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Interferon regulatory factors: at the crossroads of immunity, metabolism, and disease ☆

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ABSTRACT

The interferon-regulatory factor (IRF) family comprises nine members in mammals. Although this transcription factor family was originally thought to function primarily in the immune system, contributing to both the innate immune response and the development of immune cells, recent advances have revealed that IRFs plays critical roles in other biological processes, such as metabolism. Accordingly, abnormalities in the expression and/or function of IRFs have increasingly been linked to disease. Herein, we provide an update on the recent progress regarding the regulation of immune responses and immune cell development associated with IRFs. Additionally, we discuss the relationships between IRFs and immunity, metabolism, and disease, with a particular focus on the role of IRFs as stress sensors. This article is part of a Special Issue entitled: Autophagy and protein quality control in cardiometabolic diseases.

1. Introduction

The mammalian interferon regulatory factor (IRF) family of transcription factors comprises nine members: IRF1, IRF2, IRF3, IRF4/PIP/LSIRF/ICSAT, IRF5, IRF6, IRF7, IRF8/ICSBP, and IRF9/ISGF3γ [1,2]. All IRF proteins possess a conserved amino (N)-terminal DNA-binding domain (DBD) of ~120 amino acids that is characterized by a series of five well-conserved tryptophan-rich repeats [1]. The DBD forms a helix-turn-helix domain and recognizes DNA that is similar in sequence to the IFN-stimulated response element (ISRE, A/GNGAAANNGAAACT). The carboxy-terminal regions of IRFs exhibit greater diversity and participate in interactions with other members of the IRF family, other transcription factors, and co-factors. Thus, the carboxy-terminal region confers specificity to each IRF [1,3,4]. Two types of association modules have been identified in the carboxy-terminal regions of IRFs: IRF-associated domains 1 and 2 (IAD1 and IAD2). IAD1 is conserved in all IRFs except IRF1 and IRF2 and has a structure similar to that of the Mad-homology 2 (MH2) domains of the Smad family of transcription factors, whereas IAD2 is present only in IRF1 and IRF2.

Although IRFs were first identified as transcriptional regulators of type I IFNs and IFN-inducible genes, this family is now recognized to play a crucial role in the regulation of immune responses and immune cell development [1,5]. In addition to their contributions to immunity, accumulating evidence indicates that IRFs also have critical functions in the regulation of oncogenesis [6] and metabolism [7,8]; therefore, they are involved in the pathogenesis of the associated diseases [9–24]. IRFs were initially considered to be specifically expressed in immune cells; however, some IRFs, such as IRF4 and IRF8, have been detected in other tissues, such as the heart, kidney, brain, and liver. Here, we provide an update on the recent progress regarding the regulation of immune responses and immune cell development by IRFs and discuss the relationships between IRFs and immunity, metabolism, and related diseases.

2. Regulation of innate immune responses by IRFs

The initial sensing of infection is mediated by innate pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs) [25]. These receptors recognize various pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). In response to diverse PAMPs and/or DAMPs, the intracellular signaling cascades differentially triggered by these PRRs induce the transcription of type I IFNs, pro-inflammatory cytokines, and chemokines that coordinate the elimination of pathogens and infected cells. IRFs are essential mediators that transmit PRR signals to chromatin for immune cell activation [26].

The innate immune system utilizes different PRRs to detect pathogens depending on their modes of infection. These PRRs can be classified based on their locations: TLRs and CLRs are present on the cell membrane, whereas RLRs and NLRs are found in the cytoplasm [27].

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Here, we introduce the IRFs that function downstream of each of these PRRs.

2.1. IRFs involved in cell surface PRR signaling

2.1.1. IRFs involved in TLR signaling

TLRs are the most well characterized signal-generating receptors among the PRRs; they initiate key inflammatory responses in addition to shaping the adaptive immune response [28]. All TLRs, approximately 11 of which are known in mammals, are type I integral membrane glycoproteins comprising an extracellular domain with leucine-rich repeats (LRRs), which is responsible for ligand recognition, and a cytoplasmic Toll/IL-1R homology (TIR) domain, which is required for the initiation of signaling. These receptors are either expressed on the cell surface or associated with intracellular vesicles. TLR1, TLR2, TLR4, TLR5, and TLR6 are localized on the cell surface and are largely responsible for recognizing microbial membrane components, whereas TLR3, TLR7, TLR8, and TLR9 are expressed within intracellular vesicles and recognize nucleic acids. TLRs initiate shared and distinct signaling pathways by recruiting different combinations of four TIR domain-containing adaptor molecules: MyD88, TIRAP (MAL), TRIF (TICAM1), and TRAM [29].

Signaling through TLRs can be broadly categorized into two pathways: the MyD88-dependent pathway and the TRIF-dependent (or MyD88-independent) pathway. All TLRs, with the exception of TLR3, activate the MyD88-dependent pathway. In contrast, TLR3 and TLR4 activate the TRIF-dependent pathway. Moreover, TLR4 requires the additional adaptors TIRAP and TRAM for the recruitment of MyD88 and TRIF, respectively. To transmit signals, most TLRs directly associate with either MyD88 or TRIF.

2.1.1.1. IRFs involved in the TRIF-dependent pathway. TLR4 and TLR3 both use the TRIF adaptor protein to activate IRF3 and induce type I IFNs (Fig. 1A). TLR4 recognizes lipopolysaccharide (LPS) from gram-negative bacteria in addition to a variety of other PAMPs or DAMPs, and is the only TLR that recruits four adaptor proteins and activates two distinct signaling pathways: the MyD88-dependent and TRIF-dependent pathways [29].

TLR4 initially recruits TIRAP and MyD88. MyD88 then recruits IRAKs, TRAF6, and the TAK1 complex, leading to the early-phase activation of NF-κB and MAP kinases [29]. TLR4 is then endocytosed and delivered to intracellular vesicles to form a complex with TRAM and TRIF. This complex then recruits TRAF3 and the protein kinase TBK1, which catalyze the phosphorylation of IRF3, leading to the expression of type I IFN. TRAM-TRIF also recruits TRAF6 and TAK1 to mediate the late-phase activation of NF-κB and MAP kinases [28]. In Irf3$^{-/-}$ dendritic cells (DCs), IFNβ induction is not responsive to LPS, whereas this induction is approximately normal in Irf7$^{-/-}$ cells. Consistent with these findings, mice lacking Irf3 exhibit resistance to LPS-induced endotoxic shock, in which IFNβ plays a central role. Thus, TLR4-induced IFN-β production is primarily mediated by IRF3 through TBK1 [1].

TLR3 is expressed within intracellular vesicles and recognizes dsRNA, including the synthetic dsRNA analog poly(rI:rC) and viral dsRNA derived from either dsRNA or single-stranded RNA (ssRNA) viruses. TLR3 is also required for the recognition of some DNA viruses, such as herpes simplex virus (HSV) and murine cytomegalovirus, and parasites, such as *Leishmania donovani* and *Schistosoma mansoni* [26]. Similar to TLR4 activation, TLR3 activation also induces the expression of type I IFN via a TRIF-, TBK1-, and IRF3-dependent pathway.

2.1.1.2. IRFs involved in the MyD88-dependent pathway. TLR7 recognizes the genomic ssRNA of ssRNA viruses, whereas TLR9 recognizes hypomethylated CpG DNA motifs present in bacteria and DNA viruses [26]. In contrast to TLR3- or TLR4-mediated type I IFN gene induction, which is dependent on TRIF, TLR7 and TLR9 exclusively use MyD88 as a signaling adaptor (Fig. 1B).

IRF7 is essential for the induction of the IFNβ gene via the MyD88-dependent pathway in plasmacytoid dendritic cells (pDCs), which are characterized by their high level of type I IFN. The induction of IFNβ mRNA upon viral infection is impaired in purified pDCs from Irf7$^{-/-}$ mice but is normal in Irf3$^{-/-}$ pDCs [30]. IRF7 directly interacts with the death domain of MyD88 to form a complex that also involves IRAK1, IRAK4, and the E3 ubiquitin ligase TRAF6. Furthermore, IKKα associates with and phosphorylates IRF7. The IRAK4–IRAK1–IKKα kinase cascade functions as a signal transducer between MyD88 and TRAF6 and is required for the phosphorylation of IRF7 as well as the activation of IFN-dependent promoters [26].

IRF5 generally functions downstream of the TLR–MyD88 signaling pathway to induce the gene expression of proinflammatory cytokines, such as interleukin-6 (IL-6), IL-12, and tumor necrosis factor-α (TNF-α). IRF5 interacts with and is activated by MyD88 and TRAF6. In contrast with IRF7, IRF5 interacts with the central region (i.e., the intermediary domain and part of the TIR domain) of MyD88. Additionally, TRAF6-mediated K-63-linked ubiquitination is important for IRF5 nuclear translocation and target gene regulation [31]. Following TLR9 activation, the phosphorylation of serine/threonine residues in the carboxy-terminal autoinhibitory region of IRF5 triggers conformational rearrangements that convert the C-terminal segment from an autoinhibitory domain to a dimerization domain, thus facilitating the interaction of IRF5 with CBP/p300 in the nucleus [32].

IRF1, which is induced by IFN-γ, also interacts with and is activated by MyD88 upon TLR activation [33]. MyD88-associated IRF1 migrates into the nucleus more efficiently than non-MyD88-associated IRF1 to mediate the efficient induction of IFNβ, iNOS, and IL-12p35 expression. Thus, IRF1 activation via the TLR–MyD88 pathway links IFN-γ and TLR signaling events.

IRF4 and IRF5 bind to the same region of MyD88, which is distinct from the region that is bound by IRF7. Upon TLR activation, induced IRF4 competes with IRF5 and inhibits its sustained activity. The TLR-dependent induction of proinflammatory cytokines is markedly enhanced in peritoneal macrophages from mice lacking IRF4, whereas this induction is inhibited by the ectopic expression of IRF4 in a macrophage cell line. Mice lacking IRF4 also exhibit hypersensitivity to DNA-induced shock, as evidenced by elevated serum proinflammatory cytokine levels [34]. Therefore, IRF4 negatively regulates TLR signaling and inhibits the production of proinflammatory cytokines in response to TLR stimulation.

IRF8 has the greatest homology with IRF4 and is involved in the unmethylated CpG DNA-induced TLR9 signaling pathway. DCs from mice lacking IRF8 are unresponsive to CpG and fail to induce TNF-α and IL-6, while these cytokines are robustly induced in IRF8$^{-/-}$ DCs in response to LPS, which signals through TLR4. This effect is due to the selective inability of IRF8$^{-/-}$ DCs to activate IκB kinases α and β, which are required for NF-κB activation in response to CpG, suggesting that IRF8 acts upstream of NF-κB. Although IRF8 does not bind to MyD88, it interacts with TRAF6, which is an ubiquitin ligase that is essential for the activation of NF-κB and MAP kinases downstream of the TLR signaling pathway. IRF8 can also function as a transcription factor to promote the induction of Il12b gene expression in macrophages and DCs by directly binding to the Il12b promoter with IRF1 and NFAT. Additionally, IRF8 promotes type I interferon induction by prolonging the recruitment of the basal transcription machinery to IFN promoters in DCs, a role that is not shared by IRF7 or IRF3 [26].

2.1.2. IRFs involved in CLR signaling

Similar to TLRs, CLRs are also localized to the plasma membrane. Recent studies have identified the CLRs as an important family of PRRs that are involved in the induction of pathogen-specific gene expression profiles either by modulating TLR signaling or by directly inducing gene expression [35]. CLR ligands include carbohydrate, protein, and lipid components that are specific to both pathogens and self-antigens; these ligands can trigger endocytic, phagocytic, proinflammatory, and anti-inflammatory reactions [36]. Most cell types, including myeloid