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Viral evasion of the interferon response at a glance

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ABSTRACT

Re-emerging and new viral pathogens have caused significant morbidity and mortality around the world, as evidenced by the recent monkeypox, Ebola and Zika virus outbreaks and the ongoing COVID-19 pandemic. Successful viral infection relies on tactical viral strategies to derail or antagonize host innate immune defenses, in particular the production of type I interferons (IFNs) by infected cells. Viruses can thwart intracellular sensing systems that elicit IFN gene expression (that is, RIG-I-like receptors and the cGAS–STING axis) or obstruct signaling elicited by IFNs. In this Cell Science at a Glance article and the accompanying poster, we review the current knowledge about the major mechanisms employed by viruses to inhibit the activity of intracellular pattern-recognition receptors and their downstream signaling cascades leading to IFN-based antiviral host defenses. Advancing our understanding of viral immune evasion might spur unprecedented opportunities to develop new antiviral compounds or vaccines to prevent viral infectious diseases.

KEY WORDS: Viral evasion, Innate immunity, Interferon, Intracellular sensors

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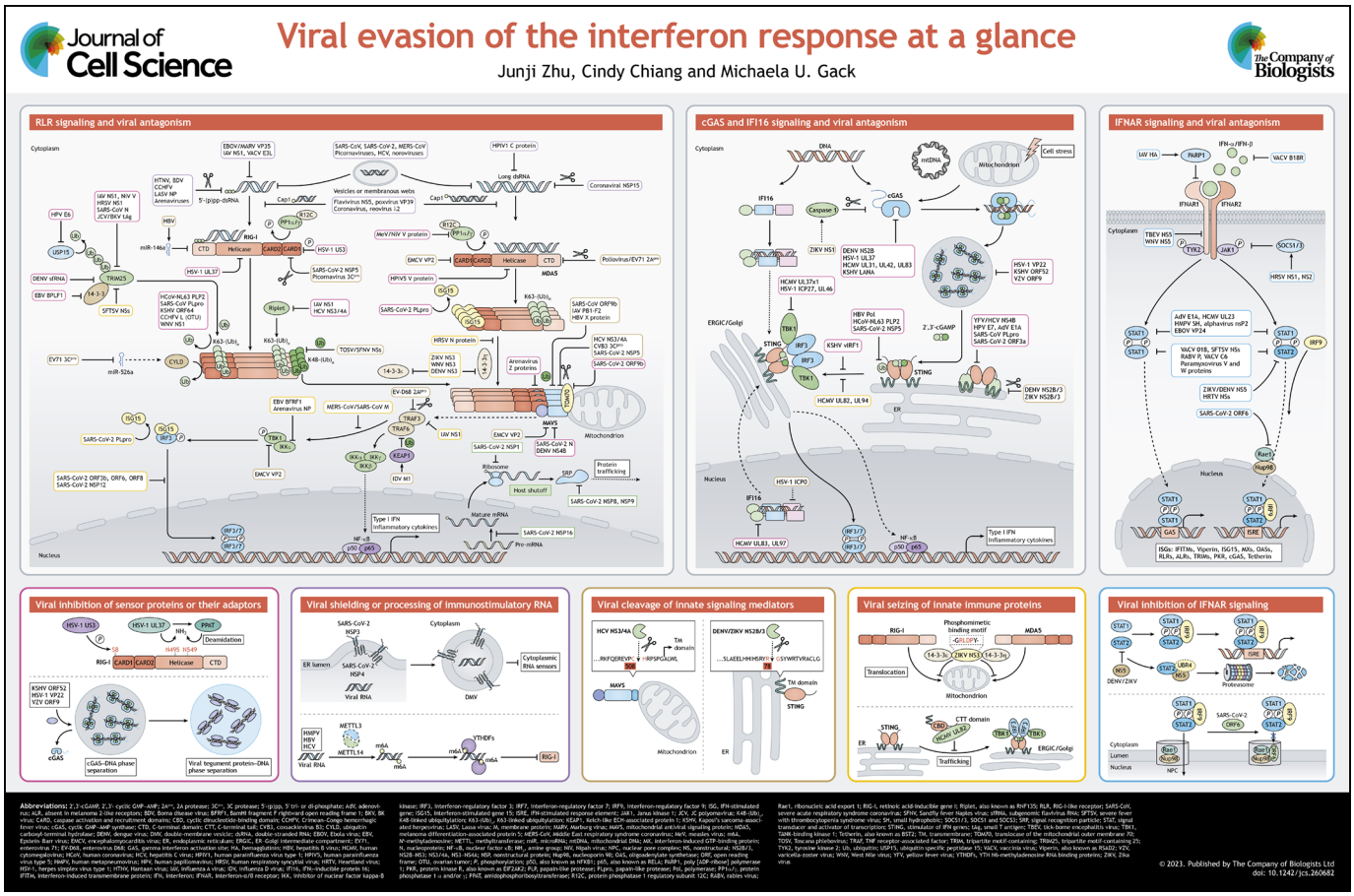
Introduction

Infectious diseases caused by persistent, emerging or re-emerging viruses have significantly affected the global human population. Successful infection and viral pathogenesis rely on the ability of viruses to thwart or divert mammalian host defenses, particularly the type I interferon (IFN) response, which involves IFN-α subtypes and IFN-β (IFNB1) (here referred to collectively as IFN-α/β) (Mesev et al., 2019). As part of the antiviral innate immune response, IFNs (and a large number of other cytokines) help create a ‘hostile’ environment that is characterized by the upregulation of cellular proteins with pathogen-restricting activities. Many viruses, however, employ tactical tricks to derail IFN production or to block



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the downstream events of IFN signaling. Here, we summarize the current state of research into antagonism of IFN-mediated innate immunity by human pathogenic viruses, with a focus on intracellular virus-sensing pathways and the human IFN-α/β response.

Antiviral interferon response and immune surveillance pathways

A successful host innate immune response against viral pathogens involves the production of hundreds of diverse cytokines and IFN-stimulated genes (ISGs) that promote an antiviral state that is effective against RNA viruses and DNA viruses (Schneider et al., 2014). Viruses from most families elicit type I IFNs, which through binding to their receptor (the IFN-α/β receptor, referred to here as IFNAR), trigger ISG transcription and antiviral protein production. Further upstream, IFN gene expression is elicited by distinct and well-characterized sensor proteins called pattern-recognition receptors (PRRs), which often recognize foreign nucleic acids, typically viral RNA or DNA. The detection of RNA viruses and DNA viruses is mediated by a number of intracellular PRRs that include the retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) family, which detect cytosolic viral RNA (Rehwinkel and Gack, 2020), and the cytoplasmic or nuclear DNA sensors IFNγ-inducible protein 16 (IFI16) and cyclic GMP–AMP synthase (cGAS) (see poster). Additionally, several other immune surveillance receptors, such as the NOD-like receptors (NLRs) and Toll-like receptors (TLRs), are vital for virus detection in the host (Fitzgerald and Kagan, 2020; Kanneganti et al., 2007).

RLR family of RNA helicases

The RLR family is made up of three DExD/H box-containing RNA helicases – RIG-I, melanoma differentiation-associated protein 5 (MDA5, also known as IFIH1) and laboratory of genetics and physiology 2 (LGP2, also known as DHX58) (with the latter not serving as a sensor per se but rather as a regulatory protein) (Rehwinkel and Gack, 2020). RIG-I and MDA5 recognize short and long double-stranded RNA (dsRNA) ligands, respectively; in the case of RIG-I, these ligands possess additional key features, including a 5′-triphosphate (5′-ppp) or 5′-diphosphate (5′-pp) moiety that is absent in many host RNAs (Gerlier and Lyles, 2011; Schmidt et al., 2009). RLR activation occurs in a well-defined sequential fashion that includes the following key steps: (1) RNA agonist binding to the C-terminal domain (CTD) and helicase region; (2) RLR oligomerization and conformational changes; (3) subcellular redistribution from the cytoplasm to the mitochondrion; and (4) interaction with the RLR-adaptor protein, mitochondrial antiviral signaling protein (MAVS) (Rehwinkel and Gack, 2020) (see poster). MAVS functions as a protein-complex assembly scaffold recruiting a variety of signaling proteins, among them TANK-binding kinase 1 (TBK1) and inhibitor of nuclear factor kappa-B kinase subunit ε (IKKε). Once activated, these effector kinases then propagate further signaling via IFN-regulatory factors [typically IFN-regulatory factor 3 (IRF3) or IFN-regulatory factor 7 (IRF7)], which induce the expression of an assortment of IFNs. IFNs, together with countless other cytokines, then initiate and contribute to antiviral responses in both the infected cell and adjacent uninfected cells. The activation of RIG-I and MDA5 is primarily regulated by certain critical post-translational modifications (PTMs) (see Box 1). It is worth noting that while K63-linked polyubiquitylation of the caspase activation and recruitment domains (CARDs) of RIG-I is crucial for RIG-I oligomerization, MAVS binding and downstream signaling, the CARDs of MDA5 necessitate ISGylation for downstream signaling. RIG-I and MDA5 sense distinct or overlapping groups of RNA viruses, such as flaviviruses, influenza viruses, picornaviruses, and paramyxoviruses (to name a few) (Loo et al., 2008). An increasing body of work has recently implicated RIG-I in detecting DNA viruses, including certain adenoviruses (Minamitani et al., 2011), herpes simplex virus type 1 (HSV-1) (Chiang et al., 2018b), Epstein–Barr virus (EBV) (Samanta et al., 2006) and Kaposi's sarcoma-associated herpesvirus (KSHV) (Inn et al., 2011; Zhao et al., 2018). In these contexts, RIG-I has been shown to recognize specific noncoding RNAs that are derived from either the host cell or the virus – primarily RNAs transcribed by mammalian RNA polymerase III (Ablasser et al., 2009; Chiang et al., 2018b; Chiu et al., 2009; Naesens et al., 2022; Zhao and Karijolich, 2019).

Box 1. Viral targeting of host 'PTMases' that regulate immune sensor proteins

The activity of RLRs, cGAS and IFI16 is regulated by numerous PTMs, including phosphorylation, deamidation, ubiquitylation and conjugation of the ubiquitin-like protein ISG15 (ISGylation) (Chiang and Gack, 2017; Song et al., 2021). Not surprisingly, modifying the regulatory PTMs of immune sensors has emerged as a major strategy by which viruses inhibit mammalian IFN responses (Chan and Gack, 2016b; Chiang et al., 2021b). Viruses can either target the responsible cellular modifying enzymes – the 'PTMases' (such as phosphatases and E3 ubiquitin ligases) – or they can actively remove or add regulatory PTMs (see poster).

Nondegradative K63-linked ubiquitylation events promote PRR signaling, and thus many viruses perturb this type of PTM to dampen IFN induction. For instance, HBV polymerase and ZIKV NS2B/3 bind to STING and reduce its K63-linked ubiquitylation (Li et al., 2019; Liu et al., 2015). Human coronavirus (HCoV)-NL63 PLP2 acts as a deubiquitylase to remove K63-linked ubiquitin chains from STING (and RIG-I) (Sun et al., 2012). Crimean–Congo hemorrhagic fever virus (CCHFV) possesses deubiquitylation and deISGylation activities that reduce the RIG-I–MAVS-mediated response (Scholte et al., 2017). Multiple viruses inhibit the K63-linked ubiquitylation of RIG-I (catalyzed by several host E3 ubiquitin ligases), preventing RIG-I oligomerization and signal transduction. For example, the E6 oncoprotein from human papilloma virus 16 blunts RIG-I signaling by forming a complex with TRIM25 and USP15 (Chiang et al., 2018a). Numerous viral proteins (IAV NS1, paramyxovirus V, HRSV NS1, JC polyomavirus small T antigen, SARS-CoV N, EBV BPLF1) target TRIM25, blocking its activity on RIG-I, although through different tactics and/or interaction modes (Ban et al., 2018; Chiang et al., 2021a; Gack et al., 2009; Hu et al., 2017; Koliopoulos et al., 2018; Sanchez-Aparicio et al., 2018; Gupta et al., 2019). The subgenomic flavivirus RNA (sfRNA) from serotype 2 DENV interacts with TRIM25 to reduce RIG-I signaling (Manokaran et al., 2015). Lastly, HCV NS3/4A specifically targets Riplet (RNF135)-induced RIG-I K63-linked ubiquitylation (Oshiumi et al., 2013).

HSV-1 UL37 collaborates with the host glutamine amidotransferase PPAT to induce RIG-I deamidation, deactivating RNA sensing (Huang et al., 2021; Zhao et al., 2016). HSV-1 UL37 also targets cGAS for deamidation, impairing its enzymatic cGAMP synthesis activity (Zhang et al., 2018).

Viral proteins can also manipulate phosphorylation events on sensor proteins or use their own kinases to add phosphate groups. HCMV UL97 phosphorylates nuclear IFI16, triggering its mislocalization to the cytoplasm where it is trapped in viral assembly complexes and mature virions (Dell'Oste et al., 2014). The HSV-1-encoded kinase US3 phosphorylates RIG-I specifically at S8 to prevent effective RIG-I signaling (van Gent et al., 2022). Some paramyxoviral V proteins obstruct MDA5 dephosphorylation by binding to the phosphatases PP1α and PP1γ (Davis et al., 2014).

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cGAS and IFI16 – intracellular sensors of DNA viruses

Several intracellular DNA sensors have been identified to date, including cGAS, IFI16, absent in melanoma 2 (AIM2), DNA-dependent activator of IFN-regulatory factors (DAI, also known as Z-DNA-binding protein 1, ZBP1) and DNA-dependent protein kinase (DNA-PK) (Paludan and Bowie, 2013). Among them, cGAS and IFI16 are considered primary sensors for inducing type I IFN responses in many different cell types in response to various DNA virus infections (see poster). Unlike RLRs, cGAS and IFI16 transmit signals via the adaptor molecule stimulator of interferon genes (STING, also known as STING1, MITA or TMEM173) (Ishikawa and Barber, 2008; Sun et al., 2013; Unterholzner et al., 2010). DNA agonist binding enables cGAS to catalyze formation of cyclic GMP–AMP (cGAMP). This small 'second messenger' molecule then binds to STING, prompting critical activation steps. Key events for downstream IRF3 activation and IFN initiation are STING dimerization, which is facilitated by nondegradative ubiquitylation mediated by several TRIM-family E3 ubiquitin ligases (Giraldo et al., 2020; van Gent et al., 2018), and its translocation from the endoplasmic reticulum (ER) to the Golgi and perinuclear sites. Although the cGAS–STING axis is canonically labeled an immune surveillance system for DNA viruses, recent reports have shown that it is also involved in recognition of RNA viruses, where leakage or mislocalization of cellular DNA can prompt cGAS activation (Webb and Fernandez-Sesma, 2022; Zevini et al., 2017). The PYHIN-family sensor protein IFI16 is predominately located in the nucleus where DNA sensing takes place. IFI16 activates a similar downstream cascade as cGAS that is mediated by STING, IRF3 and nuclear factor κB (NF-κB), and further, induces a distinct pathway leading to inflammasome activation (Kerur et al., 2011) (see poster). Of note, recent work has unveiled that cGAS and IFI16 can cooperate to potentiate DNA sensing and IFN induction (Jonsson et al., 2017; Orzalli et al., 2015).

Tactics of viral immune escape

RLRs, cGAS and IFI16 are antagonized by viruses from diverse families, which have evolved to wreck IFN-based innate immune defense in mammalian hosts. Here, we highlight the major viral strategies of immune escape, which can be grouped into five categories: (1) inhibiting critical sensor or adaptor proteins of innate immunity; (2) shielding or processing viral immunostimulatory RNA; (3) degrading or cleaving sensors or downstream signaling mediators; (4) relocalizing or 'seizing' innate signaling proteins; and (5) derailing IFNAR signaling. Lastly, many viruses obstruct innate immunity through a mechanism called 'host shutoff', which broadly impedes the production of host proteins, including those with critical roles in antiviral immunity (reviewed in detail elsewhere; see Gaucherand and Gaglia, 2022; Walsh and Mohr, 2011). Of note, the newly emerged coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has also evolved a myriad of immune escape strategies (Box 2).

'Disabling the alarm system' – inhibiting sensor proteins or their adaptors

PRRs are the 'alarm system' of mammalian cells, detecting viral 'burglars'. They sense specific immunostimulatory RNA or DNA (or other viral components, such as glycoproteins) (Boehme and Compton, 2004; Kurt-Jones et al., 2000) and then trigger antiviral downstream signaling leading to protective responses. In turn, many viruses directly disable PRRs, or they block MAVS and STING (see poster). For instance, paramyxovirus V proteins bind to the receptor MDA5, interfering with IFN-β induction (Andrejeva et al., 2004; Childs et al., 2007). Arenavirus Z proteins disrupt the association between RIG-I or MDA5 and MAVS by interacting with the CARDs of RIG-I or MDA5 (Fan et al., 2010; Xing et al., 2015). Moreover, the PB1-F2 protein from influenza A virus (IAV) targets MAVS at mitochondria (Varga et al., 2012), whereas dengue virus (DENV) NS4B induces morphological alterations in the mitochondria that affect their ability to serve as MAVS scaffolding platforms (Chatel-Chaix et al., 2016).

The cGAS and IFI16 pathways are also targeted by numerous viral proteins. For example, ORF52 from several herpesviruses, including KSHV, interacts with cGAS, disturbing its DNA-binding and enzymatic activities (Wu et al., 2015). KSHV LANA protein also interacts with cGAS, promoting KSHV reactivation (Zhang et al., 2016). An analogous strategy of negatively regulating the cGAS–STING pathway is employed by HSV-1 VP22 (Huang et al., 2018a) and human cytomegalovirus (HCMV) UL31 (Huang et al., 2018b), both of which interact with cGAS to inhibit viral sensing.

Box 2. Immune evasion tactics employed by SARS-CoV-2

As one of the viruses causing devastating pandemics in the human population, SARS-CoV-2 has developed an array of evasion strategies that lead to delayed or dysregulated IFN responses in the human organism. One of these strategies is host translational shutoff. SARS-CoV-2 NSP1 interferes with host gene translation by associating with ribosomes, inhibiting the mRNA export machinery and accelerating the degradation of cellular mRNAs (Finkel et al., 2021; Thoms et al., 2020; Zhang et al., 2021). ORF8 employs a histone mimicry strategy to block global gene expression in the infected cell (Kee et al., 2022). NSP8 and NSP9 bind to the 7SL RNA in the signal recognition particle and interfere with protein trafficking (Banerjee et al., 2020). NSP14 and NSP16 act as translational repressors, shutting down host protein synthesis (Banerjee et al., 2020; Hsu et al., 2021). All of the aforementioned actions disrupt IFN and ISG induction.

Masking of viral RNA ligands also plays an important role in immune evasion by SARS-CoV-2. The viral 2′-O-methyltransferase NSP16 (along with NSP14, NSP12 and other viral proteins) catalyzes Cap1 modifications of viral RNA to mimic host mRNA, evading detection by MDA5 (Park et al., 2022; Russ et al., 2022). A molecular pore complex consisting of NSP3, NSP4 and NSP6 spans double-membrane vesicles and allows 'guided' export of viral RNAs to the cytosol, while shielding them from innate sensors (Wolff et al., 2020) (see poster).

Mounting evidence shows that SARS-CoV-2 targets RLR–MAVS and cGAS–STING signaling cascades. For example, NSP3 has been shown to remove ISGylation from MDA5 and IRF3 via its papain-like protease activity, thereby dampening IFN gene expression (Liu et al., 2021a; Shin et al., 2020). NSP5 cleaves RIG-I, promotes the ubiquitylation and proteasome-mediated degradation of MAVS, and also impedes STING (Liu et al., 2021b; Rui et al., 2021). SARS-CoV-2 N protein undergoes liquid–liquid phase separation with RNA, which inhibits the K63-linked ubiquitylation and aggregation of MAVS (Wang et al., 2021a). ORF9b has been shown to interact with TOM70 at the mitochondrial outer membrane and to disrupt the recruitment of TBK1 to MAVS (Jiang et al., 2020). NSP12, ORF3b, ORF6 and ORF8 impair nuclear translocation of IRF3 (Kimura et al., 2021; Konno et al., 2020; Rashid et al., 2021; Wang et al., 2021b). ORF3a can interact with STING and attenuate its downstream signaling (Rui et al., 2021). IFNAR signaling can also be dysregulated by multiple SARS-CoV-2 proteins. For instance, SARS-CoV-2 ORF6 has been shown to abrogate nuclear translocation of STAT1 and STAT2 by hijacking Nup98 (Miorin et al., 2020). Of note, some SARS-CoV-2 variants of concern have differential abilities to suppress cellular IFN responses. For example, the Alpha variant displays higher levels of subgenomic RNA and protein abundances of N, ORF9b and ORF6, which are all innate immune antagonists (Thorne et al., 2022).

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Viral IFN-regulatory factor 1 (vIRF1) of KSHV competitively binds to STING, impeding TBK1 binding (Ma et al., 2015). HCMV employs, besides UL31, an arsenal of additional proteins to negatively regulate DNA-sensing mechanisms. HCMV UL37 exon 1 protein (UL37x1) interacts with TBK1 and prevents TBK1–STING–IRF3 signaling (Ren et al., 2022). Viral pp65 (UL83) inhibits IFN-β induction by binding to cGAS, impeding its enzymatic activity and disrupting the cGAS–STING–IRF3 axis (Biolatti et al., 2018). HCMV UL83 also interacts with the PYRIN domain of IFI16, preventing IFI16 from forming nuclear oligomers, which ultimately blocks IFN induction (Li et al., 2013).

The formation of liquid droplet compartments is required for cGAS activation (Du and Chen, 2018), and accordingly, ORF52 and VP22 proteins from gamma- and alpha-herpesviruses disrupt cGAS–DNA phase separation to antagonize innate immunity (Bhowmik et al., 2022; Xu et al., 2021).

Another major strategy to target RLRs, IFI16 and cGAS is to disable regulatory mechanisms required for their activation, in particular specific PTMs of these sensors (see poster and Box 1).

‘Hiding in the dark’ – shielding or processing of viral immunostimulatory RNA

RLRs and DNA sensors detect viral RNA or DNA ligands at specific subcellular locations (i.e. the cytoplasm and/or nucleus). As a countermeasure, viruses have evolved to process or modify viral nucleic acid, especially viral RNA, to remove some of the key features that are critical for PRR activation. Additionally, some viruses hide or shield their viral RNA in membranous structures or certain vesicles, escaping immune detection (see poster). For instance, several *Hantaviridae* and *Bornaviridae* family members encode phosphatases that turn 5′-ppp moieties into 5′-monophosphate moieties, which disables sensing by RIG-I (Habjan et al., 2008; Wang et al., 2011). Viral dsRNAs from certain arenaviruses harboring a single unpaired 5′-ppp-nucleotide have been found to be unable to elicit type I IFN responses and even compete with other 5′-ppp-RNA agonists for RIG-I (Marq et al., 2011). Certain viral proteins, such as the Lassa virus nucleoprotein (NP; which exhibits 3′–5′ exonuclease activity), are able to digest dsRNA, preventing detection by RIG-I (Hastie et al., 2011; Reynard et al., 2014).

The IAV nucleoprotein and polymerase subunit PB2 encapsidate and bind viral RNA to prevent RIG-I-dependent virus restriction (Weber et al., 2015). Human metapneumovirus (HMPV) RNA is modified with N^6-methyladenosine (m6A), mimicking cellular RNA. m6A-deficient recombinant HMPV induces increased expression of type I IFNs, which has been shown to be dependent on RIG-I but not MDA5 (Lu et al., 2020). m6A modification of hepatitis B virus (HBV) and hepatitis C virus (HCV) transcripts also prevents recognition by RIG-I (Kim et al., 2020). VP35 from Ebola (Cardenas et al., 2006) and Marburg (Ramanan et al., 2012) viruses, IAV NS1 (Donelan et al., 2003), as well as vaccinia virus (VACV) E3L (Valentine and Smith, 2010) all bind to viral dsRNA, contributing to immune escape. Human parainfluenza virus type 1 (HPIV1) C protein has been proposed to prevent MDA5 activation by inhibiting cytoplasmic dsRNA accumulation (Boonyaratanakornkit et al., 2011).

‘Inducing destruction’ – degrading or cleaving sensors or signaling mediators

Another effective viral strategy is to simply ‘destroy’ proteins that play critical roles in the innate immune response. To achieve this, viruses induce proteasomal, lysosomal or autophagy-based degradation, or they cleave key regulators (see poster). Virus infection can also elicit the expression of specific microRNAs (miRNAs) that subsequently ‘silence’ the expression of innate immune factors.

Examples of viral proteins inducing direct proteolytic cleavage include the HCV NS3–NS4A complex (NS3/4A), which chops MAVS off the mitochondria (Li et al., 2005; Meylan et al., 2005), and the NS2B–NS3 complex (NS2B/3) of DENV and Zika virus (ZIKV), which binds and cleaves human but not murine STING to antagonize the type I IFN response (Aguirre et al., 2012; Ding et al., 2018). Several human enteroviruses, such as coxsackievirus B3 (CVB3), enterovirus 71 (EV71) and poliovirus, use their 3C and/or 2A proteases ($3C^{pro}$ and $2A^{pro}$, respectively) to cleave specific RLRs (such as MDA5) and MAVS (Feng et al., 2014). $3C^{pro}$ from several viruses, including echovirus, rhinovirus and encephalomyocarditis virus (EMCV), cleaves and inactivates RIG-I (Barral et al., 2009; Mukherjee et al., 2011).

EMCV VP2 protein degrades MDA5, MAVS and TBK1 through proteasomal and lysosomal degradation pathways (Han et al., 2021). ZIKV NS1 triggers cGAS degradation by stabilizing caspase 1 (Zheng et al., 2018), whereas DENV NS2B mediates lysosomal degradation of cGAS (Aguirre et al., 2017). HSV-1 ICP0 promotes the proteasomal degradation of IFI16 through an indirect mechanism that likely requires other host and/or viral factors (Cuchet-Lourenco et al., 2013). KSHV also degrades IFI16 to maintain latency (Roy et al., 2016). SARS-CoV ORF9b has been shown to trigger the K48-linked ubiquitylation of MAVS by targeting two host factors, PCBP2 and AIP4 (also known as ITCH) (Shi et al., 2014). IAV PB1 promotes RNF5-mediated ubiquitylation of MAVS and recruits the selective autophagic receptor NBR1 to deliver ubiquitylated MAVS to autophagosomes for degradation (Zeng et al., 2021). Toscana phlebovirus (TOSV) NSs, which shares homology with Sandfly fever Naples virus (SFNV) NSs, has E3 ubiquitin ligase activity, directly ubiquitylating and degrading RIG-I (Gori-Savellini et al., 2013; Gori Savellini et al., 2019).

Interestingly, viruses can also modulate miRNA expression, thereby dampening RLR signaling. EV71 $3C^{pro}$ downregulates miR-526a, which targets CYLD, a cellular enzyme that removes K63-linked ubiquitylation from RIG-I that is needed for signaling (Friedman et al., 2008; Xu et al., 2014). Another example is HBV, which induces miR-146a to directly ‘silence’ the expression of RIG-I (Hou et al., 2016).

‘Holding hostage’ – relocalizing or seizing innate signaling proteins

Rather than degrade innate immune proteins, some viruses simply relocalize them or keep them captive (for example, in viral inclusion bodies). This prevents host proteins from performing their normal duties at the proper locations. For instance, the NSs protein from Dabie bandavirus (also termed severe fever with thrombocytopenia syndrome virus, SFTSV) interacts with TRIM25, one of the E3 ubiquitin ligases acting on RIG-I (Gack et al., 2007), trapping it in viral inclusion bodies. Viral ‘seizing’ of TRIM25 ultimately prevents the K63-linked ubiquitylation and activation of RIG-I (Min et al., 2020). The human respiratory syncytial virus (HRSV) N protein interacts with both MDA5 and MAVS to sequester these proteins into inclusion bodies, reducing type I IFN expression during infection (Lifland et al., 2012). The ZIKV NS3 protein binds to 14-3-3η and 14-3-3ε via a conserved RLDP motif that resembles a phosphorylated 14-3-3-binding motif in cellular proteins. By binding to these 14-3-3 proteins, ZIKV NS3 competes with RIG-I and MDA5, blocking their translocation from the cytosol to the

mitochondria, which is normally mediated by 14-3-3ε and 14-3-3η, respectively (Riedl et al., 2019). DENV and West Nile virus (WNV) NS3 proteins usurp 14-3-3 proteins in a similar manner to evade RLR signaling (Chan and Gack, 2016a; Riedl et al., 2019) (see poster).

DNA viruses also employ a number of tactics to block the relocalization of innate immune signaling proteins to specific subcellular sites or organelles that allow signal transduction. The HCMV UL82 tegument protein inhibits STING by directly binding to it and preventing its translocation from the ER to the perinuclear membrane. UL82 also prevents STING from interacting with TBK1 and IRF3 (Fu et al., 2017). In a different approach, HCMV UL94 disrupts STING dimerization and translocation to perinuclear microsomes, impairing TBK1 recruitment and ultimately type I IFN gene transcription (Zou et al., 2020).

‘Blocking protective responses’ – IFNAR signal inhibition

IFNs produced following RNA virus or DNA virus infection are secreted and activate antiviral responses in an autocrine and paracrine manner by engaging with the IFNAR. This activates the intracellular Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway (Stark and Darnell, 2012). During this key process, STAT1 and STAT2 become phosphorylated and combine with IRF9 to form the IFN-stimulated gene factor 3 (ISGF3) transcriptional complex, which binds to IFN-stimulated response elements (ISREs) in type I IFN-dependent gene promoters, leading to ISG expression that is essential to generate an antiviral state (Au-Yeung et al., 2013; O’Shea et al., 2015; Philips et al., 2022). This host protective response is also antagonized by viral proteins at multiple steps (see poster).

Members of the poxvirus and paramyxovirus families have been shown to antagonize STAT1 by preventing it from binding to the activated IFNAR. VACV (Western Reserve strain) gene 018 (also known as OPG024) and Nipah virus V protein, which share similar STAT-binding regions, compete with phosphorylated IFNAR to bind STAT1 (Talbot-Cooper et al., 2022). Some viruses, such as tick-borne encephalitis virus (TBEV) and WNV, use their NS5 proteins to bind to peptidase D (PEPD), inhibiting surface expression of the IFNAR1 subunit of the IFNAR (Lubick et al., 2015). IAV hemagglutinin (HA) has been shown to promote IFNAR1 degradation (Xia et al., 2015), which reportedly involves PARP1 (Xia et al., 2020). Some viruses such as VACV (which uses its B18R protein) employ a ‘decoy’ tactic to sequester IFNs prior to IFNAR binding (Symons et al., 1995).

Viruses also suppress the JAK–STAT pathway either by manipulating negative-feedback inhibitory proteins of the SOCS family, or by impeding phosphorylation or translocation of STAT1 and STAT2. For instance, WNV induces the expression of SOCS1 and SOCS3 in dendritic cells, resulting in SOCS1- and SOCS3-mediated inhibition of JAK1 (Mansfield et al., 2010). Similarly, varicella-zoster virus (VZV) infection induces SOCS3 expression (Choi et al., 2015), and HRSV NS1 and NS2 induce upregulation of both SOCS1 and SOCS3 (Zheng et al., 2015), all to inhibit ISG induction. Moreover, Ebola virus VP24 prevents STAT1 nuclear translocation by binding to karyopherins (Mateo et al., 2010; Reid et al., 2006). Multiple flaviviruses, such as DENV and ZIKV, degrade human STAT2 using their NS5 proteins, a phenotype that has been observed in multiple independent studies (Grant et al., 2016; Hertzog et al., 2018; Kumar et al., 2016). Numerous other viral proteins (from both RNA viruses and DNA viruses) inhibit JAK1, STAT1 and/or STAT2, sometimes due to a direct interaction with these key signaling mediators. These include certain flavivirus NS proteins (Guo et al., 2005; Munoz-Jordan et al., 2005), HCMV UL23 (Feng et al., 2021), HMPV SH protein (Hastings et al., 2016), SFTSV NSs (Chaudhary et al., 2015; Ning et al., 2015), Heartland virus (HRTV) NSs (Feng et al., 2019), adenovirus (AdV) E1A (Look et al., 1998; Sohn and Hearing, 2019), alphavirus nsP2 (Fros and Pijlman, 2016), paramyxovirus V and W proteins (Rodriguez et al., 2002; Shaw et al., 2004), rabies virus P protein (Vidy et al., 2005) and VACV C6 protein (Stuart et al., 2016).

Perspectives

Our knowledge of host–pathogen interactions in innate immunity and antagonism of type I IFN responses has grown considerably in the past two decades, and these findings might hold tremendous therapeutic value. Viruses lacking efficient IFN antagonists have gained significance in vaccine development (Fleming, 2016) and are frequently utilized in oncolytic virotherapy since they are confined to IFN-deficient cell types, such as cancer cells (Li et al., 2022). Aside from attenuating type I IFN induction and signaling as described above, numerous viruses also employ evasion strategies to impede the antiviral activities of specific ISG-encoded proteins (Schoggins, 2019; Short, 2009). Targeting specific viral antagonists (or ideally, multiple ones in a given virus) is expected not only to reduce viral replication, but also to reinstate effective immune responses, boosting antiviral defenses for faster clearance. Recently, novel upstream pathways that prompt innate immune activation – for instance, virus-induced actin cytoskeleton disturbance leading to RLR activation (Acharya et al., 2022) – have been identified. The discovery of viral inhibitory measures that counteract these new sensing pathways therefore awaits future investigation, which might in turn also offer new ways of targeting viruses for therapeutic interventions. Another exciting avenue is the combined use of classical screening approaches and artificial intelligence-based or computational approaches to identify novel viral protein targets and inhibitors to interfere with the ability of viruses to impede innate immune pathways (Ng et al., 2022).

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Competing interests

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High-resolution poster and poster panels

A high-resolution version of the poster and individual poster panels are available for downloading at https://journals.biologists.com/jcs/article-lookup/doi/10.1242/jcs.260682#supplementary-data.

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