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REVIEW ARTICLE

Interferons: cell signalling, immune modulation, antiviral responses and virus countermeasures

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Introduction

To establish infections *in vivo*, viruses must replicate in the face of powerful immune defence mechanisms including those induced by interferons (IFNs). The effectiveness of the IFN response has led to many viruses developing specific mechanisms that antagonize the production or actions of IFNs. Indeed, in order to replicate efficiently *in vivo*, it seems likely that all viruses must, at least to a degree, have some means of circumventing the IFN response either by limiting IFN production or by blocking IFN actions. However, virus countermeasures to the IFN response are rarely absolute and the IFN response, by limiting virus spread, buys time for the generation of an acquired immune response to the invading virus. Nevertheless, the speed and efficiency by which a given virus circumvents the IFN response may be critical determinants in its host range and pathogenicity. In part A of this article, we review how virus infections lead to the production of IFNs (section 1), how IFNs induce the transcription of their target genes (section 2) and how these target genes exert their antiviral effects (section 3). Part B of this article reviews the strategies used by viruses to inhibit IFN production (section 4), IFN signalling (section 5) and/or specific antiviral functions (section 6).

The IFNs are a large family of multifunctional secreted proteins involved in antiviral defence, cell growth regulation and immune activation. The IFNs may be classified into two distinct types. Type I IFNs are produced in direct response to virus infection and consist of the products of the IFN-α multigene family, which are predominantly synthesized by leukocytes, and the product of the IFN-β gene, which is synthesized by most cell types but particularly by fibroblasts. Type II IFN consists of the product of the IFN-γ gene and, rather than being induced directly by virus infection, is synthesized in response to the recognition of infected cells by activated T lymphocytes and natural killer (NK) cells (reviewed in Vilcek & Sen, 1996).

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Type I IFN (IFN-α/β) and type II IFN (IFN-γ) share no obvious structural homology. However, functional similarities exist due to a broad overlap in the types of genes that they induce (reviewed in Stark *et al.*, 1998; summarized in Fig. 1). It is clear that IFNs can induce transcription of a significant number of genes. In addition to the well-characterized gene products described below, large-scale screening using oligonucleotide arrays has identified several novel human IFN-inducible genes that are induced by either IFN-α/β or IFN-γ or both (Der *et al.*, 1998). The importance of IFN in mediating responses to virus infections is established by the fact that mice lacking IFN-α/β (Muller *et al.*, 1994; Fiette *et al.*, 1995; Hwang *et al.*, 1995; Rousseau *et al.*, 1995; Steinhoff *et al.*, 1995; van den Broek *et al.*, 1995*a*, *b*; Garcia-Sastre *et al.*, 1998; Mrkic *et al.*, 1998; Yeow *et al.*, 1998; Cousens *et al.*, 1999; Grieder & Vogel, 1999; Grob *et al.*, 1999; Johnson & Roehrig, 1999; Nunez, 1999) or IFN-γ (Huang *et al.*, 1993; Muller *et al.*, 1994; Fiette *et al.*, 1995; van den Broek *et al.*, 1995*a*, *b*; Bovolenta *et al.*, 1999; Cantin *et al.*, 1999; Dorman *et al.*, 1999; Grob *et al.*, 1999; Nunez, 1999; Tay *et al.*, 1999) receptors are unable to mount efficient responses to a large number of viruses. Importantly, there are often differences in the requirements for the two types of IFN in resolving specific virus infections, and the systems are non-redundant in many cases. Both types of IFN stimulate an 'antiviral state' in target cells, whereby the replication of virus is blocked or impaired due to the synthesis of a number of enzymes that interfere with cellular and virus processes. Both types of IFN can also slow the growth of target cells or make them more susceptible to apoptosis, thereby limiting the extent of virus spread. Finally, both types of IFN have profound immunomodulatory effects and stimulate the adaptive response. However, whilst both IFN-α/β and IFN-γ influence the properties of immune effector cells, they show significant differences, and it is these extended cytokine functions that probably account for the different spectrums of antiviral activities of the two types of IFN.

A. Production and actions of IFNs

1. Virus induction of IFN genes

The induction of IFN-β expression by virus infection of fibroblastoid cells has been the subject of intensive research. It

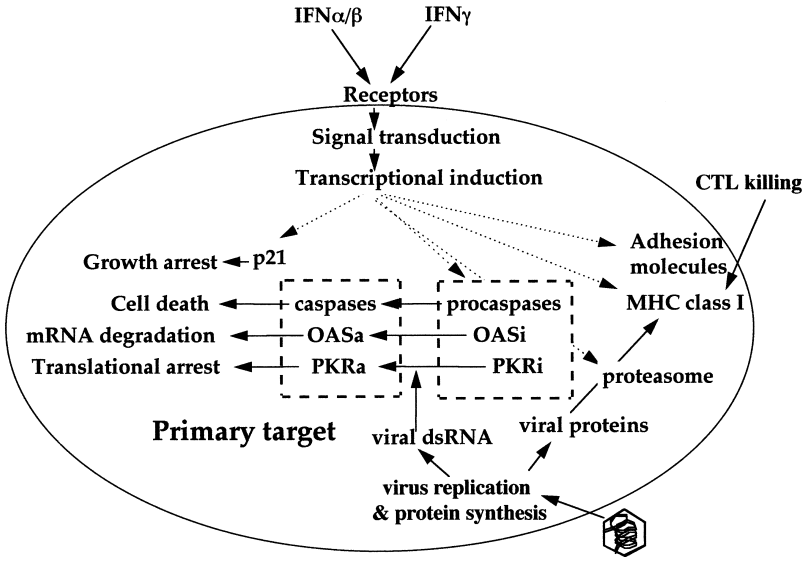

Fig. 1. The biological properties of α/β and γ IFNs. IFNs α/β and γ bind to specific surface receptors on primary target cells and induce the transcription of a variety of genes that mount an antiviral response. It is characteristic of these gene products that they often depend upon viral dsRNA as a co-factor in order to ensure that they are only active under conditions of infection. Thus, PKR and 2′–5′ oligoadenylate synthetase (OAS) are synthesized as inactive precursors (PKRi and OASi, respectively) and are activated by dsRNA (PKRa and OASa, respectively). Once activated, these gene products shut down translation. IFNs can also induce the synthesis of gene products that arrest the cell cycle (e.g. p21, an inhibitor of G_1/S phase-specific cyclin-dependent kinases), thus blocking virus replication, or induce a pro-apoptotic state (e.g. procaspases). Finally, IFNs can induce the synthesis of proteins that are involved in the processing and presentation of virus proteins to $CD8^+$ cytotoxic T lymphocytes (CTLs) (e.g. MHC class I proteins, components of the proteasome and peptide transporter molecules). Both types of IFN also have profound immunomodulatory effects that differ between types, and these are discussed in the text.

is generally assumed that the inducer is intracellular double-stranded RNA (dsRNA), provided by the viral genome itself or formed as a result of replication or convergent transcription of viral genomes (reviewed in Jacobs & Langland, 1996). The induction of IFN-β occurs primarily at the level of transcriptional initiation (see Fig. 2). The key induction event is the redistribution from the cytoplasm to the nucleus of the transcription factor NF-κB (Lenardo *et al.*, 1989; Visvanathan & Goodbourn, 1989). NF-κB plays a role in the transcriptional induction of many immunomodulatory genes, including other cytokines, MHC class I and cell adhesion molecules (reviewed in Baldwin, 1996). NF-κB is normally held in a quiescent state in the cytoplasm by association with an inhibitor molecule called IκB. Upon receipt of a wide range of stress signals [for example lipopolysaccharide, tumour necrosis factor (TNF), interleukin (IL)-1 and viral dsRNA], IκB becomes phosphorylated by a specific multicomponent IκB kinase and, in turn, the phosphorylated IκB becomes ubiquitinated by an E3 ubiquitin ligase. The ubiquitinated IκB is itself a target for degradation by proteasomes and, once the inhibitory IκB is destroyed, the associated NF-κB is freed from restraint and can enter the nucleus and activate transcription (reviewed in Israel, 2000). Exposure to dsRNA activates NF-κB via the dsRNA-dependent protein kinase R (PKR) (Maran *et al.*, 1994; Yang *et al.*, 1995; see section 3), which activates the IKKβ subunit of the multicomponent IκB kinase (Chu *et al.*, 1999; Zamanian-Daryoush *et al.*, 2000). PKR can also phosphorylate IκB directly (Kumar *et al.*, 1994; Offermann *et al.*, 1995), although the biological role for this is unclear.

NF-κB binds to the IFN-β promoter as part of a multiprotein transcription-promoting complex called the 'enhanceasome' (reviewed in Thanos, 1996), which also contains HMG-I/Y, ATF-2 homodimers or ATF-2/c-Jun heterodimers (Du *et al.*, 1993) and a factor that binds to positive regulatory domain I (PRD I). Although the latter would appear to be a member of the interferon regulatory factor (IRF) family, its identity remains the subject of debate, having been suggested to be IRF-1 (Miyamoto *et al.*, 1988; Fujita *et al.*, 1989*a*; Watanabe *et al.*, 1991; Reis *et al.*, 1992; Matsuyama *et al.*, 1993), ISGF3 (Yoneyama *et al.*, 1996), IRF-3 (Sato *et al.*, 1998*b*; Schafer *et al.*, 1998; Weaver *et al.*, 1998; Yoneyama *et al.*, 1998) or a combination of IRF-3 and IRF-7 (Wathelet *et al.*, 1998). Since many of the IRF proteins bind both PRD I and the closely related IFN-stimulated response element (ISRE; an element that is found in genes that are transcriptionally responsive to type I IFN – see section 2), there may be some functional overlap in the properties of these proteins. One consequence of this overlap may be to ensure that virus infections cannot block IFN-β induction completely by inhibiting any single IRF (see section 4).

IFN-α can also be induced by virus infection in fibroblastoid cells, and the promoters of several IFN-α genes have been studied in detail (reviewed in Pitha & Au, 1995). Unlike IFN-β, the IFN-α promoters do not have an NF-κB site, but contain

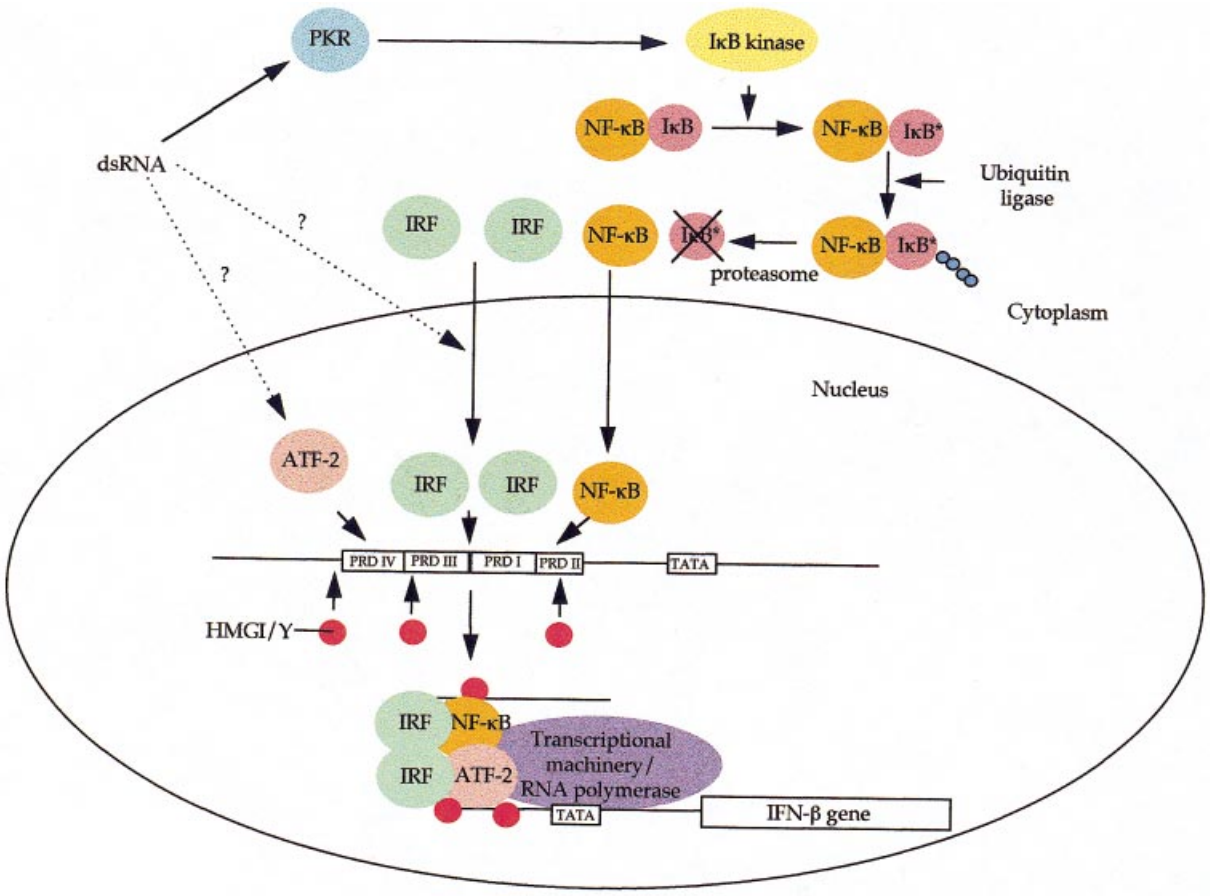

Fig. 2. Transcriptional induction of the IFN-β gene. Virus replication gives rise to dsRNA, which is able to activate PKR and perhaps additional cellular kinases. PKR in turn activates the IκB kinase and indirectly leads to the activation of the immunomodulatory transcription factor NF-κB. Together with ATF-2 and a member(s) of the IRF family, NF-κB assembles on the IFN-β promoter with the help of several copies of the accessory factor HMG-I/Y to form a multifactorial complex called the 'enhanceasome'. Components of the enhanceasome make contacts with factors that are part of the basal transcriptional machinery and, by stabilizing interactions with this machinery and causing a local 'remodelling' of the chromatin, recruit RNA polymerase II to the promoter to bring about transcription of the IFN-β gene. See text for details.

elements that are related to the PRD I- and ATF-2-binding sites, as well as distinct elements. IFN-α genes are not able to be induced in embryonic fibroblasts derived from mice lacking both copies of the IFN-β gene, implying that fibroblasts depend upon IFN receptor activation by IFN-β for IFN-α production (Erlandsson *et al.*, 1998). It is thought that IFN-β works by inducing the synthesis of IRF-7, which, following activation by virus infection, leads to stimulation of IFN-α transcription (Au *et al.*, 1998; Marie *et al.*, 1998; Sato *et al.*, 1998*a*; Yeow *et al.*, 2000). IFN-α is also induced in leukocytes by virus infection. The induction mechanism is poorly characterized in the case of these cells, but is clearly distinct from induction in fibroblasts, since IFN-β production is not required (Erlandsson *et al.*, 1998).

IFN-γ is produced by Th1 $CD4^+$ helper T cells and by nearly all $CD8^+$ cells, as a result of transcriptional activation induced by exposure to antigen-presenting cells (reviewed in Young, 1996). In naive and memory $CD4^+$ T cells, the IFN-γ promoter is under the control of two distinct regulatory elements (proximal and distal; Aune *et al.*, 1997). In contrast, only the distal element is activated in $CD8^+$ cells, leading to a significantly weaker response than that seen in $CD4^+$ cells. The proximal element is activated by complexes containing c-Jun and ATF-2, whilst the distal element is activated by GATA-3 and ATF-1 (Penix *et al.*, 1996; Zhang *et al.*, 1998*a*). The signal transduction mechanisms involved in activating transcription of the IFN-γ gene are poorly characterized, but involve the p38 and JNK2 mitogen-activated protein kinase (MAP kinase) pathways (Rincon *et al.*, 1998; Yang *et al.*, 1998; Lu *et al.*, 1999). IFN-γ production in response to antigen stimulation is enhanced markedly by IL-12 or IL-18, cytokines produced by activated antigen-presenting cells (reviewed in Okamura *et al.*, 1998). Although neither IL-12 nor IL-18 alone can stimulate IFN-γ production significantly in unstimulated T cells, together these cytokines can stimulate IFN-γ production in an antigen-independent manner (Tominaga *et al.*, 2000). The molecular

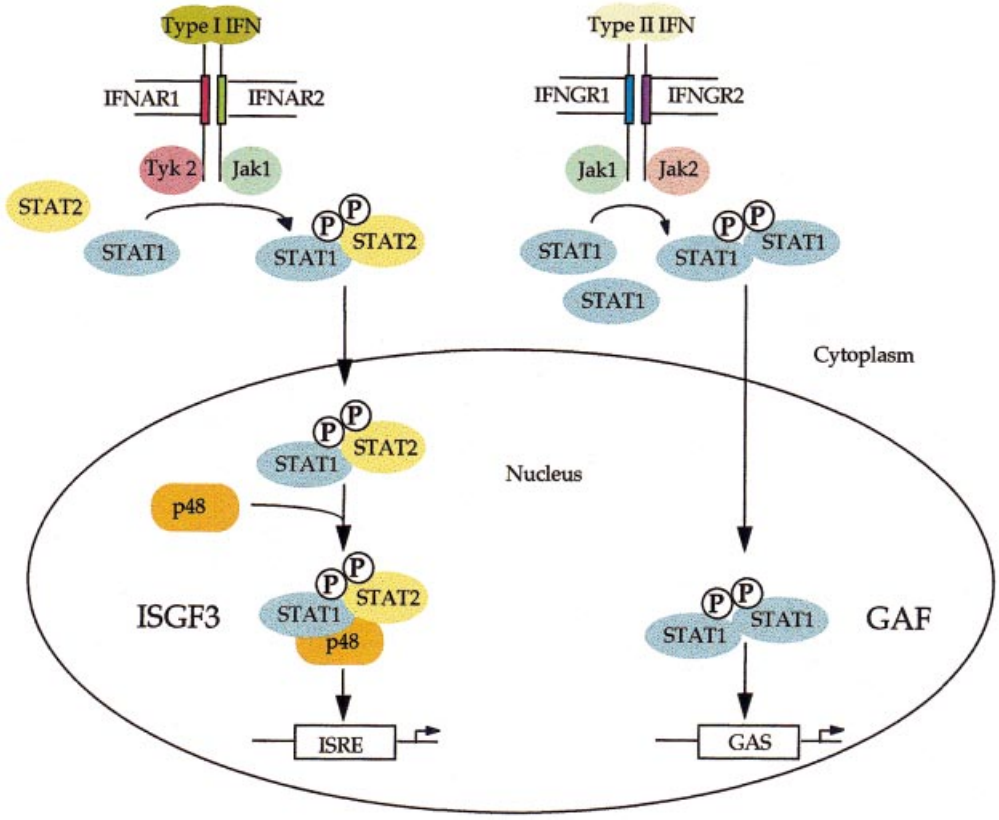

Fig. 3. Signalling pathways activated by IFN-α/β and IFN-γ. The biological activities of IFNs are initiated by binding to their cognate receptors. This leads to the activation of receptor-associated tyrosine kinases, as discussed in the text. These kinases phosphorylate members of the STAT family of transcription factors, which can enter the nucleus and, either on their own or in combination with p48, bind to the promoters of target genes and bring about gene-specific transcriptional activation. See text for details.

basis of this is unknown, but may involve activation of STAT4 by IL-12 and NF-κB by IL-18, and it may also involve an up-regulation of the IL-18 receptor by IL-12 (Yoshimoto *et al.*, 1998). IFN-γ is also produced by activated NK cells in an antigen-independent manner and this is also dependent on IL-12 production by antigen-presenting cells and is stimulated by IL-18 (Singh *et al.*, 2000).

2. Signal transduction in response to IFNs

The biological activities of IFNs are initiated by the binding of IFN-α/β and IFN-γ to their cognate receptors on the surface of cells, which results in the activation of distinct but related signalling pathways, known as the Jak/STAT pathways (reviewed in Stark *et al.*, 1998; summarized in Fig. 3). The ultimate outcome of this signalling is the activation of transcription of target genes that are normally expressed at low levels or are quiescent. The upstream regulatory sequences of most IFN-α/β-inducible genes contain a variation of the consensus sequence [GAAAN(N)GAAA] called the ISRE, whilst the upstream regulatory regions of IFN-γ-inducible genes contain a unique element called the gamma activation sequence (GAS), which contains the consensus sequence TTNCNNNAA.

The IFN-α/β receptor is composed of two major subunits, IFNAR1 and IFNAR2 (reviewed in Mogensen *et al.*, 1999). Prior to stimulation, the cytoplasmic domains of IFNAR1 and IFNAR2 are respectively associated with the 'Janus' tyrosine kinases Tyk2 (Colamonici *et al.*, 1994) and Jak1 (Novick *et al.*, 1994). IFNAR2 is also associated with the 'signal transducer and activator of transcription' (STAT) molecule STAT2 (Li *et al.*, 1997). On IFN-α/β binding, IFNAR1 and IFNAR2 associate, facilitating the transphosphorylation and activation of Tyk2 and Jak1 (Novick *et al.*, 1994). Tyk2 then phosphorylates the tyrosine at position 466 (Tyr^{466}) on IFNAR1 (Colamonici *et al.*, 1994), creating a new docking site for STAT2 through the latter's SH2 domain (Yan *et al.*, 1996). STAT2 is then phosphorylated by Tyk2 at Tyr^{690} and serves as a platform (Leung *et al.*, 1995; Qureshi *et al.*, 1996) for the recruitment of STAT1 (also through its SH2 domain), which is subsequently phosphorylated on Tyr^{701} (Shuai *et al.*, 1993). The phosphorylated STAT1/STAT2 heterodimers thus formed

dissociate from the receptor and are translocated to the nucleus through an unknown mechanism, where they associate with the DNA-binding protein p48 (Veals *et al.*, 1992) to form a heterotrimeric complex called ISGF3, which binds the ISRE of IFN-α/β-responsive genes. p48 is a member of the IRF family and is sometimes referred to as IRF-9; it should be stressed that, like the IFN-β promoter element PRD I, the ISRE sequence can also be bound by other members of the IRF family, notably IRF-1 and IRF-2, and this may have profound biological consequences (see below).

IFN-γ receptors are composed of at least two major polypeptides, IFNGR1 and IFNGR2 (reviewed in Bach *et al.*, 1997). In unstimulated cells, IFNGR1 and IFNGR2 do not pre-associate strongly with one another (Bach *et al.*, 1996), but their intracellular domains specifically associate with the Janus kinases Jak1 and Jak2, respectively (Kotenko *et al.*, 1995; Sakatsume *et al.*, 1995; Bach *et al.*, 1996; Kaplan *et al.*, 1996). Binding of the dimeric IFN-γ to the receptor triggers receptor dimerization, which brings Jak1 and Jak2 molecules on adjacent receptor molecules into close proximity (Greenlund *et al.*, 1994, 1995; Igarashi *et al.*, 1994; Bach *et al.*, 1996); Jak2 is thus activated and in turn activates Jak1 by trans-phosphorylation (Briscoe *et al.*, 1996). The activated Jaks then phosphorylate a tyrosine-containing sequence near the C terminus of IFNGR1 (Tyr^{440}–Tyr^{444}), thereby forming paired binding sites for STAT1 that interact through their SH2 domains (Greenlund *et al.*, 1994, 1995; Igarashi *et al.*, 1994) and are phosphorylated at Tyr^{701}, near the C terminus (Shuai *et al.*, 1993, 1994; Greenlund *et al.*, 1994; Heim *et al.*, 1995). The phosphorylated STAT1 proteins dissociate from the receptor and form a homodimer, through SH2 domain–tyrosine phosphate recognition, which translocates to the nucleus through a poorly characterized mechanism (Sekimoto *et al.*, 1996). Active STAT1 homodimers, also called gamma-activated factor (GAF), bind to specific GAS elements of IFN-γ-inducible genes (reviewed by Stark *et al.*, 1998) and stimulate transcription. IFN-α/β can also induce the formation of STAT1 homodimers, albeit less efficiently than IFN-γ (Haque & Williams, 1994), although the mechanism whereby STAT1 homodimers are activated by IFN-α/β remains obscure.

The transactivation function of STAT1 depends upon phosphorylation of Ser^{727} (Wen *et al.*, 1995) by a kinase with MAP-like specificity. The identity of this kinase remains controversial, although it may differ between cell types. Thus, p38 kinase has been shown to be important for Ser^{727} phosphorylation in response to IFN-α/β and IFN-γ in mouse fibroblasts (Goh *et al.*, 1999) but not in response to IFN-γ in macrophages (Kovarik *et al.*, 1999). Furthermore, the protein tyrosine kinase Pyk2 has recently been shown to be a critical mediator of the Jak-dependent activation of Ser^{727} phosphorylation of STAT1 in IFN-γ, but not IFN-α/β, signalling (Takaoka *et al.*, 1999). It has also recently been shown that PKR plays a role in Ser^{727} phosphorylation (Ramana *et al.*, 2000), but this is unlikely to be direct. The role of Ser^{727} phosphorylation is to facilitate interaction of STAT1 with the basal transcriptional machinery. Recent studies have revealed important connections between STAT1 and the CREB-binding protein (CBP)/p300 transcription factors. The CBP/p300 family of transcription factors potentiate the activity of several groups of transcription factors (reviewed in Janknecht & Hunter, 1996). Both the C- and N-terminal domains of STAT1 have been shown to bind CBP/p300 (Zhang *et al.*, 1996). STAT1 also interacts with the chromatin-associated protein MCM5 in a Ser^{727}-dependent manner (Zhang *et al.*, 1998*b*) and with Nmi, a protein that acts to enhance the association between STAT1 and CBP/p300 (Zhu *et al.*, 1999). Although STAT2 does not contain a MAP kinase consensus site and is not known to be serine-phosphorylated in response to IFN, it also binds CBP/p300 and facilitates interaction with the basal transcriptional machinery (Bhattacharya *et al.*, 1996).

A second form of STAT1 (STAT1β) can be derived by differential splicing. STAT1β contains the tyrosine at position 701 and is recruited to the receptor complex, becomes tyrosine-phosphorylated and binds DNA. However, STAT1β differs from the predominant form of STAT1 (STAT1α) by lacking the C-terminal 38 amino acids that include Ser^{727} and, thus, it cannot activate transcription (Schindler *et al.*, 1992; Shuai *et al.*, 1993). The function of STAT1β is not clear. Although it can become incorporated into ISGF3 complexes that retain their transcriptional activation potential as a result of STAT2 function (Muller *et al.*, 1993), the consequences of a potential STAT1α/STAT1β heterodimer have not been established, but these might well down-regulate transcription.

Recently, several other proteins have been identified that may also be required for IFN signalling. For example, the tyrosine phosphatase SHP-2, which pre-associates with IFNAR1, is phosphorylated in response to IFN-α/β and, in transfection experiments, a dominant-negative form of SHP-2 inhibits the IFN-α/β-induced expression of a reporter gene (David *et al.*, 1996). IFN-α/β treatment also induces the phosphorylation and activation of cytosolic phospholipase A2 (CPLA2), an event that requires Jak1 and the p38 MAP kinase (Goh *et al.*, 1999). The demonstration that CPLA2 inhibitors can block the expression of ISRE-containing genes induced by IFN-α/β implies that CPLA2 also plays a role in the trans-activation of ISRE-containing genes (Hannigan & Williams, 1991; Flati *et al.*, 1996).

As discussed above, other members of the IRF family can bind ISRE sequences and our understanding of IFN-mediated signal transduction is complicated by the fact that some of these IRF proteins are inducible by IFNs. Thus, both IFN-α/β and IFN-γ can induce IRF-1, which can then serve to sustain expression of genes that contain ISREs. Indeed, IRF-1-dependent gene expression in response to IFNs has been observed in a number of cases (see for example Kimura *et al.*, 1994; Chatterjee-Kishore *et al.*, 1998; Kano *et al.*, 1999; Salkowski *et al.*, 1999; Karlsen *et al.*, 2000). This can give rise to complex patterns of gene expression whereby, for

example, IFN-γ can induce the synthesis of genes that lack GAS sites via the induction of IRF-1 (see for example Lechleitner *et al.*, 1998; Foss & Prydz, 1999; Piskurich *et al.*, 1999).

In contrast to the mechanism of IFN signal transduction, little is known about the mechanism of signal attenuation. Several IRF proteins, including IRF-2 (Harada *et al.*, 1989) and the IFN-consensus sequence-binding protein (ICSBP, also called IRF-8; Nelson *et al.*, 1993), are known to bind ISREs and negatively regulate expression, and may help to prevent expression in the absence of IFN or down-regulate the induced response. IFN-induced proteins play a major role in signal attenuation, since protein synthesis inhibitors prolong the transcription of IFN-induced genes (Friedman *et al.*, 1984; Larner *et al.*, 1986). One group of proteins with the potential to fulfil this role is the SOCS/JAB/SSI family, which are inducible by IFN-γ and several other cytokines and bind to and inhibit activated Jaks, leading to signal down-regulation (Endo *et al.*, 1997; Naka *et al.*, 1997; Starr *et al.*, 1997; Starr & Hilton, 1999).

Activation by STAT1 is usually transient, as a result of dephosphorylation by a tyrosine phosphatase (Igarashi *et al.*, 1993; Haque *et al.*, 1995). However, it is not known whether the phosphatase acts on phosphorylated STATs in the nucleus or on phosphorylated Jaks or receptor subunits at the plasma membrane. The tyrosine phosphatase SHP-1 has been shown to be associated reversibly with IFNAR-1 after IFN-α stimulation (David *et al.*, 1995) and Jak1 and STAT1 phosphorylation is increased significantly in macrophages isolated from mice that lack SHP-1 activity compared with normal control macrophages (Haque & Williams, 1998), suggesting that SHP-1 may play a role in signal attenuation. In addition to down-regulation by dephosphorylation, STAT1 is turned over by a mechanism involving proteasome-mediated degradation, but there is no evidence that this process is important in the regulation of STAT1 function (Kim & Maniatis, 1996).

3. The antiviral response

The best-characterized IFN-inducible components of the antiviral response are PKR and the 2′–5′ oligoadenylate synthetases, although it is clear that other factors may be involved, especially molecules that regulate the cell cycle or cell death and thereby limit the extent of virus replication. In many cases, IFN-inducible enzymes are inactive until exposed to virus infection, thus ensuring that uninfected cells do not suffer undue trauma. It is thought that the virus co-factor that activates these IFN-inducible enzymes is dsRNA (reviewed in Jacobs & Langland, 1996).

(i) dsRNA-dependent protein kinase R (PKR). The IFN-inducible PKR is a serine/threonine kinase with multiple functions in control of transcription and translation (reviewed in Clemens & Elia, 1997). The PKR protein has two well-characterized domains, an N-terminal regulatory domain that contains the dsRNA-binding site and a C-terminal catalytic domain that contains all of the conserved motifs for protein kinase activity (Meurs *et al.*, 1990). PKR is normally inactive, but is activated by binding to dsRNA or other polyanions (Meurs *et al.*, 1990; Katze *et al.*, 1991; George *et al.*, 1996), whereupon it undergoes a conformational change that leads to the unmasking of the catalytic domain. The active form of PKR is postulated to be a dimer, with two PKR molecules binding one molecule of dsRNA; the juxtaposed PKR molecules trans-phosphorylate each other on several serines and threonines. PKR activation is decreased when large amounts of dsRNA are present, due to saturation of dsRNA-binding sites and a shift in the equilibrium towards monomers. There are no sequence requirements for the dsRNA, although some RNAs are more potent activators than others. However, there are size requirements, with at least 50 base pairs of duplex being necessary for activation (reviewed in Robertson & Mathews, 1996).

Activated PKR has a number of important cell-regulatory activities. Firstly, it phosphorylates the α subunit of the eukaryotic translation initiation factor eIF2 and prevents the recycling of initiation factors (Meurs *et al.*, 1992; reviewed in Clemens & Elia, 1997). In the initial step of translation, the initiator Met-tRNA is recruited to the 40S ribosomal subunit via an interaction with GTP-bound eIF2 (which consists of three subunits, α, β and γ). This complex then interacts with mRNA, other initiation factors and the large ribosomal subunit to form a pre-initiation complex, with subsequent hydrolysis of the GTP molecule bound to eIF2 and release of GDP-bound eIF2. In order to participate in another round of translational initiation, the GDP bound to eIF2 must be exchanged for GTP, a reaction that is catalysed by the guanine exchange factor, eIF2B. Phosphorylated eIF2α interacts strongly with eIF2B and traps it such that it cannot mediate the recycling of eIF2 (Ramaiah *et al.*, 1994; reviewed by Clemens & Elia, 1997). Since eIF2B is present in limiting amounts, translation is inhibited.

PKR also plays a role in mediating signal transduction in response to dsRNA and other ligands (reviewed in Williams, 1999). For example, the transcription factor NF-κB, which is essential for mediating induction of the IFN-β gene, is activated by PKR in response to dsRNA (see section 1). PKR has also been proposed to influence the activity of the transcription factors STAT1 (Wong *et al.*, 1997; Ramana *et al.*, 2000), IRF-1 (Kumar *et al.*, 1997) and p53 (Cuddihy *et al.*, 1999*a*, *b*), although the details of the activation events remain to be clarified. The elevated levels of PKR that would be found in a cell exposed to IFN would cause an enhancement of these signal transduction events, which may help to accelerate virus clearance. For example, enhanced activation of NF-κB activation would lead to increased cytokine, chemokine and MHC class I presentation.

PKR also aids in the clearance of virus infection by mediating apoptosis. It has been shown that dsRNA (and thus virus infection) can trigger apoptosis directly (Der *et al.*, 1997; King & Goodbourn, 1998; Tanaka *et al.*, 1998) and there

is considerable evidence that this effect works through PKR (Takizawa *et al.*, 1996; Der *et al.*, 1997; reviewed in Jagus *et al.*, 1999; Tan & Katze, 1999), although PKR-independent mechanisms also operate for some viruses (Balachandran *et al.*, 2000). The downstream targets for PKR-mediated apoptosis remain to be identified, but overexpression of PKR has been shown to induce apoptosis through a Bcl2- and caspase-dependent mechanism (Lee *et al.*, 1997). Intriguingly, although mice with a targetted knockout of the dsRNA-binding domain of PKR are sensitive to virus-induced apoptosis (Yang *et al.*, 1995), mice with a targetted knockout of the PKR catalytic domain are not (Abraham *et al.*, 1999).

PKR also plays a role in mediating the apoptotic effects of dsRNA in an indirect manner. In this case, effects on protein synthesis are important (Srivastava *et al.*, 1998; Gil *et al.*, 1999), as are effects on the transcription factor NF-κB (Gil *et al.*, 1999). Exposure of cells to dsRNA also enhances apoptosis by inducing the synthesis of Fas (Takizawa *et al.*, 1995; Balachandran *et al.*, 1998; Fujimoto *et al.*, 1998) and Fas receptor (Fujimoto *et al.*, 1998) in a manner that depends upon PKR (Balachandran *et al.*, 1998). Finally, the apoptotic effects of TNF on promonocytic U937 cells require p53 to ensure a response to activated PKR (Yeung *et al.*, 1996).

Although there is abundant evidence that PKR plays a major role in regulating virus infection, PKR is not sufficient to mediate the full antiviral response. Thus, mice with homozygous disruptions of the PKR gene (Yang *et al.*, 1995; Abraham *et al.*, 1999) still show resistance to virus infection, although the wild-type but not the PKR-deficient animals are protected to some extent by injection of dsRNA at virus doses that are normally lethal (Yang *et al.*, 1995).

(ii) The 2′–5′ oligoadenylate synthetase system. 2′–5′ oligoadenylate synthetases are a group of enzymes that are induced by IFNs in mammalian cells and catalyse the synthesis from ATP of oligomers (three to five units) of adenosine linked by phosphodiester bonds in the unusual conformation of 2′ to 5′ (2′5′A; Kerr & Brown, 1978). The 2′5′A molecules bind with high affinity to endoribonuclease L (RNase L) and induce its activation via dimerization. Activated RNase L catalyses the cleavage of single-stranded RNA including mRNA, thereby leading to inhibition of protein synthesis (reviewed in Silverman, 1997). It has recently been demonstrated that RNase L also cleaves 28S ribosomal RNA in a site-specific manner, leading to ribosomal inactivation and thus translational inhibition (Iordanov *et al.*, 2000). Since 2′5′A is highly labile, the activation of RNase L depends upon locally activated 2′–5′ oligoadenylate synthetase within the cell, thus ensuring that virus transcripts are destroyed preferentially over cellular mRNAs, since they are in the vicinity of the activator (viral dsRNA; Nilsen & Baglioni, 1979).

The 2′–5′ oligoadenylate synthetase/RNase L system has been suggested to play a role in the antiviral effects of IFN-α/β against vaccinia virus, reovirus and encephalomyocarditis virus (reviewed in Silverman & Cirino, 1997) and antiviral effects of IFN-α are indeed impaired in RNase $L^{-/-}$ mice (Zhou *et al.*, 1997). RNase L may also play a role in apoptosis, since RNase $L^{-/-}$ mice show defects in apoptosis in several tissues (Zhou *et al.*, 1997) whilst activation of RNase L induces apoptosis (Diaz-Guerra *et al.*, 1997). Although the exact role of RNase L in apoptosis is not clear, it seems likely that the 2′–5′ oligoadenylate synthetase/RNase L system may contribute to the antiviral activity of IFN by inducing apoptosis of infected cells (Zhou *et al.*, 1997; Castelli *et al.*, 1998*a*, *b*).

(iii) Alternative antiviral pathways. The IFN-inducible Mx proteins are highly conserved, large GTPases with homology to dynamin and have been found in all vertebrate species examined so far, including mammals, birds and fish (reviewed in Staeheli *et al.*, 1993; Arnheiter *et al.*, 1995). Mx proteins interfere with virus replication, probably by inhibiting the trafficking or activity of virus polymerases (Stranden *et al.*, 1993), thereby impairing the growth of a wide range of RNA viruses at the level of virus transcription and at other steps in the virus life-cycle. The murine nuclear protein Mx1 has been shown to suppress the growth of members of the *Orthomyxoviridae* (Staeheli *et al.*, 1986, 1988; Haller *et al.*, 1995). The human cytoplasmic protein MxA inhibits the growth of members of several RNA families, including the *Orthomyxoviridae* (Pavlovic *et al.*, 1990, 1992; Frese *et al.*, 1995, 1997), *Paramyxoviridae* (Schneider-Schaulies *et al.*, 1994; Zhao *et al.*, 1996), *Rhabdoviridae* (Pavlovic *et al.*, 1990), *Bunyaviridae* (Frese *et al.*, 1996; Kanerva *et al.*, 1996) and *Togaviridae* (Landis *et al.*, 1998). Mutant forms of Mx proteins lacking the ability to bind or hydrolyse GTP fail to suppress virus replication. Hefti *et al.* (1999) have analysed the behaviour of transgenic mice that constitutively express the human MxA gene in a mouse background lacking the IFN-α/β receptor and have shown that the MxA protein protects mice against Thogoto virus, La Crosse virus and Semliki Forest virus.

Recent studies involving the generation of mice that are triply deficient in RNase L, PKR and Mx1 indicate that there are additional antiviral effects of IFNs (Zhou *et al.*, 1999). Other factors that clearly play a role in the IFN-induced antiviral response are caspases (see below) and the dsRNA-dependent adenosine deaminase (ADAR). The enzyme ADAR recognizes dsRNA as a substrate and unwinds it as a result of systematically replacing adenosines with inosine (Bass *et al.*, 1989; Polson & Bass, 1994; O'Connell *et al.*, 1995; Patterson *et al.*, 1995). Since many viral RNAs go through a dsRNA-based replicative intermediate, this has the effect of being mutagenic, and there are several reports of genomic substitutions consistent with this activity (Bass *et al.*, 1989; Cattaneo, 1994; Casey & Gerin, 1995; Hajjar & Linial, 1995; Horikami & Moyer, 1995; Polson *et al.*, 1996). It has also been suggested that an inosine-specific ribonuclease could act in concert with ADAR to destroy modified viral RNAs (Scadden & Smith, 1997).

(iv) Antiproliferative activities of IFNs. IFNs can inhibit cell growth and thereby inhibit the replication of some viruses. However, the sensitivity of cells to the antiproliferative effects of IFNs is very cell-type dependent. For example, growth of the Daudi B cell line is arrested completely by as little as 1 unit/ml IFN-α/β, whereas many cell types are largely unresponsive at any dose tested. Because of the potential clinical importance of the cytostatic properties of IFN, the negative regulation of growth has been studied intensively and a number of aspects of this process have been described. There is evidence to support a role for PKR and RNase L in the antiproliferative functions of IFNs. The amount of PKR can vary according to the state of growth of mammalian cells in culture and this appears to correlate with the level of eIF2α phosphorylation (reviewed in Jaramillo *et al.*, 1995), suggesting that, even in the absence of viral dsRNA, PKR can exhibit residual activity, presumably due to the presence of a cellular activator. Additionally, overexpression of PKR is growth suppressive and/or toxic in insect, mammalian and yeast cells (Koromilas *et al.*, 1992; Chong *et al.*, 1992; Dever *et al.*, 1993), an effect which can also be shown to be due to eIF2α phosphorylation. Overexpression of the 40 kDa form of 2′–5′ oligoadenylate synthetase has been shown to reduce growth rates of transfected cells (Chebath *et al.*, 1987; Rysiecki *et al.*, 1989; Coccia *et al.*, 1990) and expression of a dominant-negative mutant of RNase L in murine SVT2 cells inhibited the antiproliferative effect of IFN on these cells (Hassel *et al.*, 1993).

IFNs can also exert negative regulation of the cell cycle at a more direct level. IFNs have been shown to up-regulate specifically the levels of the cyclin-dependent kinase inhibitor p21 (Chin *et al.*, 1996; Subramaniam & Johnson, 1997; Subramaniam *et al.*, 1998), which plays a crucial role in the progression from G_1 into S phase (reviewed in Harper *et al.*, 1993; Gartel *et al.*, 1996). When p21 levels are elevated, cyclin-dependent kinase activity is turned off and consequently the phosphorylation of the retinoblastoma gene product (pRb) and the related pocket proteins is suppressed (Sangfelt *et al.*, 1999). Since hypophosphorylated pRb and the related pocket proteins interact strongly with the E2F family of transcription factors, there is a consequent increase in the pRB-/pocket protein-bound E2F complexes (Iwase *et al.*, 1997; Kirch *et al.*, 1997; Furukawa *et al.*, 1999). The significance of this is that free E2F is required for the transcription of many genes that are needed for transition from G_1 to S phase and thus the elevation of pRB-/pocket protein-bound E2F complexes results in a block to the cell cycle.

Another major IFN-inducible activity that can act as a potent repressor of the cell cycle is the p202 gene product and related members of its '200 family' (Kingsmore *et al.*, 1989; Lembo *et al.*, 1995; Gutterman & Choubey, 1999). The p202 product can bind both hypophosphorylated pRb (Choubey & Lengyel, 1995) and members of the E2F transcription family (Choubey *et al.*, 1996; Choubey & Gutterman, 1997) as well as complexes containing both. The complex between E2F and p202 is unable to bind DNA and hence there is a loss of stimulation of transcription of genes important for the G_1–S transition. Since the p202 protein also contains a transcriptional repression domain (Johnstone *et al.*, 1998), any recruitment to DNA would also shut down gene expression. Finally, IFNs have been shown recently to down-regulate directly the transcription of c-myc, an essential gene product that is required to drive cell cycle progression (Ramana *et al.*, 2000).

(v) Control of apoptosis. IFNs, like other cytokines, can have either pro- or anti-apoptotic activities depending on various factors including the state of cell differentiation. For example, IFN-γ induces apoptosis of murine pre-B cells but inhibits apoptosis of chronic lymphocytic leukaemia cells (Buschle *et al.*, 1993; Grawunder *et al.*, 1993; Rojas *et al.*, 1996). However, when a cell is infected with a virus, a major function of IFN is to ensure that the cell is triggered to undergo apoptosis (Tanaka *et al.*, 1998). IFN appears to do this by inducing a pro-apoptotic state in uninfected cells (reviewed in Schindler, 1998). As discussed above, IFN-induction of PKR and the 2′5′A system plays a major role in the apoptosis response. However, IFN has also been demonstrated to induce caspase 1 (Chin *et al.*, 1997), caspase 3 (Subramaniam *et al.*, 1998) and caspase 8 (Balachandran *et al.*, 2000) and thus to enhance the sensitivity of cells to virus-induced apoptosis. IFN-γ has also been shown to influence the sensitivity to apoptosis by inducing both Fas and Fas ligand (Xu *et al.*, 1998).

(vi) Immunomodulatory functions of IFNs. Nearly all phases of innate and adaptive immune responses are affected profoundly by IFNs. All IFN family members share the ability to enhance the expression of MHC class I proteins and thereby to promote $CD8^+$ T cell responses (reviewed in Boehm *et al.*, 1997). In contrast, only IFN-γ is capable of inducing the expression of MHC class II proteins, thus promoting $CD4^+$ T cell responses. IFNs play an important role in antigen processing by regulating the expression of many proteins involved in the generation of antigenic peptides to be displayed in association with MHC class I proteins. IFN-γ modifies the activity of proteasomes (reviewed in York & Rock, 1996) such that they enhance the generation of peptides that bind class I MHC proteins. In unstimulated cells, the proteasome contains the three enzymatic subunits x, y and z. However, following IFN-γ treatment of cells, the transcription of the x, y and z genes is decreased and the transcription of three additional genes encoding enzymatic proteasome subunits LMP2, LMP7 and MECL1 is increased. This results in the formation of proteasomes with different substrate specificities, thereby altering the types of peptide produced and subsequently presented to the immune system. IFN-γ also increases the expression of TAP1 and TAP2, which are involved in the transfer of peptides (generated by the proteasome) from the cytoplasm into the endoplasmic reticulum to bind nascent MHC class I proteins (Trowsdale *et al.*, 1990; Epperson *et al.*,

1992). Thus, IFNs enhance immunogenicity by increasing the repertoire and quantity of peptides displayed to $CD8^+$ T cells.

IFN-γ also plays an important role in regulating the balance between Th1 and Th2 cells. Firstly, it increases the synthesis of IL-12 in antigen-presenting cells (Dighe *et al.*, 1995; Flesch *et al.*, 1995; Murphy *et al.*, 1995). IL-12 is the primary effector that drives developing $CD4^+$ T cells to become Th1 cells (Hsieh *et al.*, 1993; Trinchieri, 1995). Secondly, IFN-γ prevents the development of Th2 cells by inhibiting the production of IL-4, which is required for Th2 cell formation (Gajewski & Fitch, 1988; Szabo *et al.*, 1995). IFN-γ also plays an important role in macrophage activation (Adams & Hamilton, 1984; Buchmeier & Schreiber, 1985; Dalton *et al.*, 1993; Huang *et al.*, 1993). Once activated, macrophages use a variety of IFN-γ-induced mechanisms to kill microbial targets. The most important of these mechanisms involve the production of reactive oxygen and reactive nitrogen intermediates. Reactive oxygen intermediates are generated as products of the enzyme NADPH oxidase, the assembly of which is induced by IFN-γ. Reactive nitrogen intermediates, especially nitric oxide (NO), are generated in murine macrophages as a result of the IFN-γ-dependent transcription of the gene encoding the inducible form of nitric oxide synthase (iNOS), which catalyses NO formation (MacMicking *et al.*, 1997).

In addition to affecting humoral immunity indirectly by regulating the development of specific T helper cell subsets, IFNs can have direct effects on B cells by regulating development and proliferation, immunoglobulin (Ig) secretion and Ig heavy-chain switching. Since different Ig isotypes promote distinct effector functions in the host, IFNs can facilitate interactions between the humoral and cellular effector limbs of the immune response and increase the host defence against certain bacteria and viruses by selectively enhancing the production of certain Ig isotypes while inhibiting the production of others (Snapper & Paul, 1987; Snapper *et al.*, 1988, 1992).

A major immunomodulatory function of IFN-α/β is to enhance the cytotoxicity of NK cells (reviewed in Reiter, 1993; Biron *et al.*, 1999) by up-regulating the levels of perforins (Mori *et al.*, 1998; Kaser *et al.*, 1999). IFN-α/β also acts to stimulate the proliferation of NK cells to a limited degree, apparently via the induction of IL-15 from monocytes/macrophages (Ogasawara *et al.*, 1998; Fawaz *et al.*, 1999; Gosselin *et al.*, 1999; Sprent *et al.*, 1999). NK cells also synthesize and secrete IFN-γ in response to a combination of IL-12 and IL-15, which are released from infected monocytes/macrophages (Doherty *et al.*, 1996; Fehniger *et al.*, 1999). However, IFN-α/β blocks the production of IL-12 by infected monocytes (reviewed in Biron *et al.*, 1999) and thus prevents NK cells from producing IFN-γ. The biological reasons, if any, behind this are unclear. Finally, IFN-α/βs also play a role in stimulating the adaptive responses; IFN-induced IL-15 can stimulate the division of memory T cells (Tough *et al.*, 1996; Zhang *et al.*, 1998*c*; reviewed in Tough *et al.*, 1999; Sprent *et al.*, 1999), whilst IFN-α/β appears to be able to promote the survival of activated T cells directly (Marrack *et al.*, 1999).

B. Virus countermeasures to the IFN response

4. Inhibition of IFN production

Viruses vary considerably in their ability to induce IFN. This may simply reflect the amounts of dsRNA produced during their replication cycles (in general, DNA viruses produce less dsRNA than RNA viruses and are therefore less potent inducers of IFN; reviewed in Jacobs & Langland, 1996) or it may reflect the fact that many viruses produce dsRNA-binding proteins as part of their life-cycle. The sequestration of dsRNA could inhibit the induction of IFN-α/β and might also act to minimize the dsRNA-dependent activation of antiviral gene products like PKR, 2′–5′ oligoadenylate synthetase and ADAR, as well as dsRNA-dependent apoptosis. For example, the reovirus major outer capsid protein $\sigma3$ is a dsRNA-binding protein (Lloyd & Shatkin, 1992; Yue & Shatkin, 1997; reviewed in Jacobs & Langland, 1998), as is the σA protein of avian reovirus (Martinez-Costas *et al.*, 2000). Reovirus strains vary significantly in their ability to induce IFN-α/β (reviewed in Samuel, 1998); although this has not yet been shown to be a function of variation in the $\sigma3$ protein, it is interesting to note that strain differences in IFN sensitivity have been linked to differences in dsRNA affinity of the $\sigma3$ protein (Bergeron *et al.*, 1998). The multifunctional NS1 protein of influenza virus (Lu *et al.*, 1995), the E3L protein of vaccinia virus (Chang *et al.*, 1992) and products of the NSP3 gene of porcine rotaviruses (Langland *et al.*, 1994) also bind dsRNA and a number of other viruses that have been reported to block IFN production at the transcriptional level may also do so by sequestering dsRNA [e.g. the core antigen of hepatitis B virus (HBV); Twu & Schloemer, 1989; Whitten *et al.*, 1991]. The sequestration of dsRNA by viral proteins might have a wider role in protecting the virus from antiviral mechanisms; dsRNA-activated PKR can activate NF-κB and induce the synthesis of immunomodulatory genes in addition to IFN-α/β.

Since the activation of NF-κB by infection is a key trigger to inducing IFN-α/β transcription and other immune responses, it would perhaps not be surprising to find that many viruses encoded inhibitors of NF-κB activation or function. Indeed, African swine fever virus (ASFV) encodes a homologue of IκB that inhibits the activity of NF-κB (Powell *et al.*, 1996; Revilla *et al.*, 1998). However, it is well established that NF-κB, as well as inducing proinflammatory cytokines, also induces anti-apoptotic genes (Liu *et al.*, 1996; Wu *et al.*, 1996; Wang *et al.*, 1996; Van Antwerp *et al.*, 1996; reviewed in Van Antwerp *et al.*, 1998; Foo & Nolan, 1999) and any virus that blocks NF-κB activation may leave itself susceptible to enhanced induction of apoptosis. Interestingly, ASFV infections are indeed characterized by a significant degree of apoptosis (Oura *et al.*, 1998). The increased risk of apoptosis associated with inhibition of

NF-κB may be circumvented by viral gene products that act to block apoptosis; such gene products are widespread (reviewed in Cuff & Ruby, 1996; Gillet & Brun, 1996).

Another major strategy for blocking IFN-α/β production would be to target the activities of the IRF transcription factors that bind to the PRD I region of the IFN-β promoter. Intriguingly, the E6 protein of human papillomavirus type 16 (HPV-16) binds IRF-3 and can inhibit its virus-induced transcriptional activation function (Ronco *et al.*, 1998). However, induction of IFN-β is not blocked completely by the E6 protein, suggesting that other cellular factors can substitute functionally for IRF-3, and indeed, as discussed above, there are several lines of evidence consistent with this hypothesis. The potential substitutes for IRF-3 include IRF-1 (Miyamoto *et al.*, 1988; Fujita *et al.*, 1989*a*; Watanabe *et al.*, 1991; Reis *et al.*, 1992; Matsuyama *et al.*, 1993) and ISGF3 (Yoneyama *et al.*, 1996), but these factors can themselves be targetted by virus functions. For example, IRF-1 is targetted by the K9 ORF gene product of human herpesvirus-8 (HHV-8) (Zimring *et al.*, 1998), whilst the E7 protein of HPV-16 interacts with the p48 subunit of ISGF3 and prevents binding to DNA (Barnard & McMillan, 1999). Perhaps the plethora of factors that can bind to the PRD I region of the IFN-β promoter reflects a need of the cell to be able to circumvent virus blockades.

In addition to specific transcription factor blocks, viruses may inhibit the production of IFN by generally down-regulating host mRNA production or protein synthesis, and there is some evidence that these apparently non-specific effects can affect virus pathogenicity. For example, mutation in the gene encoding the matrix M protein of vesicular stomatitis virus (which in wild-type virus causes a general inhibition of host-cell transcription) leads to an attenuated virus with efficient IFN-β-inducing properties (Ferran & Lucas-Lenard, 1997). Similarly, the foot-and-mouth disease virus L proteinase gene encodes a protein that shuts off host-cell protein synthesis and mutation of this gene is sufficient to generate an attenuated strain that induces elevated levels of IFN-α/β (Chinsangaram *et al.*, 1999).

Viruses may also have more subtle and indirect methods for reducing the level of IFN produced. For example, Epstein–Barr virus (EBV) produces a homologue of IL-10 (Hsu *et al.*, 1990). Normally, IL-10 is produced by the Th2 subset of T helper cells and one of its biological functions is to inhibit the ability of monocytes and macrophages to activate Th1 cells by down-regulating the expression of class II MHC molecules. Activated Th1 cells produce a number of cytokines, including IFN-γ, that are critical for the induction of classical cell-mediated immune responses, including cytotoxic T lymphocytes. It has therefore been proposed that EBV produces the homologue of IL-10 in order to induce an inappropriate and less-effective immune response against the virus (Bejarano & Masucci, 1998). Similarly, human herpesvirus-6 may up-regulate IL-10, thereby causing immunodysregulation by causing a shift from a Th1 to a Th2 cytokine profile (Arena *et al.*, 1999).

5. Inhibition of IFN signalling

There are clear advantages to viruses in having the ability to block IFN signalling. Since there are components in common between signalling pathways, it is possible for a virus to block IFN-α/β or IFN-γ signalling or both. Using such strategies, not only would the induction of cellular antiviral enzymes, such as PKR, 2′–5′ oligoadenylate synthetase and Mx, be inhibited but there would also be no up-regulation of class I MHC molecules within infected cells, making them poorer targets for cytotoxic T cells. 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.

Blocking the IFN signalling pathways could occur at several levels and there is accumulating evidence that viruses can block at most, if not all, stages (Table 1). Several poxviruses have been shown to encode soluble IFN-receptor homologues that bind and sequester IFNs, thereby preventing their biological activity. For example, functional IFN-γ receptors are secreted by cells infected with rabbit myxoma virus, ectromelia virus, cowpox virus, camelpox virus and vaccinia virus (Upton *et al.*, 1992; Mossman *et al.*, 1995; Alcami & Smith, 1995). Vaccinia virus and most other orthopoxviruses also encode soluble IFN-α/β receptor homologues (Symons *et al.*, 1995; Colamonici *et al.*, 1995). It appears that the vIFN-α/β receptor of vaccinia virus can also bind to the surface of cells and inhibit IFN activity. Intriguingly, highly attenuated strains of vaccinia virus do not secrete the IFN-α/β receptor, consistent with its importance in virus pathogenesis. Interestingly, in terms of virus host range, both the IFN-α/β and IFN-γ receptor homologues secreted by poxviruses often have a broad species specificity, unlike their cellular counterparts.

Human cytomegalovirus (HCMV) has been shown to disrupt IFN signalling by decreasing the levels of Jak1 and p48 by a mechanism involving the proteasome (Miller *et al.*, 1998, 1999), whereas the T antigen of murine polyomavirus (MPyV) binds to Jak1 thereby blocking the activation of the IFN-α/β and IFN-γ signalling pathways (Weihua *et al.*, 1998). The STAT and p48 proteins that form part of IFN-inducible transcription complexes are targets for inhibition by several viruses. The V protein of the paramyxovirus simian virus 5 (SV5) targets STAT1 for proteasome-mediated degradation (Didcock *et al.*, 1999*b*), thereby preventing the formation of ISGF3 and GAF complexes; indeed, at least part of the host range of SV5 appears to be determined by the ability to mediate STAT1 degradation (Didcock *et al.*, 1999*a*). Surprisingly, whilst mumps virus also probably targets STAT1 for degradation (Yokosawa *et al.*, 1998), human parainfluenza virus 2 (hPIV2) (a virus very closely related to SV5 and mumps) targets STAT2 (Young *et al.*, 2000). As a consequence, whilst SV5 and mumps virus block both IFN-α/β and IFN-γ signalling, hPIV2 blocks only IFN-α/β signalling. Sendai virus (Didcock *et al.*, 1999*b*; Yokoo *et al.*, 1999) and hPIV3 also block IFN-α/β and IFN-γ signalling, although there was no evidence with these viruses that either

Table 1. Virus inhibition of IFN signalling and IFN-induced transcriptional responses

Virus	Mechanism of action/inhibition
i. Inhibition of IFN binding to cognate receptors	
Poxviruses (many)	Soluble IFN-α/β receptor
Poxviruses (many)	Soluble IFN-γ receptor
ii. Inhibition of Jak/STAT pathway	
Adenovirus	E1A decreases the levels of STAT1 and p48; sequesters the transcriptional co-activator, CBP/p300, which binds STAT1 and STAT2; interacts directly with STAT1
Ebola virus	Blocks IFN-α/β and IFN-γ signalling, mechanism unknown
Epstein–Barr virus	EBNA-2 blocks IFN signal transduction, mechanism unknown
Hepatitis C virus	Blocks IFN-α/β and IFN-γ signalling, mechanism unknown
Human cytomegalovirus	Reduces levels of Jak1 and p48
Human parainfluenza virus type 2	Blocks IFN-α/β signalling by targetting STAT2 for degradation
Human parainfluenza virus type 3 and Sendai virus	Block IFN-α/β and IFN-γ signalling by blocking STAT1 phosphorylation
Human papillomavirus type 16	E7 protein binds to p48 and blocks IFN-α/β signalling
Murine polyoma virus	T antigen binds to and inactivates Jak1
Simian virus 5 (and mumps virus?)	V protein blocks IFN-α/β and IFN-γ signalling by targetting STAT1 for proteasome-mediated degradation
iii. Miscellaneous	
Hepatitis B virus	Capsid protein specifically inhibits MxA gene expression, mechanism unknown
Human herpesvirus-8	Virus IRF homologue blocks transcriptional responses to IFN-α/β and IFN-γ

STAT1 or STAT2 was specifically degraded. These viruses seem to prevent appropriate phosphorylation of STAT1 (Young *et al.*, 2000; Komatsu *et al.*, 2000). Interestingly, whereas SV5 utilizes the V protein to block IFN signalling, Sendai virus has been shown to use the C protein (Garcin *et al.*, 1999; Gotoh *et al.*, 1999; Komatsu *et al.*, 2000). In contrast, respiratory syncytial virus (another paramyxovirus) does not inhibit IFN signalling, although it clearly has some uncharacterized mechanism for circumventing the IFN response (Young *et al.*, 2000). The adenovirus E1A protein can disrupt transcriptional responses to IFN-α/β and IFN-γ by decreasing the levels of STAT1 and p48 (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 directly with STAT1 (Look *et al.*, 1998). Furthermore, the multifunctional E7 protein of HPV-16 interacts directly with p48, preventing the formation of ISGF3 and thus the activation of IFN-α/β-inducible genes (Barnard & McMillan, 1999).

HHV-8 encodes a homologue of the IRF family that represses transcriptional responses to IFN-α/β and IFN-γ; in this case, the inhibition does not appear to act at the level of IFN signalling, but rather inhibits the function of the IFN-inducible product IRF-1 (Zimring *et al.*, 1998), thus transcriptional responses to IFN cannot be sustained. It has been reported that EBNA2 of EBV, which acts as a virus and cellular transcription factor, also inhibits IFN-α/β signalling, by an unknown mechanism that does not prevent the formation of ISGF3 complexes (Kanda *et al.*, 1992). Ebola virus (Harcourt *et al.*, 1998) and hepatitis C virus (HCV) (Heim *et al.*, 1999) also block transcriptional responses to IFN-α/β and IFN-γ, although the cellular target(s) for inhibition and the viral proteins responsible have yet to be identified in these cases. It has also been reported recently that the capsid protein of HBV inhibits IFN-induction of the MxA gene (Rosmurduc *et al.*, 1999).

Although blocking IFN signalling would seem to be of limited value to viruses in cells that had already been exposed to IFN before infection (such cells would have an established antiviral state), there is some evidence that it can still be advantageous to be able to down-regulate IFN responses. For example, although SV5 cannot initially replicate efficiently in cells that have entered an antiviral state, the ability of the virion-associated V protein to induce STAT1 degradation leads to an eventual decay of the antiviral state and subsequent virus replication (Didcock *et al.*, 1999*b*). Viral proteins that require synthesis after infection might also be able eventually to inactivate an established antiviral state and permit replication, although it should be stressed that the delay in replication induced by IFN exposure would buy time for the host to mount an acquired immune response to help to resolve the infection.

Given that the immune response has co-evolved with viruses and that blocking IFN signalling seems an obvious

Table 2. Virus inhibition of IFN-induced antiviral enzymes

Virus	Mechanism of action/inhibition
i. PKR	
Adenovirus	Produces VA RNA that binds to but fails to activate PKR
Baculovirus	PK2 binds eIF2α kinases, including PKR, and blocks their activities
Epstein–Barr virus	Produces EBER RNA that binds to but fails to activate PKR
Hepatitis C virus	NS5A binds to and inhibits PKR; E2 also interacts with PKR and may inhibit its activity
Herpes simplex virus	ICP 34.5 redirects protein phosphatase 1 to dephosphorylate (re-activate) elF2α; U_S11 blocks PKR activity
Human immunodeficiency virus	Down-regulates PKR by unknown mechanism; Tat and short Tat-responsive region RNA inhibit PKR
Influenza virus	NS1 binds dsRNA and PKR to inhibit its activity. Influenza virus also induces cellular inhibitor of PKR (p58IPK)
Poliovirus	Induces the degradation of PKR
Poxviruses (many)	Example: vaccinia virus E3L binds dsRNA and PKR; K3L binds PKR
Reovirus	σ3 binds dsRNA and thus inhibits PKR (and 2′–5′ oligoadenylate synthetase)
Rotavirus	NSP3 binds dsRNA and thus inhibits PKR (and 2′–5′ oligoadenylate synthetase)
ii. 2′–5′ Oligoadenylate synthetase/RNase L system	
Various viruses	Produce proteins that sequester dsRNA (above)
Encephalomyocarditis virus	Induces RNase L inhibitor (RLI) that antagonizes 2′5′A binding to RNase L
Herpes simplex virus	2′5′A derivatives are synthesized that behave as 2′5′A antagonists
Human immunodeficiency virus	Induces RNase L inhibitor (RLI) that antagonizes 2′5′A binding to RNase L

strategy, it would be surprising if the immune system had not evolved a mechanism(s) for recognizing and eliminating cells in which IFN signalling has been blocked. Alternatively, the cell itself may have some compensatory strategy for inducing an antiviral response in cells in which the IFN signal-transduction pathway is blocked. Indeed, this may be an important function of IRF-1, which can bind to and activate many of the promoters normally activated by IFN-α/β (Pine, 1992; Henderson *et al.*, 1997; Nguyen *et al.*, 1997). IRF-1 levels can be raised by exposure of cells to a number of cytokines whose levels are up-regulated during infection, such as TNFα, IL-1 and IL-6 (Fujita *et al.*, 1989*b*; Harroch *et al.*, 1994), and these potential alternative pathways to antiviral gene activation may be important survival mechanisms in the face of a blockade of IFN signalling.

6. Inhibition of IFN-induced antiviral enzymes

Many viruses encode factors that down-regulate the activity of IFN-induced antiviral enzymes such as PKR and 2′–5′ oligoadenylate synthetase; our current knowledge of these factors is summarized in Table 2 and is discussed below.

(i) PKR. The importance of PKR in the induction of an antiviral state can be inferred from the wide variety of mechanisms that are employed by viruses to inhibit its activity (reviewed in Gale & Katze, 1998). As discussed above, a number of viruses encode dsRNA-binding proteins that act to minimize NF-κB activation, IFN induction and apoptosis and these proteins would also inhibit PKR. Interestingly, the dsRNA-binding proteins NS1 (Tan & Katze, 1998) and E3L (Sharp *et al.*, 1998) also bind directly to PKR and inhibit its function, and this is also presumably true of the OV20.0L gene product of orf virus, which shares 33% homology with E3L (Haig *et al.*, 1998). Although the NS1 protein of influenza virus is critical for its ability to overcome the IFN response (Garcia-Sastre *et al.*, 1998; Hatada *et al.*, 1999), influenza virus has also been reported to induce the activation of a cellular inhibitor of PKR termed p58IPK (Lee *et al.*, 1990, 1992, 1994; Melville *et al.*, 1997). NS1 probably also inhibits the IFN response indirectly (as discussed above) by being involved in the virus-induced shut-off of host-cell protein synthesis. Thus, NS1 regulates nuclear export of cellular mRNA (Fortes *et al.*, 1994; Qiu & Krug, 1994) and affects pre-mRNA maturation by inhibiting splicing (Fortes *et al.*, 1994; Lu *et al.*, 1994) and poly-

adenylation-site cleavage (Chen *et al.*, 1999; Shimizu *et al.*, 1999).

In addition to binding dsRNA, viral gene products can inhibit PKR in other ways. Poliovirus induces the degradation of PKR (Black *et al.*, 1989, 1993), HCV encodes the non-structural protein NS5A, which binds PKR directly, thus blocking its activity (Gale *et al.*, 1997), whilst the baculovirus PK2 protein also binds PKR and inhibits its activity (Dever *et al.*, 1998). Furthermore, the E2 protein of HCV contains sequences identical to the phosphorylation sites on PKR and eIF2α and its interaction with PKR may also contribute to the ability of HCV to circumvent the IFN response (Taylor *et al.*, 1999). The K3L gene product of vaccinia virus has structural similarity to the N terminus of eIF2α and binds tightly to PKR, preventing autophosphorylation and hence activation of PKR and the subsequent phosphorylation of eIF2α (Davies *et al.*, 1992, 1993; Carroll *et al.*, 1993).

A more indirect method of overcoming the action of PKR is illustrated by the γ_1 ICP34.5 protein encoded by herpes simplex virus (HSV). ICP34.5 interacts with cellular protein phosphatase 1α (PP1), redirecting it to dephosphorylate, and hence reactivate, eIF2α (He *et al.*, 1997). A virus deleted in ICP34.5 is attenuated in normal mice but exhibits wild-type replication and virulence in PKR null mice, thereby demonstrating formally the importance of blocking the effects of PKR for HSV pathogenicity (Leib *et al.*, 2000). The l14L protein of ASFV is a homologue of HSV ICP34.5 that contains the sequence thought to be important in its binding to PP1. However, l14L is found predominantly in the nuclei of infected cells and it is not yet clear whether it has a role in circumventing PKR activity (Goatley *et al.*, 1999). Interestingly, HSV also encodes U_S11 (a γ_2 protein), which, when expressed in mutants from an early promoter, can compensate for mutations in ICP34.5 by inhibiting PKR activity. Since U_S11 is an abundant tegument protein brought into the cells upon infection, it may act early to block phosphorylation of eIF2α. However, it appears not to be as important as ICP34.5 in preventing PKR-induced switch-off of HSV protein synthesis, and the exact role of U_S11 in the life-cycle of HSV has yet to be resolved (Mohr & Gluzman, 1996; Cassady *et al.*, 1998).

Some viruses produce abundant short RNA molecules that inhibit PKR (reviewed in Robertson & Mathews, 1996). The adenovirus VAI transcript is an RNA molecule that can form a highly ordered secondary structure that binds avidly to the dsRNA-binding site on PKR and acts as a competitive inhibitor; the molecule is thought to be too short (160 nucleotides) to permit two molecules of PKR to juxtapose and transactivate (reviewed in Mathews, 1993, 1995). EBV also encodes two small RNAs, EBER-1 and EBER-2, that may be analogous to the VA RNAs of adenovirus. Thus, EBER-1 and possibly also EBER-2 can interfere with PKR activity (Sharp *et al.*, 1993). Furthermore, EBER RNAs can partially complement VA-negative mutants of adenovirus (Bhat & Thimmappaya, 1985). Human immunodeficiency virus type 1 (HIV-1) also produces a short Tat-responsive region (HIV-TAR) RNA that inhibits PKR activity (Gunnery *et al.*, 1990). However, HIV-1 also down-regulates PKR activity by an unknown mechanism (Roy *et al.*, 1990) and the Tat protein, as well as being an activator of virus transcription, also interacts with and inhibits PKR (McMillan *et al.*, 1995; Brand *et al.*, 1997) by both RNA-dependent and RNA-independent mechanisms (Cai *et al.*, 2000).

(ii) The 2′–5′ oligoadenylate synthetase/RNase L system. Since dsRNA is required to activate 2′–5′ oligoadenylate synthetase, virus proteins that sequester dsRNA, e.g. the E3L gene product of vaccinia virus (Rivas *et al.*, 1998), inhibit both PKR and the 2′–5′ oligoadenylate synthetase/RNase L system. Several viruses also appear to have evolved strategies that specifically counteract the antiviral activity of the latter pathway. For example, during HSV type 1 and type 2 infection, 2′5′A derivatives are synthesized that behave as 2′5′A antagonists, thereby inhibiting the activation of RNase L (Cayley *et al.*, 1984). Viruses such as HIV-1 (Martinand *et al.*, 1999) and encephalomyocarditis virus (Cayley *et al.*, 1982; Martinand *et al.*, 1998) down-regulate RNase L activity by inducing the expression of the RNase L inhibitor (RLI), which antagonises 2′5′A binding to RNase L and hence prevents its activation.

Surprisingly, a number of the small RNAs produced by viruses that inhibit PKR, including HIV-TAR, adenovirus VAI and EBV EBER-1, appear to activate 2′–5′ oligoadenylate synthetase (Desai *et al.*, 1995; Mordechai *et al.*, 1995; Sharp *et al.*, 1999), although the biological reasons for this are unclear.

Conclusion

The study of how viruses interact with the IFN system has told us much about virus pathogenesis and about the IFN system itself. Future studies on the molecular mechanisms that viruses have for circumventing the IFN response are likely to produce new and unsuspected insights into virus–host relationships. For example, given that viruses have co-evolved with the IFN system, it is possible that viruses have evolved subtle ways of exploiting the IFN response. In this context, it is intriguing to note that the IFN-α/β-inducible transcription factor IRF-7 may play a role in altering the pattern of latency in EBV infections (Zhang & Pagano, 2000), whilst HHV-8 can be induced from latency by IFN-γ (Chang *et al.*, 2000).

The ability of viruses to block the IFN response may have consequences in terms of the chronic diseases caused by viruses and their treatments. Thus, IFN may be unsuccessful in the treatment of chronic virus infections because the viruses have mechanisms for circumventing the IFN response. For example, it has been suggested that IFN is ineffective as a treatment of some hepatitis C patients because the virus blocks PKR activity (Gale & Katze, 1998).

By understanding the molecular mechanisms by which viruses circumvent the IFN response, it may be possible to

identify novel antiviral drugs that work by preventing viruses from blocking specific cellular activities. Such drugs may be particularly useful in treating chronic virus-induced diseases such as persistent hepatitis B and C infections. In addition, it may be possible to generate attenuated vaccines by altering specifically the virus gene(s) that is responsible for virus inhibition of IFN function. We anticipate that research in the area of IFN–virus interactions will yield a wealth of information that has direct application to the control of virus infections.

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