REVIEW

Clash of the Cytokine Titans: counter-regulation of interleukin-1 and type I interferon-mediated inflammatory responses

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Over the past decades the notion of 'inflammation' has been extended beyond the original hallmarks of rubor (redness), calor (heat), tumor (swelling) and dolor (pain) described by Celsus. We have gained a more detailed understanding of the cellular players and molecular mediators of inflammation which is now being applied and extended to areas of biomedical research such as cancer, obesity, heart disease, metabolism, auto-inflammatory disorders, autoimmunity and infectious diseases. Innate cytokines are often central components of inflammatory responses. Here, we discuss how the type I interferon and interleukin-1 cytokine pathways represent distinct and specialized categories of inflammatory responses and how these key mediators of inflammation counter-regulate each other.

INTRODUCTION

Inflammation is a highly complex response initiated by the host to a large variety of stimuli such as damaged and dying cells, chemical irritants, injuries and pathogens. Inflammatory responses are critical because they not only alert cells to mount effective immune responses during infections but also initiate wound repair and healing programs.[1] In contrast, excessive unresolved inflammation can lead to tissue damage and disease.[2] Therefore, understanding the unique properties of a given inflammatory response is paramount to gain new perspectives on disease pathogenesis and novel treatment strategies.

Given the diversity of inflammation-inducing insults and variations in both exposure route and duration, qualitatively and quantitatively distinct inflammatory responses must be generated that are fine-tuned to achieve the optimal response to a given stimuli. Thus, each type of inflammatory response is comprised of unique sets of molecular events, lipid mediators, cytokines and specialized cell types that nucleate inflammation, followed by equally tuned steps to ensure resolution of inflammation. We suggest here that depending on the type of insult and the ensuing inflammatory response, distinct classes of inflammatory pathways can be delineated. Moreover, we

propose that the innate cytokines interleukin-1 (IL-1) and type I interferons (IFNs) are the pillars of two major types of inflammatory responses. We discuss how the type I IFNs and IL-1 cytokine pathways represent distinct and specialized classes of innate inflammatory responses and how these mediators antagonize each other. Moreover, we highlight how studies on the innate inflammatory response to *Mycobacterium tuberculosis (Mtb)* infection, a major global health threat, uncovered key-aspects of this special antagonistic relationship between IL-1 and type I IFNs.

INTERLEUKIN-1 DRIVEN INFLAMMATORY RESPONSES

IL-1 is the prototypic pro-inflammatory cytokine and the classic fever-inducing endogenous pyrogen.[3] IL-1 mediates highly inflammatory responses via two cytokine species, IL-1α and IL-1β, respectively, which can be expressed by most cell types and signals on cells of both hematopoietic and non-hematopoietic in origin. IL-1α and IL-1β generate a vast spectrum of biological responses spanning from effects on the central nervous, hematologic and metabolic systems, and are extensively reviewed elsewhere.[4,5] Although IL-1 signaling plays pivotal roles in immunity, sterile inflammation and

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metabolism[1,6–8] excessive overproduction of IL-1 is highly detrimental and contributes to auto-inflammatory diseases, autoimmune encephalomyelitis, rheumatoid arthritis and gout.[4,9–13] IL-1 production is therefore extensively regulated and the margin between clinical benefit and undesirable pathogenic effects for IL-1 is exceedingly narrow.

IL-1R1 cytokine system

IL-1α and IL-1β share little amino acid homology (26%) yet display similar secondary structures.[14–16] In both human and mouse, the IL-1α and IL-1β genes are located next to each other on chromosome 2, and have conserved synteny in this region.[17] IL-1α and IL-1β also appear to carry out similar biological functions by binding to a common receptor comprised of the IL-1 receptor type I (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) chains.[18] The third ligand for IL-1R1, IL-1 receptor antagonist (IL-1Ra), is a naturally occurring specific IL-1R1 antagonist and prevents IL-1α and IL-1β mediated signaling. Such endogenous antagonism in form of a dedicated soluble secreted protein appears to be a unique feature of IL-1 cytokine family members and highlights the extraordinary tight regulation of the biological activity of IL-1. In addition, a second IL-1R chain, the IL-1RII, is both a surface and soluble receptor that lacks a signaling-competent cytosolic domain and therefore functions as an additional decoy receptor in limiting IL-1 driven responses.[18–22] Finally, both IL-1α and IL-1β are regulated at the post-transcriptional and translational level as outlined below. Thus, expression, generation and signaling of IL-1 are among the most highly and complex regulated checkpoints of any cytokine system.

Post-transcriptional and -translational regulation of IL-1α and IL-1β

A key feature in the regulation of IL-1α and IL-1β is that they are both translated as pro-proteins without leader sequences that require further proteolytic cleavage to gain optimal biological activity.[5,23] Processing of the IL-1α precursor is accomplished by calpain II, a membrane-associated, calcium-dependent cysteine protease,[24] and calcium influx induces IL-1α secretion of the processed form.[25,26] Pro-IL-1β is typically cleaved following activation of intracellular cysteine protease caspase-1 or caspase-11 via aggregation of intracellular multiprotein complexes called inflammasomes.[27] IL-1 release by inflammasomes is a two-step process. A Signal 1 event typically represents pro-IL-1β protein transcription and translation often as a result of nuclear-factor-kb (NF-κb) activation by toll-like receptor (TLR) ligands or IL-1 itself.[28,29] Signal 2, in contrast, is an activation step that differs for the respective inflammasome sensors such as NOD-like receptors (NLRs) and AIM2-like receptors (ALRs), and ultimately leads to the assembly of inflammasome complexes which are comprised of the NLR/ALR and adapter molecules such as apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) or NLRC4.[30,31] The inflammasome platform recruits and activates caspase-1, the enzyme that in turn coverts the 31 kD immature pro-IL-1β polypeptide to a 17-kD mature IL-1β.[32,33] The cleavage of IL-1β has been suggested

to be required for its active secretion via unconventional, endoplasmatic reticulum–Golgi independent, ill-defined processes thought to involve secretory autophagosomes, cytolysis, multi-vesicular body formation and micro-vesicle shedding.[34–40]

Increasing evidence suggests that inflammasomes and caspase-1/11 are not the only mechanism for processing IL-1 cytokines. Several studies have identified neutrophil- and macrophage-derived serine proteases such as proteinase 3, elastase and cathepsin-G, as enzymes that can process pro-IL-1β into the 17-kDa bioactive fragment.[18,41,42] In addition, two other serine proteinases, chymase and chymotrypsin, can also cleave pro-IL-1β into bioactive IL-1β. Apart from serine proteases, metalloproteinases such as Meprin can process pro-IL-1β as well as proteases released by invading pathogens.[43–46] Alternatively, it has also been suggested that inflammasome-mediated IL-1β release can be a strictly cytolysis-driven event, through necrosis or pyroptosis.[47] Pyroptosis is a form of caspase-1-dependent programmed cell death that is initiated downstream of inflammasome activation and can contribute to IL-1β release. Moreover, immature pro-IL-1 is often released by cells undergoing cytolysis and present in vast excess of mature IL-1 from cells undergoing inflammasome activation. Although the biological activity of mature IL-1β is 600 times that of pro-IL-1β, pro-IL-1β can still bind to its receptor and it remains unclear what the relative contribution of pro-IL-1β is to IL-1R1 mediated signals in vivo.[19,48,49]

IL-1 signaling pathway

Once IL-1α or IL-1β binds to the IL-1R1 chain, a ligand-induced conformational change facilitates recruitment of IL-1RAcP, the receptor chain required to form a functioning signaling IL-1 R complex.[50–52] Subsequently, the trimeric IL-1 R complex recruits the myeloid differentiation primary response gene 88 (Myd88) via its C-terminal Toll-and IL-1 R-like (TIR) domains.[53,54] MyD88 oligomerizes via its death domain (DD) and TIR domain, and interacts with the interleukin-1 receptor-associated kinase 4 (IRAK4) to form the Myddosome complex that serves as a platform to phosphorylate IRAK4, as well as IRAK2 and IRAK1.[55–57] IRAK phosphorylation is then followed by the recruitment and oligomerization with tumor-necrosis factor-associated factor (TRAF) TRAF6.[58] IRAK1 and IRAK2 serve as both adapters and protein kinases to propagate downstream signals with TRAF6 resulting in NF-κB activation.[56,58,59]

Role of IL-1 in host resistance to infection

IL-1 is most widely studied and implicated in host resistance to acute bacterial infections, such as *Staphylococcus aureus*, where rapid inflammatory responses and IL-1-induced chemokines are required for optimal neutrophil-dependent control[60,61] (also see Table 1). Indeed, this is the classic scenario for IL-1-mediated host control of acute bacterial infections and mice deficient in caspase-1 or IL-1 display increased susceptibility and mortality to infections with *Francisella tularensis*, *Legionella pneumonia*, *Shigella*, *Salmonella typhimurium*, *Bacillus anthracis* or *Pseudomonas aeruginosa*.[62–69] For instance, Gram-negative bacteria, such as *Legionella pneumophila* and *Salmonella*

Table 1 Comparison of IL-1 vs type I IFN-mediated signals in host resistance to infections and disease

Pathogen	Phenotype of mice deficient in IL-1R1 signaling	Phenotype of mice deficient in IFNAR1 signaling
Extracellular bacteria		
Pseudomonas aeruginosa	*Il1r1* −/− mice have decreased number of CFU during pulmonary infection[62]	*Ifnar1* −/− mice are more resistant to *Pseudomonas aeruginosa* infection[148]
Klebsiella spp.	No significant differences in survival rates and viable bacterial counts between WT and *Il1a,b* −/− mice[188]	–
Staphylococcus aureus	Higher mortality in *Il1r1* −/− mice[68]	*Ifnar1* −/− mice are more resistant to lethal infection of *S. aureus*[147,189]
Streptococcus spp.	*Il1b* −/−, *Il1a,b* −/− and *Il1r1* −/− mice are hypersusceptible to *Streptococcus* Spp. infection[190–192]	*Ifnar1* −/− mice are more susceptible to *Streptococcus Spp.* infection[157,193,194]
Intracellular bacteria		
Mycobacterium tuberculosis	*Il1a* −/−, *Il1b* −/− and *Il1r1* −/− mice were more susceptible to pulmonary tuberculosis[73–75,77–80]	*Ifnar1* −/− mice show significantly reduced bacterial loads and type I IFN hyperinduction exacerbates disease and bacterial growth[139,141]
Mycobacterium avium	No significant differences in CFU between WT and *Il1r1* −/− mice[195]	The continuous infusion of IFN-β leads to increased resistance to *M. avium* infection[196]
Listeria monocytogenes	IL-1 neutralization antibody treated mice show decreased anti-Listeria response[197,198]	*Ifnar1* −/− mice are more resistant to *L. monocytogenes* infection[144–146]
Legionella pneumophila	*Il1r1* −/− mice are more susceptible to *L. pneumophila* infection[66]	*Ifnar1* −/− mice have increased number of CFU[132]
Salmonella enterica	IL-1β neutralizing-antibody treated mice show increased CFU. *Il1b* −/− mice are more susceptible to *Salmonella enterica* infection[199,200]	*Ifnar1* −/− and *Ifnb* −/− mice have reduced number of CFU and increased survival[194,199]
Francisella tularensis	*Il1r1* −/− or *Il1b* −/− mice are more susceptible to infection[201]	*Ifnar* −/− mice are more resistant to intradermal infection with *F. Novicida*[158]
Bacillus anthracis	*Il1b* −/− and *Il1r1* −/− mice are more susceptible to lethal infection[69,202]	The type I IFN inducer, poly-ICLC, strongly and rapidly protects mice[135]
Fungi		
Cryptococcus	No difference between WT and *Il1r1* −/− mice[203]	*Ifnar1* −/− and *Ifnb* −/− are more susceptible to *Cryptococcus* infection[126]
Aspergillus fumigatus	*Il1r1* −/− mice displayed slightly increased survival during *Aspergillus* infection. *Il1r1* −/− mice have recently been described to be highly susceptible to *Aspergillus* infection[99,204]	PolyI:C induced Type I IFN protects mice from *Aspergillus fumigatus* infection[128,129]
Coccidioides	*Il1r1* −/− mice have higher CFU after *Coccidioides* infection[205]	–
Candida albicans	*Il1a* −/− and *Il1b* −/− mice are more susceptible to *C. albicans* infection[98]	*Ifnar1* −/− mice are more resistant to *C. albicans* infections[125,164]
Histoplasma capsulatum	*Il1r1* −/− and IL-1β neutralization treated mice are more susceptible to *Histoplasma* infection[206]	*Ifnar1* −/− mice are extremely resistant to Histoplasma infections[130]
Parasites		
Leishmania major	The course of high-dose infection in *Il1r1* −/− mice is not different from controls. In low-dose infections, *Il1r1* −/− mice develop smaller lesions. *Il1r1* −/− mice are more resistant to a non-healing strain.[207–209]	IFNα/β is important for in inducing iNOS expression during L. major infection. However, high levels of IFNα/β actually impaired iNOS induction[210–212]
Plasmodium spp.	Low dosages of IL-1 protects mice against lethal cerebral malaria[213]	*Ifna/b* can have either a host protective or detrimental effect, depending on both the stage of infection and the species of infecting *Plasmodium*[214–218]
Trypanosoma cruzi	–	Complicated outcome dependent on the route of infection[219–222]

Table 1 (Continued)

Pathogen	Phenotype of mice deficient in IL-1R1 signaling	Phenotype of mice deficient in IFNAR1 signaling
Viruses		
RSV	*Il1r1* −/− mice show similar immune response to RSV infection as compared with WT mice[223]	*Ifnar1* −/− mice have less RSV induced antiviral monocyte chemoattractants[224]
LCMV	LCMV is not cleared in *Il1r1* −/− mice, and yet the infected mice develop neither splenomegaly nor hepatitis[225,226]	IFN-I blockade both before and following establishment of persistent LCMV infection results in enhanced virus clearance[186]
Influenza A virus	*Il1r1* −/− mice show significantly increased mortality to Influenza A infection[89]	*Ifnar1* total KO mice are slightly more susceptible to Influena A infection compared with WT, but chimeric mice, in which both types I and III IFN-mediated signaling is deficient only in epithelial cells, are significantly more susceptible[227,228]
HIV	HIV-1 expression in HIV transgenic mice is decreased in *Il1a,b* −/− mice[229]	Enhanced HIV 1 expression in *Ifnar1* knockout HIV transgenic mice[230]
Autoimmune disease		
Gout	*Il1r1* −/− mice have decreased gouty inflammation, and anti-interleukin-1 therapy works in the management of gout[10,231]	–
MS (EAE)	*Il1r1* −/− mice have less IL-17 cells and lower incidence of EAE compared with WT mice[11,12]	*Ifnb* −/− and *Ifnar1* −/− mice are more sensitive to EAE[232,233]
SLE	*Il1b* −/− mice are resistant to induction of experimental SLE[13,234–236]	*Ifnar1* −/− mice are protected from experimental lupus[237]

Abbreviations: CFU, colony-forming unit; EAE, experimental autoimmune encephalomyelitis; HIV, human immunodeficiency virus; IFN, interferon; Ifnar1, interferon (alpha and beta) receptor 1; IFN-β, interferon-β; IL-1, interleukin-1; IL-1R1, IL-1 receptor type I; LCMV, lymphocytic choriomenigits virus; MS, multiple sclerosis; RSV, respiratory syncytial virus; SLE, systemic lupus erythematosus; WT, wild type.

typhimurium, trigger IL-1 responses required for host resistance by injecting virulence factors into the host cell cytosol with a specialized type III secretion system.[70–72]

In the context of chronic bacterial infections, such as with the intracellular pathogen *Mtb*, IL-1α and IL-1β are each critically required for host resistance.[73–81] *Il1a,b* −/− doubly deficient mice and *Il1r1* −/− mice develop significantly larger granulomatous lesions with neutrophil infiltration in their lungs compared with wild-type (WT) mice. Mice deficient in IL-1 signaling are more susceptible to pulmonary tuberculosis, as reflected by an increased mortality and an enhanced mycobacterial growth in lungs and spleens.[73–75,80] However, consistent with the detrimental effects of uncontrolled IL-1β production, mice deficient in inducible nitric oxide synthase (iNOS) have dysregulated inflammasome activation and IL-1 production leading to increased pathology and mortality during *Mtb* infection.[82] On the opposing role, the exact mechanisms by which IL-1 mediates protection against bacterial pathogens have only recently been studied. In the case of *Mtb*, the major protective role of IL-1 during *Mtb* infection was shown to be linked to its ability to trigger arachidonic acid derived lipid mediator prostaglandin E2 (PGE2) synthesis and COX-2 activation.[78] Thus, mice deficient in IL-1 or IL-1 signaling display major defects in PGE2 production in the lungs and increased extracellular bacteria and necrosis. Add-back of PGE2 reduces pulmonary *Mtb* loads and extends survival[78] indicating that IL-1-induced PGE2 is required for bacterial containment and control inside *Mtb*-infected macrophages.

Despite the importance of inflammasome activation in certain experimental models of inflammation *in vitro*, certain bacterial infection models in mice deficient in inflammasome components show intriguing results that question the importance of inflammasome-mediated processing of IL-1β *in vivo*.[43,83] For example, *Mtb*-infected *Il1r1* −/− or *Il1b* −/− deficient mice both display significantly increased mortality with highly increased pulmonary bacterial burden, suggesting a major role for IL-1β signaling in determining the MyD88-dependent phenotype.[77,81] However, Mtb-infected mice deficient in caspase-1/11, ASC or NLRP3, which have critical functions in inflammasome-mediated IL-1β maturation *in vitro*, showed unimpaired IL-1β production and importantly, were considerably less susceptible to infection than IL-1β-deficient mice.[77,84–86] The exact mechanisms of IL-1β activation *in vivo* during *Mtb* infection remain to be elucidated. Similarly, caspase-1 appears to be dispensable in host resistance against *Chlamydia trachomatis*, although IL-1β is critical for host defense against this pathogen.[87,88] Together these findings suggest that the production of mature host protective IL-1β during infections *in vivo* can occur independently of caspase-1/11 activation and ASC-containing inflammasomes. Possible mechanisms could involve inflammasome and caspase-1/11-independent processing of pro-IL-1β by innate immune cells derived serine proteases as mentioned above.[18,41–44]

Although IL-1 mediates host resistance most commonly in bacterial infections, IL-1 signaling can also protect against certain viral infections, including Influenza. *Il1r1* −/− deficient

mice show significantly increased mortality but markedly reduced inflammatory pathology in the lung after Influenza virus infection.[89] IL-1α/β appears not to influence the killing of virus infected cells *per se* but to enhance antibody responses and recruitment of CD4+ T cells and neutrophils to the site of infection.[89] Interestingly, data from genome-wide association studies show that genetic variants in IL-1α and IL-1β contributed to the susceptibility to 2009 pandemic H1N1 influenza A virus.[90] A more recent study using human pulmonary microvascular endothelial cells showed that IL-1β secreted by the endothelial cells contributes to influenza-induced inflammation, and blockade of IL-1β signaling is a potential treatment or therapeutic target for influenza-induced inflammation and pathology.[91] Furthermore, human immunodeficiency virus (HIV) infection IL-1 induces viral gene expression in chronically infected U1 cells and viral replication is inhibited by addition of IL-1RA.[92,93] IL-1RA gene polymorphisms have also been reported to be linked with circulating levels of HIV viral titers in Brazilian women,[94] while caspase-1-dependent pyroptosis has been suggested to play a detrimental role during HIV infection.[95,96]

During fungal infections, both IL-1α and IL-1β have been shown to play critical roles in host resistance.[23,97] Both IL-1 species are necessary for host resistance against *Candida albicans* and in the absence of IL-1α or IL-1β growth of *C. albicans* in the kidneys as well as mortality is significantly increased.[98] During pulmonary *Aspergillus fumigatus* infection, it is IL-1α rather than IL-1β that is crucial for optimal leukocyte recruitment after challenge with the fungal pathogen.[99]

TYPE I IFN DRIVEN INFLAMMATORY RESPONSES

Although IL-1 protects most commonly against bacterial infections, type I IFNs belong to a family of cytokines that are specialized to be highly protective against viral infections. In 1957 Isaacs and Lindenmann[100] observed that heat-inactivated influenza virus interfered with subsequent viral replication and identified a secreted factor responsible for this phenomenon that they called interferon. Interferons can be separated into three sub-families designated as types 1–3 IFNs. In humans and mice, the type I IFN family is composed of 13 IFNα subtypes, IFNβ, IFNε, IFNκ and IFNω.[101] The type II IFN group is comprised of one cytokine, IFNγ. The third type of IFNs are members of the IFNλ family, which includes IFNλ1 (also known as IL-29), IFNλ2 (also known as IL-28 A) and IFNλ3 (also known as IL-28B).[102]

Type I IFN induction

Most cell types express type I IFNs after detection of pathogen-associated molecular patterns by membrane bound or cytosolic pattern recognition receptors.[103] Cytosolic receptors are mainly responsible for triggering type I IFN secretion, through recognition of viral RNA or DNA. Such receptors include the retinoic acid–inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5), NOD1, NOD2 receptors, interferon gamma-inducible protein 16, DEAD-box helicase 41 and RNA polymerase III amongst others.[104–108] Cytosolic nucleotidyltransferase

GAMP synthase (cGAS) detects cytosolic DNA and stimulates cyclic GAMP (cGAMP) synthesis.[109] cGAMP engages stimulator of interferon genes (STING) as a secondary receptor and further stimulates STING-dependent inflammatory cytokine production including type 1 IFNs.[109] In addition to cytosolic signaling events, type I IFNs can also be produced in response to TLR signaling in macrophages and dendritic cells (DCs). TLR3 and TLR4 sense double-stranded (ds) RNA and lipopolysaccharide (LPS), respectively, and via TIR-domain-containing adapter-inducing interferon-β and TANK-binding kinase 1 (TBK1) activate interferon regulatory transcription factor 3 to trigger type I IFN inductions.[103] Although most cell types can produce type I IFN, plasmacytoid DCs (pDCs) represent a major source of type I IFNs in mice[110] and men.[111,112] pDCs abundantly express the TLR9 subfamily members TLR7, TLR8 and TLR9 which recognize viral single-stranded RNA (TLR7,8) or ds CpG-rich DNA (TLR9), respectively.[113]

Type I IFN signaling pathway

Type 1 IFNs bind to a heterodimeric transmembrane receptor interferon (alpha and beta) receptor 1 (IFNAR), comprised of two chains, IFNAR1 and IFNAR2. Once bound IFNAR activates Tyk2 and Jak1, which results in signal transducer and activator of transcription (STAT) STAT1-STAT2 heterodimer formation and subsequent translocation to the nucleus. In the nucleus, dimeric STATs recruit an additional transcriptional factor, IFN regulatory factor 9, forming a trimeric complex called IFN-stimulated gene factor 3 (ISGF3).[114] ISGF3 then binds to interferon-stimulated response elements, inducing hundreds of IFN-stimulated genes (ISGs).[115,116] Depending on the cell type, IFNAR-mediated activation of Tyk2 and Jak1 can promote homo-dimerization of other STATs including the formation of STAT1 and STAT3 dimers that bind to IFNγ-activated site (GAS) enhancer elements and STAT3-biding elements, respectively. It can also result in STAT4 activation, leading to IFNγ production during viral infection.[117] In addition, type I IFN can activate mitogen-activated protein kinases and phosphatidylinositol-3 kinase (MAPK) signaling pathways that contribute to antiviral effects.[102] Type I IFNs also signal through other STATs, including STAT3, STAT4, STAT5A and STAT5B.[118] The phosphoinositide 3-kinase (PI3K)–mammalian target of rapamycin (mTOR) and MAPK pathways can also be activated by IFNAR1 signaling. This large diversity of signaling pathways may contribute to the pleiotropic effects of type I IFN-driven responses, as it allows transcription of a broad range of genes besides those intended for viral restriction, such as cytokines, chemokines, pro-apoptotic and anti-apoptotic molecules, and molecules involved in lipid metabolism.[118,119]

Role of type I IFNs in host resistance

Type I IFNs are the prototypical cytokines associated with control of viral infections as they successfully restrict viral replication by an acute induction of specific sets of several hundreds of ISGs inside infected cells that can directly interrupt viral gene transcription and translation.[120] These genes are induced by type I IFNs in response to innate viral recognition

and also promote an antiviral state in bystander cells that limits viral spread. In fact, most viruses devote a significant part of their limited genome to mechanisms that modulate type I IFNs pathways so ISG induction is limited, highlighting the importance of IFNα/β in host cell protection from viral infection.[121] In most pathogenic virus infections, early and rapid production of type I IFN is required to limit initial viral replication before effective humoral or cellular adaptive immune mechanisms become operational. This is exemplified by the fact that mice deficient in IFNAR1 are highly susceptible to viral infections as extensively reviewed elsewhere.[122,123]

In addition to the protective role for type I IFNs during viral infections, they are also involved in immunity against fungal pathogens, these cytokines can have both detrimental and beneficial roles. In one study with *C. albicans*, type I IFNs were required to induce reactive oxygen species important for killing of yeast cells by infected phagocytes,[124] whereas in another study the absence of type I IFN signaling did not alter fungal burden but instead lead to lethal immunopathology.[125] During infections with *Cryptococcus neoformans* mice lacking either *Ifnar1* − / − or *Ifnb* − / − have been shown to die from unrestrained pneumonia and encephalitis when compared with control animals.[126] Consistent with this, *C. neoformans* or *C. gattii*-infected mice showed increased resistance to infection when they were intranasally administered polyinosinic-polycytidylic acid stabilized with poly-L-lysine (polyinosinic-polycytidylic acid-polylysine-carboxymethylcellulose (poly-ICLC)), a double-stranded RNA homolog which is a potent inducer of type I IFNs.[127] Although Type I IFN signaling was also reported to be required for optimal host resistance in mice infected with *Aspergillus fumigatus*,[128,129] there are also reports of a detrimental role of type I IFNs in defense against *Candida glabrata* and Histoplasma capsulatum.[130,131]

Albeit most critically required for host resistance against viral infections, Type I IFNs can contribute to protection against some bacterial infections. For example, *Legionella pneumophila* remains an important opportunistic pathogen and type I IFNs have been shown to limit its replication. IFNα significantly suppressed *Legionella pneumophila* growth in WT but not in *Ifnar1* − / − deficient macrophages and *Legionella* was able to trigger type I IFN production in an autocrine manner.[132] Treatment of mice with exogenous IFN or poly-ICLC protected mice from *Bacillus anthracis* and *Chlamydia trachomatis* infection, and inhibited intracellular replication in both human and mouse cells.[133–135] Type I IFNs may also contribute to host resistance against *Salmonella typhimurium* infection by promoting strong IFN-γ production in an IL-12-independent manner.[136]

Although in some instances, type I IFNs contribute to host resistance against bacterial pathogens, there is mounting evidence that the detrimental and pro-bacterial effects of type I IFN are far reaching.[122] The pro-bacterial effects of an inappropriate or excessive type I IFN responses accelerate the pathogenesis of disease by both intracellular and extracellular bacteria. For example, the hyper-virulence of certain *Mtb* strains correlates with enhanced type I IFN synthesis and *Ifnar1* − / − mice

infected with *Mtb* display lower bacterial loads when compared with WT animals.[137–140] *Mtb*-infected mice intranasally treated with poly-ICLC exhibit exacerbated lung pathology and increased bacterial burden.[141] The relevance of these observations to human tuberculosis is supported by whole-blood transcriptional profiles of TB patients, which were found to be dominated by a type I IFNs gene signature that closely correlated with disease severity.[142] In line with these observations, viral co-infection with influenza A virus increases susceptibility to *Mtb* infection in a type I IFN-dependent manner.[143]

Listeria monocytogenes is another intracellular bacteria that infects primarily macrophages and is most commonly associated with food-borne illness in immune compromised individuals. *Ifnar1* − / − mice are resistant to *Listeria monocytogenes* infection and display increased survival and lower spleen, and liver bacterial loads compared with WT animals.[144–146] The major mechanism attributed to this was reduced apoptotic cell death, particularly of lymphocytes, with IFNAR1 signaling sensitizing cells to the bacterial virulence factor listeriolysin O and resultant cell death in WT mice.[144,145] Moreover, *Ifnar1* − / − deficient mice were also resistant to infection with *S. aureus*, where lethal pneumonia was observed in only 10% of *Ifnar1* − / − mice as compared with 80% in the WT animals.[147] Increased resistance against *Pseudomonas aeruginosa* has also been reported in *Ifnar1* − / − mice.[148]

IL-1 AND TYPE I IFN CROSS TALK

Both the IL-1 and type I IFNs pathways can cause great harm to the human body when dysregulated or activated untimely in an inappropriate context. Studies in infants and adolescents with inborn errors of innate immunity have revealed key roles for both IL-1 and type I IFN in auto-inflammatory and immunodeficiency disorders. Mutations in *NLRP3* and *IL1RN* lead to increased IL-1 activity such as Cryopyrin-associated periodic syndromes and deficiency in IL-1RA.[149] These diseases are characterized by episodes of strong inflammation, including high fevers, urticaria-like rashes, joint pain and malaise, and present in patients early in life leading to stunted growth and high mortality.[149] In recent years it has also become evident that inborn errors in type I IFN regulation can cause inflammatory syndromes termed interferonopathies.[150] Specifically, conditions such as Aicardi–Goutieres syndrome, STING-associated vasculopathy with onset in infancy as well as certain types of systemic lupus erythematosus are characterized by an increased and dysregulated type I IFN response that underlies these diverse pathological syndromes. The severity of these inborn errors of IL-1 and type I IFN inflammation highlights the critical importance of these inflammatory pathways in the physiological state in addition to their role in response to bacterial or viral infections. Moreover, these syndromes strongly underscore the notion of distinct types of inflammatory classes and increasing evidence suggests that cross-regulation by IL-1 and type I IFN plays an important role in balancing the innate inflammatory equilibrium in both physiological homeostasis as well as infection.

Type I IFN regulation of IL-1

Inhibition of IL-1 by type I IFNs was first described in the 1990s when multiple groups observed that IL-1 levels were reduced and IL-1Ra simultaneously upregulated in *in vitro* studies of IFN-treated cells, and later, in patients who received a single dose of type I IFN.[151–154] These early observations were the foundation for subsequent studies on the anti-inflammatory properties of type I IFNs,[155] and exemplified the multi-faceted antagonism between IL-1 and type I IFNs. Importantly, both IFNα and IFNβ can suppress IL-1α and IL-1β transcription and translation in various cell types.[76–79,156] The absence of type I IFN-mediated IL-1 inhibition in *Ifnar1* or *Ifnb* deficient animals, after infection with a variety of pathogens, results in increased IL-1 concentrations in tissues and circulation and elevated IL-1-dependent IL-17 responses.[78,157–159] IL-1 and type I IFNs play divergent roles in host resistance to infections and while type I IFNs can enhance or impede host resistance, type IFN-mediated IL-1 inhibition has been observed in both scenarios. Therefore IL-1 inhibition by type I IFNs can both impair host resistance, as in the case of *Mtb* infection[78,79] as well as limit IL-1 driven immunopathology as shown recently during *S. pyogenes* infection.[157] Besides direct regulation of IL-1 protein expression, type I IFNs also potently induce anti-inflammatory IL-1Ra and IL-10, which in turn can inhibit IL-1 signaling effects.[79,160–165] In addition, 25-hydroxycholesterol has been implicated as a downstream effector mechanism of type I IFN-mediated inhibition of IL-1β expression and inflammasome activation.[166] More recently, with increased understanding of the complex regulation of IL-1β processing, we now know that type IFNs and IL-10 also potently regulate NLRP1 and NLRP3 inflammasome activation thereby further modulating IL-1 activity.[164,165]

Interestingly, antagonism of IL-1 does not seem to be limited to type I IFNs. Indeed, type II IFN, IFN-γ and recently type III IFNs, IFN-λ as well as IFN-ταυ have been reported to be able to inhibit IL-1 expression.[79,167–169] Of note, there is also evidence that type I IFN can positively regulate IL-1 expression via the AIM2 inflammasome, which is primarily activated by cytosolic DNA and operational during some select bacterial and viral infections.[170–173]

IL-1 regulation of type I IFNs

Much less is known about how IL-1 could in turn regulate type I IFN production and/or effector functions. Until recently there was limited evidence for IL-1 mediated inhibition of type I IFNs with one study showing that IL-1β was able to attenuate IFNα/β-induced STAT1 phosphorylation in hepatocytes via a proteasome-dependent mechanism.[174] Another study observed IL-1-dependent and TNF-independent inhibition of IFN-β production in a human fibroblast line, suggesting that IL-1 driven inhibition of type I IFNs is an effect unique to IL-1 rather than a general effect due to NF-κb activation via TNFα.[175] PGE2 has been shown to suppress type I IFN production in the context of LPS-induced responses in mice and more recently during Influenza infection.[176,177] However, a link

to IL-1 has not been generated in these studies and remains to be elucidated further. In fact, recent work in *Mtb*-infected cells and animals revealed that IL-1 potently antagonizes type I IFN responses by directly regulating both transcription and translation of IFN-β via induction of PGE2 and PGE2 by itself is able to inhibit and antagonize type I IFN.[78] Moreover, limiting excessive and detrimental type I IFN expression via PGE2 has proven to be a promising host-directed therapeutic approach in *Mtb* infection.[78] Although IL-1 and type I IFN cross-regulation is an emerging research area, it has become clear that the contextual differences in pathogenesis will likely determine whether the cross-regulation results in beneficial outcomes with a given pathogen or contributes to inflammatory pathology and susceptibility.

Mtb: a case study for IL-1 and type I IFN cross talk

The relevance of IL-1 and type I IFN cross talk is perhaps best studied and exemplified in the context of mycobacterial infections, where IL-1 plays a major protective and type I IFN a primarily detrimental role in host resistance to *Mtb*. Here it has been shown that, in human monocyte-derived DC and macrophages as well as murine bone marrow derived dendritic cells and bone marrow derived macrophages, IFNβ or poly-ICLC were able to potently inhibit both IL-1α and IL-1β in response to *Mtb* infection in vitro.[76,79] This inhibition was at least in part due to type I IFN-dependent induction of IL-10, an important anti-inflammatory cytokine,[79,178] previously reported to inhibit IL-1 production downstream of type I IFNs.[164] Besides inhibiting IL-1α and IL-1β cytokine expression directly, type I IFNs also potently upregulated expression of IL-1Ra during *Mtb* infection *in vitro* and *in vivo*, further amplifying the negative effects on IL-1 activity,[78,79] a central feature in type I IFN opposition of IL-1.[151] In addition to modulating IL-1RA and IL-1α, and IL-1β expression, type I IFNs also regulated expression of the decoy receptor IL-1R2 (ref. 78; Figure 1). Moreover, the type I IFN-mediated inhibition of IL-1 cytokine production observed *in vitro* was confirmed *in vivo* in *Mtb*-infected lungs using single-cell analysis of IL-1 producing myeloid subsets.[79]

A potential molecular mechanism was recently uncovered that could shed some light on the reciprocal relationship between IL-1 and type I IFNs and extends previous findings that implicated the ESAT6-secretion system (ESX)-1 in type I IFN expression and inflammasome activation.[140,179] Multiple independent groups have shown that the nucleotidyltransferase cGAS is a central component in the cytosolic surveillance pathway and recognizes *Mtb*, leading to type 1 interferon induction and autophagy.[180–183] The most recent studies identify cGAS as the sensor for *Mtb* DNA in the cytosol leading to STING activation and autophagy induction.[180–182] Wasserman *et al.* in addition showed that AIM2 recognizes cytosolic *Mtb* DNA and triggered AIM2-dependent inflammasome activation and IL-1 production. They found that virulent and attenuated *Mtb* can engage distinct cytosolic pattern recognition receptor systems, namely the cGAS-IFN-axis vs
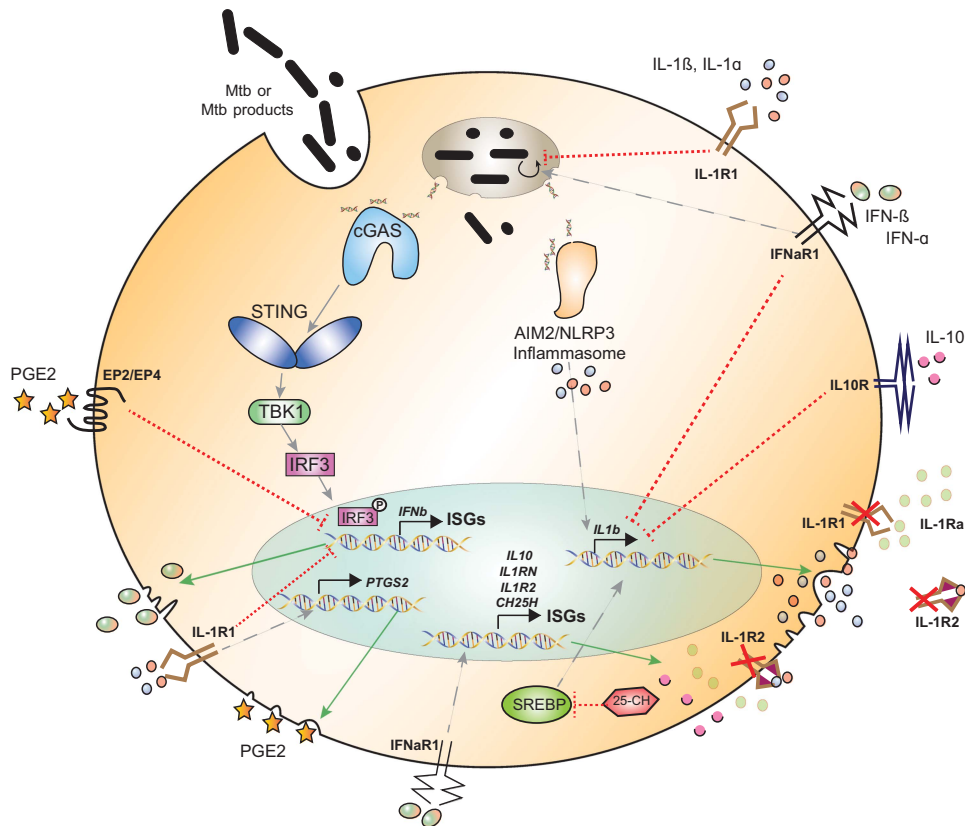
Figure 1 Cross-regulation between interleukin-1 (IL-1) and type-1 interferon (IFN) inflammatory pathways as exemplified during Mtb infection. *Mtb* infection triggers both cytosolic nucleotidyltransferase GAMP synthase-STING-TBK1-interferon regulatory transcription factor 3-interferon-β (cGAS-STING-TBK1-IRF3-IFN-β) axis and AIM2/NLRP3-IL-1β pathway in myelophagocytic cells. These two pathways exert opposite biological outcomes for host defense against *Mtb*: IL-1 is recognized as beneficial with anti-bacterial effects while type I IFNs are considered largely detrimental with replication promoting properties. IL-1α and IL-1β limit type I IFN production through direct transcriptional downregulation and *PTGS2*-mediated PGE2 production, which in turn inhibits type I IFN. Type I IFNs attenuate IL-1α/β signaling through induction of IL-10, IL-1R2, IL-1RA and CH25H.

the AIM2/NLRP3-IL-1β-pathway, and that the decision as to which pathway is triggered is determined by the relative abundance of EsxA and/or by additional ESX-1/EsxA-dependent effectors. Thus, the tug of war between IFN and IL-1 exists even at the single-cell level inside infected macrophages and centers around innate sensing of cytosolic DNA of *Mtb*.

Recent work uncovered that IL-1 can in turn counter-regulate type I IFN driven detrimental responses during *Mtb* infection.[78] In murine and human macrophages IL-1α and IL-1β potently inhibit type I IFN induction at both the mRNA and protein level, and similarly IFNβ mRNA and protein levels are upregulated in the lungs of *Mtb*-infected *Il1r1 − / −* deficient mice.[78] This inhibition is of functional importance because mice doubly deficient in *Il1r1,Ifnar1-/-* are partially protected while *Il1r1 − / −* singly deficient animals succumb rapidly to *Mtb* aerosol challenge. Moreover, when IL-1 is present in type I IFN-treated cultures, it even suppresses the pro-bacterial effects downstream of IFN that lead to increased bacterial replication. Interestingly, IL-1-induced PGE2 is also able to potently inhibit type I IFNs in a dose-dependent manner. Targeting PGE2 during *Mtb* infection, either via direct administration or its enhancement by 5 lipoxygenase blockade

with Zileuton, reversed poly-ICLC-mediated type I IFN driven mortality.[78] These data highlighted and provided proof-of-concept that the cross talk of IL-1 and type I IFN provides a valuable target for host-directed therapies of *Mtb* and plays a major role during infection in mice.[78] Thus, the above findings generated during the study of *Mtb* infection played into a broader context for previous studies that showed that IL-1 and PGE2 can inhibit type I IFN production.[176,177]

CONCLUDING REMARKS

Most of our insights into IL-1 driven inflammatory processes are based on studies during acute inflammation (or infection), where a trigger appears suddenly and leads to a rapid onset of innate and adaptive immune responses. Perhaps a key determinant in whether a particular inflammatory pathway such as IL-1 or type I IFN dominates, or the nature of the inflammatory cross talk, is whether the inflammatory stimuli is temporally limited or persistently present. For example, it has become increasingly appreciated that in particular IFNα/β can also be harmful during chronic viral infections, either by immunosuppressive effects that impair viral control or by triggering inflammation and tissue damage that exacerbates

disease.[184–187] Perhaps a contributing factor for the pronounced interplay between IL-1 and type I IFNs during pulmonary *Mtb* infection in contrast to other acute bacterial infections is the chronic nature of the infection and the slow replication time of the bacterium. The inability of a host to clear chronic pathogens promotes immunosuppressive programs that lead to sustained expression of both pro- and anti-inflammatory cytokines and vastly change the rules of engagement between inflammatory pathways. Understanding the rules of engagement, how they are influenced by both magnitude and quality of a given inflammatory trigger and how acute vs persistent stimuli influence the inflammatory equilibrium, will be key to develop novel anti-inflammatory agents and host-directed therapies for a variety of diseases.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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