

Pathogenic Viruses: Smart Manipulators of the Interferon System

O. Haller¹ · (✉) · F. Weber¹

¹Abteilung Virologie, Institut für Medizinische Mikrobiologie und Hygiene,
Universität Freiburg, 79008 Freiburg, Germany
Otto.haller@uniklinik-freiburg.de

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Abstract Vertebrate cells are equipped with specialized receptors that sense the presence of viral nucleic acids and other conserved molecular signatures of infecting viruses. These sensing receptors are collectively called pattern recognition receptors (PRRs) and trigger the production of type I (α/β) interferons (IFNs). IFNs are secreted and establish a local and systemic antiviral state in responsive cells. Viruses, in turn, have evolved multiple strategies to escape the IFN system. They try to avoid PRR activation, inhibit IFN synthesis, bind and inactivate secreted IFN molecules, block IFN-activated signaling, or disturb the action of IFN-induced antiviral proteins. Here, we summarize current knowledge in light of most recent findings on the intricate interactions of viruses with the IFN system.

1 Introduction: First Inklings of a Viral IFN Antagonist

The type I IFN system provides a powerful and universal intracellular defense mechanism against viruses. Knockout mice that are defective in IFN signaling (Muller et al. 1994) quickly succumb to viral infections of all sorts (Bouloy et al. 2001; Bray 2001; Grieder and Vogel 1999; Hwang et al. 1995; Muller et al. 1994; Ryman et al. 2000; van den Broek et al. 1995). Likewise, humans with genetic defects in interferon signaling die of viral disease at an early age (Dupuis et al. 2003).

IFNs- α/β are synthesized by virus-infected tissue and specialized immune cells. After secretion into the extracellular space, these cytokines circulate in the body and cause susceptible cells to express potent antiviral mechanisms, thus limiting viral spread. Pathogenic viruses, however, have learned to manipulate the IFN system for their own sake. They have evolved efficient escape strategies allowing them to suppress IFN production, to modulate IFN signaling, and to block the action of antiviral effector proteins. This facet of the virus life cycle is only now being fully appreciated. Nevertheless, the first inklings of an anti-IFN activity were noticed early on, soon after the discovery of interferons by Isaacs and Lindenmann in 1957 (Isaacs and Lindenmann 1957). Lindenmann himself made the surprising observation that infection of cells with a live virus inhibited the subsequent induction of IFN by an inactivated virus. This phenomenon was called inverse interference and was presumably the first description of a viral IFN-suppressive function (Lindenmann 1960). Since then, great progress has been made in our understanding of how cells recognize viral intruders and how viruses manage to survive in the face of the powerful IFN system (for reviews see Garcia-Sastre and Biron 2006; Goodbourn et al. 2000; Haller et al. 2006).

2 Host Cell Recognition of Invading Viruses: An Enigma of Self–Nonself Discrimination

It has become increasingly clear that conserved molecular signatures of viruses serve as danger signals that are recognized by specialized receptors of the host cell. These receptors are collectively called pattern recognition receptors (PRRs) because they recognize a diverse range of conserved pathogen-associated molecular patterns (PAMPs) found in infectious disease agents. The main PAMP of viruses appear to be nucleic acids, such as double-stranded RNA (dsRNA). The cellular PRRs designed to sense viruses can be divided into the extracellular/endosomal toll-like receptors (TLRs) (Akira and Takeda 2004;

Bowie and Haga 2005) and the intracellular receptors RIG-I, MDA-5, and PKR (Meylan et al. 2006). Signaling through these cellular sensors activates transcription of the IFN genes (Fig. 1). RIG-I and MDA-5 act through the adaptor protein IPS-1/MAVS and the kinases TBK-1 and IKK-ε to activate the transcription factor IRF-3. A parallel pathway involves the dsRNA-binding kinase PKR, the TRAF adaptor molecules and the NF-κB kinase IKKα/β.

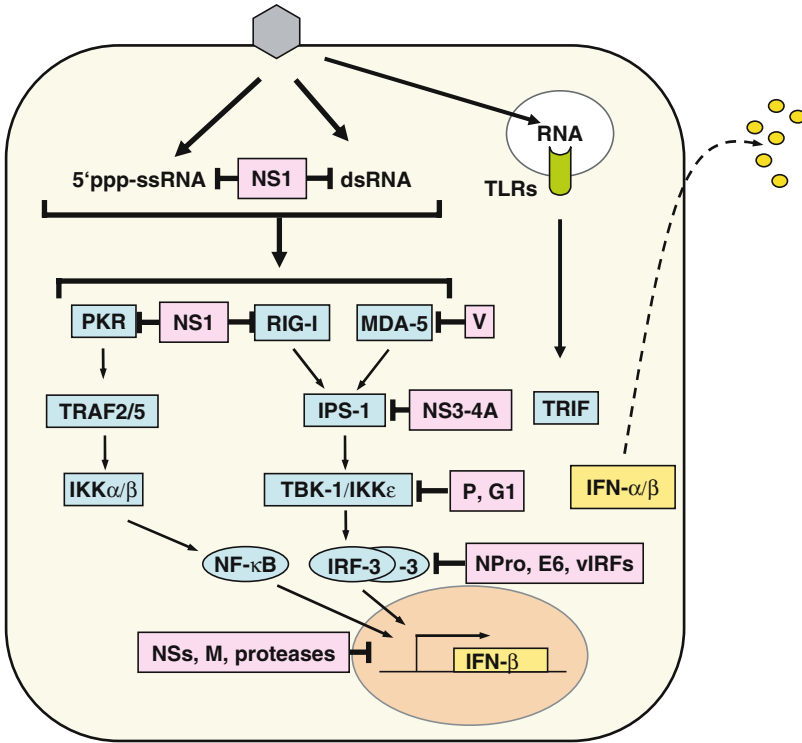


Fig.1 Viral inhibition of IFN production. Intracellular recognition of 5'-triphosphorylated ssRNA or dsRNA by the intracellular receptors RIG-I, MDA-5, and PKR leads to activation of the transcription factors IRF-3 and NF-κB via several intermediate signaling factors. The kinases TBK-1 and IKKε phosphorylate and activate IRF-3. NF-κB is mainly activated by the PKR pathway. Examples of viral IFN antagonists interfering with different steps in the IFN induction pathways are shown (see text for details)

Until very recently, it was assumed that the only molecule that clearly distinguishes viruses from their host (i.e., self vs nonself) is dsRNA, which would act as a danger signal capable of activating the IFN system. This concept was supported by data showing that many RNA and DNA viruses express proteins that bind this key molecule to avoid both IFN induction and activation of dsRNA-dependent antiviral enzymes (Jacobs et al. 1998; Langland et al. 2006). Good examples are the NS1 protein of influenza A virus (Garcia-Sastre 2001 1998; Lu et al. 1995; Min and Krug 2006), the E3L protein of poxviruses (Hornemann et al. 2003; Xiang et al. 2002), the VP35 protein of Ebola virus (Cardenas et al. 2006; Hartman et al. 2006), the sigma3 protein of reoviruses (Jacobs and Langland 1998), and the US11 protein of herpes simplex virus (Mohr 2004; Poppers et al. 2000). It came therefore as a surprise when it was realized that some viruses do not produce detectable amounts of dsRNA at all (Weber et al. 2006). This unexpected finding indicated that cells must be able to sense other viral molecules important for IFN induction. Indeed, the cytoplasmic receptor RIG-I was subsequently found to bind to the 5' end of certain viral ssRNA genomes provided they carried a 5'triphosphate group (Hornung et al. 2006; Pichlmair et al. 2006). Such 5' triphosphate moieties are usually not present on host RNA species in the cytoplasm and appear to provide an ideal recognition pattern for nonself. In line with this, it was shown that the NS1 of influenza A virus can bind ssRNA as well, and is able to form complexes with RIG-I (Mibayashi et al. 2006; Pichlmair et al. 2006).

3

Viral Subversion of Host Cell Sensors and IFN Triggering: New Approaches

To subvert innate immunity, many viruses interfere with one or several steps in the IFN induction pathway. Figure 1 shows examples of viral antagonists that work at different levels of the signaling pathway. As mentioned above, the dsRNA-binding NS1 protein of influenza A virus binds to both dsRNA and ssRNA presumably by recognizing inter- or intramolecular dsRNA regions. Importantly, NS1 also associates with RIG-I in infected cells and seems to impair its signaling function (Mibayashi et al. 2006; Pichlmair et al. 2006). In contrast, the V protein of paramyxovirus SV5 has no apparent RNA-binding activity. It inhibits IFN induction by targeting the RIG-I-related RNA sensor MDA-5 (Andrejeva et al. 2004; Childs et al. 2006). Next in line is the adaptor protein IPS-1/MAVS, which connects the RNA sensors RIG-I and MDA5 with the IRF-3 kinases TBK-1/IKK- ϵ . It is specifically cleaved by the NS3-4A protease of hepatitis C virus (HCV) and additional flaviviruses (Chen et al. 2007; Lin et al. 2006; Meylan et al. 2005)

(see also chapter by M. Gale, this volume). Activation of IRF-3 by TBK-1 is prevented by the phosphoprotein P of rabies virus (Brzozka et al. 2005) and the G1 glycoprotein of the hantavirus NY-1 (Alff et al. 2006). IRF-3 itself is degraded by the NPro proteins of pestiviruses such as classical swine fever virus and of bovine viral diarrhea virus (Bauhofer et al. 2005; La Rocca et al. 2005; Ruggli et al. 2005) via the proteasomal pathway (Bauhofer et al. 2007; Hilton et al. 2006). Also, the E6 protein of human papilloma virus 16 binds and inactivates IRF-3 (Ronco et al. 1998). A sophisticated strategy to block IRF-3 is used by certain herpesviruses. Human herpes virus 8 (HHV-8), the causative agent of Kaposi sarcoma, expresses several IRF homologs, termed vIRFs, which exert a dominant-negative effect (Burysek et al. 1999a, 1999b; Fuld et al. 2006; Li et al. 1998; Lubyova et al. 2004; Lubyova and Pitha 2000; Zimring et al. 1998).

While these IFN subversion strategies show a degree of specificity and suggest an intimate co-evolution of viruses and their immunocompetent hosts, other and more basic mechanisms are also exploited by diverse viruses. For example, viruses with a lytic life cycle can afford to target the basic cellular transcription machinery and suppress IFN gene expression through a general shutoff of host gene transcription. For example, the nonstructural NSs proteins of bunyaviruses interfere with the basic cellular transcription machinery (Billecocq et al. 2004; Le May et al. 2004; Thomas et al. 2004). Although this strategy appears to be nonspecific, *in vivo* experiments with Rift Valley Fever virus (RVFV), Punta Toro virus, and Bunyamwera virus clearly demonstrated that the biological purpose of this broad-band shut-off is to inhibit IFN synthesis (Bouloy et al. 2001; Perrone et al. 2007; Weber et al. 2002). The matrix (M) protein of vesicular stomatitis virus (VSV) is also a potent host cell shutoff factor that inhibits basal transcription (Yuan et al. 1998), impairs nuclear-cytoplasmic transport of RNAs and proteins (Her et al. 1997), and inactivates translation factors (Connor and Lyles 2002). As in the case of bunyavirus NSs, the biological significance of M-mediated shutoff is to suppress IFN induction upon VSV infection (Ferran and Lucas-Lenard 1997; Stojdl et al. 2003). Likewise, proteinases of picornaviruses (e.g., foot and mouth disease virus, Theiler's virus, poliovirus) and pestiviruses (e.g., Classical Swine fever virus) cause a shutoff of the host cell metabolism to interfere with the IFN response (de Los Santos et al. 2006; Delhaye et al. 2004; Lyles 2000; Ruggli et al. 2003, 2005; van Pesch et al. 2001).

Finally, some viruses seem to use a stealth approach: they attempt to go undetected by the sensing machinery of the cell by either disguising or invading and replicating in hidden cellular compartments. SARS coronavirus and other members of the coronavirus family do not induce IFN in certain cell types (Cervantes-Barragan et al. 2006; Spiegel et al. 2005; Zhou and Perlman 2007) and are suspected to use such trickery (Stertz et al. 2007). In addition, SARS coronavirus expresses several proteins inhibiting IRF-3 and STAT1 (Kopecky-Bromberg et al. 2006).

4 Viral Downregulation of IFN Signaling: A Top-Down Strategy

IFN- β and the various IFN- α subspecies bind to and activate a common type I IFN receptor (IFNAR), which signals to the nucleus through the so-called JAK-STAT pathway. This pathway is well characterized (Levy and Darnell 2002) and will not be described here in detail. It should be noted, however, that IFN signaling is highly regulated by cellular factors to avoid overstimulation of the system and keep a physiological balance. Negative feedback regulation is mainly mediated by IFN-induced members of the suppressor of the cytokine signaling protein (SOCS) family and the protein inhibitor of the activated STAT (PIAS) family. Essentially, SOCS members inhibit JAK tyrosine kinase activity, while PIAS members work as small ubiquitin-like modifier (SUMO) E3 ligases and inhibit transcriptional activity of activated STAT in the nucleus.

It has become increasingly clear that the IFN signal transduction pathway is also targeted by numerous viruses (Fig. 2). Different approaches are used by different viruses according to their genetic capabilities.

A seemingly simple and highly preventive strategy is used by vaccinia and other poxviruses. They express soluble IFN-binding proteins to neutralize secreted IFN molecules (Alcami and Smith 1995; Alcami et al. 2000; Puehler et al. 1998; Symons et al. 1995). These so-called viroceptors prevent the establishment of an antiviral state as well as the autocrine IFN amplification loop, which normally leads to increased IFN production.

Most viruses cannot afford the luxury of encoding viroceptors. Instead they have evolved multifunctional proteins that specifically target select components of the IFN signaling cascade. In addition, some viruses exploit the cellular feedback loop to achieve the same result. A large number of viral proteins with anti-IFN properties have been described in the past few years, and we can discuss here only a few examples.

Members of the paramyxovirus family express up to three IFN-antagonistic proteins from the P gene (named P, C, and V) that interfere with JAK-STAT function. Depending on viral origin, these IFN antagonists act either by inhibiting the JAK kinases or by binding the STAT proteins, thereby sequestering them in high molecular mass complexes or inducing their proteasomal degradation (Andrejeva et al. 2002; Garcin et al. 2002; Gotoh et al. 2003; Nanda and Baron 2006; Palosaari et al. 2003; Parisien et al. 2001; Park et al. 2003; Rodriguez et al. 2003; Shaw et al. 2004, 2005; Takeuchi et al. 2001; Ulane et al. 2003; Yokota et al. 2003). The P protein of rabies virus (a rhabdovirus) binds to tyrosine-phosphorylated STAT1 and STAT2 and retains the activated transcription factors in the cytoplasm, thereby preventing STAT-dependent expression of

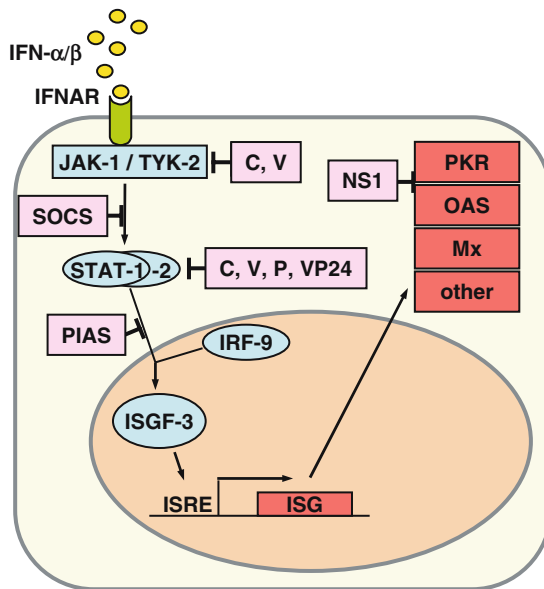


Fig. 2 Viral inhibition of IFN action. IFN- α and IFN- β bind to the type I IFN receptor (IFNAR) and activate the expression of numerous IFN-stimulated genes (ISGs) via the JAK/STAT pathway. Most viral antagonists described so far interfere on the level of either the JAK/TYK kinases or the STATs. Some also inhibit the activation and/or function of IFN-induced effector proteins (see text for details)

IFN-regulated genes (Brzozka et al. 2006). Interestingly, the paramyxoviral V protein as well as the rabies virus P protein have a dual anti-IFN function: they block both IFN induction (see above) and STAT signaling. Ebola virus, by contrast, uses a different protein, VP24, to block nuclear import of STAT by interacting with the transporter protein karyopherin alpha1 (Reid et al. 2006). STAT signaling is also disturbed by viruses causing persistent infections, such as HCV (François et al. 2000; Heim et al. 1999), herpes simplex virus (HSV) (Chee and Roizman 2004; Yokota et al. 2004), HHV-8 (Fuld et al. 2006), or cytomegalovirus (Khan et al. 2004; Zimmermann et al. 2005).

As mentioned above, some viruses exploit the cellular feedback loop to inhibit IFN signaling. HSV type 1 (HSV-1) induces SOCS-3 to downregulate JAK and STAT phosphorylation (Yokota et al. 2004). The core protein of HCV also appears to activate SOCS-3 (Bode et al. 2003), while the virulence factor NSs of RVFV activates SOCS-1 to suppress IFN action (M. Bouloy, personal communication). Again, NSs seems to have a dual function since it also inhibits IFN production by blocking IFN gene transcription (Billecocq et al. 2004).

5 Viral Inhibition of IFN Effector Proteins: A Testimony of Importance

An efficient way to escape the IFN response is to directly inhibit the specific antiviral proteins that mediate the antiviral state. The targeting of IFN-induced proteins by viral counterplayers is a telling case for the importance of these effector molecules in antiviral defense and virus–host evolution.

To date, the best studied antiviral pathways are the protein kinase R (PKR) system (Garcia et al. 2006; Williams 1999), the 2-5 OAS/RNaseL system (Silverman 1994), and the Mx system (Haller and Kochs 2002). Their importance for host survival following viral infections has been amply demonstrated (Arnheiter et al. 1996; Hefti et al. 1999; Zhou et al. 1999). Additional proteins with known antiviral activities are P56 (Guo et al. 2000; Hui et al. 2003), ISG20 (Espert et al. 2003), promyelocytic leukemia protein (PML) (Regad et al. 2001), guanylate-binding protein 1 (GBP-1) (Anderson et al. 1999), and RNA-specific adenosine deaminase 1 (ADAR1) (Samuel 2001). Mx protein expression is tightly controlled by type I IFNs, making Mx gene expression a useful marker for IFN action in clinical settings (Antonelli et al. 1999; Roers et al. 1994). In contrast, PKR and 2-5 OAS are constitutively expressed in a latent, inactive form in normal cells. Their expression is transcriptionally upregulated in IFN-treated cells. Importantly, these two enzymes need to be activated by viral dsRNA. This requirement makes them vulnerable to IFN antagonists found in many viruses. Indeed, viruses endowed with the capacity to sequester dsRNA by virtue of viral RNA-binding proteins are capable of preventing activation of PKR or the 2-5 OAS/RNaseL system (Antonelli et al. 1999; Roers et al. 1994; Weber et al. 2004). An alternative strategy used by several viruses is to encode small RNAs that compete with dsRNA for binding to PKR, thereby preventing activation. This is the case for adenoviruses (Mathews and Shenk 1991), HCV (Vyas et al. 2003), Epstein-Barr virus (EBV) (Elia et al. 1996), and HIV-1 (Gunnery et al. 1990). Some viruses express proteins that either directly bind to or otherwise inactivate PKR. For example, the γ 34.5 protein of HSV-1 triggers the dephosphorylation of eIF-2 α , thus reverting the translational block established by PKR (He et al. 1997). The E2 protein of HCV acts as pseudosubstrate for PKR (Taylor et al. 1999), as does the Tat protein of HIV-1 (Roy et al. 1990) or the K3L protein of vaccinia virus (Davies et al. 1992). Interestingly, FLUAV exploits a cellular pathway to block PKR in that it activates p58^{IPK}, a cellular inhibitor of PKR (Lee et al. 1990) and NS1 to block the 2-5 OAS/RNaseL system (Li et al. 2006; Min and Krug 2006). Poliovirus induces the degradation of PKR (Black et al. 1993). Many viruses also block the RNaseL pathway, either by expressing dsRNA-binding proteins (see above), or by other, more direct

means. Encephalomyocarditis virus as well as HIV-1 induce the synthesis of RLI, a cellular RNaseL inhibitor (Martinand et al. 1998, 1999). Infection with HSV-1 and HSV-2 activates the synthesis of 2'-5'-oligoadenylate derivatives, which bind and prevent RNaseL activation (Cayley et al. 1984). The antiviral effect of IFN is inhibited in cells infected with RSV (Atreya and Kulkarni 1999; Young et al. 2000), an effect most probably mediated by the viral NS1 and the NS2 proteins (Schlender et al. 2000; Spann et al. 2004; Wright et al. 2006).

Certain viruses induce the disruption of PML nuclear bodies (also called ND10) by proteasome-dependent degradation of PML and Sp100 (Moller and Schmitz 2003). In HSV-1 infected cells, viral ICP0 accumulates in ND10 and induces the degradation of PML and Sp100, an activity that requires the E3 ligase activity of ICP0 (Boutell et al. 2002; Van Sant et al. 2001). Similar disruptions of ND10 were observed in cells infected with CMV, EBV, HPV, and adenoviruses (Muller and Dejean 1999). It is conceivable that viruses disassemble these nuclear structures to get rid of antiviral components, but sufficient data supporting this view are not yet available.

6 The IFN Response Circuit: Inducing and Suppressing Amplification Loops

When considering the IFN-inducing and -suppressing activities of infecting viruses, it is important to keep in mind that the IFN response is generated in a cascade-like manner. As shown in Fig. 3, viral replication and genome amplification leads to accumulation of viral nucleic acids and other components that are sensed as danger signals or PAMPs. They activate the IFN induction pathway (left part of Fig. 3) via cellular sensors (RIG-I, MDA-5), adaptors (IPS-1/MAVS), protein kinases (TBK-1, IKK- ϵ), and transcription factors of the IFN regulatory factor (IRF) family (Honda and Taniguchi 2006). IFN gene expression depends on the basic cellular transcription machinery composed of the cellular RNA polymerase II (RNAPII) and essential co-factors, such as components of the transcription factor IIH (TFIIH). Secreted IFNs bind to their cognate receptors and activate the JAK-STAT signaling pathway (right part of Fig. 3), which induces the antiviral effector molecules. Most components of the IFN induction and signaling pathways are themselves IFN-inducible, representing a positive amplification loop. During viral replication, however, a number of viral IFN antagonists are produced (center part of Fig. 3) and interfere with the IFN response circuit. It is not unusual that a given virus displays more than one IFN-antagonistic protein and targets different parts of the IFN response pathway. Also, a single viral protein may inhibit quite different components of

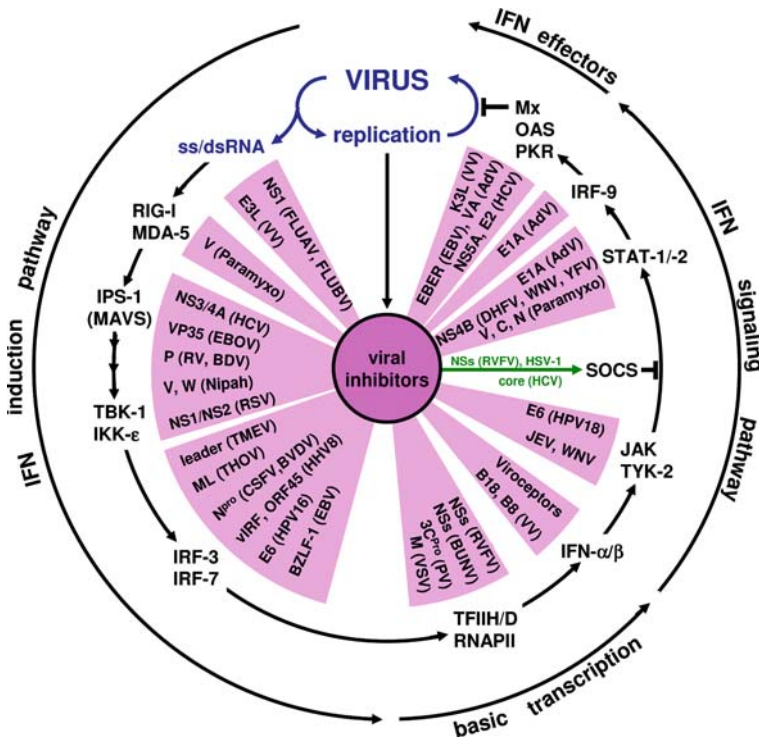


Fig.3 Induction and suppression of the IFN response circuit. Viral gene products interfere with the IFN response circuit in a negative amplification loop, resulting in a balance between virus-promoting and virus-inhibiting factors. (see text for details). (Adapted from Haller et al. 2006, with permission)

the IFN induction and signaling cascade. Thus, viral dsRNA-binding proteins have the advantage of blocking both IFN production and action. Besides, the dsRNA-binding NS1 protein of influenza A virus has additional functions and impairs also the post-transcriptional processing and nuclear export of cellular pre-mRNAs (Chen et al. 1999; Fortes et al. 1994; Kim et al. 2002; Li et al. 2001; Noah et al. 2003). Since the IFN response is generated in a cascade-like manner, viral proteins blocking one component in this circuit also affect distant signaling or effector molecules, thereby amplifying the inhibitory effect. For example, JAK-STAT inhibitors suppress not only the production of antiviral proteins, but also the expression of RIG-I, MDA-5, IPS-1/MAVS, and IRFs, which are all IFN-inducible proteins. As a consequence, a negative amplification loop is produced, which further helps the virus to suppress the IFN system as a whole.

7 Concluding Remarks

Viruses are able to negatively influence the whole spectrum of the IFN response, often affecting different parts of the IFN circuit at the same time. The interplay between viruses and the IFN system, as described here, most likely results from an evolutionary race between the two genetic systems. The race is ongoing, as emerging viruses attempt transmission across species to new hosts. This is best illustrated by recent outbreaks of SARS coronavirus or the constant threat of avian influenza A viruses to invade the human population. Our present knowledge of the IFN system and viral countermeasures is still limited. Future research should provide better insight into the intricate interplay between viruses and the innate immune defenses of the host. This knowledge is important not only for a better understanding of viral pathogenesis, but also for designing novel vaccination strategies and therapeutic approaches.

Acknowledgements We thank Peter Staeheli for critically reading the manuscript. Our own work described in the text was supported by grants from the Deutsche Forschungsgemeinschaft.

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