Microreview

Interferon signalling network in innate defence

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Summary

Interferons (IFNs) elicit multifaceted effects in host innate defence. Accumulating evidence revealed that not only the first identified Jak-Stat pathway but also other newly found signalling pathways are required for the induction of versatile responses by IFNs. In particular, type I IFNs are inducible by viral infection through the recognition of pathogen-associated molecules by pattern recognition receptors, and the induction of multiple IFN-stimulated genes through the activation of type I IFN signalling confers antiviral and immunomodulatory activities. Any step in this process is often targeted by viruses for their immunoevasion. The regulatory function of constitutive IFN-α/β signalling has been recognized in terms of its boosting effect on cellular responsiveness in host defence systems. Further comprehensive understanding of IFN signalling may offer a better direction to unravelling the complex signalling networks in the host defence system, and may contribute to their more effective therapeutic applications.

Introduction

Interferons (IFNs) are a family of structurally related cytokines with a hallmark function of antiviral activity, and are found only in vertebrates (Isaacs and Lindenmann, 1957; Pestka et al., 1987; De Maeyer and De Maeyer-Guignard, 1988; Vilcek and Sen, 1996). Despite their distinct profiles of activity, IFNs exhibit a diversity of biological functions, as represented by three major biological activities: antiviral activity, antitumour activity and immunomodulatory effects. IFNs constitute several types (Kotenko et al., 2003; Pestka et al., 2004), all members of which interact with a type-specific receptor complex, consisting of a pair of heterologous subunits. The ligand–receptor interaction triggers the main Jak-Stat pathway together with additional signalling cascades. Of note, the discovery of the Jak-Stat pathway (Schindler et al., 1992; Silvennoinen et al., 1993; Darnell et al., 1994; Ihle, 1995; Ihle and Kerr, 1995; Stark et al., 1998) has also provided a common cardinal signalling framework in signalling pathways by other cytokines as well as IFNs (Taniguchi, 1995). It is now becoming clear that there are crosstalk networks among these cytokine signalings (Haque and Williams, 1998; Takaoka et al., 2000; Mitani et al., 2001; Taniguchi and Takaoka, 2001; Heinrich et al., 2003).

The transcriptional regulation of thousands of effector genes downstream of the Jak-Stat or other IFN-regulated pathways (Der et al., 1998) contributes to pleiotropic responses elicited by IFNs. Thus, the IFN system, which triggers the induction of numerous antiviral genes during viral infection, is a formidable barrier against viral multiplication in the infected host. On the other hand, it has become clearer that there are multiple strategies that viruses evolve for the evasion from the IFN system (Goodbourn et al., 2000; Levy and Garcia-Sastre, 2001; Garcia-Sastre, 2002; Katze et al., 2002; Weber et al., 2004; Johnson and Gale, 2005). Such a better understanding of virus–host interactions is also emerging with more obvious recognition of the vital part of the IFN system in the host defence system.

In this review, we focus mainly on type I IFN-mediated signalling and their regulatory functions in host defence systems. Type I IFNs, IFN-α/β, are massively produced in most cell types in response to viral and other microbial infections, and play a vital role in innate resistance to a wide variety of viruses through the induction of antiviral effects, both directly and indirectly manner. As for their indirect role in antiviral activities, IFN-α/β also have an immunomodulatory effect of activating natural killer (NK) cells, macrophages and dendritic cells (DCs), all of which are essential effector cells in the innate immune system (Pestka et al., 1987; De Maeyer and De Maeyer-Guignard, 1988; Vilcek and Sen, 1996; Biron et al., 1999; Theofilopoulos et al., 2005). By virtue of their potentiating effect on DC maturation, type I IFNs are currently recognized as pivotal cytokines bridging two aspect of host defence, innate and adaptive immune systems. It is noteworthy that a unique subset of DCs, termed plasmacytoid DCs...
β-critical for the enhancement of other cytokine signalling, both IFN-α, IFN-β and IFN-ω, upon viral exposure or the activation of certain Toll-like receptors (TLRs) (Liu, 2005).

On the other hand, with accumulating reports about the potential role of type I IFNs in tumour suppression, we also found a new linkage between IFN-α/β signalling and the tumour suppressor p53, which provided an insight into a possible role of p53 not only in IFN-α/β-mediated anti-tumour activity but also in antiviral defence (Takaoka et al., 2003). Furthermore, Schreiber’s group recently reported that type I IFNs are important components for cancer immunediting process wherein protective antitumour responses are developed through their effect on immune and other biological systems (Takanaka et al., 2005). In this regard, it is interesting that constitutively produced type I IFNs play a role in this process.

As also indicated above, recent advances elucidating the biology of these key cytokines also contribute to a better understanding of the important role of ‘a weak signalling’ by constitutively produced IFN-α/β in the absence of viral infection in modifying cellular responsiveness in the immune and other biological systems (Taniguchi and Takaoka, 2001; Takaoka and Taniguchi, 2003). Indeed, there are accumulating reports regarding low levels of IFN-α/β production observed in the absence of viral infection, both in vitro and in vivo (Bocci, 1985; Tovey et al., 1987; De Maeyer and De Maeyer-Guignard, 1988). Our recent studies revealed that this constitutive, weak IFN-α/β signalling, transmitted independently of viral infection, is critical for the enhancement of other cytokine signalling and their induction by virus, as well as for positive regulatory functions in adaptive immune responses such as CD8+ T cell activation (Hida et al., 2000). Furthermore, this constitutive signalling has been shown to negatively regulate the differentiation of the CD8α+ myeloid DC subgroup (Honda et al., 2004a; Ichikawa et al., 2004).

In this article, we outline the signalling events induced by both type I and type II IFNs as well as recently identified IFN family members, with the main focus on the overall signalling profile of type I IFN responses during viral infection from the offensive and defensive aspects of both the host and viruses. Furthermore, we also review the regulatory mechanism and the critical roles of constitutive type I IFN-mediated signalling in several facets of host defence systems.

### Interferon family members

Although in this review we mainly focus on the signalling activated by IFNs, particularly type I IFNs, a brief explanation will be initially made about their ligands, which can be divided into three types on the basis of their structural and functional properties (Table 1).

#### Type I IFNs

The type I IFNs (Roberts et al., 1998) consist of IFN-α, -β, -ω, -ε (Langer et al., 2004; Pestka et al., 2004) and -κ (Lafleur et al., 2001) (Table 1). In addition, IFN-δ (Lefevre et al., 1998), -τ (Roberts et al., 1999) and -ζ (limitin) (Oritani et al., 2000) are included in this group, although they are only detected in pigs/cattle, ruminants and mice and their capacity to produce prodigious amounts of type I IFNs, consisting of IFN-α, IFN-β and IFN-ω, upon viral exposure or the activation of certain Toll-like receptors (TLRs) (Liu, 2005).

#### Table 1. The interferon family members.

| Types of IFNs | Receptors | Gene locusa | Amino acid residues | Molecular weight (kDa) | Expression pattern |
|---------------|-----------|-------------|---------------------|------------------------|-------------------|
| I             | IFNAR-1/IFNAR2 | 9p21 | 165–166b | 15–23 | Ubiquitously expressed |
|               | IFNAR-1/IFNAR2 | 9p21 | 166b | 15–23 | Ubiquitously expressed |
|               | IFNAR-1/IFNAR2 | None | 170 | 20 | Trophoblasts |
|               | IFNAR-1/IFNAR2 | 9p21 | 208 | 24.4 | Uterus, ovary |
|               | IFNAR-1/IFNAR2 | 9p21 | 172b | 20–23 | Leukocytes |
|               | IFNAR-1/IFNAR2 | 9p21 | 180b | 24.5 | Selectively expressed in epidermal keratinocytes |
|               | IFNAR-1/IFNAR2 | None | 191b | 20–22 | Trophoblasts |
|               | IFNAR-1/IFNAR2 | None | 161b | 20 | Spleen, thymus, lymph node |
| II            | IFNGR-1/IFNAR2 | 12q24.1 | 146b | 34 | Activated T cell, macrophage, NK cell |
| III           | IL-28Rα/IL-10R2 | 19q1 | 200 | 20–33b | Ubiquitously expressed |
|               | IL-28Rα/IL-10R2 | 19q1 | 200 | 22 | Ubiquitously expressed |
|               | IL-28Rα/IL-10R2 | 19q1 | 196 | 22 | Ubiquitously expressed |

a. Human.
b. Signal peptides are not included.
c. Found in pigs and cattle only.
d. Found in ruminants only.
e. Found in mice only.
f. Acts as a homodimers.
g. Due to its glycosylation.

Data about molecular properties were obtained from the following NCBI web site: http://www.ncbi.nlm.nih.gov except for IFN-λs (Kotenko et al., 2003).
respectively (Table 1). All these members are induced in virally infected cells to confer an antiviral state on uninfected cells. Most of the intensive studies have focused mainly on IFN-α/β. Recent rapid progress in studies about pathogen recognition by the host revealed that the induction of IFN-α/β genes are mediated by the activation of pattern recognition receptors (PRRs) including TLRs (Takeda et al., 2003; Akira and Takeda, 2004; Takeda and Akira, 2005; Kawai and Akira, 2006) and retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene 5 (Md5) (Rothenfusser et al., 2005; Yoneyama et al., 2005). IFN-α/β also show a variety of important immunomodulatory roles in not only innate immune responses but also adaptive immune responses. Additionally, a direct or an indirect tumour suppression is one of the major therapeutical activities of IFN-α/β (Parmar and Platanias, 2003). All of the members transmit signals through a receptor complex composed of two subunits, IFNAR-1 and IFNAR-2, although it seems that there are some differences in both quality and efficiency among them; e.g. a significant difference in the activity of boosting human NK cells was found among IFN-α subtypes (Ortaldo et al., 1984). Interestingly, some studies showed that although IFNAR-2 is phosphorylated by treatment with both IFN-α and IFN-β, the association of IFNAR-2 with IFNAR-1 is only detected upon IFN-β stimulation (Abramovich et al., 1994), and that Tyk2-deficient cells lose their responsiveness to IFN-α but still respond to IFN-β (Velazquez et al., 1992). These studies suggest that the interaction of IFN-β and IFN-α with the receptor might lead to a different conformational assembly of the receptor complex, resulting in a distinct activation of downstream signalling pathways.

**Type II IFN**

Type II IFN comprises solely IFN-γ (Bach et al., 1997; Pestka, 1997; Ikeda et al., 2002) (Table 1), which similarly has antiviral activity. However, this cytokine is strongly produced by activated T cells or NK cells but not by virus-infected cells. IFN-γ signalling is essential for the activation of macrophages to constitute the effective form of innate immunity to intracellular microorganisms such as Mycobacteria and Listeria, and also contributes to the promotion of the development of CD4+ Th1 cells and cytotoxic CD8+ T cells (Ikeda et al., 2002). IFN-γ signals through a pair of receptor subunits, IFNGR-1 and IFNGR-2.

**Type III IFNs**

Newly identified IFN members, IFN-λs or IL-28/29, have been identified by two different research groups (Kotenko et al., 2003; Sheppard et al., 2003; Vilcek, 2003) (Table 1). In humans, this group includes three homologous proteins, IFN-λ1-3 (IL-28A, IL-28B and IL-29). Similar to type I IFNs, they are induced upon viral infection and have their antiviral activity by inducing so-called IFN-stimulated genes such as those encoding OAS (2′,5′-oligoadenylate synthetase), PKR (protein kinase, double-stranded RNA-dependent) and MxA, through the activation of unidentified Jak kinase(s) and subsequent formation of the IFN-stimulated gene factor 3 (ISGF3) complex (Fig. 1). However, the major differences are that they are structurally distinct from type I IFNs and that they utilize their specific receptor subunit, IFN-λR1 or IL-28Rα, together with IL-10R2 that is known to be a shared receptor subunit among IL-10, IL-22 and IL-26. In this regard, they might be separated into the third group (type III IFNs). Tyk2, which was already shown to physically interact with IL-10R2 (Kotenko et al., 1996), is likely a candidate kinase, whereas the Jak kinase(s) associated with the IFN-λR1 subunit have not yet been identified. Downstream signalling pathways activated by IFN-λs remain to be clarified in further detail.

These receptors that are utilized by all types of IFNs belong to the class II cytokine receptor family (CRF2) (Langer et al., 2004), other members of which include receptors for the IL-10 family members (IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26). In all cases, ligand-binding to these receptors leads to the activation of the Jak-Stat pathway (described below).

**Overview of cardinal signalling pathways activated by type I and II IFNs**

All IFN-α/β subtypes interact with the same receptor complex, termed the IFN-α/β receptor (IFNAR), which consists of at least two subunits, IFNAR-1 and IFNAR-2 (Uze et al., 1990; Darnell et al., 1994; Novick et al., 1994; Stark et al., 1998) (Fig. 1). The intracellular domains of these two subunits, IFNAR-1 and IFNAR-2, are associated with Janus protein tyrosine kinases (Jak PTKs), Tyk2 and Jak1 respectively. As for type II IFN signalling, IFN-γ binds to the IFN-γ receptor complex (IFNGR), comprising IFNGR-1 and IFNGR-2; the IFNGR1 subunit is constitutively associated with Jak1, whereas IFNGR2 with Jak2 (Bach et al., 1997; Stark et al., 1998; Chen et al., 2004) (Fig. 1).

The binding of both types of IFNs to IFNAR or IFNGR results in the cross-activation of these Jak PTKs, which then phosphorylate their downstream substrates, which are two members of the family of signal transducers and activators of transcription (Stats), namely, Stat1 and Stat2 (Darnell et al., 1994; Ihle and Kerr, 1995; Schindler and Darnell, 1995; Stark et al., 1998). The tyrosine phosphorylation of these Stats leads to the formation of two transcriptional activator complexes, IFN-α/activated factor [AAF; also termed IFN-γ-activated factor (GAF); Decker
et al., 1991a] and IFN-stimulated gene factor 3 (ISGF3; Darnell et al., 1994; Haque and Williams, 1994; Bluyssen et al., 1996) (Fig. 1). AAF/GAF is a homodimer of tyrosine-phosphorylated Stat1, whereas ISGF3 is a heterotrimeric complex of tyrosine-phosphorylated Stat1, Stat2 and another transcription factor member, IRF-9/p48/ISGF3γ (Bluyssen et al., 1996) (Fig. 1). There is a clear difference in the activation level of ISGF3 or GAF/AAF.
between type I and type II IFN signalling (Fig. 1; the thicknesses of arrows for ISGF3 and GAF/AAF represent the extents of their involvement). Type I IFNs more strongly activate the formation of ISGF3 than type II IFN, whereas type II IFN mainly activates GAF/AAF. These complexes translocate into the nucleus; subsequently, AAF and ISGF3 bind to their specific DNA sequences containing each of the common motifs, namely, the IFN-γ-activated sequence (GAS; Decker et al., 1991b; Lew et al., 1991) and the IFN-stimulated regulatory element (ISRE; Kessler et al., 1990; Williams, 1991) respectively. The IFN stimulation of promoters containing ISRE and GAS results in the transcriptional induction of a large number of target genes (IFN-stimulated genes; ISGs) to evoke versatile biological activities.

Recent identified signalling pathways downstream of type I IFN receptor

In addition to the well-established ISGF3 complex, type I IFNs have been shown to induce other types of Stat complex (Fig. 1), such as Stat3 or Stat5 homodimer and Stat1-Stat3 or Stat5-CrKL (Fish et al., 1999) (v-crk sarcoma virus CT10 oncogene homologue) heterodimers. Stat5 constitutively interacts with Tyk2 and undergoes phosphorylation in response to stimulation by IFN, and then CrKL binds to the tyrosine-phosphorylated Stat5 via its SH2 domain. This Stat5-CrKL heterodimeric complex translocates to the nucleus and binds to the GAS element (TTCTAGGAA) (Fish et al., 1999).

Although at significantly lower levels than IL-12, recombinant murine IFN-αA induces Stat4 phosphorylation in mouse T cells, which can be observed in the absence of Stat2 (Rogge et al., 1998; Wang et al., 2003a; Berenson et al., 2004a) (Fig. 1). As for the implication of IFN-α-induced Stat4 activation, it seems that IFN-α does not play a functionally significant role in mediating the Stat4-dependent induction of Th1 differentiation or IFN-γ production (Rogge et al., 1998; Wang et al., 2003a; Berenson et al., 2004a) although this issue is currently still controversial (Berenson et al., 2004b).

Several reports further indicate that type I IFNs can activate pathways that are distinct from the canonical Jak-Stat pathway. In response to type I IFN stimulation, two of the members of insulin receptor substrate (IRS)-1 and IRS-2 become tyrosine-phosphorylated, allowing for the N- and C-terminal SH2 domain-mediated binding of the p85 subunit of phosphatidylinositol (PI) 3-kinase (Uddin et al., 1995; Platanias et al., 1996; Burfoot et al., 1997) (Fig. 1). This binding results in the activation of the p110 catalytic subunit of PI3-kinase (Uddin et al., 1995). PI3-kinase activity is not required for the induction of the ISGF3 complex or any IFN-inducible genes, whereas the association of PI3-kinase with the IFNAR-1 subunit can occur in a Stat3-dependent manner (Pfeffer et al., 1997). Presumably PI3-kinase activation may be linked to an activation pathway of the proto-oncogene product Akt (Nguyen et al., 2001) and PKCδ (Uddin et al., 2002).

The overexpression of Stat3 in IFN-resistant B cell lymphoma cells showed that Stat3 is possibly involved in the induction of antiproliferative effects by type I IFNs (Yang et al., 1998), besides the well-characterized signalling pathways involving the activation of Stat1 and Stat2. However, this finding is contradicted by the observation that Stat3 appears to be also required for the activation of PI3-kinase to promote IFN-α/β-mediated cell survival, although the direct involvement of Stat3 was not shown (Yang et al., 2001). In this regard, there is evidence showing that PI3-kinase is activated by type I IFN in a Stat3-independent manner. Although the relationship between the Stat3-dependent pathway and PI3-kinase-dependent pathway has not been fully clarified, it has been shown that the PI3-kinase-dependent pathway can mediate both proapoptotic and survival activities in IFN-mediated signalling: IFN-α/β-activated PI3-kinase signalling mediates survival signals through the activation of its downstream effector, Akt or PKCδ, in a cell-type specific manner; e.g. primary astrocytes (Barca et al., 2003) or neutrophils (Wang et al., 2003b). By contrast, the activation of PI3-kinase and its downstream molecule, mammalian target of rapamycin (mTOR) serine-threonine protein kinase, is also essentially involved in the IFN-α-induced apoptosis of multiple myeloma cells (Thyrell et al., 2004) Thus, IFN-activated PI3-kinase signalling seems to regulate apoptotic responses in a context-dependent manner.

It has been also reported that the mitogen-activated protein (MAP) kinases, extracellular-signal-regulated kinase 2 (ERK2) and p38, are activated by IFN-α/β (David et al., 1995; Goh et al., 1999) (Fig. 1). In addition, it was shown that the inhibition of p38 activity by SB203580, a pharmacological inhibitor of p38, blocks IFN-α-induced gene transcription via GAS elements as well as ISRE elements (Uddin et al., 1999; 2000a). On the other hand, the tyrosine phosphorylation of Stat1 or Stat2 is not affected by the inhibition of p38 activity, nor the serine phosphorylation of Stat1 or Stat3 (Uddin et al., 2000a). These results indicate that the suppression of the type I IFN-mediated gene transcription is independent of Stat1 activation (Uddin et al., 1999). Further studies have revealed that p38 is activated in a type I IFN-dependent manner in breakpoint cluster region-v-abl Abelson murine leukaemia viral oncogene homologue 1 (BCR-ABL)-expressing cells and in cells from patients with chronic myelogenous leukaemia (CML) (Mayer et al., 2001). In addition, p38 inhibitors abrogated the suppressive effects of type I IFN on leukaemic progenitors from the bone marrow of CML patients. These findings suggest that p38-
mediated signalling is essential for the antileukaemic effects of type I IFN (Mayer et al., 2001).

**Amplifying effect of type I IFN signalling on IFN-α/β gene induction by viral infection**

Prior to going into the details of the regulatory function of IFN-α/β signalling in their induction by viral infection, we would like to describe the current view of the mechanism underlying IFN-α/β gene induction in conjunction with PRRs and the IFN-regulatory factor (IRF) system.

The induction of IFN-α/β genes upon viral infection is transcriptionally controlled. A gene disruption study (Sato et al., 2000) revealed that among nine hitherto identified members (IRF-1 to IRF-9) of the IRF family, IRF-3 and IRF-7 are essential transcriptional factors for IFN-α/β gene induction by viruses. Consistently, no induction of IFN-α/β mRNA was detected in IRF-3- and IRF-7-doubly deficient mice (Honda et al., 2005a). In fibroblasts or conventional DCs (Fig. 2), infection by viruses such as Newcastle disease virus (NDV), Sendai virus (SeV) and vesicular stomatitis virus (VSV), is sensed by RIG-I and Mda5, which results in the stimulation of IPS-1/MAVS/VISA/Cardif-mediated downstream signalling pathways, partly leading to the activation of IRF kinases [TANK-binding kinase 1 (TBK1) and IκB kinase ε/ι (IKKe/IKIk)]. These activated kinases in turn phosphorylate the serine/threonine residues of IRF-3 and IRF-7 at their carboxyl terminal region to become an active form. The activated IRF-3 and IRF-7 undergo nuclear translocation, and subsequently bind to IRF-binding elements (IRF-Es) [i.e. positive regulatory domains (PRDs) I and III, and PRD-like elements (PRD-LEs)] in the IFN-α/β promoter.

This positive feedback regulation depends on the IFN-inducible expression of IRF-7 in an ISGF3-dependent manner (Marie et al., 1998; Sato et al., 1998). Due to the unique expression profile of IRF-7, which is expressed by the initial induction of IFN-α/β, it augments its intracellular level, leading to the amplification of IFN-α/β gene induction (Fig. 2, right panel). Therefore, massive IFN-α/β production can be achieved through this positive feedback mechanism, whereby the signalling triggered by de novo synthesized IFN-α/β amplifies IFN-α/β production through the increase in the intracellular expression level of IRF-7 (Marie et al., 1998; Sato et al., 1998; 2000).

It is of interest to determine whether this positive feedback mechanism is observed in pDCs, a specialized subset of DCs, which is characterized by the capability of producing large amounts of IFN-α/β upon viral infection (Asselin-Paturel and Trinchieri, 2005; Liu, 2005). IFN induction in pDCs is dependent on MyD88 and IRF-7, but not IRF-3, which is different from that in fibroblasts or conventional DCs (both IRF-7- and IRF-3-dependent, but MyD88-independent) (Honda et al., 2005a). Recent data
demonstrated the existence of a similar positive feedback mechanism in pDCs (Honda et al., 2005a). In fact, robust production of IFN-α in response to stimulation by CpG-A, a TLR9 ligand, is abolished in IFNAR-1-deficient or IRF-9-deficient pDCs, both of which are defective in the IFN-signal-dependent gene induction of IRF-7. This positive feedback mechanism is also regarded as an essential regulation for a robust IFN induction in pDCs, similarly in fibroblasts. In relation to this finding, our recent study demonstrated a unique spatiotemporal regulation of the signalling process for high-levels IFN induction in pDCs (Honda et al., 2005b).

Regulatory roles of weak signalling by spontaneously produced IFN-α/β

As mentioned above, IFN-α/β are massively produced upon viral infection, however, there is evidence for the constitutive expression of IFN-α/β, albeit at very low levels, in the absence of viruses or other IFN inducers (Bocci, 1985; Tovey et al., 1987; De Maeyer and De Maeyer-Guignard, 1988; Gresser, 1990). In fact, the IFN-α/β mRNAs can be detected in normally growing mouse embryonic fibroblasts (MEFs), splenocytes and bone marrow cells by reverse transcriptase polymerase chain reaction analysis (Takaoka et al., 2000; Hata et al., 2001; Takayanagi et al., 2002; Honda et al., 2004a). Although previous reports suggest the contribution of these IFNs to antiviral, antitumour activities and cell growth control (Bocci, 1985; De Maeyer and De Maeyer-Guignard, 1988; Gresser, 1990; Gresser et al., 1995) similarly to virus-induced IFNs, several studies by our group provided a mechanistic insight into this unique system (Takaoka et al., 2000; Hata et al., 2001; Mitani et al., 2001; Taniguchi and Takaoka, 2001).

Evidence has been provided that this weak signalling by the constitutively produced IFN-α/β is critical for eliciting strong responses of cells to IFN-γ and interleukin (IL)-6 (Takaoka et al., 2000; Mitani et al., 2001; Fig. 3). In fact, the IFN-γ-induced DNA-binding activity of activated Stat1 was found to be severely diminished in cells from mice deficient in IFNAR-1 (Takaoka et al., 2000). Similarly, the full activation of Stat1 and Stat3 by IL-6 did not occur in this mutant cells (Mitani et al., 2001). Further analyses revealed that this weak IFN-α/β signalling is critical for maintaining the intracellular tyrosine residues of IFNAR-1 in a phosphorylated form so as to provide niches where these Stats can dimerize efficiently upon stimulation by IFN-α/β or IL-6 (Takaoka et al., 2000; Mitani et al., 2001). In relation to the above-mentioned positive feedback system for type I IFN induction, a constitutive, weak IFN-α/β signalling was also found to contribute to the mechanism underlying the amplification of type I IFN induction by viral infection. Our recent study using IRF-7-deficient mice revealed that the viral induction of IFN-α/β genes is severely impaired in IRF-7-deficient MEFs (Honda et al., 2004a).
contribute to a more efficient operation of this mechanism to viral infection (Hou et al., 2001). Interestingly, the expression level of IFR-7 was found to correlate with that of constitutive IFN-α/β (Hata et al., 2001). Therefore, prior to viral invasion, the constitutive, weak IFN-α/β signalling renders cells in a state of 'revving up' for the robust and efficient production of IFN-α/β upon viral infection (Taniguchi and Takaoka, 2001; 2002; Takaoka and Taniguchi, 2003). Furthermore, there is also an observation that the expression levels of IFN-α/β only marginally increase upon the stimulation of CD8+ T cells by a mixed lymphocyte reaction (Ogasawara et al., 2002), suggesting that this weak IFN-α/β signalling may also plays a role in the regulation of adaptive immune responses. The level of IFN-α/β mRNA expression induced by TCR stimulation is less than 1/200 that of induction by viral infection (Buller et al., 1987). It can be speculated that the increase in local IFN-α/β concentration at the site of T cell activation, by the concomitant, massive production of IFN-α/β in response to viral infection (Hou et al., 1995; Ridge et al., 1998), may contribute to a more efficient operation of this mechanism for the activation of TCR signalling in CD8+ T cells. Consistent with this hypothesis, CD8+ T cells lacking IFNAR-1 cannot respond efficiently to antigen stimulation, and the exogenous addition of recombinant IFN-β markedly enhances the proliferation of CD8+ T cells (Ogasawara et al., 2002). These observations additionally indicate the regulatory role of weak IFN-α/β signalling in the efficient activation of CD8+ T cell upon TCR engagement.

In this context, a study with IRF-2-deficient mice demonstrated a possible outcome of a dysregulated, weak IFN-α/β signalling. IRF-2 is constitutively expressed in most cell types, and functions as an attenuator at the ISRE to suppress ISGF3-mediated signalling (Taniguchi et al., 2001; Taki, 2002). Therefore, one can postulate that IRF-2 is a negative regulator of the constitutive, weak IFN-α/β signalling. IRF-2-deficient mice were found to spontaneously develop inflammatory skin lesions accompanied by a marked upregulation of IFN-inducible genes (Hida et al., 2000). The polyclonal activation of CD8+ T cells seems to be involved in the pathogenesis of this condition (Hida et al., 2000). Furthermore, both the skin lesions and the hyperresponsiveness of CD8+ T cells are suppressed in IRF-2- and IFNAR-1-doubly deficient mice. These results suggest the importance of the IRF-2-mediated attenuating regulation of the constitutive, weak IFN-α/β signalling (Matsuyama et al., 1993). Intriguingly, additional abnormalities, such as the suppression of haematopoiesis and predisposition to pancreatitis, are also observed in IRF-2 null mice (unpublished observation).

Therefore, a weak signal by constitutively produced IFN-α/β, renders cells ‘ready-to-go’ for the enhancement of cellular responses to rapid environmental changes, such as viral infection. Analogous to a car engine revving up for a thrust start and acceleration, we figuratively termed this machinery the ‘revving-up’ system. The ‘revving up’ of cellular engines by a weak signal is implicated in the elicitation of robust cellular responses against infections (Fig. 3; Taniguchi and Takaoka, 2001; 2002; Takaoka and Taniguchi, 2003). In this regard, this ‘revving-up’ system could be considered as a unique regulatory mechanism for amplifying cellular responsiveness in host defence.

We also reported that the IFN-β gene is induced in bone marrow macrophages upon stimulation by the RANK ligand (receptor activator of NF-κB ligand), a negative regulator of osteoclast differentiation, and that this induction is not dependent on IRF-3 or IRF-7, but on RANKL-induced c-Fos, one of the essential transcriptional factors for osteoclast differentiation (Takayanagi et al., 2002). In addition, the constitutive, weak IFN-α/β signalling has been shown to negatively regulate the differentiation of CD8α-DCs from fms-like tyrosine kinase ligand (Flt3L)-stimulated bone marrow cells (Honda et al., 2004a). Consistently, the differentiation of this DC population is impaired in IRF-2-deficient DCs, whereas this abnormality is rescued in IRF-2- and IFNAR-1-doubly deficient DCs. Thus, the weak signalling by constitutive type I IFN exhibits its regulatory role in not only host defence but also in other cellular processes such as cell differentiation.

Viral evasion from IFN system

Viruses evolutionarily have acquired their own mechanisms of evading host immune responses against themselves. Viruses frequently evolve various strategies to abolish the activities of key components of the IFN system, such as the signalling molecules of the Jak-Stat pathway, or PRR-mediated pathway for IFN production (Weber et al., 2004; Johnson and Gale, 2005). In this section, we will briefly explore potential mechanisms by which viruses evade antiviral defence systems, on the basis of previous reports about viral strategies countering two major aspects of the IFN system: (i) IFN production and (ii) IFN signalling. Because there have been many excellent reviews published on this subject (Goodbourn et al., 2000; Levy and García-Sastre, 2001; García-Sastre, 2002; Katze et al., 2002), we focus on several major viruses, hepatitis C virus (HCV), Paramyxoviruses and vaccinia virus (VV) (Fig. 2).
It is well documented that most members of the Paramyxoviruses (Foy, 2005) contribute to the persistence of HCV infection (Gale and A complex combination of these evasion processes may continual viral genetic variation to evade host responses.

i. Recently, much attention has been focused on an HCV serine protease, NS3/4A, which cleaves IPS-1/VISA/MAVS/Cardif, an adaptor protein, leading to the inactivation of RIG-I- or Mda5-mediated signalling pathways including both NF-κB and IRF-3 pathways (Meylan et al., 2005) (Fig. 2). In addition, there is a report documenting that this NS3/4A protease also causes the proteolysis of TRIF (Fig. 2), which is the critical adaptor protein linking TLR3 to its downstream NF-κB and IRF-3 pathways for the double-stranded RNA (ds-RNA) response (Li et al., 2005).

ii. HCV NS5A and E2 are shown to interact with PKR, one of the IFN-inducible antiviral proteins. This interaction results in the inactivation of this kinase (He and Katze, 2002) (Fig. 2). NS5A also directly targets IFN signalling pathway by disrupting the crosstalk between the MAP kinase and Jak-Stat pathways (He and Katze, 2002).

Hepatitis C virus also exploits other strategies such as continual viral genetic variation to evade host responses. A complex combination of these evasion processes may contribute to the persistence of HCV infection (Gale and Foy, 2005).

**Paramyxoviruses**

It is well documented that most members of the Paramyxoviridae subfamily, such as simian virus 5 (SV5), NDV, SeV, measles virus, mumps virus and parainfluenza virus, circumvent the IFN system by abrogating both processes; IFN production and IFN signalling.

i. The C-terminal domain of the V protein of most paramyxoviruses binds selectively to Mda5, thereby blocking the activation of its downstream pathway for IFN production (Andrejeva et al., 2004; Yoneyama et al., 2005) (Fig. 2). There is no evidence that the V protein interacts with RIG-I, which is another caspase recruitment domain (CARD)-containing recognition receptor of intracellular ds-RNA (Yoneyama et al., 2004).

ii. The V protein of SV5 inhibits both type I and type II IFN signallings through the proteasomal degradation of Stat1 (Didcock et al., 1999) (Fig. 2). Furthermore, the V protein of other paramyxoviruses has been found to target other Stat proteins as well as Stat1 to inhibit Stat-mediated signallings through diverse mechanisms including proteasomal degradation, sequestration and blockade of nuclear translocation (Horvath, 2004) (Fig. 2).

**Vaccinia virus**

Vaccinia virus, a member of the Poxviridae, has been shown to evolve multiple evasion strategies against the IFN system (Haga and Bowie, 2005).

i. It has been shown that A52R associates with both IRAK2 and TRAF6 to block the NF-κB activation pathway by various TLRs such as TLR4 (Bowie et al., 2000), whereas another VV protein, A46R, which contains a TIR domain, can target TLR adaptors such as MyD88, TRIF and TRAM, thereby inhibiting both MyD88- and TRIF-dependent pathways (Stack et al., 2005). Furthermore, Stack et al. showed that upon TLR3 activation, A52R more potently inhibits the activation of the NF-κB pathway than A46R, whereas A46R exhibits a more prominent inhibition of the IRF-3 activation pathway (Stack et al., 2005) (Fig. 2).

ii. It has been reported that poxviruses interfere with signallings by key cytokines that function in host immune systems, by expressing a variety of viral proteins such as soluble forms of receptors of cytokines, tumour necrosis factor, interleukin-1β, chemokines and IFNs (Alcami and Smith, 1996a; Haig, 1998). One of the VV proteins, vIFN-γR (viral IFN-γ receptor), which in the VV strain Western Reserve is encoded by the viral gene BBR (Alcami and Smith, 1995), binds to IFN-γ, thereby interfering with the binding of IFN-γ to the cellular receptor, and neutralizing the ligand activity. IFN-γ plays an important role in host defence against poxvirus infections, as demonstrated by a number of reports (Karupiah et al., 1990; 1993a,b; Kohonen-Corish et al., 1990; Huang et al., 1993; Melkova and Esteban, 1994; Harris et al., 1995), including a gene knockout analysis showing that IFNGR-1-deficient mice exhibit a severe susceptibility to VV (Huang et al., 1993). These observations may provide a plausible explanation for the viral strategy targeting the host IFN-γ system by expressing a soluble homologue of the cellular IFN-γ receptor. Furthermore, the expression of such a soluble IFN-γ receptor homologue and the encoding gene are highly conserved among most of other poxviruses, including the cowpox, ectromelia, variola, myxoma and Shope fibroma viruses (Alcami and Smith, 1996b), and their IFN-γ binding activity is presumably attributable to the sequence similarity of the viral soluble receptor to the extracellular binding domain of the IFN-γ receptor although these viral receptors show a ligand-binding activity in a species-specific manner (Alcami and Smith, 1995; 1996b). In this respect, because IFN-γ shows the activity of species-specific binding to its receptor (Pestka et al., 1987), it is also speculated that the ligand specificity of poxvirus-encoded IFN-γ receptors may reflect the spectrum of the host(s) where the virus has evolved (Alcami and Smith, 1996b). Consistently, the first described poxvirus IFN-γ receptor expressed by the myxoma virus, which causes myxomatosis specifically in rabbits, binds to rabbit IFN-γ but not mouse or human IFN-γ (Upton et al., 1992).
On the other hand, the type I IFN system is important for protection against poxvirus infection, which is supported by several studies showing that pretreatment with IFN-α/β abrogated the in vivo replication of the VV (Rodriguez et al., 1991) and IFNAR-1-deficient mice are more susceptible to VV infection (Muller et al., 1994). Therefore, it is not surprising that the type I IFN system is also targeted by poxviruses; the vIFN-α/β-BP, a VV protein encoded by B18R, binds to IFN-α/β with a broad species specificity, and prevents the binding of IFN-α/β to cellular receptors, consequently leading to the inhibition of the type I IFN response (Colamonici et al., 1995; Symons et al., 1995) (Fig. 2). Although the role of this type I IFN-binding protein in natural infection remains to be clarified, it was found to be expressed by other orthopoxviruses such as the cowpox, ectromelia and camelpox viruses (Colamonici et al., 1995; Symons et al., 1995). A mechanism underlying the binding activity of the B18R protein is not clear: Colamonici et al. showed that despite showing a very limited sequence similarity, the B18R protein has significant regions of homology with mouse, human and bovine IFNAR-1 subunits, and shows binding and neutralizing activities against several recombinant human type I IFNs (Colamonici et al., 1995). On the other hand, Symons et al. demonstrated that the B18R protein has three immunoglobulin-like domains, belonging to the immunoglobulin superfamily, which is different from cellular type I IFN receptors containing fibronectin type III domains (Symons et al., 1995).

The cellular type I IFN-receptor binds to only the N-terminal region of its ligand, which is proposed to determine a strict species specificity of IFN-binding (Liptakova et al., 1997), whereas the B18R protein was shown to interact with type I IFNs through their C-terminal region as well as their N-terminal region (Liptakova et al., 1997). This distinct feature of the B18R protein may explain a possible mechanism for its broad species specificity (Liptakova et al., 1997).

In addition, the VV E3L gene product codes for ds-RNA binding proteins, thus resulting in the inhibition of the activation of PKR (Fig. 2) and OAS (2′, 5′-oligoadenylate synthetase), both of which require ds-RNA for their activation (Chang et al., 1992). On the other hand, the K3L gene product acts as a decoy of eukaryotic initiation factor (eIF)-2α to disrupt the interaction of eIF-2α with PKR (Fig. 2). Thus, K3L competitively inhibits eIF-2α phosphorylation as well as the autophosphorylation of PKR (Davies et al., 1992) (Fig. 2). In conjunction with the soluble viral type I and type II IFN receptors, E3L and K3L contribute to viral resistance to IFN signalling.

Conclusion and future prospects

Since the first discovery of the cardinal Jak-Stat pathway in the IFN system, numerous studies have contributed to not only the elucidation of involvement of other signalling molecules in the positive or negative regulation of the Jak-Stat pathway, but also the identification of non-Stat pathways. Although there is accumulating evidence regarding the important role of the cooperation of several signalling pathways for IFN activities, the underlying molecular mechanism is not fully understood.

On the other hand, as described above, viral infection triggers the gene induction of many members of the type I IFN family, all of which activate the type I IFN receptor complex in a distinct manner on the basis of the activation property of each ligand. Among these ligands, it was reported that human IFN-α subtypes contain 12 distinct proteins (Pestka, 2000; Pestka et al., 2004). It is of note that they seem to show different relative activities although they similarly utilize the identical receptor complex. In this context, interesting data obtained by Pestka’s group in their studies with recombinant IFN-αs show that there is a marked difference (by more than 10 000-fold) in increasing NK activity among the IFN-α subtypes (Ortaldo et al., 1984). IFN-α2, which is a recombinant protein corresponding to IFN-α7, exhibits virtually no capability of boosting NK activity, and can even act as an antagonist to the effects exerted by other IFN-α subtypes, whereas it has potent antiviral and antiproliferative activities (Ortaldo et al., 1984). In addition to quantitative differences between IFN-α1, -α2 and -α21 in their ability to activate Stat1–5 and ISGs, IFN-γ-inducible protein-10 (IP-10) is highly induced by IFN-α2 and -α21 but to a much lower extent by IFN-α1 in DCs (Hilkens et al., 2003).

These differences in biological activity profiles among the IFN-α subtypes may be caused by several different properties in the receptor-ligand interaction or affinity, which may result in different activations of intracellular signalling pathways in terms of intensity, quality and duration. As Pestka et al. suggested the importance of structure determination of more IFN subtypes to accurately define the molecular basis for their respective activities (Pestka et al., 2004), such analyses regarding extracellular events in relation to ligand properties and ligand–receptor interaction will be required for further clarification of regulatory mechanisms for diversified IFN responses, which could provide deep insights into the physiological roles of type I IFNs in various aspects of host defence systems. In addition, more integral studies using genomics and proteomics will be required to elucidate the molecular mechanism underlying the co-ordination and cooperation of the complex crosstalk networks of intracellular signalling pathways, which underlies diversity of biological activities induced by IFNs.

Interferon biology particularly has an important impact on the clinical field, where IFNs have been so far used in various clinical settings, including viral infections, malign-
nant tumours, immunodeficiency and autoimmune diseases (Liang et al., 2000; Malik and Lee, 2000; Parmar and Platanias, 2003). Further comprehensive understanding of IFN-mediated signalling from both intracellular and extracellular mechanistic points of view may provide some clues to the development of new agents and efficient therapeutic strategies.

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References

Abramovich, C., Shulman, L.M., Ratovitski, E., Harroch, S., Tovey, M., Eid, P., and Revel, M. (1994) Differential tyrosine phosphorylation of the IFNAR chain of the type I interferon receptor and of an associated surface protein in response to IFN-alpha and IFN-beta. EMBO J 13: 5871–5877.

Akira, S., and Takeda, K. (2004) Toll-like receptor signalling. Nat Rev Immunol 4: 499–511.

Alcamí, A., and Smith, G.L. (1995) Vaccinia, cowpox, and camelpox viruses encode soluble gamma interferon receptors with novel broad species specificity. J Virol 69: 4633–4639.

Alcamí, A., and Smith, G.L. (1996a) Soluble interferon-gamma receptors encoded by poxviruses. Comp Immunol Microbiol Infect Dis 19: 305–317.

Alcamí, A., and Smith, G.L. (1996b) Receptors for gamma-interferon encoded by poxviruses: implications for the unknown origin of vaccinia virus. Trends Microbiol 4: 321–326.

Andrejeva, J., Childs, K.S., Young, D.F., Carlos, T.S., Stock, N., Goodbourn, S., and Randall, R.E. (2004) The V proteins of paramyxoviruses bind the IFN-inducible RNA helicase, mda-5, and inhibit its activation of the IFN-beta promoter. Proc Natl Acad Sci USA 101: 17264–17269.

Asselin-Paturel, C., and Trinchieri, G. (2005) Production of type I interferons: plasmacytoid dendritic cells and beyond. J Exp Med 202: 461–466.

Bach, E.A., Aguet, M., and Schreiber, R.D. (1997) The IFNγ receptor: a paradigm for cytokine receptor signaling. Annu Rev Immunol 15: 563–591.

Barca, O., Ferre, S., Seoane, M., Prieto, J.M., Lema, M., Senaris, R., and Arce, V.M. (2003) Interferon beta promotes survival in primary astrocytes through phosphatidylinositol 3-kinase. J Neuroimmunol 139: 155–159.

Berenson, L.S., Farrar, J.D., Murphy, T.L., and Murphy, K.M. (2004a) Frontline: absence of functional STAT4 activation despite detectable tyrosine phosphorylation induced by murine IFN-alpha. Eur J Immunol 34: 2365–2374.

Berenson, L.S., Ota, N., and Murphy, K.M. (2004b) Issues in T-helper 1 development – resolved and unresolved. Immunol Rev 202: 157–174.

Biron, C.A., Nguyen, K.B., Pien, G.C., Cousens, L.P., and Salazar-Mather, T.P. (1999) Natural killer cells in antiviral defense: function and regulation by innate cytokines. Annu Rev Immunol 17: 189–220.

Blyussan, A.R., Durbin, J.E., and Levy, D.E. (1996) ISGF3 gamma p48, a specificity switch for interferon activated transcription factors. Cytokine Growth Factor Rev 7: 11–17.

Bocci, V. (1985) The physiological interferon response. Immunol Today 6: 7–9.

Bowie, A., Kiss-Toth, E., Symons, J.A., Smith, G.L., Dower, S.K., and O’Neill, L.A. (2000) A46R and A52R from vaccinia virus are antagonists of host IL-1 and toll-like receptor signaling. Proc Natl Acad Sci USA 97: 10162–10167.

Buller, R.M., Holmes, K.L., Hugin, A., Frederickson, T.N., and Morse, H.C., 3rd (1987) Induction of cytotoxic T-cell responses in vivo in the absence of CD4 helper cells. Nature 328: 77–79.

Burfoot, M.S., Rogers, N.C., Watling, D., Smith, J.M., Pons, S., Paonessaw, G., et al. (1997) Janus kinase-dependent activation of insulin receptor substrate 1 in response to interleukin-4, oncostatin M, and the interferons. J Biol Chem 272: 24183–24190.

Chang, H.W., Watson, J.C., and Jacobs, B.L. (1992) The E3L gene of vaccinia virus encodes an inhibitor of the interferon-induced, double-stranded RNA-dependent protein kinase. Proc Natl Acad Sci USA 89: 4825–4829.

Chen, J., Baig, E., and Fish, E.N. (2004) Diversity and relatedness among the type I interferons. J Interferon Cytokine Res 24: 687–698.

Colamonici, O.R., Domanski, P., Szwiercz, S.M., Larner, A., and Buller, R.M. (1995) Vaccinia virus B18R gene encodes a type I interferon-binding protein that blocks interferon alpha transmembrane signaling. J Biol Chem 270: 15974–15978.

Darnell, J.E., Jr, Kerr, I.M., and Stark, G.R. (1994) Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science 264: 1415–1421.

David, M., Petricoin, E., 3rd, Benjamin, C., Pine, R., Weber, M.J., and Larner, A.C. (1995) Requirement for MAP kinase (ERK2) activity in interferon alpha- and interferon beta-stimulated gene expression through STAT proteins. Science 269: 1721–1723.

Davies, M.V., Elroy-Stein, O., Jagus, R., Moss, B., and Kaufman, R.J. (1992) The vaccinia virus K3L gene product potentiates translation by inhibiting double-stranded-RNA-activated protein kinase and phosphorylation of the alpha subunit of eukaryotic initiation factor 2. J Virol 66: 1943–1950.

De Maeyer, E., and De Maeyer-Guignard, J. (1988) Interferons and Other Regulatory Cytokines. New York: John Wiley and Sons.

Decker, T., Lew, D.J., and Darnell, J.E., Jr (1991a) Two distinct α-interferon-dependent signal transduction pathways may contribute to activation of transcription of the guanylate-binding protein gene. Mol Cell Biol 11: 5147–5153.

Decker, T., Lew, D.J., Mirkovitch, J., and Darnell, J.E., Jr (1991b) Cytoplasmic activation of GAF, an IFN-γ-regulated DNA-binding factor. EMBO J 10: 927–932.

Der, S.D., Zhou, A., Williams, B.R., and Silverman, R.H. (1998) Identification of genes differentially regulated by interferon alpha, beta, or gamma using oligonucleotide arrays. Proc Natl Acad Sci USA 95: 15623–15628.

Didcock, L., Young, D.F., Goodbourn, S., and Randall, R.E. (1999) The V protein of simian virus 5 inhibits interferon

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signalling by targeting STAT1 for proteasome-mediated degradation. J Virol 73: 9928–9933.

Dumoutier, L., Lejeune, D., Hor, S., Fickenscher, H., and Renaud, J.C. (2003) Cloning of a new type II cytokine receptor activating signal transducer and activator of transcription (STAT) 1, STAT2 and STAT3. Biochem J 370: 391–396.

Dunn, G.P., Bruce, A.T., Sheehan, K.C., Shankaran, V., Uppaluri, R., Bui, J.D., et al. (2005) A critical function for type I interferons in cancer immunoediting. Nat Immunol 6: 722–729.

Fish, E.N., Uddin, S., Korkmaz, M., Majchrzak, B., Druker, B.J., and Platanias, L.C. (1999) Activation of a CrkL-stat5 signaling complex by type I interferons. J Biol Chem 274: 571–573.

Gale, M., Jr, and Foy, E.M. (2005) Evasion of intracellular host defence by hepatitis C virus. Nature 436: 939–945.

Garcia-Sastre, A. (2002) Mechanisms of inhibition of the host interferon alpha/beta-mediated antiviral responses by viruses. Microbes Infect 4: 647–655.

Goh, K.C., Haque, S.J., and Williams, B.R. (1999) p38 MAP kinase is required for STAT1 serine phosphorylation and transcriptional activation induced by interferons. EMBO J 18: 5601–5608.

Goodbourn, S., Didcock, L., and Randall, R.E. (2000) Interferons: cell signalling, immune modulation, antiviral response and virus countermeasures. J Gen Virol 81 Part 10: 2341–2364.

Gresser, I. (1990) Biologic effects of interferons. J Invest Dermatol 95: 665–715.

Gresser, I., Maury, C., Kaido, T., Bandu, M.T., Maunoury, M.T., et al. (1995) The essential role of endogenous IFN-α/β in the anti-metastatic action of sensitized T lymphocytes in mice injected with Friend erythroleukemia cells. Int J Cancer 63: 726–731.

Haga, I.R., and Bowie, A.G. (2005) Evasion of innate immunity by vaccinia virus. Parasitology 130 (Suppl.): S11–S25.

Haig, D.M. (1998) Poxvirus interference with the host cytokine response. Vet Immunol Immunopathol 63: 149–156.

Hata, N., Sato, M., Takaoka, A., Asagiri, M., Tanaka, N., and Taniguchi, T. (2001) Constitutive IFN-α/β signal for efficient IFN-α/β gene induction by virus. Biochem Biophys Res Commun 285: 518–525.

He, Y., and Katze, M.G. (2002) To interfere and to anti-interfer: the interplay between hepatitis C virus and interferon. Viral Immunol 15: 95–119.

Heinrich, P.C., Behrmann, I., Haan, S., Hermanns, H.M., Muller-Newen, G., and Schaper, F. (2003) Principles of interferon-IL6-type cytokine signalling and its regulation. Biochem J 374: 1–20.

Hida, S., Ogasawara, K., Sato, K., Abe, M., Takayanagi, H., Yokochi, T., et al. (2000) CD8+ T cell-mediated skin disease in mice lacking IRF-2, the transcriptional attenuator of interferon-α/β signaling. Immunity 13: 643–655.

Hilkens, C.M., Schlaak, J.F., and Kerr, I.M. (2003) Differential responses to IFN-alpha subtypes in human T cells and dendritic cells. J Immunol 171: 5255–5263.

Honda, K., Mizutani, T., and Tanimu, T. (2004a) Negative regulation of IFN-alpha/beta signaling by IFN regulatory factor 2 for homeostatic development of dendritic cells. Proc Natl Acad Sci USA 101: 2416–2421.

Honda, K., Yanai, H., Mizutani, T., Nogishi, H., Shimada, N., Suzuki, N., et al. (2004b) Role of a transudational-transcriptional processor complex involving MyD88 and IRF-7 in Toll-like receptor signaling. Proc Natl Acad Sci USA 101: 15416–15421.

Horvath, C.M. (2004) Silencing STATs: lessons from paramyxovirus interferon evasion. Cytokine Growth Factor Rev 15: 117–127.

Hou, S., Mo, X.Y., Hyland, L., and Doherty, P.C. (1995) Host response to Sendai virus in mice lacking class II major histocompatibility complex glycoproteins. J Virol 69: 1429–1434.

Huang, S., Hendriks, W., Althage, A., Hemmi, S., Bluethmann, H., Kamijo, R., et al. (1993) Immune response in mice that lack the interferon-gamma receptor. Science 259: 1742–1745.

Ichikawa, E., Hida, S., Omatzu, Y., Shimoyama, S., Takahara, K., Miyagawa, S., et al. (2004) Defective development of splenic and epidermal CD4+ dendritic cells in mice deficient for IFN regulatory factor-2. Proc Natl Acad Sci USA 101: 3909–3914.

Ihle, J.N. (1995) The Janus protein tyrosine kinases in hematopoietic cytokine signaling. Semin Immunol 7: 247–254.

Ihle, J.N., and Kerr, I.M. (1995) Jak and Stats in signaling by the cytokine receptor superfamily. Trends Genet 11: 69–74.

Ikeda, H., Old, L.J., and Schreiber, R.D. (2002) The roles of IFN gamma in protection against tumor development and cancer immunoediting. Cytokine Growth Factor Rev 13: 95–109.

Isaacs, A., and Lindenmann, J. (1957) Virus interference. I. The interferon. Proc R Soc B147: 258–273.

Johnson, C.L., and Gale, M., Jr (2005) CARD games between virus and host get a new player. Trends Immunol 27: 1–4.

Karupiah, G., Blanden, R.V., and Ramshaw, I.A. (1990) Interferon gamma is involved in the recovery of athymic nude mice from recombinant vaccinia virus/interleukin 2 infection. J Exp Med 172: 1495–1503.

Karupiah, G., Fredrickson, T.N., Holmes, K.L., Khairallah, L.H., and Buller, R.M. (1993a) Importance of interferons in recovery from mousepox. J Virol 67: 4214–4226.

Karupiah, G., Xie, Q.W., Buller, R.M., Nathan, C., Duarte, C., and MacMicking, J.D. (1993b) Inhibition of viral replication by interferon-gamma-induced nitric oxide synthase. Science 261: 1445–1448.

Katze, M.G., He, Y., and Gale, M., Jr (2002) Viruses and interferon: a fight for supremacy. Nat Rev Immunol 2: 675–687.
Kotenko, S.V., Gallagher, G., Baurin, V.V., Lewis-Antes, A., Kessler, D.S., Veals, S.A., Fu, X.Y., and Levy, D.E. (1990) Interferon-alpha regulates nuclear translocation and DNA-binding affinity of ISGF3, a multimeric transcriptional activator. *Genes Dev* 4: 1753–1765.

Kohonen-Corish, M.R., King, N.J., Woodhams, C.E., and Ramshaw, I.A. (1990) Immunodeficient mice recover from infection with vaccinia virus expressing interferon-gamma. *Eur J Immunol* 20: 157–161.

Kotenko, S.V., Izotova, L.S., Pollack, B.P., Muthukumanan, G., Paaluk, K., Silvennoinen, O., et al. (1996) Other kinases can substitute for Jak2 in signal transduction by interferon-gamma. *J Biol Chem* 271: 17174–17182.

Kotenko, S.V., Gallaghcr, G., Baurin, V.V., Lewis-Antes, A., Shen, M., Shah, N.K., et al. (2003) IFN-lambda mediates antiviral protection through a distinct class II cytokine receptor complex. *Nat Immunol* 4: 69–77.

LaFluer, D.W., Nardelli, B., Tsareva, T., Mather, D., Feng, P., Semenuk, M., et al. (2001) Interferon-kappa, a novel type I interferon expressed in human keratinocytes. *J Biol Chem* 276: 39765–39771.

Langer, J.A., Cutrone, E.C., and Kotenko, S. (2004) The Class II cytokine receptor (CRF2) family: overview and patterns of receptor–ligand interactions. *Cytokine Growth Factor Rev* 15: 33–48.

Leferve, F., Guillomot, M., D’Andrea, S., Battegay, S., and La Bonnadiere, C. (1998) Interferon-delta: the first member of a novel type I interferon family. *Biochimie* 80: 779–788.

Levy, D.E., and Garcia-Sastre, A. (2001) The virus battles: IFN induction of the antiviral state and mechanisms of viral evasion. *Cytokine Growth Factor Rev* 12: 143–156.

Lew, D.J., Decker, T., Strehol, I., and Darnell, J.E. (1991) Overlapping elements in the guanylate-binding protein gene promoter mediate transcriptional induction by alpha and gamma interferons. *Mol Cell Biol* 11: 182–191.

Li, K., Foy, E., Ferreion, J.C., Nakamura, M., Ferreion, A.C., Ikeda, M., et al. (2005) Immune evasion by hepatitis C virus NS3/4A protease-mediated cleavage of the Toll-like receptor 3 adaptor protein TRIF. *Proc Natl Acad Sci USA* 102: 2992–2997.

Liang, T.J., Rehermann, B., Seef, L.B., and Hofnung, J.H. (2000) Pathogenesis, natural history, treatment, and prevention of hepatitis C. *Ann Intern Med* 132: 296–305.

Liptakova, H., Kontsekova, E., Alcami, A., Smith, G.L., and Kontsek, P. (1997) Analysis of an interaction between the soluble vaccinia virus-coded type I interferon (IFN) receptor and human IFN-alpha1 and IFN-alpha2. *Virology* 232: 86–90.

Liu, Y.J. (2005) IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. *Annu Rev Immunol* 23: 275–306.

Malik, A.H., and Lee, W.M. (2000) Chronic hepatitis B virus infection: treatment strategies for the next millennium. *Ann Intern Med* 132: 723–731.

Marie, I., Durbin, J.E., and Levy, D.E. (1998) Differential viral induction of distinct interferon-α genes by positive feedback through interferon regulatory factor-7. *EMBO J* 17: 6660–6669.

Matsuyama, T., Kimura, T., Kitagawa, M., Pfeffer, K., Kawakami, T., Watanabe, N., et al. (1993) Targeted disruption of IRF-1 or IRF-2 results in abnormal type I IFN gene induction and aberrant lymphocyte development. *Cell* 75: 83–97.

Mayer, I.A., Verma, A., Grumbach, I.M., Uddin, S., Lekmine, F., Ravandi, F., et al. (2001) The p38 MAPK pathway mediates the growth inhibitory effects of interferon-alpha in BCR-ABL-expressing cells. *J Biol Chem* 276: 28570–28577.

Mekkova, Z., and Esteban, M. (1994) Interferon-gamma severely inhibits DNA synthesis of vaccinia virus in a macrophage cell line. *Virology* 198: 731–735.

Meylan, E., Curran, J., Hofmann, K., Moradpour, D., Binder, M., Bartenschlager, R., and Tschopp, J. (2005) Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. *Nature* 437: 1167–1172.

Mitani, Y., Takaoka, A., Kim, S.H., Kato, Y., Yokochi, T., Tanaka, N., and Taniguchi, T. (2001) Cross talk of the interferon-α/β signalling complex with gp130 for effective interleukin-6 signalling. *Genes Cells* 6: 631–640.

Muller, U., Steinhoff, U., Reis, L.F., Hemmi, S., Pavlovic, J., Zinkernagel, R.M., and Aguet, M. (1994) Functional role of type I and type II interferons in antiviral defense. *Science* 264: 1918–1921.

Nguyen, H., Ramana, C.V., Bayes, J., and Stark, G.R. (2001) Roles of phosphatidylinositol 3-kinase in interferon-gamma-dependent phosphorylation of STAT1 on serine 727 and activation of gene expression. *J Biol Chem* 276: 33361–33368.

Novick, D., Cohen, B., and Rubinstein, M. (1994) The human interferon alpha/beta receptor: characterization and molecular cloning. *Cell* 77: 391–400.

Ogasawara, K., Hida, S., Weng, Y., Saamura, A., Sato, K., Takayanagi, H., et al. (2002) Requirement of the IFN-alpha/beta-induced CXCR3 chemokine signalling for CD8+ T cell activation. *Genes Cells* 7: 309–320.

Oritani, K., Medina, K.L., Tomiyama, Y., Ishikawa, J., Oka-jima, Y., Ogawa, M., et al. (2000) Limitin: an interferon-like cytokine that preferentially influences B-lymphocyte precursors. *Nat Med* 6: 659–666.

Ortalido, J.R., Herberman, R.B., Harvey, C., Osheroff, P., Pan, Y.C., Kelder, B., and Pestka, S. (1984) A species of human alpha interferon that lacks the ability to boost human natural killer activity. *Proc Natl Acad Sci USA* 81: 4926–4929.

Parmar, S., and Platanias, L.C. (2003) Interferons: mechanisms of action and clinical applications. *Curr Opin Oncol* 15: 431–439.

Pestka, S. (1997) The interferon receptors. *Semin Oncol* 24: 8S–9S–19S–94.

Pestka, S. (2000) The human interferon alpha species and receptors. *Biopolymers* 55: 254–287.

Pestka, S., Langer, J.A., Zoon, K.C., and Samuel, C.E. (1987) Interferons and their actions. *Annu Rev Biochem* 56: 727–777.

Pestka, S., Krause, C.D., and Walter, M.R. (2004) Interferons, interferon-like cytokines, and their receptors. *Immunol Rev* 202: 1–32.

Pfeffer, L.M., Mullersman, J.E., Pfeffer, S.R., Murti, A., Shi, W., and Yang, C.H. (1997) STAT3 as an adapter to couple
phosphatidylinositol 3-kinase to the IFNAR1 chain of the type I interferon receptor. Science 276: 1418–1420.

Platania, L.C., Uddin, S., Yetter, A., Sun, X.J., and White, M.F. (1996) The type I interferon receptor mediates tyrosine phosphorylation of insulin receptor substrate 2. J Biol Chem 271: 278–282.

Ridge, J.P., Di Rosa, F., and Matzinger, P. (1998) A conditioned dendritic cell can be a temporal bridge between a CD4+ T Helper and a T Killer cell. Nature 393: 474–478.

Roberts, R.M., Liu, L., Guo, Q., Leaman, D., and Bixby, J. (1998) The evolution of the type I interferons. J Interferon Cytokine Res 18: 805–816.

Roberts, R.M., Ealy, A.D., Alexenko, A.P., Han, C.S., and Ezashi, T. (1999) Trophoblast interferons. Placenta 20: 259–264.

Rodríguez, J.R., Rodríguez, D., and Esteban, M. (1991) Interferon treatment inhibits early events in vaccinia virus gene expression in infected mice. Virology 185: 929–933.

Rogge, L., D’Ambrosio, D., Biffi, M., Penna, G., Minetti, L.J., Presky, D.H., et al. (1998) The role of Stat4 in species-specific regulation of Th cell development by type I IFNs. J Immunol 161: 6567–6574.

Rothenfusser, S., Goutagny, N., DiPerna, G., Gong, M., Monks, B.G., Schoenemeyer, A., et al. (2005) The RNA helicase Lgp2 inhibits TLR-independent sensing of viral replication by retinoic acid-inducible gene-1. J Immunol 175: 5260–5268.

Sato, M., Hata, N., Asagiri, M., Nakaya, T., Taniguchi, T., and Tanaka, N. (1998) Positive feedback regulation of type I IFN genes by the IFN-inducible transcription factor IRF-7. FEMS Lett 441: 106–110.

Sato, M., Suemori, H., Hata, N., Asagiri, M., Ogasawara, K., Nakao, K., et al. (2000) Distinct and essential roles of transcription factors IRF-3 and IRF-7 in response to viruses for IFN-α/β gene induction. Immunity 13: 539–548.

Schindler, C., and Darnell, J.E., Jr (1995) Transcriptional responses to polypeptide ligands: the JAK-STAT pathway. Annu Rev Biochem 64: 621–651.

Schindler, C., Shuai, K., Prezioso, V.R., and Darnell, J.E., Jr (1992) Interferon-dependent tyrosine phosphorylation of a latent cytoplasmic transcription factor. Science 257: 809–813.

Seth, R.B., Sun, L., Ea, C.K., and Chen, Z.J. (2005) Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-kappaB and IRF 3. Cell 122: 669–682.

Sheppard, P., Kindevogel, W., Xu, W., Henderson, K., Schlutzmeyer, S., Whitmore, T.E., et al. (2003) IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Immunol 4: 63–68.

Silvennoinen, O., Ihle, J.N., Schlessinger, J., and Levy, D.E. (1993) Interferon-induced nuclear signalling by Jak protein tyrosine kinases. Nature 366: 583–585.

Stark, G.R., Kerr, I.M., Williams, B.R., Silverman, R.H., and Schreiber, R.D. (1998) How cells respond to interferons. Annu Rev Biochem 67: 227–264.

Stack, J., Haga, I.R., Schroder, M., Bartlett, N.W., Maloney, G., Reading, P.C., et al. (2005) Vaccinia virus protein A46R targets multiple Toll-like-interleukin-1 receptor adaptors and contributes to virulence. J Exp Med 201: 1007–1018.

Symons, J.A., Alcami, A., and Smith, G.L. (1995) Vaccinia virus encodes a soluble type I interferon receptor of novel structure and broad species specificity. Cell 81: 551–560.

Takaoka, A., and Taniguchi, T. (2003) New aspects of IFN-α/β signalling in immunity, oncogenesis and bone metabolism. Cancer Sci 94: 405–411.

Takaoka, A., Mitani, Y., Suemori, H., Sato, M., Yokochi, T., Noguchi, S., et al. (2000) Cross talk between interferon-γ and α/β signalling components in caveolar membrane domains. Science 288: 2357–2360.

Takayanagi, H., Kim, S., Matsuo, K., Suzuki, H., Suzuki, T., Sato, K., et al. (2002) RANKL maintains bone homeostasis through c-Fos-dependent induction of interferon-beta. Nature 416: 744–749.

Takaoka, A., Hayakawa, S., Yanai, H., Stoiber, D., Negishi, H., Kikuchi, H., et al. (2003) Integration of interferon-α/β signalling to p53 responses in tumour suppression and antiviral defence. Nature 424: 516–523.

Takeda, K., and Akira, S. (2005) Toll-like receptors in innate immunity. Int Immunol 17: 1–14.

Takeda, K., Kaisho, T., and Akira, S. (2003) Toll-like receptors. Annu Rev Immunol 21: 335–376.

Taki, S. (2002) Type I interferons and autoimmunity: lessons from the clinic and from IRF-2-deficient mice. Cytokine Growth Factor Rev 13: 379–391.

Taniguchi, T. (1995) Cytokine signaling through nonreceptor protein tyrosine kinases. Science 268: 251–255.

Taniguchi, T., and Takaoka, A. (2001) A weak signal for strong responses: interferon-α/β revisited. Nat Rev Mol Cell Biol 2: 378–386.

Taniguchi, T., and Takaoka, A. (2002) The interferon-α/β system in antiviral responses: a multimodal machinery of gene regulation by the IRF family of transcription factors. Curr Opin Immunol 14: 111–116.

Taniguchi, T., Ogasawara, K., Takaoka, A., and Tanaka, N. (2001) IRF family of transcription factors as regulators of host defense. Annu Rev Immunol 19: 623–655.

Theofilopoulos, A.N., Baccala, R., Beutler, B., and Kono, D.H. (2005) Type I interferons (alpha/beta) in immunity and autoimmunity. Annu Rev Immunol 23: 307–336.

Thyrell, L., Hjortsberg, L., Arulampalam, V., Panaretakis, T., Uhles, S., Dagnell, M., et al. (2004) Interferon alpha-induced apoptosis in tumor cells is mediated through the phosphoinositide 3-kinase/mammalian target of rapamycin signaling pathway. J Biol Chem 279: 24152–24162.

Tovey, M.G., Streuli, M., Gresser, I., Gugenheim, J., Blanchard, B., Guymarho, J., et al. (1987) Interferon messenger RNA is produced constitutively in the organs of normal individuals. Proc Natl Acad Sci USA 84: 5038–5042.

Uddin, S., Yenus, L., Sun, X.J., Sweet, M.E., White, M.F., and Platania, L.C. (1995) Interferon-alpha engages the insulin receptor substrate-1 to associate with the phosphatidylinositol 3'-kinase. J Biol Chem 270: 15938–15941.

Uddin, S., Majchrzak, B., Woodson, J., Arunkumar, P., Alsayed, Y., Pine, R., et al. (1999) Activation of the p38 mitogen-activated protein kinase by type I interferons. J Biol Chem 274: 30127–30131.

Uddin, S., Lekmine, F., Sharma, N., Majchrzak, B., Mayer, L., Young, P.R., et al. (2000a) The Rac1/p38 mitogen-activated protein kinase pathway is required for interferon alpha-dependent transcriptional activation but not serine phosphorylation of Stat proteins. J Biol Chem 275: 27634–27640.

Uddin, S., Majchrzak, B., Wang, P.C., Modi, S., Khan, M.K., Fish, E.N., and Platania, L.C. (2000b) Interferon-dependent activation of the serine kinase PI 3'-kinase requires engagement of the IRS pathway but not the Stat pathway. Biochem Biophys Res Commun 270: 158–162.
Uddin, S., Sassano, A., Deb, D.K., Verma, A., Majchrzak, B., Rahman, A., et al. (2002) Protein kinase C-δ (PKC-δ) is activated by type I interferons and mediates phosphorylation of Stat1 on serine 727. J Biol Chem 277: 14408–14416.

Uematsu, S., Sato, S., Yamamoto, M., Hirota, T., Kato, H., Takeshita, F., et al. (2005) Interleukin-1 receptor-associated kinase-1 plays an essential role for Toll-like receptor (TLR) 7- and TLR9-mediated interferon-α induction. J Exp Med 201: 915–923.

Upton, C., Mossman, K., and McFadden, G. (1992) Encoding of a homolog of the IFN-gamma receptor by myxoma virus. Science 258: 1369–1372.

Uze, G., Lutfalla, G., and Gresser, I. (1990) Genetic transfer of a functional human interferon alpha receptor into mouse cells: cloning and expression of its cDNA. Cell 60: 225–234.

Velazquez, L., Fellous, M., Stark, G.R., and Pellegrini, S. (1992) A protein tyrosine kinase in the interferon alpha/beta signaling pathway. Cell 70: 313–322.

Vilcek, J. (2003) Novel interferons. Nat Immunol 4: 8–9.

Vilcek, J., and Sen, G.S. (1996) Interferons and other cytokines. In Fields Virology, Third Edition. Fields, D.M., Knipe, P.M., and Howley, P.M. (eds). Philadelphia, PA: Lippincott-Raven, pp. 375–399.

Wang, J., Pham-Mitchell, N., Schindler, C., and Campbell, I.L. (2003a) Dysregulated Sonic hedgehog signaling and medulloblastoma consequent to IFN-alpha-stimulated STAT2-independent production of IFN-gamma in the brain. J Clin Invest 112: 535–543.

Wang, K., Scheel-Toellner, D., Wong, S.H., Craddock, R., Caamano, J., Akbar, A.N., et al. (2003b) Inhibition of neutrophil apoptosis by type 1 IFN depends on cross-talk between phosphoinositol 3-kinase, protein kinase Cδ, and NFκB signaling pathways. J Immunol 171: 1035–1041.

Weber, F., Kochs, G., and Haller, O. (2004) Inverse interference: how viruses fight the interferon system. Viral Immunol 17: 498–515.

Williams, B.R. (1991) Transcriptional regulation of interferon-stimulated genes. Eur J Biochem 200: 1–11.

Xu, L.G., Wang, Y.Y., Han, K.J., Li, L.Y., Zhai, Z., and Shu, H.B. (2005) VISA is an adapter protein required for virus-triggered IFN-beta signaling. Mol Cell 19: 727–740.

Yang, C.H., Murti, A., and Pfeffer, L.M. (1998) STAT3 complements defects in an interferon-resistant cell line: evidence for an essential role for STAT3 in interferon signaling and biological activities. Proc Natl Acad Sci USA 95: 5568–5572.

Yang, C.H., Murti, A., Pfeffer, S.R., Kim, J.G., Donner, D.B., and Pfeffer, L.M. (2001) Interferon alpha /beta promotes cell survival by activating nuclear factor kappa B through phosphatidylinositol 3-kinase and Akt. J Biol Chem 276: 13756–13761.

Yoneyama, M., Kikuchi, M., Natsukawa, T., Shinobu, N., Imai-zumi, T., Miyagishi, M., et al. (2004) The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat Immunol 5: 730–737.

Yoneyama, M., Kikuchi, M., Matsumoto, K., Imai-zumi, T., Miyagishi, M., Taira, K., et al. (2005) Shared and unique functions of the DExD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity. J Immunol 175: 2851–2858.