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Innate immune evasion strategies of DNA and RNA viruses

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Upon infection, both DNA and RNA viruses can be sensed by pattern recognition receptors (PRRs) in the cytoplasm or the nucleus to activate antiviral innate immunity. Sensing of viral products leads to the activation of a signaling cascade that ultimately results in transcriptional activation of type I and III interferons, as well as other antiviral genes that together mediate viral clearance and inhibit viral spread. Therefore, in order for viruses to replicate and spread efficiently, they must inhibit the host signaling pathways that induce the innate antiviral immune response. In this review, we will highlight recent advances in the understanding of the mechanisms by which viruses evade PRR detection, intermediate signaling molecule activation, transcription factor activation, and the actions of antiviral proteins.

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Introduction

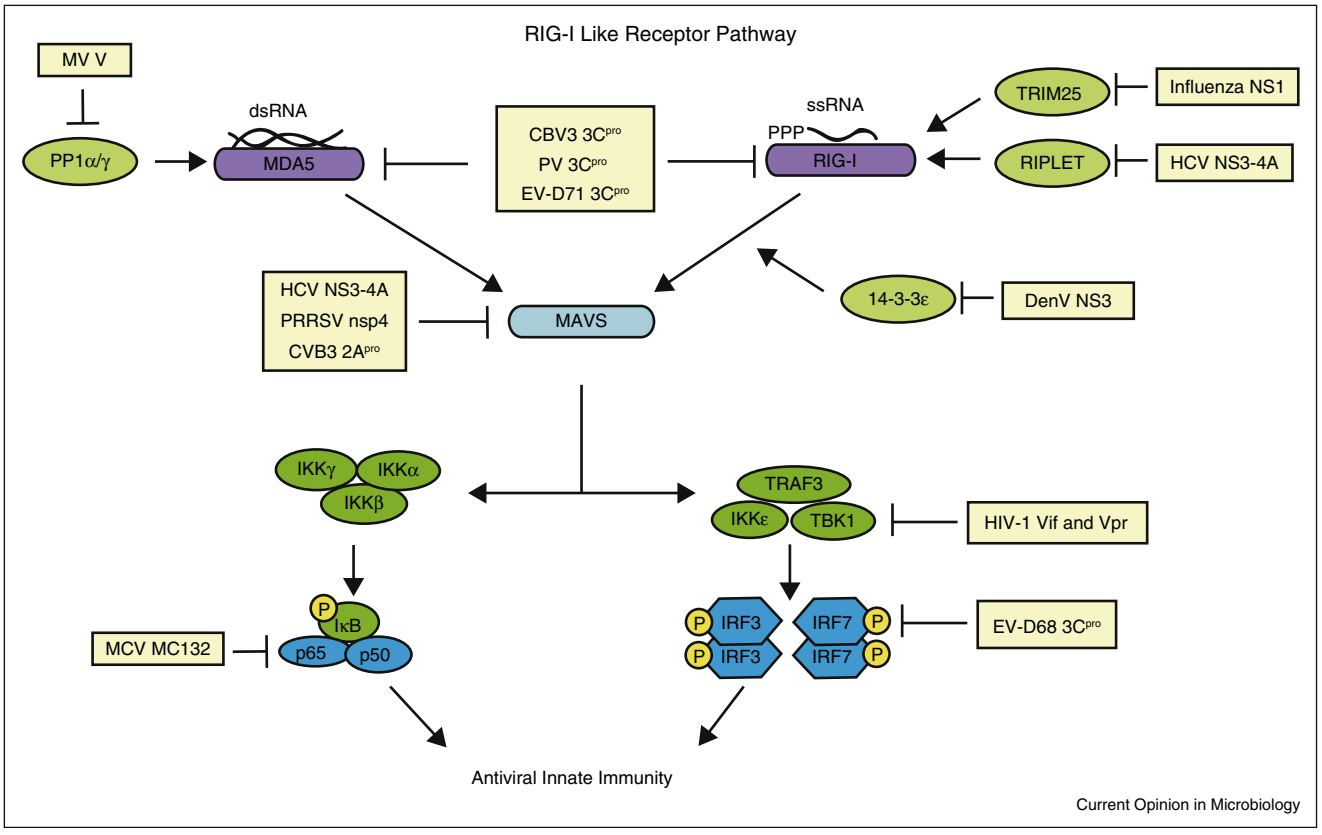
Upon virus infection, viral pathogen-associated molecular patterns (PAMPs) are sensed by host pattern recognition receptors (PRRs). PAMPs are unique features present in viruses that are not present in the host cell and therefore allow cells to distinguish self versus non-self to activate an immune response to infection. There are several types of PRRs that sense viral infection, including Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and DNA sensors, which recognize both viral nucleic acids and proteins. Activation of these PRRs leads to signaling through adaptor proteins, such as MAVS and STING. These adaptor proteins then activate kinases and transcription factors that induce the expression of type I and III interferons (IFNs), as well as antiviral proteins (PRRs are reviewed in [1]). The antiviral innate immune signaling pathways highlighted in this review are shown in Figures 1–4.

As full induction of antiviral innate immunity potently limits viral replication, viruses have evolved several general strategies to evade this innate immunity. A broad overview of many of the strategies to evade PRR signaling have been previously reviewed in detail [2,3,4•,5•]. In this review, we describe the recent advances in viral evasion of the host antiviral innate immune response, including mechanisms for viral evasion of PRR detection, intermediate signaling molecule activation, transcription factor activation, and the actions of antiviral proteins.

Evasion or targeting of PRRs

Viruses have developed several ways to evade detection by PRRs. Many RNA viruses replicate in the cytoplasm where they are sensed by the cytoplasmic PRRs, MDA5 and RIG-I (Figure 1). In contrast, most DNA viruses replicate within the nucleus and can be sensed in the nucleus or in the cytoplasm by IFI16 or cGAS, respectively (Figure 2). Thus to avoid detection by the host innate immune system at their sites of replication, viruses have evolved several evasion strategies. For example, the positive-sense single-stranded (ss) RNA virus, dengue virus (DenV), replicates in the cytoplasm where its dsRNA would be expected to be detected by the cytoplasmic RNA sensor proteins RIG-I and MDA5 to induce type I IFN. However, new work has revealed that DenV induces membrane modifications that sequester the DenV RNA away from RIG-I and MDA5, resulting in poor induction of type I IFN [6]. It has been known for some time that hepatitis C virus (HCV), which like DenV is in the *Flaviviridae* family of viruses, similarly induces membrane rearrangements to house its replication machinery [7,8]. Interestingly, it has now been suggested that similar to DenV, HCV-induced membrane rearrangement prevents recognition of HCV RNA by RIG-I [9••]. Indeed, a study by Neufeldt *et al.*, showed that HCV co-opts host nuclear pore complex proteins (NPC) to the membranous web to regulate protein transport into the replication complex. As viral proteins have cryptic nuclear localization signals they can relocalize to these sites of replication; however, as RIG-I does not, it is excluded from the sites of replication. Intriguingly, addition of a nuclear localization signal to RIG-I, allows it to sense HCV RNA and activate IFN induction, suggesting that the NPC at the membranous web acts as a regulator to determine the proteins that can access the membranous

Figure 1



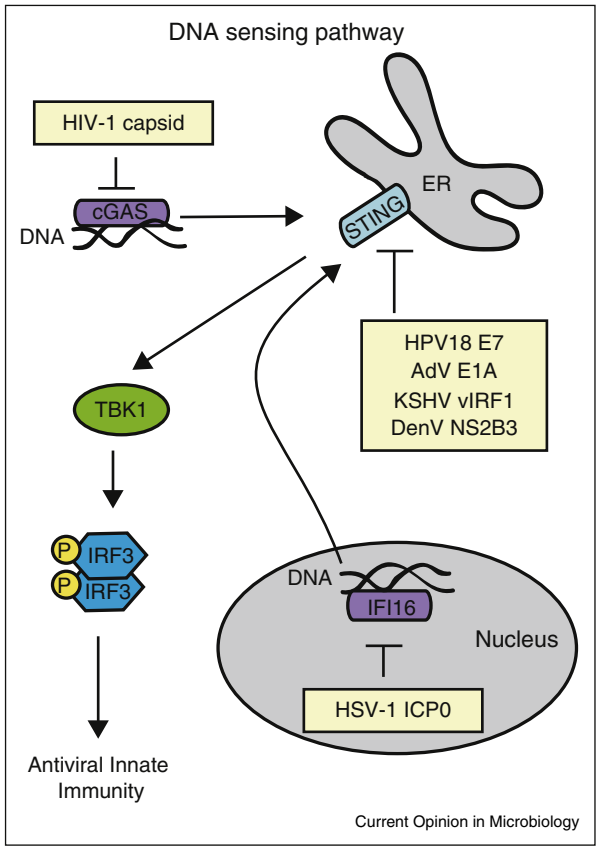
Evasion of RIG-I-like receptor signaling by viruses. The RIG-I-like receptors RIG-I and MDA5 are activated by viral dsRNA in the cell cytoplasm. PP1α/γ dephosphorylates MDA5 to allow subsequent signaling. TRIM25 and RIPLET are E3 ubiquitin ligases that ubiquitinate RIG-I for its full activation. The 14-3-3ε protein mediates RIG-I translocation to the membrane to interact with MAVS. MAVS is the adaptor protein for both RIG-I and MDA5 and recruits downstream signaling molecules to mediate signaling to the transcription factors IRF3/7 and NFκB. Several aspects of this signaling pathway are inhibited by viruses, as shown here. *Abbreviations*: coxsackievirus B3 (CVB3), dengue virus (DenV), enterovirus 68 (EV-D68), enterovirus 71 (EV-D71), hepatitis C virus (HCV), human immunodeficiency virus (HIV), molluscum contagiosum virus (MCV), poliovirus (PV), porcine reproductive and respiratory syndrome virus (PRRSV), and West Nile virus (WNV).

web [9••]. This is the first demonstration that sequestered viral replication within rearranged cytoplasmic membranes actively prevents PRR sensing of viral RNA and the subsequent induction of IFN.

The PRRs RIG-I and MDA5 are frequently inhibited by viruses to prevent activation of IFN. These proteins are activated by specific PAMPs, with RIG-I recognizing ssRNA that contains a 5′ triphosphate as well as short double-stranded (ds) RNA molecules, and MDA5 sensing longer dsRNA molecules (reviewed in [3]). Enteroviruses, including poliovirus (PV), coxsackievirus B3 (CVB3), and enterovirus 71 (EV-D71), are positive-sense ssRNA viruses sensed in the cytoplasm by MDA5 and RIG-I. These enteroviruses encode two proteases, $2A^{pro}$ and $3C^{pro}$, required for viral polyprotein processing. However, $2A^{pro}$ and $3C^{pro}$ have also been shown to cleave MDA5 and RIG-I, respectively [10]. This demonstrates that enteroviruses have converged on common strategies to evade multiple PRRs during infection further supporting the fact that PRR sensing is critical for limiting viral replication and spread.

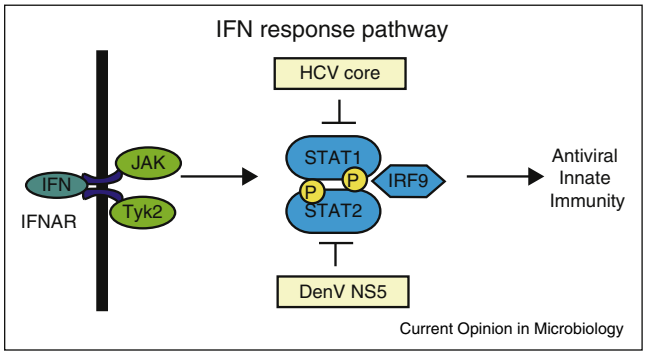
Both RIG-I and MDA5 require a coordinated set of events to go from their inactive to active state (reviewed in [11]). One of the steps to activate RIG-I and MDA5 includes removal of inhibitory phosphorylation marks by the protein phosphatases PP1α and PP1γ [12]. The negative-sense ssRNA viruses, measles virus (MV) and Nipah virus, both inhibit MDA5 activation through the actions of their V protein [13,14]. The V protein, which acts as an IFN antagonist, binds PP1α and PP1γ to prevent the dephosphorylation of MDA5 specifically during infection [13]. MV also utilizes a second strategy to prevent PP1α/γ dephosphorylation of MDA5. This strategy involves activation of a DC-SIGN signaling pathway that activates Raf1 kinase for activation of the PP1 inhibitor 1, which blocks PP1α/γ action [14].

Figure 2



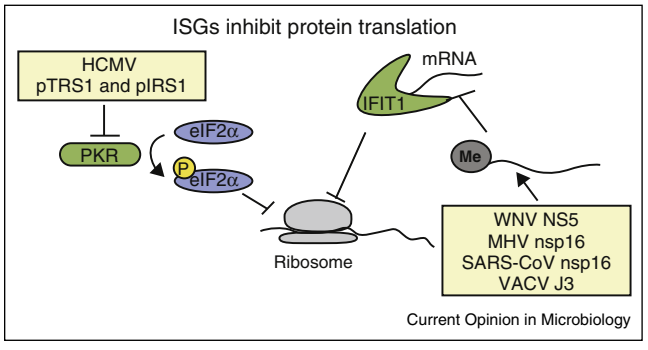
Evasion of DNA sensors by viruses. Viral DNA is sensed by cGAS in the cytoplasm and IFI16 in the nucleus. cGAS and IFI16 signal to a common adaptor protein, STING, which recruits TBK1 to activate IRF3, which induces expression of type I IFN and other antiviral genes. IFI16, cGAS, and STING have all been inhibited by viruses, as shown here. *Abbreviations*: adenovirus (AdV), herpes simplex virus-1 (HSV-1), human immunodeficiency virus (HIV), human papillomavirus 18 (HPV18), and Kaposi's sarcoma associated herpes virus (KSHV).

Figure 3



Viral evasion of the IFN response pathway. Once induced, IFNs are secreted from the infected cell and signal in an autocrine and paracrine manner through the IFN receptor complex to activate the JAK/STAT pathway. This signaling leads to the activation of the ISGF3 complex, which consists of STAT1, STAT2, and IRF9, that translocates to the nucleus to induce ISGs with broad antiviral functions. Both STAT1 and STAT2 are inhibited by viruses, as shown here. *Abbreviations*: dengue virus (DenV), hepatitis C virus (HCV), and interferon α receptor complex (IFNAR).

Figure 4



Evasion of ISGs by viruses. Both PKR and IFIT1 are ISGs that limit mRNA translation in virally infected cells. PKR phosphorylates the eukaryotic initiation factor eIF2α to inhibit translation. Several viruses, including human cytomegalovirus (HCMV) shown here, inhibit this function of PKR. As IFIT1 binds to uncapped RNAs to prevent their translation, several viruses encode 2′-O methyltransferases that cap viral RNAs to prevent inhibition of their translation during infection. *Abbreviations*: murine hepatitis virus (MHV), severe acute respiratory syndrome coronavirus (SARS-CoV), vaccinia virus (VACV), and West Nile virus (WNV).

Full activation of RIG-I requires the actions of a set of proteins, including TRIM25, RIPLET, and 14-3-3ε (reviewed in [11]). All of these proteins are targeted by viruses to prevent their activation. Both TRIM25 and RIPLET are E3 ubiquitin ligases that ubiquitinate RIG-I with K63-linked ubiquitin chains for its full activation. However, the negative-sense ssRNA virus, influenza virus, which is sensed by RIG-I [15,16], evades the actions of both TRIM25 and Riplet [17,18]. The viral NS1 protein binds to both TRIM25 and Riplet in a species-specific manner [18]. This prevents the activation of RIG-I during infection leading to a decreased induction of IFN [17,18]. Recently, it was shown that the HCV NS3-4A protease complex, which has long been known to cleave MAVS and TRIF (see below) [19–23], also cleaves RIPLET to inhibit induction of IFN [24]. The 14-3-3ε protein, which binds to RIG-I to mediate translocation of RIG-I from the cytoplasm to interact with MAVS at intracellular membranes [25], is also inhibited by viruses. The 14-3-3ε protein binds proteins like RIG-I that contain phosphorylated serine or threonine at an Rxx(pS/pT)xP motif. Interestingly, the NS3 proteases of both DenV and West Nile virus (WNV) bind to 14-3-3ε via a phosphomimetic RxEP motif, suggesting that NS3 competitively inhibits RIG-I binding to 14-3-3ε, thus blocking translocation to MAVS to prevent induction of antiviral innate immunity [26••].

Viruses also evade sensing by PRRs by encoding proteins that protect the viral nucleic acids from sensors. The cytoplasmic PRR cGAS senses viral DNA in the cytoplasm (reviewed in [27]). During HIV-1 and HIV-2 infection, the viral complementary DNA (cDNA) within the virion is sensed by cGAS after infection [28]. However, the HIV-1 but not HIV-2 cDNA is protected within the viral capsid until it is transported into the nucleus for replication. The mechanism behind this protection is due to affinity of the HIV-1, but not HIV-2, capsid with the host protein cycophilin A (CypA) which stabilizes the viral capsid to prevent exposure of the viral cDNA to cGAS in the cytoplasm [28]. In addition to cGAS, viruses target IFI16, which senses DNA viruses that replicate in the nucleus. In particular, the herpes simplex virus-1 (HSV-1) immediate early protein ICP0 has E3 ubiquitin ligase activity that ubiquitinates IFI16, resulting in its degradation by the ubiquitin proteasome and loss of IFN induction [27,29].

Targeting of adaptor proteins and their kinases

In addition to using viral proteases to cleave PRRs, as described above, viruses also utilize their proteases to target the downstream signaling molecules in antiviral innate immune pathways. In particular, the NS3-4A protease of HCV blocks antiviral signaling by cleaving at least three innate immune signaling molecules. The HCV NS3-4A protease prevents activation of the transcription factor IRF3 and induction of IFN by cleaving the signaling adaptor protein MAVS [19–21,23]. The NS3-4A protease can also cleave TRIF, an adaptor protein for TLR3, a protein that senses viral dsRNA in the endosome [22]. Finally, as described above, NS3-4A also cleaves RIPLET [24]. As the HCV NS3-4A protease cleaves two molecules in the RIG-I signaling pathway (both RIPLET and MAVS), this suggests that either the virus is ensuring that the RIG-I pathway is inhibited or that RIPLET may have additional functions within innate immunity besides activating RIG-I.

Since MAVS activation coordinates IFN-induction by both RIG-I and MDA5, it is not surprising that viruses often target MAVS or proteins that regulate its function. In addition to HCV, the positive-sense RNA viruses, porcine reproductive and respiratory syndrome virus (PRRSV) and EV-D71, use the nsp4 cysteine protease [30] and $2A^{pro}$, respectively, to cleave MAVS during infection [31]. The DenV protease NS2B3 cleaves the mitofusins, MFN1 and MFN2, known to be positive (MFN1) or negative (MFN2) regulators of MAVS function [32–36]. Therefore, as their cleavage in DenV-infected cells results in increased virus replication, it suggests that cleavage of MFN1 (vs MFN2) is required to prevent the antiviral response in DenV-infected cells.

While MAVS is the adaptor for RNA virus sensing, STING is the adaptor for DNA virus sensing via the PRRs cGAS and IFI16 (reviewed in [5•]). Interestingly, Lau *et al.* determined that both the adenovirus E1A and human papilloma virus 18 (HPV18) E7 proteins bind to STING to prevent induction of type I IFN upon DNA transfection [37••]. Additionally, the Kaposi's sarcoma-associated herpes virus (KSHV) protein vIRF1 binds to STING and prevents its interactions with TBK1 and IRF3 to block IFN induction [38]. Importantly, this inhibition of IFN induction by KSHV was found to important for reactivation of KSHV from viral latency [38].

Intriguingly, several RNA viruses have mechanisms to block the function of STING, even though it is a known adaptor for DNA virus sensing (reviewed in [2]). The HCV NS4B protein, the DenV NS2B3 protease, and the yellow fever virus NS4B protein all block STING downstream signaling to IFN ([39] and reviewed in [40]). While the mechanism of how STING senses RNA viruses remains unclear, the fact that multiple RNA viruses have strategies to antagonize its function suggests that it must play a role in IFN induction during RNA virus infection (reviewed in [40]). *Flaviviridae* virus infection may damage mitochondria, leading to the releases of mitochondrial DNA that primes the innate immune response [41••]. Indeed, HCV infection induces mitophagy, and this results in decreased IFN induction suggesting that this induction of mitophagy is a viral mechanism to protect from mitochondrial DNA induction of type I IFN [42].

Viruses also target the kinases IKKε and TBK1, which transduce signals from MAVS or STING to activate antiviral transcription factors. IKKε is inhibited by the nucleoprotein of arenaviruses, including lymphocyte choriomeningitis virus and Lassa fever virus [43]. TBK1 is inhibited by both Vpr and Vif during HIV-1 infection of dendritic cells and macrophages to prevent its autophosphorylation and activation [44]. Further, both TBK1 and IKKε are inhibited by the ebola virus Vp35 protein to prevent their interactions with the transcription factors IRF3 and IRF7 [45]. Since these kinases can be activated by multiple PRR pathways, inhibition of the kinases broadly inhibits the antiviral innate immune response.

Targeting transcription factors

Viruses also directly inhibit transcription factors that act in the IFN induction and response pathways to prevent transcriptional activation of IFNs and interferon-stimulated genes (ISGs) during virus infection. To evade IFN induction, enterovirus 68 (EV-D68) $3C^{pro}$ cleaves IRF7 during infection [46]. The human poxvirus, molluscum contagiosum virus (MCV), a DNA virus, also evades IFN induction by using its MC132 protein to recruit the Elongin B/Elongin C/Cullin-5 ubiquitin ligase complex

to ubiquitinate and degrade the p65 subunit of NFκB to prevent its activation [47]. To antagonize the transcriptional induction of the IFN response pathway, several viruses directly act on the STAT proteins. Both STAT1 and STAT2 are phosphorylated following IFN signaling thereby promoting their interaction with IRF9 to form the ISGF3 complex that transcriptionally activates ISGs (Figure 3). In particular, the DenV NS5 protein targets STAT2 for degradation, resulting in the ubiquitination and degradation of STAT2 [48]. Additionally, the HCV core protein dysregulates STAT1 signaling by increasing the levels of non-phosphorylated STAT1 in the cell [49]. Antagonism of transcription factors by viruses efficiently blocks IFN signaling and ISG induction.

Evasion of ISGs

Not surprisingly, viruses have evolved ways to inhibit the antiviral actions of ISGs that are induced by the IFN response pathway. These ISGs have broad mechanisms to confer antiviral activity [50]. In this section, we will focus on how viruses evade the antiviral actions of the ISGs IFIT1 and PKR (Figure 4). The IFIT proteins bind to uncapped RNA to prevent their translation. While many viruses have uncapped RNA and use internal ribosome entry sites for their translation (e.g. HCV), some viruses have evolved ways to cap their RNA to evade IFIT1 recognition. For example, Lassa fever virus and influenza virus snatch caps from host mRNAs. Additionally, many viruses encode proteins that can perform these capping functions (reviewed in [51]). In particular, the WNV NS5 protein contains 2′-Omethyltransferase (2′O-MT) activity to generate a cap 1 structure. This particular cap structure is not sensed by IFIT1 during infection therefore this allows the virus to evade restriction by IFIT1 [52]. Coronaviruses, positive-sense ssRNA viruses, also encode a 2′O-MT protein, nsp16 [53]. Similar to the MT activity of WNV NS5A, the MT activity of nsp16 is required for evasion of IFIT sensing during both murine hepatitis virus and severe acute respiratory syndrome coronavirus infection [52,54]. Vaccinia virus, a DNA virus that replicates exclusively in the cytoplasm, also has a 2′O-MT and disruption of its activity results in increased susceptibility of vaccinia virus to IFIT protein restriction [52]. Taken together, many viruses evade the actions of IFIT1, demonstrating that IFIT1 has the capacity for potent restriction of viral replication.

The antiviral effector ISG PKR is one of the most common proteins targeted and inactivated by viruses (reviewed in [55]). Activation of this ISG by dsRNA results in PKR autophosphorylation, dimerization, and phosphorylation of eIF2α leading to decreased protein synthesis due to translational inhibition. This inhibition of translation affects both host and viral mRNAs, which ultimately decreases viral replication. A recent example of inhibition of PKR function was described during infection with human cytomegalovirus virus (HCMV), a DNA virus of the herpesvirus family [56]. This virus encodes two proteins, pTRS1 and pIRS1, that antagonize PKR to prevent its autophosphorylation and subsequent phosphorylation of eIF2α. Importantly, deletion of the viral pTRS1 and pIRS1 proteins leads to decreased expression of viral early and late proteins, resulting in decreased viral replication [56]. This suggests that these proteins are critical for HCMV to prevent the antiviral activity of PKR for its replication.

Conclusions

Evasion of the host antiviral innate immune response is critical for virus replication and spread. Viruses have several strategies to evade IFN induction and signaling to avoid the antiviral mechanisms of the host innate immune system. In fact, some viruses utilize multiple strategies to evade antiviral innate immune signaling, as is seen with HCV. This virus evades RIG-I detection of its replicating RNA in the membranous web by co-opting the NPC to regulate protein trafficking to the these sites of replication [9••]. It also cleaves MAVS, TRIF, and RIPLET to prevent downstream signaling to IRF3 and NFκB [19–24]. Further, it induces mitophagy to limit IFN induction and it also inhibits the transcription factor STAT1 to prevent ISG induction [42,49]. Taken together, there is a strong need for viruses to evade IFN induction and signaling to prevent activation of host innate immune system to allow for viral replication.

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