Type I interferons in infectious disease

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Abstract | Type I interferons (IFNs) have diverse effects on innate and adaptive immune cells during infection with viruses, bacteria, parasites and fungi, directly and/or indirectly through the induction of other mediators. Type I IFNs are important for host defence against viruses. However, recently, they have been shown to cause immunopathology in some acute viral infections, such as influenza virus infection. Conversely, they can lead to immunosuppression during chronic viral infections, such as lymphocytic choriomeningitis virus infection. During bacterial infections, low levels of type I IFNs may be required at an early stage, to initiate cell-mediated immune responses. High concentrations of type I IFNs may block B cell responses or lead to the production of immunosuppressive molecules, and such concentrations also reduce the responsiveness of macrophages to activation by IFNγ, as has been shown for infections with *Listeria monocytogenes* and *Mycobacterium tuberculosis*. Recent studies in experimental models of tuberculosis have demonstrated that prostaglandin E2 and interleukin-1 inhibit type I IFN expression and its downstream effects, demonstrating that a cross-regulatory network of cytokines operates during infectious diseases to provide protection with minimum damage to the host.

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There are three distinct interferon (IFN) families. The type I IFN family is a multi-gene cytokine family that encodes 13 partially homologous IFNα subtypes in humans (14 in mice), a single IFNβ and several poorly defined single gene products (IFNε, IFNτ, IFNκ, IFNω, IFNδ and IFNζ)[1]. The type II IFN family consists of a single gene product, IFNγ, that is predominantly produced by T cells and natural killer (NK) cells, and can act on a broad range of cell types that express the IFNγ receptor (IFNγR)[2]. The type III IFN family comprises IFNλ1, IFNλ2 and IFNλ3 (also known as IL-29, IL-28A and IL-28B, respectively) and the recently identified IFNλ4 (REFS 3,4), which have similar functions to cytokines of the type I IFN family but restricted activity, as the expression of their receptor is largely restricted to epithelial cell surfaces[5]. Indeed, immune cells are largely unresponsive to IFNλ (reviewed in REFS 5,6). This Review focuses on IFNα and IFNβ (hereafter referred to as IFNα/β), which are the best-defined and most broadly expressed type I IFNs. These cytokines are best known for their ability to induce an antiviral state in both virus-infected cells and uninfected, bystander cells, by inducing a programme of gene transcription that interferes with multiple stages of the viral replication cycle through various mechanisms[7]. However, IFNα/β have numerous additional functions that influence the innate and adaptive immune responses not only to viruses but also to bacterial pathogens and other pathogens. The outcome of the IFNα/β response during infectious disease is highly context dependent. Different conditions are induced during specific infections and affect when and where IFNα/β signals are delivered, as well as the signalling pathways that are triggered downstream of the type I IFN receptor (IFNAR). This, in turn, influences which IFN-stimulated genes (ISGs) are activated or repressed. Overall, this can lead to beneficial or detrimental outcomes for the host. In this Review, we discuss IFNα/β-mediated effects on the host response during various infectious diseases and the mechanisms involved in conferring these effects.

Type I IFN production and signalling

Induction of IFNα/β production. Almost all cells in the body can produce IFNα/β, and this usually occurs in response to the stimulation of receptors known as pattern recognition receptors (PRRs) by microbial products. These receptors are located on the cell surface, in the cytosol or in endosomal compartments. They recognize foreign nucleic acids and self DNA (which are generally not found in the cytosol), as well as a limited

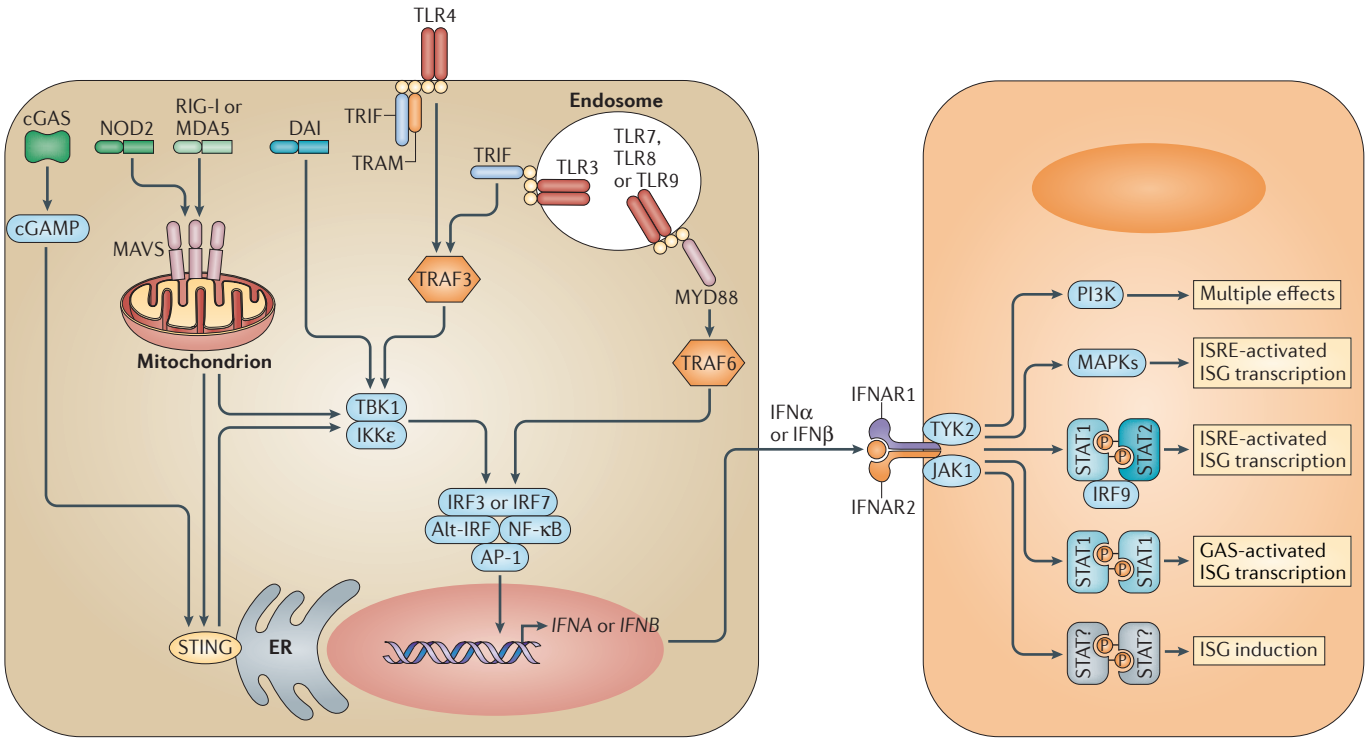

Figure 1 | **Pathways of type I interferon induction and receptor signalling.** Recognition of microbial products by a range of cell-surface and intracellular pattern recognition receptors, including Toll-like receptors (TLRs) and retinoic acid-inducible gene I (RIG-I), can lead to induction of the genes encoding type I interferons (IFNs), which is mediated by several distinct signalling pathways. On the binding of type I IFNs to their receptor (IFNAR), multiple downstream signalling pathways can be induced, leading to a diverse range of biological effects. The canonical signal transducer and activator of transcription 1 (STAT1)–STAT2–IFN-regulatory factor 9 (IRF9) signalling complex (also known as the IFN-stimulated gene factor 3 (ISGF3) complex) binds to IFN-stimulated response elements (ISREs) in gene promoters, leading to induction of a large number of IFN-stimulated genes (ISGs). Type I IFNs can also signal through STAT1 homodimers, which are more commonly associated with the IFNγ-mediated signalling pathway. Other STAT heterodimers and homodimers may also be activated downstream, including STAT3, STAT4 and STAT5. Other signalling pathways that do not rely on Janus kinase (JAK) and/or STAT activity may also be activated, including mitogen-activated protein kinases (MAPKs) and the phosphoinositide 3-kinase (PI3K) pathway, thereby leading to diverse effects on the cell. Alt-IRF, IRFs other than IRF3 or IRF7; AP-1, activator protein 1; cGAMP, cyclic di-GMP-AMP; cGAS, cytosolic GAMP synthase; DAI, DNA-dependent activator of IRFs; ER, endoplasmic reticulum; GAS, γ-activated sequence; IKKε, IκB kinase-ε; MAVS, mitochondrial antiviral signalling protein; MDA5, melanoma differentiation-associated gene 5; MYD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; NOD2, NOD-containing protein 2; STING, stimulator of IFN genes; TBK1, TANK-binding kinase 1; TRAF, TNF receptor-associated factor; TRAM, TLR adaptor molecule (also known as TICAM2); TRIF, TIR domain-containing adaptor protein inducing IFNβ; TYK2, tyrosine kinase 2.

number of other non-nucleic-acid pathogen-associated molecular patterns (PAMPs). The RNA helicases retinoic acid-inducible gene I (RIG-I; also known as DDX58) and melanoma differentiation-associated gene 5 (MDA5; also known as IFIH1) are the main cytosolic receptors that are responsible for the recognition of RNA, and they may recognize certain AT-rich DNA motifs, although this is controversial (reviewed in REF. 8). These receptors are highly associated with the induction of type I IFNs (FIG. 1). Other DNA motifs in the cytosol can be recognized by various receptors, including DNA-dependent activator of IFN-regulatory factors (DAI; also known as ZBP1), the DEAD box and DEAH box (DEXD/H box) helicases, and the recently described receptor cytosolic GAMP synthase (cGAS; also known as MB21D1) (reviewed in REFS 8,9), all of which are highly associated with the induction of type I IFN production. Finally, the cytosolic molecular sensors NOD-containing protein 1 (NOD1) and NOD2 are expressed by various cell types and recognize nucleic acids and other ligands, which can lead to IFNα/β production[10–12] (reviewed in REF. 13).

In addition to these cytosolic receptors, several Toll-like receptors (TLRs) activate pathways that lead to IFNα/β production. Of the cell-surface TLRs, TLR4, which recognizes lipopolysaccharide from bacteria, is the most potent type I IFN inducer and signals through the adaptor protein TIR domain-containing adaptor protein inducing IFNβ (TRIF; also known as TICAM1). In endosomal compartments, TLR3, TLR7 and TLR8, and TLR9 respond to double-stranded RNA, single-stranded RNA and unmethylated CpG DNA, respectively[14].

Diverse pathways downstream of these receptors transduce signals that converge on a few key molecules, such as the IFN-regulatory factor (IRF) family of

Cytosolic GAMP synthase (cGAS). A cytosolic DNA sensor that catalyses the production of the second messenger cyclic di-GMP-AMP (cGAMP) in response to DNA, which is then recognized by the sensor and signalling intermediate STING (stimulator of interferon genes), triggering type I interferon production.

transcription factors, that activate the transcription of genes encoding IFNα/β. In most cases, IRF3 and IRF7 are the fundamental IRFs that are required, although others (such as IRF1, IRF5 and IRF8) can also induce *IFNA/B* gene transcription. The central tenet of IFNα/β production is that the *IFNB* and *IFNA4* genes are induced in an initial wave of transcription that relies on IRF3. This initial IFN burst triggers the transcription of *IRF7*, which then mediates a positive feedback loop, leading to the induction of a second wave of gene transcription, including additional IFNα-encoding genes[15,16]. Nuclear factor-κB (NF-κB) is also required as a cofactor, although there is some disagreement about the importance of this pathway in IFNα/β production[15]. Immediately upstream of the IRFs, the kinases IκB kinase-ε (IKKε; encoded by *IKBKE*) and TANK-binding kinase 1 (TBK1) are responsible for the phosphorylation of IRF3 and IRF7. The cytosolic RNA sensors RIG-I and MDA5 rely on the adaptor mitochondrial antiviral signalling protein (MAVS; also known as IPS1 or VISA) to activate TBK1, whereas stimulator of IFN genes (STING; also known as TMEM173) is an important mediator of much of the response to cytosolic DNA[9]. TLR3 and TLR4 use the adaptor molecule TRIF, which activates TBK1, leading to the activation of IRF3. TLR7 and TLR9 are preferentially expressed by plasmacytoid dendritic cells (pDCs) and transduce signals for IFNα/β production through myeloid differentiation primary response protein 88 (MYD88) rather than TRIF, and the potent production of IFNα/β by pDCs is due to constitutive expression of IRF7 and to retention of the MYD88–IRF7 complex in endosomes[14,16].

Type I IFN signalling and induction of ISGs. IFNβ and all of the IFNα subtypes bind to, and signal through, a heterodimeric transmembrane receptor composed of the subunits IFNAR1 and IFNAR2. Ligation of IFNAR activates the receptor-associated protein tyrosine kinases Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2). In the canonical pathway of IFNα/β-mediated signalling, activated JAK1 and TYK2 phosphorylate signal transducer and activator of transcription 1 (STAT1) and STAT2 molecules that are present in the cytosol, leading to the dimerization, nuclear translocation and binding of these molecules to IRF9 to form the ISG factor 3 (ISGF3) complex. This complex then binds to IFN-stimulated response elements in ISG promoters, leading to the activation of ISG transcription (reviewed in REF. 17). In this manner, IFNα/β induces the expression of several hundred ISGs, a large number of which function to induce an antiviral state within the cell.

IFNα/β-mediated signalling is not limited to this canonical pathway, however. In addition to signalling through STAT1–STAT2 heterodimers, IFNα/β can signal through STAT1 homodimers, which are more commonly associated with IFNγ-mediated signalling and bind to γ-activated sequences in gene promoters[17]. IFNα/β can also signal through STATs that are usually associated with other cytokine-mediated signalling pathways, including STAT3, STAT4, STAT5A and STAT5B. The phosphoinositide 3-kinase (PI3K)–mammalian target of rapamycin (mTOR) pathway and multiple mitogen-activated protein kinase (MAPK) pathways can also be activated downstream of IFNAR. This diversity of signalling pathways may in part explain the broad effects of IFNα/β-mediated signalling, as it allows the transcription of a broad range of genes in addition to those dedicated to viral restriction (reviewed in REF. 17). These include genes that encode cytokines and chemokines, antibacterial effectors, pro-apoptotic and anti-apoptotic molecules, and molecules involved in metabolic processes[18] (FIG. 1).

Protective effects in viral infection

***Virus restriction* in vitro.** IFNs were named for their ability to restrict (that is, to 'interfere' with) viral replication in vertebrate cells, which has now been shown for many viruses both in human and mouse cells and cell lines[7]. The ability of IFNα/β to restrict viral replication is largely attributable to the induction of ISGs. These genes are either expressed constitutively in cells in response to low levels of IFNα/β in the microenvironment or, more commonly, in response to IFNα/β produced in response to infection, during which IFNα/β promote an antiviral state in bystander cells and restrict the viral replication cycle in cells that have already been infected[7]. The fact that most viruses devote part of their limited genome to mechanisms that perturb IFNα/β production and/or IFNα/β-mediated signalling, thereby preventing ISGs from being induced, illustrates the importance of this cytokine family in host cell protection against viral infection[19].

The mechanisms of action of many of these ISGs have been described. Some of the best known are myxovirus resistance 1 (MX1), IFN-inducible double-stranded RNA-dependent protein kinase (PKR; encoded by *EIF2AK2*), 2′-5′-oligoadenylate synthetase (OAS), IFN-induced transmembrane proteins (IFITMs), apolipoprotein B mRNA-editing enzyme catalytic polypeptide 1 (APOBEC1)[7] and the tripartite motif-containing (TRIM) family of molecules[7,20]. These ISGs have been reviewed in great detail elsewhere and are therefore not discussed further here[7]. However, it is worth noting interesting recent work aimed at understanding this acute ISG response at a broader level by defining the transcriptional programmes of ISGs that are induced by different viruses[21]. These studies reveal that specific sets of induced ISGs are effective in different viral infections.

***Virus restriction* in vivo.** Studying IFNAR1-deficient mice has provided definitive proof that IFNα/β mediate potent protection against viruses *in vivo*[22], although previous studies in which exogenous IFN was experimentally used to treat viral infections also strongly suggested this property of IFNα/β[23]. *Ifnar1*$^{-/-}$ mice were found to be susceptible to infection with four viruses — vesicular stomatitis virus (VSV), Semliki forest virus, vaccinia virus and lymphocytic choriomeningitis virus (LCMV) — a list that, interestingly, does not include influenza virus, as it was not tested in this study. Subsequently, *Stat1*$^{-/-}$ mice were shown to be highly susceptible to influenza virus, but the role of IFNAR1 in influenza virus infection — as tested in *Ifnar1*$^{-/-}$ mice — was less clear[24–27].

Plasmacytoid dendritic cells (pDCs). Immature dendritic cells with a morphology that resembles that of plasma cells. On a per-cell basis, pDCs are the main producers of type I interferons in response to viral infections or Toll-like receptor stimulation.

This discrepancy was explained when mice that were deficient in both IFNAR1 and IFNλR (*Ifnar1*$^{-/-}$*Ifnlr*$^{-/-}$ mice) were shown to be unable to control influenza virus infection, whereas IFNAR1-deficient mice and IFNλR-deficient mice had a mild phenotype[28,29]. This finding suggests that there is redundancy between the type I and type III IFN systems, which both require STAT1 downstream of their respective receptors. Only *Stat1*$^{-/-}$ and *Ifnar1*$^{-/-}$*Ifnlr*$^{-/-}$ mice lack all IFN responsiveness in both haematopoietic and epithelial cells; *Ifnar1*$^{-/-}$ mice retain type III IFN-mediated signalling in the epithelium and can partially control influenza virus infection[29]. In addition, when both type I and type III IFN-mediated signalling is deficient only in epithelial cells, mice succumb to influenza virus infection[30].

Naturally occurring mutations in the JAK and STAT genes in humans have provided further evidence of the importance of IFNs in host protection against viruses, as well as other types of pathogen, although the relative contribution of type I and type III IFNs is unclear, given that these mutations affect signalling downstream of both IFN receptors[31,32]. That the IFNα/β and IFNλ pathways often intersect in antiviral responses is supported by studies of patients who are infected with hepatitis C virus (HCV). In these patients, single nucleotide polymorphisms in the interleukin-28 (*IL28*) locus (which encodes IFNλ subtypes) are predictive of a successful response to treatment with IFNα (or the drug ribavirin), which is associated with a sustained virological response and clearance of the virus[33–36]. Recently, a new type III IFN (IFNλ4) has been identified and associated with impairment of spontaneous clearance of HCV[3,4].

Recently, during simian immunodeficiency virus (SIV) transmission and acute infection of rhesus macaques, blockade of IFNAR signalling was found to reduce antiviral gene expression, increase the SIV reservoir size and accelerate CD4$^+$ T cell depletion, with progression to AIDS despite a decrease in T cell activation[37]. Conversely, administration of recombinant IFNα2a initially upregulated the expression of antiviral genes and prevented systemic infection in these animals. However, with continued IFNα2a treatment, animals became desensitized to IFNα/β, and antiviral gene expression decreased, resulting in an increased SIV reservoir size and accelerated CD4$^+$ T cell loss. This study indicates that the timing of IFN-induced innate responses in acute SIV infection markedly affects the overall disease course and outweighs the detrimental consequences of increased immune activation[37], and this is likely to be the case for most infections.

So far, relatively few downstream effector ISGs (that is, molecules that are downstream of, but not involved in, the IFN-mediated signalling cascade) have been shown to control viral infection in humans. However, recent studies[38,39] found that the ISG IFITM3 controls influenza virus infection in mice *in vivo*. They also found that an allele of *IFITM3* that renders the protein ineffective at restricting the virus in cells *in vitro* is over-represented in patients requiring hospitalization due to influenza virus infection[38] and among patients suffering from severe infection with pandemic influenza virus[39]. The ISG MX1 also has important antiviral functions in influenza virus infection. Most inbred mouse strains have deletions or point mutations in *Mx1* (REF. 40), and reintroduction of a functional gene into deficient mouse strains markedly increases their resistance to influenza virus infection[41]. In keeping with this finding, type I IFNs have been shown to provide protection against influenza A virus infection in the presence of MX1 (REF. 26). However, it should be noted that the strongest phenotype of susceptibility to influenza virus infection has been observed in mice carrying deletions in both the type I and type III IFN receptors[29]. Human MX1 has antiviral effects *in vitro*, but whether polymorphisms in the *MX1* gene affect susceptibility to influenza virus infection in the human population has not been investigated[42].

Enhanced action of dendritic cells and monocytes. The effects of IFNα/β on the host response to infection are not limited to the acute, cell-intrinsic antiviral response described above. IFNα/β have effects on both the innate and adaptive cellular immune response. By contrast, the effects of type III IFNs are largely limited to non-haematopoietic cells, owing to the restricted expression of IFNλR. IFNα/β affect myeloid cells, B cells, T cells and NK cells, thereby enhancing the immune response, more effectively resolving viral infection and improving the generation of memory responses that will allow responses to future viral challenges.

Myriad studies in both human and mouse systems indicate that IFNα/β are involved at various stages in the activation of adaptive immune cell responses by dendritic cells (DCs), either activating or inhibiting these cells depending on the context. IFNα/β variously inhibit or promote the differentiation of precursors into DCs[43–46], and some viruses, such as measles virus and LCMV, can exploit this property to reduce the DC pool[47]. However, IFNα/β seem to have an activating effect on immature committed DCs, enhancing the cell-surface expression of MHC molecules and co-stimulatory molecules, such as CD80 and CD86, which is associated with an increased ability to stimulate T cells[47–49]. It has also been observed that IFNα/β promote the ability of DCs to cross-present antigens during viral infections, such as vaccinia virus and LCMV infections[50–52]. IFNα/β may also promote the migration of DCs to lymph nodes, through upregulating chemokine receptor expression, thus promoting T cell activation[53,54].

DCs are potent producers of IL-12, which is crucial for driving T helper 1 (T_H1)-type responses during some bacterial and viral infections, and important for IFNγ production by T cells and NK cells. In some settings, IFNα/β-mediated signalling has been shown to be necessary for IL-12 production by DCs following PRR stimulation[55]. However, high but physiological levels of IFNα/β strongly inhibit IL-12 production during murine cytomegalovirus (MCMV) and LCMV infections[56,57]. This suppression of IL-12 production may have developed to favour optimal cytotoxic responses by T cells and NK cells in response to virus, while limiting the pathological effects of excessive IL-12 production[56–59].

Ribavirin
A drug that interferes with RNA metabolism and blocks viral replication. Ribavirin is used in combination with interferon-α to treat hepatitis C virus infection.

However, in other situations in which IL-12 production is crucial to the host response, such as during infection with intracellular bacteria, certain pathogens may be able to exploit the suppression of IL-12 by IFNα/β for their own benefit (discussed below).

Promotion of CD4⁺ and CD8⁺ T cell responses. In addition to affecting DCs in a manner that drives or inhibits T cell activation as a downstream consequence, IFNα/β can act directly on both CD4⁺ and CD8⁺ T cells, influencing their function. IFNα/β have been described to have inhibitory and stimulatory effects on T cell survival and proliferation, cytokine (IFNγ) production, cytotoxic function and memory formation. Detailed dissection of these effects has revealed that these diverse outcomes are controlled by differential levels and differential activation of STAT molecules downstream of IFNAR.

In CD4⁺ T cells, IFNα/β enhance the ability to help B cells[60], as well as survival, and thus clonal expansion in response to viral (LCMV) but not bacterial infection[61]. In human T cells, IFNα/β promote differentiation into IFNγ-producing T_H1 cells[62]. In LCMV infection, depletion of CD4⁺ T cells has been shown to prevent lethality in LCMV-infected STAT1-deficient mice and to be associated with a reduction in tissue immunopathology[63]. In West Nile virus infection, IFNAR signalling controls CD4⁺ regulatory T cell differentiation, which suggests further effects on CD4⁺ T cell differentiation and function[64]. In addition, lymphocyte responses to type I IFNs may be reduced during viral infection, as type I IFNs have been shown to inhibit lymphocyte egress from lymphoid organs during LCMV infection[65].

IFNα/β can promote growth-inhibitory signals in CD8⁺ T cells[66–68], in line with the known, STAT1-dependent, antiproliferative effects of IFNα/β[69–71]; however, in activated CD8⁺ T cells and during viral (LCMV and VSV) infection, IFNα/β can also promote the survival and clonal expansion of the CD8⁺ T cell pool[72–76]. One possible explanation for these opposing findings may relate to differential STAT signalling downstream of IFNAR because in STAT1-deficient T cells, IFNα/β provide pro-survival and mitogenic signals, possibly through STAT3 and STAT5, rather than antiproliferative signals through STAT1 (REFS 71,77). Furthermore, activated CD8⁺ T cells 'escape' the antiproliferative effects of IFNα/β during viral (LCMV) infection by expressing lower total levels of STAT1 (REF. 78). With regard to CD8⁺ T cell function, cytotoxicity is positively regulated by IFNα/β[75,79,80], and IFNγ production is both positively[81,82] and negatively[83] affected by IFNα/β. This dichotomous outcome depends on the relative levels of STATs, with dominant STAT1 driving inhibition of IFNγ production but STAT4 activation promoting IFNγ production[82,83]. Therefore, the levels of IFNα/β expressed during a specific infection, the relative strength of the signalling pathways induced and the kinetics of this signalling seem to determine the nature of the CD8⁺ T cell response that develops[76,84]. Indeed, it is likely that both the quantity and the timing of type I IFN delivery may be crucial for the consequent adaptive immune responses to infection, as previously reported[85].

IFNα/β also influence the differentiation and function of memory CD8⁺ T cells. By affecting the initial expansion of the T cell pool after infection with viruses such as vaccinia virus, VSV and LCMV, IFNα/β also determine the size of the downstream memory T cell pool[74,84,86]. Furthermore, IFNα/β support memory T cell effector function and trafficking during secondary infection in several ways, including: driving the cytotoxicity of circulating memory T cells that are recruited to the lungs during respiratory infection with Sendai virus[87]; promoting chemokine production for the correct trafficking of central memory T cells during recall responses to LCMV[88]; and driving inflammatory monocytes to produce factors such as IL-15 and IL-18, which support memory CD8⁺ T cell survival and function in infections, including MCMV infection[89]. Finally, two recent studies indicate that type I IFNs can protect T cells against NK cell-mediated killing, through inducing the expression of inhibitory NK cell receptor ligands on the target T cells[90,91].

Enhancement of NK cell responses. Similarly to their effects on T cells, IFNα/β promote the function and survival of NK cells, through both direct and indirect means. The inflammatory conditions induced by specific viral infections seem to dictate the degree to which direct or indirect effects of IFNα/β modulate NK cell function and which NK cell function is affected. During both influenza virus[92] and vaccinia virus[93] infections, the direct action of IFNα/β on NK cells is required for the activation and expression of cytolytic effector functions and the production of IFNγ by NK cells. By contrast, in MCMV infection, IFNα/β-mediated signalling through STAT1 is required for NK cell accumulation and cytolytic function but not for IFNγ production[94]. These effects have also been described to be mediated indirectly through IL-15, with similar findings in TLR-stimulated mice[95], although others have reported no requirement for IL-15 (REF. 96). A recent study investigating the transcriptional response of NK cells and DCs during MCMV infection supports a largely IL-15-dependent role for IFNα/β in this infection[97]. In this study, the NK cell transcriptional response revealed a relatively weak IFNα/β-responsive profile but a distinct and prolific IL-15-dependent response, whereas DCs had high levels of IFNα/β-inducible gene expression[97].

As with T cells, the ability of IFNα/β to induce or restrict IFNγ production by NK cells is related to differential STAT1 and STAT4 signalling. High levels of STAT1-dependent signalling inhibit IFNγ production by NK cells, whereas high basal levels of STAT4 prime NK cells for IFNγ production[83,98]. Accordingly, the kinetics and levels of IFNα/β production and signalling during infection with viruses such as LCMV and MCMV modulate the IFNγ response by NK cells[99].

Enhancement of B cell responses. B cells have an important role in the resolution of many viral infections, largely through the production of neutralizing antibodies. Whereas some studies[100–102] indicate that IFNα/β may impair the survival and development of precursor and immature B cells, committed B cells seem to benefit from the presence of IFNα/β for various functions.

Similarly to findings with viral protein antigens[60,103,104], IFNα/β can promote B cell activation and antibody responses, including class switching, during viral infection. Within the first 48 hours of influenza virus infection, early activation of B cells has been shown to be mediated by IFNAR signalling, resulting in upregulation of activation markers and alteration of the transcriptional response[105–107]. This response involved only the respiratory tract B cells and not systemic B cells[105,106], and affected both the magnitude and quality of the antibody response[105]. IFNα/β have also been reported to 'fine-tune' B cell antibody class switching between IgG subtypes during influenza virus infection[108]. Interestingly, although IFNα/β seem to be beneficial for the antibody response early in infection, at least one study has found that at late time points after influenza virus infection, the antibody titres are higher in IFNAR-deficient mice than in wild-type mice, although the underlying biology has not been explored[27].

Similarly to influenza virus infection, IFNα/β are important for early B cell responses during VSV infection[109] and for class switching[110]. Likewise, during West Nile virus infection, IFNα/β are required for B cell activation in the lymph nodes but not in the spleen of infected animals[111]. Moreover, recent work on VSV infection shows that rather than acting as targets of IFNα/β, B cells in the lymph nodes produced lymphotoxin, driving a protective macrophage phenotype. In the absence of this lymphotoxin, the host-protective IFNα/β were not produced and the mice succumbed to VSV infection[112].

Detrimental effects in viral infection

Chronic viral infection. As described above, IFNs contribute to antiviral protection through the induction of an ISG-based cellular antiviral programme and through enhancing immune responses for the efficient termination of infection. However, there is an increasing appreciation that IFNα/β can also be harmful in virus infection, either by inducing immunosuppressive effects that impede viral control[113] or by triggering inflammation and tissue damage that exacerbate disease[114] (FIG. 2).

Comparisons of SIV infection in primate species that develop AIDS-like disease and species without disease symptoms indicate that strong IFNα/β responses occur only during pathogenic infection in macaques, whereas natural SIV hosts, without disease progression, have weaker IFNα/β responses[115,116]. Similar findings have been made in individuals infected with HIV; rapid progressors show stronger IFNα/β signatures than viraemic non-progressors[117]. These studies suggest a link between sustained IFNα/β levels and disease progression, but the mechanisms involved are as yet unclear. One possibility is that IFN-induced chronic inflammation and immune system activation facilitate the recruitment of target $CD4^+$ T cells and thereby the spread of HIV. Another possibility is that the immunosuppressive effect of IFNα/β[113] reduces T cell clonal expansion (through STAT1 signalling) and the ability of T cells to restrict HIV. The negative effects of IFNα/β on $CD8^+$ T cell proliferation may depend on the timing of IFN exposure. Exposure before an antigenic stimulus is suppressive, whereas simultaneous exposure is stimulatory[68]. It has also been demonstrated in mice that transfer of antigen-specific $CD8^+$ T cells or treatment with polyinosinic–polycytidylic acid (poly(I:C)) causes IFNα/β-dependent apoptosis and thus attrition of bystander $CD8^+$ T cells[118]. Similar type I and type III IFN-dependent suppression has been shown *in vitro* for human $CD4^+$ T cells co-cultured with monocyte-derived DCs infected with respiratory syncytial virus[119]. The signalling mechanisms that control whether T cell clonal expansion is limited after exposure to IFNα/β are relatively well described (for examples, see REFS 78,120), whereas the outcomes of viral infection in the presence of this IFNα/β-mediated suppression require more investigation.

TNF-related apoptosis-inducing ligand (TRAIL; also known as TNFSF10) and its receptor death receptor 5 (DR5; also known as TNFRSF10B) have been suggested as candidates that link high IFNα/β levels to lymphocyte death. For example, in a study of individuals infected with HIV, the IFNα/β expression by pDCs and the TRAIL and DR5 expression levels in tonsil tissue were higher in progressors than in non-progressors[121]. Similarly, an *in vitro* study showed that HIV caused IFNα/β-mediated upregulation of TRAIL expression by pDCs, enabling these cells to induce TRAIL-dependent $CD4^+$ T cell apoptosis[122]. DR5 expression has also been found to be increased on $CD4^+$ T cells in the blood of HIV-infected individuals[123], and B cells undergo apoptosis in a TRAIL-dependent manner in HIV infection[124]. In another chronic viral infection (HCV), it has been shown in the human hepatoma cell line Huh-7 that caspase 8, DR5 and TRAIL function alone or together to increase apoptosis in response to exogenously added type I IFNs[125–127]. However, the extent to which these mechanisms are mediating immunosuppression and/or immunopathology in patients with hepatitis will require further investigation.

Two recent *in vivo* studies have identified suppressive mechanisms involved in the harmful effects of IFNα/β in chronic viral infection[128,129]. Blocking IFN-mediated signalling, through antibody administration or receptor deficiency, improved $CD4^+$ T cell-mediated virus control in chronic infection with LCMV clone 13. Furthermore, IFNα/β reduced T cell responses, through the induction of immunosuppressive genes such as those encoding IL-10 and programmed cell death 1 ligand 1 (PDL1; also known as CD274).

Acute viral infection. As discussed above, both type I and type III IFNs contribute to protection against influenza virus infection. The disease-promoting effects of IFNα/β in an acute viral infection, such as influenza virus infection, were discovered more recently and were perhaps more surprising given the well-established antiviral activities of these IFNs. It was shown that severe influenza virus infection is associated with TRAIL-mediated epithelial cell damage[130] and that IFNα/β can induce TRAIL expression by inflammatory monocytes[131]. Similarly, exposure to influenza virus was shown to induce TRAIL expression by human pDCs *in vitro*[132], but the involvement of IFNα/β was not assessed in this study.

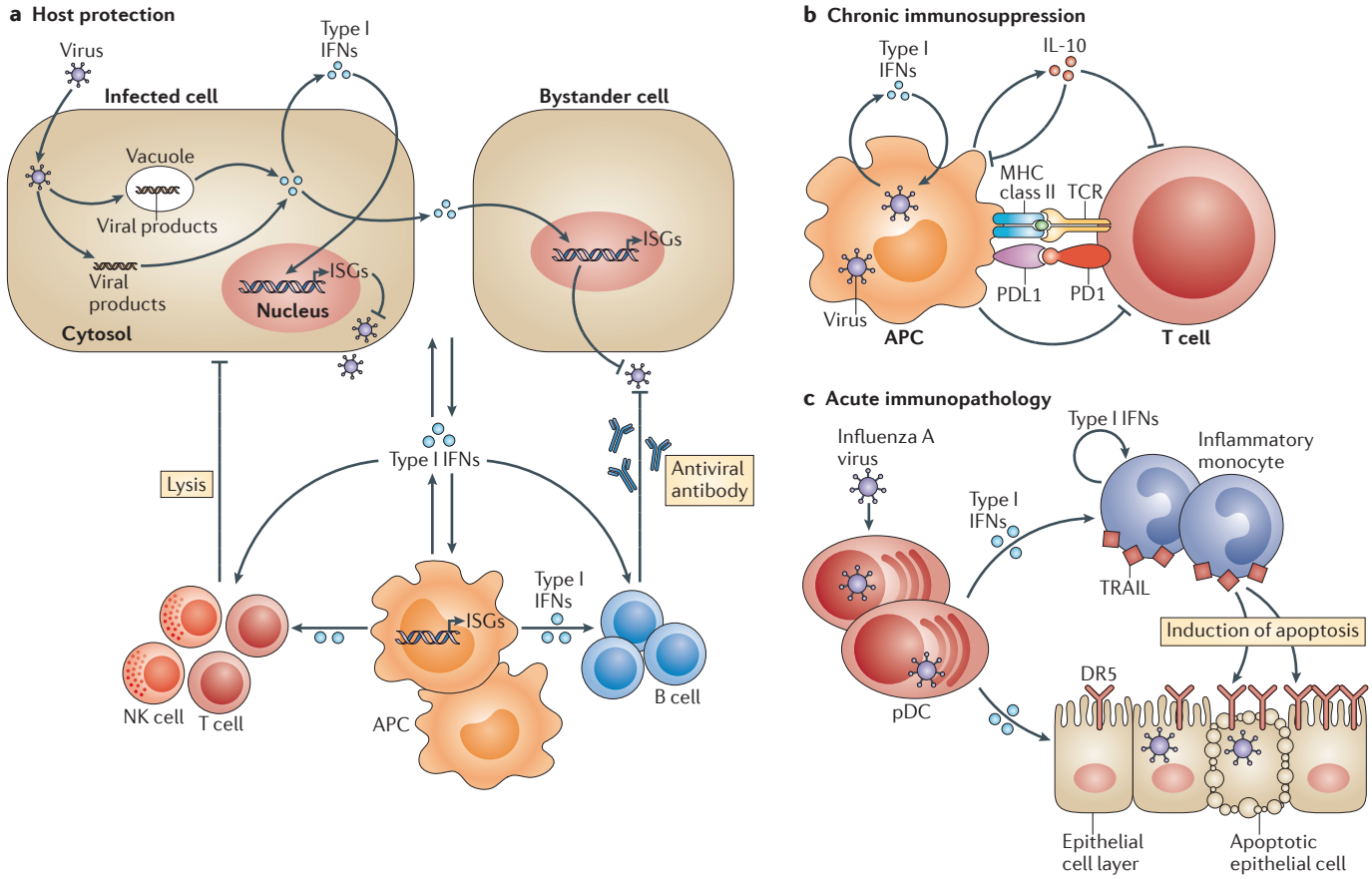

Figure 2 | **Type I interferons during viral infection.** **a** | Infected cells of the vertebrate body produce type I interferons (IFNs) in response to viral infection and/or contact with viral products. Feedback of type I IFNs onto infected and bystander cells leads to the induction of IFN-stimulated genes (ISGs), which function to block the viral replication cycle. Type I IFNs are also produced by, and act on, innate immune cells, including professional antigen-presenting cells (APCs), in response to viral infection and viral products. Type I IFNs acting on APCs can enhance the antigen-presenting function of these cells. They can also enhance the antiviral function of adaptive immune cells, including B cells, T cells and natural killer (NK) cells, which act to restrict viral infection through the production of antibody (B cells) and cytotoxic responses (T cells and NK cells). **b** | During chronic viral infection, type I IFNs can induce the production of immunosuppressive cytokines such as interleukin-10 (IL-10). They can also induce APCs to express ligands (such as programmed cell death 1 ligand 1 (PDL1)) for T cell-inhibitory receptors (such as PD1, the PDL1 receptor). These factors lead to the suppression of T cell function and failure to clear infection. **c** | During acute viral infections such as with influenza virus, type I IFN production by myeloid cells, such as plasmacytoid dendritic cells (pDCs) and inflammatory monocytes, leads to the upregulation of expression of both the death ligand TNF-related apoptosis-inducing ligand (TRAIL) on inflammatory monocytes and the TRAIL receptor death receptor 5 (DR5) on epithelial cells. TRAIL-expressing inflammatory monocytes then induce immunopathology and host morbidity and/or mortality through killing epithelial cells. TCR, T cell receptor.

When inbred mouse strains (MX1 deficient) were ranked according to susceptibility to influenza virus and their IFNα/β levels were assessed, susceptible strains were found to have a stronger and more sustained IFNα/β signal than resistant strains, even at early time points when no differences in virus titres were detected[114]. Higher pDC numbers and higher levels of pro-inflammatory cytokines were found in susceptible strains compared with resistant strains, and blocking the IFNα/β signal in susceptible strains, through receptor deficiency or pDC removal, reduced the inflammation and lung damage, resulting in improved survival[114]. The pathogenic mechanism downstream of type I IFNs was found to be upregulation of TRAIL expression by monocytes and DR5 expression by epithelial cells[114]. Thus, excessive levels of IFNα/β can contribute to immunopathology in severe influenza virus infection, mainly by inducing immune cell-mediated tissue damage, although the response in MX1-sufficient mice remains to be studied.

In addition to TRAIL, expression of the apoptosis-inducing ligand CD95 ligand (CD95L; also known as FASL) has been shown to be upregulated in an IFN-dependent manner in severe influenza virus infection, and the presence of a functional mutation in the *CD95L* gene or blockade of the CD95–CD95L interaction has been found to reduce the mortality after high-dose influenza virus infection[133]. In contrast to the effects in chronic viral infection, it seems that most of the disease-promoting effects of IFNα/β in

M1 macrophage
A pro-inflammatory, or 'classically activated', subset of macrophages that are characterized by phagocytic activity and the expression of particular pro-inflammatory cytokines (such as tumour necrosis factor) and inflammatory mediators (such as inducible nitric oxide synthase).

acute influenza virus infection involve the induction of immunopathology rather than the suppression of the antiviral adaptive immune response, as the virus titres are mostly unaffected. However, IFNα/β-dependent PDL1 expression by influenza virus-infected airway epithelial cells has been shown to suppress the function of T cells expressing programmed cell death 1 protein 1 (PD1; also known as PDCD1)[134]. Similarly, influenza virus-induced TRAIL expression by mouse $CD8^+$ T cells has been found to control the magnitude of the $CD8^+$ T cell response[135] (although the role of IFNs in this mechanism was not assessed in this study), indicating that immunosuppressive pathways similar to those in chronic viral infection are also active in acute infections such as influenza virus infection.

In conclusion, a theme emerges: IFNα/β mediate the upregulation of expression of apoptosis-inducing proteins, which, if expressed by non-haematopoietic somatic cells, mediate tissue damage. The same molecules, when induced on immune cells by IFNα/β, can contribute to immunosuppression in a similar manner to PDL1 and IL-10. Therefore, depending on the pathogen, the host and the context, type I IFNs can have protective effects in viral infection or can contribute to immunosuppression or immunopathology (FIG. 2).

Protective effects in bacterial infection

As seen in viral infection, IFNα/β can be protective or detrimental to the host during bacterial infection in a bacterium-specific manner, although less is known about the role of these IFNs in bacterial infections than in viral infections[136]. Immunity to intracellular bacteria relies on T_H1 cell responses, which activate macrophages and other phagocytic cells to kill intracellular bacteria. By contrast, immunity to extracellular bacteria typically requires a combination of antibody responses, activation of phagocytic cells (such as neutrophils) and T_H17 cell responses.

Many of the cytokines and chemokines responsible for coordinating these responses are IFN inducible (mainly through IFNγ), as are many of the antibacterial effector molecules, such as indoleamine 2,3-dioxygenase (IDO), inducible nitric oxide synthase (iNOS; also known as NOS2), immunoresponsive genes and guanylate-binding proteins[136]. Conversely, under different conditions, IFNα/β can inhibit the induction of many of these host antibacterial effector mechanisms, chemokines and pro-inflammatory cytokines. The mechanisms by which IFNα/β promote host protection or susceptibility to bacterial pathogens are as yet poorly defined, and the factors that determine whether a response will be protective or pathogenic are not yet fully understood.

Some of the earliest reports of a protective role of IFNs were in infection with chlamydial species. Treatment with exogenous IFNs or IFN-inducing agents such as poly(I:C) was shown to protect mice against *Chlamydia trachomatis* infection[137] and to inhibit intracellular replication of *C. trachomatis* in various human and mouse cell types[138]. This protection resulted from IDO-mediated depletion of intracellular L-tryptophan, thereby reducing the availability of this amino acid to intracellular pathogens and thus impeding their survival[139]. IFNα/β may also be involved in protection against *Chlamydia pneumoniae* infection, through a cooperative interaction with IFNγ that induces antimicrobial effectors and thereby suppresses bacterial survival[140,141]. However, IFNα/β are not universally protective against chlamydial species, as *Ifnar1*$^{-/-}$ mice are protected against *Chlamydia muridarum* infection, showing longer survival and lower bacterial loads than wild-type controls[142].

IFNα/β also protect macrophages and lung epithelial cells *in vitro* against infection with *Legionella pneumophila*, the causative agent of Legionnaires' disease[143–145]. *Ifnar1*$^{-/-}$ macrophages have been found to have higher bacterial loads than wild-type cells[144], and the treatment of both cell types with IFNα/β has been shown to restrict intracellular bacterial growth[143–145]. The mechanisms underlying this protective effect have not been fully elucidated but were found to be STAT1, STAT2 and STAT3 independent in macrophages, and were associated with polarization towards a classically activated M1 macrophage phenotype and the induction of iNOS expression[144]. Similar inhibition of bacterial growth has been observed in IFNα/β-treated human macrophages infected with *Bacillus anthracis,* suggesting that IFNα/β have a protective role against anthrax[146].

In addition to promoting the restriction of bacterial growth and bacterial killing within cells, IFNα/β may prevent or reduce cellular invasion by invasive gut bacteria, such as *Shigella flexneri* and *Salmonella enterica* subsp. *enterica* serovar Typhimurium. Treatment with IFNα/β increased the survival of mice infected with *S. flexneri* or *S.* Typhimurium and reduced the invasion of their intestinal epithelial cells *in vivo*, as well as the invasion of fibroblasts *in vitro*[147,148].

A protective role for IFNα/β has also been reported in mouse models of group B streptococcus, *Streptococcus pneumoniae*, *Escherichia coli*, *Helicobacter pylori* and *Streptococcus pyogenes* infections[12,149–151], as well as in a model of caecal ligation and puncture[152]. In all of these infections, *Ifnar1*$^{-/-}$ mice had a shorter survival and/or more bacterial growth than wild-type controls. By contrast, type I IFNs have been shown to have adverse effects in colon ascendens stent peritonitis, which is a model of peritoneal sepsis[153].

In the case of the immune response to group B streptococcus, *E. coli* and *S. pneumoniae*, IFNα/β-mediated signalling contributed to the optimal activation of macrophages, in terms of their ability to produce tumour necrosis factor (TNF) and nitric oxide, although the plasma TNF and IL-6 levels during *in vivo* infection were much higher in *Ifnar1*$^{-/-}$ mice than in wild-type controls, which may reflect greater inflammation as a result of the higher bacterial burden in the knockout mice or may reflect multiple effects of IFNα/β at the systemic level versus the local level[149]. IFNα/β may also contribute to the production of host-protective cytokines during *S.* Typhimurium infection, inducing strong IFNγ production in an IL-12-independent manner, although the direct contribution of this response to host protection has not been established[154].

IFNα/β-mediated signalling downstream of NOD1 signalling has been shown to have a role in protecting intestinal epithelial cells against *H. pylori* infection[12]. Although the mechanism of protection was not fully elucidated, impairment of chemokine and IFNγ production in the absence of IFNα/β-mediated signalling was implicated. In addition, the importance of the correct recruitment of host-protective phagocytic cells by IFNα/β-dependent chemokine production has been highlighted by results from a caecal ligation and puncture model of infection[152]. In this model, *Ifnar1*$^{-/-}$ mice have a shorter survival and elevated bacteraemia compared with wild-type control mice. These differences were associated with decreased levels of CXC-chemokine ligand 10 (CXCL10) and with reduced neutrophil numbers and function. Treatment of *Ifnar1*$^{-/-}$ mice with recombinant CXCL10 rescued them from fatal infection and restored neutrophil function. Conversely, during subcutaneous *S. pyogenes* infection, *Ifnar1*$^{-/-}$ mice had increased tissue damage and a shorter survival after infection than did wild-type mice, and these were associated with uncontrolled neutrophilia at the disease site, although whether neutrophils had a detrimental role in this case was not confirmed[152].

Therefore, the induction of cell-intrinsic immunity to kill bacteria or prevent their invasion and the regulation of chemokines, pro-inflammatory cytokines and phagocytic cells, are all implicated as mechanisms by which IFNα/β suppress bacterial infection, with the exact mechanisms involved being dependent on the pathogen.

Detrimental effects in bacterial infection

Perhaps the two best-described examples of a harmful role for IFNα/β are in infections with *Listeria monocytogenes* and *Mycobacterium tuberculosis*. These pathogens are intracellular, preferentially infect macrophages and require broadly similar immune responses for their control.

***Infection with* L. monocytogenes.** Three research groups initially described the first important mechanism of host immunosuppression by IFNα/β in bacterial infections: *Ifnar1*$^{-/-}$ mice are resistant to *L. monocytogenes* infection, with a longer survival, and lower spleen and liver bacterial loads after infection than wild-type mice[155–157]. The main mechanism attributed to this resistance was reduced apoptotic cell death, particularly of lymphocytes, with IFNα/β sensitizing these cells to the *L. monocytogenes* virulence factor listeriolysin O and resultant cell death in wild-type mice[156–158]. This reduced cell death was also associated with lower levels of expression of IFN-inducible apoptosis-associated genes, such as TRAIL, p53 and death domain-associated protein 6 (DAP6; also known as DAXX), in infected *Ifnar1*$^{-/-}$ mice[157]. Subsequent induction of immunosuppressive cytokines, particularly IL-10, after this large-scale apoptosis of lymphoid cells was suggested as the mechanism by which lymphocyte apoptosis led to the IFNα/β-dependent increase in susceptibility to infection[158].

Decreased expression of pro-apoptotic genes has also been reported in infected *Ifnar1*$^{-/-}$ bone marrow-derived macrophages compared with wild-type cells[157]. Several other reports have also suggested that macrophages are targets of IFNα/β-induced cell death following *L. monocytogenes* infection[159–161]. This cell death can take the form of apoptosis that is STAT1 dependent but iNOS and PKR independent[159] or of necrotic cell death that is iNOS dependent but TRAIL and PKR independent[160,161] and is related to STAT1-dependent breakdown of the plasma membrane[160]. The death of myeloid cells may be involved in pathology *in vivo*, as increased levels of host-protective TNF- and iNOS-producing DCs (TIP-DCs) have been reported in *Ifnar1*$^{-/-}$ mice following *L. monocytogenes* infection[155]. However, the overall role of TIP-DCs in this infection may be ambiguous, as it was shown in IFNβ reporter mice that they are also an important source of IFNβ during infection[162]. Interestingly, CD11b^{+} DCs seem to be one of the main IFNβ-producing cells during *L. monocytogenes* infection[163]. This finding might suggest that IFNα/β production is a method of self-regulation by immune cells, which in this case is subverted by *L. monocytogenes* for its own advantage. However, whether TIP-DCs, as well as CD11b^{+} DCs, are themselves targets of IFNα/β-induced cell death remains unclear.

A second important mechanism of host immunosuppression by IFNα/β was elucidated in later studies. During infection with pathogens such as *L. monocytogenes*, the activation of macrophages by T cell-derived and/or NK cell-derived IFNγ is crucial for inducing antimicrobial pathways and for the subsequent eradication of the intracellular bacteria[136]. Although IFNα/β can induce some of these antimicrobial pathways in particular circumstances, it has now been shown that during infection with *L. monocytogenes,* IFNα/β potently inhibit these pathways by blocking the responsiveness of macrophages to IFNγ[164]. This block in responsiveness results from downregulation of IFNγR expression by macrophages[164], owing to silencing of new transcription from the gene encoding IFNγR (*Ifngr1*) by repressive transcriptional regulators[165].

***Infection with* M. tuberculosis.** Studies performed in patients and mouse models of infection collectively point to a detrimental role of IFNα/β during tuberculosis. Several studies have reported a decreased bacterial load and/or improved host survival in the absence of IFNα/β-mediated signalling[166–169]. However, these changes have not been universally observed[170], and there has not always been concordance between studies regarding bacterial load and survival data. It is likely that the differences between studies result from differences in experimental protocols, and in the genetics of the host and the *M. tuberculosis* strain used.

The importance of type I IFNs as a potentially detrimental factor during tuberculosis was suggested by studies of patient cohorts from the United Kingdom and South Africa[171]. Patients with active tuberculosis had a prominent whole blood IFNα/β-inducible transcriptional profile that correlated with the extent of radiographic disease and diminished with successful treatment[171]. Several other studies have since verified these findings in additional patient cohorts from Africa[172,173] and Indonesia[174], suggesting that this IFNα/β-inducible signature is broadly applicable to humans and may be detrimental.

Box 1 | **IFNα/β-mediated exacerbation of bacterial infection by viruses**

Bacterial infection subsequent to or together with viral infection has long been known to be a significant cause of mortality and morbidity in humans, particularly following influenza virus infection[225]. Intensive research has therefore gone into understanding how viral infection sensitizes the host to bacterial infection. Perhaps unsurprisingly, interferon-α/β (IFNα/β) have emerged as important players in this phenomenon. Influenza virus-infected *Ifnar1*$^{-/-}$ mice survive secondary infection with *Streptococcus pneumoniae* better than wild-type controls, with increased bacterial clearance[226–228]. This has been attributed to increased production of the neutrophil chemoattractants CXC-chemokine ligand 1 (CXCL1) and CXCL2 (REF. 228), to increased production of the macrophage chemoattractant CC-chemokine ligand 2 (CCL2)[227] and to an enhanced response by γδ T cells[226]. Similar results were reported with *Staphylococcus aureus* secondary infection when poly(I:C) was administered as a surrogate for viral infection[229]. Likewise, influenza virus infection has a harmful effect on the host response to *Mycobacterium tuberculosis*, in an IFNα/β-dependent manner, although the underlying mechanism is currently unclear[178]. Negative effects on granulocyte generation in the bone marrow were also implicated in a model of lymphocytic choriomeningitis virus–*Listeria monocytogenes* superinfection[230]. Finally, viral infection or poly(I:C) administration together with *Escherichia coli* or *M. tuberculosis* superinfection leads to enhanced lethality in mice, owing to excessive inflammation in an IFNα/β- and NOD-containing protein 1 (NOD1)- and/or NOD2-dependent manner[175,231]. Thus, IFNα/β contribute to priming of the host to clear the virus, increasing host susceptibility to bacterial assault. Interestingly, in this scenario, IFNα/β produced in response to infections are damaging to the host but would normally be protective during a primary infection (for example, with *S. pneumoniae* or *E. coli*). Again, these findings support the idea that the circumstances of IFNα/β production and action are crucial in determining host protection versus pathogenesis and highlight the opposing role of IFNα/β in inflammation during viral infections and certain bacterial infections.

IFNα/β overexpression during *M. tuberculosis* infection in experimental mouse models has provided additional robust evidence for the detrimental effects of the IFNα/β system during tuberculosis. Studies of infection with hyper-virulent *M. tuberculosis* strains showed a correlation between increased levels of IFNα/β and increased virulence[166,167,169]. Direct instillation of IFNα/β into the lungs during infection was also injurious to the host[169]. Similarly, enhanced induction of IFNα/β expression during *M. tuberculosis* infection via administration of a TLR3 ligand derivative led to an increased severity of infection[175,176]. Likewise, deletion of the gene encoding a negative regulator of IFNα/β, MAPK kinase kinase 8 (MAP3K8; also known as TPL2), that functions downstream of TLRs led to increased levels of IFNα/β production and increased bacterial burdens[177], and these increases were abrogated in *Map3k8*$^{-/-}$*Ifnar1*$^{-/-}$ (double knockout) mice during *M. tuberculosis* or *L. monocytogenes* infection. Control of the bacterial load in *Map3k8*$^{-/-}$*Ifnar1*$^{-/-}$ mice was correlated with reduced IL-10 levels and increased IL-12 levels in the serum. Finally, concurrent co-infection of mice with influenza A virus and *M. tuberculosis* results in increased bacterial loads in an IFNα/β-dependent manner[178], as seen for other pathogen co-infections as outlined in BOX 1.

The mechanisms that mediate the IFNα/β-driven exacerbation of disease are not fully understood but seem to be multifactorial. Data from investigations of hyper-virulent *M. tuberculosis* strains initially suggested that the suppression of pro-inflammatory cytokines and of T_H1-type immunity are important[166,167,169], and there is good evidence both in human cells and in mouse models that IFNα/β suppress the production of host-protective cytokines following *M. tuberculosis* infection. The production of IL-1α and IL-1β, which are crucial for host defence against *M. tuberculosis*[179], is inhibited by IFNα/β, both *in vitro* in infected human and mouse cells and *in vivo* in mouse models[176,180–182]. This finding is in line with a previous study using lipopolysaccharide that showed that IFNα/β can potently inhibit the NOD-, LRR- and pyrin domain-containing 1 (NLRP1) and NLRP3 inflammasomes, which are responsible for the post-translational maturation of IL-1β[183].

In addition, cell-intrinsic type I IFN signals have been shown to negatively regulate iNOS production by pulmonary myeloid cells, particularly TIP-DCs[176]. The production of other pro-inflammatory cytokines such as TNF and IL-12 is also negatively affected[177,180,182] (K.M.-B. and A.S., unpublished observations). The induction of the immunosuppressive cytokines IL-10 and IL-1 receptor antagonist by IFNα/β seems to have an important role in this suppression of pro-inflammatory cytokines[176,177,180,182].

In turn, IL-1α and IL-1β have recently been shown to inhibit IFNα/β induction in mouse and human macrophages, and when IL-1 was present in IFNα/β-treated cultures, it also suppressed the pro-bacterial effects downstream of IFNβ[184]. Interestingly, IL-1-induced prostaglandin E2 was also able to potently inhibit IFNα/β in this context[184], as observed previously in lipopolysaccharide-induced IFNα/β responses[185] and more recently during influenza virus infection[186]. Moreover, investigating the effects of prostaglandin E2 during *M. tuberculosis* infection, either by directly administering this prostanoid or by increasing its level through 5-lipoxygenase blockade with zileuton, reversed poly(I:C)-mediated IFNα/β-driven mortality[184].

Similarly to the findings in *L. monocytogenes* infection, the repression of innate cell responsiveness to IFNγ is emerging as an important mechanism of IFNα/β-mediated immunosuppression during mycobacterial infection[180,182,187]. However, direct downregulation of IFNγR expression may not be the central mechanism by which IFNα/β exert their effects on IFNγ activity[176]. Instead, in both mouse and human cells, it has been shown that IFNα/β potently suppress the ability of macrophages to upregulate antimycobacterial effector molecules and to restrict bacterial growth, in response to both *Mycobacterium leprae* and *M. tuberculosis*[180,187] (F.M., J. Ewbank and A.O., unpublished observations; K.M.-B., unpublished observations). The importance of this mechanism of action of IFNα/β is further suggested by experiments using *Ifngr1*$^{-/-}$*Ifnar1*$^{-/-}$ mice, which suggest that IFNα/β contribute to host protection in the absence of the IFNγ pathway[188]. Furthermore, the observation of naturally occurring mutations in the host-protective gene *ISG15* in humans suggests that IFNα/β can induce host-protective responses to mycobacterial infection, although the circumstances under which IFNα/β induce this gene during *M. tuberculosis* infection are unclear[189].

Additionally, the production of innate cytokines such as IL-12p70 has also been shown to be suppressed by IFNα/β during *M. tuberculosis* infection[180,182,187] (K.M.-B., unpublished observations). This suppression could

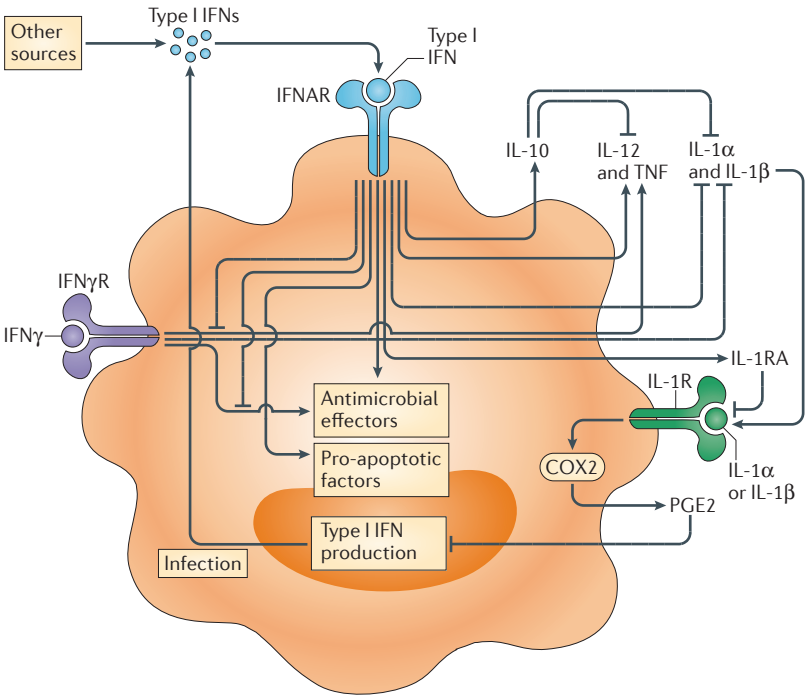

Figure 3 | **Positive and negative effects of type I interferons during bacterial infection.** Low level autocrine interferon-α/β (IFNα/β)-mediated signalling primes the production of interleukin-10 (IL-10), pro-inflammatory cytokines and antimicrobial effector mechanisms. Type I IFNs induce IL-1 receptor antagonist (IL-1RA), which in turn inhibits IL-1-mediated signalling. IL-10 mediates a negative feedback loop, suppressing the production of pro-inflammatory cytokines, including IL-12, tumour necrosis factor (TNF) and IL-1α/β. On infection, high levels of IFNα/β, which affect myeloid cells, can be contributed by autocrine production, as well as from exocrine cellular sources. IFNα/β can also suppress pro-inflammatory cytokine production in an IL-10-independent manner. A major type I IFN-suppressive mechanism is downregulation of the IFNγ receptor (IFNγR), thus abrogating IFNγ-dependent host-protective immune responses. IFNα/β-mediated signalling can promote the production of high levels of IL-10, as well as the induction of pro-apoptotic factors. IL-1α and IL-1β induce cyclooxygenase 2 (COX2)-dependent prostaglandin E2 (PGE2). PGE2 and IL-1 inhibit type I IFN expression and the downstream effects. IFNAR, type I IFN receptor; IL-1R, IL-1 receptor.

result from the presence of IL-10, the downregulation of IFNγR and/or the induction of negative regulators of IFN-mediated signalling such as protein arginine methyltransferase 1 (PRMT1)[180,182,187]. Finally, IFNα/β, possibly by influencing chemokine expression, have been shown to be involved in the generation and trafficking of *M. tuberculosis*-permissive innate cells to the lungs in a mouse model, thus contributing to the exacerbation of infection[175,190].

***Infection with* Francisella tularensis *and* Francisella tularensis *subsp.* novicida.** The facultative intracellular bacterium *F. tularensis* and the subspecies *F. tularensis* subsp. *novicida*, which is highly pathogenic in mice, have been investigated for a possible role of IFNα/β in the immune response to infection[191–193]. Two studies found that type I IFNs were necessary for activation of the inflammasome during *F. t. novicida*[192] or *F. tularensis*[191] infection and that the AIM2 inflammasome, in turn, was necessary for host protection against *F. tularensis*[191]. This finding is in contrast to those of another study showing that IFNα/β inhibit inflammasomes (see above) and that type I IFN-dependent AIM2 inflammasomes were triggered *in vitro* during mycobacterial infection but that their role is unclear *in vivo*[194], suggesting that IFNα/β may have differential effects on inflammasome activity, depending on the type of inflammasome involved.

Similarly to infection with *L. monocytogenes*, IFNα/β have been shown to be involved in the apoptosis of macrophages during *F. t. novicida* infection[192], although this cell death did not correlate with the outcome for the host. Despite these data indicating that IFNα/β may mediate some host-protective mechanisms during these infections, a comparison of wild-type and *Ifnar1*$^{-/-}$ mice infected with *F. t. novicida* revealed that IFNα/β are detrimental to the host, restricting the development of a protective IL-17-producing γδ T cell response[193].

Infection with other bacteria. A limited range of studies further implicate IFNα/β in enhancing susceptibility to various other bacterial agents. IFNα/β have been suggested to be detrimental factors during Whipple's disease (caused by *Tropheryma whipplei*), diverting macrophages to an alternatively polarized, permissive state and promoting macrophage apoptosis[195].

IFNα/β are also detrimental during *Brucella abortus* infection, with *Ifnar1*$^{-/-}$ mice having lower bacterial loads than wild-type controls[196]. Bacterial control in these mice is correlated with increased IFNγ and nitric oxide production, and reduced TRAIL expression and apoptosis[196]. *Ifnar1*$^{-/-}$ mice are also reportedly more resistant to infection with the plague agent *Yersinia pestis*[197]. This resistance was associated with an increased number of neutrophils and enhanced function of phagocytic cells[197]. In contrast to earlier reports[147,154], it has been found that IFNα/β were harmful to the host during *S.* Typhimurium infection[198]. Protection in these mice was associated with macrophage resistance to necroptosis rather than to alterations in cytokine production or inflammasome activation.

IFNα/β have also been implicated in mediating deleterious inflammation during infection with a large range of Gram-negative bacteria through the activation of caspase 11, leading to the production of IL-1β and IL-18, and caspase 1-independent cell death[199]. Another study also found a role for IFNα/β in inducing the activation of caspase 11 during *S.* Typhimurium infection. This activation resulted in macrophage cell death that was injurious to the host, but only in the absence of caspase 1, which was required for the antibacterial function of neutrophils[200].

IFNα/β are detrimental for the host during *Staphylococcus aureus* infection, with more *Ifnar1*$^{-/-}$ mice than wild-type mice surviving after intranasal infection[201]. Protection correlated with an increased proportion of CD11c^{+} cells within the total population of airway and lung immune cells, and reduced pro-inflammatory cytokine production in the lungs.

In conclusion, IFNα/β may contribute to host protection against bacterial infection by upregulating antimicrobial effectors, such as IDO, iNOS and pro-inflammatory cytokines. Conversely, IFNα/β may impair the host response to bacteria by eliciting the production

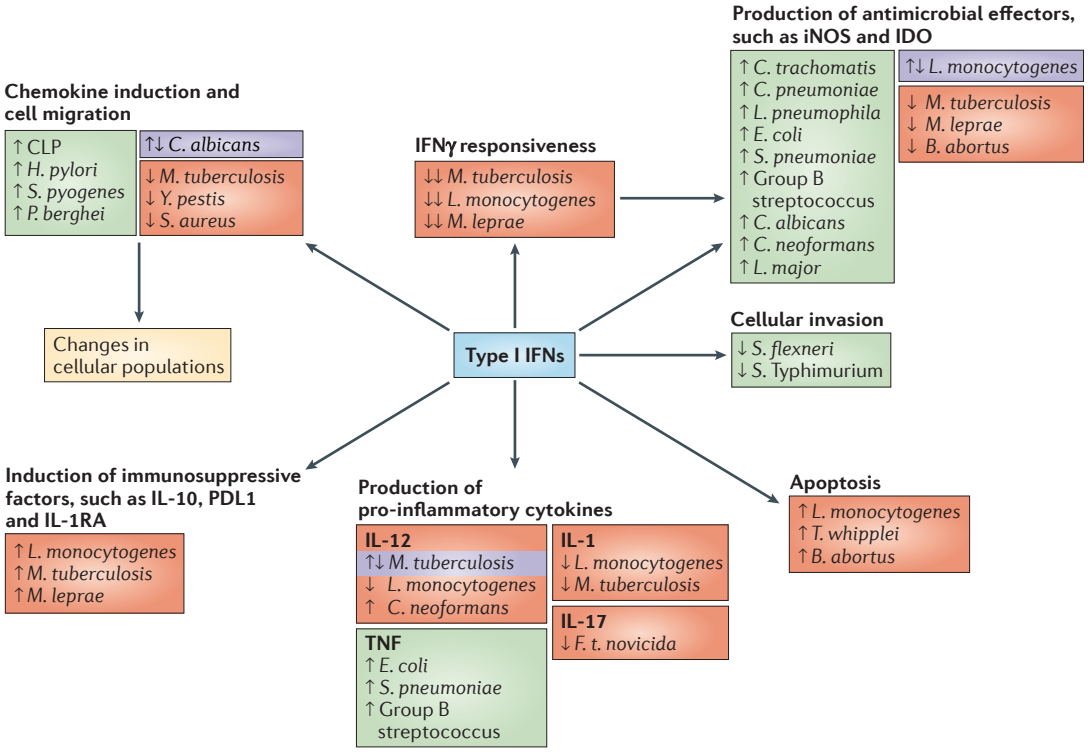

Figure 4 | **Mechanisms of interferon action in non-viral infections.** The diagram indicates the mechanistic processes that are influenced by interferon-α/β (IFNα/β) during bacterial infections. The small vertical arrows indicate whether IFNα/β promote (arrow pointing upwards), suppress (arrow pointing downwards) or have variable, context-dependent effects (two arrows) on the associated process. For each process, the organisms that cause infections in which IFN-mediated effects may occur are shown. In green are those infections in which IFNα/β are thought to be protective, in red are those in which IFNα/β have host-detrimental effects, and in purple are those in which IFNα/β have both host protective and detrimental effects. For example, IFNα/β have variable effects on chemokine production and cell migration. In *Streptococcus pyogenes* infection (in which IFNα/β are protective), IFNα/β have promoting effects on chemokine production and cell migration. *B. abortus*, *Brucella abortus*; *C. albicans*, *Candida albicans*; CLP, caecal ligation and puncture; *C. neoformans*, *Cryptococcus neoformans*; *C. pneumoniae*, *Chlamydia pneumoniae*; *C. trachomatis*, *Chlamydia trachomatis*; *E. coli*, *Escherichia coli*; *F. t. novicida*, *Francisella tularensis* subsp. *novicida*; *H. pylori*, *Helicobacter pylori*; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; IL-1RA, IL-1 receptor antagonist; iNOS, inducible nitric oxide synthase; *L. major*, *Leishmania major*; *L. monocytogenes*, *Listeria monocytogenes*; *L. pneumophila*, *Legionella pneumophila*; *M. leprae*, *Mycobacterium leprae*; *M. tuberculosis*, *Mycobacterium tuberculosis*; *P. berghei*, *Plasmodium berghei*; PDL1, programmed cell death 1 ligand 1; *S. aureus*, *Staphylococcus aureus*; *S. flexneri*, *Shigella flexneri*; *S. pneumoniae*, *Streptococcus pneumoniae*; S. Typhimurium, *Salmonella enterica* subsp. *enterica* serovar Typhimurium; TNF, tumour necrosis factor; *T. whipplei*, *Tropheryma whipplei*; *Y. pestis*, *Yersinia pestis*.

of IL-10 and IL-1 receptor antagonist, suppressing pro-inflammatory cytokine production, inducing immune cell death (including apoptosis) and restricting host responses to IFNγ (FIGS 3,4).

Effects in parasitic and fungal infection

Analyses of the effects of IFNα/β on the course of disease during parasitic and fungal infections have been relatively limited, with most work carried out in *Leishmania major*, *Plasmodium* spp. and *Trypanosoma cruzi* models of parasite infection and *Candida* spp. (yeast) models of fungal infection (FIG. 4).

Parasitic infection. Work conducted during the late 1990s and early 2000s elucidated an important role for IFNα/β in inducing iNOS expression during *L. major* infection[202–204]. Interestingly, it was noted that high levels of IFNα/β actually impaired iNOS induction, implicating IFN levels as important in determining whether IFNα/β had a host-protective or pathogenic role[203,204]. More recent work with different strains of *Leishmania* spp. suggests a detrimental role for IFNα/β, through inhibiting macrophage function and regulating neutrophil number and function[205,206].

During malaria, IFNα/β can have either a host-protective or detrimental effect, depending on both the stage of infection and the species of infecting *Plasmodium*. In the blood stages of infection with the mouse malaria parasites *Plasmodium berghei* and *Plasmodium chabaudi*, IFNα/β enhance infection through inhibiting $CD4^+$ T cell function[207]. By contrast, studies of *Plasmodium yoelii* infection indicate a protective role for IFNα/β, possibly through inhibiting reticulocytosis, a condition in which immature red blood cells accumulate[208]. Treatment with recombinant IFNα also has been reported to protect mice from developing the cerebral malaria induced

Box 2 | **Commensal microbiota and the type I interferon response**

The ability of the resident microbial flora to influence the homeostasis and function of the host immune system has attracted growing attention in recent years[232]. At least three studies published in the past two years define a role for interferon-α/β (IFNα/β) as mediators of host–microbiota interactions and/or as downstream targets of these interactions, leading to further effects on immune system function. Both Ganal *et al.*[233] and Abt *et al.*[234] found that in mice lacking commensal microorganisms, either through antibiotic treatment or being bred in germ-free conditions, the IFN-inducible, inflammatory transcriptional response was greatly reduced. In both cases, antiviral immunity was severely compromised, as mononuclear phagocytes had a defective response to viral challenge, with an abrogated ability both to limit viral replication and to prime other aspects of the antiviral response such as natural killer cell activation. A recent study suggests that an absence of type I IFN receptor (IFNAR) signalling in intestinal epithelial cells leads to the proliferation of Paneth cells and consequently to an alteration in the intestinal microbiota composition[235]. Microbiota-induced production of IFNβ by dendritic cells (DCs) in the intestine has also recently been shown to protect mice from colitis induced by dextran sulphate sodium[236]. In this model, Toll-like receptor 3 activation by double-stranded RNA allowed DCs to discriminate between non-pathogenic commensal bacteria and harmful pathogens, with only non-pathogenic bacteria inducing protective IFNβ production[236]. These findings extend our understanding of IFNα/β as factors that are important for homeostasis of the immune response and may explain the putative role of constitutive type I IFN production in modulating basal signal transducer and activator of transcription (STAT) expression[17,237].

by the *P. berghei* strain ANKA, in part through enhancing the T_H1 cell response[209]. However, using *Ifnar1*$^{-/-}$ mice, another study has reported only a minor influence of IFNα/β during acute *P. chabaudi* infection[210]. An interesting recent report has shown that during the liver stage of infection, *P. berghei* induces an IFNα/β response that is essential for host protection[211]. This protection, mediated through cytosolic recognition of parasite RNA by the PRR MDA5, was associated with IFNα/β-dependent recruitment of leukocytes to infectious foci. It remains to be seen whether this host resistance-promoting function of IFNα/β in the liver stages of malaria is specific to the parasite species and whether it occurs in human malarial infection.

Studies of infection with the protozoan parasite *T. cruzi* show various effects of IFNα/β on host immunity, including positive effects[212–214], negative effects[215] and no difference[216]. The reasons for these differences are not fully understood but may relate to the route of infection, as studies showing a positive role for IFNα/β used the intraperitoneal route[212–214], whereas those showing a negative role used intradermal infection[215]. The levels of IFNα/β-mediated signalling that are induced may also be crucial, as *Ifnar1*$^{-/-}$ mice reportedly succumbed earlier than wild-type mice, yet mice lacking the ubiquitin-specific protease UBP43, which are hyper-responsive to IFNα/β, were also more susceptible than wild-type mice[214]. Finally, the relative balance between the effects on the innate immune response and the adaptive immune response seems to be important. In the absence of the innate immune signalling molecules MYD88 and/or TRIF, IFNα/β are important for host protection[213], as well as for nitric oxide generation[212]. However, IFNα/β also inhibit the production of the host protective cytokine IFNγ during *T. cruzi* infection[215], and this cytokine is most probably produced by T cells, because NK cells reportedly do not require IFNα/β for IFNγ production in this infection[216].

Fungal infection. Studies of IFNα/β during fungal infection have generated conflicting results. Several findings suggest that IFNα/β have a host-protective contribution to immunity to *Candida albicans*, *Saccharomyces cerevisiae* and *Cryptococcus neoformans*[217–219]. IFNα/β-mediated signalling has been found to be required for various processes, including inducing the reactive oxygen intermediates that are necessary for the killing of *C. albicans* by phagocytic cells[218], for maintaining a T_H1-like immune response (high IFNγ, TNF, iNOS and CXCL10 levels) to *C. neoformans*[217] and for attracting leukocytes (particularly neutrophils) to the disease site during *C. albicans* infection[219]. Interestingly, another study of *C. albicans* infection, in wild-type and *Ifnar1*$^{-/-}$ mice, found a similar requirement for IFN-mediated signalling for attracting neutrophils and inflammatory monocytes to the disease site; however, in this study, these cells had no effect on fungal burden but rather caused lethal immunopathology[220]. The reason for these opposing findings is unclear; however, given the very similar infection protocols used, it is possible that the differences are due to variations in the microbiota at different animal facilities. IFNα/β have also been found to mediate the poly(I:C) sensitization of mice to *C. albicans*, through suppressing IL-1β[183]. IFNα/β have also been implicated in sensitizing the host in infections with *Candida glabrata* and *Histoplasma capsulatum*, although the mechanism was not investigated in these cases[221,222].

Studies of humans with inherited errors in immune signalling components may provide the strongest clues to the role of IFNα/β in fungal infections. Whole exome sequencing and genome-wide association studies looking for the genetic aetiologies of chronic mucocutaneous candidiasis have identified mutations in *STAT1* in some patients[223,224] (reviewed in REF. 31). The same *STAT1* mutations were also found in patients with disseminated disease caused by other fungal pathogens such as *H. capsulatum*[31]. Interestingly, these mutations are gain-of-function and dominant, suggesting that IFNα/β potentially has a detrimental role in the response to fungal infection, possibly through suppressing T_H17 cell responses[223]. However, other cytokines that depend on STAT1 for signalling, such as IFNγ and IL-27, may also be responsible (FIG. 4).

Closing remarks

Type I IFNs are among the first cytokines whose production is induced by a plethora of cells during infection. Owing to the broad distribution of expression of IFNAR, IFNα/β have wide-ranging effects, on epithelial cells and innate and adaptive immune cells. The net effect of IFNα/β on protection or pathogenesis during infection is determined by the type and dose of pathogen, as well as by the genetic background of the host and possibly the microbiota (BOX 2). Progress is needed to better understand, first, the precise regulation of the induction of IFNα/β at the transcriptional and post-transcriptional levels and, second, the factors that determine responsiveness to IFNα/β. Such knowledge will allow researchers to uncover mechanisms to harness the immune response for maximum host protection with minimum damage.

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Competing interests statement
The authors declare no competing interests.