

Type I IFN-mediated regulation of IL-1 production in inflammatory disorders

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Abstract Although contributing to inflammatory responses and to the development of certain autoimmune pathologies, type I interferons (IFNs) are used for the treatment of viral, malignant, and even inflammatory diseases. Interleukin-1 (IL-1) is a strongly pyrogenic cytokine and its importance in the development of several inflammatory diseases is clearly established. While the therapeutic use of IL-1 blocking agents is particularly successful in the treatment of innate-driven inflammatory disorders, IFN treatment has mostly been appreciated in the management of multiple sclerosis. Interestingly, type I IFNs exert multifaceted immunomodulatory effects, including the reduction of IL-1 production, an outcome that could contribute to its efficacy in the treatment of inflammatory diseases. In this review, we summarize the current knowledge on IL-1 and IFN effects in different inflammatory disorders, the influence of IFNs on IL-1 production, and discuss possible therapeutic avenues based on these observations.

Keywords Type I IFN · IL-1 · Inflammasome · Inflammatory disorders · Autoimmunity · Multiple sclerosis · Anti-IL-1 therapy

Introduction

In this review, we focus on IFNs and give a background on their biological functions, emphasizing their anti-inflammatory effects in infections as well as in their therapeutic use. We summarize the knowledge on the complex mechanisms leading to IL-1 production and on its role in the development of various inflammatory disorders. Increasing evidence underlines the ability of IFNs to affect IL-1 production, and these findings potentially impact the management of infectious and inflammatory disorders. Here, we concentrate on the interplay between these two cytokines and possible clinical implications.

Inflammation

An inflammatory reaction is initiated whenever the normal equilibrium of the tissue is altered. Inflammation is required to remove the agent that caused the damage and to restore normality [1]. This is mainly achieved by cells of the immune system and by the action of different factors found in blood plasma and in extracellular fluids.

The classical signs of inflammation were already recognized by Celsus at the time of Ancient Greece and are described as the characteristic redness (rubor), swelling (tumor), increased temperature (calor), and pain (dolor) in the inflamed area. In fact, the primary goal of inflammatory responses is to increase blood supply and vessel permeability within the damaged tissues, thus promoting plasma protein and immune cell exudation. This facilitates tissue repair

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processes and minimizes the risk of infection. Indeed, when tightly controlled and actively terminated, inflammation represents a protective response, which coordinates tissue healing as well as immune cell activation and migration.

However, if not properly held in check, overriding inflammatory reactions can be detrimental to the tissue and lead to important collateral damage. This is the reason why a fifth hallmark, the ‘*Functio laesa*’ (i.e., loss of function), attributed to the Roman physician Galen, has been added to the four cardinal signs of inflammation. Importantly, chronic inflammation-driven diseases are a major health issue, particularly in developed countries, and selected examples are discussed later.

Mechanisms inducing innate-driven inflammation

Classical triggers of inflammatory responses are tissue damage and infectious agents. Innate immune cells, being strategically located at the site of injury, propagate the first alarm signal to recruit immune cells and to coordinate local tissue repair. Cells of the innate immune system have the ability to immediately respond to pathogen- and danger-associated molecular patterns (PAMPs and DAMPs, respectively) through dedicated germ-line encoded receptors, the so-called pattern recognition receptors (PRRs). Whilst PRRs lack the specificity and plasticity of their more sophisticated adaptive counterparts (T and B cell receptors), they mediate rapid and robust innate immune responses. Upon engagement, these receptors activate multiple signaling pathways that orchestrate the overall immune response, including the adaptive system.

To date, several classes of innate receptors have been defined [2–5]. We mainly focus on Toll-, Retinoic acid-inducible gene (RIG)-, and Nucleotide-binding oligomerization domain (NOD)-like receptors (TLRs, RLRs, and NLRs, respectively), that are particularly relevant to the induction of IFNs and IL-1.

Interleukin-1

The IL-1 family consists of 11 related ligands. Although a few members have been extensively investigated, others are neglected and await more in depth analysis. The most studied family members are the functionally related IL-1 α and IL-1 β (IL-1 α and IL-1 β are referred here as to ‘IL-1’), IL-1 receptor antagonist (IL-1Ra), and the IFN- γ -inducing cytokine IL-18.

Biological effects of IL-1

IL-1 α and IL-1 β , which share 26 % sequence homology, exert pleiotropic activities. Interleukin-1 represents an

important mediator linking the immune, the endocrine, and the central nervous system, therefore affecting several physiological functions [6–8]. Yet, IL-1 is best known for its ability to induce fever and for this reason was formerly called ‘endogenous pyrogen’ [7].

In fact, this cytokine is instrumental in inducing inflammation through activation of the nuclear factor- κ B (NF- κ B) pathway. Both IL-1 α and IL-1 β signal via a common IL-1 receptor (IL-1R) that is formed by the association of IL-1RI and the IL-1R accessory protein [9]. Interleukin-1R represents the prototypical NF- κ B activating Toll/Interleukin-1 receptor (TIR) domain-containing receptor and engages the NF- κ B signaling cascade through the adapter myeloid differentiation factor 88 (MyD88) and the IL-1 receptor-associated kinases (IRAKs) [10–13].

Interleukin-1 induces a variety of inflammatory mediators, such as the neutrophil chemoattractant CXCL1, and promotes growth/activation of hematopoietic cells by inducing cytokines such as IL-6 or the granulocyte-macrophage colony-stimulating factor [14–18]. In the early 1990s, the properties of IL-1 in helping hematopoietic reconstitution in bone marrow-transplanted patients have been evaluated, as summarized by Dinarello [15]. Unfortunately, side effects such as inflammation and hypotension were too severe to pursue the use of IL-1 as a therapeutic agent. However, IL-1 α and IL-1 β were efficacious in reducing thrombocytopenia and leucopenia, in particular with regard to neutrophil counts. Another name that has been assigned to IL-1 in the past was ‘lymphocyte activating factor’, due to its ability to promote lymphocyte proliferation [19]. The interest in this field was recently revitalized, as it was shown that IL-1 plays a crucial role in promoting CD4⁺ T cell polarization towards a T helper type 17-phenotype (Th17) [20, 21]. These are helper T cells secreting IL-17 (also known as IL-17A), which are mainly involved in autoimmune diseases and antifungal responses. Furthermore, another report demonstrated that IL-1 had the property of opposing the function of regulatory T cells, thus restoring the response of conventional T lymphocytes [22]. Altogether, these studies highlight the contribution of IL-1 in both innate and adaptive immune responses.

Such important inflammatory effects require tight regulation of IL-1 production and signaling. As discussed in more detail in the next paragraph, the generation of bioactive IL-1 is a complex process controlled at multiple levels. In addition, IL-1 signaling is held in check by its antagonist IL-1Ra, which is a protein sharing 26 % homology with IL-1 β and 18 % with IL-1 α . This naturally occurring inhibitor strongly binds IL-1RI without activating it and defects in its production lead to early onset life-threatening inflammatory diseases [23–26]. The crucial role of IL-1 in the development of inflammatory

pathologies has been increasingly studied and recognized over the past few years (reviewed in [14, 27]).

Multilevel control of bioactive IL-1 production

Interleukin-1 is mainly, but not exclusively, produced by myeloid cells. Given its strong and complex effects, its production is regulated at the transcriptional, translational, and posttranslational levels (Fig. 1). In fact, IL-1 α and the inactive precursor of IL-1 β (called pro-IL-1 β) are virtually undetectable in blood cells under normal conditions, and their induction needs the presence of stress signals [28]. In well-studied myeloid immune cells, IL-1 transcription relies on NF- κ B activating signals, such as tumor necrosis factor (TNF) or lipopolysaccharide (LPS) [29]. This ‘priming’ step is thus essential to raise intracellular levels of IL-1 α and pro-IL-1 β , along with enhancing the competence of the cell to proteolytically activate and secrete IL-1 β [30–32].

Interleukin-1 β mRNA is short-lived, giving rise to a tightly controlled burst of protein [33, 34]. Moreover, dissociation between the transcriptional and the translational regulation of this gene has been observed. Whereas, the stimulation of peripheral blood mononuclear cells with LPS increased both *IL-1 β* mRNA and protein, the adhesion of these cells to plastic surface or exposure to the complement system factor C5a augmented transcript abundance, leading, however, to abortive translation [35–37]. Under such conditions, *IL-1 β* transcripts assemble into large polyribosomes without giving rise to substantial protein levels.

Whereas IL-1 α is biologically active as it is synthesized, IL-1 β is produced as a precursor protein, which is per se inactive; proteolytic processing is required to convert the

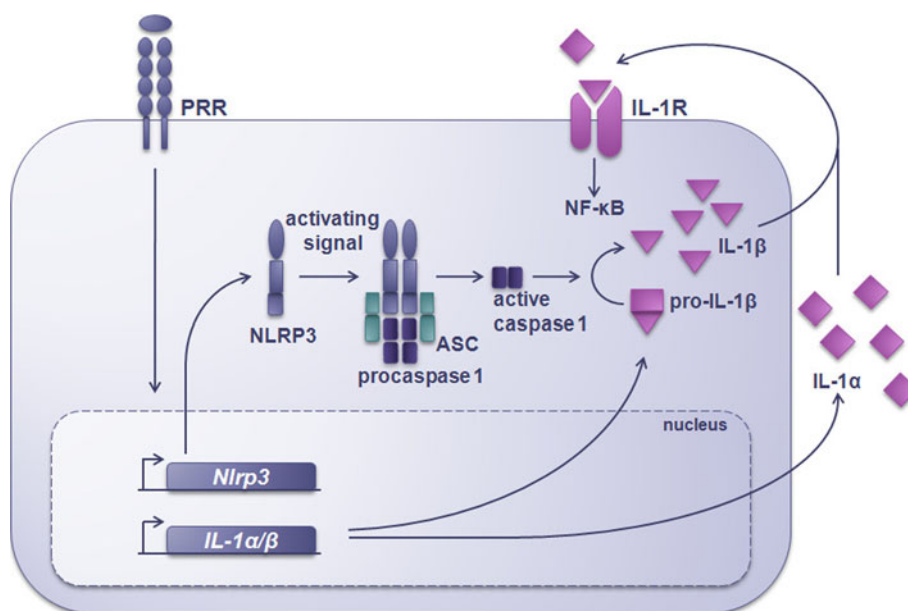
precursor protein into its active counterpart [38]. Several years ago, caspase-1 was identified as the crucial protease responsible for pro-IL-1 β maturation and was called ‘IL-1 β -converting enzyme’ thereafter [39–41]. However, the molecular mechanism leading to caspase-1 activation has only been described recently [42]. Its activation is accomplished upon formation of multiprotein complexes, called inflammasomes, which are able to bring caspases in close proximity to promote their autoactivation (discussed in more detail in the next section). A second member of the IL-1 family, IL-18, also requires caspase-1-dependent processing in order to be bioactive. Notably, although IL-1 α activity is independent of its cleavage, its secretion has often been observed in association with inflammasome function [17, 40, 43, 44].

NLRs and inflammasomes

NOD-like receptors are mainly recognized for their important role in the activation of inflammatory cascades in response to different PAMPs and DAMPs [4, 45, 46]. This family of proteins is characterized by a tripartite structure. The N-terminus, which is also called ‘effector domain’, is responsible for the recruitment of downstream executioner proteins and consists in most cases of a caspase recruitment or a pyrin domain (CARD or PYD, respectively). In addition, NLRs have a central NOD domain and a C-terminal tail of leucine-rich repeats (LRRs) [45].

Amongst the best-characterized NLRs, we find NLRP3 (previously called NALP3 or cryopyrin), NLRP1, and NLR family CARD-containing (NLRC) 4 (previously known as IPAF). These three family members share the ability to form inflammasome platforms, which have been studied in

Fig. 1 The production of bioactive IL-1. Pattern recognition receptor engagement enhances NLRP3 expression and induces IL-1 α and pro-IL-1 β . Upon sensing specific inflammasome-activating stimuli, NLRP3 assembles into and recruits ASC and procaspase-1 to the inflammasome complex. This multi-protein platform leads to the activation of caspase-1, which proteolytically converts pro-IL-1 β into bioactive IL-1 β . In contrast, pro-IL-1 α does not require cleavage for its activity. The release of both cytokines triggers NF- κ B signaling by binding to IL-1R



detail by means of biochemical and genetic approaches. Upon activation, NLRP3 recruits caspase-1 into the inflammasome complex via the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), which is a bipartite protein formed by a CARD and a PYD domain. ASC joins the oligomerized NLRP3 proteins through PYD–PYD interactions, while its CARD is available for homotypic interaction with the N-terminal CARD of caspase-1. In contrast to NLRP3, NLRC4 bears an N-terminal CARD, whereby caspase-1 can be directly recruited into the complex via homotypic CARD–CARD interactions. Nonetheless, the presence of ASC has been shown to favor NLRC4 inflammasome activity [47].

NOD-like receptor family CARD-containing protein 4 (NLRC4) with the assistance of neuronal apoptosis inhibitory proteins (NAIPs), another subgroup of NLR proteins, senses distinct Gram-negative bacteria. In particular, the role of NLRC4 in the response to flagellin has been investigated (Table 1) [46, 48–50]. The NLRP1 inflammasome was historically the first to be described, and the NLRP1b murine paralog activates caspase-1 upon exposure to lethal toxin of *Bacillus anthracis* [42, 51] (Table 1). To date, the activation of the NLRP3 inflammasome remains the most enigmatic. Indeed, this cytoplasmic protein leads to inflammasome assembly upon an ever-growing number of triggers, which belong to completely different chemical and physical categories (as summarized in Table 1, and reviewed in several articles [46, 52–54]). For example, NLRP3 can respond to stimulation with extracellular ATP, with pathogens and PAMPs, or to particulate stimuli such as monosodium urate crystals and asbestos fibers. How such diverse stimuli activate inflammasome formation specifically through NLRP3 is subject of intense research, and proposed models suggest the activation or induction of a common secondary effector molecule [31, 53]. Recent reports on *Nlrp6*-knockout animals and on human *NLRP12* variants support the idea that these NLRs may be similarly involved in inflammasome complex formation [55–57].

Finally, also absent in melanoma 2 (AIM2), not belonging to the NLR family, has been shown to form an inflammasome. This protein of the IFI200 family of proteins recruits and activates caspase-1 upon binding to double-stranded (ds) DNA in the cytoplasm (Table 1) [58].

Interferons

IFNs were discovered over half a century ago as endogenous antiviral effector molecules. These cytokines were named after their ability to ‘interfere’ with viral replication in the host cell. However, IFNs mediate a variety of

Table 1 List of inflammasome activators

Origin	Trigger	Sensor protein	
Sterile activators			
Endogenous signals	ATP	NLRP3	
	MSU crystals	NLRP3	
	CPPD crystals	NLRP3	
	BCP crystals	NLRP3	
	Cholesterol crystals	NLRP3	
	Glucose/hyperglycemia	NLRP3	
	Amyloid- β	NLRP3	
	Hyaluronan	NLRP3	
	Environmental-derived	Skin irritants	NLRP3
		UV	NLRP3
Alum		NLRP3	
Asbestos		NLRP3	
Silica		NLRP3	
		NLRP3	
Microorganisms—PAMPs			
Viral	RNA	NLRP3, AIM2	
	DNA	AIM2	
Bacterial	RNA	NLRP3	
	DNA	AIM2	
	Flagellin	NLRC4	
	Type III secretion system	NLRC4, NLRP3	
	Cell wall components	NLRP1, NLRP3	
	Pore-forming toxins	NLRP1, NLRP3	
Fungal	Hyphae, β -glucan	NLRP3	
Protozoan-derived	Haemozoin	NLRP3	
Helminth-derived	(unknown)	NLRP3	

biological functions not limited to the defense against viral infections, extending to antitumor and immunomodulatory effects [59]. According to their amino acid sequence, chromosomal location, and receptor specificity, IFNs are further subdivided into three groups, which we describe below.

IFN subtypes

Introduction to type I IFNs

Interferon- α and - β are the most studied and therefore best-characterized members of this class. Interferon- β is encoded by a single gene in human and mouse, and more than 20 different genes code for IFN- α , thereof 13 give rise to a functional protein in humans and 14 in mice. Whereas IFN- α and - β regulate a widely overlapping set of genes, these two cytokines are described as slightly differing in their downstream effects and in their expression pattern, which varies depending on the stimulation, on the cell type, and among individuals [60–63].

Other type I subtypes are IFN- ϵ , - κ , - ω , - δ , and - τ . Interferon- δ and - τ are only found in pigs and cattle, respectively, and have no human homologs. IFN- ϵ , - κ , and - ω exist in humans but are less well described and show restricted tissue distribution [60]. Induction, signaling, and downstream effects of IFN- α and - β are discussed in detail in the following sections.

Type II IFN

The type II IFN subtype is constituted by a single gene product, IFN- γ . It is structurally different from type I IFNs, but was classified in the IFN family due to its antiviral effects [64, 65]. Interferon- γ binds to the nearly ubiquitously expressed IFN- γ receptor (IFNGR), and signals through Janus kinase 1 (JAK1) and JAK2 to phosphorylate signal transducer and activator of transcription 1 (STAT1), thereby allowing STAT1 homodimer formation and nuclear translocation.

Interferon- γ is involved in the modulation of immune and inflammatory responses and is predominantly produced by NK, NKT, and activated T cells. In the latter, IFN- γ leads to the upregulation of the transcription factor T-bet, which is crucial for controlling commitment to the Th1 phenotype [66]. T helper 1 cells are characterized by IFN- γ production and suited to fight viral infections. In fact, T-bet upregulation drives IFN- γ expression and creates a positive feedback loop, which forces undifferentiated CD4⁺ cells to Th1 polarization. Furthermore, IFN- γ favors Th1 commitment indirectly by suppressing polarization to Th17 and Th2 [66, 67], the latter being a subtype of helper T cells mainly involved in allergic and helminth responses, distinguished by the production of IL-4 and IL-13.

Interferon- γ also exerts immunomodulatory effects on innate immune cells, primarily by increasing lysosomal enzymatic activity and bactericidal oxidative burst [68]. Moreover, type II IFN directly enhances antigen presentation by promoting antigen processing and by inducing the expression of major histocompatibility complex (MHC) molecules [65, 68].

Type III IFNs

The third class of IFNs is composed of IFN- λ 1, - λ 2, and - λ 3, or IL-28A, IL-28B, and IL-29, respectively. They are produced by most cell types, but particularly by plasmacytoid dendritic cells (DCs) in response to viral or bacterial infection [69, 70]. λ -Interferons form a separate group as they signal through a distinct receptor complex, consisting of IL-10R2 and IL-28R, which is expressed on a limited number of cells like hepatocytes and epithelial cells [70, 71]. However, type III IFNs activate similar signaling

pathways and partly induce the same genes as type I IFNs, resulting in a potent antiviral response [72, 73].

Type I IFN production

Interferon- α and - β can be produced by almost all cell types upon stimulation of PRRs. Constitutive expression of low type I IFN levels is maintained by macrophages, skin DCs, and thymic epithelial cells and is also found in organs like liver, spleen, and kidney [74–77]. Basal IFN signaling is important to keep immune cells in a ‘primed’ state to rapidly and effectively mount an antiviral immune response [78].

Cytoplasmic receptors

Most cell types can induce type I IFN in response to the activation of cytoplasmic RLRs (Fig. 2a), which are nearly ubiquitously expressed [5]. Importantly, the strategic intracellular location of these PRRs allows infected cells to activate the antiviral response. Retinoic acid-inducible gene-like receptors detect microbial ribonucleic acids, which can derive from the genome of RNA viruses or from replication intermediates of DNA viruses [79]. These receptors therefore enable infected cells to locally produce antiviral type I IFNs, which are essential in opposing a number of viral infections [5, 80].

Retinoic acid-inducible gene-like receptors include the two DExD/H-box helicases RIG-I and melanoma differentiation-associated gene 5 (MDA5), which are engaged by distinct ribonucleic acid species. Retinoic acid-inducible gene-I detects 5' triphosphate single-stranded (ss) RNA with pairing at the 5' end and rather short dsRNA, while MDA5 is activated by long dsRNA [5].

Retinoic acid-inducible gene-I and MDA5 have a common downstream adaptor, called mitochondrial antiviral signaling protein (MAVS) (Fig. 2a) [5]. Engagement of MAVS is followed by signaling through TBK1 [TNF receptor-associated factor (TRAF) family member-associated NF- κ B activator (TANK)-binding kinase 1] and the I κ B kinase ϵ (IKK ϵ), leading to the activation of the transcription factors interferon-regulatory factor (IRF) 3, IRF7, and NF- κ B [5, 80, 81]. Phosphorylation of IRFs allows their homo- or heterodimerization and promotes their subsequent localization to the nucleus, where they cooperate with NF- κ B to stimulate the transcription of type I IFN genes [82] (Fig. 2a). In most cells, IRF3 is the only constitutively expressed IRF. The phosphorylation of IRF3 results in the induction of IFN- β and low levels of IFN- α 4 [83]. IRF3-triggered type I IFN increases IRF7 levels, which then lead to the proficient expression of IFN- α [84].

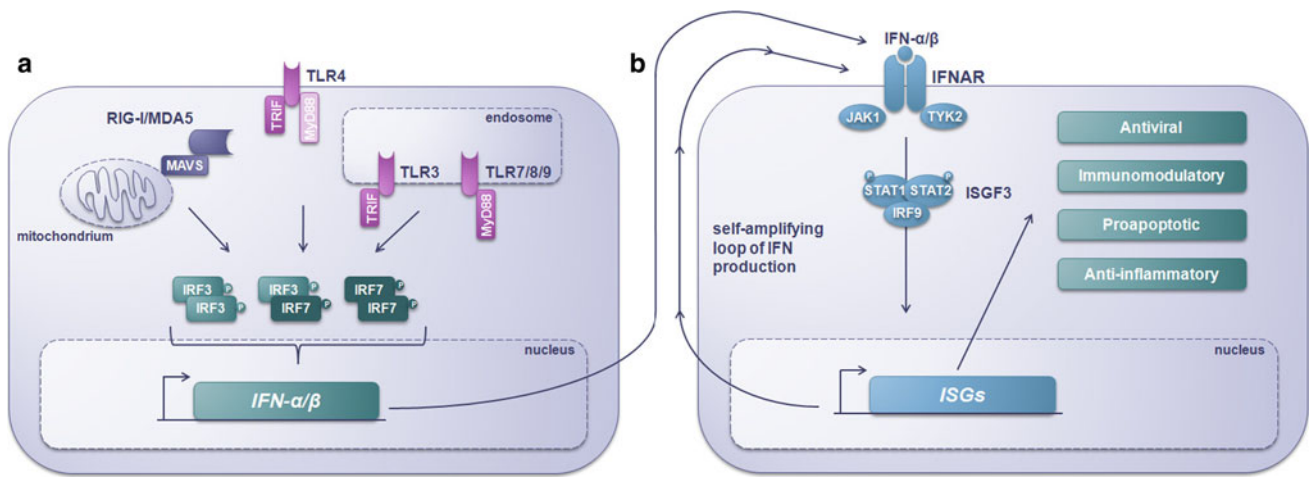


Fig. 2 Induction and effects of type I IFNs. **a** The best characterized mechanisms leading to type I IFN induction are initiated by cytoplasmic RLRs and transmembrane TLRs. Signaling pathways activated by these receptors converge in the phosphorylation of IRFs, which translocate into the nucleus and activate the transcription of type I IFN genes. **b** Type I IFNs signal through a dimeric receptor and

activate JAK1 and TYK2. In turn, these kinases phosphorylate STAT1 and STAT2, enabling recruitment of IRF9 to the so-called ISGF3 complex. This trimeric complex binds to ISREs, thereby modulating the expression of ISGs exerting antiviral, immunomodulatory, proapoptotic, and anti-inflammatory functions

In addition to RNA, sensing of cytoplasmic DNA also results in the induction of type I IFNs. Proposed DNA receptors are the DNA-dependent activator of IRFs (DAI) and the DNA-dependent RNA polymerase III [85]. The latter transcribes dsDNA into a 5′triphosphate dsRNA, which is recognized by RIG-I. More recently, the AIM2-like molecule IFI16 and other members of the DExD/H-box helicase superfamily have been described as contributing to the sensing of cytoplasmic DNA [85]. Downstream of these DNA sensors, the ER-localized stimulator of IFN genes (STING) serves as a recruitment platform to activate TBK1, which in turn phosphorylates IRF3/7, resulting in the induction of type I IFNs [86].

Transmembrane receptors

Interferon production in immune cells can also be induced by the activation of transmembrane TLRs (Fig. 2a). The expression of TLRs is mainly restricted to tissues and cell types involved in innate immunity, such as macrophages and dendritic cells (DCs) [87, 88]. Toll-like receptors recognize structurally conserved molecules derived from microbes through their LRRs. While TLR3 senses viral dsRNA, TLR7 and TLR8 recognize ssRNA. Toll-like receptor 9 detects unmethylated CpG-containing oligonucleotides, typical of microbial DNA, and TLR4 responds to LPS, a cell wall component of Gram-negative bacteria (a detailed description of TLR ligands can be found in [2, 88]). These receptors are localized either in endosomal compartments (TLR3, 7, 8, 9,) or at the cell surface (TLR3, 4). They are thus devoted to the recognition of PAMPs

upon phagocytosis or after lysis and release of material by a pathogen or an infected cell.

All TLRs except TLR3 trigger signaling cascades via MyD88. TLR3 associates instead with TRIF (TIR-domain-containing adapter inducing IFN- β), whereas TLR4 uses both TRIF and MyD88 [2]. Similarly to RLRs, engagement of the TRIF-dependent pathway downstream of TLR3 and TLR4 activates TBK1 and IKK ϵ , leading to the phosphorylation of IRFs. Type I IFN induction by endoplasmic TLR7, TLR8, and TLR9 is instead mediated by an MyD88-dependent complex including IRAK1 and IKK α , which phosphorylate and thereby activate IRF7 [89].

The main producers of type I (and III) IFNs are plasmacytoid DCs, a population of circulating DCs [90]. These ‘specialized IFN-producing cells’ are characterized by rapid and potent IFN production, which is dependent on the activation of TLR7 and TLR9. Indeed, high constitutive expression of these TLRs and of the downstream signaling molecule IRF7 leads to a very efficient coupling of ligand detection to cytokine production [91]. Thus, plasmacytoid DC are particularly important to produce systemic type I IFN, which is crucial to alert the entire organism.

Type I IFN signaling

Interferon- α and - β share a common receptor, the IFN- α receptor (IFNAR), composed of a IFNAR1 and a IFNAR2 subunit (Fig. 2b) [64]. These cytokines can signal in virtually every cell, as the receptor is ubiquitously expressed. Ligand-induced receptor dimerization leads to the auto- and trans-phosphorylation of receptor-associated tyrosine

kinases JAK1 (on IFNAR2) and TYK2 (on IFNAR1). Janus kinase 1 and Tyrosine kinase 2 then phosphorylate the intracellular domain of IFNAR, which creates docking sites for STAT1 and STAT2. These two transcription factors heterodimerize, bind to IRF9, and translocate to the nucleus (Fig. 2b) [92]. This heterotrimer [also known as IFN-stimulated gene factor 3 (ISGF3)] binds to genomic IFN-stimulated response elements (ISREs), thereby modulating the expression of numerous IFN-stimulated genes (ISGs). Interferon-stimulated genes encode factors involved in the antiviral and anti-inflammatory response, in immunomodulation, and factors endowed with pro-apoptotic and anti-proliferative activities (Fig. 2b) [61, 93].

Importantly, ISGs also code for proteins that augment IFN signaling by a positive feedback loop. Firstly, the expression of the nucleic acid receptors RIG-I, MDA5, DAI, and of TLRs is positively regulated by type I IFNs [94]. Secondly, ISGs encode signaling molecules involved in the IFN pathway, such as IRF7 and STAT1. Furthermore, all genes encoding type I IFNs contain ISREs in their promoters, resulting in a self-amplifying loop (Fig. 2b) [61, 95].

Although ISGF3 mediates the most studied and probably the major effects of type I IFNs, other STAT family members can participate in type I IFN signaling. Homodimers and heterodimers of STAT1, STAT3, STAT4, STAT5, and STAT6 can play a role downstream of IFNAR [64]. Moreover, type I IFNs have also been described to activate other signaling pathways such as mitogen-activated protein and phosphatidylinositol-3 kinases [96].

Effects of type I IFNs

The following sections focus on the antiviral, pro-apoptotic, immunomodulatory, and in particular anti-inflammatory activities of type I IFNs. Emerging evidence indicates that IFN- β and the different α -subtypes can vary in these effects [97, 98]. This may be explained by the different binding properties of IFN- α and - β to IFNAR, influencing downstream signaling [97, 99]. Therefore, in some cases, we discuss the diverging activities of β - and α -IFNs.

Antiviral effects

Type I IFNs were initially discovered and best described as effector molecules in the protection against viral infections. They have the ability to induce an antiviral state in infected, but also in neighboring cells by autocrine and paracrine effects. Interferon-stimulated genes code for proteins that target virtually all steps of the virus life cycle, including entry, transcription, and translation, and lead to viral RNA degradation.

A prime example of an antiviral effector molecule is the dsRNA-dependent protein kinase R (PKR). Upon PKR

activation, the α -subunit of the eukaryotic translational initiation factor 2 (eIF2 α) is phosphorylated, which results in the inhibition of cellular as well as viral mRNA translation [100]. Further, the translational suppression triggered by PKR is also linked to IFN-induced cell-cycle arrest and apoptosis [101–103]. Not being central to this work, we refer the reader to excellent reviews in which the antiviral effects of IFNs have been summarized [103, 104].

Immunomodulation

In addition to their direct antiviral effects, type I IFNs play a major role in modulating innate and adaptive immunity. Notably, they are involved in regulating homeostasis, survival, differentiation, and trafficking of immune cells [105].

To start with, these cytokines play an important role in promoting the maturation of DCs, which are required for efficient activation of T cells [106, 107]. In fact, type I IFNs enhance antigen presentation, in particular by increasing the expression of costimulatory and MHC class I molecules [108, 109].

Type I IFN signaling has also been described to directly act on T cells as it can induce the production of IFN- γ through activation of STAT4, thereby favoring induction and maintenance of Th1 cells [110, 111]. Some reports claim that type I IFNs are, however, not sufficient to promote Th1 differentiation as the phosphorylation of STAT4 occurs only transiently. In both human and mouse cells, IL-12 has been proven to be necessary to induce adequate levels of the transcription factor T-bet, thereby leading to Th1 polarization [112, 113]. Nevertheless, IL-18 has been described to act with type I IFNs to activate STAT4 in the absence of IL-12 [114]. Type I IFNs are likely to also indirectly contribute to Th1 differentiation. They do so by inhibiting the ability of IL-4 to promote Th2 commitment and to antagonize Th1 development [115, 116]. Similarly, IFNs are involved in the negative regulation of Th17 development [117, 118]. Interferon- β has been described to induce the expression of IL-27 via STAT1. Interleukin-27 in turn downregulates IL-17 and IL-23, the latter being required for Th17 maintenance [119, 120].

In addition, type I IFNs seem to play a role in the survival of activated CD4⁺ T cells. Despite the fact that IFNs have been described as promoting cell growth arrest and even apoptosis [121, 122], these cytokines seem to protect T cells from apoptosis induction upon antigen encounter and enhance the development of central memory-like CD4⁺ T cells [123, 124].

Type I IFNs are also able to induce efficient CD8⁺ T cell responses by promoting DC cross-presentation. This process defines the ability of DCs to take up extracellular antigens by endocytosis and present them via MHC I to CD8⁺ T cells [107]. Furthermore, the augmented MHC I

levels increase the presentation of peptides to cytotoxic T cells, thus leading to augmented recognition and killing of infected cells. Type I IFNs also support CD8⁺ T cell responses by directly enhancing effector functions, including IFN- γ secretion and expression of perforin and granzymes [125, 126]. An increase in the cytotoxic capacity has also been observed for NK cells and macrophages [127], highlighting the immunomodulatory effects of type I IFNs on these cell types as well. Notably, high levels of IL-15 induced in DCs by type I IFNs during their maturation lead to a selective stimulation and maintenance of memory CD8⁺ T cells [128, 129] and also favor NK cell development and differentiation [130]. Besides modulating T cell activation, type I IFNs also influence their migration by the induction of chemoattractants, such as CXCL10 and CXCL11 [131].

Direct and indirect effects of type I IFNs have also been described for B cells. These cytokines can enhance antibody production by promoting isotype switch and by inducing two TNF-family members important for B cell survival and homeostasis, namely B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) [132, 133]. In addition, treatment with type I IFNs has been shown to protect B cells from apoptosis [134]. Therefore, these cytokines seem to also contribute to the induction and maintenance of a potent humoral immune response [132]. Altogether, type I IFNs play a crucial role in the regulation of immune responses, by directly affecting functions of lymphocytes and antigen presentation.

Apoptosis

In contrast to the aforementioned anti-apoptotic effects in lymphocytes, type I IFNs have often been described to have anti-proliferative activity and to sensitize infected or transformed cells to apoptosis [122, 135]. These anti-proliferative effects were correlated with an inhibition of the NF- κ B pathway [136], which, however, requires higher doses of IFNs than the induction of an antiviral state.

Although type I IFNs are insufficient per se to induce death in most cell types, they can sensitize cells to apoptosis via upregulation of caspases, pro-apoptotic, and tumor suppressor genes [137–139]. Furthermore, the induction of multiple antiviral proteins affects viral replication by significantly interfering with essential cellular processes. As an example, several studies have assigned a pro-apoptotic role to the IFN-inducible PKR, which is in part linked to the translation blockade induced by this kinase [140–142]. Type I IFNs have also been shown to have in vivo anti-tumor effects by promoting cell cycle arrest and apoptosis in transformed cells [135, 143, 144].

Moreover, engagement of RIG-I and MDA5 is known to induce pro-apoptotic signaling in addition to transcription

of IFNs themselves [145, 146]. Similarly, apoptosis induction has been described downstream of TLR3 and 4 [142, 144, 147]. Interferons positively regulate the expression of these receptors, thereby rendering cells further susceptible to death. Altogether, certain effects of type I IFNs might cumulate, thereby sensitizing cells to apoptosis.

Autoimmunity and pro-inflammatory effects

Although beneficial for host immune responses, type I IFNs are also involved in the pathogenesis of certain diseases. Type I IFNs marry immuno-stimulatory to pro-apoptotic effects, which together make these cytokines particularly suited to favor autoimmune manifestations. Indeed, elevated production of inflammatory cytokines, such as type I IFNs, activates DCs. Moreover, these cytokines can promote tissue damage, therefore inducing the release of apoptotic material, which can be further phagocytosed and presented by activated antigen-presenting cells. These effects might be detrimental in individuals prone to develop autoimmunity due to an increased risk of activating autoreactive lymphocytes [148–150].

First indications that type I IFNs might be key players in autoimmunity came from the observation that the administration of these cytokines as antiviral or anti-proliferative therapy was associated with autoimmune manifestations [149, 151]. However, most of the time, symptoms resolved when the therapy was stopped, indicating that type I IFNs may initiate the development of autoimmunity but other factors are required to sustain the disease [97, 149]. Administration of IFN- α more than IFN- β was found to be associated with the onset of such autoimmune manifestations, which supports the hypothesis that there are differences in the action of type I IFN subtypes. Accordingly, reports suggest a more pronounced pathologic and driving role for systemic IFN- α in the development of autoimmunity [97, 98].

Indeed, an ‘IFN signature’, characterized by elevated IFN- α levels and expression of type I IFN-regulated genes, is found in systemic lupus erythematosus (SLE) patients and correlates with immune cell activation and clinical disease manifestations (Table 2). Systemic lupus erythematosus is a systemic autoimmune disorder that can affect any part of the body. This disease is characterized by the deposition of immune complexes leading to inflammation, and one of the pathologic features and diagnostic criteria of SLE is the presence of anti-nuclear antibodies.

Dying cells release cellular material, which is then recognized by PRRs, inducing an inflammatory response. Released intracellular components are also antigenic determinants for B cells, triggering antibody production against self-DNA and -RNA. This leads to the formation of immune complexes, which may even promote delivery of

Table 2 Current understanding of the role of IL-1 and type I IFNs in selected inflammatory disorders

	Disease	Main trigger, involved genes	Role for IL-1	IL-1-blocking agents in patients	Refs	Rec. IFN therapy	Refs
Monogenic auto-inflammatory diseases	FMF	MEFV mutations	a	a	[288–295]	a	[296]
Polygenic auto-inflammatory diseases	IBD	NOD2, ATG16L1, IRGM, IL-12R β , IL-23R, STAT3, IL-10R β mutations	a	n.d.	[304], [306]	a	[310–312]
Mixed pattern diseases	Behçet	HLA-B51 association, IL-12R β , IL-23R, IL-10 variants	b	a	[295], [318]	a	[319]
Atopic disorders	Allergy	Allergens, complex	a	n.d.	[322–332]	a	[336]
Autoimmune diseases	SLE	IRF5, STAT4, TLR7, TYK2, IRAK1, IKK- ϵ variants	b	b	[344–347]	n.d. (pathological role)	
	MS	Specific HLA alleles, complex	a	n.d.	[20], [241–244]	a	[228, 229]

refs references, rec recombinant, n.d. not determined, a established, b potential role

nucleic acids to immune cells, therefore enhancing IFN production [152–154]. The overproduction of type I IFNs results in a chronic activation of DCs, which further sustains the response of autoreactive lymphocytes in predisposed individuals, thus promoting the vicious circle [133].

The specific nature of the autoantigens in SLE may be instrumental in dictating the deleterious role of IFN- α in this disease. Cytoplasmic delivery of nucleic acids leads to activation of innate immune sensors, including the AIM2 inflammasome, whose components are further induced by type I IFNs, as discussed below. Under these circumstances, AIM2 inflammasome engagement may lead to enhanced IL-18 production, which has been involved in disease progression [155]. Interestingly, AIM2 belongs to the *Ifi200* gene family, which in the mouse clusters within the *Nba2* lupus susceptibility locus [156].

Although the strongest genetic factor associated to SLE is the human leukocyte antigen (HLA) region on chromosome 6 [157], many polymorphisms map to genes of the type I IFN pathway, further suggesting that these cytokines might play a detrimental role in this disease. In fact, IRF5 and TYK2 polymorphisms have been linked to increased risk of SLE [97, 158]. Moreover, a pathological role of type I IFNs is supported by studies from mouse lupus models showing that genetic ablation of *Ifnar1* leads to less severe autoimmune manifestations [159, 160]. Against this commonly accepted view, few recent reports claim a protective role for type I IFNs in SLE, a surprising finding that requires more in-depth analysis [161, 162].

An IFN signature could also be detected in other autoimmune diseases like Sjögren's syndrome and in a subgroup of rheumatoid arthritis patients [97, 163, 164]. Rheumatoid arthritis is mainly characterized by inflammation of the joints and autoantibody production, while Sjögren's

syndrome is a lymphoproliferative disease characterized by xerostomia (dry mouth) and xerophthalmia (dry eyes). Whereas, in SLE, a pathologic role for type I IFNs is established, a causative role for these cytokines in rheumatoid arthritis and Sjögren's syndrome has not been determined, leaving open the possibility that they are produced in the inflammatory context as anti-inflammatory mediators [97, 163, 164]. In the case of Sjögren's syndrome, this is supported by the fact that elevated levels of IL-1Ra have been detected in the cerebrospinal fluid of patients, and that oromucosal administration of IFN- α significantly increased unstimulated whole saliva flow, thus having a modest therapeutic effect [165, 166]. In the case of rheumatoid arthritis, a possible anti-inflammatory function of type I IFN is suggested by the protective role of IFN- β in animal models of collagen-induced as well as antigen-induced arthritis [167–169]. Moreover, an open phase I study, in which 12 patients with rheumatoid arthritis were treated with IFN- β subcutaneously, demonstrated modest clinical improvement [170]. However, a double-blinded placebo-controlled trial of IFN- β -1a (recombinant IFN- β produced in mammalian cells) in rheumatoid arthritis patients did not show any significant difference in radiological scores or clinical outcomes [171].

Anti-inflammatory effects of type I IFNs

Experimental evidence

Anti-inflammatory effects in sterile and infectious models

Multiple lines of evidence indicate that type I IFNs also exert anti-inflammatory functions. It has been known for a

long time that type I IFN administration can be beneficial in a number of sterile inflammatory models, such as skin reactivity test, collagen-induced arthritis, or allotransplant rejection [59, 172–174]. Interferon- β also leads to a reduced reaction upon neutrophil-induced blood–brain barrier rupture [175] and in experimental autoimmune encephalomyelitis (EAE) [176], both models mimicking inflammatory aspects of the central nervous system found in MS. Interestingly, IFN has a direct stabilizing effect on cerebral endothelial cells lining the blood–brain barrier in *in vitro* and EAE models [176, 177]. These data suggest that the decreased passage of autoreactive lymphocytes through the endothelium might be one of the modes of action of IFN- β in MS, as discussed later.

In addition, while in virtually all viral and most bacterial infections type I IFNs are advantageous or even required for resistance [178], recent evidence shows that in some instances IFN induction can also have unfavorable outcomes. On the one hand, these effects can be due to a disproportionate production of type I IFN leading to an excessive inflammation, such as for cerebral malaria [179]. On the other hand, anti-inflammatory effects can dampen the immune response, which results in an exacerbated infection. This is the case for *Francisella tularensis* [180] and *Listeria monocytogenes*, as well as for the protozoan *Leishmania amazonensis* [181–183]. These infections were found to be less detrimental and also have reduced infectious burden in *Ifnar*^{-/-} mice, showing that IFNs can indirectly favor microbial outgrowth.

Mycobacterium tuberculosis infection was also shown to be less severe in *Ifnar*^{-/-} mice, with similar or reduced bacterial burdens as compared to control mice [184, 185]. Of note, patients infected with *M. tuberculosis* show an IFN signature, which might therefore have a pathogenic role during infection [186].

Finally, another line of evidence for the anti-inflammatory effects of IFNs comes from superinfections. In most cases, influenza-related deaths do not derive from the viral infection per se but from bacterial superinfections. A recent study revealed that secondary *Streptococcus pneumoniae* infections are worsened by the anti-inflammatory effects of influenza-induced type I IFNs [187]. Similarly, fungal infections can be exacerbated by type I IFNs. Mice pretreated with type I IFN-inducing RNAs are more susceptible to candidiasis than untreated controls, an effect abolished in *Ifnar*^{-/-} mice [188–190].

Type I IFN-dependent inhibition of IL-1 production

The first molecular mechanisms for these anti-inflammatory phenomena was proposed in 1990 when Schindler et al. showed that IFN- α has the ability to reduce IL-1 production [191, 192]. As discussed above, production of

active IL-1 has to fulfill several conditions, and its activity is further regulated by the existence of a natural antagonist and a decoy receptor, IL-1RII. Additionally, IL-1 synthesis and inflammasome function are targeted by several negative regulatory mechanisms (reviewed in [46, 193]). Interestingly, type I IFNs have the ability to suppress pro-IL-1 levels and decrease the activity of NLRP1 and NLRP3 inflammasomes [188]. The effects of type I IFNs on IL-1 production have been known for decades, and several studies contributed to the understanding of the underlying mechanisms, as schematically illustrated in Fig. 3 [59, 188, 192, 194–196]. Of note, both IFN- α and - β are able to exert this anti-inflammatory effect.

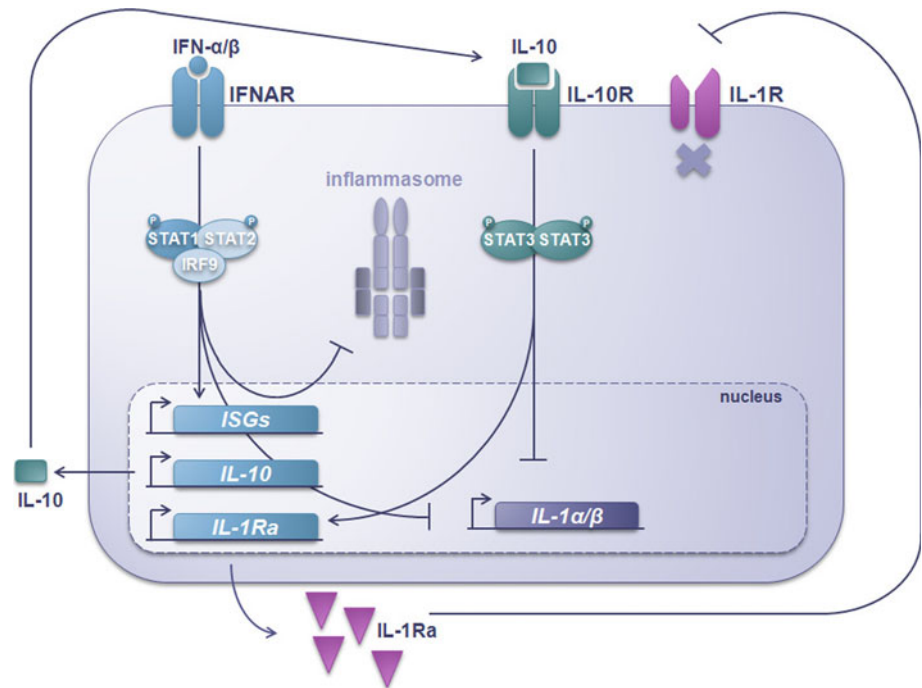
In addition to reducing the expression of a number of inflammatory genes, including TNF and the IL-12/IL-23 subunit p40, type I IFNs reduce the levels of IL-1 α and pro-IL-1 β [120, 188, 192, 194–198]. Suppression of IL-1 α and - β has been reported to occur both at the transcriptional as well as at the translational level [199, 200].

It recently became clear that this mechanism is relevant to infectious diseases. In fact, IL-1 is instrumental for resistance to both *M. tuberculosis* infection and systemic candidiasis, suggesting that IFN-dependent suppression of IL-1 production might be one mechanism explaining the detrimental effects of type I IFN in these models [184, 199, 201–204]. Interestingly, in the context of *M. tuberculosis* infection, adaptive immune cell-derived type II IFN has also been found to suppress IL-1 production [184]. Although the anti-inflammatory contribution by IFN- γ is controversial, emerging evidence highlights an inhibitory role of type II IFN on IL-1 levels, which seems to be dependent on the context and on the target cell type [184, 188, 192, 205].

Additionally, type I IFNs induce the expression of anti-inflammatory genes, such as IL-1Ra and IL-10 (Fig. 3) [194, 195, 206]. In fact, type I IFNs synergize with LPS to induce IL-10 [188, 207–210]. In the human system, this effect is thought to occur through the transcription factor STAT3 or the PI3K pathway [211, 212]. However, the use of macrophages derived from different knockout mice indicated that IL-10 induction downstream of type I IFNs depends on STAT1, most likely as part of the canonical signaling complex comprising STAT2 and IRF9 [188].

Interleukin-10 is one of the major anti-inflammatory cytokines, which increases IL-1Ra transcription and negatively regulates IL-1 α and pro-IL-1 β levels (Fig. 3) [188, 208, 209, 213, 214]. We found that the inhibitory effects of type I IFNs on pro-IL-1 levels in macrophages are in part achieved through autocrine IL-10 signaling [188]. Interleukin-10-dependent regulation of pro-IL-1 has been shown to mainly occur at the transcriptional level [208, 213, 214]. Furthermore, as IL-10 induces IL-1Ra [214], the question arises as to which extent the IFN-dependent

Fig. 3 Type I IFNs inhibit IL-1 production. Type I IFN signaling suppresses caspase-1-dependent IL-1 β maturation by a STAT1-dependent mechanism, which might involve de novo transcription of a target protein. In addition, type I IFNs induce the expression of IL-1Ra, the natural IL-1R antagonist, and the anti-inflammatory cytokine IL-10. In murine macrophages, enhancement of IL-10 production by type I IFNs also requires the transcription factor STAT1. Interleukin-10, in turn, contributes to the induction of IL-1Ra and to the decrease of pro-IL-1 levels in a STAT3-dependent manner



IL-1Ra induction could also be mediated by autocrine IL-10 signaling.

Emphasizing their highly complex role in the balance between inflammatory and anti-inflammatory effects, it has been shown that type I IFNs have the ability to both positively and negatively regulate inflammasome activity. In fact, IFNs play an important pro-inflammatory role, for instance in sensitizing cells to certain bacterial inflammasome activators such as *F. tularensis*, and in the maintenance of AIM2 expression [215, 216]. Interferons are thus favoring the activity of the DNA-sensing AIM2 inflammasome, which is important upon infection by cytosolic bacteria and DNA viruses [215, 216]. In addition, caspase-1 itself, although being constitutively expressed, is a transcriptional target of type I IFN [155, 217]. Interestingly, IFNs not only seem to alter the activity of different inflammasomes but also the abundance of their substrates; while IL-1 α and pro-IL-1 β levels are decreased, the amount of pro-IL-18 is augmented [155, 198].

In contrast, exogenous type I IFNs are clearly anti-inflammatory, suppressing the activity of the NLRP3 inflammasome, which is a sensor for a broad range of stimuli [188]. This effect is transient and requires higher doses of IFNs than the one on pro-IL-1, at least in macrophages [188]. Although experimental data indicate that this inhibitory effect requires the transcription factor STAT1, the underlying mechanisms currently remain unclear. Interestingly, it was recently suggested that IFI16, which is strongly induced by type I IFN treatment, might be involved in this process [218]. In fact, knockdown of this

DNA-binding protein in THP1 cells, a monocytic myeloid cell line, clearly increased the basal caspase-1 processing, indicating an augmented inflammasome activity.

Altogether, the complex effects of type I IFNs on inflammasome activity suggest that these cytokines favor the activity of the AIM2 inflammasome, possibly in concert with the production of IL-18, while impairing the activity of the NLRP3 inflammasome along with the production of IL-1. In the case of a viral infection, this might hinder development of a Th17 and favor a tailored Th1 type of response.

Established type I IFN-based clinical treatments

Therapeutic use of type I IFNs in viral and neoplastic diseases

Type I interferons are classical antiviral effector molecules. It is therefore not surprising that they have been studied as potential therapies for a number of viral diseases. Interferon- α is currently used in combination with other medications as a standard treatment for hepatitis B and C infections and may also reduce the occurrence of associated hepatocellular carcinoma [219–221]. Moreover, IFN- α was shown to be effective against human herpesvirus 8-driven Kaposi sarcoma and genital warts caused by papilloma viruses [222, 223]. Although its antiviral properties could per se explain the beneficial effects of IFN- α in these virus-associated neoplasms, the synergy with its ability to promote apoptosis, modulate immune functions,

and alter tumor microenvironment is likely to contribute to this outcome [224]. On the one hand, IFN-dependent reduction of viral load could alone decrease inflammation by removing viral-derived PAMPs. On the other hand, IFN- α has also been successfully used in the therapy of malignancies, which are not considered to be associated with viral infections, where its effects are not mediated by the control of viral load. In particular, beneficial effects were observed in hairy cell leukemia, chronic myeloid leukemia, and melanoma [224–226].

Therapeutic use of type I IFNs in multiple sclerosis

Furthermore, for almost 20 years, IFN has been known to reduce inflammation in MS (Table 2) [97]. Multiple sclerosis is an inflammatory autoimmune disorder of the brain and the spinal cord and represents the second most common cause of neurological disability in young adults, exceeded only by trauma [227]. Affected patients suffer from relapses of neurological deficits that affect the white matter of the brain and the spinal cord. These are caused by autoreactive T cells that attack the myelin sheath, resulting in defective neural transmission. At least in the early stage of the disease, there is a more or less full recovery after each relapse, a form named relapsing-remitting phase (RR-MS). However, more than 80 % of patients with RR-MS, after 10–15 years, see their neurological symptoms progress unremittingly, without any relapses. At this stage, one speaks of secondary-progressive MS.

Interferon- β is used for the treatment of patients suffering from a first episode suggestive of MS (clinically isolated syndrome) and of patients with RR-MS. Pivotal studies have shown a reduction in the frequency of relapses by about 30 % over 2–3 years of treatment with IFN (reviewed in [228]). In a large clinical trial, administration of IFN- β was shown to marginally, but still significantly, decrease the rate of accumulation of disability over 3 years [229]. However, once the secondary progressive stage of the disease is reached, these therapies lose their efficacy, suggesting that IFN- β acts more on the inflammatory than on the neurodegenerative phase of the disease.

Interferon- α has also been studied as a treatment modality in MS. In one small study, IFN- α -2a (recombinant IFN- α produced in *Escherichia coli*) has been found to be effective in reducing exacerbations in MS patients as compared to placebo [230]. Additional encouraging findings have been reported in a trial of natural human leukocyte IFN- α in MS patients [231]. However, several reports have appeared on the potential of recombinant IFN- α to exacerbate the course of MS, including in patients with the progressive form of the disease [232, 233]. An MS-like syndrome has also been reported in a patient with

chronic myeloid leukemia treated with IFN- α [234]. Thus, currently, IFN- α is not recommended as a treatment for MS.

Autoreactive lymphocytes are traditionally considered to be the primary immuno-pathogenic mechanism in MS for several reasons: (1) the adoptive transfer of myelin-specific autoreactive T cells induces EAE in mice [235], (2) perivascular cuffs of T lymphocytes are found in the center of demyelinating lesions in the white matter in human MS [236], (3) there is an oligo-clonal expansion of CD8⁺ T cells in brain lesions of MS patients, suggesting that these cells recognize an antigen in the central nervous system [237], (4) the central role of T cells is supported by genetic association of specific HLA alleles with MS [228], and (5) B cell infiltration and immunoglobulins are detected in MS lesions [238].

However, despite a sustained effort in research, the precise etiology(ies) of MS remain(s) to be established. Comprehensive studies of the adaptive immunity have not provided the whole picture of its immuno pathogenesis, which points to the fact that MS is a complex and/or heterogeneous disease. In particular, no consistent auto-antigen has been found. Therefore, an alternative model proposes a pivotal role of a dysregulated innate immune response that may impact the adaptive immune system by the generation of autoreactive T and B cells [239, 240]. Interestingly, experimental evidence highlights a role for inflammasome components and IL-1 in EAE progression, as mice deficient for caspase-1, ASC, NLRP3, IL-1RI, or IL-1 α/β were significantly protected, while EAE in animals deficient for IL-1Ra showed exacerbated progression [20, 241–244]. The fact that IFN- β targets the innate at least as much as the adaptive arm of the immune system supports the aforementioned hypothesis [245].

Proposed mechanisms of IFN- β efficacy in multiple sclerosis

Originally, the efficacy of IFN- β in MS was attributed to its ability to decrease inflammatory cytokine production while increasing the expression of anti-inflammatory mediators [191, 192, 194–198, 206]. Of note, monocytes derived from IFN- β -treated MS patients produced significantly lower amounts of IL-1 β upon ex vivo challenge with inflammasome activators, as compared to monocytes from healthy donors [188]. This suggests that the efficacy of IFN- β treatment might in part be caused by this anti-inflammatory mechanism. Moreover, the pro-apoptotic effects on activated autoreactive T cells, which cause damage in the central nervous system, were believed to contribute to IFN- β effectiveness in MS treatment [192, 194, 195, 246]. Later studies added IFN- β -activated STAT3 signaling as a main player in the anti-inflammatory

effects. It does so by promoting the expression of Src homology phosphatase-1, an inhibitor of cytokine signaling, and blocking the activation of inflammatory mediators, such as NF- κ B and STAT6 [247–249].

Moreover, IFN- β has been proposed to negatively influence trafficking of immune cells to the inflamed central nervous system. One mechanism involves the inhibition of lymphocyte egress from lymph nodes. Sphingosine 1-phosphate receptor-1 is required for this process and is negatively regulated by type I IFNs, thus reducing the number of circulating effector T cells [250]. In addition, IFN- β also decreases the ability of T cells to migrate to the central nervous system by stabilizing the blood–brain barrier, downregulating integrin expression on T cells, and affecting the function of matrix metalloproteases, which are important for cell migration and adhesion [177, 251–254].

More recently, the Th17-opposing effects of type I IFNs have gained attention. In fact, studies in MS patients and EAE have shown that Th17 cells are involved in these autoimmune manifestations [255]. Interferons could therefore also exert their beneficial effects in the treatment of MS by hindering the development of Th17, a possible mechanism being the reduction of IL-1 levels [120].

Only about two-thirds of MS patients respond well to treatment with IFN- β in terms of decreased relapse rates and fewer new brain and spinal cord lesions [256]. Identifying so-called ‘non-responders’ prior to the initiation of therapy is of obvious clinical interest, and multiple studies have looked at ways to predict a patient’s ‘responder’ status. One study of MS patients treated with IFN- β demonstrated that non-responder and responder phenotypes differ in their *ex vivo* gene expression profiles as assessed by magnetic resonance imaging scanning and clinical disease activity. In particular, *IL-8*, an important chemotactic mediator recruiting neutrophils to sites of inflammation, was found to be significantly downregulated *ex vivo* and *in vitro* in IFN- β treated responders but not in non-responders. In addition, expression of a number of genes involved in either regulation of proliferation or apoptosis were modified in responders towards an anti-proliferative pro-apoptotic state. In non-responders, however, this shift was either absent or observed to a significantly lesser degree [257]. Another study has suggested that high concentration of IL-17F, another member of the IL-17 family, in the serum of patients with RR-MS is associated with non-responsiveness to IFN- β therapy [258]. Furthermore, it has been proposed that, in certain subpopulations of MS patients, IFN- β treatment could worsen the disease [259]. This differential response to therapy highlights the fact that MS is a heterogeneous disease and that other factors, such as genetic ones, are

important players in the susceptibility to the treatment [238].

Adverse effects and drawbacks of IFN treatment

Just as any treatment, type I IFNs can have side effects. Up to 75 % of patients treated with IFN- β experience flu-like symptoms such as fever, headache, muscle pain, fatigue, and chills [260]. The most common observed laboratory abnormalities are elevation of liver enzymes and leukopenia. These changes are seldom serious, generally reversible, and rarely warrant the discontinuation of the treatment [261–267]. However, reports on fulminant liver failure as well as on unmasking of pre-existing autoimmune hepatitis or psoriasis do exist [268–270]. Hence, the regular monitoring of liver enzymes is recommended.

Reports of depression associated with IFN therapy (both IFN- α and - β) are well known. However, controversy still exists on whether it is caused by IFN. For instance, depression is quite common in MS patients irrespective of the treatment they are undergoing. A recent review has described 11 cases of severe depression with suicide attempts among patients treated with IFN- β who had no prior psychiatric history [271]. Yet, other studies found no evidence to support the claim that IFN- β can cause or exacerbate depression [272].

Occasionally, IFN therapy can lead to the development of autoimmune manifestations in the form of SLE, arthritis, and diabetes [97, 149, 151]. However, most of these complications resolve upon discontinuation of treatment. Rarely, a syndrome resembling thrombotic thrombocytopenic purpura with fever, thrombocytopenia, and renal failure has been reported in MS patients treated with IFN- β -1a [260].

In addition, chronic therapy with IFN- β can be associated with development of antibodies neutralizing IFN. In initial trials of different IFN- β preparations in MS patients, frequencies of neutralizing antibodies varied from 7 to 42 % [262, 273–275]. However, these percentages often depend on the method used to detect antibodies. It has previously been reported that up to 80 % of serum samples from patients treated with IFN- β for more than 1 year contained measurable amounts of neutralizing antibodies when assessed with an optimized assay [276]. It has been demonstrated that the presence of antibodies against IFN- β in the sera of MS patients may reduce the clinical efficacy of this medication as manifested by increased relapse rates [277]. Switching the therapy is recommended for neutralizing antibody-positive patients that have experienced worsening of their disease course. However, provided that the patient is without exacerbations on IFN- β treatment, it is generally not necessary to check the neutralizing antibody status.

Potential clinical treatments based on type I IFN

Excessive inflammatory reactions can originate from a disproportioned inflammatory response or from a malfunctioning control mechanism, and can have an acquired or a genetic origin. In fact, we define a wide range of pathological manifestations with the term ‘inflammatory disorders’, all sharing inflammatory features, but resulting from profoundly different causes [278]. Thus, the spectrum of inflammatory diseases spans from pure ‘auto-inflammatory’ ones, which are disorders without any involvement of the adaptive immune system, to classical autoimmune pathologies.

The origin of several auto-inflammatory diseases can be solely attributed to deregulated IL-1 signaling [27]. This is the case for diseases such as cryopyrin-associated periodic syndromes (CAPS; which include: familial cold auto-inflammatory syndrome, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease), where activating mutations within the *NLRP3* gene lead to constitutive inflammasome activity [279]. The pathological role of excessive inflammasome activity and IL-1 signaling in this disorder has been irrevocably proven by the therapeutic efficacy of agents blocking IL-1 [280–285]. Given the clear molecular basis and the straightforward therapeutic approaches, we do not discuss such auto-inflammatory disorders in this review. Instead, we focus on diseases with more complex origin, with IL-1 being involved but not being the unique cause of the pathogenesis, and where novel therapeutic approaches are needed.

In the following paragraphs, we therefore discuss representative disorders with regard to the role of type I IFNs, inflammasomes and IL-1 (as summarized in Table 2).

Familial Mediterranean fever

Familial Mediterranean fever (FMF) is manifested by fever episodes along with local inflammatory reactions such as peritonitis, arthritis, skin rashes, and in some cases amyloidosis. Patients bear mutations in the Mediterranean fever (*MEFV*) gene, also known as pyrin, and such variants are encountered with higher frequency in populations from the Mediterranean basin and the Middle East [286, 287]. Although to date an excessive IL-1 production in FMF patients has not been consistently measured and the nature of mutations affecting pyrin is not firmly established, it is clear that these patients respond to IL-1 blocking biologics [27, 288–295]. Interestingly, IFN- α treatment was also found to be promising in the management of colchicine-resistant FMF patients [296]. This suggests that the ability of type I IFN to interfere with IL-1 production may be relevant in this therapeutic context.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a heterogeneous group of inflammatory disorders of the intestinal tract, including Crohn’s disease and ulcerative colitis. Crohn’s disease is characterized by discontinuous and transmural inflammatory manifestations. In 2001, two independent studies showed a clear association of this disease with variants of NOD2, a member of the NLR family [297, 298]. Later studies identified a number of other genes as hotspots for mutations, including *IL-23R*, *STAT3*, immunity-related GTPase family M (*IRGM*), and autophagy-related 16-like 1 (*ATG16L1*) [299–303]. Nucleotide-binding oligomerization domain-containing protein 2 (NOD2), immunity-related GTPase family M protein (IRGM) and autophagy-related protein 16-1 (ATG16L1) control autophagy, which interestingly seems to be an important negative regulator of inflammasome activity as shown in IBD models [304–306]. Furthermore, *Atg16L1*-deficient mice show increased intestinal inflammation and IL-1 secretion [304, 306].

Whereas in Crohn’s disease the inflammation can be found anywhere in the digestive tract, ulcerative colitis is characterized by an inflamed large intestine and rectum, only in some cases spreading to the small intestine. A direct cause of ulcerative colitis is so far not known, but environmental factors, immune dysfunction, and a presumed genetic predisposition were proposed to contribute to disease pathology. Interestingly, *IL-23R*, and *STAT3* are common risk loci associated with both ulcerative colitis and Crohn’s disease. Interleukin-23R also signals through the transcription factor STAT3, clearly identifying the IL-23 pathway as a key player in the development of IBD. Interleukin-23 plays a very important role in Th17 responses and has been associated with autoimmune disorders, thus highlighting the contribution of the adaptive immune branch to this disease. However, STAT3 is also implicated in signaling downstream of the anti-inflammatory IL-10, and several reports strongly link IBD to mutations affecting IL-10 signaling [301, 307, 308].

Besides the classical anti-inflammatory treatments, anti-TNF biologics have been successfully used in the management of IBD, and shown to prevent deleterious tissue damage [309]. Interestingly, type I IFNs have been reported to be beneficial in the treatment of ulcerative colitis [310, 311]. A proposed mechanism is the shift towards a Th1 polarization mediated by type I IFNs in a Th2-predominant disease like ulcerative colitis [312].

Behçet disease

Behçet disease is a chronic multifocal inflammatory disorder with mucocutaneous, ocular, vascular, skeletal, and central nervous system manifestations. Strong associations

with specific HLA alleles have been identified, and also, albeit less pronounced, with IL-10 and IL-23 signaling pathways [313, 314]. Despite the strong link to certain HLAs and the important presence of CD4⁺ T cells in inflamed areas, direct contribution by these HLAs to a potential autoreactive response has not been determined [315].

For patients refractory to traditional immunosuppressive and anti-inflammatory therapies, encouraging results have been observed using TNF and IL-1 antagonist, and, interestingly, IFN- α [295, 316–319]. Therefore, both IL-1 inhibition and type I IFN treatment are helpful for the management of Behçet disease, suggesting that part of type I IFN efficacy in this context might be due to its suppression of IL-1 production.

Atopic disorders

Allergies are frequent inflammatory disorders originating from both genetic and environmental factors. One of the hypotheses to explain the widespread prevalence of these disorders in developed countries relies on the hygienic habits adopted by our society. Under these circumstances, the immune system would compensate its inactivity towards pathogens by attacking otherwise inert antigenic determinants, such as pollen-derived ones [320]. Nonetheless, several allergens are endowed with enzymatic functions, thus having immuno-stimulatory properties [321].

Atopic responses can be found in different tissues, including skin, airway mucosa, and conjunctiva, and are associated with Th2 polarization. In fact, Th2 inflammatory cytokines promote all the typical features of allergic reactions, such as excessive production of immunoglobulin E, mast cell activation, and eosinophilia. Antibody-allergen complexes are crucial to crosslink Fc-receptors on mast cells, thus leading to the release of pre-stored granules containing, among other substances, histamines.

Multiple links between IL-1 and allergy have been reported. Firstly, IL-1 supports the production of several chemokines and cytokines, which are involved in atopic reactions, and can synergize with other Th2 cytokines to activate mast cells [321–323]. Secondly, IL-1 is detected upon allergen challenge, and mast cells are capable of producing bioactive IL-1 [324, 325]. Besides their role in Th17 differentiation, inflammasome activators have also been suggested to promote Th2-biased polarization, although a specific role for inflammasome or IL-1 in this process has not been unambiguously shown [326–335]. Interestingly, IFN treatment alleviates asthma; this could rely on a type I IFN-induced Th2 to Th1 shift, and the suppression of IL-1 production could also contribute to this effect [336].

Cancer

Our understanding of the interplay between inflammation and cancer has profoundly changed. A decade ago, an increased inflammation within tumor environment was perceived as a potentially beneficial feature, able to attract and activate immune cells. However, there is now increasing evidence that inflammation can also exert detrimental effects, favoring tumor growth, angiogenic switch, and metastasis [337]. This makes IL-1 a double-edged sword, which in some settings favors tumor regression, but in others helps its progression (for a more detailed discussion, see [46, 338]).

Interferon- α therapy has proven efficacious for treating several virus-associated tumors, myeloproliferative disorders, hairy cell leukemia, and melanomas, particularly ulcerated ones, as discussed in the section “[Therapeutic use of type I IFNs in viral and neoplastic diseases](#)” [224, 226]. Besides its pro-apoptotic features, the anti-angiogenic properties of type I IFNs could play an important role in the case of solid tumors [339].

Interestingly, the properties of IL-1 in promoting myeloproliferation through positive regulation of granulocyte-macrophage colony-stimulating factor, and in induction of vascular endothelial growth factor have been consistently reported [14, 340–343]. This suggests that the action of IFN- α on IL-1 production might also contribute to the suppressive effects of IFNs on myeloproliferative disorders and angiogenesis.

Concluding remarks

As discussed, IFN therapies are effective in the management of viral, malignant, and autoimmune disorders. It goes without saying that in diseases of viral origin, such as hepatitis, the contribution by IFNs in controlling viral load is crucial. Nonetheless, suppression of certain inflammatory components can be beneficial in all these diseases. Indeed, the anti-inflammatory effects of IFN- α and - β have been recognized in sterile and infectious experimental models as well as in the clinic. The strongest evidence for the surprising anti-inflammatory role of type I IFNs comes from the treatment of MS, where pro-apoptotic, immunomodulatory, and anti-inflammatory effects of IFN- β converge to a beneficial outcome. Whereas IFN- β is virtually uniquely used in the treatment of MS, the therapeutic administration of IFN- α ranges from viral infections to tumors. However, a comprehensive analysis of the possible molecular mechanisms behind this divergent use of type I IFNs is so far missing.

One important feature of inflammatory pathologies resides in the nature of the inflammation; at one extreme, we can place disorders of pure innate origin. In many of

these pathologies, IL-1 plays an important role, as witnessed by the efficacy of treatments targeting this cytokine. It is, however, important to mention that in some auto-inflammatory syndromes, a possible contribution of auto-reactive T and B cells has so far been disregarded. At the opposite end of the inflammatory disease spectrum are rare monogenic autoimmune disorders affecting the adaptive immune system, such as autoimmune polyendocrinopathy syndrome. Inbetween these extremes, there are disorders that involve both innate and adaptive immune cells. Recently, the effectiveness of anti-IL-1 treatment is becoming appreciated in disorders with such complex etiology as Behçet or Type 2 diabetes. These observations encourage extending the use of anti-IL-1 agents, which are specific, safe, and well tolerated [283–285].

In addition, experimental results point to a crucial contribution of IL-1 in a number of inflammatory syndromes, including those currently treated with IFNs. Given the strong ability of type I IFNs to dampen IL-1 production, it is conceivable that IFNs might be considered as anti-inflammatory agents in a broader range of complex inflammatory diseases where a role for IL-1 has been reported. The combined administration of type I IFNs together with IL-1 neutralizing agents might enforce the anti-inflammatory properties of IFNs, thus increasing treatment efficacy. Possibly, this may also allow the reduction of the administered dose of IFNs, thereby improving tolerability.

However, the effects of IFNs are pleiotropic and their use warrants caution because of their potential side effects. Instead of broadening the use of type I IFNs in the clinic, we might take advantage of the growing knowledge on the multiple anti-inflammatory effects of type I IFNs and use agents that specifically target selected pathways downstream of these cytokines. Such approaches might represent valuable alternatives to the use of IFNs. We have highlighted how therapies targeting IL-1 signaling can mimic one of the important anti-inflammatory effects of IFNs. Another example are sphingosine analogs, which have been recently approved for MS treatment and that act by sequestering lymphocytes within lymph nodes. Finally, it is possible that IL-1-blocking agents could be well complemented by or even synergize with treatments that target other specific aspects of inflammatory diseases and could therefore provide an even more efficient therapy.

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