Review

Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures

Richard E. Randall[1] and Stephen Goodbourn[2]

[1]School of Biology, University of St Andrews, The North Haugh, St Andrews KY16 9ST, UK

[2]Division of Basic Medical Sciences, St George's, University of London, London SW17 0RE, UK

Correspondence

Richard E. Randall

rer@st-andrews.ac.uk

Stephen Goodbourn

s.goodbourn@sgul.ac.uk

The interferon (IFN) system is an extremely powerful antiviral response that is capable of controlling most, if not all, virus infections in the absence of adaptive immunity. However, viruses can still replicate and cause disease *in vivo*, because they have some strategy for at least partially circumventing the IFN response. We reviewed this topic in 2000 [Goodbourn, S., Didcock, L. & Randall, R. E. (2000). *J Gen Virol* **81**, 2341–2364] but, since then, a great deal has been discovered about the molecular mechanisms of the IFN response and how different viruses circumvent it. This information is of fundamental interest, but may also have practical application in the design and manufacture of attenuated virus vaccines and the development of novel antiviral drugs. In the first part of this review, we describe how viruses activate the IFN system, how IFNs induce transcription of their target genes and the mechanism of action of IFN-induced proteins with antiviral action. In the second part, we describe how viruses circumvent the IFN response. Here, we reflect upon possible consequences for both the virus and host of the different strategies that viruses have evolved and discuss whether certain viruses have exploited the IFN response to modulate their life cycle (e.g. to establish and maintain persistent/latent infections), whether perturbation of the IFN response by persistent infections can lead to chronic disease, and the importance of the IFN system as a species barrier to virus infections. Lastly, we briefly describe applied aspects that arise from an increase in our knowledge in this area, including vaccine design and manufacture, the development of novel antiviral drugs and the use of IFN-sensitive oncolytic viruses in the treatment of cancer.

Biology of the interferon system

The interferons (IFNs) are a group of secreted cytokines that elicit distinct antiviral effects. They are grouped into three classes called type I, II and III IFNs, according to their amino acid sequence. Type I IFNs (discovered in 1957; Isaacs & Lindenmann, 1957) comprise a large group of molecules; mammals have multiple distinct IFN-α genes (13 in man), one to three IFN-β genes (one in man) and other genes, such as IFN-ω, -ε, -τ, -δ and -κ. The IFN-α and -β genes are induced directly in response to viral infection, whereas IFN-ω, -ε, -δ and -κ play less well-defined roles, such as regulators of maternal recognition in pregnancy. Thus, rather than use the term 'type I IFN', we will use IFN-α/β when referring to the virally induced cytokines. Although the multigenic nature of IFN-α has been known for over 20 years, the significance of this is still debated – i.e. whether these genes are expressed differentially in distinct cell types, whether they are inducible by different

types of viruses or whether they are functionally specialized (Brideau-Andersen *et al.*, 2007). For the rest of this review, we will not distinguish between IFN-α subtypes. Type III IFNs have been described more recently and comprise IFN-λ1, -λ2 and -λ3, also referred to as IL-29, IL-28A and IL-28B, respectively (reviewed by Ank *et al.*, 2006; Uze & Monneron, 2007). These cytokines are also induced in direct response to viral infection and appear to use the same pathway as the IFN-α/β genes to sense viral infection (Onoguchi *et al.*, 2007). Type II IFN has a single member, also called IFN-γ or 'immune IFN', and is secreted by mitogenically activated T cells and natural killer (NK) cells, rather than in direct response to viral infection, and will not be considered in depth in this review.

IFN-α/β acts through a common heterodimeric receptor (see below), which appears to be expressed ubiquitously, to activate a signal-transduction pathway that triggers the transcription of a diverse set of genes that, in total, establish an antiviral response in target cells. These genes are referred to as IFN-inducible genes or IFN-stimulated genes (ISGs). A subset of ISGs can also be induced directly

(i.e. in an IFN-independent manner) by viral infection, perhaps offering a degree of protection in the primary infected cells, although the dramatic viral sensitivity of IFN-α/β receptor-knockout mice suggests that this is much less effective than the IFN response itself. In addition to the cell-autonomous activities of IFN-α/β, these cytokines modulate the immune system by activating effector-cell function and promoting the development of the acquired immune response. The IFN-α/β system is summarized in Fig. 1.

Type III IFNs are also secreted and bind to receptors on cells (the IL-28 receptor, which comprises a heterodimer of IL10R2 and IFNLR1) and elicit an equivalent antiviral response to IFN-α/β. Like IFN-α/β, type III IFNs can be induced in many cells but, unlike IFN-α/β, the type III IFN receptor shows a limited tissue distribution (Meager *et al.*, 2005; Mennechet & Uze, 2006; Zhou *et al.*, 2007). The role of the type III IFNs remains to be established but, to date, there is little evidence to support an essential role for host survival in response to infection.

Induction of IFN by viruses

In recent years, our understanding of the nature of the signalling processes in response to viral infection has evolved significantly. Studies on synthetic inducers of IFN throughout the late 1960s and 1970s demonstrated that double-stranded RNAs (dsRNAs), especially poly(rI). poly(rC), were extremely efficient inducers (reviewed by De Clercq, 2006). Seminal studies by Marcus and colleagues in the 1970s and 1980s generated a paradigm in which both RNA and DNA viruses induced IFN through the production of viral dsRNA (Marcus & Sekellick, 1977; Marcus, 1983). Thus, negative-stranded RNA viruses were proposed to generate a dsRNA molecule dependent upon transcription, positive-stranded RNA viruses to generate a dsRNA molecule via replication, and even DNA viruses were proposed to generate dsRNA as a result of convergent transcription.

However, whilst dsRNA, either viral or synthetic, is an efficient inducer of IFN-α/β, it is not the only inducer. There are several ways in which a cell can recognize the presence of an invading micro-organism, and multiple distinct routes by which hosts can recognize viruses and signal the induction of IFN through the recognition of pathogen-associated molecular patterns (PAMPs) by pattern-recognition receptors. The importance of any individual route of induction depends upon the specific virus, the cell being infected or the stage of infection, and requires a lot more investigation. The known routes of activation are discussed in detail below.

Before considering the specifics of each route of induction, it is worth reviewing our knowledge of the downstream components, namely the transcription factors, as these may be common to many of the induction pathways. The best-studied model for IFN-α/β induction is the production of IFN-β in fibroblastoid cells in response to either the synthetic dsRNA poly(rI).poly(rC) or to simple RNA viruses, such as Sendai virus (SeV; see Table 1 for a list
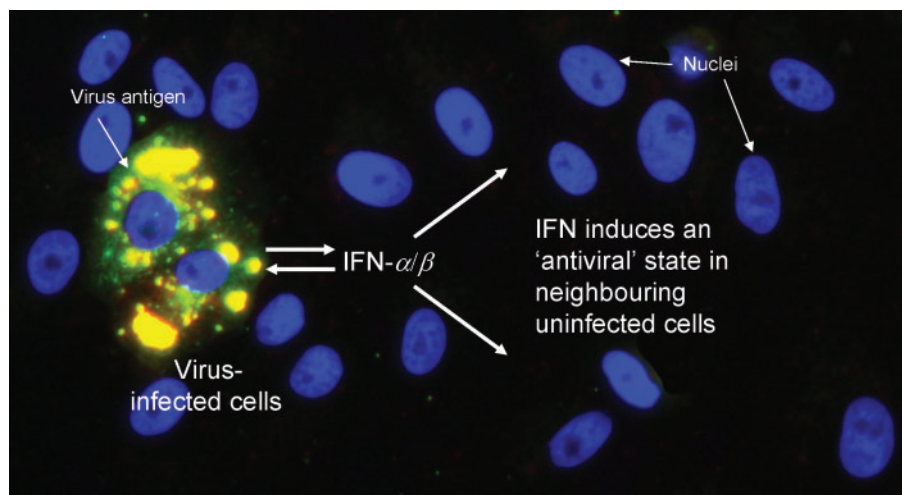

Fig. 1. Overview of the IFN-α/β system. Cells that secrete IFN-α/β have pattern-recognition receptors (PRRs) to detect molecules associated with infection. These molecules include viral nucleic acids such as dsRNA. These PRRs, once stimulated by their appropriate ligands, activate intracellular signalling cascades leading to transcription of IFN-α/β genes. Once secreted, IFN-α/β binds to the IFN-α/β receptor on neighbouring uninfected cells (as well as on the initial infected cell) and activates an intracellular signalling cascade leading to upregulation of several hundred IFN-α/β-responsive genes, many of which have direct or indirect antiviral action. Viruses released from the primary infected cell replicate inefficiently in cells that are in the antiviral state. The image shows a monolayer of cells infected at 0.01 p.f.u. per cell with PIV5 and, 24 h later, the cells were stained with antibody to the viral nucleocapsid protein (virus antigen) and DAPI (4,6-diamidino-2-phenylindole) to stain the nuclei.

Table 1. Virus abbreviations

Virus	Abbreviation
Adenovirus	AdV
African swine fever virus	ASFV
Borna disease virus	BDV
Bovine herpesvirus 1	BHV-1
Bovine respiratory syncytial virus	BRSV
Bovine viral diarrhea virus	BVDV
Bunyamwera virus	BUNV
Camelpox virus	CMLV
Canine distemper virus	CDV
Classical swine fever virus	CSFV
Cowpox virus	CPXV
Crimean Congo hemorrhagic virus	CCHV
Dengue virus	DV
Eastern equine encephalitis virus	EEEV
Ebola virus	EBOV
Ectromelia virus	ECTV
Encephalomyocarditis virus	EMCV
Epstein–Barr virus	EBV
Foot-and-mouth-disease virus	FMDV
Hantavirus	HTNV
Hendra virus	HeV
Hepatitis A virus	HAV
Hepatitis B virus	HBV
Hepatitis C virus	HCV
Herpes simplex virus	HSV
Human cytomegalovirus	HCMV
Human herpesvirus	HHV
Human immunodeficiency virus	HIV
Human papillomavirus	HPV
Human respiratory syncytial virus	HRSV
Japanese encephalitis virus	JEV
Kunjin virus	KUNV
La Crosse virus	LACV
Langat virus	LGTV
Lymphocytic choriomeningitis virus	LCMV
Mapuera virus	MPRV
Measles virus	MeV
Mumps virus	MuV
Murine cytomegalovirus virus	MCMV
Murine polyomavirus	MPyV
Myxoma virus	MYXV
Newcastle disease virus	NDV
Nipah virus	NiV
Parainfluenza virus	PIV
Poliovirus	PV
Rabies virus	RABV
Rift Valley fever virus	RVFV
Rinderpest virus	RPV
Sendai virus	SeV
Severe acute respiratory syndrome coronavirus	SARS Co-V
Simain virus	SV
Sindbis virus	SINV
Theiler's virus	TMEV
Thogoto virus	THOV
Vaccinia virus	VACV
Vesicular stomatatis virus	VSV
West Nile virus	WNV
Yaba-like disease virus	YLDV
Yellow fever virus	YFV

of virus abbreviations) or Newcastle disease virus (NDV). In this case, the induction is at the level of transcription and requires no new cellular protein synthesis, indicating that cells contain all of the required signalling components and transcription factors. In its simplest form, induction of IFN-β requires the activation of nuclear factor kappa B (NF-κB) and IFN regulatory factor-3 (IRF-3) although, as discussed below, certain other members of the ten-member IRF family (reviewed by Honda & Taniguchi, 2006; Paun & Pitha, 2007) may play a role under some circumstances.

Prior to induction, IRF-3 and NF-κB are both cytoplasmic. Upon receipt of an appropriate signal (see below), the C terminus of IRF-3 is phosphorylated, causing a conformational change leading to dimerization and the unveiling of a nuclear-localization signal (NLS) (Lin *et al.*, 1998; Dragan *et al.*, 2007; Panne *et al.*, 2007a). Translocated IRF-3 is retained in the nucleus until it is dephosphorylated (Kumar *et al.*, 2000). NF-κB is held in the cytoplasm by association with the inhibitor molecule named inhibitor of NF-κB (IκB). Signals generated during viral infection cause phosphorylation of IκB and its subsequent ubiquitination and degradation by proteasomes; freed of association with its inhibitor, the NLS of the p65 subunit of NF-κB becomes accessible and NF-κB is translocated to the nucleus (reviewed by Hayden & Ghosh, 2004; Wullaert *et al.*, 2006).

Optimal induction of the IFN-β gene also requires binding of a c-jun/ATF-2 heterodimer to the promoter. The IRF-3, NF-κB and c-jun/ATF-2 complexes assemble on the promoter in a co-operative manner to form the so-called enhanceasome, and formation of this complex is aided by the high-mobility group (HMG) chromatin-associated protein HMGI(Y) (also known as HMGA) (reviewed by Merika & Thanos, 2001). The assembled enhanceasome components aid the recruitment of CREB-binding protein (CBP)/p300 that, in turn, promote the assembly of the basal transcriptional machinery and RNA polymerase II. Although the proposed model for the IFN-β enhanceasome features HMGI(Y) as a structural component, NF-κB, IRF-3, and c-jun/ATF-2 can each form a stable structure with the promoter without HMGI(Y) (Berkowitz *et al.*, 2002; Panne *et al.*, 2004). Indeed, although HMGI(Y) could aid crystal formation, it could not be positioned within the resolved structure of NF-κB bound to the IFN-β promoter. A revision of the enhanceasome model thus suggests that any role for HMGI(Y) is limited to enhancing complex assembly through modulation of the DNA structure.

A feature of the enhanceasome model is that each of the transcription factors binds the IFN-β promoter with limited affinity and that cooperativity between factors is required for optimal induction. However, promoter-mapping studies have shown that the individual binding sites from the IFN-β promoter can respond independently to inducers and that a subset of binding sites will confer some degree of response to inducers. The consensus view is that binding of IRF-3 and/or IRF-7 (see below) is indispensable for induction, but that activation of both

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NF-κB and c-jun/ATF-2 may not be essential; indeed, IFN induction has been reported under conditions where NF-κB or c-jun/ATF-2 are not activated or their binding sites are not required (Goodbourn *et al.*, 1985; Ellis & Goodbourn, 1994; King & Goodbourn, 1994; Peters *et al.*, 2002; Poole *et al.*, 2002). Presumably, the relative contributions that the individual transcription factors make to IFN-β induction will vary depending on cell type and inducer, and there might be alternative enhanceasome structures.

An analysis of IFN-β induction is complicated by the fact that pre-treatment of cells with IFN can sometimes enhance the IFN yield (an effect called priming) and the distinct possibility of positive autoregulation, where IFN produced during the induction cycle can enhance ongoing production by inducing the synthesis of alternative signalling or transcriptional components. The production of IFN during viral infection leads to the induction of at least three transcription factors (IRF-1, IRF-7 and IRF-9) that, under some circumstances, play a role in the induction process (Matsuyama *et al.*, 1993; Kawakami *et al.*, 1995; Sato *et al.*, 1998, 2000; Honda *et al.*, 2005b). The precise role of each of these factors is unclear. IRF-7 expression levels are undetectable or very low in tissues other than plasmacytoid dendritic cells (pDCs – see below) or cells exposed to IFN. Thus, positive-feedback models have been proposed in which direct induction of the 'primary' IFN genes (IFN-β and murine IFN-α4) (Erlandsson *et al.*, 1998; Marie *et al.*, 1998) takes place, utilizing IRF-3 as the IRF family member; the IFN thus produced feeds back onto cells and induces the synthesis of IRF-7, which, in the presence of a continued infection, then enhances the transcription of the primary IFN genes and allows transcription of the 'secondary' IFN genes (the remaining IFN-α genes) (Marie *et al.*, 1998; Sato *et al.*, 1998; Prakash *et al.*, 2005). In support of this model, IRF-7 can bind to the IFN-β promoter (Wathelet *et al.*, 1998; Panne *et al.*, 2007b) and can enhance transcription dramatically (Yang *et al.*, 2004). However, in addition to this feedback role, it remains possible that, even at very low levels, IRF-7 may function as a primary transcription factor in IFN-β induction in fibroblasts. Mouse embryonic fibroblasts (MEFs) from both IRF-3$^{0/0}$ and IRF-7$^{0/0}$ mice show impaired induction of IFN-β (Sato *et al.*, 2000; Honda *et al.*, 2005b), indicating that, although neither factor is essential, both appear important in induction in these cells, although it remains uncertain whether the IRF-7 effect is direct or indirect.

Induction of the IFN-α genes is less well understood (reviewed by Civas *et al.*, 2002). In fibroblastoid cells, these genes do not display a primary induction profile, with the exception of murine IFN-α4. Unlike the IFN-β promoter, the IFN-α genes lack NF-κB sites in their promoters, but contain several binding sites for members of the IRF family, including some sites that fit poorly to the consensus. The identity of the IRF family member that stimulates IFN-α gene transcription is uncertain, but it is notable that IRF-7 has a more relaxed DNA-binding specificity for IRF sites than other members of the IRF family (Morin *et al.*, 2002), and there is considerable evidence that IRF-7 stimulates IFN-α gene transcription preferentially (Au *et al.*, 1998; Lin *et al.*, 2000), probably in association with IRF-3 (Morin *et al.*, 2002). The apparent requirement for IRF-7 is consistent with the lack of primary IFN-α gene induction in fibroblasts, where induction would be dependent upon the feedback induction of the IRF-7 gene (Yeow *et al.*, 2000).

Whilst the general applicability of this model remains to be seen, there are clearly many situations where different profiles are observed. In lymphocytes, viral infection leads to the production of IFN-α without the need to pre-produce IFN-β, indicating that these cells are somehow primed constitutively (Hata *et al.*, 2001). This may correlate with the pre-existence of IRF-7 in these cells, although the evidence for this is equivocal. However, in the case of pDCs, there is constitutive IRF-7 expression, and these cells respond to IFN inducers by making massive amounts of IFN-α/β (hence their alternative name of IFN-producing cells or IPCs). Recent work has also suggested a role for IRF-1 in the induction of IFN-β in myeloid-derived dendritic cells (mDCs) in response to the Toll-like receptor 9 (TLR9) ligand CpG (Negishi *et al.*, 2006; Schmitz *et al.*, 2007).

We will next consider the known individual routes of activation in more detail.

(i) Extracellular dsRNA or dsRNA delivered through endosomes. It has been known for over 30 years that many cell lines and cell types respond to the addition of synthetic dsRNA to the culture medium (referred to here as extracellular dsRNA). Given the size of this molecule, it seemed likely that cells either have a surface-bound dsRNA receptor or contain such a receptor in endosomes, which is activated by internalizing dsRNA by endocytosis. As the kinetics of response to extracellular dsRNA can vary widely between cells, it is probable that a dsRNA receptor can be localized in both compartments. The nature of this receptor remained elusive until 2001, when TLR3 was identified as a molecule that permitted signal responses to added dsRNA (Alexopoulou *et al.*, 2001). TLR3 shows a relatively wide tissue distribution, but is expressed at a high level in mDCs, especially the CD4$^-$CD8$^+$ subset. TLR3 relocalizes from the endoplasmic reticulum to endosomes in mDCs (Johnsen *et al.*, 2006), to lysosomes in bone marrow-derived macrophages (de Bouteiller *et al.*, 2005; Lee *et al.*, 2006) and to both endosomes and the cell surface in fibroblasts (Matsumoto *et al.*, 2002). The location of TLR3 (and, indeed of TLR7 and TLR9 – see below) enables the detection of viral nucleic acid present in the extracellular environment or produced by uncoating or degradation of entering viral particles; these features permit the development of an IFN response without the need for viral replication. Furthermore, under some circumstances, pDCs can respond through TLR3 to the dsRNA presented

in the phagocytosed apoptotic cells derived from viral infection (Schulz et al., 2005).

The importance of TLR3 in antiviral defence has been probed by using knockout mice; TLR3-deficient mice succumb to infection by murine cytomegalovirus (MCMV) due to reduced IFN production (Tabeta et al., 2004), but remain resistant to some other viruses, such as lymphocytic choriomeningitis virus (LCMV), vesicular stomatatis virus (VSV) and reovirus (Edelmann et al., 2004). Engagement of TLR3 by dsRNA triggers a complex signal-transduction pathway (summarized in Fig. 2), starting with the dimerization of TLR3 and its tyrosine phosphorylation (Sarkar et al., 2004) and recruitment of an adaptor called

Toll–interleukin (IL)-1-resistance (TIR) domain-containing adaptor inducing IFN-β (TRIF) (Hoebe et al., 2003; Yamamoto et al., 2003a), as well as phosphatidylinositol 3 (PI3) kinase (Sarkar et al., 2004). Engagement of TRIF signals the activation of both the NF-κB and the IRF-3 'arms' of the IFN-induction pathway (Jiang et al., 2004). In the NF-κB 'arm', TRIF activation leads to the recruitment of tumour necrosis factor (TNF) receptor-associated factor 6 (TRAF6) (Sato et al., 2003; Jiang et al., 2004) and receptor-interacting protein 1 (RIP1) (Meylan et al., 2004; Cusson-Hermance et al., 2005). TRAF6 recruitment and oligomerization activate its lysine 63-linked ubiquitin E3 ligase activity, leading to polyubiquitination of itself and RIP1 (reviewed by Chen, 2005). The polyubiquitin chains
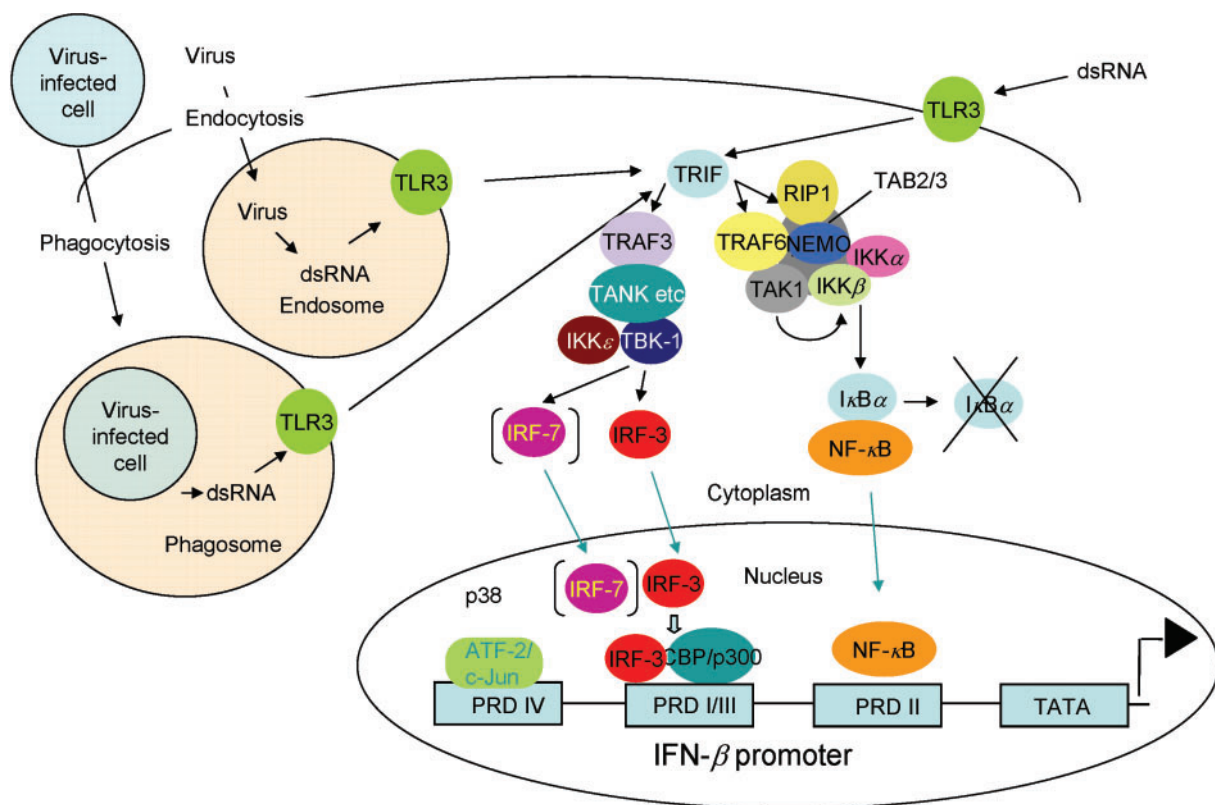

Fig. 2. TLR3-dependent signalling in response to dsRNA. dsRNA, presented to the outside of the cell or presented to endosomes by endocytosis of extracellular dsRNA, uncoating of endocytosed viral particles or degradation of engulfed apoptotic cells, binds to TLR3. Activated TLR3 recruits the adaptor TRIF that, in turn, acts as a scaffold to recruit signalling components that feed into either the IRF-3 or the NF-κB pathways. NF-κB activation requires TRAF6 and RIP1 recruitment to TRIF and their co-operation in recruiting the IKK complex and TAK1. TAK1 phosphorylates the IKKβ subunit of the IKK complex, leading to its activation and phosphorylation of IκB. Phosphorylated IκB is ubiquitinated and subsequently degraded by proteasomes, releasing NF-κB for migration to the nucleus (green arrow) and assembly on the IFN-β promoter. IRF-3 activation requires recruitment of TRAF3 to TRIF. TRAF3 binds to TANK, which then binds to TBK-1 and/or IKKε, which are activated in an uncharacterized manner and can phosphorylate IRF-3 directly. The related proteins NAP1 and SINTBAD may function in a non-redundant manner at the same level as TANK (indicated as TANK etc.). IRF-7, where present due to the feedback action of IFN, is activated by TBK-1 and IKKε in a similar manner (NB this is distinct from the TLR7- and TLR9-dependent pathway described in Fig. 3). The activated IRFs also migrate to the nucleus (green arrows) and assemble on the IFN-β promoter with NF-κB and ATF-2/c-jun, leading to the recruitment of co-factors such as CBP/p300 and RNA polymerase II and, ultimately, stimulation of transcription. See text for more details and references.

are recognized by TAK1-binding proteins 2 and 3 (TAB2 and TAB3) (Kanayama *et al.*, 2004), which chaperone transforming growth factor β-activated kinase 1 (TAK1) to the complex (Deng *et al.*, 2000; Wang *et al.*, 2001). Polyubiquitinated RIP1 is recognized by the NF-κB essential modifier (NEMO) [also known as the γ subunit of the IκB kinase (IKK) complex; Ea *et al.*, 2006; Li *et al.*, 2006a; Wu *et al.*, 2006] and thus the IKK complex is recruited to the TRIF–RIP1–TRAF6–TAB–TAK1 complex; as a result of this juxtaposition, the IKKβ subunit of the IKK complex is phosphorylated directly by TAK1 (Wang *et al.*, 2001), leading to the downstream phosphorylation of IκB, its subsequent ubiquitination and degradation and the eventual nuclear uptake of NF-κB. To emphasize the importance of the ubiquitination profile of this complex in innate immune responses, the de-ubiquitination enzyme A20 is required for the termination of TLR-dependent NF-κB activation, in a manner that requires the removal of ubiquitin from TRAF6 (Boone *et al.*, 2004).

The IRF-3 'arm' is less well understood. Activated TRIF recruits TRAF3, a molecule that is essential for IFN induction in response to TLR stimulation (Hacker *et al.*, 2006; Oganesyan *et al.*, 2006). TRAF3 interacts directly with TRAF family member-associated NF-κB activator (TANK) (Li *et al.*, 2002), a protein that also associates directly with TANK-binding kinase 1 (TBK-1) (Pomerantz & Baltimore, 1999). TBK-1 and the related IKKε (also known as IKKi) are the kinases that interact with and phosphorylate IRF-3 (Fitzgerald *et al.*, 2003; Sharma *et al.*, 2003). The associations offer a means to explain the observed recruitment of TBK-1 to TRIF in response to TLR3 stimulation (Sato *et al.*, 2003). The precise role of TANK remains uncertain, as two related proteins, NF-κB-activating kinase-associated protein 1 (NAP1) and similar to NAP1 TBK1 adaptor (SINTBAD), have also been implicated in TLR3-mediated responses (Sasai *et al.*, 2005, 2006; Guo & Cheng, 2007; Ryzhakov & Randow, 2007) and appear to have many of the same properties as TANK without apparently being redundant (Ryzhakov & Randow, 2007). It is also interesting to note that TANK interacts specifically with NEMO, suggesting a potential means to co-regulate the IRF-3 and NF-κB arms of the signalling response (Chariot *et al.*, 2002; Zhao *et al.*, 2007).

(ii) ssRNA delivered through endosomes. During some viral infections, pDCs can make up to half of the circulating IFN (reviewed by Cao & Liu, 2007). One key feature of pDCs is their TLR-expression profile. They are one of the few cell types that express TLR7, and this is expressed exclusively in endosomes. The ligands for TLR7 include immunomodulatory compounds such as imiquimod and R848 (Hemmi *et al.*, 2002; Jurk *et al.*, 2002; Heil *et al.*, 2003) and single-stranded RNA (ssRNA) molecules, either synthetic (Diebold *et al.*, 2004) or derived from viruses such as human immunodeficiency virus (HIV), influenza and VSV (Diebold *et al.*, 2004; Heil

et al., 2004; Lund *et al.*, 2004). TLR7 shows no sequence specificity for the ssRNA, requiring only the presence of several uridines in close proximity (Diebold *et al.*, 2006). Interestingly, RNA modifications such as those found in mammalian tRNA and rRNA suppress the TLR7-agonist properties, suggesting that these modifications may have evolved to enable discrimination between host and pathogen RNA (Kariko *et al.*, 2005).

Thus, pDCs can mount robust IFN responses when exposed to ssRNA viruses. Uniquely, these cells are dependent on TLRs for IFN induction by NDV, with the RNA helicases melanoma differentiation-associated gene-5 (mda-5) and retinoic acid-inducible gene-I (RIG-I) (discussed below) playing no part (Kato *et al.*, 2005). There is a functional diversity within RNA viruses, in that some (such as influenza A virus; Diebold *et al.*, 2004) can activate TLR7 signalling without the need for replication, and presumably do so as a consequence of uncoating and RNA release within the endosome, whilst others (such as VSV and SeV) require replication to activate TLR7 signalling. This observation was puzzling, because the replication would be cytoplasmic and therefore in a different subcellular compartment from TLR7. A recent observation has offered a resolution of this issue by showing that cytoplasmic material (including replicated viruses) can be engulfed by autophagy and the resultant vesicles can fuse back to endosomes to present nucleic acids to TLR7 (Iwasaki, 2007; Lee *et al.*, 2007). It remains to be seen how this system prevents the sensing and response to cellular RNAs.

The mechanism of induction of IFN follows a different profile from dsRNA-induced activation of TLR3, in that ssRNA-activated TLR7 recruits a distinct adaptor called myeloid differentiation factor 88 (MyD88) that, in turn, recruits a complex containing the kinases interleukin-1 receptor-associated kinase 4 (IRAK-4), IRAK-1 and TRAF6 (Fig. 3); there is also an involvement of TRAF3 in this process (Hacker *et al.*, 2006). TRAF6 recruitment can activate NF-κB through TAK1–TAB2–TAB3 and the canonical IKK complex, and this route is followed for NF-κB activation in response to TLR7 engagement. However, in contrast to the activation of IRF-3 seen in response to TLR3 engagement (discussed above), the unique presence of significant constitutive levels of IRF-7 in pDCs offers an alternative route for induction of IFN. In these cells, the MyD88–IRAK-1–IRAK-4–TRAF6 complex binds directly to IRF-7 (Honda *et al.*, 2004; Kawai *et al.*, 2004; Uematsu *et al.*, 2005) and TRAF6 uses its ubiquitin E3 ligase function to polyubiquitinate IRF-7 (Kawai *et al.*, 2004). This process also requires RIP1, and IRF-7 interacts preferentially with polyubiquitinated RIP1 (Huye *et al.*, 2007). Recruited IRF-7 is phosphorylated by IRAK-1 in a TBK/IKKε-independent manner and translocates into the nucleus (still in association with MyD88, TRAF6 and IRAK-1), where it can bind to DNA and stimulate transcription. Recent results also suggest a role for IKKα (Hoshino *et al.*, 2006) and osteopontin (Shinohara *et al.*, 2006) in IRF-7 activation.
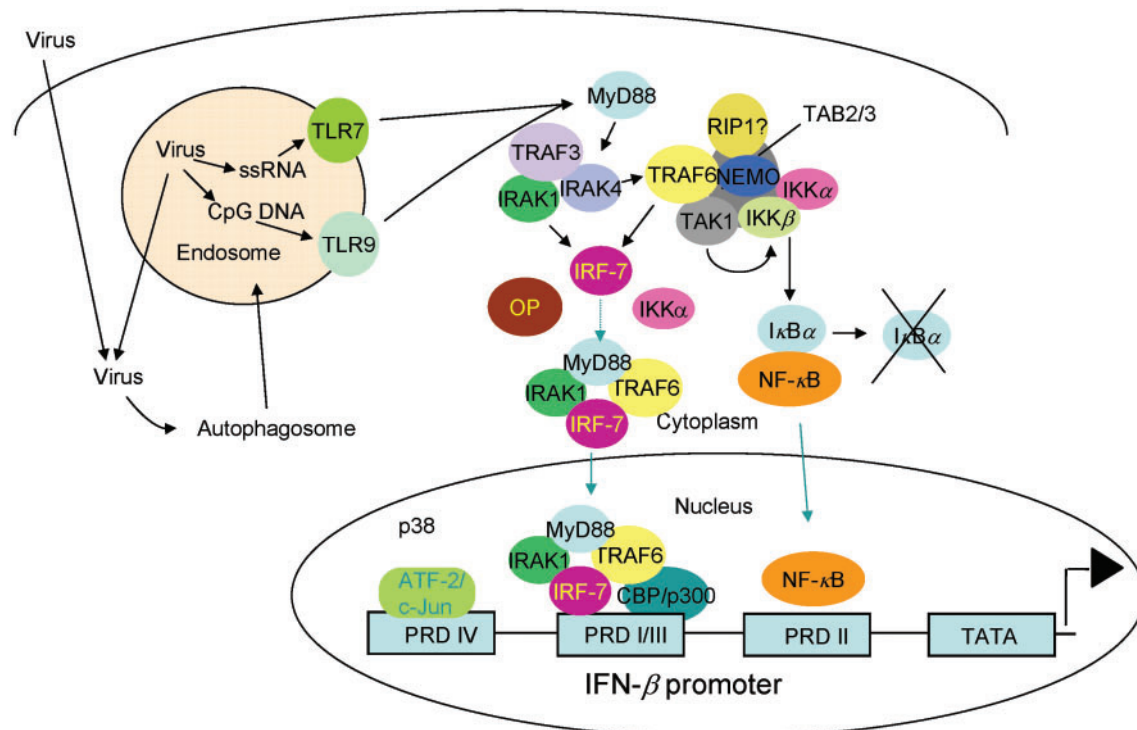
Fig. 3. TLR7- and TLR9-dependent signalling. In pDCs, ssRNA or CpG DNA is presented to TLR7 or TLR9, respectively, in endosomes by endocytosis of extracellular nucleic acids or uncoating of endocytosed viral particles, or by degradation of engulfed apoptotic cells. TLR7 is also stimulated by viral PAMPs taken into the endosomes from the cytoplasm by autophagy. Activated TLRs recruit the adaptor MyD88 that recruits IRAK-4 and IRAK-1. This complex acts as a scaffold to recruit signalling components that feed into either the IRF-7 or NF-κB pathways. NF-κB activation follows a route similar to that described in Fig. 2, although the role for RIP1 remains to be clarified. IRF-7 recruitment to the MyD88 adaptor complex requires polyubiquitination by TRAF6 in a RIP1-dependent manner. IRF-7 is phosphorylated by IRAK-1 and a complex containing IRF-7, MyD88, TRAF6, IRAK-1 and possibly IRAK-4 is released and migrates to the nucleus (green arrows). Here, it assembles on the IFN-β promoter with NF-κB and other factors, leading to the stimulation of transcription. IRF-7 can also stimulate IFN-α promoters strongly. See text for more details and references.

It should be emphasized that this mode of activation is distinct from the 'feedback' activation of IRF-7 discussed above. In the latter situation, the TBK-1 and IKKε kinases can phosphorylate the C terminus of IRF-7 in the same way as IRF-3 in the TLR3 pathway (Caillaud *et al.*, 2005). Recent evidence indicates that IRF-7 activation by this TLR-independent pathway requires the activity of the Fas-associated death domain (FADD) protein (Balachandran *et al.*, 2007). Additionally, IRF-7 can also interact with small/mothers against decapentaplegic 3 (SMAD3) to enhance induction of IFN-β in a TGF-β-dependent manner (Qing *et al.*, 2004).

(iii) DNA delivered through endosomes. Certain peripheral blood mononuclear cells (PBMCs) show responses to engulfed 'foreign' DNA and can activate IFN production. In this case, the receptor is TLR9, again localized on the endosomes, and the DNA is recognized as foreign because it is usually unmethylated (CpG), unlike host genomic DNA. The importance of TLR9 in innate antiviral immunity is illustrated by the susceptibility of TLR9-deficient mice to MCMV, as a result of reduced IFN production (Krug *et al.*, 2004; Tabeta *et al.*, 2004; Delale *et al.*, 2005).

pDCs, mDCs and macrophages each mount responses to TLR9 agonists, but these cell types use distinct signalling pathways. In pDCs, IFN induction requires endosomal retention of the CpG ligand (Honda *et al.*, 2005a) and involves a MyD88-dependent signalling pathway that is identical to the TLR7-mediated activation of IRF-7 and NF-κB, as discussed above (Fig. 3). However, mDCs are unable to retain CpG ligands in their early endosomes and are unable to use this IRF-7 pathway, although they still activate NF-κB; rather, they use IRF-1 (Negishi *et al.*, 2006; Schmitz *et al.*, 2007), which is also activated by TLR9-dependent engagement of the MyD88 adaptor and IRAK kinases.

IRF-5 is also involved in the production of IFN by pDCs in response to TLR7 and TLR9 agonists (Barnes *et al.*, 2004;

Schoenemeyer *et al.*, 2005; Takaoka *et al.*, 2005; Yasuda *et al.*, 2007). IRF-5 is not involved in IFN production by fibroblasts, but makes a contribution to serum IFN levels during viral infection (Yanai *et al.*, 2007). TLR7 or TLR9 engagement activates IRF-5 via the MyD88 pathway, as discussed above for IRF-7. Mutations in the IRF-5 promoter or allelic variations in the structure of the IRF-5 protein are associated with a predisposition to systemic lupus erythematosus (reviewed by Graham *et al.*, 2007; Kozyrev *et al.*, 2007; Kyogoku & Tsuchiya, 2007) and arthritis (Sigurdsson *et al.*, 2007).

(iv) Intracellular viral RNA. Cells possess TLR-independent pathways that respond to viral nucleic acids generated in the cytoplasm by viral replication. The activities of two widely expressed RNA helicase molecules (RIG-I and mda-5) are linked to these responses. Although the nature of the activators of RIG-I and mda-5 remain uncertain (see below), RIG-I was identified initially as an essential regulator for poly(rI).poly(rC)-induced signalling in a functional screen (Yoneyama *et al.*, 2004) and binds to poly(rI).poly(rC) *in vitro* (Rothenfusser *et al.*, 2005;

Yoneyama *et al.*, 2005). Ectopic expression of RIG-I enhances poly(rI).poly(rC) responses, and small interfering RNA (siRNA) knockdowns limit IFN-β induction by poly(rI).poly(rC) (Yoneyama *et al.*, 2004, 2005). The related protein mda-5 was identified initially as a binding partner for the IFN-induction antagonist protein of PIV5 (Andrejeva *et al.*, 2004) and has similar properties to RIG-I (Andrejeva *et al.*, 2004; Yoneyama *et al.*, 2005), although it binds less avidly to poly(rI).poly(rC). When activated, these molecules recruit and activate a mitochondrion-associated adaptor called CARD adaptor inducing IFN-β (Cardif)/virus-induced signalling adaptor (VISA)/mitochondrial antiviral signalling protein (MAVS)/IFN-β promoter stimulator protein 1 (IPS-1) (Kawai *et al.*, 2005; Meylan *et al.*, 2005; Seth *et al.*, 2005; Xu *et al.*, 2005; reviewed by Hiscott *et al.*, 2006a; Johnson & Gale, 2006; summarized in Fig. 4). Experiments with knockout mice indicate that this adaptor is essential for responses to both helicases (Kumar *et al.*, 2006; Sun *et al.*, 2006). Strikingly, although these mice have functionally intact TLR-signalling systems, they are extremely susceptible to RNA viruses, indicating that IFN production by the TLR and
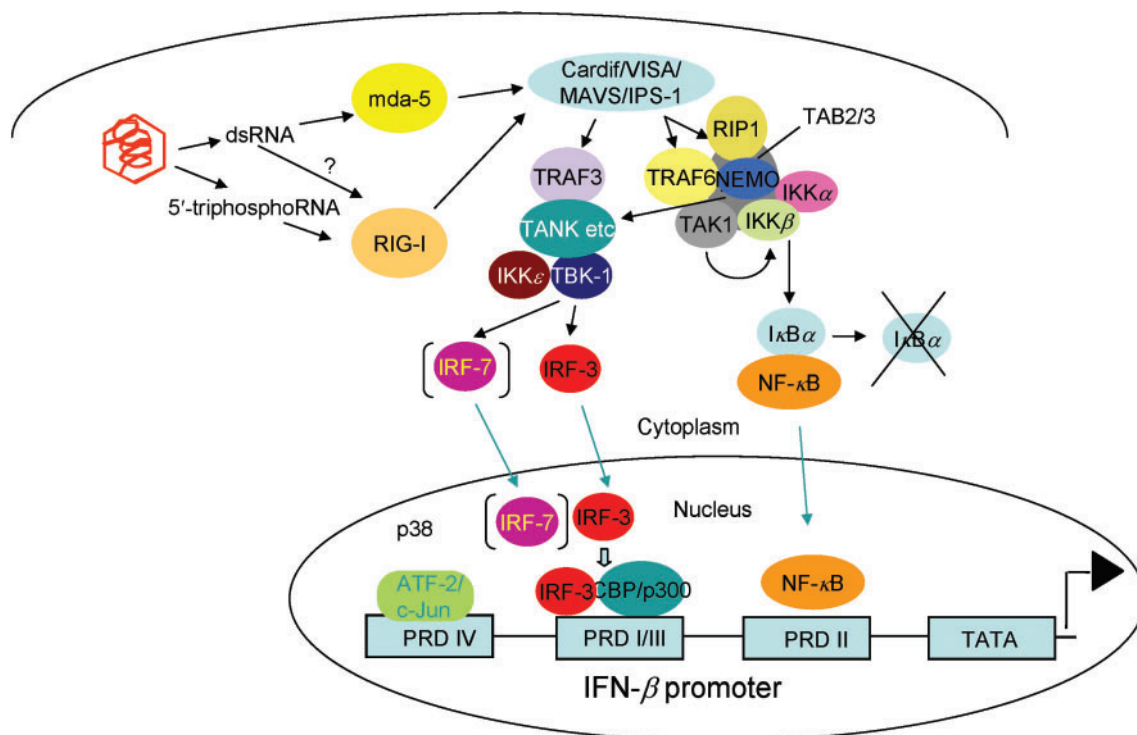

Fig. 4. mda-5- and RIG-I-dependent signalling. Viral RNA, generated in the cytoplasm by uncoating, transcription or replication, activates the RNA helicases mda-5 and RIG-I. mda-5 and RIG-I are both activated by dsRNA, whilst RIG-I can also be activated by RNA molecules with 5′ triphosphates. Both helicases have N-terminal CARD domains that recruit the adaptor Cardif/VISA/MAVS/IPS-1. This adaptor, in turn, acts as a scaffold to recruit signalling components that feed into either the IRF-3 or the NF-κB pathways. Although the details of these downstream signalling pathways remain incomplete, for Cardif/VISA/MAVS/IPS-1 activation, they seem very similar to those events described in Fig. 2 downstream of TRIF. The assembly of an enhanceasome complex on the IFN-β promoter is also equivalent to that described in Fig. 2. See text for more details and references.

helicase pathways is not redundant and that IFN production by the helicase pathway is essential for controlling infection by these viruses.

RIG-I, but not mda-5, requires ubiquitination by TRIM25 to interact with Cardif/VISA/MAVS/IPS-1 (Gack et al., 2007), and mda-5, but not RIG-I, interacts with dihydroacetone kinase in a manner that suggests its negative regulation (Diao et al., 2007), although the significance of these findings is unknown. Both RIG-I and mda-5, as well as the Cardif/VISA/MAVS/IPS-1 adaptor, interact with the atg5/atg12 components of the autophagy machinery (Jounai et al., 2007). This interaction inhibits signalling downstream of Cardif/VISA/MAVS/IPS-1. It remains to be seen whether this is a means to ensure that the induction of autophagy and IFN production are mutually exclusive in infected cells.

A third member of the helicase family (LGP2) has also been described; this protein lacks the CARD domains present in mda-5 and RIG-I and appears to function as a negative regulator of IFN production (Rothenfusser et al., 2005; Yoneyama et al., 2005; Saito et al., 2007). However, this simple model has been challenged by the phenotypes of LGP2$^{0/0}$ mice, which show unpredictable antiviral phenotypes (Venkataraman et al., 2007). Engagement of Cardif/VISA/MAVS/IPS-1 leads to independent signalling to both the NF-κB and IRF-3 'arms' of the IFN-induction pathway, as discussed above for the TLR3 adaptor TRIF. Cardif/VISA/MAVS/IPS-1 interacts directly with TRAF6 (Xu et al., 2005) and probably with TRAF3, and the activation pathways are very similar. Specifically, in the context of intracellular RNA signalling, the IKK component NEMO acts as an essential adaptor both for NF-κB activation and TBK-1/IRF-3 activation, through its interaction with TANK (Zhao et al., 2007).

The relative roles of mda-5 and RIG-I have been studied intensively to determine whether the helicases are redundant parallel sensors or whether they sense different virus-derived signals. In cell-culture systems, both mda-5 and RIG-I signal responses to transfected poly(rI).poly(rC) (Andrejeva et al., 2004; Yoneyama et al., 2004, 2005; Yamashita et al., 2005; Cardenas et al., 2006; Taima et al., 2006). Furthermore, helicase domain-swap experiments have revealed that there are no detectable differences between mda-5, RIG-I or either chimaera in their ability to respond to poly(rI).poly(rC) (Childs et al., 2007). However, studies on knockout mice indicate that mda-5 plays a much more important role than RIG-I in the regulation of total serum IFN-α/β levels in response to injected poly(rI).poly(rC) (Kato et al., 2006), in IFN-β production in poly(rI).poly(rC)-treated dendritic cells or macrophages (Gitlin et al., 2006; Kato et al., 2006) and in poly(rI).poly(rC)-transfected embryo-derived fibroblasts (Kato et al., 2006). Curiously, RIG-I plays a limited role in poly(rI).poly(rC) responses in these systems (Kato et al., 2006).

Despite the ability of both helicases to mediate responses to poly(rI).poly(rC), the two molecules differ in their abilities to recognize other types of RNA. The observation that RIG-I was much more efficient than mda-5 at responding to dsRNA generated by in vitro transcription raised the possibility that the two helicases recognized different types of structures within dsRNA. However, RIG-I can bind and respond to ssRNA molecules that contain a 5′ triphosphate (Hornung et al., 2006; Pichlmair et al., 2006). Such a triphosphate moiety is present on the RIG-I-activating in vitro-transcribed dsRNA and on many RNA molecules generated during viral replication, but absent from most cellular cytosolic RNAs. For example, cellular mRNAs have 5′ cap structures, and RNA polymerase I and most RNA polymerase III transcripts have 5′ monophosphates. Specifically, mda-5 was not activated by 5′ triphosphate-containing RNAs. The well-documented response of RIG-I to poly(rI).poly(rC) is not explained by these findings, because the bulk of poly(rI).poly(rC) contains little or no 5′ triphosphate. Probably, RIG-I can be activated by both 5′ triphosphate RNAs and dsRNAs or, alternatively, the 5′ triphosphate RNAs examined may contain some secondary structure.

Intriguingly, the magnitude of IFN induction is enhanced by the activation of RNase L (Malathi et al., 2007), an endonuclease that degrades both cellular and viral RNAs to generate short fragments with 3′ monophosphates. The induction of IFN by RNase L utilized both mda-5 and RIG-I, and the activation of both was limited by removal of the 3′ monophosphates. The authors speculate that the degradation products contain both ssRNA and dsRNA components, but these would both lack 5′ triphosphates. Overall, knowledge of the ligands for both helicases remains incomplete, and a full understanding may require the structures of the helicases to be solved.

The above properties offer some explanation for the relative importance of mda-5 and RIG-I in inducing IFNs in response to different RNA viral infections. Experiments on knockout mice show that mda-5 is essential for IFN production in response to picornaviruses (Gitlin et al., 2006; Kato et al., 2006), but is less important in responses to other types of RNA virus, such as influenza A virus, where RIG-I is critical (Kato et al., 2006). These results are consistent with the properties of mda-5 and RIG-I discussed above and the reported status of viral RNA structure generated during the viral infection. Thus, the picornaviruses poliovirus (PV) and encephalomyocarditis virus (EMCV) depend on mda-5 for IFN-β induction and generate detectable levels of dsRNA during infection, whilst influenza A virus and paramyxoviruses do not generate dsRNA and depend on RIG-I (Pichlmair et al., 2006). However, results from cell culture suggest a less clear-cut situation. Ectopic overexpression or gene knockout achieved in cell culture by using siRNA or dominant interfering forms of factors indicate a role for both RIG-I and mda-5 in IFN induction by NDV and SeV (Andrejeva et al., 2004; Yoneyama et al., 2004, 2005; Melchjorsen et al., 2005), whilst mda-5, but not RIG-I, is required for IFN-β induction by measles virus (MeV) (Berghall et al., 2006)

and picornaviruses (Kato *et al.*, 2006). In all of these experiments, it should be remembered that the viruses will often encode inhibitors of IFN induction. For example, most paramyxoviruses (including NDV, SeV and MeV) encode an inhibitor of mda-5 (the V protein) that would help to explain why mda-5 gives the impression of making only a limited contribution to IFN induction. It is also important to stress that different preparations of some viruses might produce distinct types of IFN-inducing signal and, if so, that this might influence the apparent contribution of RIG-I and mda-5 to IFN induction. For example, the optimal induction of IFN by SeV was achieved with a mixture of live virus and defective interfering (DI) particles (Johnston, 1981), due to the presence of copyback DI genomes that could self-anneal and form dsRNA (Strahle *et al.*, 2006). It is probable that, during a viral infection, cells may be exposed to and need to block signals emanating from more than one type of PAMP.

(v) Cytoplasmic DNA. Some mammalian cells, most notably macrophages and DCs, respond to 'foreign' DNA present in the cytoplasm (Ishii *et al.*, 2006; Stetson & Medzhitov, 2006a). Such DNA might be distinguished from self DNA by its lack of methylation, higher A + T content (perhaps on the basis of minor-groove topology) or cytoplasmic localization. There seems a considerable degree of disagreement in the literature about the nature of the foreign DNA-recognition system, for example over the involvement of Cardif/VISA/MAVS/IPS-1 (Stetson & Medzhitov, 2006a; Cheng *et al.*, 2007; Takaoka *et al.*, 2007) or whether NF-κB is activated (Ishii *et al.*, 2006; Stetson & Medzhitov, 2006a; Cheng *et al.*, 2007). It is possible that there are several distinct novel components, perhaps expressed in a tissue-specific manner. Studies utilizing transfected DNA generally do not investigate whether the DNA remains cytoplasmic, or indeed whether it is transcribed into RNA.

The receptor for cytoplasmic DNA is probably distinct from the TLRs and RIG-I/mda-5, and a candidate receptor molecule called DAI/DLM-1/ZBP1 was identified recently (Takaoka *et al.*, 2007). Consistent with a role in signalling responses to foreign DNA, depletion of DAI/DLM-1/ZBP1 led to a decrease in IFN-β mRNA production during herpes simplex type 1 (HSV-1), but not NDV, infection (Takaoka *et al.*, 2007). The induction of IFN-β by DAI/DLM-1/ZBP1 in response to cytoplasmic DNA involves the activation of TBK1 and IRF-3, but the potential involvement of NF-κB remains to be resolved.

(vi) Induction of IFN by viral proteins. In addition to viral nucleic acids, several viral envelopes or particles can induce IFN-α/β, although this is not a general feature of viruses. For example, HIV gp120 is a potent inducer of IFN-α/β in PBMCs (Capobianchi *et al.*, 1992), but the best-studied systems in this regard are herpesviruses. In response to exposure to either human cytomegalovirus (HCMV) or HSV-1, human fibroblasts activate IRF-3 complex

formation without new protein synthesis (Navarro *et al.*, 1998; Mossman *et al.*, 2001; Preston *et al.*, 2001). Moreover, for herpesviruses, the activation of ISGs by IRF-3 seems sufficient to establish an antiviral state without NF-κB activation or IFN production (Mossman *et al.*, 2001). Importantly, although both HCMV and HSV-1 activate IRF-3 rapidly, these viruses encode powerful antagonists of IFN production to counteract activation. Whether viral recognition at the cell surface or viral entry is required to initiate IRF-3 activation is uncertain. However, HSV-1 virions deficient in glycoprotein D (gD), gH, gB or gI were unable to activate IRF-3, suggesting that viral entry is required (Mossman *et al.*, 2001; Preston *et al.*, 2001). Similarly, HCMV-mediated ISG induction was blocked by fusion inhibitors (Netterwald *et al.*, 2004). On the other hand, soluble HSV-1 gD (Ankel *et al.*, 1998) and soluble HCMV gB (Boehme & Compton, 2004) induced IFN-β or IRF-3 activation in some cell types. In contrast to HCMV or HSV-1, Kaposi's sarcoma-associated herpesvirus (KSHV)/human herpesvirus 8 (HHV-8) virions do not activate IRF-3 or IFN-β, despite soluble envelope glycoprotein gpK8.1 doing so (Perry & Compton, 2006), suggesting that HHV-8 has evolved a mechanism to avoid this effect.

In addition to IRF-3 activation, efficient induction of IFN-β usually requires the activation of NF-κB. At low m.o.i., HSV-1 and HCMV particles do not induce NF-κB in the absence of viral replication (Paladino *et al.*, 2006), implying the existence of a signalling mechanism that activates IRF-3, but not NF-κB. Interestingly, at higher m.o.i. with HCMV, NF-κB activation and IFN-α/β production were observed (Paladino *et al.*, 2006).

Expression of MeV nucleocapsid can activate IRF-3 and cause IFN induction (tenOever *et al.*, 2002), but the generality of this phenomenon remains uncertain. Moreover, the nucleocapsid is an avid RNA-binding protein and could function simply to present RNA to the signalling system.

Macrophages and conventional DCs respond to bacterial pathogens and lipopolysaccharide (LPS) by making IFN. This activation is TLR4-dependent and, as for TLR3, TLR7/8 and TLR9 (discussed above), TLR4 activates IRF-3 in addition to NF-κB. However, TLR4 is unique among these TLRs in responding entirely to an extracellular signal. Whilst the biological significance of induction of IFN in response to LPS remains unclear, there is evidence that respiratory syncytial virus (RSV) can induce IFN synthesis through TLR4 via recognition of its F protein (Kurt-Jones *et al.*, 2000; Haynes *et al.*, 2001). Furthermore, VSV gG can activate IFN-α/β production through a TLR4-dependent pathway (Georgel *et al.*, 2007).

Although TLR4 utilizes MyD88 to activate NF-κB, it uses the same adaptor as TLR3 (namely TRIF) to activate IRF-3 (Yamamoto *et al.*, 2002; Oshiumi *et al.*, 2003). Both MyD88 and TRIF are recruited indirectly to TLR4, via the TIRAP/MyD88 adaptor-like (Mal) (Fitzgerald *et al.*,

2001; Horng *et al.*, 2001) and TRIF-related adaptor molecule (TRAM) (Yamamoto *et al.*, 2003b) proteins, respectively.

Signalling responses to IFN

The basic signalling pathway activated in response to IFN-α/β has been characterized in detail and reviewed comprehensively (Platanias, 2005; Fig. 5). Key players in this signalling pathway are the Janus/just another kinase (JAK) family (cytoplasmic tyrosine kinases that are recruited to a range of receptors in response to ligand binding) and the signal transducers and activators of transcription (STATs) (members of a family of transcription factors that are phosphorylated by JAKs and bind to DNA; reviewed by Murray, 2007).

In outline, all type I IFNs binds to a common hetero-dimeric receptor (composed of the products of the *IFNAR1* and *IFNAR2* genes), inducing oligomerization. Prior to activation, the cytoplasmic tail of IFNAR1 is associated with tyrosine kinase 2 (Tyk2) and the IFNAR2 subunit is associated with the tyrosine kinase JAK1. STAT2 is also bound to IFNAR2 before induction and is associated weakly with STAT1 (Stancato *et al.*, 1996; Precious *et al.*, 2005a; Tang *et al.*, 2007). Ligand-induced dimerization of the receptor causes a conformational change, such that Tyk2 phosphorylates tyrosine 466 on IFNAR1, creating a strong docking site for STAT2. Tyk2 then phosphorylates STAT2 on tyrosine 690, and STAT1 is phosphorylated by JAK1 on tyrosine 701; the phosphorylated STAT1 and STAT2 now form a stable heterodimer. Phosphorylation of STAT1 and its subsequent dimerization with STAT2 create a novel NLS (Banninger & Reich, 2004) and, simulta-neously, phosphorylation of STAT2 inactivates the dominant constitutive nuclear export of STAT2 (Frahm *et al.*, 2006) so that the dimers become transported into and retained in the nucleus until their dephosphorylation (reviewed by Reich & Liu, 2006). The STAT1–STAT2 complex associates with a monomer of IRF-9 to form the ISGF3 heterotrimer that binds to the IFN-stimulated response element (ISRE), present in the promoters of most IFN-responsive genes, and enhances transcription. Until recently, it was thought that the assembly of ISGF3 took place in the nucleus, but a recent study suggested that assembly may be co-ordinated at the receptor (Tang *et al.*, 2007). In response to IFN stimulation, the transcriptional co-factor CBP is recruited to the IFNAR2 chain of the receptor and catalyses IFNAR2 acetylation; the acetylation of IFNAR2 creates a docking site for IRF-9 that, in turn, also gets acetylated, as do the receptor-bound STAT1 and STAT2. Acetylation of IRF-9 is required for DNA binding, and acetylation of the STAT factors may aid ISGF3 complex assembly (Tang *et al.*, 2007).

Signalling in response to type III IFN follows a very similar pattern to that in response to type I IFN (Zhou *et al.*, 2007), and signalling in response to type II IFN also shares some features of these pathways. The IFN-γ receptor is also a heterodimeric glycoprotein, comprising two species of major subunit, IFNGR1 and IFNGR2, that pre-associate weakly in unstimulated cells. The cytoplasmic domains of the IFNGR1 and IFNGR2 receptor subunits are associated with a different set of JAKs, JAK1 and JAK2, respectively. When dimeric IFN-γ binds to the receptor subunits, the signalling pathway is initiated by triggering receptor dimerization. This brings JAK1 and JAK2 into close proximity, resulting in the activation of JAK2 which, in turn, *trans*-phosphorylates JAK1, thereby activating it. Subsequently, the activated JAKs phosphorylate a
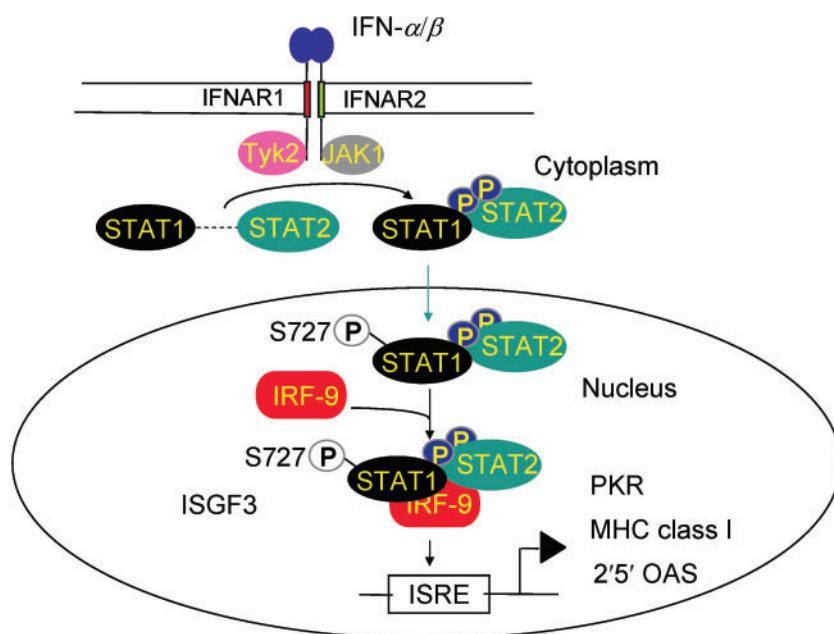

Fig. 5. Signalling pathway activated by IFN-α/β. The biological activities of IFN-α/β are initiated by binding to the type I IFN receptor. This leads to the activation of the receptor-associated tyrosine kinases JAK1 and Tyk2, which phosphorylate STAT1 on tyrosine 701 and STAT2 on tyrosine 690. Phosphorylated STAT1 and STAT2 interact strongly with each other by recognizing SH2 domains, and the stable STAT1−STAT2 heterodimer is translocated into the nucleus, where it interacts with the DNA-binding protein IRF-9. The IRF-9−STAT1−STAT2 heterotrimer is called ISGF3 and it binds to a sequence motif (the IFN-stimulated response element or ISRE) in target promoters and brings about transcriptional activation. In addition to the phosphorylation of tyrosine, STAT1 also requires phosphorylation on serine 727 for function. See text for more details and references.

tyrosine-containing region in the C terminus of IFNGR1 (between tyrosine 440 and tyrosine 444), creating a pair of binding sites for STAT1. Two STAT1 molecules then interact via their SH2 domains with IFNGR1 and are phosphorylated at tyrosine 701, resulting in their activation and dissociation from the receptor. The activated STAT1 molecules dimerize through SH2 domain–tyrosine phosphate recognition, forming a STAT1–STAT1 homodimer. This homodimer translocates to the nucleus and binds to the unique element of ISGs, the gamma-activation sequence (GAS), and stimulates transcription. Importantly, this sequence is distinct from the ISRE, and the binding of the STAT1–STAT1 homodimer does not require IRF-9.

Although not a major component in IFN-α/β signalling, STAT1 homodimers can also be activated by IFN-α/β (the so-called AAF complex) and trigger the transcription of some genes (Decker et al., 1991). Furthermore, the STAT1–STAT2 heterodimers formed by IFN-α/β stimulation bind to some promoters and stimulate transcription (Li et al., 1996), but the importance of this in the overall antiviral response is unknown.

Additional signalling pathways that can influence the outcome of IFN-induced transcription are activated by IFN (reviewed by Platanias, 2005). Transcriptional activation by STAT1, whether activated by IFN-α/β or IFN-γ, also requires phosphorylation on serine 727 for full activity and for mounting a full antiviral response. Several kinases catalyse this phosphorylation, including the protein kinase C isoform PKC-δ, which interacts directly with STAT1 (Uddin et al., 2002; Deb et al., 2003). PKC-δ is activated by the PI3 kinase pathway that is also activated by IFN-α/β (reviewed by Kaur et al., 2005). Serine 727 phosphorylation facilitates the interaction of STAT1 with the basal transcription machinery and with other adaptor proteins. STAT2 is not serine-phosphorylated in response to IFN, but it also binds CBP/p300 (see above) and facilitates interaction with the basal transcriptional machinery (Bhattacharya et al., 1996). Treatment of cells with IFN-α/β also activates the p38 MAP kinase (mitogen-activated protein kinase) pathway, which can have important effects on the antiviral programme, although the molecular basis of this is unknown (reviewed by Katsoulidis et al., 2005).

Whilst the activation of an IRF-9–STAT1–STAT2 heterotrimer is the canonical mode of ISRE activation, there are alternative transcription-factor arrangements that activate ISGs through ISREs, and which may show promoter-specific effects or distinct kinetic profiles (reviewed by van Boxel-Dezaire et al., 2006). Activation of a subset of ISRE-dependent genes by IFN-α/β depends on the phosphorylation of STAT1 on tyrosine 708 by IKKε (which is activated in infected cells) and this phosphorylation may stabilize the association of ISGF3 with these ISREs (tenOever et al., 2007). A heterotrimer containing IRF-9 and two molecules of STAT1 (as opposed to a STAT1–STAT2 pair) is activated by IFN-γ (Bluyssen et al., 1995) and activates several ISRE-containing promoters, including the CXCL10

promoter (Majumder et al., 1998). This type of complex, activated differentially by IFN-γ, may mediate the observed subtle differences in transcript profile induced by IFN-γ and IFN-α/β. STAT2–STAT2 homodimers can form a complex with IRF-9 (Bluyssen & Levy, 1997), although the biological role of this is unclear.

Importantly, many ISGs show either sustained induction in response to IFN or biphasic induction kinetics. These responses are dependent on new protein synthesis and, in many cases, depend on IRF-1, which binds to most, if not all, ISREs. In several cases, IRF-1 interacts with STAT1 for optimal transcriptional activation (e.g. Chatterjee-Kishore et al., 2000a, b). Although IRF-1 is induced by IFN-α/β and IFN-γ, it is more responsive to IFN-γ and this is probably a major reason for the difference in gene expression between the two types of IFN. Notably, all of the components of ISGF3 are themselves IFN-inducible, and the increase in subunit concentration may permit the formation of an ISGF3-like complex that does not require STAT tyrosine phosphorylation. In this context, IRF-9 induction by IFN-β requires IRF-9 and STAT1 without a requirement for STAT1 phosphorylation (Rani & Ransohoff, 2005).

Nature of the IFN-induced antiviral state

Treatment of cells with IFN-α/β upregulates the expression of several hundred genes and, in combination, these specify the antiviral state (Fig. 6). No single gene is pivotal and, for any given virus, a subset of genes is probably required to limit viral replication. Several of the upregulated genes encode enzymes that have been studied intensively and reviewed comprehensively, e.g. dsRNA-dependent protein kinase R (PKR) (Garcia et al., 2006), 2′5′-oligoadenylate synthetase (OAS) (Clemens, 2005; Silverman, 2007) and Mx (Martens & Howard, 2006; Haller et al., 2007).

(i) Protein kinase R (PKR). PKR is synthesized in an inactive form and, in response to the cofactor dsRNA, produced during viral replication, undergoes dimerization and activation. In addition to activation by dsRNA, PKR is activated by a stress-activated protein called protein kinase R (PKR)-activating protein (PACT) (Ito et al., 1999; Patel et al., 2000). The best-characterized substrate for PKR is the α subunit of the eukaryotic translational initiation factor 2 (eIF2α). Phosphorylation by PKR prevents recycling of eIF2α such that initiation is halted. Additionally, eIF2α phosphorylation can activate autophagy, by which the contents of a cell can be degraded (Talloczy et al., 2002; reviewed by Espert et al., 2007) and, for HSV-1, this limits viral replication (Talloczy et al., 2006). As discussed below, the involvement of PKR has been invoked in a number of other antiviral mechanisms, including the induction of apoptosis and cell-cycle arrest.

(ii) 2′5′ OAS. Like PKR, OAS is synthesized in an inactive form and utilizes dsRNA as a cofactor. Activation allows

OAS to oligomerize ATP through an unusual 2′5′ phosphodiester linkage, and the 2′5′-oligoadenylates bind to and activate RNase L, which degrades cellular and viral RNAs. As discussed above, the OAS/RNase L system has been linked to the induction of IFN and, as discussed below, may also affect apoptosis.

(iii) Mx. Mx and the Mx family of genes encode large GTPases related to dynamin; the precise functions of Mx and the superfamily of GTPases are unknown, but they show antiviral activity against a wide range of RNA viruses. The Mx proteins act by recognizing nucleocapsid-like structures and restricting their localization within the cell, thereby restricting virus replication. For example, human MxA recognizes the viral nucleoprotein of Thogoto virus (THOV) and prevents transport of the incoming viral nucleocapsids into the nucleus (Kochs et al., 1998; Weber et al., 2000).

(iv) ISG15, ISG54 and ISG56. In addition to PKR, OAS and Mx, other enzymes have important roles in the antiviral response. Early studies showed that several genes were upregulated dramatically in response to IFN, and these were named according to the molecular mass of the protein (e.g. ISG54 is a 54 kDa protein induced by IFN). Of all the genes upregulated by IFN-α/β, ISG15 is one of the most inducible, and yet little is known about its function (reviewed by Kerscher et al., 2006). ISG15 is related to ubiquitin and, like ubiquitin, it becomes joined covalently to many cellular proteins (Giannakopoulos et al., 2005; Zhao et al., 2005). Interestingly, ISG15 is also released from IFN-treated cells and acts as a cytokine. Evidence for the importance of ISG15 in the antiviral response comes from studies of knockout mice that are deficient in Ubp43 (also called Usp18), a deconjugating enzyme that removes ISG15 from substrates. These mice are hypersensitive to IFN and poly(rI).poly(rC) (Malakhova et al., 2003) and resistant to LCMV and VSV (Ritchie et al., 2004), and MEFs derived from these mice show restricted replication of VSV and Sindbis virus (SINV) (Ritchie et al., 2004). Similarly, siRNA directed against Ubp43 enhances the ability of IFN to inhibit hepatitis C virus (HCV) replication and infectious particle production (Randall et al., 2006). Mice lacking the *ISG15* gene are more susceptible to infection by influenza A and B viruses, SINV
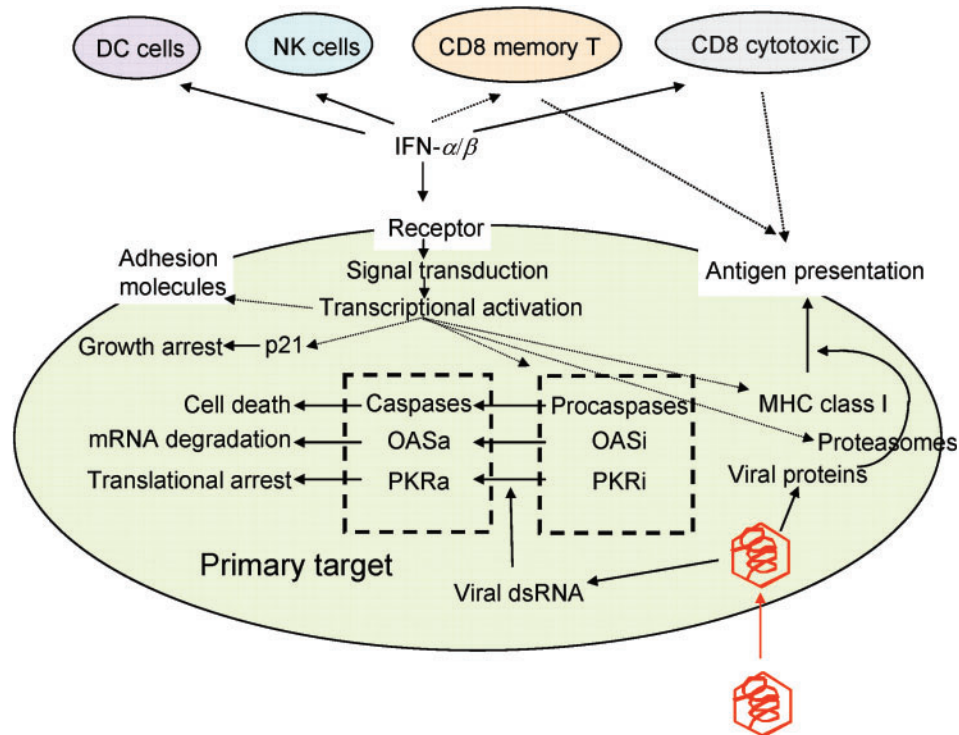

Fig. 6. Biological properties of IFN-α/β. IFN-α/β binds to its receptor and initiates the signalling programme outlined in Fig. 5. The IFN-induced transcripts encode proteins that mediate the antiviral response. Some of these proteins (e.g. PKR and OAS) are enzymes whose activities are dependent upon viral co-factors (e.g. dsRNA) and, when such co-factors are provided, the enzymes can bring about dramatic changes in cellular function (such as translational arrest). Other IFN-inducible factors trigger cell-cycle arrest (e.g. the G_1/S phase-specific cyclin-dependent kinase inhibitor p21) and others promote the presentation of viral antigens to the adaptive immune response (e.g. by upregulating MHC class I and the antigen-processing machinery). IFN-α/β also has immunomodulatory functions, by promoting the maturation of DCs, upregulating the activities of NK cells and CD8^{+} T cells and inducing the synthesis of IL-15, a factor that promotes the division of memory CD8^{+} T cells.

and several herpesviruses although, curiously, these mice show no alteration in sensitivity to VSV infection (Lenschow et al., 2007). It seems likely that ISG15 acts to upregulate the efficiency of the IFN response globally; thus, macrophages from Ubp43$^{0/0}$ mice show an increase in the strength and duration of the IFN-inducible transcription response (Zou et al., 2007) and MEFs from these mice show prolonged IFN-signalling responses (Malakhova et al., 2003). Interestingly, many of the defined substrates for ISG15 modification play important roles in the innate immune response [including JAK1, Erk1 and STAT1 (Malakhov et al., 2003), PKR, MxA and RIG-I (Zhao et al., 2005) and IRF-3 (Lu et al., 2006)], and the consequences of ISG15 conjugation include stabilizing proteins against degradation (Lu et al., 2006) and downregulating cap-dependent translation (Okumura et al., 2007). The importance of ISG15 modification is underscored by the fact that the influenza B virus non-structural protein 1 (NS1) protein interacts with ISG15 and prevents its activation and conjugation to its substrates (Yuan & Krug, 2001).

Two other highly IFN-inducible genes have attracted attention. ISG54 and ISG56 are related proteins that inhibit translation by interacting with the multiprotein translation initiation factor eIF3 complex. Human ISG56 interacts with the eIF3e subunit (Guo et al., 2000) and inhibits its ability to stabilize the eIF2–GTP–tRNAi^{Met} complex (Hui et al., 2003). Curiously, whilst murine ISG56 also targets eIF3, it does not recognize the eIF3e subunit, but rather interacts with the eIF3c subunit, a property that it shares with murine ISG54 (Terenzi et al., 2005). Murine ISG56 inhibits the ability of eIF3 to promote the formation of the eIF2–GTP–tRNAi^{Met}–mRNA–40S ribosomal subunit translational initiation complex (Hui et al., 2005).

(v) Promyelocytic leukaemia (PML) nuclear bodies. The role of PML nuclear bodies in the antiviral response has been of considerable interest recently (reviewed by Everett & Chelbi-Alix, 2007). These bodies are heterogeneous in size and composition, and so are functionally poorly defined, but contain, amongst other proteins, the IFN-inducible protein PML and other IFN-inducible proteins, such as Sp100. They play roles in transcriptional responses to stress and may regulate chromatin structure and promoter accessibility (e.g. Kumar et al., 2007). Overexpression of certain isoforms of PML impairs the replication of both RNA and DNA viruses, and depletion of key PML nuclear-body components enhances the growth of herpesviruses, indicating that the PML nuclear bodies do indeed play a role in restricting viral replication, although the details of their involvement remain to be determined. The best evidence that these functions are antiviral is that some viruses [e.g. HSV and adenovirus (AdV)] encode factors to disrupt these bodies (discussed under 'PML and PML nuclear bodies' in section on 'Viral evasion strategies').

(vi) APOBECs and TRIMs. Extensive studies on cellular genes that restrict the replication of retroviruses have revealed the existence of 'restriction factors'. These factors are members of protein families that control normal cellular functions, and the antiviral family members are evolving rapidly, suggesting that they are under positive selection pressure. The best characterized of these restriction factors are the apolipoprotein B mRNA-editing enzyme–catalytic polypeptide-like (APOBEC) 3F and 3G genes (APOBEC3F and 3G), and the unrelated tripartite motif-5α (TRIM5α) gene. Although expressed constitutively (as are many of the 'classical' IFN-response genes, such as PKR), these proteins are upregulated strongly by IFN-α/β in certain cell types (Asaoka et al., 2005; Bonvin et al., 2006; Chen et al., 2006; Peng et al., 2006; Sarkis et al., 2006; Argyris et al., 2007; Sakuma et al., 2007; Ying et al., 2007), indicative of a role in the innate immune response. APOBEC3F and 3G show antiviral activity against a range of retroviruses (reviewed by Malim, 2006; Soros & Greene, 2007) and against hepatitis B virus (HBV) (Baumert et al., 2007). The mechanism of action of these enzymes involves both cytidine deamination and subsequent mutation of template, and inhibition of reverse transcription. Both APOBEC3F and 3G can be incorporated into retroviral virions; the HIV Vif protein prevents this, and also targets these two proteins for degradation by cellular proteasomes. TRIM5α shows species-specific antiviral activity against retroviruses. For example, TRIM5α restricts HIV-1 strongly in rhesus monkeys, but only weakly in humans (Hatziioannou et al., 2004; Keckesova et al., 2004; Stremlau et al., 2004; Yap et al., 2004; Song et al., 2005). TRIM5α interacts with incoming viral capsids and forms a complex in which the virion is rendered non-infectious, at least in part by being targeted for destruction by proteasomes (reviewed by Towers, 2007).

(vii) Adenosine deaminases. Members of another class of RNA-editing enzyme, the adenosine deaminases, also function in antiviral defence (reviewed by Toth et al., 2006). Specifically, the large isoform of 'adenosine deaminase acting on RNA' (ADAR1-L) is cytoplasmic and upregulated by IFN. In vitro, this enzyme deaminates adenosines within double-stranded regions of RNA to generate inosines and this activity might thereby mutate viral RNA, although experimental evidence for this is limited. Thus, hypermutation has been observed in the genomes of distinct RNA viruses (reviewed by Cattaneo, 1994; Zahn et al., 2007), whilst the enhanced hepatitis delta virus RNA editing observed in IFN-treated cells is associated with increased ADAR1-L activity (Hartwig et al., 2006).

(viii) Viperin. Recent work has indicated that a protein referred to as viperin (also known as CMV-inducible gene 5, cig5) may play an important role in the IFN-induced antiviral response. Expression of viperin in cell-culture systems demonstrated potent antiviral activity against

HCMV (Chin & Cresswell, 2001), HCV (Helbig *et al.*, 2005), HIV (Rivieccio *et al.*, 2006), alphaviruses (Zhang *et al.*, 2007) and influenza A virus (Wang *et al.*, 2007). The mode of action of viperin is unclear, but it has recently been shown that viperin expression disrupts the formation of lipid rafts (which are important in the budding process of some viruses) on the plasma membrane by binding to and inhibiting an enzyme involved in the biosynthesis of isoprenoid-derived lipids (Wang *et al.*, 2007).

(ix) IFN-inducible microRNAs (miRNAs). Recently, it has been reported that IFN induces the expression of several cellular miRNAs and that some of these have sequence-predicted targets within HCV genomic RNA (Pedersen *et al.*, 2007). Neutralization of these miRNAs with anti-miRNAs reduced the antiviral effects of IFN-β against HCV, whilst the introduction of synthetic miRNA mimics that corresponded to these miRNAs reduced HCV replication, suggesting that IFN-inducible miRNAs may have activity against HCV (and thus potentially other viruses). However, given the high mutation rates of RNA viruses, it might be expected that viruses such HCV would rapidly evolve resistance to such miRNAs. Furthermore, as it is not clear that HCV has played a significant role in human evolution, it is debatable as to how anti-HCV IFN-inducible miRNAs might have evolved. Nevertheless, this is a potentially important area of research in which progress into the possible roles, and importance, of IFN-induced miRNAs is likely over the coming years.

(x) IFN and apoptosis. Another important function of IFNs is to establish a pro-apoptotic state in target cells (reviewed by Clemens, 2003; Maher *et al.*, 2007); this helps to remove infected cells, especially in circumstances where apoptosis depends on viral co-factors such as dsRNA. The molecular basis for the role of IFN remains unclear and there are several distinct pathways by which IFN can act. For instance, procaspase genes are IFN-inducible (Tamura *et al.*, 1996; Chin *et al.*, 1997; Dai & Krantz, 1999), and both PKR (reviewed by Garcia *et al.*, 2006) and OAS (mediated through the actions of RNase L; Castelli *et al.*, 1998) affect apoptosis and are activated by viral dsRNA. Indeed, several viruses induce apoptosis in a PKR-dependent manner (Balachandran *et al.*, 2000a; Gaddy & Lyles, 2007; Zhang & Samuel, 2007), although this is not universal (Zhang & Samuel, 2007). The apoptotic functions of PKR are sometimes mediated by eIF2α-dependent pathways (Srivastava *et al.*, 1998; Gil *et al.*, 1999; Scheuner *et al.*, 2006). dsRNA can probably activate a 'classical' apoptosis pathway similar to that activated by TNF. Consistent with this, dsRNA treatment leads to the formation of a complex containing both FADD and procaspase-8 (Iordanov *et al.*, 2005), with subsequent cleavage of procaspase-8 to the active form (Iordanov *et al.*, 2005; Takahashi *et al.*, 2006). The formation of this complex may involve PKR (Balachandran *et al.*, 1998, 2000a). Finally, the apoptosis-activating gene p53 is also IFN-inducible and can be activated indirectly in response to dsRNA or virus infection to trigger an apoptotic response (Takaoka *et al.*, 2003). Mice lacking PKR are especially sensitive to VSV (Takaoka *et al.*, 2003), whereas mice expressing an extra copy of p53 show increased resistance to VSV, due to enhanced apoptosis (Munoz-Fontela *et al.*, 2005). The mechanism linking viral infection to p53 activation remains obscure, but p53 can be phosphorylated directly by PKR, and p53 activity is enhanced by PKR (Cuddihy *et al.*, 1999a, b). However, it is unlikely that p53-mediated apoptosis is essential for clearing all types of viral infection, and one report shows that p53 actually protects cells against dsRNA-induced apoptosis (Marques *et al.*, 2005).

(xi) IFN and cell-cycle arrest. In addition to establishing an antiviral state, IFNs are often profoundly cytostatic, triggering a growth arrest at the G_1/S transition point in many cell types, and this has led to IFNs being used against a variety of cancers (reviewed by Ferrantini *et al.*, 2007). As discussed above for apoptosis, there are several mechanisms by which this is achieved. The best understood is the IFN-induced upregulation of the G_1/S cyclin-dependent kinase (CDK) inhibitor p21 (also known as pWAF, CIP), and other CDK inhibitors can also be upregulated. IFNs also upregulate the levels of a group of IFN-inducible proteins (the 'p200' family) that affect cell-cycle progression (reviewed by Asefa *et al.*, 2004). The best characterized of this group is p202 which binds to, amongst other targets, the transcription factors pRB, p53 and E2F. It also inhibits E2F-dependent gene expression of S-phase-specific genes, and it seems probable that other family members have similar activities. p53 activation may also play a role because its induction can be associated with either apoptosis or cell-cycle arrest, depending on the extent of DNA damage or the concentration of other cellular factors.

(xii) IFN-α/β in immunomodulation. Although IFN-γ plays a major role in promoting the transition from innate to adaptive immune responses, IFN-α/β is also important in this regard and has profound immunomodulatory activity (reviewed by Le Bon & Tough, 2002). The most obvious example is the upregulation of class I major histocompatibility complex (MHC) molecules and components of the antigen-presenting machinery [for example, transporter associated with antigen processing 1 (TAP-1); Epperson *et al.*, 1992]. This mechanism helps to counter the frequently observed downregulation of class I MHC associated with specific viruses, which is beyond the scope of this review. Downregulation of class I MHC leaves infected cells open to attack by NK cells. IFNs also help to activate NK cells by complex processes including the upregulation of perforin and granzymes (reviewed by Bolitho *et al.*, 2007).

IFN-α/β also has less obvious immunomodulatory functions. Production of IFN by infected cells can promote the maturation of DCs (Le Bon *et al.*, 2003) and, whilst IFN

inhibits the proliferation of naïve CD8^{+} T cells (Petricoin et al., 1997; Sun et al., 1998), it can also sustain the proliferation of antigen-specific CD8^{+} T cells (Tough et al., 1996; Marrack et al., 1999; Honda et al., 2005b; Kolumam et al., 2005; Le Bon et al., 2006). Thus, it seems likely that, once a CD8^{+} T cell has been engaged by an antigen-presenting cell (APC), the production of cytokines by that APC can play a crucial role in stimulating the expansion of the CD8^{+} T-cell clone. During viral infections, the presentation of processed antigens on MHC class I (either through direct cytoplasmic infection of the DC or, more likely, through the degradation of an engulfed infected cell, a process called cross-priming) would be accompanied by the stimulation of TLRs by the engulfed infected cell and the induction of IFN-α/β, hence ensuring the delivery of a high local concentration of cytokine to the selected CD8^{+} T cell. Interestingly, there are specialized types of CD8^{+} effector T cell that require IFN for their expansion (Honda et al., 2005b; Stetson & Medzhitov, 2006b). In addition to this mitogenic role, IFNs upregulate the effector mechanisms of cytotoxic T cells and promote NK-cell maturation. Finally, IFNs can trigger the production of IL-15 by APCs, and this cytokine plays an important role in stimulating the division of memory cytotoxic T cells (reviewed by Surh et al., 2006; Boyman et al., 2007) and the maintenance of NK-cell populations (Nguyen et al., 2002).

Viral evasion strategies

General considerations of how viruses evade the IFN response

There are five main ways by which viruses circumvent the IFN response, namely by: (i) interfering globally with host-cell gene expression and/or protein synthesis; (ii) minimizing IFN induction by limiting the production of viral PAMPs and/or by specifically blocking IFN-induction cascades; (iii) inhibiting IFN signalling; (iv) blocking the action of IFN-induced enzymes with antiviral activity; and (v) having a replication strategy that is (largely) insensitive to the action of IFN. Within each of these strategies, different viruses have evolved a great diversity of molecular mechanisms to achieve similar ends. Furthermore, to circumvent the IFN response, it may be necessary for viruses to use combinations of these strategies. Thus, if a virus blocks IFN signalling but fails to limit IFN production, the virus may not spread rapidly from the infected cell to neighbouring cells, because the latter would be in an IFN-induced antiviral state. Probably because of this, viruses that block IFN signalling often limit IFN production specifically, and some even inactivate specific IFN-induced proteins with antiviral activity, e.g. PKR.

Despite the production of some extremely powerful IFN antagonists, there must be a balance between the ability of viruses to block the IFN response and the cells' ability to produce and respond to IFN. Consistent with this, many wild-type viruses form bigger plaques on cells engineered to be non-responsive to IFN than on the parental cells

(Young et al., 2003). Consequently, until viruses can synthesize enough of the viral IFN antagonist(s) to limit the IFN response, it is also important for viruses to keep production of any potential inducer(s) of IFN to a minimum. This may manifest itself in the mode and kinetics of virus transcription and replication. Indeed, any viral defect, be it in attachment, entry, RNA synthesis or packaging, has the potential to tip the balance of this race against the virus. This implies that, in a normal acute infection, the IFN response probably constitutes a constant selective pressure that keeps viruses maximally fit in terms of replication speed and competence, and in the maintenance of mechanisms to circumvent the IFN response. It also suggests that the efficiency by which a given virus overcomes the IFN response may be extremely important in terms of its pathogenesis and host range (Young et al., 2003).

Viral IFN antagonists are often multifunctional proteins and their different properties may vary in importance at different stages of the virus replication cycle. For example, the NS1 protein of most strains of influenza A virus blocks expression of cellular genes by interfering with stability, processing or export of mRNA from the nucleus (Fortes et al., 1994; Chen et al., 1999; Li et al., 2001b; Kim et al., 2002; Noah et al., 2003; Satterly et al., 2007). However, the NS1 protein of some influenza virus strains also inhibits RIG-I-mediated inhibition of the IFN pathway (Guo et al., 2006; Opitz et al., 2006; Pichlmair et al., 2006; Mibayashi et al., 2007). This may be because there is a window of opportunity for an infected cell to respond to influenza virus infection before the NS1 protein accumulates to sufficient levels to block cellular mRNA processing and export from the nucleus completely. However, influenza viruses may also be able to exploit this window to upregulate specific cellular genes to their own advantage, e.g. by the NS1 protein activating PI3 kinase (Hale et al., 2006; Ehrhardt et al., 2007; Shin et al., 2007). In addition to these properties, NS1 also binds dsRNA (and thus blocks OAS activity) and interacts with PKR to block its activity (all of these activities are described in more detail below). Thus, the relative affinity of NS1 for its cellular targets, its cellular location and the relative abundance of free NS1 will all influence the biological properties of NS1 at any given point in the virus replication cycle. However, it should be noted that although a great many viral IFN antagonists with multiple functions have been identified in vitro by using genetic approaches, often there is no formal proof that the supposed targets have relevance in vivo. One approach to address such questions is to infect animals with null mutations in host defence genes with (recombinant/mutant) viruses with specific defects in their IFN antagonist(s) in order to provide a formal genetic test for identifying in vivo mechanisms and targets of virus virulence (Leib et al., 2000).

Whilst over the last few years we have learnt a great deal about the molecular mechanisms of how different viruses block the IFN response, it is less clear what all the biological

consequences may be, both for the virus and host. Undoubtedly the mechanism employed by a given virus to circumvent the IFN response will be a major factor that will influence the molecular pathogenesis of virus infections. This may be especially true for simple RNA viruses, where most of the virus-encoded proteins will be involved in virus replication rather than in 'luxury' functions.

(i) Interfering with host gene expression and/or protein synthesis globally. Many viruses that cause acute infections have developed a variety of mechanisms to inhibit cellular protein expression globally, including inhibition of cellular gene transcription, mRNA processing or export or cellular protein synthesis (specific examples of how viruses inhibit cellular protein expression are illustrated in Table 2). Whilst many host-cell functions will be affected by general inhibition of cellular gene expression, there is good evidence that one major reason that viruses do this is to circumvent the IFN response. For example, the NSs protein of Bunyamwera virus (BUNV) inhibits cellular mRNA transcription by blocking the activity of RNA polymerase II (Thomas *et al.*, 2004). However, a recombinant BUNV that does not encode a NSs protein is pathogenic in IFN-α/β receptor-knockout mice and grows to high titres in cells that do not produce IFN (Weber *et al.*, 2002; Young *et al.*, 2003). Similarly, the NSs protein of La Crosse virus (LACV) serves primarily to suppress the IFN response of mammalian hosts (Blakqori *et al.*, 2007). A mutation in the VSV matrix (M) protein (which, in wild-type virus, causes a general inhibition of host-cell transcription and translation) also leads to an attenuated virus with efficient IFN-β-inducing properties (Ferran & Lucas-Lenard, 1997). Similarly, foot-and-mouth-disease virus (FMDV) L proteinase shuts off host-cell protein synthesis, and mutation of this protein generated an attenuated strain that induced elevated levels of IFN-α/β (Chinsangaram *et al.*, 1999).

Whilst there are many potential advantages in having a mechanism that prevents host-cell gene expression in some way, there are also many disadvantages. On the upside, by inhibiting cellular gene expression, the cell will not produce IFN (or other cytokines) or respond to IFN by upregulating the production of IFN-inducible proteins. On the downside, if a virus inhibits host-gene expression, then the cell will die fairly rapidly and thus the virus will have only a limited time to replicate. Also, by inhibiting global expression of cellular proteins, the virus will be unable to manipulate the cell to its own advantage, e.g. by forcing it to enter the cell cycle to provide the enzymes that might be necessary for virus replication. Furthermore, a virus cannot establish a persistent or latent infection in cells in which

Table 2. Examples of viruses that inhibit host-cell gene expression globally

Mode of action	Virus	References
Virus-encoded proteases cleave translation initiation factor eIF4-G, poly(A)-binding protein, TATA box-binding protein (TBP) and other cellular factors, including nucleoporins	PV	Etchison *et al.* (1982); Clark *et al.* (1993); Das & Dasgupta (1993); Yalamanchili *et al.* (1996); Gradi *et al.* (1998); Joachims *et al.* (1999); Gustin & Sarnow (2001); Belov *et al.* (2004)
Virus-encoded proteases cleave translation initiation factors eIF4-G and eIF4A	FMDV	Devaney *et al.* (1988); Kirchweger *et al.* (1994); Chinsangaram *et al.* (1999); Belsham *et al.* (2000); Li *et al.* (2001a); de Los Santos *et al.* (2006)
M protein inhibits host-cell transcription and translation	VSV	Ferran & Lucas-Lenard (1997); Her *et al.* (1997); Ahmed & Lyles (1998); Yuan *et al.* (1998); Connor & Lyles (2002, 2005); Ahmed *et al.* (2003); Stojdl *et al.* (2003); Whitlow *et al.* (2006)
Disrupts nucleocytoplasmic transport and affects translation of capped mRNAs	EMCV	Svitkin *et al.* (2005); Porter *et al.* (2006)
L protein interacts with Ran-GTPase to interfere with nucleocytoplasmic trafficking	TMEV	van Pesch *et al.* (2001); Delhaye *et al.* (2004); Porter *et al.* (2006)
Virus-encoded NS1 protein inhibits processing and export of cellular mRNAs	Influenza A virus	Fortes *et al.* (1994); Chen *et al.* (1999); Li *et al.* (2001b); Kim *et al.* (2002); Noah *et al.* (2003); Satterly *et al.* (2007)
Virion host-cell shut off protein [vhs/U(L)41] together with ICP27 interfere with host-cell transcription and mRNA stability	HSV-1	Everly *et al.* (2002); Murphy *et al.* (2003); Chee & Roizman (2004); Doepker *et al.* (2004); Smiley (2004)
Virus-encoded NSs protein inhibits RNA polymerase II (RNAP II) to inhibit host-cell transcription	BUNV	Weber *et al.* (2002); Thomas *et al.* (2004)
Virus-encoded NSs protein inhibits host-cell transcription by interacting with the transcription factor TF$_{II}$H	RVFV	Bouloy *et al.* (2001); Billecocq *et al.* (2004); Le May *et al.* (2004)
Capsid protein, mechanism unknown	EEEV	Aguilar *et al.* (2007)
nsP2 inhibits cellular transcription (and translation)	SINV	Frolova *et al.* (2002); Gorchakov *et al.* (2005); Garmashova *et al.* (2006)

cellular protein synthesis is inhibited. Cells in which cellular protein synthesis is blocked might also be killed more rapidly by other innate immune responses, including the induction of apoptosis by cytokines such as TNF. It may be for these reasons that other viruses have evolved more subtle means to circumvent the IFN response.

(ii) Minimizing IFN production. As discussed above, different viruses, different virus strains and even different laboratory preparations of the same virus strain can vary considerably in their ability to induce IFN. The amount of IFN induced by a virus is dependent upon a number of factors that include (i) the amount and type of IFN inducer(s) produced by virus infection (this can be influenced heavily by the presence of DI particles), (ii) whether a virus produces a specific inhibitor of the IFN-induction pathways, its mode of action and its kinetics of synthesis, and (iii) the type of cell infected. Furthermore, the source of the virus may influence the induction of IFN. Thus, it has been reported that alphaviruses derived from mosquito cells induce less IFN than viruses derived from mammalian cells and that this might have an impact on the ability of the mosquito-borne virus to transfer to the vertebrate host (Shabman et al., 2007).

Clearly, in vivo, it would be expected that viruses would keep the production of viral PAMPs to a minimum. This may be achieved by having a replication strategy that minimizes the production of PAMPs by: (i) tightly controlling virus transcription and replication to minimize the production of PAMPs such as dsRNA [e.g. poxviruses minimize the production of overlapping mRNAs by (a) transcribing genes in blocks in the same direction and (b) having multiple transcriptional terminators in intergenic regions where two early genes are transcribed convergently; reviewed by Smith et al., 1998]; (ii) encapsidating both genomic and antigenomic RNA, in the case of negative-strand RNA viruses; (iii) protecting the 5′ end of their mRNA from recognition by RIG-I, e.g. by capping their mRNAs (e.g. paramyxoviruses) or 'cap-snatching' (e.g. influenza viruses), coupling a protein to the 5′ end of their RNA (e.g. picornaviruses) or not having 5′ triphosphate ends of the genomic RNAs (e.g. hantaviruses); (iv) integrating their genomes into host chromosomes and thereafter using cellular machinery for virus transcription and replication (retroviruses); (v) 'hiding' any viral PAMPs from their cellular receptors (e.g. by positive-strand RNA viruses replicating within intracellular membrane vesicles).

However, it is likely that small amounts of dsRNA are produced as a by-product of the replication of most viruses and, thus, many viruses produce dsRNA-binding proteins that sequester dsRNA. This strategy has the additional advantage that it also minimizes the dsRNA-dependent activation of antiviral gene products such as PKR, OAS and ADAR, as well as blocking dsRNA-induced apoptosis. The reovirus major outer capsid protein sigma3 is a dsRNA-binding protein (Imani & Jacobs, 1988; reviewed by Jacobs & Langland, 1998; Olland et al., 2001), as is the sigma A

protein of avian reovirus (Martinez-Costas et al., 2000) and the NSP3 protein of porcine rotaviruses (Langland et al., 1994). Reovirus strains vary significantly in their abilities to induce IFN-α/β (reviewed by Samuel, 1998), and strain differences in IFN sensitivity have been linked to differences in dsRNA affinity of the sigma3 protein (Bergeron et al., 1998). The E3 protein of vaccinia virus (VACV) (Chang et al., 1992) also binds dsRNA, as does the US11 protein of HSV-1 and the VP35 protein of Ebola virus (EBOV) (Cardenas et al., 2006; Hartman et al., 2006; Feng et al., 2007). However, as with the NS1 protein of influenza A viruses (below), the importance of the dsRNA-binding activity of the VP35 protein of EBOV in blocking IFN induction is not clear (Cardenas et al., 2006; Feng et al., 2007). The nuclear protein BS-MLF1 (SM) of Epstein–Barr virus (EBV) (Poppers et al., 2003) and TRS1 protein of HCMV (Cassady, 2005; Hakki & Geballe, 2005) bind dsRNA, whilst the m142 and m143 proteins of MCMV form a heterodimeric complex that binds dsRNA (Child et al., 2006; Valchanova et al., 2006). Furthermore, even though dsRNA is present in very low amounts in cells infected with negative-strand RNA viruses, including influenza virus (Weber et al., 2006), the NS1 protein of influenza virus has a dsRNA-binding motif (Lu et al., 1995). Whilst the primary function of this domain may be to mop up dsRNA to prevent activation of OAS (Min & Krug, 2006), depending on the virus strain (Hayman et al., 2006; Kochs et al., 2007), it may also play an important role in preventing dsRNA-mediated induction of IFN (Talon et al., 2000a; Wang et al., 2000; Li et al., 2006b). Several other viral IFN antagonists, e.g. the HBV core antigen (Twu & Schloemer, 1989; Whitten et al., 1991), may block IFN production at the transcriptional level by sequestering dsRNA.

Intriguingly, there are examples of virus proteins that intervene specifically at most points in IFN-induction cascades (Fig. 7; Table 3). Bovine viral diarrhea virus (BVDV) secretes a glycoprotein termed E^{rns} with dsRNA-binding and RNase activities that blocks the ability of extracellular dsRNA to activate TLR3 (Iqbal et al., 2004). This may play an important role in preventing the induction of IFN by released PAMPs/apoptotic bodies in neighbouring or immune cells, such as pDCs. The NS3/4a protein of HCV cleaves the TLR3 adaptor protein TRIF, thereby blocking TLR3 signalling (Li et al., 2005a). VACV proteins A52 and A46 target multiple TIR proteins, including TRIF, to block TLR3 and TLR4 induction of IFN (Harte et al., 2003; Stack et al., 2005). Other viruses can block TLR3 (and TLR7, 8 and 9, e.g. RSV and MeV; Schlender et al., 2005) signalling by inhibiting downstream intracellular signalling components such as TBK and IRF-3 (below). The need to block TLR signalling within infected cells (including pDCs that may be infected productively or abortively) may reflect a requirement to prevent IFN induction through TLR activation following autophagy-dependent viral recognition (Lee et al., 2007). Furthermore, the need to limit IFN induction by this
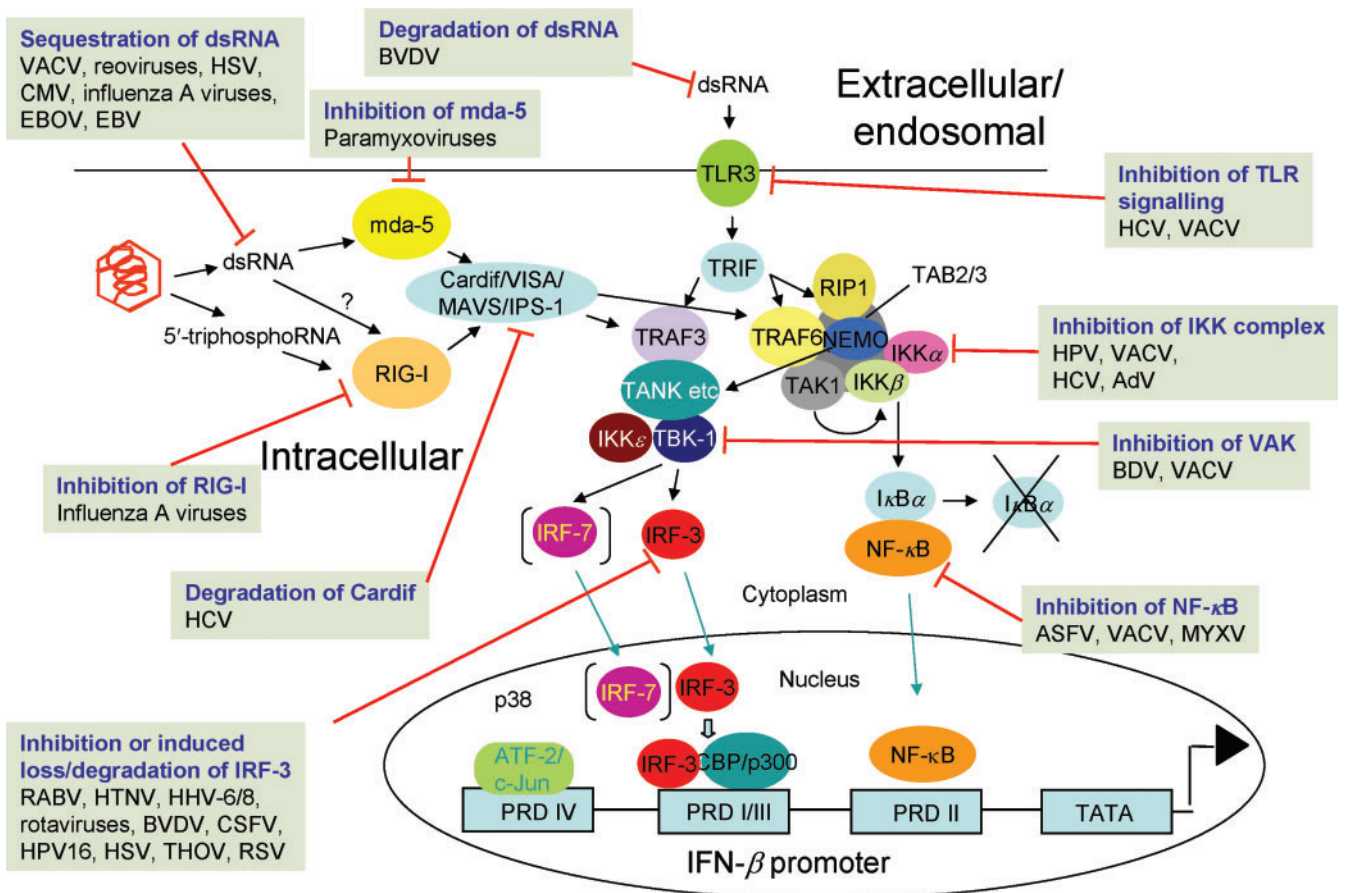
Fig. 7. Examples of viral IFN antagonists that block/limit the production of IFN-α/β from virus-infected cells. The signalling scheme presented is a composite of that shown in Figs 2 and 4 and shows IFN-β induction via both TLR3- and RNA helicase-dependent pathways. The sites of intervention by several antagonists are indicated. Note that some antagonists, such as N^{pro} of BVDV, are extremely effective in blocking IFN-α/β induction from a variety of PAMPs, because they target signalling molecules (IRF-3) that are far downstream in the IFN-induction cascades, whilst others, such as the V proteins of paramyxoviruses, act further upstream and may block only one arm of the induction pathway (mda-5). Also note that other IFN antagonists, such as HCV NS3/4a, have more than one cellular target. See text for details.

pathway may also partially explain why HSV-1 has evolved a mechanism to block autophagy specifically (Orvedahl *et al.*, 2007). In contrast, it has been suggested that some RNA viruses may activate components of the autophagic machinery both to promote their replication on cellular membranes (Prentice *et al.*, 2004; Jackson *et al.*, 2005) and to limit IFN production (Jounai *et al.*, 2007). This is because, during autophagy, the autophagy-related Atg family members Atg5 and Atg12 form conjugates that, amongst other functions, prevent the CARD domains of RIG-I/mda-5 from interacting with Cardif/VISA/MAVS/IPS-1, thereby preventing the induction of IFN through activation of RIG-I/mda-5 (Jounai *et al.*, 2007). Thus, given that autophagy appears to be an ancient pathway that plays an important role in innate and adaptive immune resistance to pathogens (Schmid *et al.*, 2006), we will probably soon learn more about how viruses specifically block or usurp this pathway.

Some viruses inhibit intracellular detectors of viral PAMPs. The V protein of most paramyxoviruses interacts with, and inhibits the activity of, mda-5 (Andrejeva *et al.*, 2004), but not RIG-I (Yoneyama *et al.*, 2005; Childs *et al.*, 2007; Komatsu *et al.*, 2007). It has also recently been reported that the C proteins of the paramyxovirus SeV can block RIG-I activation of the IFN-induction cascade (Strahle *et al.*, 2007). However, not all paramyxoviruses encode C proteins, suggesting that it may be more important for some paramyxoviruses, such as parainfluenza virus type 5 (PIV5; previously referred to as simian virus 5, SV5) and mumps virus (MuV), that do not encode C proteins to inhibit the function of mda-5 than RIG-I. However, this conclusion appears to contradict observations made on transgenic RIG-I or mda-5 knockout mice that suggest that the primary route for IFN induction by negative-strand viruses, including paramyxoviruses, is through RIG-I rather than mda-5 (Kato *et al.*, 2006; reviewed by Fujita

Table 3. Examples of viruses that block or limit IFN production specifically by infected cells

Mode of action	Virus	References
Degradation of dsRNA	BVDV (E^{rns} has RNase activity)	Iqbal et al. (2004)
Sequestration of dsRNA	VACV (E3)	Chang et al. (1992)
	Reoviruses (sigma3/A)	Imani & Jacobs (1988); Martinez-Costas et al. (2000); Olland et al. (2001); reviewed by Jacobs & Langland (1998)
	Rotaviruses (NSP3)	Langland et al. (1994)
	Influenza A virus (NS1)	Lu et al. (1995); Talon et al. (2000a); Wang et al. (2000); Li et al. (2006b)
	HSV (US11)	Poppers et al. (2000); Mohr (2004)
	HCMV (TRS1)	Cassady (2005); Hakki & Geballe (2005)
	MCMV (m142/143)	Child et al. (2006); Valchanova et al. (2006)
	EBOV (VP35)	Cardenas et al. (2006); Hartman et al. (2006); Feng et al. (2007)
	EBV (SM)	Poppers et al. (2003)
Inhibition of TLR signalling	HCV (NS3/4a)	Li et al. (2005c); Kaukinen et al. (2006)
	VACV (A52, A46)	Harte et al. (2003); Stack et al. (2005)
Inhibition of mda-5/RIG-I	Paramyxoviruses (V)	Andrejeva et al. (2004); Yoneyama et al. (2005); Childs et al. (2006); Komatsu et al. (2007)
	Influenza A virus (NS1)	Hornung et al. (2006); Pichlmair et al. (2006); Mibayashi et al. (2007); Guo et al. (2006); Opitz et al. (2006)
Inactivation of Cardif/ VISA/MAVS/IPS-1	HCV (NS3/4a)	Li et al. (2005c); Meylan et al. (2005); Cheng et al. (2006); Lin et al. (2006a); Loo et al. (2006)
Interferes with VAK	BDV (P)	Unterstab et al. (2005)
	VACV (N1)	DiPerna et al. (2004)
Inhibition or degradation of IRF-3	RABV (P)	Brzozka et al. (2005)
	HTNV (G1)	Alff et al. (2006)
	HHV-6 (E1)	Jaworska et al. (2007)
	Rotaviruses (NSP1)	Graff et al. (2007)
	BVDV (N^{pro})	Hilton et al. (2006)
	CSFV (N^{pro})	Bauhofer et al. (2005, 2007); La Rocca et al. (2005); Ruggli et al. (2005)
	HPV 16 (E6)	Ronco et al. (1998)
	HSV (ICP0)	Lin et al. (2004a); Melroe et al. (2004, 2007)
	BHV-1 (bICP0)	Saira et al. (2007)
	THOV (ML)	Hagmaier et al. (2004); Jennings et al. (2005)
	Bovine RSV	Bossert et al. (2003)
	Human RSV	Spann et al. (2005)
	SARS Co-V	Kopecky-Bromberg et al. (2007)
Interferes with IKK complex	HPV (E7)	Spitkovsky et al. (2002)
	HCV (core)	Joo et al. (2005)
	VACV	DiPerna et al. (2004)
	AdV (E3)	Friedman & Horwitz (2002)
Inhibition of NF-κB	ASFV (A238L)	Powell et al. (1996); Revilla et al. (1998); Tait et al. (2000)
	VACV (N1)	Shisler & Jin (2004)
	MYXV (MNF)	Camus-Bouclainville et al. (2004)
Interfere with IFN-β promoter activation	HHV-8 (IRF orthologues)	Offermann (2007)

et al., 2007). Whilst there are a number of potential explanations for these observations, including the fact that the paramyxoviruses used in these studies will have inhibited mda-5 activity (Childs et al., 2007), an important consideration when interpreting such data is that different virus preparations used for experimentation, both in tissue culture and in animal studies, may not produce the same spectrum of IFN inducers as in nature. Indeed, viruses grown in tissue culture are not under the same set of selective pressures as those encountered during replication in vivo, and this may lead to apparent inconsistencies. This is well illustrated by the ease with which DI particles, which are powerful inducers of IFN, are generated in cell culture (Johnston, 1981; Poole et al., 2002; Strahle et al., 2006).

In contrast to the V proteins of paramyxoviruses, the NS1 protein of influenza virus associates, either directly or indirectly, with RIG-I (but not mda-5) to inhibit its activity

(Guo *et al.*, 2006; Opitz *et al.*, 2006; Pichlmair *et al.*, 2006; Mibayashi *et al.*, 2007). As discussed previously, influenza viruses may need to inhibit RIG-I activity because uncapped ssRNAs with a 5′ triphosphate group that may activate RIG-I may be produced at early times post-infection, before the virus can inhibit host gene expression.

Further downstream in the intracellular IFN-induction cascade, the HCV NS3/4a protein cleaves the C-terminal mitochondrial anchor of Cardif/VISA/MAVS/IPS-1, thereby disrupting its ability to signal to TBK1 and IKKε (Li *et al.*, 2005c; Meylan *et al.*, 2005; Cheng *et al.*, 2006; Kaukinen *et al.*, 2006; Lin *et al.*, 2006a; Loo *et al.*, 2006). Hepatitis A virus (HAV) inhibits RIG-I activation of the IFN-induction cascade at some point upstream of TBK1/IKKε (Fensterl *et al.*, 2005). Rabies virus (RABV) P protein (Brzozka *et al.*, 2005) and the G1 protein of hantavirus (HTNV) (Alff *et al.*, 2006) inhibit the activation of IRF-3 by TBK-1, as does the borna disease virus (BDV) P protein (Unterstab *et al.*, 2005) and the N1 protein of VACV (DiPerna *et al.*, 2004). N^{pro} of both BVDV and classical swine fever virus (CSFV) (Bauhofer *et al.*, 2005, 2007; La Rocca *et al.*, 2005; Ruggli *et al.*, 2005) blocks IFN induction by targeting IRF-3 for proteasome-mediated degradation (Hilton *et al.*, 2006), whilst the E6 protein of human papillomavirus (HPV) 16 sequesters IRF-3 (Ronco *et al.*, 1998). Rotavirus non-structural protein 1 (NSP1) also targets IRF-3 for degradation (Graff *et al.*, 2007), as well as IRF-5 and IRF-7 (Barro & Patton, 2007). Similarly, ICP0 of HSV-1 inhibits IRF-3 and IRF-7 (Lin *et al.*, 2004a; Melroe *et al.*, 2004), reportedly by recruiting activated IRF-3 and CBP/p300 to nuclear structures away from host chromatin (Melroe *et al.*, 2007). In contrast, it appears that bovine herpesvirus 1 (BHV-1) bICP0 targets IRF-3 for degradation (Saira *et al.*, 2007). The ML protein of THOV acts as an IFN antagonist by blocking IRF-3 dimerization to inhibit its transcriptional activity (Hagmaier *et al.*, 2004; Jennings *et al.*, 2005), whilst severe acute respiratory syndrome coronavirus (SARS Co-V) appears to have multiple methods to inhibit IFN production (Spiegel *et al.*, 2005; Kopecky-Bromberg *et al.*, 2007). The immediate-early 1 protein of HHV-6 also inhibits IRF-3 function (Jaworska *et al.*, 2007), whilst that of HHV-8 targets IRF-7 for degradation (Yu *et al.*, 2005). HHV-8 also produces IRF orthologues, such as vIRF3, which interacts with IRF7 (Joo *et al.*, 2007), and these interfere with the activation of both the IFN-β promoter (Lin *et al.*, 2001) and IFN-responsive genes (reviewed by Rezaee *et al.*, 2006; Offermann, 2007). A number of other viral IFN antagonists, including the NS1 and NS2 proteins of bovine and human RSV (Bossert *et al.*, 2003; Spann *et al.*, 2005), also interfere with IRF-3 activation, by unknown mechanisms.

As discussed above, NF-κB is also involved in the activation of the IFN-β promoter (as well as other cytokine genes) and its activity is manipulated by some viruses (reviewed by Hiscott *et al.*, 2006b). However, although most viruses do not normally activate NF-κB (perhaps because they inhibit upstream targets in the IFN-induction

cascade), a few do suppress NF-κB function directly. Thus, African swine fever virus (ASFV) encodes an IκB orthologue that inhibits the activity of NF-κB (Powell *et al.*, 1996; Revilla *et al.*, 1998; Tait *et al.*, 2000). The HPV type 16 E7 protein (Spitkovsky *et al.*, 2002) and the HCV core protein (Joo *et al.*, 2005) target the IKK complex to inhibit NF-κB signalling. The AdV E3 protein also inhibits the activation of NF-κB (Friedman & Horwitz, 2002), as do the VACV K1 (Shisler & Jin, 2004) and N1 (DiPerna *et al.*, 2004) proteins, and the MNF protein of myxoma virus (MYXV) (Camus-Bouclainville *et al.*, 2004). However, as NF-κB, as well as inducing proinflammatory cytokines, also induces anti-apoptotic genes (Li & Verma, 2002; Li *et al.*, 2005b; Karin, 2006), any virus that blocks NF-κB activation specifically may leave itself susceptible to enhanced induction of apoptosis. Notably, the VACV N1 protein resembles Bcl-2 structurally and, as well as inhibiting NF-κB activation, blocks apoptosis. Indeed, this latter function may be its more relevant biological function (Cooray *et al.*, 2007).

As well as inhibiting IFN induction, viruses may limit the release of IFN by inhibiting cellular protein secretion, as suggested for PV (Choe *et al.*, 2005). As PV also switches off host-cell protein expression (Table 2), this may reflect the need for PV (like other viruses) to inhibit several cellular process to inhibit the IFN response efficiently.

(iii) Inhibition of IFN signalling. There are clear advantages to viruses in blocking IFN signalling and, as there are components in common between signalling pathways for type I, II and III IFNs, it is possible for a virus to block multiple pathways simultaneously. Using such strategies, not only would the induction of cellular antiviral enzymes, such as PKR, OAS, Mx, ISG15, PML and Sp100, be inhibited, but also there would be no upregulation of class I MHC molecules within infected cells, making them poorer targets for cytotoxic T lymphocytes (CTLs). Furthermore, virus-infected cells would be resistant to the actions of IFNs, regardless of whether the IFNs were produced by infected cells or by activated leukocytes. As with the IFN-induction cascade, there are examples of virus proteins blocking all aspects of the IFN-signalling cascade, from receptor signalling to the formation and activity of IFN-induced transcription factors (Fig. 8; Table 4). Furthermore, some viruses target multiple points of the IFN-signalling cascade. By blocking IFN signalling, some viruses also dismantle the IFN-induced antiviral state in cells. For example, although initially PIV5 cannot replicate efficiently in cells that have entered an antiviral state (Didcock *et al.*, 1999b; Carlos *et al.*, 2005), the degradation of STAT1 by the virion-associated V protein leads to an eventual decay (24–48 h) of the antiviral state (as cells cannot maintain their antiviral state indefinitely without continuous IFN signalling), thereby facilitating subsequent viral replication (Didcock *et al.*, 1999a). However, even if a virus can eventually dismantle the antiviral state of cells, the delay in virus replication induced by IFN should buy
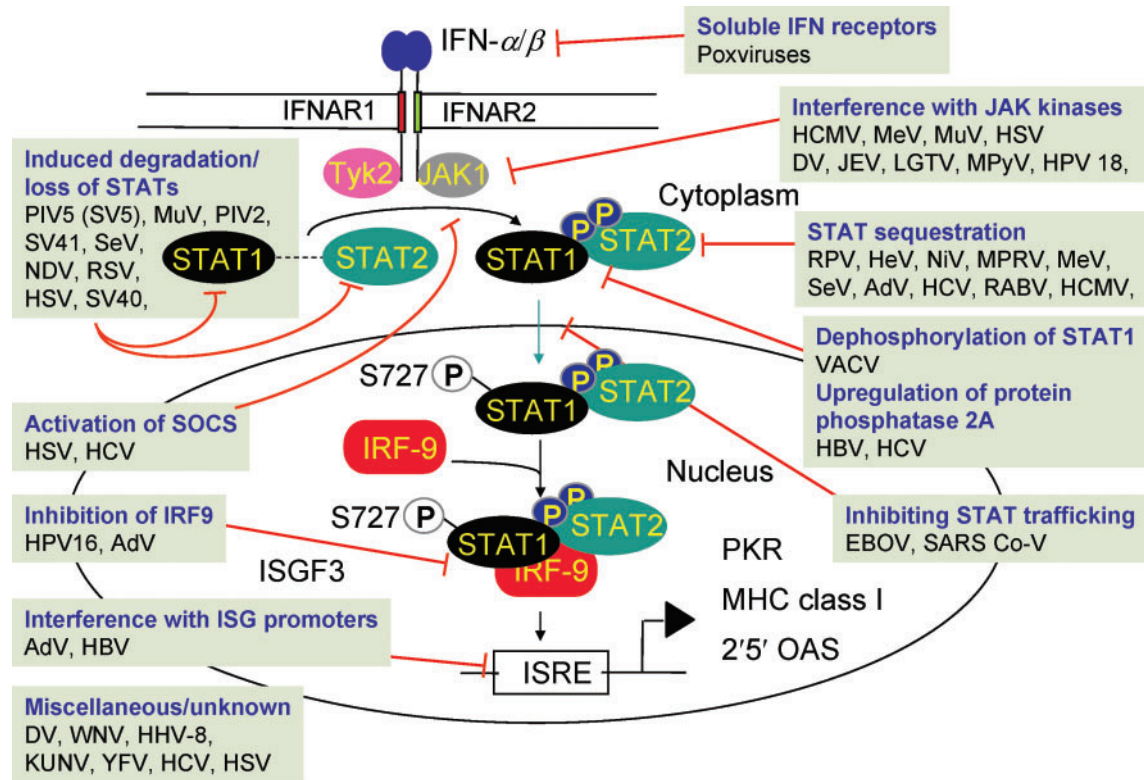
Fig. 8. Examples of viral IFN antagonists that inhibit IFN-α/β signalling specifically within virus-infected cells. The signalling scheme presented is that shown in Fig. 5. Sites of intervention by several antagonists are indicated. Note that many, but not all, of these IFN antagonists will also inhibit IFN-γ signalling. For example, the V protein of PIV5 targets STAT1 for degradation and thus blocks IFN-α/β, IFN-γ and type III IFN signalling, whilst the V protein of hPIV2 targets STAT2 for degradation (in human cells) and thus does not block IFN-γ signalling. See text for details.

time for the host to mount an acquired immune response to help resolve the infection, and this may be why viruses that block IFN signalling also need to limit IFN production.

The diversity of molecular mechanisms that viruses have evolved to block IFN signalling is enormous. For example, viral IFN-γ-binding proteins, which can bind IFN-γ and thus neutralize it, are secreted by cells infected with MYXV, ectromelia virus (ECTV), cowpox virus (CPXV), camelpox virus (CMLV) and VACV (Upton et al., 1992; Alcami & Smith, 1995; Mossman et al., 1995a, b). Similarly, VACV and most other orthopoxviruses also encode soluble IFN-α/β-binding proteins (Colamonici et al., 1995; Symons et al., 1995). Furthermore, the secreted vIFN-α/β-binding protein of VACV (B18 of VACV strain Western Reserve) also binds to the surface of infected and uninfected cells and prevents them from entering an antiviral state in response to IFN-α/β (Alcami et al., 2000). Yaba-like disease virus (YLDV) has a protein (YLDV 136) related to VACV B18, but this protein binds and inhibits both type I and type III IFNs (Huang et al., 2007). The K3 and K5 proteins of HHV-8 downregulate IFNGR1 by targeting it for ubiquitination, endocytosis and degradation

(Li et al., 2007). There are several viruses that interfere directly with IFN-receptor activity. The NS5 protein of Japanese encephalitis virus (JEV) interferes with Tyk2 activation, possibly by activating protein tyrosine phosphatases (Lin et al., 2004b, 2006b). Other flaviviruses, including dengue virus (DV) (Ho et al., 2005) and Langat virus (LGTV) (Best et al., 2005; Park et al., 2007), also disrupt the IFN-receptor complex. HCMV has been reported to disrupt IFN signalling by (i) decreasing the levels of JAK1 (and IRF-9) by a mechanism involving the proteasome (Miller et al., 1998, 1999), and (ii) by the HCMV immediate-early 1 (IE1) 72 kDa protein sequestering STAT1 and STAT2 (Paulus et al., 2006). The T antigen of murine polyomavirus (MPyV) binds to JAK1, thereby blocking the activation of IFN-α/β- and IFN-γ-signalling pathways (Weihua et al., 1998). HSV-1 gene products occlude IFN signalling at multiple points, including by rapidly reducing the levels of JAK1 and STAT2 (Chee & Roizman, 2004). Some paramyxoviruses, including MeV and MuV, as well as interfering with STAT function (below), have been reported to inhibit JAK kinase signalling by interacting with the scaffolding protein RACK1 (receptor for activated C kinase) (Kubota et al., 2002; Yokota et al., 2003).

Table 4. Examples of viruses that inhibit IFN signalling specifically

Mode of action	Virus	References
Sequestration of IFN through soluble IFN receptor homologues	VACV, MYXV, ECTV, CPXV, CMLV, YLDV	Upton et al. (1992); Alcami & Smith (1995); Colamonici et al. (1995); Mossman et al. (1995a, b); Symons et al. (1995); Puehler et al. (1998); Alcami et al. (2000); Huang et al. (2007)
Downregulation of IFN receptor	HHV-8	Li et al. (2007)
Interference with JAK kinases	JEV	Lin et al. (2004b, 2006b)
	DV	Ho et al. (2005)
	LGTV	Best et al. (2005); Park et al. (2007)
	HCMV	Miller et al. (1998, 1999)
	MPyV	Weihua et al. (1998)
	MeV	Yokota et al. (2003)
	MuV	Croze et al. (2000); Usacheva et al. (2001); Kubota et al. (2002)
	HSV	Chee & Roizman (2004)
	HPV18	Li et al. (1999)
Interference with STAT activity by:		
Inducing the degradation/loss of STATs	PIV2	Young et al. (2000); Nishio et al. (2001); Parisien et al. (2001); Ulane & Horvath (2002)
	PIV5	Didcock et al. (1999a); Young et al. (2000); Andrejeva et al. (2002a, b); Parisien et al. (2002a, b); Ulane & Horvath (2002); Precious et al. (2005a, b); Ulane et al. (2005)
	SV41	Kozuka et al. (2003)
	MuV	Croze et al. (2000); Kubota et al. (2001); Nishio et al. (2002); Ulane et al. (2003); Kubota et al. (2005)
	NDV	Huang et al. (2003)
	RSV	Ramaswamy et al. (2004, 2006); Elliott et al. (2007)
	SeV	Garcin et al. (2002)
	HSV	Chee & Roizman (2004)
Sequestration of STATs or altering their phosphorylation	NiV	Rodriguez et al. (2002); Park et al. (2003); Butler (2004); Rodriguez & Horvath (2004); Shaw et al. (2004, 2005)
	HeV	Rodriguez et al. (2003)
	MeV	Palosaari et al. (2003); Shaffer et al. (2003); Takeuchi et al. (2003); Ohno et al. (2004)
	RPV	Nanda & Baron (2006)
	HCV	Lin et al. (2006c)
	HCMV	Paulus et al. (2006)
	RABV	Brzozka et al. (2006); Vidy et al. (2007)
	SeV	Garcin et al. (1999, 2000, 2001); Kato et al. (2001); Takeuchi et al. (2001); Komatsu et al. (2002); Saito et al. (2002); Garcin et al. (2002, 2003); Gotoh et al. (2003a, b); Young et al. (2000); Marq et al. (2007)
	AdV	Look et al. (1998)
	HBV	Christen et al. (2007)
	VACV	Najarro et al. (2001)
	MPRV	Hagmaier et al. (2007)
Inhibiting STAT trafficking	EBOV	Reid et al. (2006)
	SARS Co-V	Frieman et al. (2007)
Interfering with IRF-9	HPV16	Barnard & McMillan (1999); Barnard et al. (2000)
Induction of SOCS	HSV	Yokota et al. (2004)
	HCV	Bode et al. (2003)
Upregulation of protein phosphatase 2A	HBV	Christen et al. (2007)
	HCV	Duong et al. (2006)
Interference with ISG promoter activity	HHV-8	Reviewed by Lin et al. (2001); Rezaee et al. (2006); Offermann (2007)
	HBV	Fernandez et al. (2003)
	AdV	Leonard & Sen (1996)
Miscellaneous/unknown	SARS Co-V	Kopecky-Bromberg et al. (2007)
	DV, KUNV, WNV, YFV	Munoz-Jordan et al. (2003, 2005); Liu et al. (2004, 2005, 2006)
	HCV	de Lucas et al. (2005); Ciccaglione et al. (2007)
	HSV	Chee & Roizman (2004)

STAT and IRF-9 proteins that form part of IFN-inducible ISGF3 and GAF transcription complexes are the targets for inhibition by several viruses. Most paramyxoviruses inhibit STAT function to block IFN signalling. However, the molecular mechanisms by which they achieve this differ. In human cells, the V protein of PIV5 blocks IFN signalling by targeting STAT1 for degradation; parainfluenza virus type 2 (HPIV2) targets STAT2 primarily, whilst MuV targets both STAT1 and STAT3. In contrast, the V and P proteins of Nipah (NiV) and Hendra (HeV) viruses sequester STAT1 and STAT2. SeV also blocks IFN signalling by sequestering STATs, increasing their turnover and altering the pattern of STAT1 phosphorylation, although it is another set of proteins encoded by the P/V/C gene, namely the C proteins, that are responsible for this aspect of IFN antagonism. The RSV NS1 protein also targets STAT2 for degradation (see Table 4 for references; for more extensive reviews of how paramyxoviruses block IFN signalling, see Horvath, 2004; Nagai & Kato, 2004; Conzelmann, 2005; Stock et al., 2005).

The RABV P protein also interacts with STAT1 and STAT2, forming an inactive complex (Brzozka et al., 2006; Vidy et al., 2007). Amongst the reported ways that HCV blocks IFN signalling (see also below), the core protein interacts with STAT1 to inhibit its phosphorylation and interaction with STAT2 (Lin et al., 2006c). However, whether this mechanism also operates in vivo is not clear, because treatment of HCV-infected or HCV-transfected cell cultures with IFN potently reduces HCV RNA replication (Frese et al., 2001; Windisch et al., 2005; Kim et al., 2007). In contrast, DV clearly blocks IFN signalling (Munoz-Jordan et al., 2003, 2005) and, indeed, in replicon-containing cells, DV RNA replication is resistant to IFN-α treatment (Jones et al., 2005). The VH1 structural protein of VACV is a phosphatase that dephoshorylates STAT1 and has been reported to block IFN-γ signalling (Najarro et al., 2001). Similarly, Kunjin virus (KUNV) and West Nile virus (WNV) (Liu et al., 2004, 2005, 2006) also circumvent the IFN response at least partially by blocking IFN signalling. The HPV 16 E7 multifunctional protein interacts directly with IRF-9, preventing the formation of ISGF3 and thus the activation of IFN-α/β-inducible genes (Barnard & McMillan, 1999; Barnard et al., 2000). In contrast to interfering directly with STAT1 or STAT2, VP24 of EBOV (Reid et al., 2006) and the ORF6 protein of SARS-CoA (Frieman et al., 2007) interact with karyopherin to inhibit the nuclear import of STATs. As part of its mechanism to circumvent the IFN response, HSV rapidly induces the expression of SOCS3, a cellular inhibitor of JAK/STAT pathways (Yokota et al., 2004), as reportedly does the HCV core protein (Bode et al., 2003). HCV and HBV have also been reported to upregulate the expression of protein phosphatase 2A (PP2A), which can interfere with STAT signalling (Duong et al., 2004; Christen et al., 2007). Furthermore, HBV core/precore proteins interact directly with the MxA gene promoter (Fernandez et al., 2003). The AdV E1A protein disrupts transcriptional responses to

IFN-α/β and IFN-γ by decreasing the levels of STAT1 and IRF-9 (Leonard & Sen, 1996), by sequestering the transcriptional co-activator CBP/p300, which binds STAT1 and STAT2 and is involved in transcription responses mediated by these proteins (Bhattacharya et al., 1996; Zhang et al., 1996), and by interacting with STAT1 directly (Look et al., 1998). Furthermore, viruses may limit long-term IFN signalling by targeting other transcription factors. For example, HCV core protein interferes with IRF-1, which, as discussed above, is a secondary transcription factor responsible for the prolonged induction of several IFN-stimulated antiviral and immunomodulatory genes (Ciccaglione et al., 2007).

(iv) Inhibition of IFN-induced antiviral enzymes. Many viruses have evolved specific mechanisms to circumvent indirect IFN-induced antiviral responses, including stimulating cells to enter their cell cycle, inhibiting apoptosis and blocking the activity of CTLs and NK cells. However, here we will only briefly review the mechanisms that viruses have evolved to block IFN-induced enzymes with more direct effects on virus replication.

(a) PKR and OAS/RNase L. Several virus types, including pox-, herpes-, influenza and reoviruses, encode proteins that sequester dsRNA to minimize the activation of IFN-induced antiviral proteins PKR, OAS and ADAR by dsRNA. However, sequestration of dsRNA will not prevent the activation of PKR by PACT (PKR-associated activator), which is activated by different cellular-stress pathways that may be activated by virus infection, and it may be for this reason that some viruses, including influenza virus (Tan & Katze, 1998; Li et al., 2006b), have evolved specific mechanisms to inhibit PKR activity or escape its action downstream. Furthermore, inhibition of PKR may also be important for viral evasion of autophagy (Talloczy et al., 2006; Orvedahl et al., 2007; reviewed by Munz, 2007). The mechanisms that viruses use to inhibit PKR have recently been reviewed extensively by Langland et al. (2006) and include the production of: (i) small, highly structured RNA molecules that prevent dimerization of PKR by dsRNA and hence its activation [VA-RNA of AdVs, possibly Epstein–Barr-encoded (early) RNAs, the internal ribosome entry sequence (IRES) of HCV]; (ii) proteins that bind directly to, and inhibit the activity of, PKR (HCV NS5A and E2, influenza virus NS1, HSV-1 US11, EBV SM, HHV-8 vIRF-2, baculovirus PK2, VACV E3); (iii) proteins that are pseudosubstrate competitive inhibitors of PKR (HIV Tat, VACV K3); (iv) proteins that degrade PKR (PV protease); (v) proteins that induce the expression of p58^{IPK} (influenza virus NS1), which is a cellular inhibitor of PKR; (vi) proteins that act indirectly on PKR activity, for example the $_{\gamma 1}$ICP34.5 protein of HSV-1 redirects the cellular protein phosphatase 1α to dephosphorylate, and hence reactivate, eIF-2α [as does the MyD116 protein of ASFV (Rivera et al., 2007)]. For references, see Langland et al. (2006).

Unlike PKR, OAS lack canonical dsRNA-binding motifs and have a relatively low affinity for dsRNA (Hartmann *et al.*, 2003). Consequently, viral proteins that bind dsRNA (above) are particularly potent inhibitors of OAS, even if they also have relatively low affinity for dsRNA, such as influenza virus NS1 (Min & Krug, 2006). However, a few viruses may have evolved strategies that specifically counteract the antiviral activity of the OAS/RNase L system. For example, HIV-1 (Martinand *et al.*, 1999) and EMCV (Martinand *et al.*, 1998) apparently downregulate RNase L activity by inducing the expression of the cellular RNase L inhibitor (RLI), which antagonizes 2′5′-oligoadenylate binding to RNase L and hence prevents its activation. With regards to HIV, potentially the TAR sequence structural element could also bind and activate OAS and PKR, but this is prevented by the virus Tat protein binding the TAR element (Maitra *et al.*, 1994).

(b) ISG15. As described above, ISG15 is a ubiquitin-like molecule that is induced rapidly by IFN and has antiviral activity (Lenschow *et al.*, 2007). Indeed, overexpression of ISG15 in recombinant SINV attenuated the virus in in IFN-α/β receptor-knockout mice (Lenschow *et al.*, 2005). Although its mechanism(s) of action remain(s) unknown, its importance as an antiviral is suggested because several viruses interfere with its activity. It has been reported (Garcia-Sastre, 2007) that the N-terminal domain of the L protein of Crimean Congo hemorrhagic virus (CCHV) has de-ISGylating and de-ubiquitinating activity, which can restore the pathogenicity of the recombinant SINV that overexpresses ISG15 (above) in IFN-α/β receptor-knockout mice. The influenza B virus NS1 protein also binds to ISG15 and prevents it from interacting with its E1 ligase, thereby inhibiting conjugation of ISG15 to its target proteins (Yuan & Krug, 2001).

(c) PML and PML nuclear bodies. Much remains to be discovered of the role of PML and PML nuclear bodies both in virus replication and in antiviral defence (reviewed by Everett, 2001, 2006). Nevertheless, it is clear that many adenoviruses and herpesviruses encode regulatory proteins that localize to, and disrupt the functions of, PML nuclear bodies (reviewed by Everett & Chelbi-Alix, 2007). For example, to aid replication, the AdV E4orf3 protein reorganizes PML nuclear bodies into thread-like structures (Doucas *et al.*, 1996; Stracker *et al.*, 2005; Hoppe *et al.*, 2006; Ullman *et al.*, 2007); the ICP0 protein of HSV-1 has E3 ligase activity that induces the degradation of PML and SUMO-modified forms of Sp100 (reviewed by Hagglund & Roizman, 2004); EBV nuclear antigen 5 (EBNA5) interacts with Sp100A, but this may be to release PML-associated factors from PML nuclear bodies to aid viral gene expression (Ling *et al.*, 2005); HCMV IE72 induces the loss of SUMO-modified forms of PML to disrupt PML nuclear bodies (Ahn & Hayward, 2000; Kang *et al.*, 2006), and pp71 localizes to PML nuclear bodies to induce the

degradation of hDaxx, which inhibits HCMV IE gene expression (Cantrell & Bresnahan, 2006; Preston & Nicholl, 2006; Saffert & Kalejta, 2006). Even certain RNA viruses that replicate in the cytoplasm may block PML function. For example, PV induces the recruitment of p53, mdm2 and proteasome components to PML nuclear bodies, resulting in the degradation of p53 (Pampin *et al.*, 2006). Although it is not yet clear whether PML has a role in antiviral defence against LCMV and RABV, it may be significant that the LCMV Z protein and the RABV P protein, as well as smaller truncated products, interact with PML to cause a reorganization of PML nuclear bodies (Borden *et al.*, 1998a, b; Djavani *et al.*, 2001; Blondel *et al.*, 2002). HCV core protein can co-localize with PML and p53 in PML nuclear bodies (Herzer *et al.*, 2005), although the relevance of this is debated (Rouille *et al.*, 2006).

(d) APOBECs. As discussed earlier, the cytidine deaminases APOBEC3F and 3G, which are inducible by IFN in certain cell types, have antiviral activity against a broad range of retroviruses. However, HIV (and most other lentiviruses) ameliorate the effects of these enzymes at least partially by encoding a protein, termed vif, that forms a complex with components of cellular E3 ligases to target APOBEC3 proteins for ubiquitination and subsequent degradation by proteasomes (reviewed by Malim, 2006; Soros & Greene, 2007). Although it has been reported that these proteins also have activity against HBV, they are not primarily responsible for the anti-HBV activity of IFNs. Thus, HIV vif, even when used in combination with RNA interference to specific APOBEC3 proteins, does not abrogate the inhibitory effect of IFN on HBV (Jost *et al.*, 2007).

Consequences for the virus and host

(i) Consequences for the virus. It is increasingly clear that viruses have evolved an amazing variety of mechanisms to circumvent the IFN response. However, the knock-on consequences that a particular mechanism may have for both the virus and host are less clear. Intuitively, it would be expected that antagonists that block downstream in the IFN-induction cascade would be more effective than those that block upstream, because the multiple signalling pathways that can activate IFN production converge upon IRF-3 and NF-κB. For example, although PIV5 blocks mda-5 activity (Andrejeva *et al.*, 2004), it does not block RIG-I-induced responses (Childs *et al.*, 2007) and is therefore much less effective in blocking IFN induction than N^{pro} of BVDV, which targets IRF-3 for degradation (Hilton *et al.*, 2006) and, consequently, blocks IFN induction from a number of convergent pathways. Presumably, PIV5 (and closely related paramyxoviruses) are less concerned with the RIG-I-induction pathway, as they limit the production of the inducer of RIG-I (Dillon & Parks, 2007). Nevertheless, it is of note that the ability of paramyxoviruses to circumvent the IFN response may not be absolute (Young *et al.*, 2003).

Although apparently less efficient, viruses may block upstream in the IFN-induction pathway because there may be negative consequences for viruses in blocking further downstream; for example, it may make the cells more susceptible to other host-defence responses. Indeed, given that the IFN response is a near-universal target for viruses, it would be surprising if, in the context of an infection, the immune system had not evolved ways to recognize and eliminate cells with defects in their IFN response.

Although the IFN response is an extremely powerful response that is critical in helping to control most virus infection, it is a programmed response in that, if stimulated in a given way, it will respond predictably. Consequently, as well as blocking the IFN response specifically, viruses may also have more subtle ways to take advantage of the IFN response by evolving particular lifestyles. For example, to survive in nature, certain simple RNA viruses, such as BVDV and HCV, establish persistent infections in a proportion of infected hosts. These relatively simple RNA viruses do not have the ability to establish latent infections in the way that herpesviruses or retroviruses do. Thus, it is possible that their ability to manipulate, and be manipulated by, the IFN response may be critical for the ability of small RNA viruses to establish persistent infections. Indeed, we have suggested such a scenario for PIV5 (Chatziandreou et al., 2002; Carlos et al., 2005). IFN may also help herpesviruses to establish and maintain latency. HSV-1 latency in neurons is characterized by low-level viral gene expression in some neurons, and HSV-1-specific CD8$^+$ T cells in close proximity to the neurons prevent full reactivation by the production of IFN-γ and other factors (Khanna et al., 2004; Decman et al., 2005). As latency is central to the life cycle of HSV, if this model is correct, it could be argued that the virus has evolved a strategy to exploit the predictable CD8$^+$ T-cell response and the resulting release of IFN-γ. It has also been reported that EBV latent membrane protein 1 (LMP-1) primes viral latency cells for production of IFN-α/β and this would help to preserve EBV latency in two ways; firstly, by preventing the cells from being superinfected by other viruses, and secondly, by inhibiting EBV replication itself (Zhang et al., 2004; Xu et al., 2006).

Viruses may also make use of IFN-induced antiviral proteins. For example, it is surprising that HIV has evolved such a complicated mechanism for controlling the activity of APOBEC3 proteins when it would seem easier to simply avoid packaging APOBEC3F and 3G into virions. An intriguing possibility is that HIV controls APOBEC activity, rather than eliminating it entirely, to increase virus sequence diversity in a way that is not lethal to the virus (Malim, 2006). Consequently, in the future, we are likely to learn more of the ways in which viruses have evolved lifestyles to take advantage of the programmed IFN response for their own benefit.

(ii) **Consequences for the host.** As long as a viral antagonist does not interfere with host-cell protein expression in a gross way, persistently infected cells can survive with defects in their IFN response. However, their normal cellular functions may be affected adversely by the continuous expression of the viral IFN antagonist and this may lead to long-term sequelae. Indeed, certain cellular functions may be controlled by the actions of IFN in the absence of virus infection. For example, the activity of osteoclasts, which are involved in bone reabsorption, is regulated negatively by their release of small amounts of IFN (Takayanagi et al., 2002, 2005). Paget's bone disease, in which there is thinning of the bone, has been linked both to increased osteoclast activity and to persistent paramyxovirus infections (Bender, 2003). As paramyxoviruses interfere with both IFN production and signalling, there is potentially a mechanistic link between these observations. Others have disputed this link (Nuovo et al., 1992; Ooi et al., 2000; Rima et al., 2002; Ralston et al., 2007), but the picture is complicated by the fact that most paramyxoviruses, and many other viruses, block the IFN-signalling pathways, raising the possibility that persistent infections by different viruses may cause the same manifestations of a chronic disease. Indeed, a number of different paramyxoviruses, including MeV, canine distemper virus (CDV), RSV, PIV3 and PIV5, have been reported to infect osteoclasts persistently (Mills et al., 1984; Basle et al., 1985, 1986, 1987; Gordon et al., 1991; Mee et al., 1998; Reddy et al., 1999; Friedrichs et al., 2002; Hoyland et al., 2003). Whether or not paramyxoviruses are related to Paget's bone disease, the possibility that different viruses may cause similar chronic disease manifestations should be considered, especially as this scenario is well established for acute infections, e.g. respiratory and enteric viral diseases.

As well as possible adverse consequences of persistent/latent infections and their effects on the IFN response, perversely, the host may benefit from chronic/latent virus infections and the production of IFN. For example, mice infected latently with herpesviruses are more resistant to bacterial infections than non-infected mice (Barton et al., 2007). The latency-induced protection was not antigen-specific, but rather correlated with the production of IFN-γ and systemic activation of macrophages. Furthermore, as IFNs also induce the production of IL-15, which stimulates memory CTLs (discussed above), chronic virus infections, in which there is continuous production of IFN, may help to maintain immune memory. Thus, it is important to be aware not only of surprising adverse consequences of virus–host relationships, but also of possible benefits.

(iii) **IFN response and virus host range.** Given that viruses must at least partially circumvent the IFN response, it is not surprising that an inability to do this can restrict host range. There are many examples where this is known to be the case. MYXV infects rabbits but will not replicate efficiently in murine or human cells unless their IFN response is disabled (Wang et al., 2004; Johnston et al., 2005; reviewed by McFadden, 2005). Neither MeV nor PV will replicate efficiently in mouse models unless the IFN

system has been compromised [and, for MeV, only if the appropriate virus receptors are expressed (Mrkic *et al.*, 1998; Ohka *et al.*, 2007; Ohno *et al.*, 2007)]. One restriction on the replication of human RSV in bovine cells, and bovine RSV in human cells, is their inability to circumvent the IFN response efficiently in cells of the other species (Schlender *et al.*, 2000; Bossert & Conzelmann, 2002; Young *et al.*, 2003). The IFN response can limit the replication of avian influenza viruses in human cells and thus contribute to host-range restriction (Hayman *et al.*, 2007). Similarly, PIV5 can not replicate in murine cells because it fails to block the IFN response in these cells (Didcock *et al.*, 1999b; Young *et al.*, 2001); furthermore, whilst PIV5 is non-pathogenic in SCID (severe combined immunodeficient) mice (which cannot make an adaptive immune response; Young *et al.*, 1990; Didcock *et al.*, 1999b), the virus kills STAT1$^{0/0}$ mice (He *et al.*, 2001, 2002), because they cannot mount an effective IFN response. The failure of PIV5 to block IFN signalling in mice is because its V protein does not target STAT1 for proteasome-mediated degradation (Didcock *et al.*, 1999b; Young *et al.*, 2001; Chatziandreou *et al.*, 2002; Parisien *et al.*, 2002a), although only a single amino acid change is required for it to become functional in murine cells (Young *et al.*, 2001). Thus, the ability of a virus to adapt (mutate) so that its antagonist becomes functional in a new host species is unlikely to prove more or less of a barrier than any other virus function that requires a virus protein to interact with a cellular protein.

The failure of a virus to circumvent the IFN response in a particular species could be the result of (i) the viral IFN antagonist not functioning correctly in cells of its non-natural species, (ii) the virus replication cycle being too slow, thereby buying time for the cell to mount an effective antiviral response before the virus can produce enough of its antagonist to block the IFN response, or (iii) the production of more, or different, inducers of IFN, such as dsRNA, by the virus, due to a loss of control of virus transcription and replication. Thus, even if a particular viral IFN antagonist is fully functional, the IFN response may still be critical in controlling the infection, as there will be a race between the ability of a virus to block the IFN response and the host's ability to mount one. For example, one reason that the HTNV Andres strain is pathogenic in humans, whereas the Prospect Hill strain is not, may be because Prospect Hill induces more IFN at early times in infection, rather than the inability of the Prospect Hill strain to downregulate IFN signalling (Spiropoulou *et al.*, 2007).

Conversely, there are many examples where a viral IFN antagonist works in several species that are not the natural host for the virus. For example, soluble IFN-binding proteins released from orthopoxvirus-infected cells bind IFNs from a wide variety of species (Alcami & Smith, 1995; Symons *et al.*, 1995; Liptakova *et al.*, 1997); N^{pro} of BVDV blocks IFN production in cells from many species that it does not infect naturally, including human, monkey and

canine cells (Hilton *et al.*, 2006; M. C. Galiano & R. E. Randall, unpublished observations); and the V protein of Mapuera virus (MPRV) blocks IFN signalling in human, monkey, equine, porcine and canine cells, amongst others, even though MPRV does not infect these species naturally (Hagmaier *et al.*, 2007). Thus, whilst the IFN response is undoubtedly a major barrier that all viruses must overcome to jump species, it is only one of many potential barriers that define species specificity for viruses.

Vaccines, antiviral drugs and oncolytic viruses
IFN-sensitive viruses as attenuated virus vaccines

As our molecular understanding of how viruses block the IFN response has increased, so new possibilities for the control of virus infections have opened up. Thus, attenuated virus vaccines may be developed by isolating viruses that are unable to circumvent the IFN response. This may be achieved either by using reverse genetics to target known genes that encode viral IFN antagonists or by selecting mutants that are sensitive to IFN. There are a number of examples where such an approach has been, or is being, tried, e.g. influenza virus (Talon *et al.*, 2000b; Ferko *et al.*, 2004; Fernandez-Sesma *et al.*, 2006; Richt *et al.*, 2006), paramyxoviruses (Teng *et al.*, 2000; Valarcher *et al.*, 2003; Bartlett *et al.*, 2006; Van Cleve *et al.*, 2006; Wright *et al.*, 2006), BUNV (Weber *et al.*, 2002), EBOV (Hartman *et al.*, 2006) and flaviviruses (Liu *et al.*, 2006). However, there are a number of difficulties in using IFN-sensitive viruses as vaccines. The virus may not be as attenuated as expected or required or, alternatively, if the virus is completely sensitive to IFN, the vaccine candidate may be over-attenuated and thus not immunogenic enough. For example, IFN antagonists are often multifunctional proteins, and thus simple gene deletions may overattenuate the virus. Consequently, a better approach may be to introduce/select for point mutations that knock out the IFN-antagonist function of the protein without affecting its other functions. However, single point mutations raise the possibility that such attenuated viruses may revert relatively quickly to wild-type phenotypes. In addition, such IFN-sensitive viruses may be difficult to grow in culture, because most tissue-culture cells can produce and respond to IFN following infection. Vero cells can be used, as they do not produce IFN due to natural deletion of the IFN genes (Desmyter *et al.*, 1968; Mosca & Pitha, 1986). They have the additional advantage that they are already used in manufacture of virus vaccines. However, not all viruses grow in Vero cells, due to other host-cell restrictions, but in such cases it is possible to engineer cells to express different viral IFN antagonists constitutively, to prevent IFN synthesis or the response to IFN (Young *et al.*, 2003).

Antiviral drugs

Viral IFN antagonists might also be targets for novel antiviral drugs. Excitingly, although viruses have many ways to circumvent the IFN response, certain viruses target

the same cellular protein, raising the possibility of antiviral drugs with a fairly wide spectrum of activity. For example, the V proteins of most paramyxoviruses have a conserved cysteine-rich C-terminal domain that interacts with, and blocks the activity of, mda-5 (Andrejeva et al., 2004; Childs et al., 2007). Therefore, a drug or peptide that inhibits the ability of V proteins to interact with mda-5 may inhibit a wide spectrum of paramyxoviruses, including highly pathogenic zoonotic viruses, such as NiV and HeV. In addition, if antiviral drugs/peptides that bind to the cellular targets of viral IFN antagonists can be developed, it may be more difficult for the viruses to acquire drug resistance.

Although antiviral drugs that block viral circumvention of the IFN response may help to control acute infections, they may be particularly useful in chronic virus diseases. Indeed, one reason that IFN treatment of patients infected chronically with HCV or HBV is not always successful may be because these viruses interfere with IFN signalling (Heim et al., 1999; Blindenbacher et al., 2003; Bode et al., 2003; Duong et al., 2004; Christen et al., 2007). If this is correct (see above), then drugs that prevent viral inhibition of IFN signalling may result in either the natural IFN response clearing the infection or a significant improvement in the success of IFN therapy. Similarly, the ability of the HPV E7 protein to block IFN signalling may be important/necessary for the development of papilloma-virus-derived cancers (Barnard & McMillan, 1999; Barnard et al., 2000; Antonsson et al., 2006). Thus, a drug preventing E7-mediated inhibition of IFN signalling might be effective in treating certain types of papillomavirus-related cancers.

IFN-sensitive oncolytic viruses

There is a great deal of interest in using oncolytic viruses for cancer therapy, particularly viruses unable to circumvent the IFN response in human cells, including NDV (Elankumaran et al., 2006; Krishnamurthy et al., 2006), VSV (Stojdl et al., 2000, 2003; Gaddy & Lyles, 2007; Wollmann et al., 2007), mutants of HSV (Mineta et al., 1995; Hunter et al., 1999) and poxviruses. Such viruses may be useful in treating cancers containing tumour cells deficient in their IFN response (Perou et al., 1999; Pitha, 2000), because these viruses would replicate and lyse the tumour cells, but not normal cells with an intact IFN response.

Concluding remarks

In recent years, there has been a resurgence of interest in how viruses interface with the IFN response. This has been due to (i) an increased appreciation of the importance of innate immunity in controlling virus infections, (ii) the elucidation of the molecular pathways by which IFNs are induced and of the signalling response to IFN, and (iii) a realization that all mammalian viruses must have some

strategy for circumventing the IFN response. Ten years ago, it was not generally appreciated that even small RNA viruses with limited coding capacity could produce proteins whose primary function is to target some aspect of the IFN pathway. Whilst over the coming years we can expect an increase in our understanding of how viruses block the IFN response, it is likely that more attention will be placed on how IFN controls virus infections, the interplay between the IFN response and other host-defence mechanisms, and not only how viruses block the IFN response, but also how they have adapted the programmed IFN response to their own advantage. The application of the knowledge gained from such studies should enable better control of virus infections and other diseases.

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