Review

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Focus: Type-I interferons

Dynamic control of type I IFN signalling by an integrated network of negative regulators

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Whereas type I interferons (IFNs) have critical roles in protection from pathogens, excessive IFN responses contribute to pathology in both acute and chronic settings, pointing to the importance of balancing activating signals with regulatory mechanisms that appropriately tune the response. Here we review evidence for an integrated network of negative regulators of IFN production and action, which function at all levels of the activating and effector signalling pathways. We propose that the aim of this extensive network is to limit tissue damage while enabling an IFN response that is temporally appropriate and of sufficient magnitude. Understanding the architecture and dynamics of this network, and how it differs in distinct tissues, will provide new insights into IFN biology and aid the design of more effective therapeutics.

A regulatory network controlling type I IFN production and signalling

Type I IFNs are a family of cytokines (including α subtypes, β, ε, and others) with critical importance in controlling the innate and adaptive immune response to infection, cancer, and other inflammatory stimuli. IFNs have important roles in the protection of cells from viral and some bacterial infections, and are generally associated with the induction of protective immunity. However, the proinflammatory functions of IFNs can have potent adverse effects and can contribute to the pathogenesis of some bacterial infections [1]; in addition, uncontrolled activation of downstream pathways is associated with autoimmune diseases, including systemic lupus erythematosus (SLE), Sjögren's syndrome, rheumatoid arthritis and Aicardi–Goutieres syndrome (AGS) [2,3]. IFNα therapy is used to treat some chronic viral infections and cancers, while IFNβ therapy has been used to treat multiple sclerosis [4]; however, these therapies have dose-limiting toxicities, including nausea and malaise, and long-term treatment has been associated with adverse neurological effects, autoimmune type symptoms, and even death [3,5]. Thus, effective IFN responses require balance: sufficient IFN must be produced to elicit effective protective responses, but the amount and duration of the IFN response must be limited to minimise tissue damage and potential toxicities.

Type I IFNs elicit their effects through the activation of signalling proteins and the subsequent regulation of gene expression. In recent years, it has emerged that many IFN-regulated genes feedback on the signalling system to negatively regulate both type I IFN production and response. These negative feedback mechanisms involve a diverse range of molecules that act at all points throughout the IFN signalling pathway to control type I IFN production, signal transduction, and IFN-mediated transcription and translation. Ultimately, these negative feedback mechanisms form a finely balanced regulatory network that results in transient type I IFN production and controlled signalling outputs in response to infection, facilitating clearing of pathogens and a return to homeostasis, while limiting toxicities.

Here, we review evidence for the fine-tuning of the IFN response by extensive and integrated negative regulators of type I IFN production and action, operating at multiple levels of the response. We focus in particular on IFN-stimulated genes (ISGs), which are negative regulators, forming self-regulating feedback loops.

Pathways triggering production of type I IFNs

All nucleated cell types can produce type I IFN upon pathogenic infection via the detection of pathogen-associated molecular patterns (PAMPs). However, plasmacytoid dendritic cells (pDC) are specialised IFN-producing cells that can produce large amounts of IFN [6]. Type I IFNs can also be produced through rare cases of 'physiological' stimulus, such as in response to colony stimulating factor 1 (CSF1) or receptor activator of nuclear factor kappa-B (NF-κB) ligand (RANK) (for IFNβ production) or estrogen (for IFNε production) (Box 1) [7–9]. Recent evidence also demonstrates that RNA species produced following transcriptional depression of endogenous repeats, due to loss of p53 and DNA methylation, result in IFNβ production [10].

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Box 1. 'Physiological' production of type I IFNs

In addition to being produced in response to infection or other products associated with disease, there are several physiological situations where type I IFNs are produced. It has long been known that IFNβ is produced in response to macrophage colony-stimulating factor (M-CSF) stimulation of macrophage progenitors [8]. Similarly, RANKL induces the production of IFNβ in macrophages during osteoclast differentiation [9]. In both cases, *IFNB* gene expression is stimulated via the AP1 site in the IFNβ promoter [99]. The IFNβ produced in these circumstances has an antiproliferative effect on the respective myeloid lineage cells. Absence of these signals, for example in mice with null mutations in *Ifnar1*, results in higher numbers of myeloid progenitors [100] and osteoporosis due to increased numbers of osteoclasts [9]. Nonpathogenic activation of IFN production, specifically production of IFNβ, has also been observed in response to commensal organisms, such as *Lactobacillus* [101]. The molecular mechanisms involved are incompletely characterised, and the 'physiological' implications of this response remain unknown.

Another case of 'physiological' type I IFN production is the recently characterised IFNε, which is predominantly expressed in the female reproductive tract (FRT) [7]. IFNε is unusual because it is not induced by pathogens, but rather by estrogen, and its levels fluctuate during the menstrual cycle and pregnancy. It is important for optimal protection of the FRT from viral and bacterial infection. This novel IFN is also controlled by a unique form of negative regulation, being suppressed by progesterone [7]. This suppression may be important in the increased susceptibility to FRT infections in women during different hormonal states (stage of cycle or menopause) or in women taking particular formulations of oral contraceptives [102].

There are several pathways for pathogen detection via pattern recognition receptors (PRRs) that ultimately lead to the activation of one or more members of the interferon regulatory family (IRF) transcription factors, mainly IRF3 and IRF7, but also IRF1 and IRF5, as well as activation of NF-kB (in the case of IFNβ), to induce type I IFN expression [11]. PRRs include the transmembrane toll-like receptors TLR3, TLR4, TLR7, TLR8, and TLR9, which recognise PAMPs from a range of microorganisms and activate the myeloid differentiation primary response 88 (MYD88)-dependent pathway leading to IRF7 activation through a tumour necrosis factor receptor-associated factor 6 (TRAF6)-dependent mechanism (TLR7/8/9) or the Toll/interleukin-1 (IL-1) receptor-domain-containing adapter-inducing IFN-β (TRIF)-dependent pathway that leads to IRF3 and IRF7 activation through a TRAF family member-associated NF-κB activator-binding kinase 1 (TBK1)-dependent mechanism (TLR3/4) [12]. The retinoic acid-inducible gene (RIG)-I-like helicases, RIG-I and Melanoma Differentiation-Associated protein 5 (MDA5), are cytosolic receptors that recognise viral RNA leading to IRF3 and IRF7 activation through mitochondrial antiviral signalling protein (MAVS) and TBK1 [12]. The stimulator of IFN genes (STING)-dependent pathway, which is activated in response to cyclic dinucleotides and is downstream of cyclic GMP-AMP synthase (cGAS), results in TBK1 activation, IRF phosphorylation, nuclear translocation, and induction of IFN gene expression [13]. The DEAD/H-box helicases recognise cytosolic RNA (DDX1, DDX21 and DHX36) and DNA (DHX36 and DHX9) to induce type I IFN [14,15]. The NOD-like receptors (NLRs) can also recognise bacterial antigen (NOD1 and NOD2) and cytosolic DNA (NOD2) to induce type I IFN [12]. Therefore, the primary negative feedback mechanisms that exist to control type I IFN production target the PRRs, the intermediate signalling molecules, and the IRFs activated downstream. We discuss these further in later sections.

Type I IFN signalling and effector functions

Upon induction, type I IFNs act in an autocrine, paracrine, or systemic manner to stimulate a range of responses, of which the best characterised is the ability to induce an antiviral state within a cell through the upregulation of antiviral genes, such as myxovirus (influenza virus) resistance 1 *Mx1*, protein kinase R (*Pkr*), *Irf1 and* interferon, alpha-inducible protein 6 (*Ifi6*) among many [16]. However, they can also act on multiple cell types to modulate basic cellular processes, such as proliferation, differentiation, survival, and migration, and these functions have a significant role in the overall impact of type I IFNs on the cellular immune response to infectious and other diseases [17]. For example, IFNs mediate the clearing of viral infection through the expression of the cytokine chemokine (C-C motif) ligand 2 (CCL2) and recruitment of monocytes to the site of infection [18]. IFNs can induce DC maturation and MHC II-mediated antigen presentation to T cells [19]. They are major mediators of natural killer (NK) cell function [20] and can also act directly on B cells to enhance the antibody response [21], and on T cells to induce or inhibit survival, depending on the context of stimulation (activated versus naïve T cells) [17,22,23].

Type I IFN responses are all mediated via the IFNα receptor (IFNAR), comprising the subunits IFNAR1 and IFNAR2, which appear to be expressed on all cell types (see also Schreiber and Piehler, this issue). Binding of IFN to the receptor results in the phosphorylation and activation of the IFNAR1- and IFNAR2-associated tyrosine kinases tyrosine kinase 2 (TYK2) and Janus kinase 1 (JAK1). These in turn phosphorylate receptor tyrosine residues, resulting in the recruitment and activation of a range of signalling molecules, such as members of the signal transducer and activator of transcription (STAT) family of transcription factors. STAT phosphorylation and activation by type I IFNs results in their homo- or heterodimerisation, translocation to the nucleus, and regulation of gene expression. IFN-stimulated gene factor 3 (ISGF3), comprising STAT1, STAT2, and IRF9, binds to IFN stimulated responses elements, and can regulate the transcription of a set of IFN-stimulated genes (ISGs). Although this is the most thoroughly characterised type I IFN-stimulated STAT complex, type I IFNs can also activate STAT1 and STAT3 homo- and heterodimers, and STAT5 complexes [24–27]. STAT4 and STAT6 activation by type I IFNs has also been documented in certain cell types, including some endothelial and lymphoid cells [26,28]. Furthermore, there are numerous STAT-independent pathways activated by type I IFNs, including the Crk-like protein (CrkL)–Ras related protein 1 (RAP1) pathway, the p38 mitogen-activated protein kinase (MAPK) pathway (which is required for optimal transcription of ISGs), the extracellular signal-regulated kinase (ERK) pathway, the c-Jun N-terminal kinase (JNK) pathway, and the mammalian target of rapamycin (mTOR) pathway, which has an important role in mRNA translation of ISGs [29]. It is these pathways and

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