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# Ten Strategies of Interferon Evasion by Viruses

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Viruses infecting vertebrate hosts must overcome the interferon (IFN)-mediated antiviral response to replicate and propagate to new hosts. The complex regulation of the IFN response allows viruses to antagonize IFN at multiple levels. However, no single strategy appears to be the golden ticket, and viruses have adopted multiple means to dampen this host defense. This Review does not exhaustively cover all mechanisms of viral IFN antagonism. Rather it examines the ten most common strategies that viruses use to subvert the IFN response with examples from publications appearing in the last 10 years of *Cell Host & Microbe*. The virus-host interactions involved in induction and evasion of IFN represent a fertile area of research due to the significant large number of host and viral products that regulate this response, resulting in an intricate dance between hosts and their pathogens to achieve an optimal balance between virus replication, host disease, and survival.

## Introduction

Since their discovery, interferons (IFNs) have been shown to be the most important innate antiviral cytokines of vertebrates. Almost every cell in the body responds to IFN exposure by the rapid induction of a complex transcriptional program involving more than 300 IFN-stimulated genes (ISGs) that makes the cell refractory to virus replication. Most cells have also the ability to respond to viral infection by secreting IFNs, warning the neighboring cells and inhibiting viral spread. Nevertheless, specific cell types, such as plasmacytoid dendritic cells (pDCs) and proinflammatory monocytes, have been specialized to produce more IFN than other cell types upon viral exposure. IFNs can be classified in three types according to their receptor utilization. Type I IFNs include mainly the  $\alpha$  IFNs and IFN $\beta$ , and they signal through the type I IFN receptor (IFNAR). Type II IFN, or IFN $\gamma$ , is mainly produced by immune cells, signals through the IFN $\gamma$  receptor, and, even though it has direct antiviral activity, its main role is shaping the adaptive immune response. Type III IFNs, or IFN $\lambda$ s, have similar activities as type I IFNs, but its receptor is not ubiquitously expressed. Type III IFN receptor expression is restricted to specific cell types, such as epithelial cells. For simplicity, we will use the term IFN in this Review to refer to IFN $\alpha/\beta$ .

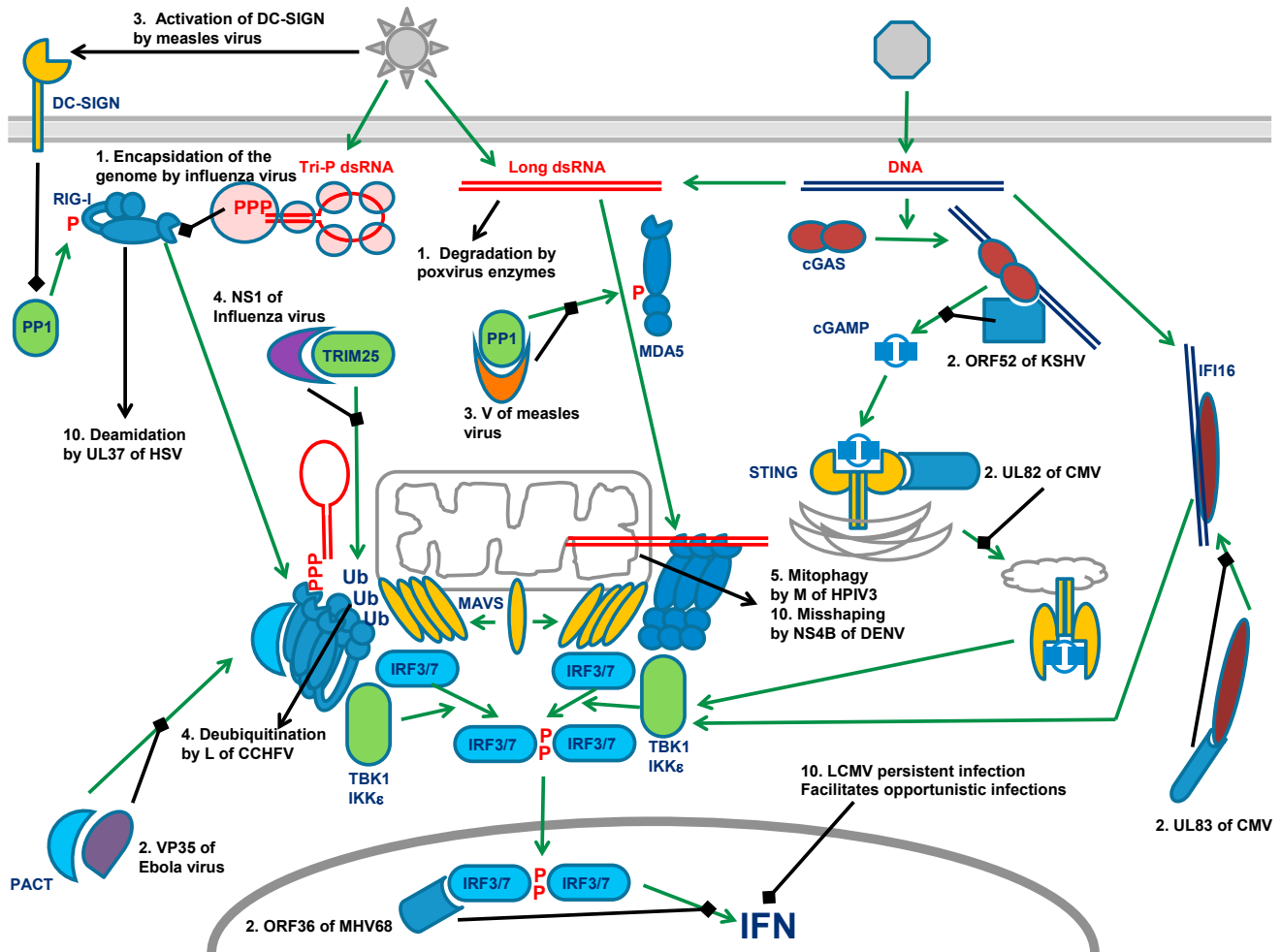
IFN is responsible for eliminating many viruses that otherwise will be pathogenic. For instance, it has been demonstrated that in the absence of STAT1, a critical transcription factor required for the transcriptional activation of IFN-stimulated antiviral genes, both mice and humans become highly susceptible to virus infections (Dupuis et al., 2003; Durbin et al., 1996). However, each vertebrate species is still infected by multiple viruses despite having an intact IFN response. Host survival in the face of virus infection depends on a robust IFN system, but virus survival depends on its ability to replicate and propagate in the host, which in turn requires viral mechanisms of evasion or subversion of the host IFN response. During co-evolution of viruses and hosts, this tension has shaped an intricate and complex web of

interactions between host factors that regulate the IFN response and viral factors that inhibit this response. These interactions have been the result of what has been many times referred by analogy as an “arms race” between viruses and hosts in which a balance needs to be reached, since a complete inhibition of the host antiviral defenses by the virus would result in host elimination and, by default, in virus elimination too.

An unchecked IFN response leads to pathological consequences, such as autoimmune disorders and immunopathology. By contrast, a weak and inefficient IFN response makes the host more susceptible to severe disease by viruses. Hosts evolved more and more complex regulatory mechanisms to achieve a balanced IFN response. On top of that, viruses evolved multiple ways to dampen the host IFN response by interfering or evading specific host regulators of this response. The ways viruses counteract the host IFN system are diverse and represent critical determinants of virulence. This complicated dance between viruses and hosts for the regulation of the IFN response has been a very rich area of research, with implications in vaccine and antiviral development. It is not surprising that many research articles in *Cell Host & Microbe* since its inception have helped expand our knowledge on how viruses evade the IFN system. To commemorate the tenth anniversary of the journal, I will discuss ten different strategies that viruses have evolved to overcome the host IFN response, with examples of original research articles published in *Cell Host & Microbe*. Importantly, such examples should not be taken as the only mechanism by which a virus or a viral product antagonizes the IFN system, as very often viral IFN antagonists are multifunctional and inhibit the IFN-mediated antiviral response at multiple steps.

## Strategy 1. Hiding the Viral Genome

Induction of the IFN system starts by cellular detection of viral infection. Since virus components are made of cellular components, discrimination of viral from cellular factors represents a challenging task. Hosts have solved this challenge using



**Figure 1. Examples of Viral Strategies of Evasion of Induction of IFN**

IFN-inducing pathways are shown with green arrows. Virus antagonistic pathways are represented by black lines and arrows. Numbers indicate the specific strategy described in the text.

sophisticated viral sensors that take into account both specific structural features of viral genomes as well as their location within the cell. A set of Toll-like receptor (TLR) sensors, TLR3, TLR7, TLR8, and TLR9, scan the extracellular and endosomal space for the detection of RNA and DNA, detecting viral genomes from lysed virus particles outside the cell, and initiating a signaling cascade leading to the secretion of IFN and other pro-inflammatory molecules (Kawai and Akira, 2006). TLRs however only partially explain viral detection, as many cell types do not express TLRs and still respond to virus infection by IFN production. While multiple intracellular sensors of viral products and virus-induced biological processes have been described, two types of sensors have emerged as the main mechanisms that detect intracellular virus infection: the RIG-I-like receptors (RIG-I, MDA5, and LGP2) and cGAS, all of which detect viral genomes in the cytoplasm (Figure 1). RIG-I recognizes tri-phosphate and di-phosphate at the end of a dsRNA stem, a hallmark of the viral RNAs of the majority of the RNA viruses (Pichlmair et al., 2006). MDA5 senses long dsRNAs, which are believed to represent replicative intermediates for many RNA viruses (Kato

et al., 2006). LGP2 is a protein structurally related to both RIG-I and MDA5 that appears to be a cofactor in viral RNA sensing through a still not completely clear mechanism that most likely involves making the viral RNA more accessible to RIG-I or MDA5 (Venkataraman et al., 2007). For DNA viruses, the presence of cytoplasmic DNA associated with their infection is the trigger for IFN induction. Specifically, the cellular sensor cGAS binds to cytoplasmic DNA, becomes activated, and generates a dinucleotide, cGAMP, which stimulates the IFN inducing cascade (Li et al., 2013b).

As viral RNA and DNA genomes need to be present at some time point in the cytoplasm, they become susceptible to these cytoplasmic RNA and DNA sensors. However, viruses have developed strategies to avoid cytoplasmic detection of their viral nucleic acids. Viruses that replicate in the cytoplasm do so in association with compartmentalized structures that are induced upon viral infection and separated from the rest of the cytoplasm. For instance, positive-strand RNA viruses generate membranous webs where their genomes replicate and produce mRNA (Miller and Krijnse-Locker, 2008). The cytoplasmic DNA vaccinia virus

and many negative-strand RNA viruses generate proteinaceous cytoplasmic viral factories that likely exclude the cellular nucleic acid sensors. Two negative-strand RNA viruses, influenza and Borna viruses, the retroviruses, and most of the DNA viruses replicate in the nucleus away from the cytoplasmic DNA and RNA sensors. Nevertheless, complete avoidance of the cytoplasm by viral nucleic acids is unlikely and additional mechanisms to avoid detection have been developed by many viruses.

In a 2015 *Cell Host & Microbe* publication, [Weber et al. \(2015\)](#) demonstrated that even though RIG-I has the ability to recognize the 5'-triphosphate (5'-triP) of the influenza virus RNA genome as it traffics to the nucleus at the initiation of infection, encapsidation of the viral RNA by the viral nucleoprotein and polymerase prevents RIG-I binding and its subsequent activation ([Figure 1](#)). Mutations in the viral polymerase associated with nucleocapsid instability make the viral RNA accessible for RIG-I recognition ([Weber et al., 2015](#)). Genome encapsidation might also allow many other negative strand RNA viruses to avoid RIG-I recognition. In addition, specific RNA viruses have adopted strategies to modify the 5'-triP of their viral RNAs, by cleavage ([Habjan et al., 2008](#)), by covalently attaching a viral protein ([Goodfellow, 2011](#)), or by capping and methylating their 5' ends, mimicking cellular mRNAs ([Daffis et al., 2010](#)). Moreover, many viruses encode dsRNA-binding proteins (such as influenza virus NS1, vaccinia virus E3L, Ebola virus VP35, reovirus  $\sigma 3$ , bunyavirus NSs, or herpesvirus US11), which have been postulated to sequester the viral dsRNA from cellular dsRNA sensors ([Versteeg and Garcia-Sastre, 2010](#)). Consistent with this hypothesis, the introduction of mutations in viral dsRNA-binding proteins results in virus mutants that induce more IFN and/or are more sensitive to the action of IFN. DNA viruses also activate RNA sensors by promoting bidirectional transcription that results in generation of cytoplasmic dsRNA. In a 2015 *Cell Host & Microbe* publication, [Liu et al. \(2015\)](#) showed that poxviruses prevent the accumulation of viral dsRNA by using their decapping enzymes to facilitate enzymatic degradation of dsRNA ([Figure 1](#)).

### Strategy 2. Inhibiting Interactions with Key Host Inducers of the IFN Response

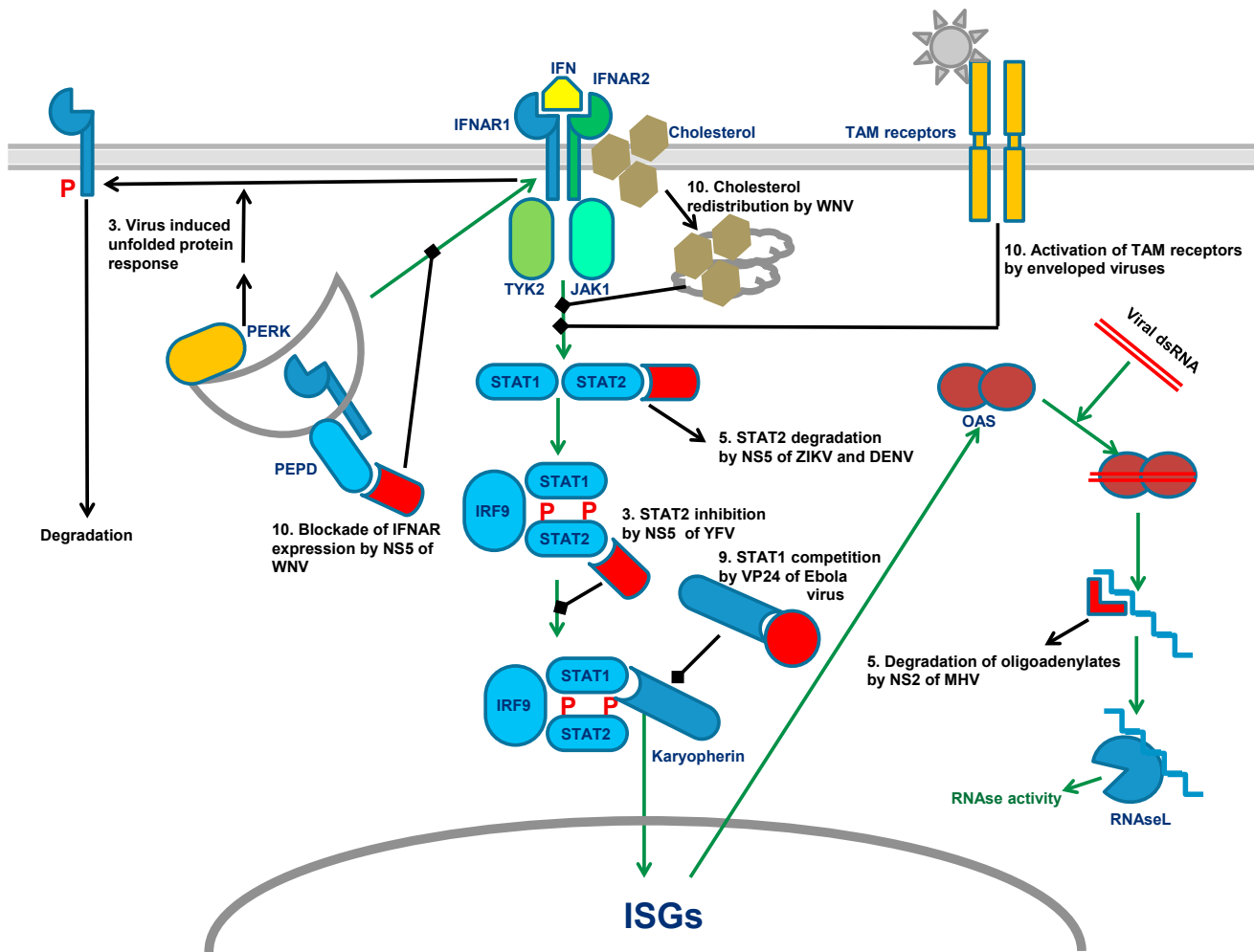
Upon activation, the cellular sensors of viral infection initiate a signaling cascade resulting in transcriptional induction of IFN. These signaling events involve many cellular adaptor molecules, regulatory enzymes, and transcription factors, notably the IFN regulatory factors (IRFs), many of which are targets for direct inhibition by viral products that bind to them and prevent their function ([Figure 1](#)). Similarly, interaction of secreted IFN with its receptor triggers phosphorylation and activation of STAT transcription factors that promote the expression of IFN-stimulated genes (ISGs) and the establishment of the antiviral state ([Figure 2](#)). Viruses have developed strategies that avoid the action of IFN by preventing the binding of viral products to cellular sensors and by inactivating downstream cellular factors involved in IFN signal transduction or in the establishment of the antiviral state. The proliferation of viral strategies that target specific cellular factors downstream of cytoplasmic viral sensors illustrates the need for viruses to inhibit the IFN response in addition to avoidance of detection. In some instances, interaction of a viral product with a host protein involved in the IFN response results in changes in phosphorylation or ubiquitinylation, cleavage,

or degradation, but these specific inhibitory activities will be covered in the next strategies.

The relatively large coding capabilities of many DNA viruses, such as herpesviruses, as compared with RNA viruses, has resulted in a plethora of viral proteins encoded by this group of viruses that short-circuit signaling pathways by interacting with cellular proteins at various stages of the IFN response. For example, direct inhibition of the DNA sensor cGAS by a herpesvirus has been described in the *Cell Host & Microbe* 2015 publication by [Wu et al. \(2015\)](#): the ORF52 protein of Kaposi's sarcoma-associated herpesvirus (KSHV) directly inhibits cGAS enzymatic activity and thus prevents generation of the signaling molecule cGAMP by binding to both cGAS and DNA ([Figure 1](#)). Similarly, inhibition by herpesviruses of the ER-located cellular factor STING, which is directly downstream cGAS and binds to cGAMP to become an active signaling platform for IFN induction ([Chen et al., 2016](#)), has also been described in another *Cell Host & Microbe* publication by [Fu et al. \(2017\)](#). In this instance, the human cytomegalovirus (HCMV) UL82 tegument protein binds to STING and prevents its translocation from the ER to the perinuclear membrane. UL82 also prevents STING from interacting with TBK1 and IRF3, which are necessary for cGAMP signaling ([Figure 1](#)). Direct binding of another HCMV protein, pUL83, to another DNA sensor molecule, IFI16, has also been described in a 2013 *Cell Host & Microbe* publication by [Li et al. \(2013a\)](#). Collectively, these findings underscore the presence of multiple nucleic acid-sensing pathways that viruses need to overcome ([Figure 1](#)). Among RNA viruses, there are also many different viral proteins that bind to and inhibit members of the RIG-I-like receptors, such as the arenavirus Z protein ([Fan et al., 2010](#)) and the paramyxovirus V proteins ([Andrejeva et al., 2004](#)), or to the downstream adaptor mitochondrial protein MAVS, such as the influenza virus PB1-F2 protein ([Varga et al., 2012](#)). An interesting mechanism of viral inhibition of RIG-I is that described by [Luthra et al. \(2013\)](#) in a 2013 *Cell Host & Microbe* publication in which the Ebola virus VP35 protein binds to the cellular protein PACT, a cellular dsRNA binding protein required for activation of RIG-I ([Figure 1](#)).

Once activated, both STING (DNA-sensing) and MAVS (RNA-sensing) signaling platforms recruit multiple kinases, ubiquitin ligases, and adaptors leading to the phosphorylation and activation of latent transcription factors involved in IFN promoter activation ([Figure 1](#)). Among these transcription factors, the IRF factors, especially IRF3 and IRF7, are critical for IFN induction ([Honda et al., 2005](#); [Sato et al., 1998](#)). In addition, IRF7 is also required for IFN induction upon TLR activation. It is then not surprising that the IRFs are attractive host factors for inhibition by viral-encoded IFN antagonists. As an example, [Hwang et al. \(2009\)](#) described in a 2009 *Cell Host & Microbe* publication that the ORF36 protein of murine gamma-herpesvirus binds to activated IRF3 in the nucleus and prevents its interaction with transcriptional co-factors to induce IFN mRNA synthesis ([Figure 1](#)). Interestingly, a mutant virus lacking this IRF3 inhibitory factor not only induces more IFN upon infection, but also exhibits compromised persistent infection, indicating a direct relationship between inhibition of the IFN response by herpesviruses and their ability to persist ([Hwang et al., 2009](#)).

STAT1 and STAT2 are the essential transcription factors, together with IRF9, that mediate IFN signaling and IFN-induced



**Figure 2. Examples of Viral Strategies of Inhibition of IFN Signaling**

IFN signaling pathway is shown with green arrows. Virus antagonistic pathways are represented by black lines and arrows. Numbers indicate the specific strategy described in the text.

expression of ISGs (Figure 2). Their crucial function in executing the action of IFN is again manifested by being among the preferred targets for viral IFN antagonism. An example of STAT2 targeting by a viral IFN antagonist is provided by the 2014 *Cell Host & Microbe* publication by Laurent-Rolle et al. (2014). This paper describes how the NS5 protein of yellow fever virus binds to STAT2 upon exposure to IFN, preventing binding of this transcription factor to the IFN-responsive promoter elements of the ISGs, and inhibiting the antiviral action of IFN (Figure 2). The binding-dependent inhibition of STAT1 and STAT2 have also been demonstrated for other viral proteins encoded by a diverse range of viruses, such as the V and W proteins of paramyxoviruses (Rodríguez et al., 2002; Shaw et al., 2004), the P protein of rabies virus (Vidy et al., 2005), or the C6 protein of vaccinia virus (Stuart et al., 2016), among others.

### Strategy 3. Regulating Phosphorylation Events

Activation of the IRFs and STATs transcription factors is triggered by specific kinases, including TBK1 and IKKε for IRF3 and IRF7 (Figure 1), and JAK1 and TYK2 for STAT1 and STAT2

(Figure 2), that become activated upon initiation of signaling. These kinases have also become attractive host factors for viral antagonism of IFN, exemplified by TBK1 inhibition by the NS4B protein of flaviviruses (Dalrymple et al., 2015), IKKε inhibition by the N protein of arenaviruses (Pythoud et al., 2012), JAK1 inhibition by VP40 of Ebola virus (Valmas et al., 2010), and TYK2 inhibition by LMP1 of Epstein-Barr virus (Geiger and Martin, 2006). However, regulation of the IFN response by phosphorylation is not only restricted to the transcription factors, as many other host factors involved in IFN induction are also regulated by phosphorylation. For instance, it is known that both RIG-I and MDA5 sensors remain in an inactivated state due to phosphorylation, and they require the action of the phosphatase PP1 to remove the inhibitory phosphorylation mark and become activated. Interestingly, the 2015 *Cell Host & Microbe* publications by Davis et al. (2014) and by Mesman et al. (2014) show how measles virus uses two different strategies to inhibit PP1 and maintain RIG-I and MDA5 in a phosphorylated inactive state (Figure 1). First, measles virus activation of the C-type lectin DC-SIGN in dendritic cells promotes PP1 association with the PP1 inhibitor I-1

(Mesman et al., 2014). Second, the V protein of measles virus binds to PP1 and prevents PP1-mediated dephosphorylation of MDA5 (Davis et al., 2014).

IFN signaling is also subjected to phosphorylation-mediated regulation at different steps other than JAK1/TYK2 kinase activation and STAT phosphorylation. For example, the IFNAR1 chain of the IFN receptor can be targeted for degradation by phosphorylation on specific serine residues (Kumar et al., 2004). Virus infection can induce this IFNAR1 inactivation pathway by activating the PERK stress kinase and promoting IFNAR1 phosphorylation, preventing IFN signaling (Figure 2), as illustrated in a 2009 *Cell Host & Microbe* publication by Liu et al. (2009). Another host kinase that is often targeted by viruses for inactivation is PKR, a host kinase that in addition to being transcriptionally induced by IFN, requires dsRNA to be activated. Activated PKR contributes to the antiviral action of IFN by phosphorylating the translation initiation factor eIF2 $\alpha$  and inducing translational shut-off. Although specific viruses could use PKR activation for their own advantage (see Strategy 8), the majority encodes inhibitors of PKR, from dsRNA-sequestering proteins to inhibitors of the kinase activity of PKR, PKR substrate decoys (see Strategy 9), or activator of phosphatases that dephosphorylate eIF2 $\alpha$  (Langland et al., 2006).

#### Strategy 4. Regulating Ubiquitylation and Related Pathways

In addition to phosphorylation, ubiquitin modification by attachment of ubiquitin chains or ubiquitin-like molecules to proteins has emerged not only as a mechanism to target proteins for degradation, but also to regulate signaling pathways by mediating the activation and/or the recruitment of proteins. In fact, the sensing pathways for IFN induction are heavily controlled by the activity of multiple ubiquitin ligases and deubiquitinating enzymes that are recruited to the STING or MAVS signaling platforms and are either essential for activation or promote their inactivation. Even RIG-I activation is heavily regulated by ubiquitylation. In fact, K63 polyubiquitin generated by the E3 ligase TRIM25 is needed for RIG-I oligomerization upon RIG-I binding to viral RNA and for subsequent interaction with and activation of MAVS (Gack et al., 2007). RIG-I association with polyubiquitin can be targeted by viral IFN antagonists that prevent RIG-I activation, as illustrated by the 2009 *Cell Host & Microbe* publication by Gack et al. (2009). In this report, the authors identified the mechanism of RIG-I inhibition by the NS1 protein of influenza virus. NS1 binds to TRIM25 and prevents its E3 ligase activity and thus the activation of RIG-I by TRIM25 synthesized K63 polyubiquitin chains (Figure 1). Inhibition or activation of other E3 ligases that act at other steps of the IFN signaling pathways has also been demonstrated for other viruses (see Strategy 5).

A more general means by which viruses interfere with ubiquitin-regulated pathways involves viral proteases that cleave poly-ubiquitin chains, i.e., deubiquitinating enzymes or DUBAs. This was also illustrated by a *Cell Host & Microbe* publication in 2007 by Frias-Staheli et al. (2007). In this published study, a protease motif at the N-terminal domain of the L protein of the tick-borne bunyavirus Crimean-Congo hemorrhagic fever virus is characterized as having deubiquitinating activity (Figure 1). Expression of this domain in virus-infected cells deregulates ubiquitin-dependent pathways and inhibits IFN induction. Inter-

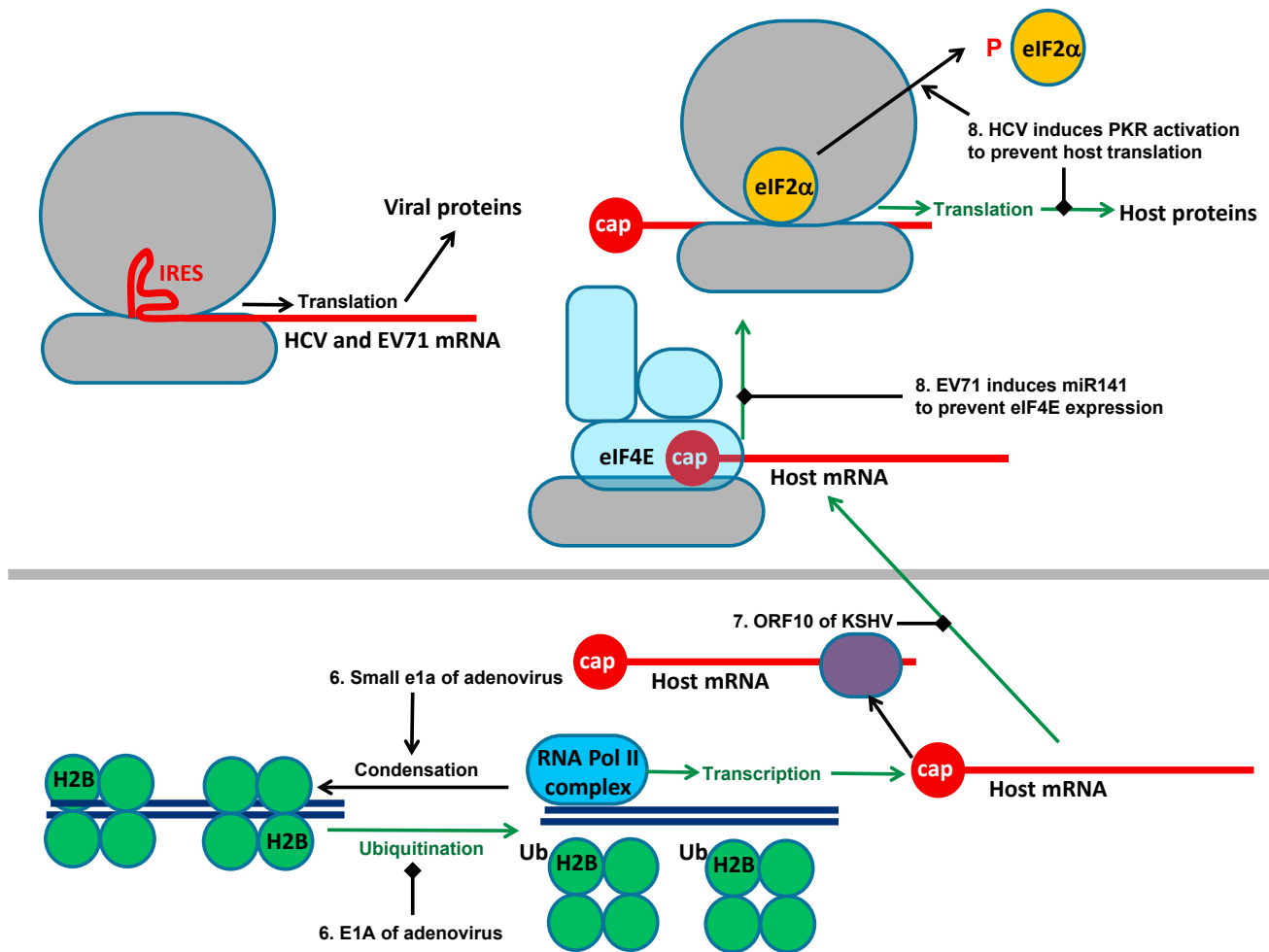
estingly, this viral DUBA domain not only cleaves ubiquitin chains, but also removes the ubiquitin-like molecule ISG15 from their target proteins. ISG15 is an ISG whose structure resembles a dimer of ubiquitin and, as ubiquitin, becomes covalently bound to target proteins by an enzymatic process analogous to that of ubiquitylation. ISGylation is part of the IFN-induced antiviral response, as it results in viral inhibition through still not well-known mechanisms. Viral DUBAs with dual specificity for both ubiquitin and ISG15 have then the ability to inhibit the IFN response at two different levels.

#### Strategy 5. Cleavage and Degradation

Many viral proteases that participate in cleavage and processing of viral polyproteins, typical of positive-strand RNA viruses, have also been shown to trigger the cleavage of factors essential for the IFN response. For example, the hepatitis C virus protease cleaves MAVS (Li et al., 2005; Meylan et al., 2005), while the dengue virus protease cleaves STING (Aguirre et al., 2012; Yu et al., 2012). By contrast, other viruses achieve the same effects without specifically targeting one single factor. The recent 2017 *Cell Host & Microbe* publication by Ding et al. (2017) shows how a single virus protein, in this case the M protein of human parainfluenza virus type 3, induces mitophagy and targets the whole mitochondria to the autophagosome, effectively blocking the generation of the mitochondrial-based MAVS signaling platform (Figure 1).

Degradation of essential factors for the IFN response can also be achieved by viruses through subversion of ubiquitin pathways that mark a protein for proteosomal degradation by attachment of K48 polyubiquitin chains. In this respect, the STATs appear to be once more attractive targets for viral proteins to direct to proteosomal degradation. For example, in the 2016 *Cell Host & Microbe* publication by Grant et al. (2016), it is shown that the NS5 of Zika virus targets human STAT2 for proteosomal degradation in infected cells (Figure 2). However, mouse STAT2 is spared from degradation, and this might explain the poor replication of Zika virus in mice unless the IFN system is inhibited or eliminated. Interestingly, this is reminiscent of a similar host specificity for dengue virus NS5 to degrade human, but not mouse, STAT2 that was published in an earlier *Cell Host & Microbe* publication (Ashour et al., 2010). Although Zika and dengue viruses are evolutionarily related and both target STAT2 to degradation through their NS5 proteins, the mechanisms through which they achieve this degradation are different (Grant et al., 2016), which underscores the amazing versatility that viruses have to deal with the IFN response. Lentiviruses encode viral proteins, e.g., HIV-1 VPU and VIF and HIV-2 VPX, that are known to mediate degradation of host antiretroviral effector factors induced by IFN, such as tetherin, APOBEC3G, and SAMHD1 (Kirchhoff, 2010).

Viruses may also target host factors different from proteins to prevent antiviral responses. One of the IFN-induced effector antiviral pathways is the OAS-RNaseL system. OASs are IFN-induced enzymes that become activated by viral dsRNA and then synthesize 2',5'-oligoadenylates, which in turn activate a latent RNase, RNaseL, resulting in cellular and viral RNA degradation and inhibition of viral replication. The 2012 *Cell Host & Microbe* publication by Zhao et al. (2012) show us how a coronavirus, mouse hepatitis virus (MHV), employs a viral enzyme with



**Figure 3. Examples of Viral Strategies of Inhibition of Host Gene Expression**

Host gene expression is shown with green arrows. Virus antagonistic pathways and virus protein expression are represented by black lines and arrows. Numbers indicate the specific strategy described in the text.

2',5'-phosphodiesterase activity to degrade the products of OAS and effectively shut down the RNaseL antiviral pathway (Figure 2).

### Strategy 6. Transcriptional Shut-Off

Viral interference with host transcription is a very common mechanism for viruses to prevent host responses to viral infection, including the IFN antiviral system, which depends on transcriptional induction of IFN and ISGs. Two *Cell Host & Microbe* publications (Ferrari et al., 2014; Fonseca et al., 2012) illustrate some of the ways viruses can inhibit transcriptional induction of antiviral genes (Figure 3). Fonseca et al. (2012) demonstrated that the adenovirus E1A protein binds to and dissociates a host nuclear complex that is needed for histone monoubiquitination at H2B lysine 120. In the absence of this epigenetic regulation that is responsible for opening the chromatin to allow transcription, IFN is unable to activate transcription of the ISGs. Interestingly, Ferrari et al. (2014) found that the adenovirus small e1a protein makes a complex with the host lysine acetylase p300 and tumor suppressor RB1 that condenses chromatin and represses antiviral gene expression. Obstruction of chromatin

activation has also been shown to take place during influenza H3N2 virus infection by virtue of the viral NS1 protein, whose C terminus mimics a histone tail and interferes with histone function (Marazzi et al., 2012).

### Strategy 7. RNA Processing and Trafficking Regulation

In addition to transcriptional interference, viruses can prevent host gene expression by postranscriptional inhibition of cellular RNA processing and trafficking. In general, this inhibition is believed to be unspecific, as exemplified by the NS1 protein of influenza virus, which prevents proper termination and polyadenylation of cellular mRNA (Nemeroff et al., 1998) and by the M protein of VSV, which inhibits RNA export from the nucleus by targeting nuclear pore components (von Kobbe et al., 2000). However, sometimes viral inhibition of host mRNA processing and export can be selective. As an example, a 2016 *Cell Host & Microbe* publication by Gong et al. (2016) depicts how the ORF10 of Kaposi's sarcoma-associated herpesvirus inhibits the mRNA export of a subset of host mRNA transcripts based on their 3' UTRs (Figure 3). Interestingly, the subset of host transcripts that are specifically retained in the nucleus by ORF10

does not belong to the traditional category of host genes involved in the IFN signature but correspond to genes enriched for biological processes such as mitosis, gene silencing, DNA metabolic process, chromosome organization, cell cycle, and transcription regulation. This may represent a subset of host genes whose expression might be detrimental for herpesvirus replication.

### Strategy 8. Translational Shut-Off

Many viruses prevent host gene expression by inducing translational shut-off. However, this approach of preventing the synthesis of antiviral genes requires a balancing act, as viruses use the same cellular translational machinery as host mRNAs to produce viral proteins from viral mRNAs. An interesting translational shut-off strategy is the one that hepatitis C virus has adopted, described in a 2009 *Cell Host & Microbe* publication by [Garai-gorta and Chisari \(2009\)](#). This virus takes advantage of a specific ISG, PKR, whose activation results in general translational inhibition and, therefore, in inhibition of viral replication. But hepatitis C virus promotes and takes advantage of PKR activation during viral infection to inhibit the translation of antiviral effector proteins induced by IFN. While most cellular translation is inhibited in hepatitis C virus-infected cells by PKR-mediated phosphorylation of the eukaryotic translation initiation factor eIF2 $\alpha$ , hepatitis C virus mRNA translation is not inhibited as it depends on a 5' internal ribosomal entry site (IRES) that is insensitive to PKR-mediated translational inhibition ([Figure 3](#)).

Picornaviruses also use viral IRES for viral mRNA translation, and as IRES-dependent translation is cap independent, these viruses target host factors required for cap-dependent translation to shut off host protein expression. This is well depicted in the 2011 *Cell Host & Microbe* publication by [Ho et al. \(2011\)](#). Using enterovirus EV71, these authors show that viral infection induces expression of microRNA-141, which in turn targets the expression of the host protein eIF4E, a critical component in the cap-dependent translation machinery ([Figure 3](#)). By reducing eIF4E levels, cap-dependent translation is reduced without an impact in cap-independent, IRES-mediated translation. Thus, translation of IFN effector proteins from ISG mRNAs is inhibited. Picornaviruses are also well known to inhibit cap-dependent translation by cleaving cell factors involved in cap-dependent translation, such as eIF4G ([Etchison et al., 1982](#)).

### Strategy 9. Decoys

Several viruses have also been demonstrated to encode decoy proteins that sequester a host protein from its targets, preventing their function. Classical virus decoys involved in inhibition of the IFN response are the poxvirus-encoded soluble IFN receptors, such as the B18R protein of vaccinia virus, that sequester IFN prior to its binding to the IFN receptor ([Symons et al., 1995](#)), and the also poxvirus-encoded K3L protein, that act as a decoy for PKR substrates ([Beattie et al., 1991](#)). An interesting viral decoy strategy to inhibit IFN signaling is described in the 2014 *Cell Host & Microbe* publication of [Xu et al. \(2014\)](#). Ebola virus VP24 protein competes with STAT1 for binding to the nuclear import factor karyopherin  $\alpha$ 5, efficiently inhibiting the nuclear translocation of STAT1 and preventing transcriptional induction of ISGs ([Figure 2](#)).

### Strategy 10. Everything Counts

Viruses are not just limited to nine strategies to antagonize IFN responses. The following *Cell Host & Microbe* publications illustrate several other strategies that do not necessarily belong to the previously discussed categories, but they nevertheless also achieve their desired effect, namely evasion from the host IFN response. [Zhao et al. \(2016\)](#) describe a herpes simplex virus deamidase, UL37, that deamidates two asparagine residues in RIG-I, inactivating this sensor ([Figure 1](#)). [Chatel-Chaix et al. \(2016\)](#) found that the NS4B protein of dengue virus induces morphological changes in the mitochondria that prevent their ability to serve as signaling platforms for the MAVS complexes ([Figure 1](#)). [Lubick et al. \(2015\)](#) describe how the NS5 of West Nile and tick-borne encephalitis viruses binds to and inhibits a cellular dipeptidase, PEPD, that is required for proper surface expression of the IFNAR1 component of the IFN receptor ([Figure 2](#)). West Nile virus infection has also been shown by [Mackenzie et al. \(2007\)](#) to redistribute cholesterol from the plasma membrane to the viral replication membranes, and this results in inhibition of JAK/STAT activation by IFN signaling ([Figure 2](#)). [Bhattacharyya et al. \(2013\)](#) have shown how enveloped viruses can take advantage of incorporating phosphatidylserine on their membranes, through which they engage and activate TAM receptors in dendritic cells, which are negative regulators of IFN signaling ([Figure 2](#)). Interestingly, opportunistic viruses can piggy bag on the capacity of other viruses to inhibit IFN, as demonstrated by [Zuniga et al. \(2008\)](#), who found that persistent LCMV infection renders mice more susceptible to murine cytomegalovirus infection by LCMV-mediated inhibition of IFN induction by pDCs ([Figure 1](#)).

### Concluding Remarks

In this Review, we have summarized many ways that viruses evade and inhibit the host IFN response to establish successful replication cycles on their hosts, using as examples *Cell Host & Microbe* publications. It is remarkable the number of multiple strategies that viruses have adopted to antagonize the IFN system, and it is likely that we still have many undiscovered mechanisms of IFN antagonism. The use of multiple mechanisms by single viruses to dampen the IFN response likely reflects their need to inhibit at multiple points this antiviral host response to efficiently spread to new hosts. As we expand our knowledge on the virus-host interactions responsible for induction and inhibition of IFN responses, we might find rational ways to tip this response for a better advantage for the host, which could lead to the design of novel antivirals and vaccines.

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