

Interferons and inflammasomes: Cooperation and counterregulation in disease



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Interferons and the IL-1 family of cytokines have important roles in host defense against invading viruses and bacteria. Inflammasomes, multimeric cytosolic sensors of infection, are required for IL-1 β and IL-18 processing and release. Interferons, IL-1 β , and IL-18 are also implicated in autoimmune disease and chronic inflammation. Although independent but complementary pathways induce these cytokine subsets during infection, in some circumstances the cross-talk between these key inflammatory mediators is a particular requirement for effective host defense. In this review we will summarize recent discoveries concerning the potentiation of inflammasome responses by type I interferons, particularly in patients with gram-negative bacterial infections, and reflect on the molecular mechanisms of IFN- β 's immunosuppressive effects through modulation of inflammasome and IL-1 β signaling in patients with tuberculosis and multiple sclerosis. (J Allergy Clin Immunol 2016;138:37-46.)

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The innate immune system has several critical functions in host defense: it recognizes invading pathogens, initiates host responses, and subsequently mediates repair processes for

Abbreviations used

AIM2:	Absent in melanoma 2
ALR:	AIM2-like receptor
ASC:	Apoptosis-associated speck-like protein containing a carboxy-terminal CARD
CARD:	Caspase activation and recruitment domain
cGAS:	Cyclic GMP-AMP synthase
CNS:	Central nervous system
DAMP:	Danger-associated molecular pattern
DC:	Dendritic cell
dsDNA:	Double-stranded DNA
EAE:	Experimental autoimmune encephalomyelitis
GBP:	Guanylate-binding protein
25-HC:	25-Hydroxycholesterol
IFI16:	IFN- γ -inducible protein 16
IFNAR:	IFN- α/β receptor
IL-1R:	IL-1 receptor
IL-1RA:	IL-1 receptor antagonist
iNOS:	Inducible nitric oxide synthase
IRF:	Interferon regulatory factor
ISG:	Interferon-stimulated gene
MS:	Multiple sclerosis
NAIP:	NLR family apoptosis inhibitory proteins
NF- κ B:	Nuclear factor κ B
NLR:	Nucleotide-binding domain, leucine-rich repeat-containing protein
NO:	Nitric oxide
PAMP:	Pathogen-associated molecular pattern
PRR:	Pattern recognition receptor
ROS:	Reactive oxygen species
SREBP:	Sterol regulatory element-binding protein
STAT:	Signal transducer and activator of transcription
TLR:	Toll-like receptor
T3SS:	Type III secretion system

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restoring homeostasis. Cells of the innate immune system, such as macrophages, recognize conserved microbial patterns, termed pathogen-associated molecular patterns (PAMPs). PAMPs, such as bacterial cell-wall components, are recognized through specialized innate signaling receptors termed pattern recognition receptors (PRRs). In addition to PAMPs, these PRRs are also able to recognize endogenous stimuli, termed danger-associated molecular patterns (DAMPs), which are often released by dying cells and are a sign of injury or infection. In general, PRR activation by a ligand (either a PAMP or DAMP) leads to proinflammatory gene expression through activation of the key inflammatory transcription factor nuclear factor κ B (NF- κ B) and/or expression of antiviral mediators, such as interferons, through activation of interferon regulatory factors (IRFs). This culminates in the release of proinflammatory cytokines, chemokines, and antimicrobial effectors in a general process termed inflammation.

The inflammatory response triggered in situations in which damage occurs without the contribution of microbes, such as during sterile tissue damage, is important for initiation of tissue repair processes. However, when inflammation is dysregulated or occurs persistently in the absence of an infection (so-called sterile inflammation),¹ it is generally considered detrimental.²

Interferons, IL-1 β , and IL-18 are among the key cytokines released upon PRR activation. Each of these potent cytokines has broad pathogen-neutralizing effects, but although they work in concert in some infectious circumstances, they are antagonistic in other settings. This review will provide an overview of the induction of interferons and IL-1 cytokines and their function, with a particular focus on the inflammasomes. We will discuss the interplay of these 2 cytokine families in 3 main disease settings: gram-negative bacterial infections, tuberculosis, and multiple sclerosis (MS).

INTERFERONS

Interferons can be subcategorized into 3 mammalian interferon families. Type I interferons include IFN- α , with its 13 homologous subtypes in human subjects; a single IFN- β ; and some other less characterized interferon subtypes (IFN- ϵ , IFN- τ , IFN- κ , IFN- ω , IFN- δ , and IFN- ζ).³ Of these, IFN- α and IFN- β are the best-characterized interferons. They are induced in a wide number of cell types upon infection and signal through the same receptor (ie, the IFN- α/β receptor [IFNAR]) to induce a broad antiviral state.³

IFN- γ is the sole type II interferon, is structurally different from the type I and III interferons, and signals through a different receptor: the IFN- γ receptor.^{2,4} IFN- γ is primarily induced by the cytokines IL-12 and IL-18 in a variety of immune cells, including CD4 T_H1 cells, CD8 cytotoxic cells, and natural killer cells, as well as macrophages and dendritic cells (DCs), where it can act in an autocrine manner.⁴ IFN- γ primes macrophages for antimicrobial actions, such as inducing nitric oxide (NO) production, and thus can potentiate proinflammatory signaling.⁴ IFN- λ 1, IFN- λ 2, IFN- λ 3, and IFN- λ 4 make up the type III family of interferons, which function similarly to type I interferons but are restricted to epithelial cells, where their receptor is expressed.³ This review will focus primarily on type I interferons and their regulation of inflammasomes.

Type I interferons are typically induced in response to virally derived ligands but can also be activated in response to bacterial infection. Microbial RNAs are detected in the cytosol by retinoic acid-inducible gene I (RIG-I)⁵ and melanoma differentiation-associated gene 5 (MDA5),⁶ whereas microbial DNA is detected by cytosolic receptors, including cyclic GMP-AMP synthase (cGAS)⁷ and IFN- γ -inducible protein 16 (IFI16).⁸ Endosomally expressed Toll-like receptors (TLRs) also sense nonhost nucleic acids through TLR3 (double-stranded RNA),⁹ TLR7/8 (single-stranded RNA),^{10,11} or TLR9 (unmethylated CpG DNA).¹² Finally, LPS, a component of gram-negative bacteria, is recognized by TLR4 at the cell surface before being endocytosed, whereupon it can induce IFN- β expression.¹³ Signaling by these receptors and their adaptors typically converges at the key transcription factors IRF3 and IRF7.¹⁴ Although IRF3 is constitutively expressed in many cell types, IRF7 is only constitutively expressed in plasmacytoid DCs or is induced after a primary wave of IFN- α/β production, thus forming part of a positive feedback loop.¹⁵

The transcriptional regulation of the *Ifnb1* “enhanceosome” is particularly well studied, and cooperation between various transcription factors, including IRFs, NF- κ B, and activating protein 2 (AP2) proteins, are required for efficient *Ifnb1* induction.¹⁶ Two recent studies further identified a site approximately 15 kb upstream of the *Ifnb1* transcription start site, which controls the magnitude of *Ifnb1* expression and might be regulated by the macrophage transcriptional repressor ATF3 and by sumoylation.^{17,18} Whether these 2 mechanisms are directly related remains to be determined.

IFN- α and IFN- β induce an antiviral state in both an autocrine and paracrine manner by signaling through the heterodimeric receptor IFNAR, which is composed of 2 subunits: IFNAR1 and IFNAR2.¹⁵ IFNAR binding of type I interferons activates downstream signaling cascades, which lead to phosphorylation of the signal transducer and activator of transcription (STAT) transcription factors and their subsequent nuclear translocation.¹⁹ STAT1 can heterodimerize with STAT2 and form a further complex with IRF9, which constitutes the transcriptional activator complex interferon-stimulated gene factor 3, which in turn binds to interferon-stimulated response elements. Interferon-stimulated response element target genes are termed interferon-stimulated genes (ISGs).¹⁵ Examples of ISGs include antiviral proteins that directly target conserved aspects of viral replication, as well as both positive and negative regulators of the interferon signaling cascade.²⁰ Many PRRs, including the cytosolic nucleic acid receptors, such as RIG-I and cGAS, are themselves ISGs.²¹ IFNAR engagement can also induce STAT1 or STAT3 homodimerization, which bind specific motifs (termed gamma-activated sequences) in target inflammatory gene promoters.¹⁵

IL-1 β AND IL-18

IL-1 β was originally identified as a proinflammatory cytokine able to induce both local and systemic inflammation and a febrile response in response to infection or injury.²² Therapeutically targeting IL-1 β by blocking its engagement with its cognate receptor, IL-1 receptor (IL-1R), has proved remarkably successful in patients with a wide range of inflammatory diseases.²³ IL-1 β is part of an 11-member IL-1 family of cytokines, including IL-1 α , which also signals through IL-1R.²² IL-18, which binds to and signals through the IL-18 receptor, was first characterized for its ability to induce IFN- γ in natural killer cells, thereby inducing a T_H1 inflammatory response.²⁴ IL-1R and IL-18 receptor engagement, similar to TLR engagement, initiates myeloid differentiation primary response gene-88—dependent signaling to activate NF- κ B and further induce proinflammatory gene expression.²⁵ Excessive or inappropriate expression of these proinflammatory cytokines can lead to tissue damage and various disease pathologies, including autoimmune diseases, metabolic syndromes, and cryopyrin-associated periodic syndromes (see Garlanda et al²² for an extensive review), and therefore these cytokines and their activity are tightly regulated at various levels. In addition to decoy receptors and soluble receptor antagonists, both cytokines are uniquely regulated at the posttranslational level by inflammasomes.

Although IL-1 α is constitutively expressed as an active protein in many cells and released as an alarmin upon necroptosis, IL-1 β and IL-18 are both translated as inactive proforms, which require cleavage of an N-terminal sequence for activation.²² This cleavage event entails formation of cytosolic oligomeric

signaling platforms, which are known as inflammasomes. Inflammasomes consist of the inflammasome receptor molecule, which senses either the PAMP or the DAMP, and the adaptor apoptosis-associated speck-like protein containing a carboxy-terminal CARD (ASC), which, through a helical fibrillation process, forms a large protein assembly termed the ASC speck. ASC specks act as platforms for the protease caspase-1, which, after autoproteolysis, activates IL-1 β and IL-18 by means of cleavage.²⁶ In addition, inflammasome activation results in proinflammatory cell death, termed pyroptosis.²⁷ Pyroptosis involves cell swelling, membrane rupture and release of the cytoplasmic content into the extracellular space.²⁷ Secretion of mature IL-1 β , which lacks appropriate target sequences for conventional secretion, might require pyroptosis of the cell, at least in macrophages,²⁸ although other mechanisms of IL-1 β secretion are likely to exist because other cells, such as neutrophils²⁹ and human monocytes,³⁰ can release IL-1 β without pyroptosing.

INFLAMMASOMES: CANONICAL ACTIVATION

The inflammasome receptor proteins are key cytosolic PRRs that either sense or directly bind their ligands. Several PRR families can form inflammasomes, including the nucleotide-binding domain, leucine-rich repeat containing proteins (NLRs); the absent in melanoma 2 (AIM2)-like receptors (ALRs); and the tripartite-containing motif family, which includes the PYRIN inflammasome.³¹ These proteins contain a ligand-sensing domain (eg, the leucine-rich repeat for the NLRs or the HIN200 domain for the ALRs) and a signaling domain, which can be a pyrin domain (eg, AIM2 for NLRP3) or a caspase activation and recruitment domain.²⁶ Many inflammasome-specific ligands have already been characterized, although in many cases these were identified in mice and subsequently shown to have a different specificity in human subjects. For example, mice express 3 NLRP1 isoforms, of which certain alleles of NLRP1b can sense anthrax lethal toxin, whereas human subjects only express 1 NLRP1 isoform, which senses bacterial products, such as muramyl dipeptide and a component of *Toxoplasma gondii*.³² Similarly, murine NLRC4 forms an inflammasome in response to the highly conserved bacterial virulence factors flagellin and the type III secretion system (T3SS) inner rod and needle proteins, which are required for bacterial motility or injecting effector proteins into target host cells, respectively.³³ In contrast, human NLRC4 is only activated in response to the T3SS needle protein, and human monocyte-derived macrophages do not pyroptose or release IL-1 β when stimulated with flagellin or the T3SS rod protein.³⁴

This discrepancy between mouse and human macrophages was explained when it was discovered that NLRC4 does not actually bind directly to these bacterial proteins but rather that these ligands are bound by the NLRC4 coreceptors; the NLR family apoptosis inhibitory proteins (NAIPs).³³ On binding their ligands, NAIPs oligomerize with NLRC4 to form an active inflammasome.³³ Mice express 7 NAIP proteins, with NAIP5 and NAIP6 binding flagellin, NAIP2 binding the T3SS rod protein, and NAIP1 binding the T3SS needle protein.³⁵ Human subjects only express 1 NAIP protein, the ortholog of murine NAIP1, which detects the T3SS needle protein, and as such, human NLRC4 is only activated in response to this bacterial ligand.³⁵

NLRP6, which is highly expressed in the gastrointestinal tract, also forms inflammasomes with ASC and caspase-1³⁶ and has a key role in maintaining colonic microbiota homeostasis in an

IL-18-dependent manner.^{36,37} NLRP6 deficiency results in dysbiosis in the gut, with colonization of nonindigenous microbiota resulting in local inflammation, all of which are likely to contribute to gastrointestinal diseases, such as colitis and inflammatory bowel disease.^{36,37} NLRP6, together with the RNA helicase Ddx15, can also sense viral RNAs from enteric viral infections and induce a type I interferon response to induce an antiviral state in the gastrointestinal tract.³⁸ Interestingly, NLRP6 can also negatively regulate both NLRP3 and NF- κ B signaling in response to bacterial pathogens in myeloid cells,³⁹ suggesting it plays different roles depending on local context.

The physiologic role of NLRP12 is still controversial. By using *in vitro* biochemical assays, NLRP12 was shown to interact with ASC and caspase-1 to process IL-1 β ,⁴⁰ and similar to NLRP3, mutations in NLRP12 can cause periodic fevers resulting from overproduction of IL-1 β and other proinflammatory cytokines, such as TNF.^{41,42} NLRP12 also appears to be required for protective IL-18 processing in response to *Yersinia pestis*, the gram-negative bacterium that causes plague.⁴³ NLRP12 was also shown to drive excessive IL-1 β production in secondary sepsis after malaria infection in murine models.⁴⁴ In addition to its potential inflammasome-related actions, NLRP12 has also been described to negatively regulate NF- κ B and extracellular signal-regulated kinase signaling in macrophages and thereby dampen inflammation, particularly in models of colonic inflammation and tumorigenesis.⁴⁵⁻⁴⁷ A role for NLRP12 in contact hypersensitivity has also been described, whereby NLRP12 was required for chemokine-induced DC migration.⁴⁸ However, a recent study was unable to reproduce either the inhibitory effect of NLRP12 on macrophage signaling or the effect of NLRP12 on DC migration.⁴⁷ In contrast, these authors found that NLRP12 is primarily expressed by neutrophils and acts as a modulator of neutrophil migration.⁴⁷

Finally, the PYRIN inflammasome detects pathogen-induced modifications (and thereby inactivation) of Rho-GTPases, which provides a broad sensing mechanism for a wide range of pathogens, such as gram-positive *Clostridium difficile*.⁴⁹ Mutations in the gene encoding PYRIN (*MEFV*) cause the autoinflammatory disorder familial Mediterranean fever, which, similar to the cryopyrin-associated periodic syndrome disorders, results in excess circulating proinflammatory cytokines, including IL-1 β and TNF.⁵⁰ Although for most of the above-described inflammasomes the exact physiologic roles, microbial or sterile ligands, and mechanisms of activation remain to be fully elucidated, their activation nevertheless results in ASC recruitment, caspase-1 processing, IL-1 β and IL-18 release and pyroptosis.

NLRP3

NLRP3 is activated by a multitude of pathogens, including bacteria, viruses, and fungi, and its ligands include pore-forming toxins, such as hemolysin and nigericin; DAMPS, such as ATP; crystalline ligands, such as uric acid or cholesterol crystals; particulate matter, including silica and asbestos; or peptide aggregates, such as β -amyloid.^{51,52} How NLRP3 recognizes these diverse ligands is still unclear and it is generally agreed that NLRP3 senses particular perturbations in the cell rather than directly binding any of these ligands.²⁶ Several cellular events upstream of NLRP3 activation have been described including potassium efflux; mitochondrial dysfunction, such as production of mitochondrial reactive oxygen species (ROS) and release of

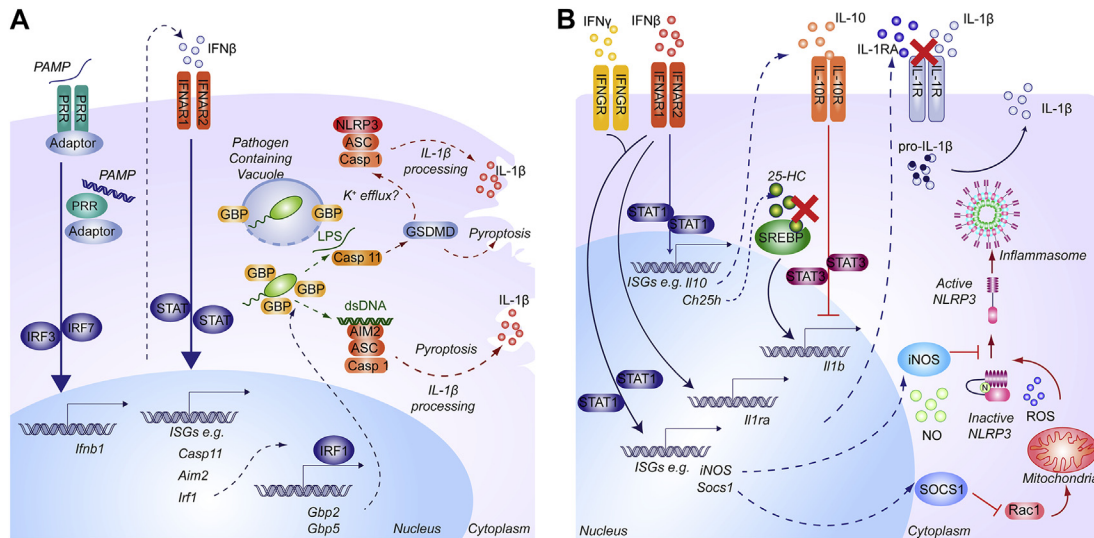


FIG 1. A, Interferon and inflammasome cooperation in infection. Initial PAMP recognition triggers IFN-β production, which can signal in an autocrine or paracrine manner to induce key ISG production, including the inflammasome components caspase-11 and AIM2, as well as IRF1, which can induce GBP expression. GBPs restrict bacteria that have escaped into the cytosol and expose PAMPs, such as LPS and dsDNA, to cytosolic PRRs. Caspase-11 recognizes cytosolic LPS and induces IL-1β processing in an NLRP3-dependent manner and triggers pyroptosis through gasdermin D (*GSDMD*). AIM2 recognizes cytosolic dsDNA to form its own inflammasome and trigger IL-1β release and pyroptosis. **B, Interferons** negatively regulate IL-1 release and activity. IFN-β or IFN-γ signaling induces expression of ISGs, including IL-10, Ch25h, iNOS, and suppressor of cytokine signaling 1 (*SOCS1*). IFN-β also induces expression of IL-1R antagonist to block IL-1R signaling. IL-10 can signal through its cognate receptor to inhibit pro-IL-1β mRNA expression in a STAT3-dependent manner. Ch25h, which encodes the enzyme 25-hydroxycholesterolase, increases the amount of 25-HC present in the cell, which blocks pro-IL-1β expression by blocking SREBP activity. iNOS increases cellular NO levels, which results in NLRP3 S-nitrosylation, keeping it in an inactive conformation and preventing its activation by various ligands. Finally, SOCS1 inhibits Rac activation, which prevents mitochondrial ROS release and activation of the NLRP3 inflammasome.

mitochondrial DNA or cardiolipin into the cytosol; and lysosomal damage, resulting in release of lysosomal proteases, including cathepsins.³¹ However, a definitive common mechanism of NLRP3 activation remains elusive because some of the above mechanisms either do not occur in response to all NLRP3 activators, or can also occur with other inflammasomes or the data are controversial.³¹

However, NLRP3 activation is tightly regulated at both the transcriptional and posttranscriptional levels. It has long been known that NLRP3 inflammasome activation in macrophages requires 2 steps: an initial signal that activates NF-κB to induce pro-IL-1β and NLRP3 mRNA expression (priming),⁵³ followed by an NLRP3 activator, which induces inflammasome formation.²⁶ Recent studies also suggest that the priming step can occur without inducing *de novo* NLRP3 protein synthesis, although how this occurs remains controversial.^{54,55} Additionally, NLRP3 activation can be regulated through direct posttranslational modifications, such as ubiquitination.⁵⁶ Considering the broad range of ligands that NLRP3 recognizes and the variety of chronic inflammatory diseases to which NLRP3 contributes, including Alzheimer disease,⁵⁷ atherosclerosis,⁵⁸ and type II diabetes,⁵⁹ understanding how NLRP3 is activated and regulated is of major therapeutic interest.

DNA-RECOGNIZING INFLAMMASOMES

AIM2 and IFI16 are members of the ALR family of inflammasomes.⁸ These proteins contain DNA-binding HIN200 domains, as well as a pyrin domain through which they can trigger

ASC speck formation and caspase-1 activation.⁶⁰⁻⁶⁴ AIM2 and IFI16 both recognize DNA inside cells, optimally 80 bp or longer, in a manner independent of sequence or GC (guanine - cytosine) content.⁶⁵ However, although AIM2 and IFI16 recognize similar ligands, their subcellular localization can be different; AIM2 recognizes double-stranded DNA (dsDNA) in the cytosol of cells, whereas IFI16 can be activated by dsDNA both in the cytosol and nucleus.⁶⁶ IFI16 can also induce type I interferon,⁶⁰ although interestingly, it seems that the inflammasome-activating and interferon-inducing effector functions of IFI16 can be separated in different cell types. For instance, during HIV infection, IFI16 induces IFN-β responses in human macrophages⁶⁷ or activated CD4 T cells but causes pyroptotic cell death of quiescent CD4 T cells.⁶⁸ As such, IFI16-dependent pyroptosis can contribute to HIV-driven depletion of CD4 T cells.⁶⁹

NONCANONICAL INFLAMMASOME ACTIVATION: CASPASE-11

Caspase-1, which is required for IL-1β cleavage and pyroptosis downstream of canonical inflammasome activation, is part of a larger family of caspases, which include both apoptotic (initiators 2, 8, 9, and 10 and effectors 3, 6, and 7) and inflammatory caspases.⁷⁰ The inflammatory caspases in human subjects include caspase-1, caspase-4, caspase-5, and caspase-12. In mice caspase-11 is the ortholog of human caspase-4 and caspase-5.⁷⁰ The role of caspase-11 in noncanonical inflammasome activation was initially described in 2011, in which caspase-11 was required for IL-1β secretion and pyroptosis in response to gram-negative

bacteria.⁷¹ Further studies elucidated that caspase-11 was involved in the response to cytosolic LPS, independently of TLR4,⁷² and was integral to the pathology of LPS-mediated endotoxic shock in mice. Unexpectedly, instead of a separate PRR upstream of caspase-11, Shi et al⁷³ showed that human caspase-4 and caspase-5 and mouse caspase-11 bound directly to LPS in the cytosol through the caspase activation and recruitment domain (CARD). Although in canonical inflammasome activation the receptor (eg, NLRP3) and ASC form a scaffold on which caspase-1 can oligomerize, caspase-11 oligomerization occurs directly upon binding to LPS.⁷³ This oligomerization is required for LPS-induced pyroptosis and IL-1 α release.⁷³ Caspase-4/5/11 subsequently cleave the protein gasdermin D, the N-terminal fragment of which is able to induce pyroptosis.^{74,75} These studies also indicated that gasdermin D might be required for NLRP3-dependent, caspase-1-mediated pyroptosis, but the exact mechanism requires further investigation (Fig 1, A).^{74,75} Interestingly, IL-1 β processing in response to LPS detection by caspase-4/5/11 requires potassium efflux from the cell to induce canonical NLRP3 inflammasome activation, whereas pyroptosis and IL-1 α release occur in an NLRP3-independent fashion (Fig 1, A).⁷⁶⁻⁷⁸ The discovery of the noncanonical inflammasome and the contribution of caspase-4/5/11-mediated pyroptosis to the LPS might provide important novel clues for our understanding of the pathogenesis of sepsis.

Unsurprisingly, many bacteria and viruses can induce both type I interferon and inflammasome signaling through the various receptors described above, and both cytokine responses have key roles to play in clearance of infection. However, in some instances type I interferons and IL-1 cytokines have a strong level of interplay, which we will describe in more detail below.

COOPERATION OF INTERFERONS AND INFLAMMASOME SIGNALING DURING BACTERIAL INFECTION

Gram-negative bacteria

Interferons and inflammasome signaling cooperate to a large extent in the initial innate immune response to certain intracellular bacterial infections. In particular, noncanonical caspase-4/5/11 activation requires interferon priming for effective activation against gram-negative bacteria. Early studies had shown that caspase-11 expression was IFN- β or IFN- γ inducible in mouse macrophages,^{79,80} although a basal level of caspase-11 expression appeared to be sufficient for activation by intracellular LPS.⁷² Human caspase-4 was constitutively expressed in monocytic cell lines⁷³ and also in keratinocytes and epithelial cells. The initial requirement for interferon signaling was first apparent when enteric bacteria, such as enterohemorrhagic *Escherichia coli*, were only able to induce caspase-1 and caspase-11 processing and IL-1 β release in mouse macrophages when IFNAR signaling was intact.⁸⁰ Similarly, *Salmonella enterica* serovar *Typhimurium*-induced caspase-1 and caspase-11 inflammasome activation was also interferon dependent.⁸¹ Rathinam et al⁸⁰ suggested that transcriptional induction of caspase-11 by type I interferons was enough to induce both its expression and autoactivation (Fig 1, A). Subsequent findings by Kayagaki et al⁷² found that the interferon pathway was dispensable for caspase-11 inflammasome activation by

intracellular LPS (ie, when it has been directly transfected into a cell). The requirement for type I interferon in caspase-11-mediated responses to cytosolic bacteria but not LPS was reconciled in recent studies, in which interferon-inducible guanylate-binding proteins (GBPs) were shown to destroy pathogen-containing vacuoles, thereby exposing gram-negative bacteria, such as *Salmonella typhimurium*⁸² or *Legionella pneumophila*,⁸³ and their components (eg, LPS) to cytosolic PRRs, such as caspase-11 (Fig 1, A). Although GBPs 1, 3, 5, and 7 can also contribute to this effect, it appears that GBP2 is the key GBP that is first induced by type I or II interferons and exposes gram-negative bacteria-derived LPS to caspase-11.⁸² Of note, GBP5 has also been implicated in NLRP3 inflammasome assembly in response to pathogenic bacteria,⁸⁴ although other studies with different experimental conditions have not replicated these findings.⁸²

Francisella tularensis

GBPs also play a role in the interferon-mediated recognition of *Francisella tularensis* subspecies *novicida* (*Francisella novicida*) DNA by the AIM2 inflammasome. Although AIM2 is also an ISG, it is constitutively expressed at high enough levels in macrophages that transcriptional induction is not required for its activation.⁸⁵ Initial studies showed that AIM2 inflammasome activation by *F novicida* was also type I interferon dependent,⁸⁶⁻⁹⁰ whereas type I interferons were not required for AIM2 detection of transfected dsDNA. Recent work has shown that type I interferons trigger the *de novo* synthesis of IRF1, itself a transcription factor, which subsequently induces a subset of ISGs, in particular GBP2 and GBP5, which are required for AIM2 inflammasome activation in response to *F novicida* (Fig 1, A).^{91,92} It appears that in *F novicida* infection the GBPs target bacteria already present in the cytosol and might compromise bacterial cells such that bacterial DNA is exposed to the cytosol for AIM2-mediated detection (Fig 1, A).⁸⁵ The mechanism by which GBPs target cytosolic bacteria for destruction and exposition of their PAMPs remains to be elucidated. Furthermore, whether other ISGs or machinery of the cell autonomous defense system are also required for effective presentation of PAMPs to cytosolic PRRs will be of further interest in the future.

COUNTERREGULATION OF INFLAMMASOME SIGNALING BY INTERFERONS

Although type I interferons are highly protective in patients with acute infections, they are also known to be immunosuppressive in chronic viral and bacterial infections.³ For this reason they are often considered anti-inflammatory and are even used in treating autoimmune diseases such as MS (see below).⁹³ A key mechanism through which IFN- β is immunosuppressive is by inhibiting inflammasome-IL-1 β axis. IFN- β can directly attenuate IL-1 signaling by inducing expression of the IL-1R antagonist (Fig 1, B).⁹⁴ Type I interferons also directly suppress IL-1 β release from macrophages in a STAT1-dependent manner.⁹⁵ IFN- β is thought to inhibit macrophage IL-1 β release in 2 main ways.

First, IFN- β induces expression of IL-10, the major anti-inflammatory cytokine, which has pleiotropic immunosuppressive effects, including on a variety of immune cells.⁹⁶ IFN- β -induced IL-10 then signals through the IL-10

receptor (IL-10R), which activates STAT3 signaling and inhibits pro-IL-1 α and pro-IL-1 β mRNA expression (Fig 1, B).⁹⁵ IFN- β -mediated induction of another ISG, *Ch25h*, encoding the enzyme 25-hydroxycholesterolase, which converts cholesterol to the antiviral lipid 25-hydroxycholesterol (25-HC), might be involved in suppression of pro-IL-1 β transcription.⁹⁷ 25-HC is a regulatory ligand for the master cellular cholesterol regulator sterol regulatory element binding protein (SREBP), and IFN- β -induced 25-HC inhibits SREBP activity, which is required for IL-1 β mRNA induction through an as yet undefined mechanism (Fig 1, B).⁹⁷

Second, IFN- β ⁹⁵ and IFN- γ ⁹⁸ are able to target NLRP3 inflammasome activation directly by stimulating inducible nitric oxide synthase (iNOS) expression, which increases the amount of endogenous NO.^{98,99} NO inhibits NLRP3 oligomerization by means of direct S-nitrosylation of the NLRP3 protein, preventing full inflammasome assembly (Fig 1, B).^{98,99} Finally, IFN- β might be able to target NLRP3 activation by suppressing ROS generation. In macrophages IFN- β also induced expression of the negative regulator suppressor of cytokine signaling 1 (SOCS1), which suppressed Rac1-mediated generation of ROS, which might also account for IFN- β -dependent inhibition of NLRP3 activation (Fig 1, B).¹⁰⁰ Thus both type I and II interferons are able to directly regulate NLRP3 inflammasome assembly, as well as control IL-1 β mRNA expression, and thereby inhibit inflammasome activation and IL-1 β release.

Counterregulation in infectious disease: *Mycobacterium tuberculosis*

The counterregulation of IL-1 and interferon signaling has particular implications in *Mycobacterium tuberculosis* infection, which causes tuberculosis, an airborne disease that can result in wide-ranging symptoms, including fever, weight loss, severe coughing, and chest pain.¹⁰¹ Upon *M tuberculosis* infection, active tuberculosis develops in some patients, whereas others contain the initial infection, and the disease is considered latent (asymptomatic).¹⁰¹ Five percent to 10% of patients with latent tuberculosis (approximately one third of the world's population) will go on to have active tuberculosis, amounting to almost 9 million cases of active tuberculosis annually.¹⁰¹ Current understanding suggests that in patients with latent tuberculosis, the infection is kept in check by an active host immune system, whereas in patients with active tuberculosis, the bacteria subvert cellular processes, particularly in macrophages, for intracellular replication and subsequent spread in the absence of an effective adaptive immune response.¹⁰¹ Studies in knockout mice and correlation studies in human subjects established early on that CD4⁺ T cells and the cytokines IFN- γ , TNF, and IL-12p40 are all critical for resolving *M tuberculosis* infections (see Mayer-Barber and Sher¹⁰² for a detailed review). Recent murine models have shown that intact IL-1R signaling downstream of IL-1 β and IL-1 α are also key for effective clearance of *M tuberculosis* infection,^{103,104} whereas IFNAR-deficient mice are protected from pulmonary *M tuberculosis* disease.¹⁰⁵

In a murine model of tuberculosis infection, type I interferons inhibited macrophage- and DC-produced IL-1 α and IL-1 β production, which were critical for host defense.¹⁰⁴ Similarly, in

human macrophages *M tuberculosis*-induced type I interferon suppressed IL-1 β production.¹⁰⁶ An elegant study by Berry et al¹⁰⁷ identified a strong type I interferon signature in the whole-blood transcriptomes of patients with active tuberculosis that was absent in healthy control subjects or those with latent tuberculosis, indicating that type I interferon-mediated suppression of IL-1 signaling could have direct implications on disease progression. Virulent *M tuberculosis* strains were also shown to preferentially induce type I interferon expression *in vitro* and *in vivo*, thereby potentially suppressing both IL-1 signaling¹⁰⁶ and the expression of other proinflammatory cytokines required for effective *M tuberculosis* clearance (eg, IL-12 and TNF).^{108,109} The mechanism by which virulent *M tuberculosis* strains achieve this was recently elucidated: the type VII secretion system of virulent *M tuberculosis*, ESX-1, secretes *M tuberculosis* DNA into the cytoplasm, which is then sensed by the cytosolic DNA sensor cGAS,¹¹⁰⁻¹¹² resulting in a type I interferon response.¹¹³ This cGAS-driven interferon counteracts NLRP3 and AIM2 inflammasome activation by other *M tuberculosis*-derived ligands, thereby suppressing IL-1 β release.¹¹⁰

Conversely, IL-1 signaling can also suppress IFN- β mRNA and protein induction during *M tuberculosis* infection through induction of the eicosanoid mediator prostaglandin E₂.¹¹⁴ The balance of eicosanoids, between prostaglandin E₂ (which confers resistance) and products of the 5-lipoxygenase axis (which enhance bacterial growth), strongly influences the outcome of *M tuberculosis* infection in murine models of the disease.¹⁰² In the case of tuberculosis infection, as well as in other bacterial infections, the counterregulatory actions of type I interferons and IL-1 family cytokines and how they affect pathogen clearance through both the innate and adaptive immune systems are likely to be dependent on the local environment and stage of infection.

Counterregulation in autoimmune disease: MS

Inflammation can also be present, even in the absence of infection,¹ and both interferons and IL-1 cytokines contribute strongly to sterile inflammation. Although in many disease settings interferons and IL-1 contribute to autoinflammatory and autoimmune pathologies, in patients with MS, IFN- β might be protective by counterregulating inflammasome activation.

MS is an autoimmune neurodegenerative disease and is the most common cause of nontraumatic neurologic disability in young adults. Some hallmarks of MS include central nervous system (CNS) demyelination, axonal damage, and infiltration of immune cells into the CNS.¹¹⁵ T cells that recognize myelin antigens primarily drive MS. These autoreactive T cells are primed in the periphery, infiltrate the brain, and, on secondary activation, initiate an immune response, leading to demyelination.¹¹⁶ Many insights into the molecular mechanisms of MS disease development and progression were gained by using experimental autoimmune encephalomyelitis (EAE) as an animal model of MS. EAE is induced by immunization with myelin antigens or adoptive transfer of myelin-specific T cells.¹¹⁷ Although disease progression in patients with EAE is thought to be driven by T_H1 and T_H17 cells and their signature cytokines, IL-17 and IFN- γ , type I interferons and IL-1, specifically the

NLRP3 inflammasome, are also critical modulators of MS and EAE.¹¹⁶

IL-1 β and IL-18 have long been associated with MS, even preceding discovery of the inflammasomes. PBMCs from patients with MS had increased IL-18 and caspase-1 expression,¹¹⁸ and IL-1 β was also detectable in the cerebrospinal fluid of patients with MS.¹¹⁹ Furthermore, a high IL-1 β /IL-1 receptor antagonist (IL-1RA) ratio is associated with increased susceptibility to relapse onset of MS,¹²⁰ whereas polymorphisms in the IL-1 β and IL-1RA genes are associated with increased disease severity.¹²¹ These cytokines promote demyelination, increased blood-brain barrier permeability,¹²² microglial activation,¹²² and IL-17 production by both CD4 T cells and $\gamma\delta$ T cells.¹²³⁻¹²⁵

Numerous studies have shown that NLRP3-deficient mice are protected against EAE, as measured by decreased demyelination and less infiltration of pathogenic T_H1 and T_H17 cells, macrophages, and DCs into the CNS.^{126,127} Furthermore, ASC-deficient¹²⁸ and caspase-1-deficient^{126,127} mice are also protected from EAE, suggesting that the detrimental effects of NLRP3 are mediated through inflammasome-derived IL-1 β and IL-18, possibly because of decreased immune cell infiltration into the CNS.¹²⁸ However, the exact contribution of IL-18 and IL-1 β is controversial: in some studies NLRP3-deficient mice had decreased IL-18 levels in the serum and cerebrospinal fluid, whereas IL-1 β levels were unaffected.¹²⁶ Furthermore, animals deficient in IL-18 were protected against EAE to the same extent as NLRP3-deficient animals.¹²⁶ Considering that various studies have shown that IL-1 β signaling drives EAE development,¹²³ particularly by enhancing IL-17 production and driving T_H17 responses,^{124,125} reconciling these conflicting reports merits further investigation of the actions of IL-1 and IL-18 in EAE and MS. Finally, the contribution of NLRP3 to EAE development is also controversial, and it appears that there are distinct subtypes of EAE that develop, one that is NLRP3 dependent and a second more aggressive form of EAE that is NLRP3 independent,¹²⁹ although the relevance of both of these for human MS remains unclear.

Considering that one of the key functions of IL-18 is to induce IFN- γ , there are also conflicting reports concerning IFN- γ 's role in EAE pathogenesis. For instance, IFN- γ ⁺ cells were shown to accumulate in the CNS in the early stages of EAE and therefore were thought to drive disease progression.^{130,131} This was supported by studies with T-bet-deficient mice: T-bet-deficient CD4 T cells did not secrete IFN- γ on activation, and T-bet-deficient mice are protected against EAE,^{132,133} suggesting that T cell-derived IFN- γ can drive EAE. However, anti-IFN- γ treatment was shown to exacerbate disease progression,¹³⁴ whereas administration of recombinant IFN- γ suppressed EAE development.¹³⁵ Genetic evidence also supports a protective role for IFN- γ in EAE development because mice lacking either IFN- γ or the IFN- γ receptor are more susceptible to EAE.¹³⁶⁻¹³⁸ Therefore whether IFN- γ potentiates or suppresses EAE progression requires further investigation.

IFN- β is a US Food and Drug Administration–approved, first-line treatment for MS. Reduced lesions, delayed disease progression, and decreases in relapse rates have all been observed in response to IFN- β treatment in different clinical trials.^{139,140} Considering the promise of IFN- β as a therapeutic agent, the

putative mechanism of its action in patients with MS has been extensively investigated in both patient samples and in the EAE model. In line with clinical trials, IFN- β deficiency aggravates demyelination and increases relapses in an EAE mouse model.¹⁴¹ IFN- β can also impair lymphocyte migration, especially across the blood-brain barrier.¹⁴² An elegant study using conditional IFNAR knockout mice showed that IFN- β exerts its beneficial effects mainly by acting on myeloid cells.¹⁴³ Specifically, myeloid IFNAR deficiency promoted EAE disease progression, whereas neuron-, B cell-, and T cell-specific IFNAR deficiency did not have a strong effect.¹⁴³

IFN- β also modulates inflammasome action in patients with MS/EAE. Ramgolam et al¹⁴⁴ showed that IFN- β reduced IL-1 β mRNA expression in DCs from patients with MS by suppressing IL-1 β priming, whereas Guarda et al⁹⁵ showed that monocytes from patients with MS receiving IFN- β treatment produced less IL-1 β compared with healthy donor control subjects. IFN- β also antagonizes mature IL-1 β action by inducing IL-1RA: patients with MS treated for 6 months with IFN- β had increased circulating IL-1RA levels (Fig 1, B).¹⁴⁵ IFN- β was also able to target NLRP3 inflammasome activation in patients with EAE directly: IFNAR signaling inhibited Rac1-dependent ROS generation to block inflammasome activation (Fig 1, B).¹⁰⁰ This study also found that IFN- β was only therapeutic in EAE models when the disease developed in an NLRP3-dependent manner,¹⁰⁰ which could explain why a considerable proportion of patients do not respond to IFN- β treatment.¹⁴⁶ A recent study showed that patients with MS who do not respond to IFN- β treatment have higher basal NLRP3 and IL-1 β mRNA expression in their PBMCs, although IFN- β treatment actually increased both NLRP3 and IL-1 β mRNA expression in responders.¹⁴⁷ Therefore the exact role of NLRP3 and IFN- β in MS progression remains to be determined and could have implications for the stratification and treatment of patients with MS.

CONCLUSION

Inflammasomes, IL-1 β , IL-18, and type I interferons are key players in both infectious and autoimmune diseases. As this review has outlined, rather than mediating purely separate functions in disease clearance or progression, interferons and IL-1 cytokines have significant cross-talk. What remains to be elucidated is whether interferon potentiation of inflammasome activation occurs in settings beyond gram-negative bacterial or *F. tularensis* infection and whether other ISGs are also involved. Current efforts to decipher the specific functions of individual ISGs should help resolve this. Similarly, the immunosuppressive effects of IFN- β on the NLRP3 inflammasome are, for the most part, molecularly elucidated, although how IFN- β (through IL-10) is mechanistically targeting IL-1 β transcription and whether other inflammasomes are also targeted remains to be determined. Furthermore, as in patients with *M. tuberculosis* infection or MS, the balance of the IFN β /IL-1 β axis can strongly influence the outcome of the disease. Understanding when during infection and pathogen replication and by which cells IFN- β or IL-1 β are being released will lead to better understanding and more effective targeting of these pathways for treating both infectious and autoimmune diseases.

Key concepts and therapeutic implications

- Interferons are induced by a multitude of viruses and bacteria and are required for host resistance.
- Inflammasomes are multimeric signaling platforms that detect various pathogens, as well as some endogenous ligands; they are required for IL-1 β and IL-18 processing and are essential to host defense.
- In patients with gram-negative bacterial infections, type 1 interferons are required for caspase-11 inflammasome activation or for AIM2 inflammasome activation by *F. tularensis*.
- Interferons induce cellular restriction factors, the GBPs, which attack cytosolic bacteria and expose PAMPs for inflammasome recognition.
- This cooperation can enhance clearance of infection but in extreme cases can contribute to the development of sepsis.
- Interferons can counteract IL-1 β signaling at a number of levels: IL-1 β mRNA transcription, NLRP3 inflammasome activation, and IL-1R antagonism.
- Interferon antagonism of IL-1 β signaling can be immunosuppressive, which can be detrimental in patients with infectious diseases, such as tuberculosis, but beneficial in patients with autoimmune diseases, such as MS.

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