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# Regulation of type I interferon signaling in immunity and inflammation: A comprehensive review

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ABSTRACT

Type I interferons (IFNs) play essential roles in establishing and modulating host defense against microbial infection via induction of IFN-stimulated genes (ISGs) through Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling pathway. However, dysregulation of IFNs production and function could also mediate immune pathogenesis such as inflammatory autoimmune diseases and infectious diseases via aberrantly activating inflammatory responses or improperly suppressing microbial controls. Thus, IFN responses need to be tightly regulated to achieve protective immunity against microbial infection while avoiding harmful toxicity caused by improper or prolonged IFN signaling. Multiple levels of cellular and molecular events act in a cooperated manner to regulate IFN responses, in especial, post-translational modification (PTMs) of signaling molecules and epigenetic modification of gene expression programs are two important mechanisms for regulation of IFN signaling and thus critical for orchestrating IFN-mediated host immune response to the complex pathogenic or environmental stimuli. Conventional PTMs such as phosphorylation and polyubiquitylation, as well as numerous other PTMs including acetylation, ISGylation, SUMOylation and methylation have been shown to potently modulate type I IFN signaling transduction via targeting distinct signaling steps or components. Moreover, epigenetic mechanisms, such as histone modification, DNA methylation, non-coding RNAs play critical roles in regulating chromatin structure and function, leading to flexible and dynamic gene expression patterns downstream type I IFN signaling. Herein, we summarize the recent advances in the PTMs and epigenetic mechanisms in regulation of type I IFN signaling and responses. The involvement of dysregulated IFN signaling in inflammatory and autoimmune diseases are also discussed.



**Contents**



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## 1. Introduction

Interferon (IFN) was first identified by Alick Isaacs and Jean Lindenmann in 1957, as a strong interference of life cycle of influenza virus in chicken embryo [1]. Since then, IFNs provide a robust first line of host innate defense against pathogenic infection. Upon detection of microbial products via pattern-recognition receptors (PRRs), multiple types of immune and non-immune cells produce and secret IFNs, which subsequently orchestrate innate and adaptive immunity via multiple mechanisms. IFNs are a superfamily of cytokine which are now classified into three subtypes: type I, type II and type III. All these three types of IFNs trigger intracellular signaling cascades generally via Janus kinase (JAK)−signal transducer and activator of transcription (STAT) pathway, leading to diversified immunological functions under biological and pathological conditions.

In humans and mice, the type I IFN family includes 16 members, including 12 IFNα subtypes, IFNβ, IFNε, IFNκ and IFNω [2]. While macrophages and dendritic cells (DCs) mainly produce IFNβ, haematopoietic cells and plasmacytoid dendritic cells (pDC) predominantly produce IFNα. When pathogens are sensed by PRRs, IFNs are induced by activation of transcriptional factor IRF3 [3–5], which is controlled by multiple transcriptional regulatory mechanisms [6]. Following production, type I IFNs trigger the downstream signals to stimulate a wide range of genes transcription in an autocrine and paracrine manner. Canonically, type I IFNs initiate the signaling via binding to a heterodimeric receptor complex IFNAR, which consists of IFNAR1 and IFNAR2 subunits. Then IFNAR phosphorylates and activates the associated tyrosine kinases JAK1 and non-receptor tyrosine kinase 2 (TYK2) [7], which subsequently induces phosphorylation of transcription factors STAT1 and STAT2. Phosphorylated STAT1 and STAT2 dimerize and in turn recruit IFN-regulatory factor 9 (IRF9) to form STAT1-STAT2-IRF9 tri-complex (ISGF3). This complex then translocates into the nucleus, where it binds to DNA sequence motif known as IFN-stimulated response elements (ISRE; conserved sequence is TTTCNNTTTC) to activate transcription of a group of genes termed as IFN stimulated genes (ISGs) [8]. Proteins encoded by most ISGs contribute to protection of host cells from viral infection by different mechanisms, such as inhibition of virus entry, replication, translation, assembly and release [9]. In addition to form the ISGF3 complex, type I IFNs can also induce STAT1 to form homodimer which does not assemble with IRF9. This homodimer then binds to a distinct consensus sequence TTCNNNGAA named as gamma-activated sequence (GAS) in the promoters of ISGs [9] (Fig. 1). Furthermore, unphosphorylated STAT1 was shown to prolong the expression of a set of ISGs [10]. STAT2/IRF9 complex can also induce expression of ISG in STAT1-independent manner [11].

Except for the JAK-STAT dependent pathway, type I IFN can also active downstream signaling through STAT-independent pathways. Mitogen activated protein kinases (MAPKs) including p38 and extracellular signal regulated kinases (ERKs) play critical roles in IFN-mediated genes expression [7]. Inhibition of p38 activity blocked IFNα-induced transcriptional activation of genes via ISREs elements, nevertheless without affecting the phosphorylation of STAT1 or STAT2, or formation of ISGF3 complex and GAS elements [12]. Thus, kinase p38 is required for IFN-mediated signaling which is independent of STATs activity. In addition to the p38, other MAPKs pathways are also reported to involve IFN downstream signaling, such as MEK-ERK pathway. Myxoma virus induces an ERK1/2 signaling which is required for further type I IFN production and IFN signaling [13]. Besides, the phosphatidylinositol 3-kinase (PI3K) pathway is demonstrated to mediate type I IFNs-stimulated gene transcription as well. Type I IFNs can induce phosphorylation of insulin receptor substrate 1 (IRS1), which in turn associates with the regulatory subunit of PI3K-p85, and then activates PI3K's catalytic subunit p110. Activated PI3K promotes gene transcription through phosphorylating protein kinase C (PKC) [7]. Another downstream signaling component of PI3K-Akt pathway is mammalian target of rapamycin (mTOR), a key protein regulating mRNA translation. The mTOR pathway kinase- p70 S6K is found to be rapidly phosphorylated and activated in response to IFNα and IFNβ stimulation, which then inactivates and dissociates the 4E-BP-1 repressor from the eukaryotic initiation factor-4E (eIF4E) complex to upregulate IFN-induced mRNA translation [14] (Fig. 1).

In a general sense, the canonical and uncanonical IFN signaling elicit multiple immunological functions via affecting various cellular processes including proliferation, differentiation, activation, migration, apoptosis, *etc*. For example, IFNs have been shown to promote antigen-presentation activity, inhibit inflammasome activation, upregulate pro-inflammatory cytokines production [15], or regulate the function or activation of innate lymphoid cells [16,17] or T cells [18]. Notably, dysregulated IFN responses are increasingly shown to be associated with many immune disorders such as chronic infection, autoimmune and inflammatory diseases. Therefore, an integrated regulation is required to shape the overall outcome of IFN responses to achieve the balance between IFN-mediated protective immunity and tissue toxicity from aberrant IFN signaling.

Post-translational modifications (PTMs) and epigenetic modifications are two emerging critical molecular mechanisms for modulation of intracellular signaling transduction and gene expression, respectively [19]. Cellular response to type I IFNs varies according to different cell types, during different phases of infection, or under different host or environmental stimuli. This heterogeneity and flexibility of IFN signaling derives from the precise and dynamic regulatory networks at both cellular and molecular level [20,21]. Upon infectious stimuli, the IFN signaling must be immediately activated to establish the first line of protective immunity, while after clearance of infection, IFN response should be appropriately and timely controlled to avoid the harmful tissue damage. To achieve this, type I IFN signaling is modulated via various mechanisms, such as 1) alteration of the activity and interaction of signaling components via PTMs, and 2) modulation of IFN-dependent gene transcription by changing chromatin states and function via