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Immunomodulatory functions of type I interferons

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Abstract

Interferon-α (IFNα) and IFNβ, collectively known as type I IFNs, are the major effector cytokines of the host immune response against viral infections. However, the production of type I IFNs is also induced in response to bacterial ligands of innate immune receptors and/or bacterial infections, indicating a broader physiological role for these cytokines in host defence and homeostasis than was originally assumed. The main focus of this Review is the underappreciated immunomodulatory functions of type I IFNs in health and disease. We discuss their function in the regulation of innate and adaptive immune responses, the response to bacterial ligands, inflammasome activation, intestinal homeostasis and inflammatory and autoimmune diseases.

The inhibitory effect that one viral infection often exerts on the infectivity of a different virus was first observed in 1804 by Edward Jenner, who reported that herpetic infections could prevent the development of vaccinia lesions[1]. In retrospect, this observation might be the first documented description of what was later coined as the viral interference phenomenon. This phenomenon was first described in detail for plant viruses in the early 1930s[2]. After that, similar observations were made with bacteriophages[3] and with animal viruses[4]. In 1954, Nagano and Kojima reported the inhibition of viral growth in areas of rabbit skin that had been previously inoculated with ultraviolet-inactivated vaccinia virus, and in 1957, during a study of the interference produced by heat-inactivated influenza virus, Isaacs and Lindenmann identified that a secreted factor was responsible for this phenomenon and they termed it interferon (IFN)[5].

Type I IFNs belong to a family of cytokines that attracted much attention owing to their protective role against viral infection. IFNs are widely expressed cytokines that possess strong antiviral and immunomodulatory properties. The IFN family can be classified into three main types of cytokines — type I, type II and type III IFNs. In humans and mice, the type I IFN family is composed of 16 members, namely 12 IFNα subtypes, IFNβ, IFNε, IFNκ and IFNω[6]. By contrast, the type II IFN family includes only one cytokine: IFNγ, which also exhibits antiviral activities. The third type of IFNs is the IFNλ family, which includes IFNλ1 (also known as IL-29), IFNλ2 (also known as IL-28A) and IFNλ3 (also known as IL-28B). On the basis of protein sequence and structure, type III IFNs are

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markedly different from type I and type II IFNs and are more similar to members of the interleukin-10 (IL-10) family; however, they provoke antiviral responses and induce the activation of IFN-stimulated genes (ISGs)[7].

Recent evidence has uncovered new roles for this family of cytokines beyond their well-known function in viral interference. This article highlights the function of type I IFNs in modulating immune responses. We map the molecular signalling pathways activated by type I IFNs, and describe the function of these cytokines in the response to bacterial ligands and their role in inflammasome activation. In addition, we discuss the role of type I IFNs in intestinal homeostasis and in inflammatory and autoimmune diseases such as coeliac disease, psoriasis, multiple sclerosis and cancer.

Type I IFN production and signalling

Induction of type I IFNs by bacterial ligands

Type I IFNs can be produced by almost every cell type, including leukocytes, fibroblasts and endothelial cells. The signalling pathways that lead to the induction of type I IFNs differ depending on the stimulus and the responding cell types, but they ultimately lead to the activation of some common signalling molecules, including TNF receptor-associated factor 3 (TRAF3)[8] and the transcription factors IFN regulatory factor 3 (IRF3) and IRF7. Dimerized IRF3 and IRF7 translocate to the nucleus and, concomitantly with the transcription factor nuclear factor-κB (NF-κB), bind to both the *IFNA* and *IFNB* promoters[9] to initiate the transcription of these IFN genes. Although the most important function of type I IFNs is typically considered to be in the induction of an antiviral immune response, these cytokines are also induced in response to many bacterial pathogens or their products, mainly through Toll-like receptor (TLR)-dependent pathways[10,11].

TLRs are the key sensors of microbial invasion in mammals[12], and they activate an innate defence programme that is crucial for host survival. Each TLR senses a particular subset of microbial signature molecules. Most TLRs that recognize bacterial products are linked to the induction of type I IFNs[10]; these TLRs include TLR3, TLR4, TLR7 and TLR9. Signalling through TLR3 and TLR4 induces type I IFN production in a broad range of cell types in a manner dependent on TIR-domain-containing adaptor protein inducing IFNβ (TRIF). By contrast, TLR7, TLR8 and TLR9 induce type I IFN production in dendritic cells (DCs) — mainly plasmacytoid DCs (pDCs) — via a pathway dependent on myeloid differentiation primary-response protein 88 (MYD88) (TABLE 1).

However, it became evident that TLR-deficient animals can still produce type I IFNs in response to RNA and DNA ligands[13,14]. These TLR-independent pathways include the cytoplasmic sensors retinoic-acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5). In addition, stimulator of IFN genes (STING) and DNA-dependent activator of IRFs (DAI; also known as DLM1 and ZBP1) have been reported to induce type I IFNs in response to cytosolic DNA[15,16]. STING is an endoplasmic reticulum-associated protein that has been shown to respond to DNA from various pathogens — including *Listeria monocytogenes* and the DNA virus herpes simplex virus 1 (HSV-1) — in macrophages, DCs and epithelial cells[15]. DAI, which was the first cytosolic DNA receptor to be described, recognizes viral, bacterial and mammalian double-stranded DNA and induces type I IFN production through the activation of TANK-binding kinase 1 (TBK1), which subsequently phosphorylates IRF3 (REF. 16). In addition, DAI stimulates the production of pro-inflammatory cytokines — such as IL-6 and tumour necrosis factor (TNF) — through the activation of the kinase receptor-interacting protein 1 (RIP1), which leads to the phosphorylation of NF-κB inhibitor-α (IκBα) and the subsequent activation of NF-κB[17]. However, DAI-deficient cells can still induce type I IFN production in response to

foreign DNA[18], suggesting the existence of additional mechanisms that contribute to type I IFN production in response to cytosolic DNA. Indeed, a recent study showed that DNA-dependent RNA polymerase III can use cytosolic DNA as a template to synthesize RNA containing a 5′-triphosphate group, and that this RNA activates the RIG-I–IPS1 (*IFNB*-promoter stimulator 1; also known as MAVS) signalling pathway[19].

Signalling pathways activated by type I IFNs

Type I IFNs signal through a common heterodimeric receptor, known as the IFNα/β receptor (IFNAR), which is expressed by nearly all cell types. This receptor consists of two subunits — IFNAR1 and IFNAR2 (REF. 20) — that are constitutively associated with Janus kinase 1 (JAK1) and non-receptor tyrosine kinase 2 (TYK2)[21]. Activation of JAK1 and TYK2 results in the tyrosine phosphorylation and activation of several signal transducer and activator of transcription (STAT) family members; in most cells these include STAT1, STAT2, STAT3 and STAT5, but in lymphocytes type I IFNs also activate STAT4 and STAT6 (REFS 22,23).

Activation of STAT1 and STAT2 leads to the recruitment of IRF9 and the formation of a STAT1–STAT2–IRF9 complex, which is known as the IFN-stimulated gene factor 3 (ISGF3) complex. This complex then migrates to the nucleus and binds to IFN-stimulated response elements (ISREs) in the promoters of ISGs to initiate gene transcription. Other STAT complexes that do not recruit IRF9, including STAT1 homodimers, bind to IFNγ-activated site (GAS) enhancer elements in the promoters of ISGs[24,25]. Both type I and type II IFNs can induce the activation of GAS elements through, for example, the formation of STAT1 homodimers. However, in contrast to type I IFNs, IFNγ cannot induce the formation of ISGF3 complexes and therefore is not able to promote the engagement of ISRE sites to activate those genes that have only ISREs in their promoters[21] (FIG. 1).

In addition, both type I and type II IFNs can induce the recruitment and phosphorylation of STAT3 (REFS 21,26). Following its phosphorylation, STAT3 forms homodimers that translocate to the nucleus, where they bind to STAT3-binding elements (SBEs). STAT1 and STAT3 have a high level of sequence similarity and can heterodimerize and activate similar genes *in vitro*[27]. However, *in vivo*, the sets of genes that are activated by these two factors are very different[28] and depend on the cell type and the activating cytokine, and in many physiological contexts STAT1 and STAT3 exert opposing effects. For example, in most cell types, STAT1 activates several proapoptotic and anti-proliferative genes[29,30], whereas STAT3 inhibits apoptosis and promotes proliferation through the induction of anti-apoptotic genes of the B cell lymphoma (BCL) family and of oncogenes such as *MYC*[31,32].

STAT1 and STAT3 also have opposite roles in inflammation. IFNγ-dependent STAT1 activation usually mediates a pro-inflammatory response that favours the recruitment of immune cells to the site of inflammation[33], and this increases the production of pro-inflammatory mediators[34] and enhances antigen processing and presentation by MHC class I and II molecules[35,36]. By contrast, STAT3 is a key mediator of IL-10 signalling, which negatively regulates pro-inflammatory responses by activated macrophages and DCs and can directly inhibit STAT1 activation[37]. Interestingly, other receptors, such as the IL-6 receptor, can activate STAT3, but this does not result in an anti-inflammatory response, possibly owing to the participation of additional regulatory factors, such as members of the suppressor of cytokine signalling (SOCS) family[38,39]. This dual ability of STAT3 to differentially regulate inflammation in different scenarios might explain some of the controversial roles that type I IFNs have in different human conditions (discussed below). Several studies also suggest that cross-regulation between STAT1 and STAT3 and their relative abundance in a cell are the defining factors that determine the biological effects of their upstream activators, such as IL-6 and IFNs[40,41].

Type I IFNs were also shown to promote the production of IL-10 by lipopolysaccharide (LPS)-stimulated macrophages[42] and by LPS-stimulated human peripheral blood mononuclear cells (PBMCs)[43]. This effect was initially attributed to the activation of STAT3 and IRF1 in IFNα-stimulated human monocytes[44]. However, another study indicated that IFNβ stimulates IL-10 production independently of STAT3, by activating a signalling pathway mediated by JAK1 and phosphoinositide 3-kinase (PI3K). This pathway increases the phosphorylation and nuclear translocation of cAMP-responsive-element-binding protein (CREB), which promotes IL-10 production in human DCs[45] (FIG. 1). It is not clear why IL-10 production is mediated by different signalling pathways in response to IFNα (the STAT3 pathway) and IFNβ (the PI3K pathway). However, the differential activation of STAT3 versus STAT1, the ability to induce IL-10 production and/or the participation of additional regulatory elements may explain the diverse effects of type I IFNs in several pathological conditions.

In addition to the JAK–STAT signalling pathways, there is evidence that type I IFNs activate other (non-STAT) signalling pathways that have crucial roles in their different biological properties. For example, it has been shown that type I IFNs activate signalling pathways mediated by mitogen-activated protein kinases (MAPKs), specifically p38 and extracellular signal-regulated kinase 1 (ERK1) or ERK2. p38 activity is required for type I IFN-dependent transcription of several genes that are regulated by ISREs and GAS elements in an STAT-independent manner[46–48]. The functional relevance of this signalling pathway in the biological effects of type I IFNs was evidenced by several studies indicating that p38 is required for the growth-inhibitory and antiviral effects of type I IFNs[49,50]. In addition to the induction of the p38 signalling cascade, the MAPK/ERK kinase (MEK)–ERK pathway is activated by type I IFNs[51] and participates in the response to viral infection[52]. Finally, as mentioned above, type I IFNs can also induce the activation of the PI3K signalling pathway in a STAT-independent manner[53,54]. The PI3K pathway has an important role in mediating gene transcription in response to both type I and type II IFNs and is essential for mediating their antiviral effects against the encephalomyocarditis virus *in vitro*[55]. Activation of the PI3K signalling cascade controls the activation of mammalian target of rapamycin (mTOR), which regulates mRNA translation. Notably, it was shown that type I IFNs activate pathways for the initiation of mRNA translation that are downstream of mTOR, such as the pathway that involves the activation of p70 S6 kinase and the subsequent phosphorylation of the S6 ribosomal protein[56,57]. The activation of mTOR by type I IFNs was unrelated to the activation of STAT family members and had no effect on gene transcription[56,57], indicating that mTOR selectively regulates IFN-induced mRNA translation. In terms of biological relevance, the activation of mTOR signalling has been shown to mediate the antiviral effects of IFNα against the hepatitis C virus[58].

Modulating immune responses by type I IFNs

Type I IFNs and suppression of intestinal inflammation

The intestinal microbiota influences the development of local and systemic immune responses and the proliferation and barrier functions of the intestinal epithelium, in part via the activation of host TLRs[59]. Over the last few years, data from our laboratory and others have shown that the systemic administration of TLR9 ligands reduces the severity of colonic injury and inflammation in models of experimental colitis[60–62], in part through the TLR9-induced production of type I IFNs by DCs[60]. In addition, IFNα enhances the barrier function of intestinal epithelial cells *in vitro* by activating STAT3, which maintains the expression of several key tight junction molecules, such as members of the claudin family (J.L., unpublished observations). Similarly, activation of TLR3 by the synthetic viral RNA polyinosinic–polycytidylic acid (polyI:C), which induces type I IFN production in many cell types, was shown to protect mice from experimental colitis[62]. Furthermore, *Ifnar*$^{-/-}$ mice

were extremely susceptible to dextran-sulphate sodium (DSS)-induced colitis[60,63], and the administration of recombinant IFNβ to DSS-treated wild-type mice mimicked the anti-inflammatory effects of TLR9 ligands[60].

Different types of haematopoietic cells contribute to DSS-induced colonic inflammation. The depletion of $CD11c^{hi}$ DCs after DSS administration showed that type I IFNs induced by TLR9-activated $CD11c^{hi}$ DCs attenuate the severity of colitis in this model[64]. This study also showed that, depending on their mode of activation, DCs can enhance or inhibit acute DSS-induced colitis by secreting various cytokines (such as TNF, IL-6, IL-10 and type I IFNs), by regulating the production of chemokines that affect the composition of the cellular infiltrate, and by affecting the rate of resolution of inflammation in the colon[64]. In addition, a recent study using a genetically modified strain of *Lactobacillus acidophilus* that constitutively expresses IFNβ reported that the local expression of IFNAR1 by $CD103^+$ DCs in the Peyer's patches is necessary for protection against DSS-induced intestinal inflammation[63]. In this study, saturating expression of IFNβ before the induction of colitis resulted in the transient suppression of IFNAR1 expression on intestinal $CD103^+$ DCs; this prevented IFNβ from signalling during the inflammatory period, mimicking the phenotype of $Ifnar^{-/-}$ mice with DSS-induced colitis[63].

Regulation of adaptive immune responses by type I IFNs

In addition to the T cell-independent protective effects of TLR9-mediated type I IFN induction, the role of TLR9 agonist-induced protection in T cell-dependent intestinal inflammation has also been evaluated. TLR9 signalling in DCs in the lamina propria of the small intestine was shown to regulate the functions of regulatory T (T_{Reg}) cells and effector T cells[65]. In this study, T_{Reg} cell induction was inhibited by DNA derived from commensal bacteria through TLR9, and this was shown to favour the development of protective mucosal immune responses; however the role of type I IFNs in these effects was not clarified[65]. In a T cell-transfer model of colitis, treatment with a TLR9 ligand in the absence of type I IFN signalling failed to induce functionally suppressive $CD4^+CD62L^+$ T cells, whereas pretreatment of the donor mice with recombinant IFNβ and subsequent T cell transfer resulted in reduced intestinal inflammation and decreased secretion of pro-inflammatory cytokines[66]. Indeed, a role for type I IFNs in TLR9-induced protection in T cell-dependent colitis was previously shown in germ-free mice; in this study, type I IFNs were shown to induce the expression of regulatory markers on $CD4^+CD62L^+$ T cells[67]. These data correlate with previous reports that type I IFNs induce regulatory capacities in T cells[68,69]. Therefore, type I IFNs seem to exert a protective effect in the intestinal mucosa in both acute and chronic models of colitis.

Type I IFNs have been shown to have an important role in the differentiation of both $CD4^+$ and $CD8^+$ T cells. Initial studies found that IL-12 signalling in $CD4^+$ T cells and the subsequent activation of STAT4, which in turn promotes T-bet expression, are crucial events in T helper 1 (T_H1) cell differentiation[70]. In addition to IL-12, type I IFNs were shown to induce the tyrosine phosphorylation and DNA binding of STAT4 (REF. 71) and to act directly on human T cells, but not mouse T cells, to drive T_H1 cell development[72]. However, it was later reported that type I IFNs activate STAT4 directly and that this activation is required for IFNγ production during viral infections in mice[73,74]. Thus, phosphorylation of STAT4 has been detected in response to type I IFN treatment of both human and mouse T cells[74–76] but, in contrast with IL-12, type I IFNs were unable to sustain STAT4 phosphorylation and therefore were not sufficient to drive T_H1 cell commitment *in vitro*[75,77]. However, type I IFNs regulate T_H1 cell differentiation and effector functions *in vivo* by synergizing with other cytokines, such as IL-18 and IL-21 (REFS 78–80). Moreover, type I IFNs have been associated with the suppression of T_H2 and T_H17 cell-mediated responses. In human cells, type I IFNs reversed T_H2 cell commitment

by suppressing the expression of the T_H2 cell-associated transcription factor GATA-binding protein 3 (GATA3)[78]. Similarly, type I IFNs also suppress the differentiation of T_H17 cells in both mice[81] and humans[82].

Forkhead box P3 $(FOXP3)^+$ T_{Reg} cells have a pivotal role in maintaining immunological tolerance and homeostasis. IFNβ treatment markedly improved the frequency and suppressive function of T_{Reg} cells in patients with relapsing–remitting multiple sclerosis[9,83] and in patients with chronic hepatitis C virus infection[84], and also increased *Foxp3* mRNA expression in PBMCs from patients with relapsing–remitting multiple sclerosis[85]. $FOXP3^+$ T_{Reg} cells show functional and phenotypical plasticity in response to environmental cues and are capable of secreting pro-inflammatory cytokines, for example during severe inflammation[86,87]. Recently, a higher frequency of IFNγ-secreting T_{Reg} cells has been reported in untreated patients with relapsing–remitting multiple sclerosis compared with the frequency in control individuals[88]. By contrast, in patients treated with IFNβ, the frequency of $IFN\gamma^+FOXP3^+$ T cells was similar to that in healthy controls[88]. In addition, ongoing studies in our laboratory indicate that type I IFN signalling is essential for the maintenance of FOXP3 expression *in vivo* and for the suppressive activity of T_{Reg} cells in a model of T cell-mediated colitis in mice (S. E. Lee, J.M.G.-N. and E.R., unpublished observations). These data suggest a novel role for type I IFNs in T_H cell differentiation, as well as in the suppressive function of T_{Reg} cells.

Type I IFNs and inflammasome activation

Four different initiator components that activate different types of inflammasome in response to different stimuli have been identified: NOD-, LRR- and pyrin domain-containing 1 (NLRP1), NLRP3, NOD-, LRR- and CARD-containing 4 (NLRC4; also known as IPAF) and absent in melanoma 2 (AIM2)[89].

Recently, an inhibitory role for type I IFNs in the activation of the inflammasome has been reported[90]. In this study, type I IFNs inhibited IL-1β production through two different mechanisms. First, IFNβ signalling directly inhibited the NLRP1 and NLRP3 inflammasomes (but not the NLRC4 and AIM2 inflammasomes) in a STAT1-dependent manner. Second, type I IFNs induced the production of IL-10, which in turn activated the transcription factor STAT3 in an autocrine manner to reduce the levels of pro-IL-1α and pro-IL-1β[90] (FIG. 2a). Furthermore, type I IFNs increased the susceptibility of mice to *Candida albicans* infection, an effect that was attributed to the reduction in IL-1β production[90]. Therefore, these data suggested an inhibitory role of type I IFNs in inflammasome activation.

By contrast, previous work reported a positive effect of type I IFNs in inflammasome activation during *Francisella tularensis* infection[91]. The cytosolic pathogens *F. tularensis* and *L. monocytogenes* were both shown to induce a type I IFN response that was essential for caspase 1 activation and IL-1β production. Consistent with this, *F. tularensis* DNA released into the cytosol activated the production of type I IFNs via IRF3, and this was necessary for the activation of the DNA-sensing AIM2 inflammasome[92] (FIG. 2b). The discrepancies regarding the role of type I IFN signalling in the production of IL-1β might be related to the type of inflammasome; that is, type I IFNs mediate the inhibition of the NLRP3 inflammasome but the activation of the AIM2 inflammasome. Of particular interest, however, is the case of *L. monocytogenes,* which has been shown to activate the NLRP3 inflammasome[89] and to increase IL-1β production in an IFNβ-dependent manner.

The cytokines IL-1α and IL-1β both bind to IL-1 receptor type 1 (IL-1R1), leading to the activation of NF-κB, MAPKs and certain IRFs[93,94]. In a recent study, we showed that IL-1R1 is necessary for the TLR9-dependent activation of a type I IFN and IL-10

response[95]. The mechanism by which IL-1R1 signalling modulates type I IFN production involves changes in the ubiquitylation profile of TRAF3, an E3 ubiquitin ligase that interacts with both MYD88 and TRIF, and the type of ubiquitylation determines whether type I IFNs or pro-inflammatory cytokines are produced[8,96]. Lysine 48 (K48)-linked polyubiquitylation of TRAF3 leads to its proteosomal degradation and the activation of MAPKs and pro-inflammatory cytokines, whereas K63-linked polyubiquitylation of TRAF3 results in the activation of IRFs and subsequent type I IFN production[96,97]. K63-linked, but not K48-linked, polyubiquitylation of TRAF3 is greatly reduced in the absence of IL-1 signalling. This effect is mediated by deubiquitylating enzyme A (DUBA; also known as OTUD5)[95], which specifically cleaves the K63-linked polyubiquitin chain on TRAF3 (REF. 97). Together, these data suggested a model in which IL-1R1 positively regulates TLR-induced type I IFN production (FIG. 3). This mechanism may explain previous observations of IL-1R1-mediated protection against intestinal damage from *Citrobacter rodentium* infection[98] and DSS-induced colitis[98,99].

Type I IFNs and bacterial infections

Although type I IFNs are induced by bacterial pathogens, the role of type I IFNs in the context of bacterial infections is not completely understood. Bacterial induction of type I IFNs can be mediated through the TLR-dependent recognition of bacterial products, such as LPS, or through the TLR-independent recognition of bacterial ligands that are delivered to the host cytosol. Many investigators have reported a variety of beneficial but also detrimental immune functions for type I IFNs during bacterial infection. For example, type I IFNs have an important role in mediating the pathology of LPS-induced septic shock[84]. By contrast, type I IFNs impair the clearance of *L. monocytogenes*[100,101], *Mycobacterium tuberculosis*[102] and *Chlamydia muridarum*[83,103], and they are detrimental to host survival after infection with *F. tularensis*[104].

Two mechanisms have been proposed to explain these phenomena. The first mechanism suggests that microorganisms induce type I IFN production as a strategy to induce apoptosis in lymphocytes, resulting in the suppression of adaptive immune responses[105]. The second mechanism proposes that type I IFNs suppress the production of IL-17A and IL-17F, which are necessary for neutrophil-mediated bacterial clearance[104]. By contrast, type I IFNs are necessary for host resistance against other bacterial pathogens. Mice deficient in IFNAR showed decreased survival and increased bacterial burdens after infection with *Streptococcus pneumoniae* or *Escherichia coli*[106], and this was attributed to the reduced expression of certain cytokines, such as TNF or IFNγ. Moreover, type I IFNs were shown to play an important part in restricting the growth of *Legionella pneumophila* in macrophages[107]. Taken together, these data show that type I IFNs have a wide range of immunomodulatory effects in response to bacterial infections, and this clearly expands the old notion that type I IFNs serve only as antiviral cytokines.

Type I IFNs in autoimmune disease

The connection between type I IFNs and several autoimmune and inflammatory disorders is well known, although there is considerable variation in the precise mechanisms and in the role of these cytokines in each condition. Some autoimmune diseases (such as psoriasis and systemic lupus erythematosus (SLE)) are improved by the inhibition of type I IFNs or their upstream regulators. By contrast, other conditions that are characterized by strong T_H1 and/or T_H17 cell responses — such as arthritis, inflammatory bowel disease (IBD) and multiple sclerosis — benefit from the administration of type I IFNs (FIG. 4). All these inflammatory conditions have an important impact on public health and are the focus of numerous analyses that are readily available in the literature. Therefore, they are only briefly discussed here.

Inflammatory bowel disease

IBD encompasses two major clinical entities: Crohn's disease and ulcerative colitis. Conventional therapies for IBD include 5-aminosalicylic acid (5-ASA), antibiotics (such as ciprofloxacin and metronidazole), corticosteroids, immunosuppressants and TNF-specific antibodies (such as infliximab and adalimumab)[108]. However, poor efficacy in some cases (with 5-ASA or antibiotic treatment) or the development of serious side effects (with corticosteroid treatment) led to the search for other biological therapies. Given their mechanisms of action and their beneficial effects on intestinal homeostasis in animal models, type I IFNs have been tested as a treatment for IBD. Although a few clinical studies of IFNα or IFNβ therapy in patients with ulcerative colitis initially showed promising results[109–111], most of these studies failed to demonstrate a beneficial therapeutic effect[112–115]. Furthermore, documented cases of the exacerbation of ulcerative colitis during IFNα therapy for chronic hepatitis C infection[116,117] and of the development of ulcerative colitis in patients with multiple sclerosis following treatment with IFNβ1a[118] call into question whether type I IFNs have a therapeutic role in IBD.

Coeliac disease

Coeliac disease has a strong genetic component, as it is highly associated with HLA-DQ2 and HLA-DQ8 alleles[119]. The pathogenesis of coeliac disease involves the polarization of T cells into T_H1 cells and the production of high levels of IFNγ in response to gluten[120]. T_H1 cell polarization is driven by many cytokines, including IL-21, IL-18 and IFNα[121], the levels of which are usually elevated in the mucosa of untreated patients with coeliac disease[122]. Interestingly, the addition of IFNα-specific, but not IL-18-specific, blocking antibodies to biopsy specimens from patients with coeliac disease inhibits IFNγ production in *ex vivo* organ cultures[123]. Activation of gluten-specific $CD4^+$ T cells requires that gluten antigens be presented by antigen-presenting cells (APCs) that express HLA-DQ2 or HLA-DQ8 (REFS 124,125). The expression of these alleles is relatively low in normal mucosa, but can be upregulated on APCs by type I and type II IFNs, and this facilitates the activation of other inflammatory cells, thereby favouring an inflammatory response to gluten peptides[122,126,127]. Notably, enteric viruses can induce the production of type I IFNs, leading to the upregulation of HLA-DQ2 or HLA-DQ8 on APCs, and this would result in the perfect milieu for the activation of gluten-specific T_H1 cells. The development of coeliac disease in patients undergoing treatment with recombinant type I IFNs, such as patients with hepatitis C virus infection[122,128], also supports this hypothesis.

Psoriasis

Psoriasis is a T cell-mediated chronic inflammatory skin disease that is characterized by the production of large amounts of type I IFNs by pDCs that are recruited to and accumulate in the dermis. High levels of type I IFNs are responsible for the local activation and expansion of pathogenic T cell populations, which in turn trigger the abnormal proliferation and differentiation of keratinocytes and the development of diffuse epidermal hyperplasia, known as acanthosis. The activation of T_H17 cells has been associated with this phenomenon[129], and the blockade of type I IFN signalling by IFNAR-specific antibodies effectively inhibited the activation of autoreactive T cells and the development of skin lesions in a xenograft model of psoriasis[130]. In addition, antibodies specific for blood DC antigen 2 (BDCA2; also known as CLEC4C) suppressed the production of type I IFNs by pDCs through the activation of SRC family protein tyrosine kinases, and this also inhibited the activation of autoreactive T cells and the development of skin lesions[131].

Systemic lupus erythematosus

The activation of pDCs by nucleic acid-containing immune complexes leads to the production of large amounts of type I IFNs, and elevated levels of IFNα are detected in the blood of patients with SLE[132,133]. Type I IFNs in the serum of patients with SLE were responsible for the differentiation of monocytes into DCs and the expression of MHC class II molecules and the co-stimulatory molecules CD80 and CD86 by these DCs. In addition, normal monocytes cultured with serum from patients with SLE, but not those cultured with autologous serum, could present self antigens to autoreactive T cells[134]. In another study, type I IFNs produced by pDCs, together with IL-6, were also shown to induce plasma cell differentiation[135]. Patients with SLE are treated with various medications, including non-steroidal anti-inflammatory drugs, glucocorticoids and immunosuppressants. Many of these therapies are associated with severe adverse effects. Therefore, there is a medical need for more-specific and safer therapies that target selective pathways involved in the pathogenesis of SLE. Recent data from a Phase I clinical trial showed that the administration of neutralizing antibodies specific for IFNα effectively inhibited the overexpression of IFNα-inducible genes in skin lesions of patients with SLE[136].

Multiple sclerosis

It is generally considered that both T_H1 and T_H17 cells are involved in the pathogenesis of multiple sclerosis and experimental autoimmune encephalomyelitis (EAE; an animal model of multiple sclerosis). Human recombinant IFNβ therapy is widely prescribed for certain stages of multiple sclerosis, particularly relapsing–remitting multiple sclerosis[137]. Two human recombinant IFNβ forms are currently used: IFNβ1a, which is produced in Chinese hamster ovary cells; and IFNβ1b, which is produced in *E. coli*[138]. The exact mechanism behind the beneficial effect of type I IFNs in multiple sclerosis and EAE is not known, but recombinant IFNβ reduces the attack frequency and severity of multiple sclerosis[138,139]. However, not all patients with relapsing–remitting multiple sclerosis respond to treatment, and the development of IFNβ-specific autoantibodies may cause relapses and side effects.

IFNβ-deficient mice are more susceptible to EAE development[140], and type I IFNs can attenuate EAE in mice[141], suggesting that IFNβ modulates both multiple sclerosis and EAE. In addition, the conditional deletion of *Ifnar1* showed that specific myeloid cells, such as monocytes and macrophages[142] or DCs[143], modulate autoimmune inflammation of the central nervous system in an IFNAR-dependent manner. The expression of IFNAR by microglial cells (brain-endogenous macrophages) also modulates the severity of EAE[142]. IFNβ reduces the ability of microglial cells to present antigens, and this in turn reduces the recruitment and effector functions of encephalitogenic T cells[144]. Another mechanism that was proposed to explain the immunomodulatory effects of IFNβ in patients with multiple sclerosis involves the induction of IL-10. Indeed, upregulation of IL-10 production is a hallmark of IFNβ treatment in patients with multiple sclerosis[145].

Cancer

Type I IFNs have been extensively used for the treatment of several types of cancer, including haematological malignancies (for example, hairy cell leukaemia and some B or T cell lymphomas) and solid tumours (for example, melanoma, renal cell carcinoma and Kaposi's sarcoma)[146,147].

IFNα1-producing tumour cells were shown to be less tumorigenic and less able to metastasize when transferred into mice, and this was attributed to the activation of several host antitumour mechanisms at the tumour site[148]. These studies suggested that type I IFNs could act as an adjuvant in cancer vaccines[133]. Indeed, IFNα showed an effective adjuvant activity in patients with melanoma[149]. In addition to their putative role as adjuvants in

antitumour vaccines, type I IFNs inhibit angiogenesis and act on DCs to enhance the ability of these cells to cross-present apoptotic antigens to $CD8^+$ T cells[150] to trigger a cytotoxic T lymphocyte response[151,152].

The main pitfall for the use of type I IFNs as an anti-tumour therapy is the frequent severe side effects, which decrease the enthusiasm for the application of type I IFNs in this clinical setting.

Concluding remarks

Our understanding of the functions of type I IFNs and the mechanisms that control these functions is continuously evolving. Since their discovery, type I IFNs have been associated with host defence responses to viral infections, and it is only recently that their functions in bacterial infections and in immune-mediated and inflammatory disorders have been appreciated. The molecular mechanisms by which type I IFNs exert their immunomodulatory functions and the reasons why they restrain the development of some immunopathologies while increasing the severity of others are still largely unknown. One possible explanation for these opposing effects could be found in the differential regulation of STAT family members in different tissues or organs under different physiological and/or inflammatory conditions. A better understanding of the underlying pathophysiology is mandatory for the design of effective treatments with type I IFNs or with type I IFN-specific neutralizing antibodies.

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Glossary

Viral interference	The antagonistic or inhibitory effect induced by one virus or its components on the propagation of another virus.
IFN-stimulated genes (ISGs)	These genes contain promoters that are responsive to interferon (IFN) signalling, and they are responsible for the antiviral and immunomodulatory properties of IFNs. Over 400 such genes have been identified by microarray analyses. Some, such as RNA-activated protein kinase, ribonuclease L, MX1 (myxovirus resistance 1) and ISG15 (IFN-stimulated gene of 15 kDa), have well-documented antiviral activities, but the precise biological function of most of these genes is unknown.
Inflammasome	A cytosolic multiprotein complex that activates caspase 1 and regulates the release of IL-1β and IL-18 in response to exogenous pathogens and endogenous danger signals. This complex minimally consists of a danger-sensing initiator component and the effector component, which is mature caspase 1.
Coeliac disease	An immune-mediated enteropathy triggered by intolerance to dietary ingestion of glutamine- and proline-rich proteins, collectively known as gluten, which is present in wheat, barley, rye and other grains. This disease results in gastrointestinal

	symptoms such as diarrhoea, nutrient malabsorption and weight loss.
Multiple sclerosis	A chronic inflammatory disease of the central nervous system that causes the progressive destruction of the myelin sheaths around axons in any area of the brain, optic nerve and spinal cord. This results in slower nerve impulses.
Peyer's patches	Collections of lymphoid tissue that are located in the mucosa of the small intestine, with an outer epithelial layer that consists of specialized epithelial cells called M cells.
Systemic lupus erythematosus (SLE)	An autoimmune disease characterized by the presence of circulating immune complexes that contain antinuclear antibodies bound to self nucleic acids and other nuclear antigens.
Inflammatory bowel disease (IBD)	A chronic inflammatory condition that affects the intestinal tract. The proposed pathogenesis of IBD involves a complex model that includes abnormalities of innate immune function and their relationship with the commensal microbiota, inappropriate release of pro-inflammatory cytokines and other mediators, alterations of the intestinal epithelial barrier, and a cytokine imbalance that promotes the pro-inflammatory activity of adaptive immune cells.

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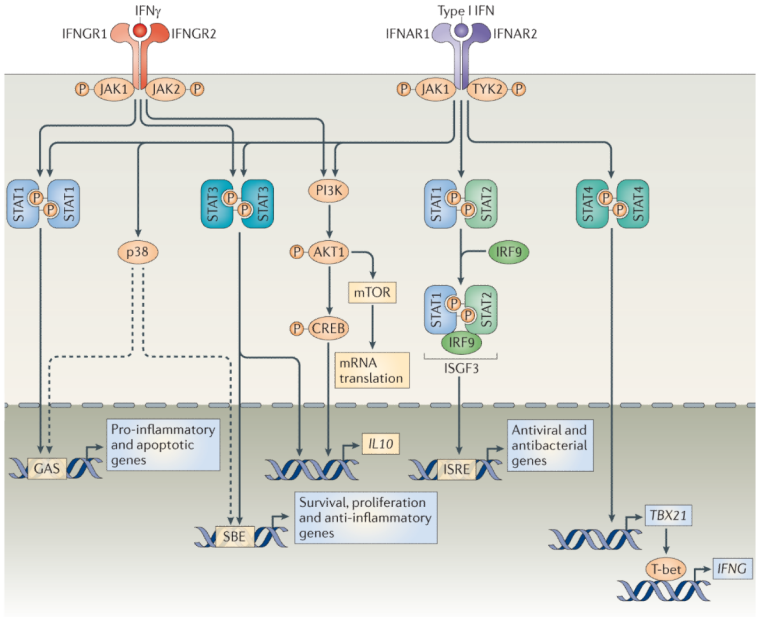

Figure 1. Signalling pathways activated by type I and type II IFNs

Different signal transducer and activator of transcription (STAT) family members can be activated by interferons (IFNs). STAT1 homodimers can be formed in response to both type I IFNs and type II IFN (IFNγ). These homodimers bind to IFNγ-activated site (GAS) enhancer elements in the promoters of IFN-stimulated genes, and this results in the induction of genes encoding pro-inflammatory cytokines and apoptotic factors. Type I and type II IFNs can also activate STAT3 homodimers, and this can result in the production of both pro-inflammatory cytokines and anti-inflammatory cytokines (such as interleukin-10 (IL-10)), although the underlying mechanisms are not known. STAT1–STAT2 heterodimers, which are activated by type I IFNs, bind to IFN regulatory factor 9 (IRF9) in the cytosol to form the IFN-stimulated gene factor 3 (ISGF3) complex, which in turn migrates to the nucleus to bind to IFN-stimulated response elements (ISREs) and activate antiviral and antibacterial genes. In addition, type I IFNs stimulate IL-10 production either through the phosphoinositide 3-kinase (PI3K)–AKT pathway or through STAT3 homodimers. Finally, in a STAT-independent manner, type I IFNs activate both p38, which is an upstream activator of several genes regulated by ISREs and GAS elements, and mammalian target of rapamycin (mTOR), which regulates mRNA translation. CREB, cAMP-responsive-element-binding protein; IFNAR, IFNα/β receptor; IFNGR, IFNγ receptor; JAK, Janus kinase; SBE, STAT3-binding element; *TBX21*, T box 21; TYK2, non-receptor tyrosine kinase 2.

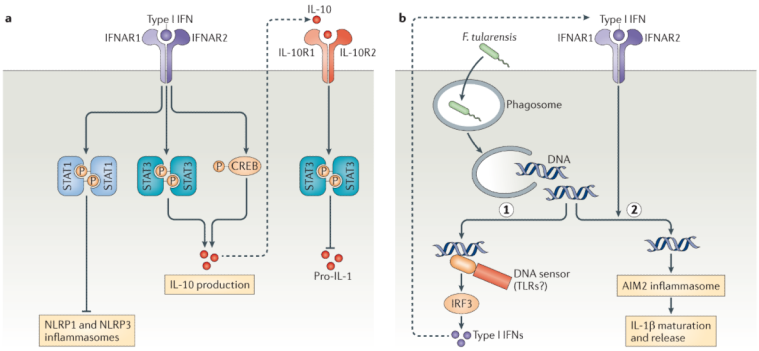

Figure 2. Type I IFNs regulate inflammasome activation

a | Type I interferons (IFNs) inhibit the production of IL-1β by the inflammasome through two different mechanisms. First, they activate signal transducer and activator of transcription 1 (STAT1), which directly inhibits the NOD-, LRR- and pyrin domain-containing 1 (NLRP1) and NLRP3 inflammasomes but not the absent in melanoma 2 (AIM2) or NOD-, LRR- and CARD-containing 4 (NLRC4) inflammasomes. Second, type I IFNs induce the production of interleukin-10 (IL-10), which binds to the IL-10 receptor (IL-10R) in an autocrine manner and activates STAT3, which in turn reduces the levels of the precursors pro-IL-1α and pro-IL-1β. **b** | Type I IFN signalling is required for efficient activation of the AIM2 inflammasome in response to *Francisella tularensis*. After the bacterium enters the phagosome, the phagosome is rapidly acidified. Acidification causes the release of bacterial DNA into the cytosol, and this DNA activates an unidentified DNA sensor, which in turn activates IFN regulatory factor 3 (IRF3) to initiate the production of type I IFNs. IFNβ then binds to the IFNα/β receptor (IFNAR) in an autocrine manner to enhance the activation of the AIM2 inflammasome, possibly by increasing phagosomal acidification and/or bactericidal activity, thereby favouring the release of more bacterial DNA. CREB, cAMP-responsive-element-binding protein; TLR, Toll-like receptor.

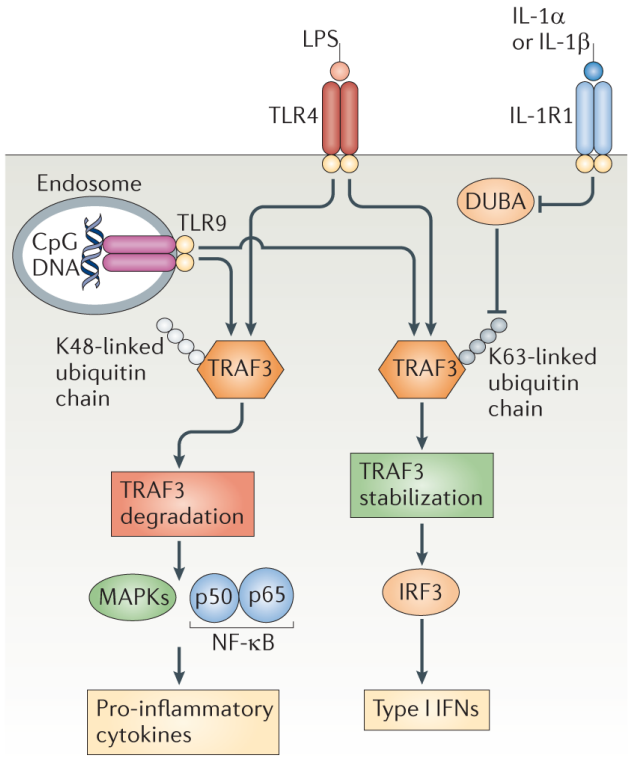

Figure 3. IL-1R1 signalling regulates type I IFN production

Interleukin-1 receptor 1 (IL-1R1) signalling positively modulates the production of type I interferons (IFNs) through the differential ubiquitylation of TNF receptor-associated factor 3 (TRAF3). Lysine 48 (K48)-linked polyubiquitylation of TRAF3 leads to its proteosomal degradation and the production of pro-inflammatory cytokines. By contrast, K63-linked polyubiquitylation of TRAF3 triggers the activation of IFN regulatory factor 3 (IRF3) and the subsequent production of type I IFNs. The absence of IL-1 signalling results in increased levels of deubiquitylating enzyme A (DUBA), which cleaves the K63-linked but not the K48-linked ubiquitin chains on TRAF3. LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; TLR, Toll-like receptor.

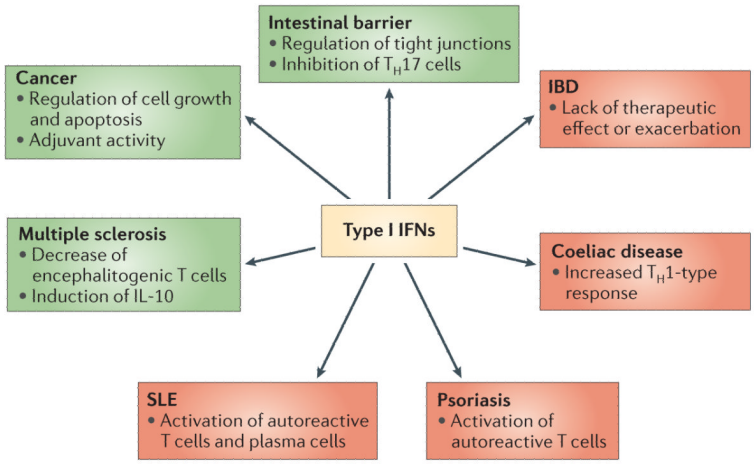

Figure 4. Type I IFNs in human diseases

Type I interferons (IFNs) are implicated in different human diseases, although their role in each condition varies. Type I IFNs usually have a beneficial impact in inflammatory syndromes, such as inflammatory bowel disease (IBD) and multiple sclerosis. By contrast, some autoimmune diseases, such as psoriasis and systemic lupus erythematosus (SLE), are improved by type I IFN inhibition. This figure summarizes the positive (green) and negative (red) roles of type I IFNs in different human conditions. IL-10, interleukin-10; T_H, T helper.

Table 1

Inducers of type I IFNs and responding cells

Inducer	Source	Receptor	Localization	Responding cell
ssRNA, dsRNA	Viruses	RIG-I and MDA5	Cytoplasm	Multiple cell types
Cytosolic DNA	Viruses or bacteria	STING, DAI and RNA polymerase III	Cytoplasm	Multiple cell types
dsRNA	Viruses	TLR3–TRIF	Endosomes	Macrophages, cDCs and epithelial cells
LPS	Gram-negative bacteria	TLR4–TRIF	Plasma membrane	Macrophages and cDCs
Viral glycolipids	Viruses	TLR4–TRIF	Plasma membrane	Macrophages and cDCs
ssRNA	Viruses or damaged host cells	TLR7–MYD88	Endosomes	pDCs, cDCs and macrophages
Imiquimod	Synthetic	TLR7–MYD88	Endosomes	pDCs, cDCs and macrophages
ssRNA	Viruses	TLR8–MYD88	Endosomes	cDCs
CpG DNA	Bacteria or viruses	TLR9–MYD88	Endosomes	pDCs, cDCs and macrophages

cDC, conventional DC; DAI, DNA-dependent activator of IRFs; DC, dendritic cell; dsRNA, double-stranded RNA; IFN, interferon; LPS, lipopolysaccharide; MDA5, melanoma differentiation-associated gene 5; MYD88, myeloid differentiation primary-response protein 88; pDC, plasmacytoid DC; RIG-I, retinoic-acid-inducible gene I; ssRNA, single-stranded RNA; STING, stimulator of IFN genes; TLR, Toll-like receptor; TRIF, TIR-domain-containing adaptor protein inducing IFNβ.