its vital role in viral replication, SARS-CoV N protein was reported to be involved in suppressing host innate immunity by targeting the upstream event of RNA sensing (Lu et al., 2011) or by suppressing RIG-I ubiquitination mediated via tripartite motif containing 25 (TRIM25) through direct binding to TRIM25 (Lu et al., 2011). For SARS-CoV-2, N protein suppresses the IFN signaling pathway through a different mechanism by inhibiting the phosphorylation of STAT1 and STAT2, resulting in their retention in the cytoplasm (Jiang et al., 2020). It is fascinating that there are such differences in their functions even though the N proteins from both SARS viruses are highly conserved, with only 5 substitutions in their corresponding consensus sequences (Wu et al., 2020).

### 3. Conclusions

It is crucial to understand how SARS-CoV-2 compromises the host IFN-I responses, and understanding this will shed light on the pathogenesis of SARS-CoV-2. Like other betacoronaviruses, SARS-CoV-2 possesses multiple mechanisms inhibiting various innate immune responses, which results in a failure of fine-tuned innate immune activation. Therefore, the skewed host defense causes enhanced disease severity and mortality rather than protection. This knowledge will also provide a rationale for developing novel therapeutics targeting the distorted immune escape mechanisms of SARS-CoV-2 and their role in compromising infection. Furthermore, studies have already shown that SARS-CoV-2 is sensitive to IFN-I inhibition (Lokugamage et al., 2020; Felgenhauer et al., 2020). A more detailed understanding of the interplay between SARS-CoV-2 and the host will warrant a reliable and practical IFN-based medical intervention for COVID-19 treatment, particularly during the early stage of infection (Lokugamage et al., 2020; Blanco-Melo et al., 2020; Hadjadj et al., 2020).

With the accumulating evidence from more studies on SARS-CoV-2 proteins that antagonize IFN-I response, we are also aware that there are discrepancies for some of these factors. For example, some reports found that NSP12 inhibits the IFN-I response, whereas some did not (Xia et al., 2020; Yuen et al., 2020; Lei et al., 2020; Li et al., 2021; Wang et al., 2021). The differences might be caused by the different experimental conditions used in these studies. Therefore, it is important to validate these results in the context of viral replication. Using reverse genetic systems, recombinant viruses should be generated to carry the specific mutations and examined for their abilities to suppress IFN-I signaling. These discrepancies also reflect that we are still at the early stages of understanding the underlying mechanisms of host-virus interactions during SARS-CoV-2 infection. Follow-up research is still required to reveal the authentic picture of this virus-host arms race. It is even more important to identify mutations located in the domains of the corresponding viral IFN antagonists so that we will be better prepared for the ongoing emergence of SARS-CoV-2 variant strains.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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