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REVIEW

# Viral pathogen-induced mechanisms to antagonize mammalian interferon (IFN) signaling pathway

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## Abstract

Antiviral responses of interferons (IFNs) are crucial in the host immune response, playing a relevant role in controlling viralw infections. Three types of IFNs, type I (IFN-α, IFN-β), II (IFN-γ) and III (IFN-λ), are classified according to their receptor usage, mode of induction, biological activity and amino acid sequence. Here, we provide a comprehensive review of type I IFN responses and different mechanisms that viruses employ to circumvent this response. In the first part, we will give an overview of the different induction and signaling cascades induced in the cell by IFN-I after virus encounter. Next, highlights of some of the mechanisms used by viruses to counteract the IFN induction will be described. And finally, we will address different mechanism used by viruses to interference with the IFN signaling cascade and the blockade of IFN induced antiviral activities.

**Keywords** IFN-I pathway · Antiviral responses · Viral evasion mechanisms

## Introduction

Innate immune responses are the first host defense against viral infections. Conserved pathogen structures are recognized by pattern recognition receptors (PRRs) on the host cells [1], that recruit a variety of adaptor proteins to signal downstream and activate the IFN response. The IFN system is present in all vertebrates and is central to antiviral responses [2]. IFNs are classified into three different families according to their receptor usage, mode of induction, biological activity and amino acid sequence [3]: type I, type II and type III IFNs. Type I IFNs, originally identified by their antiviral activity [4], include multiple IFN-α subtypes (13 in humans and 14 in mice), and a single IFN-β, and IFN-ε, IFN-κ, IFN-ω (humans) and IFN-ξ (mice) subtypes [5]. In mammals, type I IFN (IFN-I) response is essential for innate antiviral responses. They all bind to the same ubiquitously expressed receptor, IFNAR receptor, but they differ in their biological functions, due partially to the different binding affinities to the IFNAR receptor [6]. This differences in affinity results in different downstream signaling cascades [7]. For IFN-α subtypes, the quantity of the receptor on the surface of a target cell correlates also with their biological activities suggesting that the amount of IFNAR expression might compensate the weak affinity of some IFN-α subtypes [6, 8].

Type II IFNs include only one member, IFN-γ, secreted by activated T cells, natural killer (NK), NKT cells and dendritic cells with pro-inflammatory and immunomodulatory functions [9]. In general, type II IFN acts as a link between the innate immune response and the activation of the adaptive immune response [10]. Type III IFNs include IFN-λ1, IFN-λ2 and IFN-λ3, and, although genetically different to type I IFNs and signaling through different receptors, they are induced by PPRs and activates antiviral pathways similar to type I IFNs [11, 12].

Viruses use multiple mechanisms to by-pass the host IFN responses so that they can replicate and continue their infectious cycle. The present review will focus on how viruses interfere with IFN-I responses. Viruses can act at different levels of the signaling cascades involved in IFN-I responses. They can inhibit the induction of the IFN response, block the IFN signaling, and/or interfere with the antiviral activities induced by IFN. We will review some of the emerging

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themes and new insights from the past years of the IFN evasion mechanism employed by viruses in these contexts.

## Type I IFN induction

The antiviral state of an infected cells is attained by the initial induction of type I IFN expression, followed by IFN signaling transduction, which finally leads to the expression of multiple genes (Fig. 1). IFNs are the main group of cytokines secreted by host cells in response to the presence of "aberrant" nucleic acids such as double-stranded RNA (dsRNA) molecules generated as viral intermediates during viral transcription in infected cells, to CpG DNA, or uncapped ssRNA with 5′ triphosphate present in some viruses. These elements are known as pathogen-associated molecular patterns (PAMP) [13, 14] that can be recognized by PRRs. Four main types of PRRs have been described to detect virus-derived genetic materials: Toll-like receptors (TLRs) 3/7/8/9 [15]; retinoic acid-inducible gene-I (RIG-I) like receptors (RLRs) which include the cytosolic sensor RIG-I, the melanoma differentiation-associated factor 5 (MDA-5) and laboratory of genetics and physiology (LGP2) [16]; and nucleotide oligomerization domain-like receptors (NLRs) [17] and the cytosolic DNA sensors [18]. For a host to establish an antiviral state it first requires the production of type I (α/β) IFNs in direct response to virus infection and recognition of virus-derived genetic material. Hence,

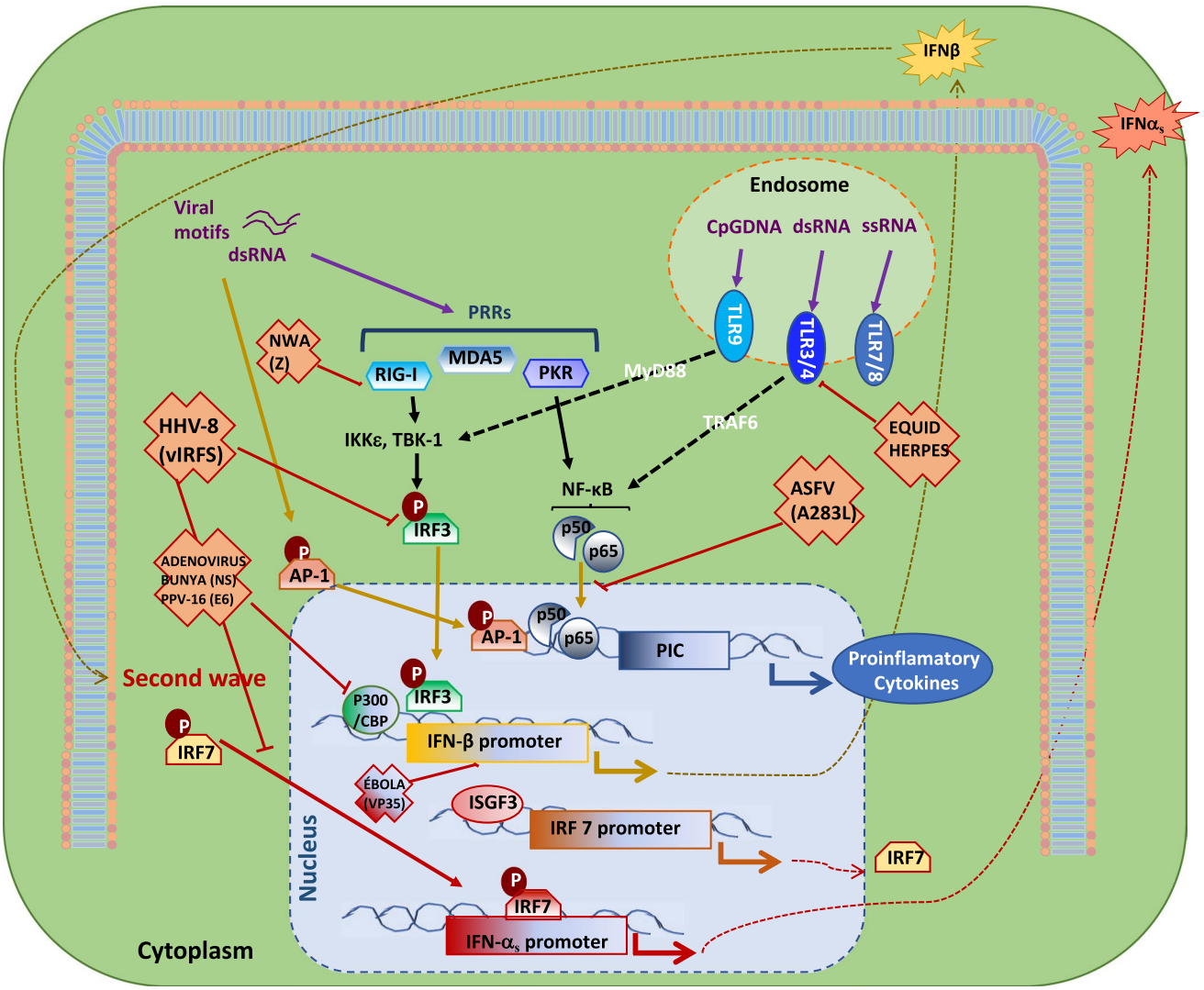


**Fig. 1** IFN-I induction and viral counteracting actions. Viral motifs (e.g. dsRNA), are recognized by PPRs. This leads to the activation of adaptor proteins such as NFκB, TBK-1, IKKε and AP-1. TBK-1 and IKKε phosphorylate IRF3, which translocate to the nucleus and induce IFN-I expression. In a second IFN signaling wave, IRF7 is phosphorylated and translocated to the nucleus, creating an amplification loop of IFN-I induction. Several viruses have developed mechanisms to block several steps of this IFN induction cascade, indicated in red blades in the figure

TLR-7 and 8 become active with the detection of ssRNA in the acidic compartment of endosomes [19] while TLR3 and 9 are receptors for dsRNA and unmethylated DNA, respectively [20].

Both RIG-I and MDA-5 sense cytosolic dsRNA. RIG-I also specifically senses 5′ triphosphate RNA generated during infection, while MDA-5 detects longer dsRNA sequence generated during virus replication. RIG-I and MDA5 contain two caspase activation and recruitment domains (CARDs) at the N-terminal. Activation of RIG-I and MDA5 liberates these CARD domains and drives the interaction of these tandem CARDs with the CARD of the mitochondrial activation signaling (MAVS) protein [21]. MAVS aggregates in filaments that provide a platform for the recruitment of the elements involved in the subsequent signaling cascade such as the tumor necrosis factor receptor-associated factor (TRAF) 3 and TRAF6, the TANK binding kinase 1 (TBK1) and IKKε ultimately drives the activation of transcription factors as IRF3/7, NFκB and AP-1, leading the production of type I IFN and pro-inflammatory cytokines [22]. IRF3 is constitutively expressed in many cell types, and after phosphorylation, IRF-3 forms a homodimer that translocates into the nucleus, activating the transcription of early transcribed type I and III IFN genes, IFN-β, IFN-α4 and IFN-α1 [23, 24].

The activation of IRF-7, expressed only in B cells, monocytes and plasmacytoid dendritic cells (pDCs) [25], with high levels of expression on pDCs [26] requires a second IFN signaling wave to be activated by phosphorylation. IRF7 induces the transcription of a set of delayed IFNα genes [24]. This creates an amplification loop in which type I IFN induces more IRF7, leading to the production of more IFN, with an important role in the generation of a potent response to viral infections [26].

The aberrant presence of DNA can also be sensed by PRRs during viral infection. Two main sensors for DNA during viral infection have been described so far: the IFN-γ inducible protein 16 (IFI16) and the cGAS cyclic-GMP-AMP synthetase (cGAS) (reviewed in [18]). IFI16 appears to have a preferential affinity for quadruplex DNA structures [27] that can be found in some viral genomes [28]. cGAS recognizes the presence of DNA in the cytosol. This includes viral, bacterial, or leaked cellular DNA [29, 30]. Upon the recognition cGAS catalyze the production of cGAMP that interacts with the stimulator of IFN gene (STING). STING possesses a pocket where it binds cyclic dinucleotides such as cGAMP resulting in conformational changes that lead to activation [31]. Once activated, STING acts as an adaptor protein located in the ER that traffics through the Golgi to perinuclear regions. During trafficking, STING recruits and activates TBK1, which leads to IRF3 activation and type I IFN induction [32]. While cGAS activation of STING involves the second messenger cGAMP, IFI16 appears to interact with STING to induce TBK1-dependent IFN induction [33].

## IFN signaling in antiviral defense

All type I IFNs signal through the same heterodimeric transmembrane receptor termed the IFNα receptor (IFNAR), containing the subunit 1 and 2 (IFNAR1 and IFNAR2). In a first step, IFN-I binds with high affinity to IFNAR1, and then recruit IFNAR2 [34]. IFNAR engagement with IFN-I promotes the induction of an antiviral state in cells. This involves the upregulation of products from a large subset of genes named IFN-stimulated genes (ISG) that protect the cell from viral replication. Broadly speaking, ISG products modulate and mediate IFN activity in the cells. This includes for instance cooperating in PRR recognition of viral PAMPs, stabilizing signaling complexes to improve their resistance to degradation, stopping virus entry, blocking viral capsid formation, impairing trafficking and budding of virions from the infected cells, but also modulating the IFN response to avoid the toxicity of these potent immune mediators. An important feature of the IFN signaling is the rapid speed at which the response happens, which is possible because protein synthesis is not required in an initial stage.

The interaction of type I IFNs with their universally expressed receptor (IFNAR) elicits an intracellular signaling cascade through the Janus protein kinase (JAK) family members, JAK and Tyk2, that successively phosphorylate signal transducer and transcription activator (STAT) family proteins [35]. The phosphorylated STAT1/STAT2 heterodimer associates with interferon regulatory factor 9 (IRF9) to form the transcriptional factor complex ISGF3, which translocate to the nucleus and binds the IFN-response elements (ISRE) in ISG promoters leading to the expression of ISG products [36] (Fig. 2). ISGs target different steps of viral replication, amplifying the IFN signaling cascades to strength the antiviral activities [37]. Hence, the ISGs can exert a complex and wide range of functions, providing a significant redundancy in the system that fights against viral infections (reviewed in [38]).

The so-called classical ISGs pathways belong to one of the following three gene families: Mx proteins, 2′,5′-oligoadenylate synthetase (2-5OAS) or ds RNA-activated protein kinase (PKR) [39, 40]. Evidences of the role of these genes in establishing an antiviral state came from studies of infected knock out mice for PKR, 2-5OAS or Mx, individually and/or together [41]. The Mx family GTPases includes Mx1 and Mx2 proteins that function as an inhibitor of viral entry. Mx1 acts before genome replication at a very early time of the virus life cycle, inhibiting the replication of several viruses belonging to

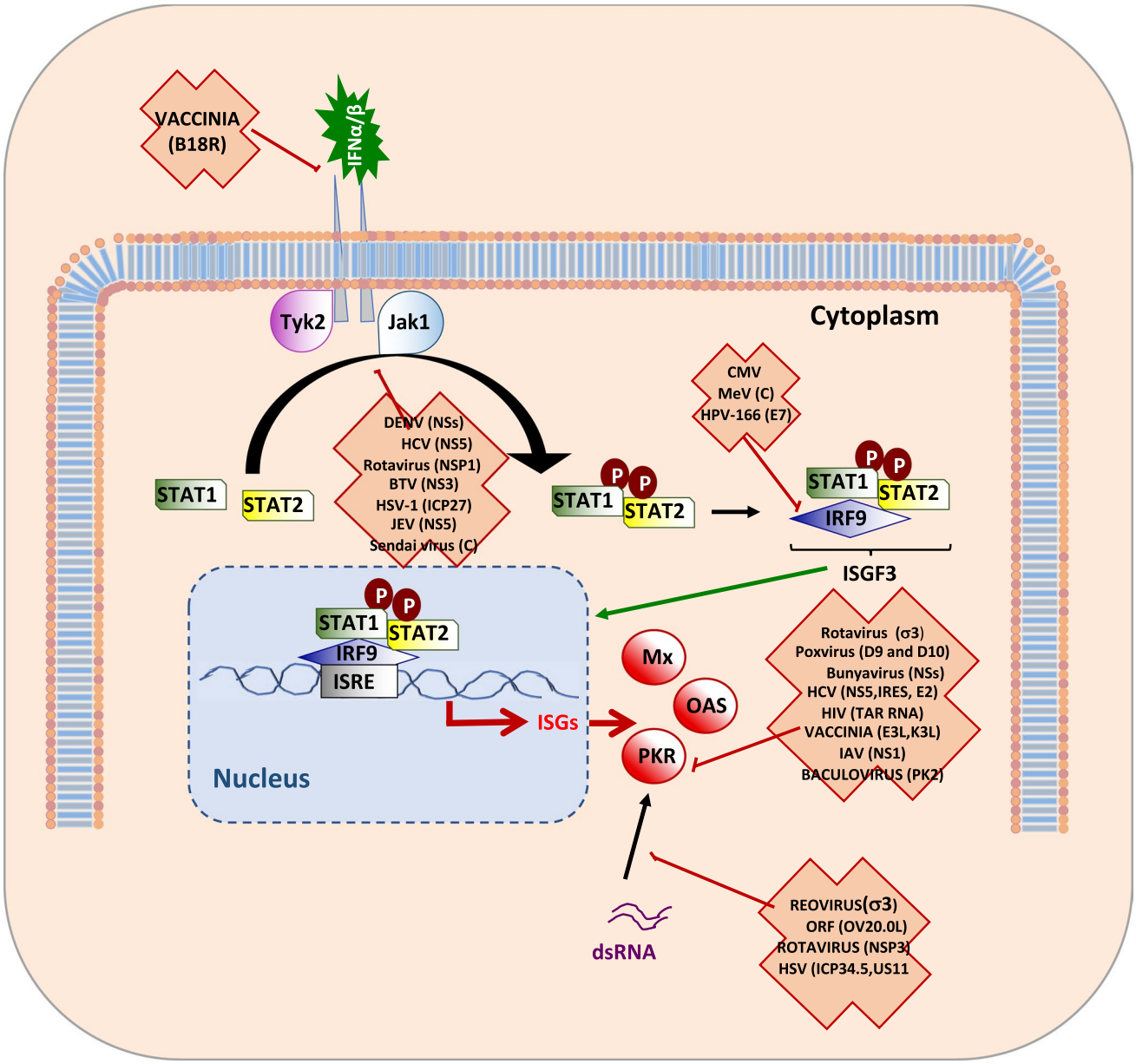


**Fig. 2** Type I IFN signaling and viral countermeasures. IFN binds to the receptor IFNAR and triggers a signaling cascade that is summarized in this figure. Viruses has developed strategies to counteract different steps on this signaling cascade. It is marked in red blades the main signaling targets of viruses

Orthomyxo-, Paramyxo-, Rhabdo- and Bunyaviridae families by interfering with the traffic or synthesis of the viral ribonucleoprotein complexes [42]. Mx2 acts as an antiretroviral protein by inhibiting chromosomal integration, a key event in the retrovirus life cycle [43].

The oligoadenylate synthetase (OAS)-latent RNase (RNase L) pathway is another IFN-inducible pathway that provides the cell with an effector mechanism upon recognition of viral dsRNA (reviewed in [44]). When the OAS senses dsRNA activates the production of 2′,5′-oligoadenylates that act as a second messenger on the inactive monomeric RNaseL [45]. The 2′,5-oligoadenylates binding to RNase L produces a catalytically active dimer that cleaves ssRNA [46]. This leads to the translational arrest and prevent viral replication and spreading [47].

RNA-activated protein kinase is an ISG product that detects cytosolic dsRNA. PKR recognition of its dsRNA substrate leads to dimerization and autophosphorylation which in turn leads to the phosphorylation of the

eukaryotic initiation factor 2α (eIF2α) required for translation initiation [48]. eIF2α phosphorylation results in the shutdown of all translation of 5′capped mRNA, thus preventing the synthesis of viral proteins. This also usually results in the formation of stress granules (SG) that consist of the accumulation of RNA and proteins from the stalled translation complexes. SG formation has been linked to antiviral responses, and their formation is often inhibited in viral infections. In general, the antiviral activity of PKR is related to apoptosis induction [49], regulation of IFN-β synthesis and NF-κB pathway [50–52], serine kinase activity for STAT1 that also regulate the IFN-I signaling pathway [53].

A family of proteins with a wide range of anti-viral functions are the interferon-induced proteins with tetratricopeptide repeats (IFITs) [54]. These genes are expressed at very low basal levels, but their transcription is rapidly increased after activation by IFN signaling. IFIT detect the lack of 2′-O-methylation on RNAs species, a methylation absent in some viral RNA but present in eukaryotic mRNA [55]. IFIT1 has also been shown to bind to the 5′-triP end of some viral RNA [56]. IFIT1 can sequester viral RNA or interact with the eukaryotic translation initiation factor 3 to inhibit the translation initiation of IFIT1-bound RNA species.

In addition to these ISGs, one highly upregulated gene in the initial stage of the antiviral immune response is ISG15 (interferon-stimulated gene 15), which encodes an ubiquitin-like protein involved in a post-translational process termed ISGylation [57]. This process allows ISG15 to bind covalently to a range of target proteins, both viral and cellular [58], by a process that is reversible due to the action of the ubiquitin-specific protease 18 (USP18), an event regulated by type I IFN [59]. ISGylation appears to modulate the activity of multiple elements involved in the IFN response. For instance, ISGylation has been shown to sustain STAT1 or IRF3 activity [60, 61], downregulate the turnover of ubiquitinated proteins [62], but also to negatively regulate RIG-I signaling [63]. ISG15 acts during viral replication by interfering with the endogenous proteins that the virus needs to replicate. Thus, ISG15 conjugates to the eukaryotic factor 4E (eIF4E) homologous protein (4EHP) that binds to the capped mRNA, inhibiting in this way the viral RNA translation of those viruses that contains a capped positive-sense RNA such as flaviviruses [64]. ISG15 also exists as an unconjugated protein that acts as a cytokine, regulating viral replication and host responses [65, 66].

The role of the ISGs members mentioned above clearly illustrates the breadth and diversity in the function of this protein group. A database has been created, called Interferome (https://www.interferome.org/interferome/home.jspx), in which ISGs are catalogued and incorporated into a database, based on the information obtained from all published reports where cells were treated with IFN, Thus, this database will allow to identify ISG signatures from high-throughput data, having implications for determining the role of ISGs. Viruses employ mechanisms that impair ISG activity to enhance their evasion from the IFN system. The mechanisms will be discussed in another section of this review.

## Viral evasion strategies: inhibition of interferon induction

As discussed previously, PRR activation leads to the production of IFN-I, -III, and pro-inflammatory cytokines such as IL-1β. The present section will be centered on how viruses affect IFN-I induction. Typically, virus genetic material triggers IFN-I induction when recognized by viral nucleic acid sensors that are membrane bound or present in the cytoplasm/nucleus. This recognition leads to activation of signaling cascades that converge towards the induction of IFN-I production in infected cells. Viruses are known to interfere at every point of this process. Viruses can interfere with the sensing of their genetic material, impair the signaling cascade that leads to IFN-I induction, and/or antagonize the activity of the transcription factors involved in IFN-I gene expression. The present section aims at providing a non-exhaustive overview of some of the most commonly used viral mechanisms to counter IFN-I induction in the host with a focus on recent findings in the field.

### Virus interference with viral sensors of genetic material

Viruses use different mechanisms to counteract the recognition of their genetic material by the host cell so that IFNs are not induced (Table 1). Viruses can sequester, modify or even degrade their nucleic acids to avoid detection by PRRs. For instance, during replication most flaviviruses create vesicular structures in the ER membrane which physically shield the viral genetic material from cytosolic RLRs [67–69]. Influenza A virus (IAV) uses the nucleus for replication, atypically for an RNA virus, so that its genetic material remains hidden from cytosolic RLRs [70]. Vaccinia virus (VV), a large double-stranded DNA virus has the peculiarity of replicating in the cytoplasm, where DNA sensors like cGAS are present, which potentially renders the viral genetic material susceptible to recognition by PRR. VV replication, however, occurs in organelles similar to micronuclei [71] that probably render viral DNA inaccessible to recognition by cytoplasmic DNA sensors. Rotaviruses (RV) concentrate their replication in a cytoplasmic structure called viroplasms where dsRNA genome is generated for packaging so that it is not exposed to the cytoplasmic PRR [72].

**Table 1** Virus interference with viral sensors of genetic material

| Virus | Cellular target | Viral protein | References |
|---|---|---|---|
| Flavivirus, IAV, Rotavirus | Detection by PRRs | | [67–70, 72] |
| Reovirus | dsRNA | σ3 | [73] |
| Ebola virus | dsRNA | VP35 | [74] |
| IAV | dsRNA, RIG-I | NS1, NS1 | ], [108, 109] |
| Lassa virus | dsRNA | NP | [78] |
| Kaposi's sarcoma-associated virus | Inhibit cGAS | ORF52 | [84] |
| HSV-1 | Inhibit cGAS, IFI16 | VP22, ICP0 | [85], [91] |
| DENV | cGAS, 14-3-3ε (RIG-I) | NS2B, NS3 | [93], [111] |
| Hantavirus, Crimean-Congo and Borna disease virus | RIG-I recognition | – | [80] |
| New World Arenavirus | RIG-I | Z | [86] |
| Coronaviruses | RIG-I | M, PLP | [87, 94] |
| Picornavirus | RIG-I, MDA5 | $L^{pro}$, $3C^{pro}$, $2A^{pro}$ | [88–90] |
| Paramyxovirus | MDA5 | V | [98–100] |

Many viruses also encode proteins that help conceal their genetic material from PRR. Some viruses possess dsRNA binding proteins that could potentially sequester these PAMPs from PPR recognition, such as VP35 from Ebola virus or σ3 from reovirus [73, 74]. The encapsidation of the viral RNA can also impair RLR recognition. For instance, IAV nucleoprotein and polymerase prevents RIG-I binding to viral RNA during transit through the cytoplasm [75]. IAV NS1 protein also possesses a dsRNA binding site that prevents recognition by RIG-I [76]. *Calicivirus* and *picornavirus* ssRNA (+) is covalently linked to a capping protein that could prevent recognition of the 5′ viral RNA extremity by RIG-I [77]. Lassa virus (LASV) nucleoprotein (NP) can act as a capping enzyme with exonuclease activity specific for dsRNA, which has been shown to antagonize IFN induction [78, 79]. Other viruses can modify their 5′tri-P motifs recognized by RIG-I to evade this cytoplasmic RNA sensor. Hantaan virus, Crimean-Congo hemorrhagic fever virus and Borna disease virus can process their 5′ genome extremity to form 5′mono-P forms, evading RIG-I recognition [80]. Poxvirus decapping enzymes D9 and D10 can prevent the accumulation of dsRNA, an intermediate necessary in viral replication, and thereby evade RLR recognition [81]. Measles virus (MeV) encodes for the non-structural C protein that can impair IFN response by modulating viral RNA replication [82] and improving the polymerase processivity [83], thus probably limiting the amount of viral material recognizable by cytosolic PRR.

Another mechanism employed by viruses to limit detection by PRR is to interact with these sensors to impair their activation. The Kaposi's sarcoma-associated virus (KSHV) uses the tegument protein ORF52 to bind to cGAS and inhibit cGAMP production, the second messenger used for STING (stimulator of interferon response cGAMP interactor 1) activation [84]. Homologues of ORF52 in other gammaherpesviruses have also been described to act similarly, indicating that inhibition of this PRR pathway is probably shared by gammaherpesvirus. The Herpes simplex virus 1 (HSV-1) tegument protein VP22 has also been shown to inhibit cGAS enzymatic activity, indicating that other *Herpesviridae* can directly target cGAS [85]. Other viruses can sequester PRR so that they are unable to relocate to their activity site. For instance, the protein Z of new world arenaviruses binds to RIG-I and prevents its association with the signaling platform MAVS protein [86]. Severe acute respiratory syndrome coronavirus (SARS-CoV) M protein has been shown to associate with RIG-I and can potentially sequester this PRR [87].

Viruses can also promote PRR degradation, thus reducing the number of cellular sensors capable of detecting viral infection (Fig. 3). This can be done directly by proteases encoded by the viral genome. Foot and mouth disease virus (FMDV) $L^{pro}$ and $3C^{pro}$ protease can reduce RIG-I intracellular protein levels [88]. The $3C^{pro}$ protease of other picornaviruses has also been shown to degrade RIG-I [89], indicating that this is a shared mechanism of RLR evasion by this viral family. RIG-I is not the sole PRR that picornavirus proteases can target; the poliovirus and enterovirus 71 (EV71) $2A^{pro}$ protease can also degrade MDA5 [90]. Viruses also encode for proteins that indirectly promote PRR degradation. The nuclear sensor of DNA IFI16 is degraded during HSV-1 infection through a mechanism dependent on the viral ICP0 protein that is not fully understood but probably involves targeting the DNA sensor for proteasomal degradation [91]. A E3 ligase activity on the NSs protein of the phlebovirus Toscana virus was recently identified that allowed the ubiquitination of RIG-I CARD domains and the subsequent proteasomal degradation of the PRR [92]. The NS2B protein of the flavivirus Dengue virus (DENV) can target the cytosolic DNA sensor cGAS for lysosomal degradation. Although this

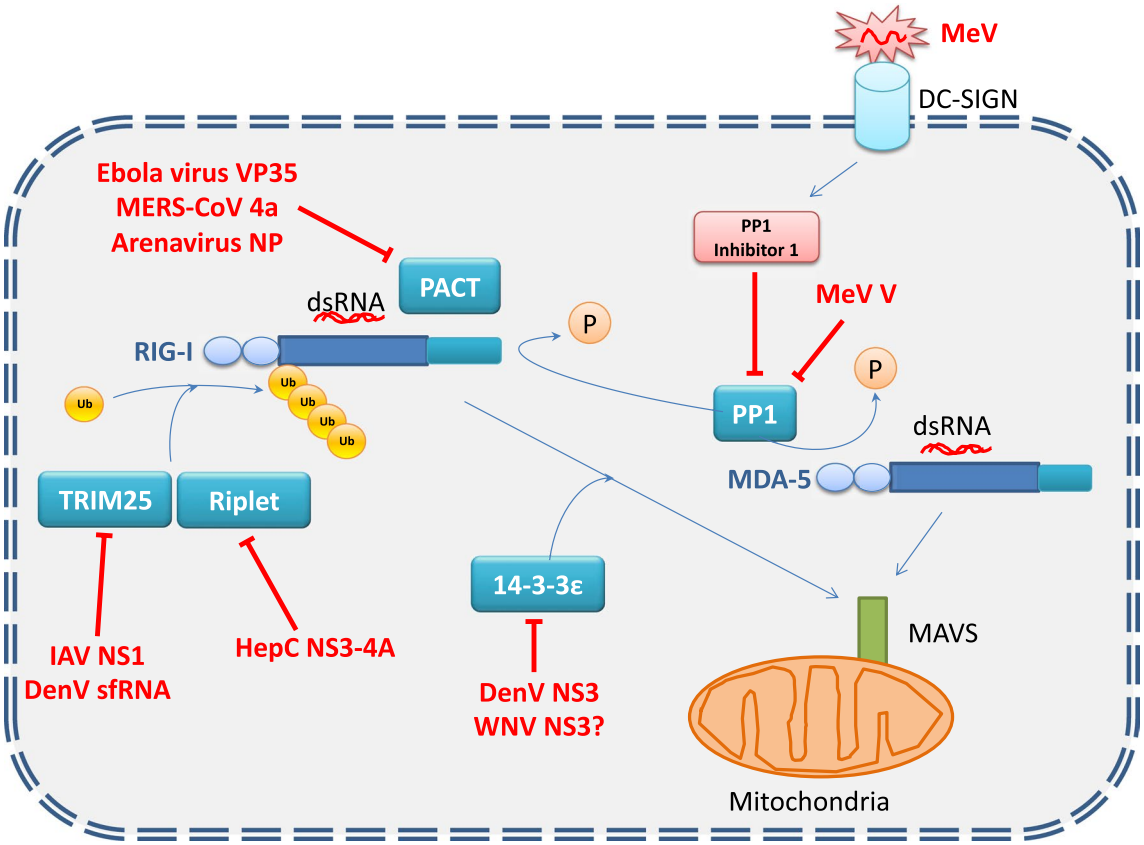


**Fig. 3** Viral interference with accessory cellular components involved in PRR activation. MeV can interfere with RLR activation by targeting the phosphatase PP1 using 2 distinct mechanisms. MeV V protein can interact with PP1 to prevent the dephosphorylation of MDA-5 required for activation. MeV can interact on the cell surface with the C-lectin receptor DC-SIGN which results in the association of PP1-inhibitor 1 with PP1 thus preventing RLR dephosphorylation. Ebola virus VP35 protein, MERS-CoV 4a protein and arenavirus NP can interfere with PACT binding to dsRNA, a mechanism that potentiates RLR activation. RLR ubiquitination is also essential for adequate activation and transport to MAVS for subsequent IFN signaling events to take place. Riplet and TRIM25 are critical to RIG-I ubiquitination. IAV-NS1 and Denv sfRNA can interfere with TRIM25 activity, whereas Hepatitis C NS3-4A protease can cleave Riplet to impair RIG-I ubiquitination. The mitochondrial-targeting chaperone 14-3-3ε is responsible for RIG-I translocation to the mitochondrial membrane. DenV NS3 protein targets 14-3-3ε using a phosphomimetic domain that displaces activated RIG-I from this chaperone. WNV NS3 possesses a similar domain

mechanism could at first glance seem counterproductive for an RNA virus, it actually allows DenV to evade the recognition of the mitochondrial DNA that becomes exposed during infection [93].

Other viruses alter the post-translational modifications essential to PRR signaling so that the PPR remains inactive. Some viral-encoded proteins achieve this directly, as in the case of the deubiquitinase activity of coronaviruses papain-like protease (PLP) that removes the K63 ubiquitin tail from RIG-I that is essential for RIG-I translocation to the MAVS protein platform [94]. This deubiquitination activity has been characterized in several coronaviruses thus suggesting that this mechanism is central to coronavirus evasion from the IFN system [95–97]. Paramyxovirus V protein binds to MDA5 and impairs its dephosphorylation by blocking the ATP hydrolysis necessary for MDA5 folding to its active state, thus impairing the adequate activation of this PRR [98].

Viruses can also impair PRR activity by interfering with the functionality of accessory cellular components required for PRR activation. MeV has been shown to act on the phosphatase PP1 required for RLR activation using two distinct mechanisms. The MeV V protein can bind PP1 which prevents MDA5 dephosphorylation [99]. MeV infection in dendritic cells also produces recognition of the viral particle through the C-lectin receptor DC-SIGN [100]. This triggers a signaling cascade that results in Raf-1 kinase activation and the association of the PP1 inhibitor I-1 with PP1 that prevented RLR dephosphorylation thus impairing IFN induction. Several viruses have also been shown to interact with the dsRNA binding protein PACT that potentiates RLR activation [101, 102]. For instance, Ebola virus VP35 protein, Middle East respiratory syndrome

coronavirus (MERS-CoV) 4a protein and arenavirus nucleoproteins have been shown to interfere with PACT binding to RLR [103–105]. As previously stated, RIG-I activation is associated to its ubiquitination with K63 Ub chains that liberates its autorepressed N-terminal CARD domains, a mechanism dependent on the activity of the cellular proteins TRIM25 and Riplet [106, 107]. This mechanism can be targeted by viral products such as the IAV NS1 protein that impairs TRIM25-mediated RIG-I ubiquitination [108, 109], or the hepatitis C virus NS3-4A protease that cleaves Riplet [106]. Intriguingly, not only protein products appear to interfere with the RIG-I activation complex. The subgenomic flavivirus RNA (sfRNA) generated during DenV infection can bind to TRIM25 and prevent the deubiquitination step required for TRIM25 activity to take place [110]. DenV uses yet another mechanism to avoid PRR detection. DenV NS3 protein possesses a phosphomimetic domain that binds the mitochondrial-targeting chaperone protein 14-3-3ε [111]. 14-3-3ε is responsible for RIG-I translocation to the mitochondrial membrane where the subsequent steps of the IFN induction signaling cascade take place. By binding 14-3-3ε, DenV NS3 displaces the activated RIG-I complex and prevents IFN induction. Interestingly, a similar phosphomimetic domain is also present in West Nile Virus (WNV) NS3 protein [111].

## Virus interference with the IFN-I induction signaling cascade

Viruses not only interfere with the PRR capable of detecting their presence during infection, they also commonly affect the activity of the signaling complexes in charge of signal transduction. Indeed, this is a strategy employed by most viruses to limit IFN responses. Viruses can antagonize these signaling cascades at multiple levels and through varied mechanisms (Table 2). This can be achieved by impairing the post-translational modifications required for signaling, i.e. by altering the phosphorylation or ubiquitinylation status of signaling intermediates. For instance, SARS-CoV and human coronavirus NL63 (HCoV-NL63) PLPs have been shown to prevent STING dimerization and thus subsequent activation of the TBK1 pathway possibly through the PLP deubiquitinase activity [112, 113], as STING dimerization is dependent on the attachment of K63Ub chains [114]. Similarly, SARS-CoV PLP can inhibit TLR7 signaling by removing K63-Ub chains from TRAF3 and TRAF6 and thus blocking TBK1 activation [115]. Another strategy to prevent post-translational modification of IFN-I pathway signaling components consists of sequestering these components so that they do not reach the adequate cellular location for activation. The NS3 protein from the economically important orbivirus Bluetongue Virus (BTV) binds to the ubiquitin-binding protein optineurin in the Golgi apparatus [116]. This prevents optineurin from recruiting ubiquitinated TBK1 at the Golgi apparatus, a necessary step for subsequent TBK1 phosphorylation to occur [116]. Recently, it has been described that cGAMP, the second messenger generated by cGAS and that activates STING, can be cleaved by poxvirus-encoded nucleases (named poxins) [117]. This allows poxvirus blockade of the cGAS-STING signaling axis.

Viral proteins can also prevent the adequate formation of signaling complexes by steric hindrance. For instance, human adenovirus type 5 E1A protein has been shown to bind to STING and thus antagonize IFN signaling [118]. MERS-CoV and SARS-CoV M proteins can interact with TRAF3 and thus disrupt the TRAF3-TBK1 association

**Table 2** Virus interference with the IFN-I induction signaling cascade

| Virus | Cellular target | Viral protein | References |
|---|---|---|---|
| Coronavirus | STING dimerization, TLR7 | PLP, PLP | [112, 113], [115] |
| BTV | TBK1 phosphorylation | NS3 | [116] |
| Poxvirus | c-GAS-STING | Poxins | [117] |
| Adenovirus | STING | E1A | [118] |
| MERS-CoV | TRAF3a, TBK1/IKKε | M, ORF4b | [119], [121] |
| SARS-CoV | TRAF3a, MAVS | M, ORF9b | [120],[134] |
| KSHV | TBK1-STING | vIRF1 | [122] |
| HSV-1 | TBK1 | ICP27 | [123] |
| Phlebovirus | TBK1 | NS | [124] |
| Flavivirus | STING | NS2B3 | [125–127] |
| Picornavirus | MAVS | $3C^{pro}$ | [128, 129] |
| PPRSV | MAVS | 3C-like protease | [130] |
| HCV | MAVS | NS3/4A | [131] |
| DENV | Mitofusins-MAVS | NS2B3 | [136] |
| Parainfluenza virus 3 | Mitophagy-MAVS | M | [140] |
| IAV | Mitophagy-MAVS | PB1-F2 | [141] |

[87, 119, 120]. MERS-CoV ORF4b protein can associate with the TBK1/IKKε complex to impair signaling [121], indicating that coronaviruses encode for multiple proteins that affect IFN induction at different stages of the signaling cascade. KSHV encodes for viral interferon regulatory factor 1 (vIRF1), a protein that binds to STING and block the association of TBK1 with STING, thus hindering the consequent IRF3 phosphorylation [122]. HSV-1 encodes for the ICP27 protein that can interact with the active STING-TBK1 complex and inhibit the subsequent TBK1-mediated phosphorylation of IRF3 [123]. The NSs protein from some phleboviruses has also been described to antagonize IFN induction by targeting TBK1 [124]. TBK1 activity is thus commonly targeted by both RNA and DNA viruses to antagonize IFN induction.

Viruses can also promote the degradation of signaling proteins involved in IFN induction. Virally-encoded proteases can directly cleave some of the components of these pathways. STING can be directly cleaved by the NS2B3 protease from several flaviviruses such as DenV, Zika virus, WNV, or Japanese encephalitis virus (JEV), but not others like yellow fever virus [125–127]. Indeed, this specific cleavage could partially explain some of the host range and pathogenicity of these flaviviruses in humans, as the identified STING cleavage site for the NS2B3 protease is only partially conserved among species [125]. Similarly, the $3C^{pro}$ from several *Picornoviridae* has been described to cleave MAVS proteins, thus inhibiting signal transduction [128, 129]. The 3C-like protease from the arterivirus porcine reproductive respiratory syndrome virus (PRRSV) and the NS3/4A protease complex from the flavivirus hepatitis C virus (HCV) have also been described to cleave MAVS protein [130, 131]. Other viruses encode proteins that promote the degradation of signaling complexes involved in the IFN responses. RV NSP1 and VP3 proteins have been shown to target MAVS protein for proteasome-dependent degradation and thus impair IFN induction [132, 133]. SARS-CoV ORF9b protein localizes in the mitochondrial membrane where it interacts with MAVS protein and promote its degradation [134]. This mechanism probably involves the recruitment of the MAVS protein cellular regulator PCBP2 [135] to the mitochondrial membrane by SARS-CoV ORF9b protein, which favors MAVS protein ubiquitination through K48-Ub chains and thus subsequent proteasomal degradation.

Since MAVS protein represents an important signaling platform in the IFN induction cascade triggered by RLR activation, some viruses use strategies to alter mitochondria structure to impair MAVS protein assembly. DenV NS2B3 protease can cleave mitofusins, which alters mitochondria dynamics and impair their fusion [136]. In other cases, viruses can also promote mitophagy to promote their replication and potentially impair IFN responses. Mitophagy has been described in MeV, hepatitis B virus (HBV) or Newcastle disease virus infections [137–139]. The protein M from the human parainfluenza virus 3 has also been shown to promote mitophagy and thus trigger MAVS protein degradation to antagonize IFN induction [140]. Recently, IAV has also been shown to employ a similar mitophagic strategy to reduce MAVS protein levels through the expression of its PB1-F2 protein [141].

## Virus interference with IFN-I transcription factors

Viruses can also act on the transcription factors that bind to the IFN-I promoter and trigger the expression of ISGs. Viruses use multiple strategies to impair the binding of the transcription factors to the IFN-I promoters (Table 3). They can impair the phosphorylation by the TBK1/IKKε complex

**Table 3** Virus interference with IFN-I transcription factors

| Virus | Cellular target | Viral protein | References |
|---|---|---|---|
| Paramyxovirus | IRF7 phosphorylation, IRF3 | C, V | [142], [160] |
| DENV | IRF3 phosphorylation | NS2B3 | [143] |
| LCMV | IRF3 phosphorylation, NF-κB | NP, NP | [144, 145], [147] |
| Hepatitis A | NEMO | $3C^{pro}$ | [148] |
| FMDV | NEMO// | $3C^{pro}$ | [149] |
| Porcine epidemic diarrhea virus | NEMO | 3C-like protease | [150] |
| PRRSV | NEMO | 3C-like protease | [151] |
| Rotavirus | IRF3/7, NF-κB, IκB phosphorylation | NSP1, NSP1, NSP1 | [152], [154], [155] |
| VV | IκB phosphorylation | A49 | [158] |
| Epstein–Barr | IκB phosphorylation | LMP-1 | [157] |
| HIV | IκB phosphorylation | Vpu | [156] |
| KSHV | IRF3 | vIRF1 | [159] |
| V | IRF3 | NS5 | [161] |
| Murine gamma-herpesvirus | IRF3 | ORF36 | [166] |

of IRF3/7 that activates dimerization and transport to the nucleus. For instance, the paramyxovirus C protein inhibits IRF7 phosphorylation and thus its activation [142]. The DenV NS2B3 protease can impair IRF3 phosphorylation by masking the IKKε kinase domain necessary for IRF3 activation [143]. Lymphocytic choriomeningitis virus (LCMV) nucleoprotein was also shown to bind to the IKKε kinase domain, thus preventing IRF3 phosphorylation [144] indicating that arenavirus NP-mediated inhibition of IRF3 phosphorylation [145] uses a similar mechanism.

Viruses not only target IRF3/7 activation to antagonize IFN induction, they can also interfere with the activation of NF-κB, as this transcription factor collaborates with IRF3 in the early activation of the IFN-β promoter [146]. Most arenavirus nucleoproteins not only block IRF3 phosphorylation but they can also impair NF-κB activity [147]. Viruses can also target adaptor molecules that regulate NF-κB activity. The NF-κB essential modulator (NEMO) is part of the kinase complex that controls NF-κB release from its inhibitor IκB. The $3C^{pro}$ from Hepatitis A virus or FMDV and the 3C-like proteases from porcine epidemic diarrhea virus or PRRSV cleave NEMO thus preventing IκB release from NF-κB and consequently antagonizing IFN-β production [148–151].

The degradation of the transcription factors involved in IFN induction is also the target of different viral proteins, as in the case of the NSP1 from RV that promote the degradation of several IRFs including IRF3 and 7 [152]. RV NSP1 appears to target IRFs by interacting with their dimerization domain and thus preventing their association in active form [153]. NSP1 has also been described to impair NF-κB by promoting the degradation of β-transducing repeat-containing protein (β-TrCP) [154], the protein responsible for substrate recognition of the E3 ligase complex that targets for degradation IκB, the associated inhibitor of NF-κB. Similarly, to other viral products, such as HIV-1 Vpu, VV A49, or Epstein–Barr virus LMP-1, RV NSP1 associates with β-TrCP through mimicry of the phosphorylated IκB that requires degradation [155–158]. RV NSP1, however, presents the particularity of not only blocking the interaction of IκB with the E3 ligase complex but also of targeting β-TrCP for degradation.

Viruses can also impair IRF3/7 activity downstream of their activation by phosphorylation. The vIRF1 encoded by KSHV can block IRF3 activity downstream of IRF3 activation by impairing the recruitment of the CBP-p300 coactivators to the IRF3 complex [159]. This can also be achieved by blocking the transport of activated transcription factors to the nucleus. For instance, some paramyxoviruses use their V protein to impair IRF3 translocation to the nucleus [160]. JEV NS5 blocks IRF3 and p65 subunit from NF-κB transport to the nucleus by interacting with nuclear transport proteins [161]. The NSs from the emerging bunyavirus severe fever with thrombocytopenia syndrome virus have also been described to sequester the TBK1–IKKε–IRF3 complex in viral inclusion bodies to prevent the trafficking of IRF3 to the nucleus [162].

Some viruses also code for proteins that interfere with IFN induction in the nucleus. In many instances, the exact mechanisms of IFN antagonism by viral products in the nucleus are not fully resolved. MERS-CoV ORF4b protein impairs IFN induction in the nucleus by a mechanism yet to be elucidated [121]. BTV encodes non-structural protein 4 (NS4) that localizes in cell nucleoli and possess IFN antagonist activity [163]. MeV C protein can interfere with IFN-β promoter activation in the nucleus and this property has been linked to the virus pathogenicity [164]. The NSs protein from the Phlebovirus Sandfly fever Sicilian virus can prevent IRF3 activity by interacting with the DNA binding domain of IRF3 [165]. The protein ORF36 from the murine gammaherpes virus 68 was shown to bind to IRF3 and to prevent its association with the co-transcriptional activator CBP, thus impairing IRF3 binding to the IFN-β promoter [166].

Viruses have developed strategies to antagonize IFN induction at multiple stages of the signaling cascade. This includes limiting the recognition of their genetic material, impairing the activation of PRRs or their signaling partners, promoting the degradation of key components of the signaling cascade, sequestering signaling complexes away from their site of action, or impairing DNA binding of the transcription factors involved in IFN induction. In viruses, multiple mechanisms have also often evolved to target several elements in these pathways, and hence augment their capacity to evade innate immunity.

## Viral evasion strategies: blockade of IFN signaling

### Intracellular blockade of IFN signaling pathways

Viruses can suppress the IFN signaling at different levels (Table 4). In this section, we will discuss some of the mechanisms that viruses use to counteract the action of this signaling cascade.

One of the first steps in the signaling cascade is the phosphorylation of JAK1 and TYK2, relevant for initiating the JAK-STAT signaling. By directly promoting the dephosphorylation of the JAK/STAT pathway, viruses counteract the IFN response. For instance, Sendai virus (*Respirovirus*) C protein inhibits the phosphorylation of receptor-associated kinases JAK1 and TYK2 by binding to the IFN receptor subunit IFN-α/β [167]. The NS5 protein of the JEV blocks the tyrosine phosphorylation of TYK2 and STAT1 [168]. STAT1 phosphorylation is targeted by several viruses, using different mechanisms. The *Paramyxovirus* family, that

**Table 4** Blockade of IFN signaling

| Virus | Cellular target | Viral protein | References |
|---|---|---|---|
| Orthopoxviruses | IFNAR, PKR | IFN-I BP (B18), D9 and D10 | [216, 217], [81] |
| Sendai virus | JAK1/TYK2 phosphorylation | C | [167] |
| JEV | TYK1/STAT1 phosphorylation | NS5 | [168] |
| Paramyxovirus | STAT1 phosphorylation | V and P | [169, 170] |
| HSV-1 | STAT1 phosphorylation | ICP27 | [171] |
| DENV | STAT1 phosphorylation, STAT2, SG assembly | NS2A, NS4A, NS4B, NS5, sfRNA | [172], [180], [191] |
| HCV | STAT1 phosphorylation | NS5 | [173] |
| Rotavirus | STAT1 phosphorylation, PKR, RNaseL | NSP1, σ3, VP3 | [174], [192], [198] |
| BTV | STAT1 phosphorylation, STAT2 | NS3, NS3 | [175, 176], |
| MeV | STAT2, SG inhibition | V, C | [177, 178], [190] |
| Yellow fever virus | STAT2 | NS5 | [179] |
| PPRS | STAT2 | nsp11 | [181] |
| Simian virus 5 | STAT1 | V | [182] |
| Mumps virus | STAT1 | V | [183] |
| HPV-16 | IRF-9 | E7 | [184] |
| CMV | JAK1 and IRF-9 | | [187] |
| Murine polyomavirus | JAK1 | Large T antigen | [188] |
| FMDV | G3BP1, ISG15 | $L^{pro}$, $L^{pro}$ | [189], [209] |
| Bunyavirus | PKR | NSs | [194] |
| Coronavirus | RNaseL, ISG15 | NS2, PLP | [199], [95–97] |
| HCMV | RNaseL | pUL26, pUL50 | [210, 211], [212] |

includes MeV, peste des petits ruminants virus (PPRV) and mumps, express V and P proteins that interact directly with STAT1, inhibiting phosphorylation [169, 170]. The immediate-early protein ICP27 of HSV-1 downregulate STAT1 phosphorylation and prevent the accumulation of STAT1 in the nucleus [171]. The DENV proteins NS2A, NS4A, NS4B block the phosphorylation of STAT1 [172]. The NS5 protein of HCV interacts with STAT1, interfering with its phosphorylation [173]. Among the *Reoviridae* family, the NSP1 protein encoded by rotavirus block the phosphorylation of STAT1 [174], and the NS3 protein encoded by BTV blocks STAT1 phosphorylation [175, 176].

Many viruses target STAT2 to antagonize IFN signaling. Thus, MeV V protein binds to STAT2 [177, 178]. Yellow fever virus NS5 protein also binds STAT2 but this interaction requires STAT2 activation by IFN [179]. Other example is DENV NS5 protein acts as a bridge between UBR4 and STAT2, driving STAT2 to degradation through the proteasome [180]. The nsp11 protein of PPRS degrades STAT2 via proteasome [181]. The proteasome is not the only catabolic cellular machinery that viruses can highjack to degrade signaling components of the IFN signaling pathway. BTV was recently shown to use ubiquitination of its NS3 protein to drive STAT2 degradation by an autophagy-dependent mechanism [175].

Another strategy used by viruses includes the interference with IFN signal transduction by modification of the constitutive or basal levels of molecules involved in the JAK/STAT pathway that viruses members of the *Rubulavirus* genus like Simian virus 5, mumps virus or human parainfluenza virus type 2, use [182, 183]. The human Papillomavirus-16 (HPV-16) expresses the viral E7 protein that binds the p48 protein blocking its translocation to the nucleus, impeding the association of IRF-9 with the STAT-1/STAT-2 heterodimer (ISGF3), and thereby inhibiting the induction of IFN-I inducible genes [184].

Viruses involved in persistent infections, such as cytomegaloviruses (CMV), polyomaviruses, HCV [185], or HSV-1 [186] use similar strategies. CMV affects the expression levels of JAK1 and IRF-9 [187], and the viral large T antigen of murine polyomavirus binds to JAK1 inactivating the transduction signal through IFN receptors [188].

## Blockade of IFN induced antiviral activities

Viruses employ mechanisms that impair ISG activity to enhance their evasion from the IFN system. In this section, we will discuss some of these mechanisms. As previously mentioned, some ISG products enhance the recognition of viral PAMPs and provide the cell with effector mechanisms that block viral replication. Thus, FMDV $L^{pro}$ cleaves G3BP1, an RNA-binding protein essential to stress granules (SG) assembly, to impair the formation of these structures

[189]. MeV C protein has been involved in SG inhibition through blockade of PKR-induced SG by the activity of the adenosine deaminase acting on RNA 1 (ADAR1) [190]. DENV sfRNA can bind to various components involved in SG assembly. This property of DENV sfRNA also led to impaired ISG mRNA translation, thus dampening IFN responses [191].

To overcome recognition by ISG products, some viral mechanisms are discussed. The reovirus σ3 protein was shown to inhibit PKR activity probably through its ability to bind dsRNA [192, 193]. NSs protein from bunyavirus can promote PKR degradation [194]. Poxvirus D9 and D10 decapping enzyme promote dsRNA degradation, thus preventing PKR recognition [81]. Viruses can also highjack regulatory ISG pathways to evade ISG product action. For instance, ADAR1 is an ISG involved in RLR regulation. ADAR1 has an important physiological function as it edits adenosines to inosines in RNA, a feature that destabilize the structure of complementary dsRNA strands, thus preventing RLR or PKR recognition. This is an important mechanism in the prevention of autoimmunity, as it limits the recognition of cellular dsRNA. Viruses such as MeV, VSV or HIV-1 have been shown to use ADAR1 function to block PKR activation and thus evade translation shutdown [195–197].

Viruses can also interfere with the OAS-RNase L pathway. Rotavirus VP3 protein blocks RNaseL activation [198] by cleaving the 2′,5′-oligoadenylates produced by OAS. The NS2 protein from coronavirus murine hepatitis virus has been shown to act similarly [199].

The IFIT is another ISG that contribute to viral RNA recognition. Some viruses have developed 2′-*O* methyltransferase activities on their gene products to prevent translation blockade of their RNA by IFIT. This has been described for WNV, coronaviruses, RV and poxvirus [200–204].

The IFN-induced transmembrane proteins (IFITM) expression is greatly enhanced upon IFN activation, but these proteins are also expressed ubiquitously in the absence of IFN. The family of IFITM proteins has been shown to block IAV, WNV and DENV cell entry, a mechanism that probably involves viral hemagglutinin recognition [205]. HCoV-OC43 has been shown to highjack IFITM2 and IFITM3 for cell entry. This mechanism could be important for virus entry in lower respiratory tract under inflammatory conditions induced by IFN [206]. In HIV-1, Vpu and Env proteins can mutate to increase infectivity and overcome IFITM1-mediated restriction of replication [207]. Mutations to overcome the activity of the ISG product MxGTPase have also been described for IAV, indicating that multiple ISG products probably exert a selective pressure on viruses. For instance, pandemic avian IAV strains appear to adapt to human through evasion of the NP recognition by MxA GTPase [208].

Viruses have evolved strategies to dampen ISG15 effects on IFN signaling. For instance, the PLP from HCoV-NL63, SARS-CoV and MERS-CoV have been shown to not only act as a deubiquitinase but also as a deconjugating protease for ISG15 chains [94, 96, 97]. FMDV Lpro has also been associated with cleavage of ISG15, but instead of targeting the isopeptide bond used in ISG15 conjugation, it hydrolyzes the peptide bond preceding the ISGylation motif [209]. Human cytomegalovirus (HCMV) tegument pUL26 protein prevents ISGylation [210]. pUL26 activity appears to be supported by two other tegument proteins pUL25 and pp65 [211]. HCMV also uses another tegument protein pUL50 to affect ISGylation by targeting UBE1L, an important ligase responsible for ISG15 linkage, for proteasomal degradation [212]. Since ISGylation also regulates the activation of IFN-related pathways, some viruses have harnessed ISGylation to favor their replication. HCV has also been described to use ISGylation to favor its replication and develop persistent infections [213, 214]. Recently, ISGylation was also associated with increased replication in HBV infections [215].

Multifaceted strategies have evolved in viruses to circumvent ISG product activity and thus enhance their replication and spreading. These range from directly impairing the activity of ISG products involved in host cellular defense to highjack the IFN modulating activity of some ISG products. Understanding these mechanisms of evasion will undoubtedly shed light on some of the pathogenic processes induced by viral infections.

## Viral evasion strategies: secreted IFN binding proteins

A unique strategy to inhibit the activity of IFN was described in 1995 with the identification of a poxviral secreted IFN type I binding protein (IFN-I BP) encoded by the B18R gene of Vaccinia virus (VV) [216] a well characterized member of the Orthopoxvirus genus that contains the strains used for the efficacious worldwide vaccination campaigns against smallpox. The protein was found to be a secreted glycoprotein of about 60 kDa expressed early during infection. While its sequence is unrelated to either of the two subunits of the cellular IFN-I receptor, IFNAR1 or IFNAR2, the IFN-I BP was found to bind with high affinity ($K_D = 175$ pM for hIFNα2) to several subtypes of human IFN-Is, inhibiting their binding to the receptor and thus abrogating their biological activity [217]. In stark contrast to the high species specificity observed for the cellular receptor, the viral protein is able to bind and inhibit the activity of IFN from different species, including mouse, rat, bovine and rabbit ligands, suggesting different interaction modes. Currently, all human IFN-I molecules tested including 8 (out of 13) IFNα, IFNβ, IFNϖ as well as the more divergent IFNκ

and IFNε are known to be bound and inhibited by B18 [218–220], although with varying affinities. Interestingly, murine IFNα, but not murine IFNβ are inhibited by the poxviral IFN-I BP in spite of being bound with high affinity, as assessed by surface plasmon resonance [219, 221]. Competition studies using anti IFN monoclonal antibodies (mAbs) showed that the binding interface of IFNs with B18 is larger than the one with their cellular receptor, which could probably account for its broad species specificity and inhibitory capacity over a wide range of affinities [222].

Further examinations substantiated an additional property of the poxviral IFN-I BP which is its saturable binding to the cell surface after secretion, where the protein is active and can inhibit IFN as efficiently as the secreted one [221]. This suggested that the main site of action is the cell surface, providing local tissue protection by protecting neighboring, still uninfected cells from entering into an IFN mediated antiviral state. Examination of a truncated version of B18 expressed by the attenuated Wyeth VACCV strain lacking its third, C-terminal immunoglobulin (Ig) domain showed that cell binding capacity is mediated by the N-terminal regions of the protein [221]. Additional transfection analyses with different constructs suggested that cell binding activity is mediated by Ig domain 1, while IFN blocking activity requires Ig domains 2 and 3 [223] Site directed mutagenesis assays identified stretches of basic residues at the N terminus of B18 to mediate high affinity binding to cell surface sulfated glycosaminoglycans, preferentially heparan sulfate [224] and showed that mutants lacking GAG binding activity could still bind and inhibit IFN efficiently.

The IFN-I BP protein has been found to be conserved in other orthopoxviruses including cowpox virus and ectromelia virus (ECTV), a natural mouse pathogen, as well as the two viruses causing significant disease in humans, monkeypox virus and variola virus, the causative agent of smallpox [219]. Interestingly, the human viruses show an enhanced affinity for the human ligands, possibly reflecting the host adaptation of the virus, as occurs with other secreted cytokine binding receptors in this family. While possible orthologues can be readily found in virus species from several other poxvirus genera, these are frequently more distantly related, and their properties have not been extensively studied. The single exception to this is protein Y136 of the Tanapoxvirus Yaba-like disease virus (YLDV), a primate virus causing infection restricted to the skin. This protein, which shares only 27% aminoacid identity to the VACV B18, can bind and inhibit both human (and monkey) IFN- I as well as the more recently described family of type III IFNs [218]. The latter are a specialized group of IFNs mediating antiviral response specifically at mucosal sites without compromising barrier integrity of the epithelia and promoting long-lasting humoral and cellular responses which signal through a distinct, specific heterodimeric cellular receptor (reviewed by [225]). The authors have proposed that inhibition of these IFNs might be related to the specific tissue tropism of YLDV, although information on its role in vivo has not yet been provided.

Insights into the biological role of poxviral IFN-I BPs comes from murine infection models using VACCV and ECTV, the latter naturally causing fatal mousepox in susceptible mouse strains. Early reports showed that deletion of IFN-I BP gene from VACV attenuated the virus in vivo both in intranasal [216] as well as intracranial [217] infection models. In ECTV, absence of IFN-I BP resulted in a completely attenuated phenotype upon footpad inoculation ($LD_{50}$ reduction at least $10^7$-fold) with severely impaired dissemination of virus to its secondary replication sites, liver and spleen, as well as enhanced NK cell recruitment and both $CD4^+$ and $CD8^+$ T cell activation [226] Crucially, these effects were shown to be dependent on IFNAR signaling by the use of knockout mice. The IFN-I BP was found to bind to uninfected cells around infection foci in the liver and spleen protecting these tissues locally from IFN induced antiviral activity [227]. The biological relevance of tissue retention of this inhibitory protein was shown using recombinant ECTV that express a mutated IFN-I BP unable to bind to the cell surface but still able to inhibit IFN-I efficiently. Infection with these recombinants resulted in non-lethal infection as in the case of the virus lacking IFN-I BP altogether [228]. Interestingly, it was found that immunization of mice with recombinant IFN-I BP could prevent the development of mousepox upon challenge [226], probably through the development of antibodies capable of impairing its interaction with its ligands [227] and also pointing to a novel therapeutic target for the treatment of poxviral infections in humans.

The structure of the complex of ECTV IFN-I BP with murine IFNα-5 has been solved to high resolution (PDB entry 3OQ3, deposited by Fremont and Lee, results to be published). Comparisons with the ternary complexes of different IFN-I with their cellular receptor [229, 230] will be crucial to disentangle the structure function relationships in the interaction and inhibition of the biological activities of IFN-I ligands by the poxviral IFN-I BPs.

The particular properties of the poxviral IFN-I BP, especially its broad species and type specificity as well its high affinity have been instrumental to its use as a biotechnological tool. Thus, B18 has been used to determine the implication of IFN-I in diverse processes, such as the monocyte-derived macrophage-mediated inhibition of human cytomegalovirus (HCMV) spread [231]. In addition, recombinant oncolytic herpes simplex viruses expressing B18 have been developed to improve their infectivity in the face of antiviral responses [232]. Finally, B18 has been used to block IFNα mediated HIV associated encephalitis in a murine model [233] or to inhibit the detrimental IFN

mediated effects produced by mRNA exposure in induced pluripotent stem (iPS) cell reprogramming [234].

Secreted IFN-I BPs have been exclusively found in poxviruses to date. A recent report described the murine norovirus NS1 protein, which is secreted by an unconventional caspase-3 mediated pathway, to be essential for tuft cell infection in gastrointestinal tissue through blockade of IFN type III signaling [235]. While a direct inhibition of IFN type III could not be demonstrated in the reporter assay used, the molecular mechanism employed by this protein remains unsolved and raises the question as to whether additional and different soluble IFN-I or IFN-III BPs might be identified in other virus species.

## Concluding remarks

IFN responses are a complex and important component of the innate immune system. This is reflected in the vastness and complexity of ISGs roles, not only involved in antiviral responses but also in several immunomodulatory functions. Viruses can disrupt IFN responses leading to the antiviral state to promote their successful replication. Indeed, viruses often interfere with multiple pathways involved in the IFN response to evade innate immunity. The importance of the IFN system in host antiviral responses is highlighted by the fact that viruses dedicate some of their genetic material to encode for IFN antagonists. The viral mechanisms of IFN evasion can be mediated directly by viral gene products. Viruses also often usurp components of the cellular machinery to carry out their IFN antagonistic activity. There is no doubt that understanding how viruses evade the IFN system will shed some light on the pathogenicity and allow for a better design of therapeutic approaches. The interaction of these pathogens with the IFN system can also shed some light on some of the regulatory cellular mechanisms that control the IFN response. Studying the interaction of viral components with the IFN system remains essential to understand the pathogenesis of emergent viruses that threatened global health.

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