JOURNAL OF INTERFERON & CYTOKINE RESEARCH
Volume 41, Number 6, 2021

DOI: 10.1089/jir.2021.0060

REVIEW

Control of Innate Immune Activation by Severe Acute Respiratory Syndrome Coronavirus 2 and Other Coronaviruses

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The ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents a public health crisis of unprecedented proportions. After the emergence of SARS-CoV-1 in 2002, and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, this is the third outbreak of a highly pathogenic zoonotic coronavirus (CoV) that the world has witnessed in the last 2 decades. Infection with highly pathogenic human CoVs often results in a severe respiratory disease characterized by a delayed and blunted interferon (IFN) response, accompanied by an excessive production of proinflammatory cytokines. This indicates that CoVs developed effective mechanisms to overcome the host innate immune response and promote viral replication and pathogenesis. In this review, we describe the key innate immune signaling pathways that are activated during infection with SARS-CoV-2 and other well studied pathogenic CoVs. In addition, we summarize the main strategies that these viruses employ to modulate the host immune responses through the antagonism of IFN induction and effector pathways.

Keywords: SARS-CoV-2, coronavirus, innate immunity, interferon, immune evasion

Introduction

In early December of 2019, an outbreak of pneumonia of unknown etiology was reported in Wuhan, China. One month later, viral sequencing identified a novel coronavirus (CoV) as the causative pathogen of this new disease that quickly spread around the globe and has now caused the greatest pandemic the world has seen in a century. As of now, this novel coronavirus disease 2019 (COVID-19) pandemic resulted in over 142 million confirmed infections and 3 million deaths (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of COVID-19, is an enveloped positive-sense single-stranded RNA (ssRNA) virus that belongs to lineage B of the *Betacoronavirus* genus, and it is closely related to SARS-CoV-1 that caused the first SARS epidemic in the early 2000s (Lu and others 2020; Wu and others 2020; Zhu and others 2020). In addition to SARS-CoV-1 and SARS-CoV-2, 5 other human coronaviruses (hCoVs) have been reported: Middle East respiratory syndrome coronavirus (MERS-CoV), a highly pathogenic lineage C Betacoronavirus, 4 seasonal hCoVs: 2 Betacoronaviruses (OC43 and HKU1), and 2 Alphacoronaviruses (229E and NL63).

While seasonal CoVs primarily cause upper respiratory tract infection and mild disease (reviewed in Forni and others 2017; Fung and others 2020), infection with high pathogenic CoVs is associated with a wide range of symptoms that can range from mild to severe respiratory illness, including acute respiratory distress syndrome, which requires mechanical ventilation and intensive care (Drosten and others 2003; Fowler and others 2003; Yang and others 2020a). Aberrant activation of the innate immune response by these viruses is believed to contribute significantly to the development of severe symptoms (Faure and others 2014; Channappanavar and others 2016; Blanco-Melo and others 2020). However, there are also great differences between COVID-19, MERS, and SARS. In fact, despite resulting in

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similar clinical manifestations, MERS and SARS are more likely to be fatal or severe than COVID-19, but their transmissibility is much lower (Liu and others 2020).

Molecular clock analysis indicates that Alphacoronaviruses entered the human population in spillover events from wildlife between 800 and 200 years ago, while the seasonal Betacoronaviruses OC43 and HKU1 emerged more recently (120 and 60 years ago, respectively) (Vijgen and others 2005; Huynh and others 2012). In addition, as mentioned above, in the last 2 decades, the world has seen the emergence of 3 novel highly pathogenic Betacoronaviruses: MERS-CoV, SARS-CoV-1, and more recently SARS-CoV-2.

Genomic analyses have proposed that all hCoVs emerged from bat or rodent reservoirs and could have either directly jumped into human populations or were introduced via intermediate species like cattle, camels, or palm civets (Guan and others 2003; Li and others 2005; Vijgen and others 2006; Corman and others 2015; Lau and others 2015). For instance, while SARS-CoV-2 has been shown to be very closely related to bat CoV isolates, SARS-CoV-2 related viruses were also identified in the Malayan pangolin (*Manis javanica*), suggesting they may have served as an intermediate host for the transmission to humans (Lam and others 2020; Zhou and others 2020). Interestingly, the current COVID-19 pandemic may not have been the first global outbreak caused by a CoV. In fact, it has been proposed that the seasonal CoV OC43 spilled over from a bovine reservoir in the late 19th century and was the etiological agent of the ''Russian flu''-pandemic that caused over 1 million reported deaths worldwide (Vijgen and others 2005).

In this review, we briefly describe our understanding of how CoV infection is sensed by the host innate immune system. In addition, we discuss the main strategies that CoVs employ to modulate and effectively blunt innate immune activation, with an emphasis on the interferon (IFN) induction pathways.

Genome Organization and Life Cycle

All CoVs have a linear genome of 26–30 kb that encode for 16 nonstructural proteins (NSPs), 4 structural proteins, and an array of accessory proteins (reviewed in Fehr and Perlman 2015).

The NSPs of CoVs are encoded by 2 open reading frames (ORFs), *ORF1a* and *ORF1b* that are translated into polyproteins pp1a and pp1ab. Autoproteolytic cleavage of these polyproteins generates 15–16 NSPs with different functions during the viral life cycle.

The structural and accessory genes instead are translated from subgenomic RNAs (sgRNAs) that are generated during genome transcription and replication. Among the structural proteins, the spike protein (S) is responsible for attachment to the host receptors and membrane fusion for almost all CoVs (Li 2016). The nucleocapsid protein (N) binds to the RNA genome to form the ribonucleocapsid and facilitate packaging. Membrane (M) and envelope (E) are anchored in the viral envelope to regulate particle maturation and provide structural integrity (Vennema and others 1996). Conversely, the accessory proteins are not essential for virus replication, and their number varies significantly among different CoVs. Notably, they have been shown to play an important role in viral pathogenesis, in some cases by antagonizing the IFN induction and signaling pathways, as discussed more in more detail below (Siu and others 2009; Lu and others 2011; Lui and others 2016; Hu and others 2017; Chang and others 2020).

The CoV life cycle is completely cytoplasmic. Upon binding to the receptor and fusion of the virus with the target membrane, the genomic RNA (gRNA) is released into the cytosol of the infected cells and serves as a transcript to allow translation of the viral polyproteins that are then processed to form functional replication and transcription complexes that are tightly associated with host's cellular membranes. Importantly, the full-length gRNA is replicated via a negative-sense intermediate that serves as a template for the synthesis of new gRNAs. Particle assembly occurs at the ER–Golgi intermediate compartment (ERGIC), and mature virions are released through vesicle fusion with the cell membrane (Romero-Brey and Bartenschlager 2014; Klein and others 2020).

Recognition of Viral Infection by Innate Immune Sensors

Vertebrates have evolved a highly organized defense network against invading pathogens. The innate immune system relies on the recognition of conserved pathogen associated molecular patterns (PAMPs) by a limited number of germline-encoded pattern-recognition receptors (PRRs) (reviewed in Riera Romo and others 2016; Pelka and De Nardo 2018). Type I IFN is an integral component of this defense network and coordinates the expression of antiviral effector genes and the establishment of the adaptive immune response (Le Bon and Tough 2002; Stetson and Medzhitov 2006). In addition, mammalian cells are also equipped with an array of constitutively expressed genes with intrinsic antiviral activity. These proteins, known as restriction factors, inhibit viral replication directly, often before the onset of the IFN response. However, most of these proteins can also be further induced by IFN to amplify their activity (Colomer-Lluch and others 2018).

The importance of these highly coordinated defense mechanisms for the resolution of infection is further emphasized by the fact that pathogenic viruses have developed multiple tools to escape or at least counteract innate immune responses (Garcia-Sastre 2017; Miorin and others 2017). Indeed, while the seasonal CoV 229E has been shown to induce high levels of IFN and IFN stimulated genes (ISGs) (Mesel-Lemoine and others 2012; Loo and others 2020), infection with SARS-CoV-1, MERS-CoV, and SARS-CoV-2 is known to induce only low levels of IFN, likely due to the expression of numerous innate immune antagonists by these highly pathogenic viruses (reviewed in de Wit and others 2016; Xia and Shi 2020).

Virus infections are mainly sensed by PRRs that recognize nucleic acids. These PRRs include retinoic acid associated gene-I (RIG-I)-like receptors (RLRs), the heterogeneous groups of cytosolic DNA sensors (CDSs), and some Toll-like receptors (TLRs) (Baccala and others 2009; Wu and Chen 2014), among others (Fig. 1).

TLRs are exclusively expressed in lymphocytes and are responsible for detection of a wide range of PAMPs (Baccala and others 2009; Riera Romo and others 2016). TLR3, TLR7, and TLR9 are involved in viral sensing and are all expressed in endosomes or lysosome-related organelles (Kawasaki and Kawai 2014). TLR7 and TLR9 trigger the MyD88 pathway, while TLR3 signals via TRIF to activate

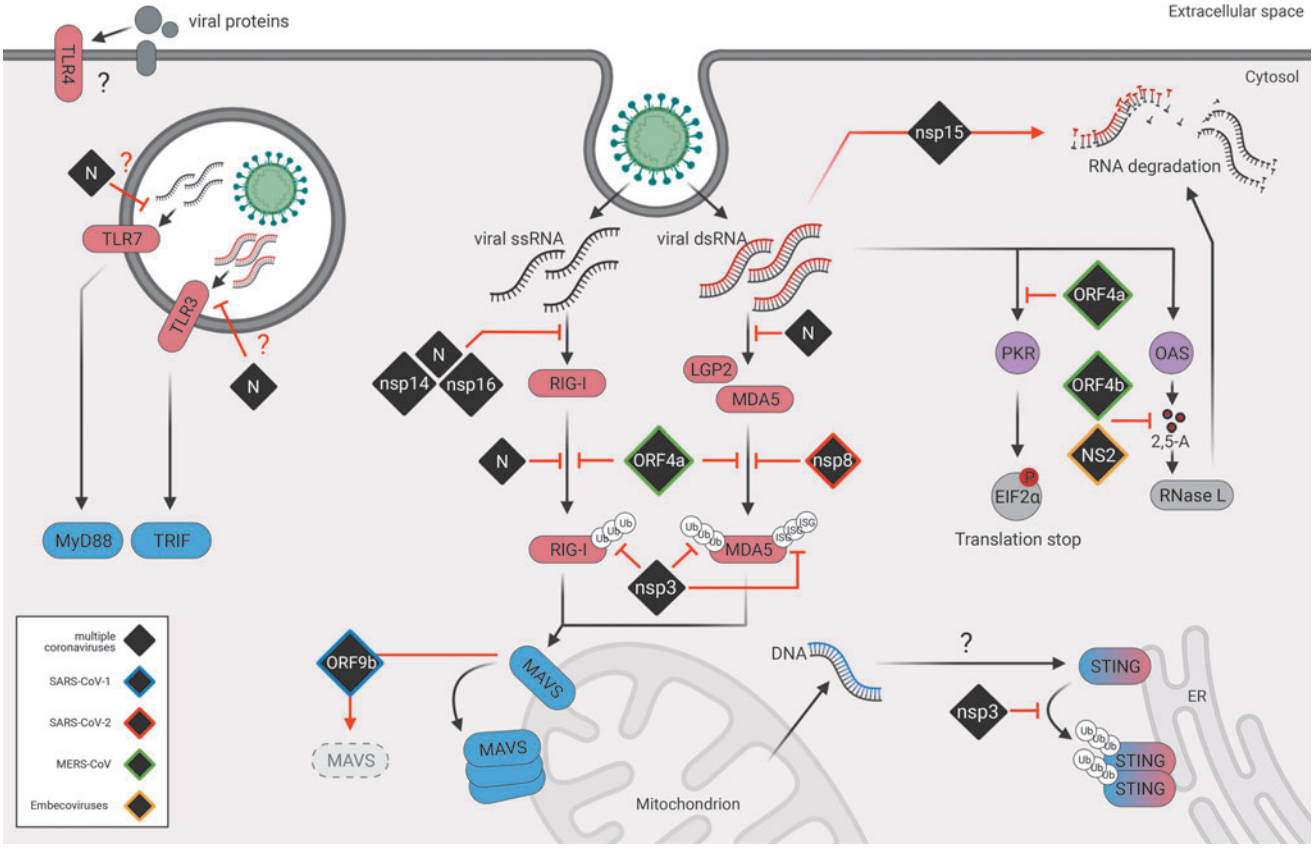

FIG. 1. Sensing of coronavirus infection and viral antagonism. Upon entry, viral nucleic acids are sensed by PRRs (*red*). While TLR3 and TLR7 sense endosomal viral RNA and TLR4 recognizes viral glycoproteins in the membrane, the RLRs RIG-I, MDA5, and LGP2 sense cytosolic RNAs. PRRs then activate adaptor proteins MAVS, MyD88, and TRIF (*blue*) to trigger downstream signaling. Additionally, cytosolic dsRNA also triggers PKR and OASes (*purple*), which in turn phosphorylates eIF2a to shut down protein translation and activate RNaseL to degrade cytosolic RNA, respectively. Viral infection may also lead to cell damage and subsequent release of DNA into the cytosol, which can trigger cytosolic DNA sensors such as the sensor-adaptor molecule STING (*blue-red*). Viral proteins (*black*) that have been described to interfere with interferon induction are depicted in black and have *color* coded borders to indicate their origin (*blue* = SARS-CoV-1, *red* = SARS-CoV-2, *green* = MERS-CoV, *yellow* = Embecoviruses, *black* = multiple coronaviruses). dsRNA, double-stranded RNA; eIF2a, eukaryotic translation initiation factor; LGP2, laboratory of genetics and physiology 2; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation-associated gene 5; MERS-CoV, Middle East respiratory syndrome coronavirus; OASes, 2′,5′-oligoadenylate synthases; PKR, protein kinase R; PRR, pattern-recognition receptor; RIG-I, retinoic acid-associated gene-I; RLR, retinoic acid-associated gene-I (RIG-I)-like receptor; SARS-CoV, severe acute respiratory syndrome coronavirus; TLR, Toll-like receptor.

an immune response (Kawai and Akira 2007). The group of CDSs comprises proteins like cGAS and IFI-16 that recognize non-self and cellular DNA in the cytoplasm, and signal through the adaptor protein STING, which mainly resides in ER membranes (Ishikawa and Barber 2008; Burdette and Vance 2013; Wu and Chen 2014; Aguirre and Fernandez-Sesma 2017).

The RLR family comprises 2 major sensor proteins RIG-I and melanoma differentiation associated gene 5 (MDA5) and the less characterized regulator laboratory of genetics and physiology 2 (LGP2), and signals through the adaptor protein mitochondrial antiviral-signaling protein (MAVS) (Yoneyama and others 2015).

Upon viral sensing, all the PRRs described above trigger the initiation of harmonized signaling pathways that ultimately lead to the expression of IFN and inflammatory cytokines via transcription factors like NFKB and interferon regulatory transcription factor 3 (IRF3) (reviewed in Wu and Chen 2014; Chen and others 2017).

Secreted IFN then binds to the IFN receptors (IFNAR) in an autocrine and paracrine fashion and activates Janus kinase 1 (JAK1) and Tyrosine kinase 2 (TYK2) (Platanias 2005). These events trigger the phosphorylation of signal transducer and activator of transcription 1 and 2 (STAT1 and STAT2), which then dimerize and interact with IRF9 to form the IGF3 complex (Schindler and others 2007). ISGF3 in turn translocates into the nucleus and binds to the Interferon-Stimulated Response Element (ISRE) promoter to initiate the expression of hundreds of ISGs and the establishment of an antiviral state (reviewed in Schneider and others 2014).

Innate Immune Sensing of CoV Infection

CoVs are RNA viruses that generate double-stranded RNA (dsRNA) intermediates during replication and are therefore subjected to cytosolic RNA recognition by RLRs. While RIG-I senses short dsRNAs carrying a triphosphate or

diphosphate moiety at the 5′ terminus, MDA5 has been described to sense primarily long dsRNAs as those generated during picornavirus and CoV replication (Pichlmair and others 2009; Zalinger and others 2015; Yin and others 2021). Interestingly, LGP2, the third member of the family, has the highest affinity to RNA of all RLRs, which may play a key role in its regulatory function (Takahasi and others 2009). However, the physiological RNA agonists of both MDA5 and LGP2 during infection still remain enigmatic.

Both RIG-I and MDA5 have been shown to be involved in the detection of mouse hepatitis virus (MHV) in a cell type-dependent manner (Roth-Cross and others 2008; Li and others 2010). In addition, MDA5-deficient mice failed to induce a protective IFN response and exhibited more severe disease than wild-type mice following MHV infection (Zalinger and others 2015). In line with this observation, we and others have recently shown that MDA5 and its positive regulator LGP2, but not RIG-I, act as the key innate immune sensors in lung epithelial cells during infection with SARS-CoV-2 (Rebendenne and others 2021; Yin and others 2021). However, whether SARS-CoV-2 replication only generates MDA5-dependent agonists, or simply better antagonizes RIG-I activation still remains unclear.

In contrast, RLR signaling appeared to be dispensable for IFN induction during MERS-CoV infection. Indeed, TLR7/MyD88 knockout mice but not MAVS-deficient mice showed more severe disease and reduced IFN induction with respect to control animals after infection with MERS-CoV (Zhao and others 2014; Channappanavar and others 2019).

TLR signaling has also been implicated in the control of other CoV infections. Indeed, several studies have shown that mice deficient in different TLRs or downstream adaptor molecules exhibit increased mortality, weight loss, and viral titers in response to infection. Specifically, TLR3 and TLR7 appear to be of particular importance. Interestingly, both proteins localize at the endosomal membrane, however, while TLR3 is known to sense dsRNA, TLR7 specifically recognizes ssRNA (Alexopoulou and others 2001; Heil and others 2004).

TLR7 has been shown to be critical for the secretion of IFN by plasmacytoid dendritic cells upon infection with both MHV and MERS-CoV (Cervantes-Barragan and others 2006; Scheuplein and others 2015). In addition, mice deficient in MyD88 were shown to be unable to mount a protective immune response and to succumb in response to a SARS-CoV-1 and MERS-CoV challenge (Sheahan and others 2008; Zhao and others 2014).

Interestingly, a similar protective role in the host response to SARS-CoV-1 has also been attributed to TLR3 and the adaptor molecule TRIF. TRIF knockout animals had mortality, weight loss, and viral titers that were comparable to those of the MyD88 knockout mice. However, rather that showing an impaired IFN response, they exhibited elevated levels of IFN and proinflammatory cytokines late in infection that resulted in increased lung pathology This suggest that some additional sensing pathways may compensate for the lack of TLR3 during SARS-CoV-1 infection (Totura and others 2015).

Surprisingly, TLR4, which recognizes bacterial lipopolysaccharides and viral glycoproteins, has also been shown to play an important role in the control of CoV infection. Indeed, TLR4 knockout mice appeared to be more susceptible to MHV and SARS-CoV-1 infection. This may be due to the recognition of the heavily glycosylated spike protein by TLR4 receptors on the surface of innate immune cells (Totura and others 2015). Additionally, the important role of TLR signaling in the establishment of a balanced innate immune response to pathogenic CoV infection has also been recently highlighted by the identification of TLR7 and TLR3 loss-of-function mutations in patients with severe COVID-19 (van der Made and others 2020; Zhang and others 2020).

As mentioned above, virus infected cells can also rapidly trigger expression of different auxiliary RNA-binding proteins with antiviral activity. The interferon-induced proteins with tetratricopeptide repeats (IFITs) belong to this class of antiviral factors, and are among the highest expressed genes during the innate antiviral responses. In addition to antagonizing translation initiation by direct interaction with eukaryotic initiation factor 3 (eIF3), IFIT proteins have been also shown to inhibit infection by sequestering viral RNAs with specific 5′-motifs moieties from the replication sites or by promoting RNA degradation (reviewed in Diamond 2014; Mears and Sweeney 2018).

Specifically, IFIT proteins have been shown to restrict viral replication upon recognition of messenger RNAs (mRNAs) lacking a 2′-*O*-methylated cap and therefore, CoVs express a 2′-*O*-methyltransferase to overcome this restriction (Daffis and others 2010). In addition, several studies have indicated that IFIT proteins are important for the immune response against CoV infection. In this respect, knock-down of both IFIT1 and IFIT2 in Vero cells resulted in increased viral titers upon infection with SARS-CoV-1. Moreover, enhanced SARS-CoV-1 replication was also observed in the lungs of IFIT1 deficient mice with respect to control animals (Menachery and others 2014). Similarly, IFIT2 knockout mice also exhibited increased viral replication in the central nervous system and liver in addition to increased morbidity and mortality upon infection with MHV (Butchi and others 2014).

Lastly, increasing evidence suggests that the cGAS-STING pathway, in addition to recognizing dsDNA from DNA viruses, is also playing a role in restricting RNA virus infection by sensing nuclear or mitochondrial DNA that is released in the cytoplasm due to infection-mediated collateral damage (Aguirre and Fernandez-Sesma 2017). In this respect, a recent study suggested that while SARS-CoV-2 infection poorly triggers the activation of the IRF3 and IFN pathways, it quite effectively triggers the activation of NFkB by the cGAS-STING pathway (Neufeldt and others 2020). In addition, the papain-like protease (PLP) of SARS-CoV-1, NL63 and more recently also SARS-CoV-2, which is part of the *nsp3* gene, are able to inhibit ubiquitination and activation of STING (Sun and others 2012; Rui and others 2021). However, more studies are needed to explore the impact of the activation of the cGAS-STING pathway in the pathogenesis of hCoV infection.

Mechanisms of Innate Immune Evasion by hCoVs

IFN is the master regulator of the innate antiviral immune response. It can modulate the expression of hundreds of genes and it is extremely effective in restricting viral replication. As a consequence, SARS-CoV-2 and many other CoVs are known to be sensitive to treatment with IFNs (Hensley and others 2004; Li and others 2010; Lei and others 2020; Miorin and others 2020). Therefore, it is not

surprising that CoVs developed multiple mechanisms to evade or inhibit IFN induction and signaling pathways during evolution.

Here, we will address the key viral strategies that CoVs exploit to control IFN induction: (1) hiding or modifying viral RNA to avoid recognition by host antiviral sensors; (2) inhibition of PRR activation; and (3) disruption of signaling pathways responsible for IFN induction (Figs. 1 and 2). The existence of these mechanisms explains why IFN induction is significantly attenuated in cells infected with CoVs (Spiegel and others 2005; Kindler and others 2013; Blanco-Melo and others 2020).

Evasion of Recognition by Host Antiviral Sensors

Like other positive-sense RNA viruses, CoVs assemble their transcription/replication complexes into membrane-associated compartments that are believe to help concentrating viral and host factors required for efficient replication, while shielding viral nucleic-acids from recognition by host antiviral sensors (Stertz and others 2007; Knoops and others 2008; Paul and Bartenschlager 2013; Snijder and others 2020; Wolff and others 2020). In addition, viral RNA recognition is also prevented by several other mechanisms. For instance, the CoV nucleocapsid protein (N), which has the structural function of encapsidating the viral genome, has also been shown to interfere with IFN induction at different levels.

At the very early steps of infection, N is believed to protect viral RNA from recognition by PRRs through its RNA binding ability (Kopecky-Bromberg and others 2007; Lu and others 2011; Lei and others 2020). In addition, at later steps in the RIG-I activation pathway, both MERS-CoV and SARS-CoV-1 N proteins are able to interact with the E3 ubiquitin ligase TRIM25 to block RIG-I ubiquitination and activation of downstream signaling (Hu and others 2017; Chang and others 2020).

CoV NSP14 and NSP16, which are part of the replicase complex, have also been involved in IFN antagonism. NSP14 has guanine-N7-methyltransferase and is involved in the formation of a 5′ terminal cap structure on the viral RNA that can mimic host mRNA (Chen and others 2009). In addition, NSP16 has 2′-*O*-MTAse activity that is critical to evade RNA recognition by MDA5 and IFIT proteins. Indeed, MHV mutant viruses that lack 2′-*O*-MTAse activity trigger and enhanced IFN response and are attenuated *in vivo* (Daffis and others 2010; Menachery and others 2014, 2017).

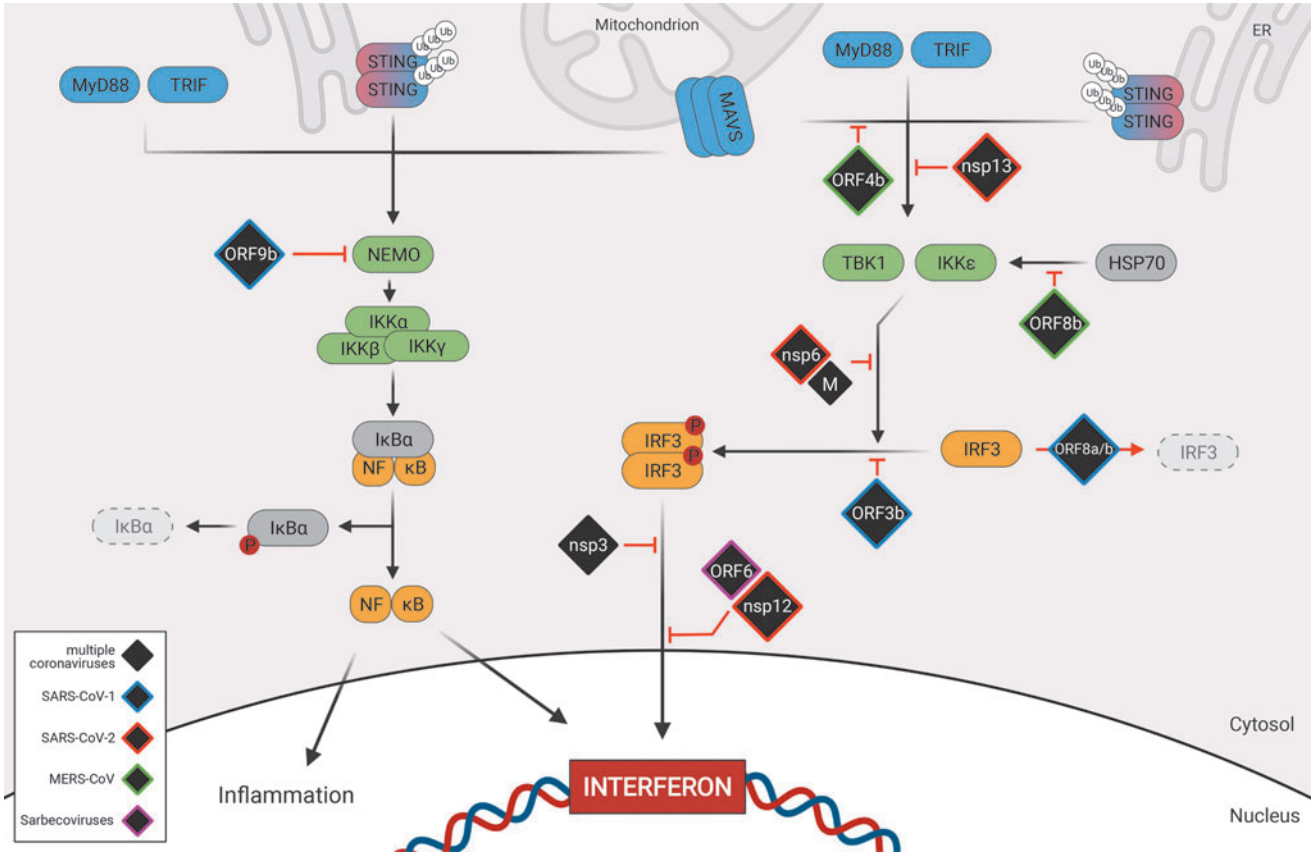

FIG. 2. Signaling downstream of PRRs activation and viral antagonism. After PRR activation, adaptor molecules initiate the formation of different signaling complexes. TBK1 and IKKe form a complex with other proteins to phosphorylate IRF3, which can then dimerize and translocate into the nucleus. Simultaneously, NEMO triggers the formation of the IKK complex, which then initiates degradation of IKBa and allows for nuclear translocation of NFKB. In the nucleus, the 3 transcription factors IRF3, NFKB, and AP1 together stimulate the production of type I/type III interferon and proinflammatory cytokines. Viral proteins (*black*) that have been described to interfere with interferon induction are depicted at the step of signaling cascade they antagonize. Viral proteins have *color* coded borders to indicate their origin (*blue* = SARS-CoV-1, *red* = SARS-CoV-2, *purple* = Sarbecoviruses, *green* = MERS-CoV, *black* = multiple coronaviruses). IRF3, interferon regulatory transcription factor 3.

Similarly, loss of NSP15 endoribonuclease activity also resulted in robust activation of host dsRNA sensors and MHV attenuation due to an increase in the number of free-dsRNA foci that are not confined within the viral replication compartment (Deng and others 2017; Yuen and others 2020). Finally, the MERS-CoV ORF4a protein has been shown to bind to the RLR cofactor PACT in an RNA-dependent manner to suppress antiviral signaling and promote viral replication (Almazan and others 2013; Yang and others 2013; Siu and others 2014).

Inhibition of PRRs Activation

A rapid and tightly controlled activation of RLR signaling is a crucial step for the initiation of an effective antiviral response. Therefore, the activities of RIG-I, MDA5, and LGP2 are regulated by several types of posttranslational modifications, including ubiquitination, conjugation of ubiquitin-like molecule, and phosphorylation, among others (Cadena and Hur 2019; Kato and others 2021). As a consequence, pathogenic CoVs also evolved strategies to target these critical regulatory mechanisms.

As mentioned above, the N protein of SARS-CoV-1 and MERS-CoV can interact with TRIM25 and impair RIG-I ubiquitination (Hu and others 2017; Chang and others 2020). Similarly, NSP8 of SARS-CoV-2 has recently been described to bind to the CARD domains of MDA5 to suppress its K63-linked polyubiquitination and prevent expression of type I IFN and inflammatory cytokines (Yang and others 2020b). In addition, CoVs also express proteins with deubiquitinase activity (DUBs) that have been shown to target key components of the IFN induction pathway (Devaraj and others 2007; Frieman and others 2009; Bailey-Elkin and others 2014; Shin and others 2020; Liu and others 2021). In this respect, the PLPs of many CoVs have been suggested to remove ubiquitin and the ubiquitin-like molecule ISG15 from cellular proteins (Clementz and others 2010; Klemm and others 2020).

Porcine epidemic diarrhea virus (PEDV) PLP2 has been shown to have DUB activity and interact with RIG-I and STING (Xing and others 2013). Consequently, PLP2 catalytically inactive mutants do not affect ubiquitination of their targets and are less efficient at suppressing IFN induction. MERS-CoV PLP has also been shown to exert DUB and deISGylase activity. However, its substrates still remain to be identified (Mielech and others 2014).

Interestingly, it was recently shown that while SARS-CoV-1 preferentially cleaves Ub from its substrates, SARS-CoV-2 PLP more efficiently reduce the appearance of ISGylated protein substrates (Shin and others 2020). Mechanistically, SARS-CoV-2 PLP was shown to specifically bind to MDA5, but not to RIG-I, and to suppress MDA5 CARD ISGylation to prevent its oligomerization and the activation of downstream signaling events. Notably, this PLP-dependent mechanism of antagonism of MDA5 activation appears to be widely conserved among different CoVs (SARS-CoV-1, MERS, MHV, and NL63), highlighting the key role of MDA5 ISGylation in the IFN induction during CoV infection (Liu and others 2021).

Disruption of Signaling Pathways Responsible for IFN Induction

As mentioned briefly above, upon viral infection, RLR stimulation results in the activation of the adaptor protein MAVS that in turn recruits TNF receptor-associated factors (TRAFs) and NEMO to activate the kinases IKK and TBK1 (Ea and others 2006; Saha and others 2006). While IKK triggers the NFKB pathway through IKBα, TBK1 phosphorylates IRF3, which dimerizes and translocates into the nucleus (Wu and others 2006; Liu and others 2013). IRF3 and NFKB, together with other factors serve as transcription factors for type I IFN induction (Fig. 1, left panel) (Yoneyama and others 2002; Liu and others 2015).

Interestingly, the SARS-CoV-1 accessory protein ORF9b has been shown to localize at the mitochondria and to inhibit RLR signaling by targeting MAVS for ubiquitin-mediated proteasomal degradation (Shi and others 2014). In addition, the ORF9b proteins of both SARS-CoV-1 and SARS-CoV-2 were recently shown to bind to, and colocalize with the mitochondrial outer membrane protein Tom70, which is known to be involved in the activation of MAVS signaling and apoptosis (Lin and others 2010; Gordon and others 2020). However, the functional significance of this interaction remains to be elucidated.

MERS-CoV ORF4b is also an important antagonist of IFN induction. Ectopically expressed ORF4b was shown to interact with IKKe and TBK1 to prevent their interaction with MAVS and inhibit IRF3 phosphorylation (Yang and others 2015). In addition, the MERS-CoV ORF8b protein has been shown to counteract IKKε activation by disrupting IKKe-HSP70 interaction, which is known to enhance IRF3 activation. Consistently, infection with a recombinant virus carrying a deletion in ORF8b resulted in an enhanced IFN induction and in the rescue of the colocalization between HSP70 and IKKe (Wong and others 2020).

Moreover, both SARS-CoV-2 NSP6 and NSP13 were shown to bind to TBK1 to prevent IRF3 activation. Interestingly, while binding of NSP13 to TBK1 resulted in an impaired TBK1 phosphorylation, the NSP6-TBK1 interaction resulted in a block of IRF3 phosphorylation (Gordon and others 2020; Xia and others 2020; Yuen and others 2020). More studies will be required to define the detailed molecular mechanism by which these viral proteins exert their antagonistic functions. Interestingly, the M proteins of all 3 highly pathogenic CoVs have also been shown to target TBK1. In fact, M has been proposed to block IRF3 phosphorylation by preventing the formation of a protein complex between TBK1, TRAF3, IKKe, and other factors. However, the specific interactors of M differ between SARS-CoV-1, SARS-CoV-2, and MERS-CoV (Siu and others 2009; Lui and others 2016; Zheng and others 2020).

The key transcription factor IRF3 is also directly targeted by several viral proteins. SARS-CoV-1 ORF8ab and ORF8b have been shown to actively degrade IRF3 in a ubiquitin-dependent fashion (Wong and others 2018). In addition, overexpression of SARS-CoV-1 ORF3b could also inhibit IFN induction by blocking IRF3 phosphorylation and nuclear translocation (Kopecky-Bromberg and others 2007). Interestingly, despite that ORF3b protein of SARS-CoV-2 has relatively low homology with the SARS-CoV-1 protein, due to the presence of a premature stop codon, it appears to exert the same function. Indeed, a recent overexpression study indicates that SARS-CoV-2 ORF3b is able to suppress IFN induction even more efficiently than ORF3b of SARS-CoV-1 (Konno and others 2020). Furthermore, the same study also identified a SARS-CoV-2 *ORF3b* variant that expresses an elongated protein due to a mutation on the

premature stop codon, with even more increased anti-IFN activity *in vitro*. However, the specific effect of this variant on IFN induction and viral replication during infection, still remains to be addressed.

The PLP proteins of MHV, SARS-CoV-1, and SARS-CoV-2 were also shown to target IRF3. Interestingly, while MHV PLP could interact with IRF3 and block IRF3 ubiquitination and nuclear translocation (Zheng and others 2008), SARS-CoV-1 PLP was shown to inhibit IFN induction at a step downstream of IRF3 nuclear localization and DNA binding (Matthews and others 2014). Conversely, SARS-CoV-2 PLP was recently reported to cleave IRF3 *in vitro* via its protease activity (Moustaqil and others 2021).

The ORF6 proteins of both SARS-CoV-1 and SARS-CoV-2 have also been proposed to block IRF3 in addition to STAT1 and STAT2 nuclear translocation (Frieman and others 2007; Kopecky-Bromberg and others 2007; Lei and others 2020; Miorin and others 2020; Xia and others 2020; Yuen and others 2020). However, while we could show that IFN-dependent STAT translocation is blocked by direct interaction of ORF6 with the nucleoporin NUP98, it still remains to be clarified whether ORF6 affects IRF3 nuclear import through the same mechanism. Lastly, a recent study also demonstrated that SARS-CoV-2 NSP12 can block nuclear translocation of IRF3 without impairing its phosphorylation. While the polymerase function of NSP12 was dispensable for this phenotype, the exact mode of action needs to be further explored (Wang and others 2021).

Induction and Evasion of the Protein Kinase R and OAS/RNAseL Pathways

dsRNA-dependent protein kinase R (PKR) and 2′,5′-oligoadenylate synthases (OASes) constitute 2 other antiviral defense systems that are activated upon the recognition of cytosolic dsRNAs (reviewed in Sadler and Williams 2008).

PKR is a serine/threonine kinase that is constitutively expressed at basal levels in all tissues and is upregulated in response to IFN (Haines and others 1998). Binding to dsRNA triggers PKR activation and results in its dimerization and autophosphorylation at multiple residues. Active PKR then phosphorylates the alpha subunit of the eukaryotic translation initiation factor (eIF2a) to inhibit viral and host cell translation and trigger stress granule (SGs) formation (Balachandran and others 2000). In addition, PKR can also regulate other signaling pathways to control apoptosis, cell growth, and differentiation through mechanisms that are incompletely understood (Ishii and others 2001; Bonnet and others 2006; Taghavi and Samuel 2012).

Similar to PKR, the OAS family of proteins consists of a homologous set of enzymes that are encoded by ISGs that are also constitutively expressed at low levels at steady state and therefore can act as PRRs for the recognition of cytoplasmic viral RNA. Binding of dsRNA by OASes results in the conversion of ATP into 2′,5′-oligoadenylates (2–5A) that serve as second messengers to activate latent endoribonuclease (RNaseL) (reviewed in Sadler and Williams 2008; Taghavi and Samuel 2012). Activated RNaseL monomers then dimerize and cleave viral and cellular ssRNAs with little specificity to trigger apoptosis of the infected cells (Zhou and others 1997).

Both of these pathways have been shown to be activated during CoV infection. In fact, several studies have shown that infection with multiple CoVs generally triggers the phosphorylation of both PKR and eIF2a, suggesting that dsRNA recognition by PKR is common during CoVs infections (Bechill and others 2008; Wang and others 2009; Cruz and others 2011; Liao and others 2013). Interestingly, infection with SARS-CoV-1 and SARS-CoV-2 was shown to trigger the activation of both PKR and RNAseL in a cell type-dependent manner (Li and others 2021). However, while RNAseL was required to restrict viral replication, eIF2a phosphorylation levels and viral titers were not affected in PKR-deficient cells, indicating that infection with these 2 highly pathogenic CoVs is likely to trigger activation of multiple kinases in the cell stress response (Krahling and others 2009; Li and others 2021).

In contrast to SARS-CoVs, MERS-CoV and MHV appear to be more effective at inhibiting these pathways. In this respect, the accessory protein NS2 of MHV and related betacoronaviruses was shown to have 2′-5′-phosphodiesterase activity that triggers 2–5A cleavage to prevent activation of RNAseL and to block viral RNA degradation. Consistently, a recombinant virus carrying a mutation that abrogates the NS2 enzymatic activity was significantly attenuated in wild-type mice but was highly pathogenic in RNaseL-deficient mice, highlighting the important role of this pathway for viral restriction (Zhao and others 2012; Goldstein and others 2017).

In addition, multiple studies have shown that MERS-CoV ORF4a can bind to dsRNA to block PKR activation and SG formation (Rabouw and others 2016; Comar and others 2019); and ORF4b, similar to NS2, is able to prevent RNAseL activation by degrading 2–5A (Thornbrough and others 2016; Comar and others 2019). However, in this case, recombinant viruses carrying mutations or deletions in these proteins were only modestly attenuated, strongly suggesting that MERS-CoV might have evolved multiple mechanisms for inhibiting the actions of these antiviral host factors (Comar and others 2019; Li and others 2021).

Conclusions

As described above, CoVs have evolved a plethora of mechanisms to control innate immune activation at multiple levels (Table 1). This highlights the importance of bypassing the establishment of a timely and harmonized host response for efficient viral replication. Importantly, the poor and delayed activation of the IFN response combined with excessive production of proinflammatory cytokines constitute the hallmark of the immune dysregulation that is associated with severe illness and poor disease outcome in SARS, MERS, and COVID-19 patients. This model is supported by several studies showing that an appropriate IFN response is necessary to control virus replication and spread in hamsters and mice (Zhao and others 2014; Channappanavar and others 2016, 2019; Boudewijns and others 2020; Hoagland and others 2021).

In addition, autoantibodies against IFN, and monogenic inborn errors of innate immunity have been found in patients with severe COVID-19 (Bastard and others 2020; Zhang and others 2020), further highlighting the key role of the IFN-mediated response in the control of CoV infection and disease progression. Depending on the virus, the efficiency of IFN inhibition may vary significantly, and it is clearly more pronounced during infection with highly pathogenic CoVs. However, there are only a couple of studies that directly

Table 1. Interferon Antagonistic Functions of Viral Proteins

Protein	*Target/mechanism*	*Virus*	*Citation*
Nonstructural			
NSP1	Inhibition of mRNA export; binding of 40S ribosomal subunit	SARS-CoV-1; SARS-CoV-2; MERS-CoV; hCoV-NL63; hCoV-OC43; MHV	Lei and others (2013); Lokugamage and others (2015); Wang and others (2010); Schubert and others (2020); Zhang and others (2021)
NSP3	Deubiquitylation of RIG-I; deubiquitylation of STING; deubiquitylation and DeISGylation of MDA5	SARS-CoV-1; SARS-CoV-2; MERS-CoV; HCoV-NL63; MHV, PEDV	Clementz and others (2010); Xing and others (2013); Mielech and others (2014); Klemm and others (2020); Shin and others (2020)
NSP6	Interaction with TBK1 prevents IRF3 phosphorylation	SARS-CoV-2	Xia and others (2020)
NSP8	Prevention of MDA5 polyubiquitylation	SARS-CoV-2	Yang and others (2020b)
NSP12	Inhibition of IRF3 nuclear translocation	SARS-CoV-2	Wang and others (2021)
NSP13	Interaction with TBK1 prevents TBK1 phosphorylation	SARS-CoV-2	Xia and others (2020); Yuen and others (2020)
NSP14	Capping of viral RNAs	SARS-CoV-2	Chen and others (2009); Yuen and others (2020)
NSP15	Degradation of viral dsRNA	SARS-CoV-2; MHV	Deng and others (2017); Yuen and others (2020)
NSP16	Capping of viral RNA	SARS-CoV-1; SARS-CoV-2; MERS-CoV; MHV	Daffis and others (2010); Menachery and others (2014); Menachery and others (2017)
Structural			
M	Disruption of TBK1-dependent IRF3 phosphorylation	SARS-CoV-1; SARS-CoV-2; MERS-CoV	Siu and others (2009); Lui and others (2016); Zheng and others (2020)
N	Shielding of viral RNA; inhibition of TRIM25-dependent RIG-I ubiquitylation	SARS-CoV-1; SARS-CoV-2; MERS-CoV	Kopecky-Bromberg and others (2007); Lu and others (2011); Lei and others (2020)
Accessory			
ORF3b	Block of IRF3 phosphorylation	SARS-CoV-1; SARS-CoV-2	Kopecky-Bromberg and others (2007); Konno and others (2020)
ORF4a	RNA-dependent sequestration of PACT (RLR cofactor); sequestration of dsRNA to prevent PKR activation	MERS-CoV	Almazan and others (2013); Yang and others (2013); Siu and others (2014); Rabouw and others (2016); Comar and others (2019)
ORF4b	Degradation of 2′,5′-oligoadenylate prevents RNaseL activation; disruption of MAVS interaction with TBK1/IKKe	MERS-CoV	Yang and others (2015); Thornbrough and others (2016); Comar and others (2019); Li and others (2021)
ORF6	Inhibition of IRF3 nuclear translocation	SARS-CoV-1; SARS-CoV-2	Frieman and others (2007); Kopecky-Bromberg and others (2007); Xia and others (2020); Yuen and others (2020)
ORF8(a/b)	Ubiquitin-dependent degradation of IRF3	SARS-CoV-1	Wong and others (2018)
ORF8b	Inhibition of HSP70-dependent activation of IKKe	MERS-CoV	Wong and others (2020)
ORF9b	Ubiquitin-dependent degradation of MAVS	SARS-CoV-1	Shi and others (2014)
NS2	Degradation of 2′,5′-oligoadenylate prevents RNaseL activation	HCoV-OC43; MHV; ECoV; BEV	Zhao and others (2012); Goldstein and others (2017)

dsRNA, double-stranded RNA; hCoV, human coronavirus; IRF3, interferon regulatory transcription factor 3; M, membrane; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation-associated gene 5; MERS-CoV, Middle East respiratory syndrome coronavirus; MHV, mouse hepatitis virus; mRNA, messenger RNA; N, nucleocapsid protein; NSP, nonstructural protein; ORF, open reading frame; PEDV, porcine epidemic diarrhea virus; PKR, protein kinase R; RIG-I, retinoic acid-associated gene-I; RLR, retinoic acid-associated gene-I (RIG-I)-like receptor; SARS-CoV, severe acute respiratory syndrome coronavirus.

compare antagonistic proteins of different CoVs to each other, and even less studies that do it in the context of infection. More comparative studies, especially between low and highly pathogenic viruses are needed to dissect pathogenesis and to identify common and unique mechanisms of CoV-related diseases.

Importantly, differences in the ability of viral proteins to interact with key innate immune factors may also play a critical role in cross-species transmission. For instance, mouse adaptation of both SARS-CoV-1 and SARS-CoV-2 resulted in the acquisition of nonsynonymous mutations in different nonstructural and accessory proteins, some of which are known to antagonize the IFN response (Roberts and others 2007; Leist and others 2020; Rathnasinghe and others 2021). This suggests that additional mutations, which are not related to receptor-binding, are likely required for adaptation to a new host.

Finally, while CoV innate immune antagonism mechanisms have been extensively explored, much less is known about viral RNA sensing during infection. The importance of some PRRs such us TLRs, MDA5, LGP2, and PKR has been demonstrated. However, we still lack a detailed understanding of the molecular mechanisms underlying their activation. More is to be discovered as to where viral PAMPs are being sensed within the cell, and about the kinetics of sensing during the course of infection.

Most importantly, almost nothing is known about the nature of the viral agonists that are detected. Gaining better insight into sensing, viral antagonistic strategies, and innate immune responses to this family of viruses is crucial to develop better antiviral treatments, but also preventive medicines such as vaccines. The attention CoVs have gotten during the last 2 decades, and especially in the last year, must be used to gain a deep understanding of virus–host interactions that result in the activation and evasion of innate immunity, for not only CoVs but also other viral pathogens.

Acknowledgments

We thank Ms. Anastasija Cupic and all members of the A.G.-S. laboratory for helpful feedback. Due to space constraints, we regret our inability to cite all relevant studies. Biorender was used to make all figures.

Author Disclosure Statement

The A.G.-S. laboratory has received research support from Pfizer, Senhwa Biosciences, Kenall Manufacturing, Avimex, Johnson & Johnson, Dynavax, 7Hills Pharma, Pharmamar, ImmunityBio, Accurius, Nanocomposix and Merck. A.G.-S. has consulting agreements for the following companies involving cash and/or stock: Vivaldi Biosciences, Contrafect, 7Hills Pharma, Avimex, Vaxalto, Pagoda, Accurius, Esperovax, Farmak and Pfizer. A.G.-S. is inventor on patents and patent applications on the use of antivirals and vaccines for the treatment and prevention of virus infections, owned by the Icahn School of Medicine at Mount Sinai, New York.

Funding Information

Research on CoV in the A.G.-S. laboratory is partly funded by CRIPT (Center for Research on Influenza Pathogenesis and Transmission), a National Institute of Allergy and Infectious Diseases (NIAID) supported Center of Excellence for Influenza Research and Response (contracts 75N93019R00028 and HHSN272201400008C); by supplements to NIAID grants R35HL135834, U19AI135972, and U19AI142733 and NIAID contract 75N93019C00045; by a National Cancer Institute (NCI) grant U54CA260560; by a supplement to DoD grant W81XWH-20-1-0270; by the Defense Advanced Research Projects Agency (DARPA) grant HR0011-19-20020; by a Fast/Mercatus grant and by the generous support of the JPB Foundation, the Open Philanthropy Project [research grant 2020–215611 (5384)] and anonymous donors to A.G.-S.

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Received 5 May 2021/Accepted 7 May 2021