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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: From Genome to Function.

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

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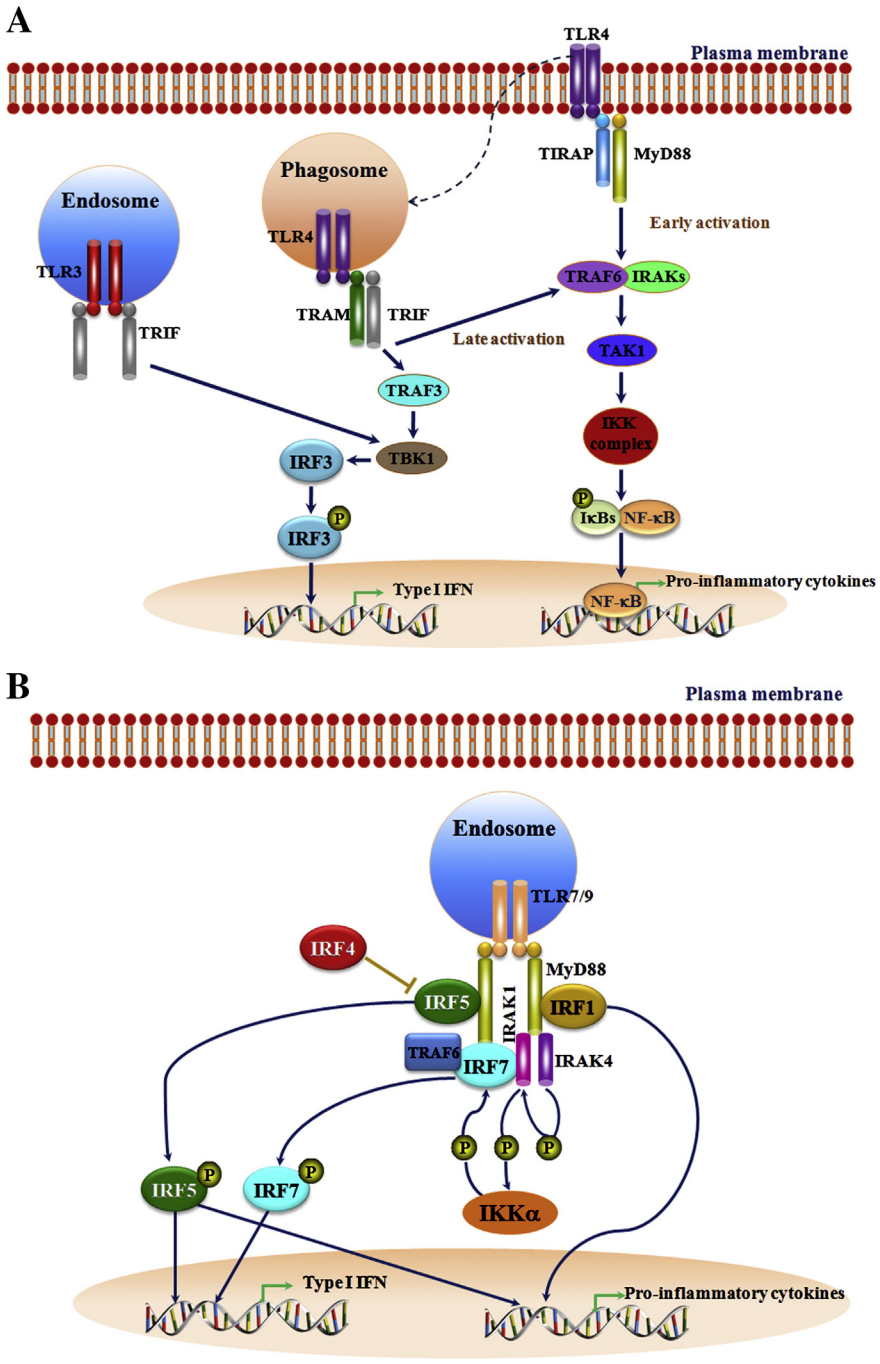

Fig. 1. IRFs involved in TLR signaling. (A) TLR4 initially recruits TIRAP and MyD88 for the early-phase activation of NF-κB. TLR4 is then transported into phagosomes, where it recruits TRAM and TRIF and activates TRAF3, TBK1, IRF3 as well as late-phase NF-κB activation for the induction of type I IFN. TLR3 also recruits TRIF and activates TBK1, IRF3 to induce the expression of type I IFN. Upon activated by TBK1, IRF3 is phosphorylated and translocated to the nucleus. (B) TLR7 and TLR9 are located in the endosomal compartment, where they engage with their ligands. After activation, IRF7 binds to MyD88 to form a complex that involves IRAK1, IRAK4, and TRAF6 and is activated by IRAK4–IRAK1–IKKα kinase cascade. IRF1 and IRF5 also interact with MyD88. IRF4 and IRF5 bind to the same region of MyD88, thus blocking the interaction of IRF5 with MyD88.

cells such as macrophages and DCs, express CLRs. CLR-induced signal transduction appears to primarily activate or modulate NF-κB functions; however, the regulation of other transcription factors by CLRs has received little attention to date.

A recent study described a pathway for IFNβ production by DCs that depends on the activation of Dectin-1 and Dectin-2, which are CLRs that recognize the complex β-glucan cell wall of *C. albicans* [37]. Moreover, Dectin-1-induced IFNβ production is dependent on Syk- and Card9-driven signaling as well as IRF5 but is independent of IRF3 and IRF7. IRF5 was found to be strongly required for Dectin-1-mediated IFNβ production, as demonstrated using bone marrow-derived DCs (BMDCs) from Irf5$^{-/-}$ mice. Together, the production of type I IFN by renal-infiltrating DCs, mediated by Dectin-Syk-IRF5 signaling, plays a crucial role in defense against *C. albicans* infection [37]. The question of whether there are other relationships between CLRs and IRFs requires further study.

2.2. IRFs involved in cytosolic PRR signaling

In addition to membrane-bound PRRs, PAMPs and DAMPs can also be recognized by cytosolic PRRs, including RLRs, cytosolic DNA sensors, and NLRs [25]. RLRs, such as RIG-I and MDA5, as well as cytosolic DNA

sensors are primarily involved in cytosolic RNA and DNA detection, respectively (Fig. 2). In contrast, NLRs are primarily involved in recognizing the peptidoglycans of intracellular bacteria.

2.2.1. IRFs involved in RLR signaling

Viruses such as the Newcastle disease virus (NDV) and Sendai virus (SV), which enter the cytoplasm of cells directly, as well as dsRNA that is synthesized during active viral replication cannot be detected by membrane-bound PRRs. Members of the RLR family, which comprises RIG-I and melanoma differentiation-associated gene 5 (MDA5), are intracellular sensors that have evolved to detect such viruses. RLRs are RNA sensors that are composed of two N-terminal caspase recruitment domains (CARDs), a central DEAD box helicase/ATPase domain, and a C-terminal regulatory domain. RIG-I and MDA5 show both selectivity and redundancy in their ability to detect virus infection, and they recognize different RNA viruses by detecting short dsRNAs (up to 1 kb) with 5' triphosphate ends and long dsRNAs (more than 2 kb), respectively. Moreover, mouse embryonic fibroblasts (MEFs) derived from RIG-I$^{-/-}$ MDA5$^{-/-}$ mice fail to produce type I IFNs in the presence of any of the RNA viruses tested, indicating that RIG-I and MDA5 are essential and sufficient for evoking type I IFN production in response to RNA viruses [25].

The CARDs of RIG-I and MDA5 are responsible for triggering signaling cascades by interacting with the N-terminal CARD-containing adaptor IFNβ-promoter stimulator 1 (IPS-1) [38](also known as MAVS, CARDIF, and VISA). IPS-1, which is localized on the mitochondrial membrane, then relays signals to TBK1 and IKKε, which phosphorylate IRF3 and IRF7.

IRF3 and IRF7 share the greatest structural homology and have essential roles in the RIG-I/MDA5-mediated type I IFN gene induction pathway. IRF3 is constitutively expressed and is initially restricted to the cytoplasm in a latent form in unstimulated cells due to its carboxy-terminal auto-inhibitory domain. Upon viral infection, RIG-I- or MDA5-activated TBK1 phosphorylates IRF3 at Ser396, 398, 402, 404, and 405 in site 2 of the carboxy (C)-terminal regulatory region, which alleviates auto-inhibition and causes IRF3 nuclear translocation. Once in the nucleus, IRF3 interacts with the coactivator CBP, which facilitates phosphorylation of IRF3 at site 1 (Ser385 or Ser386). Phosphorylation at site 1 is, in turn, required for IRF3 dimerization. IRF3 dimerizes with itself or with IRF7 to form a holocomplex that also contains coactivators such as CBP and p300 [2]. This holocomplex binds to the promoters of type I IFN genes and other target genes to facilitate their expression.

In contrast with IRF3, IRF7 is initially expressed at a low level prior to virus infection but is strongly induced by ISGF3 (a heterotrimeric complex consisting of Stat1, Stat2, and IRF9) through the Jak-STAT signaling pathway via IFN receptor activation in an autocrine manner. Similar to IRF3, IRF7 exists in a latent form in the cytoplasm of resting cells, and upon stimulation, the TBK1-induced phosphorylation of serine residues in its carboxy-terminal region causes it to translocate into the nucleus, enabling the induction of type I IFN gene expression. IRF7 forms a heterodimer with IRF3 to induce the production of IFNα4 and IFNβ in the early phase of the response. The initially induced type I IFN then, in turn, activates the expression of IRF7, which participates in the induction of most IFNα subtypes, thus functioning as a key mediator of the type I IFN amplification loop in the later phase of the response. IRF7 is expressed constitutively in certain cells, including pDCs and macrophages, readying them for rapid IFNα production. Thus, the positive feedback regulation of IRF7 allows for the full induction of type I IFN genes [2,4].

In addition to IRF3 and IRF7, IRF5 can also contribute to the RLR signaling pathway after viral infection. Mice lacking IRF5 are highly sensitive to viral (VSV or NDV) infection and possess lower levels of type I IFN in the serum. IFN production is also impaired in infected macrophages, whereas no decrease is observed in Irf5$^{-/-}$ MEFs, suggesting that the function of IRF5 may be cell-type-specific. It has recently been demonstrated that the IPS-1-dependent induction of ISGs can occur through an IRF5-dependent, yet IRF3- and IRF7-independent, pathway during West Nile virus (WNV) infection, which suggests a signaling link between the RLR pathway and IRF5 [39]. However, the precise mechanism by which IRF5 is activated by RIG-I, including how IRF5

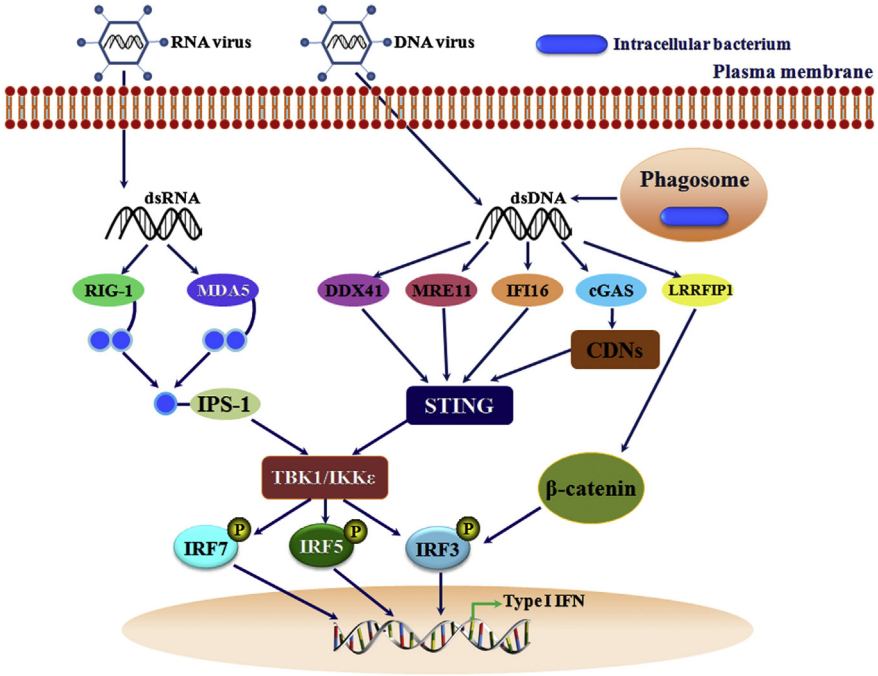

Fig. 2. IRFs involved in cytosolic nucleic acid mediated signaling. Cytosolic dsRNA are recognized by RIG-1 or MDA5 and triggers their interaction with the adaptor protein IPS-1, which leads to the activation of TBK1. Cytosolic dsDNA are recognized by DDX41, MRE11, IFI16, and cGAS to induce STING-dependent pathway and then activate TBK1/IKKε, which phosphorylate IRF3, IRF5, and IRF7. Independent of STING, β-catenin is activated by LRRFIP1 then interacts with IRF3. Activated IRFs translocate to the nucleus to induce the expression of type I IFNs and pro-inflammatory cytokines.

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dimerizes with IRF3 or IRF7 and contributes to the transcriptional regulation of type I IFN and proinflammatory genes, requires further investigation.

2.2.2. IRFs involved in cytosolic DNA-mediated signaling

In addition to RNA-mediated signaling pathways, cytosolic signaling pathways that sense microbial and host DNA in the cytoplasm have recently been discovered [40,41]. During infection or in response to stress signals, aberrantly localized DNA, such as that in the cytoplasm and endosomes, can induce type I IFN and proinflammatory cytokine expression. As discussed above, the endosomal-based DNA sensor TLR9 is responsible for recognizing unmethylated CpG DNA; however, several cytosolic sensors involved in the recognition of both foreign and host DNA have also been identified [40,41].

Cytosolic DNA can induce a caspase-1- and stimulator of interferon genes (STING)-dependent pathway in which IRF3 is activated downstream of STING via TBK1. STING (also known as MITA, ERIS, and TMEM173) is an adaptor protein localized in the endoplasmic reticulum (ER), where it relays signals from cytosolic DNA sensors [42]. In response to cytosolic dsDNA, the C-terminal tail (CTT) of the carboxy-terminal domain (CTD) of STING functions as a scaffold for the assembly of IRF3 in close proximity to TBK1, thus promoting the TBK1-dependent phosphorylation of IRF3 [43]. Therefore, STING directs TBK1 to activate IRF3 for DNA-sensing pathways. Although STING is not a direct sensor of DNA, it directly recognizes bacterial second messenger molecules termed cyclic dinucleotides (CDNs), such as cyclic di-GMP (c-di-GMP), which are produced by cGAMP synthetase (cGAS) in response to cytosolic DNA [44–47].

Upstream of STING, direct DNA sensors such as IFN-γ-inducible 16 (IFI16) [48–50] and DEAD-box-polypeptide 41 (DDX41) [51,52] bind to DNA motifs and subsequently associate with STING to induce type I IFN gene expression. Additionally, one study demonstrated that LRRFIP1 binds exogenous nucleic acids and increases the dsRNA- and dsDNA-induced expression of IFNβ. LRRFIP1 interacts with β-catenin and promotes its activation. In turn, activated β-catenin increases IFNβ expression by binding to the C-terminal domain of IRF3 and recruiting the acetyltransferase p300 to the IFNβ enhanceosome via IRF3 [53]. Another report showed that meiotic recombination 11 homolog A (MRE11), initially identified as a factor functioning in DNA damage responses, also serves as a cytosolic sensor for dsDNA. In association with its binding protein RAD50, MRE11 physically interacts with dsDNA in the cytoplasm and is required for the activation of STING and IRF3 [54].

2.2.3. IRFs involved in NLR signaling

Similar to RLRs, NLRs are cytoplasmic pathogen sensors that are composed of a central nucleotide-binding domain and C-terminal leucine-rich repeats [55]. The NLR family consists of three distinct subfamilies: the NODs (NOD1-2, NOD3/NLRC3, NOD4/NLRC5, NOD5/NLRX1, and CIITA), the NLRPs (NLRP1-14, also referred to as NALPs), and the IPAF subfamily, among which IRF3 and IRF5 are reported to be involved in NOD2-mediated IFN induction [56,57].

After recognizing the ssRNA genome of respiratory syncytial virus (RSV), Nod2 has been reported to use the adaptor protein IPS-1 to activate IRF3. Nod2-deficient mice fail to produce IFN efficiently and show enhanced susceptibility to virus-induced pathogenesis [56]. Another study reported that Nod2 is a significant activator of IRF5 via receptor-interacting protein 2 (RIP2) [57]. However, it is not clear whether other IRFs are involved in NLR signaling. Of note, a major function of one subfamily of NLR proteins is the activation of inflammasomes, which are molecular platforms that trigger the maturation of IL-1β to activate components of the innate immune system. However, the question of whether IRFs are involved in regulating the inflammasome system requires further study.

As we have described above, in innate immune responses, IRFs can be activated by various PRRs; a single IRF can be involved in several signaling pathways downstream of different PRRs, and a single PRR can activate several IRFs. These complex interactions are possible because IRFs can interact with common adaptors or kinases in diverse signaling pathways, such as MyD88 and TBK1 in the TLR and RLR signaling pathways, respectively. Active IRFs then induce shared but distinct sets of target genes, which eventually determine the specific immune response directed at clearing the pathogen. This phenomenon indicates the possibility of cross-talk between these pathways, and the question of how the pathways might interact with each other is currently under investigation [26,58]. Furthermore, the specificity and level of IRF binding to the genome are controlled based on the cooperation of IRFs with other transcription factors, such as PU.1 and BATF (also see below). Thus, the integration of signaling pathways and the interaction of transcription factors with chromatin remodeling complexes constitute a regulatory network that appropriately shapes the immune response.

3. Regulation of immune cell development and functions by IRFs

As discussed above, IRFs function as important mediators that respond to a variety of upstream PRRs, and they translate stress signals, such as those induced by infection or injury, into downstream transcriptional outputs, such as the expression of type I IFN and proinflammatory cytokines. In addition to the signal transduction functions of IRFs in innate immune responses, multiple IRFs (IRF1, IRF2, IRF4, and IRF8) also play essential roles in the development of immune cells, including dendritic, myeloid, natural killer (NK), B, and T cells.

3.1. IRFs in the development and function of DCs

DCs are essential for antigen presentation and the initiation of protective T-cell responses; thus, they bridge the innate and adaptive immune systems. DCs recognize pathogens using PRRs, as described above, and subsequently present pathogen-derived antigens to antigen-specific T cells. Activated DCs up-regulate co-stimulatory molecules and major histocompatibility complex (MHC) II for antigen presentation and produce cytokines that activate various types of immune cells.

DCs are a heterogeneous group of cells that have been divided into different subsets. The four major categories of DCs are conventional DCs, Langerhans cells, plasmacytoid DCs (pDCs), and monocyte-derived DCs [59]. Conventional DCs can be further grouped into two main classes: migratory DCs (consisting of CD11b + DCs and CD103 + DCs) and lymphoid tissue-resident DCs (consisting of CD4 + DCs, CD8α + DCs, and CD4-CD8α − DCs [typically referred to as double-negative DCs]). Functionally, CD103 + DCs correspond to lymphoid tissue-resident CD8α + DCs, whereas CD11b + DCs correspond to lymphoid tissue-resident CD4 + DCs [59].

DC development is controlled by a group of transcription factors, including IRFs, which specify and direct the differentiation of the different subsets of DCs. The development of a DC subset is primarily determined by IRF4 and IRF8. These IRFs have overlapping activity and stimulate a common process of DC development; nonetheless, each IRF also possesses the ability to stimulate subset-specific gene expression, leading to the generation of functionally divergent DCs. For example, IRF4 is required for the generation of CD4 + DCs, whereas IRF8 is essential for CD8α + DCs. Both IRF4 and IRF8 support the development of CD4-CD8α − DCs. IRF8 and, to a lesser degree, IRF4 contribute to pDC development. Consistent with these roles, IRF4, but not IRF8, is expressed in CD4 + DCs, whereas only IRF8 is expressed in CD8α + DCs. Both CD4-CD8α − DCs and pDCs express IRF4 and IRF8 [5].

Moreover, a recent finding indicates that IRF4 promotes cutaneous DC migration to lymph nodes but is dispensable for DC development [60]. CD11b + dermal DCs in IRF4$^{-/-}$ mice do not express the chemokine receptor CCR7 and fail to migrate to cutaneous lymph nodes. Thus, IRF4 is not only involved in the differentiation of DCs but is also important for their proper functioning during homeostasis and inflammation. Recently, two reports [61,62] have shown that IRF4 is required

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for the development of intestinal CD103+ CD11b+ DCs, which represent the major migratory DC population within the small intestinal lamina propria (SI-LP). Furthermore, these cells secrete the cytokines IL-6 and IL-23 to induce Th17 cell differentiation. Similarly, the development of a dermal DC subset (CD301b+) that appears to be specialized for the regulation of Th2 cell responses is also dependent on IRF4 [63,64]. The targeted deletion of Irf4 specifically in CD11c-expressing cells leads to the absence of CD301b+ (CD8α−) migratory DCs in skin-draining lymph nodes. Thus, the lack of certain populations of CD11b+ CD8α− DCs from the lamina propria, the lung, and tissue-draining lymph nodes in DC-Irf4-deficient mice indicates the importance of IRF4 in specifying the CD4+/CD11b+ DC subsets [61,62,64].

Consistent with the role of IRF8 in the development of pDCs, granulocyte macrophage colony-stimulating factor (GM-CSF) suppresses the differentiation of pDCs by employing STAT5 to inhibit IRF8 and the pDC transcriptional network [65]. Although CD8α+ DCs and pDCs both require IRF8 for development, the mechanisms underlying the development of these DC subsets are different. A point mutation in the Irf8 gene that changes arginine (R) to cysteine (C) at position 294 (IRF8R294C) results in the failure of IRF8 to interact with its partner transcription factors, including IRF2, PU.1, and SpiB, and abolishes the development of CD8α+ DCs without impairing pDC development [66]. In addition to its involvement in the later stages of CD8α+ DC and pDC development, IRF8 also regulates common DC progenitor (CDP) development and the initial commitment to the DC lineage through the suppression of neutrophil potential in both myeloid and lymphoid progenitors [67]. Irf8-deficient DC progenitors show reduced expression of several important transcription factors, including Id2, Bach2, Klf4, and Bcl, all of which are required for the development of different DC subsets. Importantly, a clinical study has also revealed that the K108E and T80A mutations impair the transcriptional activity of IRF8 by disrupting its interaction with DNA, leading to defects in DC and monocyte development in addition to severe opportunistic infections [68].

Similar to IRF8, the AP1 family member Batf3 is required for the development of CD8α+ classical dendritic cells (cDCs) and related CD103+ DCs [69]. However, a recent study identified a BATF3-independent pathway for CD8α+ cDC development that results from molecular compensation for BATF3 by BATF and BATF2 [70]. BATF (basic leucine zipper transcription factor ATF-like), BATF2 and BATF3 comprise the BATF family, which is a subgroup of basic leucine zipper transcription factors. Functional compensation for Batf3 provided by Batf and Batf2 is based on the shared specificity defined by the BATF basic leucine zipper domain to interact with IRF4 and IRF8 to mediate cooperative gene activation. Several studies have reported chromatin innunoprecipitation-coupled with massively parallel sequencing (ChIP–Seq) analyses of IRF4 and BATF in Th17 cells and demonstrated the presence of AP1 and IRF composite elements (AICEs) in several important genes in Th17 cells. The AICE motif directs the assembly of IRF4 or IRF8 with BATF heterodimer, and is also found in B cells and Th2 cells (see sections on B and T cells) [71].

In addition to IRF4 and IRF8, IRF1 and IRF2 are also involved in DC subset development. IRF1-deficient mice ($IRF1^{-/-}$) exhibit a predominance of pDCs and a selective reduction of conventional DCs, particularly the CD8α+ subset [72]. Accordingly, $IRF1^{-/-}$ DCs are unable to fully mature, and they retain plasmacytoid and tolerogenic characteristics following virus infection ex vivo and in vivo. In contrast, IRF2 is essential for the development of splenic and epidermal CD4+ DCs by negatively regulating IFN-α/β signals. $IRF2^{-/-}$ mice exhibit a selective, cell-autonomous deficiency in the CD4+ DC subset, and this deficiency is rescued by introducing an additional null mutation in the IFN receptor complex [73,74].

3.2. IRFs in the development and function of myeloid cells

In the bone marrow, hematopoietic stem cells (HSCs) give rise to the common myeloid progenitors (CMPs), granulocyte/macrophage progenitors (GMPs), and macrophage/DC progenitors (MDPs), with successive restriction of the developmental potential of these progenitor cells. These successive specifications and commitments of progenitor cells along the differentiation pathway are determined by lineage-specific transcription factors.

IRF8 is expressed in CMPs and GMPs as well as in macrophages [75]. IRF8-deficient mice show decreased numbers of macrophages and decreased M-CSF-dependent colony formation, whereas the numbers of myeloid progenitors, granulocytes, and osteoclasts are increased [76]. IRF8-deficient mice develop a disease involving the marked expansion of undifferentiated cells, which frequently progresses to a fatal blast crisis, thus resembling human chronic myelogenous leukemia (CML). These progenitor cells are hyper-responsive to both GM-CSF and G-CSF but are hypo-responsive to M-CSF in vitro. Even in the presence of M-CSF, most $Irf8^{-/-}$ CMPs differentiate into granulocytes. Accordingly, the restored expression of IRF8 in myeloid progenitors from IRF8-deficient mice induces macrophage differentiation but inhibits granulocyte differentiation. Thus, these results indicate a role for IRF8 in the promotion of M-CSF-dependent macrophage development and the inhibition of granulocytic differentiation during the divergence of granulocytes and monocytes [76].

Mechanistically, IRF8 regulates important genes involved in the differentiation, cell growth, and apoptosis of myeloid cells in combination with partner proteins such as PU.1 and IRF1. Indeed, IRF8 has been shown to activate Blimp-1, METS/PE1, CDKN2B (INK4B), NF1, and PML and repress Bcl-XL, Bcl2, Dab2, and GAS2 [5]. Microarray gene expression analysis has also been used to identify genes altered by IRF8 during macrophage differentiation, and some lysosomal/endosomal enzyme-related genes have been found to be direct targets of IRF8 [77]. Interestingly, IRF8 protein can be posttranslationally modified by small ubiquitin-like modifier (SUMO) 2/3 [78]. IRF8 is SUMOylated in resting macrophages, and SUMO conjugation abrogates the transcriptional activity of IRF8. During macrophage activation, the deSUMOylating enzyme SENP1 removes SUMO3 from IRF8 and enhances the expression of IRF8 target genes such as IL12p40 [78]. With the combined use of chromatin immunoprecipitation coupled with DNA microarrays (ChIP-chip), ChIP-Seq, and gene expression profiling technology, IRF8 binding sites were identified throughout the genome of differentiation-arrested monocytic cell lines, pathogen-infected mouse lungs tissues, and monocytic cells during differentiation [79,80]. These sites were located in both promoter-proximal and promoter-distal regions. Additionally, functional target genes of IRF8, such as OAS1, IRF9, KLF4, and members involved in the antigen presentation pathway, were also identified. Importantly, many of the promoter-distal IRF8 binding sites coincide with histone H3 lysine 4 monomethylation, a signature for enhancers, indicating that functionally significant binding occurs at these sites [79].

IRFs also play important roles during the functional specialization of macrophages. A recent study has shown that IRF5 directs the proinflammatory polarization of human macrophages [81]. IRF5 expression is induced in response to inflammatory stimuli and directly activates the transcription of IL-12 and IL-23 while actively repressing IL-10. A global gene expression analysis revealed that IRF5 reciprocally regulates the M1 and M2 genes by activating proinflammatory genes and repressing the expression of M2 markers [81]. Additionally, IRF4 has been shown to regulate M2 macrophage polarization and host responses against helminth infection. The expression of IRF4 is under the control of Jmjd3, a histone H3K27 demethylase [82].

In addition to macrophages, IRF8 is reportedly involved in regulating the development of eosinophils. IRF8 deficiency in mice leads to a reduction in the number of eosinophils in different tissues [83]. Additionally, IRF2 plays an inhibitory role in basophil generation, and naive mice lacking IRF2 show basophil expansion, leading to excessive IL-4 production and a Th1/Th2 imbalance [84]. IRF1 also plays a pivotal role in the early phases of myelopoiesis, and bone marrow cells of IRF1-deficient mice show an increased number of immature granulocytic progenitors, which is suggestive of a defective maturation process [85].

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3.3. IRFs in the development and function of NK cells

NK cells are part of the innate lymphoid cell (ILC) family and represent the main cytotoxic cell population. IRF1 [86] and IRF2 [87] are required for the development of NK cells. Mice lacking IRF1 have been shown to exhibit a severe deficiency in NK, NKT, and intestinal intraepithelial T cells [88]. A subsequent study demonstrated that the lack of IRF1 affected the radiation-resistant cells that constitute the microenvironment required for NK-cell development but not the NK-cell progenitors themselves. IRF1 transcriptionally regulates IL-15, which is essential for the development of NK cells in bone marrow stromal cells [89]. IRF2 is also required for the development of NK cells, as mice lacking IRF2 exhibit NK-cell deficiency [87]. IRF2-deficient NK cells undergo accelerated apoptosis, leading to compromised maturation [90].

3.4. IRFs in the development and function of B cells

B cells develop from hematopoietic precursor cells in an ordered maturation and selection process that includes the DNA rearrangement of immunoglobulin genes, somatic hypermutation (SHM), class-switch recombination (CSR), and the generation of plasma cells. IRF8 and IRF4 are involved in the regulation of B-cell development at multiple stages.

There are significantly fewer pre-pro-B cells in the bone marrow of IRF8$^{-/-}$ mice compared with that of wild-type (WT) controls, which indicates that IRF8 drives common lymphoid progenitors (CLPs) to the B-cell lineage [91]. Mechanistically, IRF8 activates Pax5, Tcf3 (E2A), and Ebf1 and represses Sfpi1 (PU.1) in common lymphoid progenitors and pre-pro-B cells [91]. IRF8 and IRF4 function redundantly to regulate the pre-B-to-B transition, as an even more severe defect in pre-B-cell development is observed in mice lacking both IRF8 and IRF4. Indeed, these mice exhibit a complete blockade of small pre-B-cell differentiation [92], and either IRF4 or IRF8 is capable of rescuing this blockade [93]. IRF8 and IRF4 suppress surrogate light chain expression and down-regulate the pre-B cell receptor (pre-BCR) by inducing the expression of Ikaros and Aiolos in pre-B cells [92,93]. IRF8 and IRF4 target the Igκ 3′ and Igλ enhancers, and a κ allele is positioned away from pericentromeric heterochromatin to induce the expression of the conventional immunoglobulin (Ig) light chain gene [94]. Furthermore, IRF4 also induces the expression of the chemokine receptor Cxcr4 and promotes the migration of pre-B cells in response to its ligand CXCL12, which is expressed by a distinct set of bone marrow stromal cells that are spatially separated from IL7-expressing stromal cells. Therefore, this migration of pre-B cells results in the attenuation of IL7 signaling and leads to the activation of the intronic enhancer of Igκ [94].

IRF8 and IRF4 are also required in the later regulation of germinal center (GC) B cell differentiation. In GC centroblasts, the expression level of IRF8 is high, whereas IRF4 is absent [95]. However, as centrocytes mature into plasma cells, IRF8 expression decreases and IRF4 is re-expressed in a stepwise manner [95,96]. IRF8 activates the expression of AICDA (encoding an activation-induced cytidine deaminase), BCL6, and Mdm2, all of which are important in GC programming, as well as genes involved in innate and adaptive immunity, which have been identified via ChIP-chip analyses and transcriptional profiling [97,98]. However, the B-cell lineage-specific deficiency of IRF8 is associated with increased production of marginal zone (MZ) and follicular (FO) B cells but has little effect on B-cell function, which may result from an IRF8 partner that can compensate for the functions of IRF8 in its absence [99].

IRF4 is essential for the function and homeostasis of B cells, as IRF4-deficient mice show a profound reduction in serum immunoglobulin concentrations and do not mount detectable antibody responses despite the presence of normal numbers of mature B cells in secondary lymphoid organs. Upon antigen recognition, activated B cells can directly differentiate into IgM-secreting plasma cells or undergo CSR/SHM (in GCs) prior to differentiating into high-affinity antibody-secreting plasma cells (PCs). Interestingly, differing IRF4 concentrations underlie the generation of these alternative cell states [96,100]. IRF4 regulates CSR and plasma cell differentiation by up-regulating AID (encoded by Aicda) and Blimp1 (encoded by Prdm1) expression, respectively. Moreover, IRF4 is also required for the initiation and termination of the GC reaction by controlling the expression of Bcl6 [101]. Although transient IRF4 expression in vivo induces GC B cells, sustained high expression of IRF4 drives the generation of plasma cells while antagonizing the GC fate. The concentration-dependent actions of IRF4 in regulating the GC and PC programs of gene expression are proposed to result from differences in the affinity of IRF4 for various motifs [100]. When bound to PU.1 or BATF, IRF4 has a higher affinity for the Ets or AP-1 composite motifs, which are associated with the GC program, whereas it has a lower affinity for interferon sequence response motifs, which are associated with the PC program. Taken together, these results support a model of "kinetic control" in which the dynamics of IRF4 accumulation in activated B cells determine their cell fate [102].

In the spleen, bone marrow-derived B cells can develop into FO B cells or MZ B cells, and IRF4 has recently been reported to play a role in preventing B-cell retention in the MZ [103]. The inducible deletion of Irf4 specifically in B cells in vivo leads to the aberrant accumulation of Irf4-deleted follicular B cells in the MZ. This accumulation is associated with elevated protein expression and activation of NOTCH2, which is required for the development of MZ versus FO B cells [103].

3.5. IRFs in the development and function of T cells

T cells can differentiate into multiple types of effector and memory T cells, including CD8 + T cells and CD4 + T cells. Mice lacking IRF1 have reduced numbers of mature CD8 + cells within the thymus and peripheral lymphatic organs. The absence of IRF1 results in the decreased expression of LMP2, TAP1, and MHC class I in thymic stromal cells. Despite decreased MHC class I expression on IRF1$^{-/-}$ thymic stromal cells, the defect in CD8 + T-cell development is not observed in the thymic environment. Instead, IRF1$^{-/-}$ thymocytes show an intrinsic signaling defect and are hyporesponsive to negative selection. Thus, in developing thymocytes, IRF1 regulates the gene expression program that is required for lineage commitment and the selection of CD8 + thymocytes. In contrast, mice lacking IRF2 spontaneously develop an inflammatory skin disease due to the hyper-responsiveness of CD8 + T cells to antigen stimulation, which is accompanied by a notable up-regulation of IFNα/β-induced genes [1,5].

Recently, three studies have indicated that, although it is dispensable for early CD8 + T-cell activation, IRF4 is crucial for the sustained expansion and effector function of cytotoxic CD8 + T lymphocytes [104–106]. CD8 + T cells with a conditional IRF4 deletion proliferate less, are more prone to apoptosis, and produce fewer of the effector molecules that are crucial for viral clearance, such as granzyme B and IFNγ. Mechanistically, IRF4 promotes the expression and function of Blimp1, T-bet, and HIF1α, which are crucial transcription factors for CD8 + T-cell effector differentiation. IRF4 simultaneously represses genes that mediate cell cycle arrest and apoptosis and regulates the expression of key molecules that are required for the aerobic glycolysis of effector T cells. Interestingly, the expression of IRF4 critically depends on the strength of the T-cell receptor (TCR)-ligand interaction and on the activity of mammalian target of rapamycin (mTOR) [104]. Thus, IRF4 functions as a molecular "rheostat" that "translates" TCR affinity into the appropriate transcriptional programs that link metabolic function to the clonal selection and effector differentiation of T cells [106].

Additionally, IRF4 has been shown to be required for the development of IL17-producing CD8 + T (Tc17) cells, which exert effector functions that are less cytotoxic than those of canonical CTLs [107]. IRF4 regulates Tc17 differentiation by increasing the amounts of transcription factors that are crucial for type 17 helper cell differentiation (RORγt and RORα) and by decreasing transcription factors that regulate

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alternative fates, such as regulatory T (Treg) cell-specific Foxp3 and cytotoxic T lymphocyte (CTL)-specific eomesodermin (Eomes) [107].

IRF1 is also required for the T helper type 1 (Th1) cell differentiation of CD4+ T cells. Indeed, T cells from mice lacking IRF-1 fail to mount Th1 responses and instead exclusively undergo Th2 differentiation [1,5]. Both the defective production of IL-12 by APCs and the intrinsic defect of CD4+ T cells in response to IL-12 signaling contribute to this Th1/Th2 imbalance caused by IRF1 deficiency, as IL-12 is a major Th1-promoting cytokine. IRF1 is critical for the expression of both Il12p35 and Il12p40, which encode the IL-12 p35 and p40 subunits, respectively, in macrophages and DCs. Moreover, IRF1, which can be induced by IL-12, also directly activates Il12rβ1, which encodes the IL-12 receptor β1 subunit (IL-12Rβ1) in CD4+ T cells [108]. Additionally, the lack of NK cells in Irf1$^{-/-}$mice impairs the production of IL-12, as NK cells produce IFNγ to stimulate macrophages to secrete IL-12 [89].

Similarly to mice lacking IRF1, mice lacking IRF2 also exhibit a defect in Th1 differentiation due to the impaired production of IL-12 in macrophages; together with IRF1 and other transcription factors, IRF2 contributes to the optimal expression of IL-12 p40 [87]. The defective development of NK cells in mice lacking IRF2 may also contribute to impaired Th1 differentiation [87].

Similar to IRF2, IRF8 promotes Th1 differentiation by maintaining the proper function of macrophages and DCs [1,5]. Mice lacking IRF8 have problems mounting a Th1 response; however, when transplanted into Rag2$^{-/-}$ mice, IRF8$^{-/-}$ T cells are able to promote the elimination of intracellular infection. Thus, the Th1 defect is not T-cell intrinsic. Mechanistically, IRF8 activates the expression of IL-12 in macrophages and supports the development of CD8+ DCs, which also produce IL-12.

In contrast to IRF8, IRF4 plays a critical role in the differentiation of Th2 cells [1,5]. Mice lacking IRF4 have a defective Th2 response and reduced responsiveness to IL-4, which is a Th2-promoting cytokine. IRF4 synergizes with NFATc2 and NFATc1 to enhance the activation of the IL-4 promoter and endogenous IL-4 production. Following IL-4 treatment, Irf4$^{-/-}$CD4+ T cells show defects in proliferation, and their ability to induce GATA3 and Gfi-1 is impaired. Because, both GATA3 and Gli-1 are involved in Th2 development, this result suggests that IRF4 affects Th2 cell differentiation in a T-cell-intrinsic manner. However, a late study using Th2-biased BALB/c mice showed that IRF4 differentially regulates the production of Th2 cytokines in naïve vs. effector/memory CD4+ T cells. IRF4 inhibits IL-4 production in naïve CD4+ T cells, whereas it promotes IL-4 production in effector/memory CD4+ T cells [109].

In addition to Th2 differentiation, IRF4 is also critical for the generation of IL-1-producing T helper cells (Th17 cells) [110]. Irf4-deficient mice lack Th17 cells and are completely resistant to experimental autoimmune encephalomyelitis (EAE). Consistent with its role in EAE susceptibility, IRF4 is required for the induction of RORγt, a transcription factor that is important for the differentiation of Th17 cells upon exposure to Th17-polarizing cytokines [110]. RhoA-associated kinase 2 (ROCK2) is activated under Th17-skewing conditions and phosphorylates IRF4, which directly binds to the IL-17A and IL-21 promoters and induces their transcriptional activation [111]. In accordance with the role of IRF4 in Th17 promotion, Prostaglandin E2 (PGE2) inhibits IRF4 and represses the production of IL-17, suppressing antifungal immunity, while T-bet, the master regulator of Th1 lineage commitment, negatively regulates Th17 differentiation via the direct repression of IRF4 [112]. Consistent with the interaction of IRF4 and IRF8 with BATF as discussed above, recent genome-wide ChIP-Seq analyses reveals that IRF4 or IRF8 target sequences enriched for AP-1-IRF4 composite elements (AICEs) that are co-bound by BATF in Th17 cells. Importantly, IRF4 and BATF binding is interdependent which indicates a functional cooperation between these factors. Upon binding, chromatin modifications are triggered, which allow the Th17-cell-specific transcription factor RORγt to access its DNA binding sites [113–115].

In contrast to the role of IRF4 in Th2 cell differentiation, IRF4 expression endows regulatory T cells (Tregs) with the ability to suppress Th2 responses [116]. IRF4 is directly activated by Foxp3, which acts as a master regulator for Tregs. IRF4 also directly regulates Blimp1 expression in Tregs and is indispensable for the generation of all effector Tregs [116]. Moreover, IRF4 is crucial for the development and function of an IL-9-producing CD4+ T-cell subset designated Th9 [117]. IRF4 directly binds to the Il9 promoter in Th9 cells and regulates IL-9 expression in cooperation with Smad2/3 [118]. IRF4 is also reportedly involved in T follicular helper (Tfh) cell differentiation. Based on these findings and the role of IRF4 in GC formation (discussed above), IRF4 plays an essential role in antibody production [119].

This overview of the roles of IRFs in immune cell development and function reveals a complex picture. It appears that IRFs, such as IRF4, can play different and even opposing roles according to their level of expression and the differentiation stage of the cell. Of note, the maturation of a specific immune cell is orchestrated by its intrinsic transcriptional programs and the surrounding microenvironment, the latter of which is shaped by other cells. Thus, the specific contributions of each IRF must be clarified in a lineage-specific manner and at different developmental stages.

4. IRFs in disease

IRFs are critical regulators of immune responses and immune cell development, and abnormalities in IRF expression and/or function have increasingly been linked to numerous diseases. The pathogenesis of many autoimmune disorders, such as systemic lupus erythematosus (SLE), is due to the inappropriate regulation of immune cell activation and differentiation. As expected, IRFs have been reported to be associated with the development of these diseases. Immunity against pathogens and tumor suppression are two aspects of host defense, and accumulating evidence indicates that IRFs have a critical function in the regulation of cellular responses linked to oncogenesis [6]. Thus, IRFs connect the mechanisms governing immunity and cancer [1].

Interestingly, we and others have found that IRFs are also involved in the pathogenesis of metabolic, cardiovascular, and neurological diseases, such as hepatic steatosis, diabetes, cardiac hypertrophy, atherosclerosis, and stroke [9–24]. It is not surprising that a regulator originally considered to be involved in the immune system has been subsequently shown to play a role in metabolism, as numerous studies have reported that the immune and metabolic systems are intrinsically interconnected [120]. Additionally, the progression of some cardiovascular diseases has been attributed to low-grade inflammation [121]. Different subsets of lymphocytes and their cytokines are involved in vascular remodeling in hypertension and heart disease. In the case of neurological disease, there is mounting evidence linking the inappropriate or chronic production of type I IFN in the central nervous system (CNS) to the development of several severe neuroinflammatory disorders [122]. These findings lead us to question whether the involvement of IRFs in the progression of specific diseases is solely dependent on their roles in the immune response (e.g., their roles in type I IFN production and inflammation). New discoveries have shown that IRFs can also function independent of their immune-related effects, as discussed in additional detail below.

In this section, we summarize recent knowledge regarding the role of IRFs in metabolic, cardiovascular, and neurological diseases. The contributions of IRFs to immune diseases and cancer have been extensively discussed in several excellent and comprehensive reviews [1,6,123,124].

4.1. IRFs in metabolic diseases

The evolutionary need for survival has led to the integration of the metabolic and immune systems, which resulted in the synergistic development of the organ and signaling pathways that interconnect these two processes [120]. Many immune regulators, such as IKKε, IKKβ, and NF-κB, have been associated with metabolic disorders such

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as obesity and diabetes. However, it is unclear whether IRFs also participate in the pathophysiological regulation of metabolic processes and disease. Nonetheless, as discussed below, the roles of IRFs are beginning to be elucidated.

IRFs were initially found to be involved in adipogenesis in a study that used an unbiased approach to identify transcription factors in regulatory regions surrounding key adipocyte genes [7]. DNase I hypersensitive sites (DHSs) are chromatin regions that are sensitive to cleavage by DNase I, and these regions are often associated with protein binding, suggesting the existence of regulatory elements such as enhancers, promoters, silencers, insulators, and locus control regions. By applying high-throughput DNase hypersensitivity analysis and computational motif identification, one top-scoring motif corresponding to a binding site for IRFs was identified, indicating an important role for the IRF proteins in adipocyte biology. The expression of all nine mammalian IRF mRNAs is regulated during adipogenesis, and IRF1, IRF3, and IRF4 exhibit anti-adipogenic properties in cultured adipocytes. Further study has shown that IRF4 is indeed a critical determinant of the transcriptional response to nutrient availability in adipocytes [8]. Mice lacking IRF4 expression in adipocytes exhibit increased adiposity and deficient lipolysis. Mechanistically, IRF4 is required for lipolysis, at least in part due to its direct effects on the expression of adipocyte triglyceride lipase and hormone-sensitive lipase. Recently, IRF4 has been shown to be a negative regulator of inflammation in diet-induced obesity, in part through the regulation of macrophage polarization [125]. Myeloid cell-specific IRF4 knockout mice develop significant insulin resistance on a high-fat diet, whereas $Irf4^{-/-}$ adipose tissue macrophages (ATMs) express markers that are suggestive of enhanced M1 polarization.

In addition to IRF4, other members of the IRF family have also been demonstrated to play important roles in metabolic disorders, including hepatic steatosis and insulin resistance [9–11]. In high-fat diet (HFD)-induced obese mice, IRF7 expression increases while the expression of IRF3 and IRF9 decreases, indicating that these IRFs respond to overnutrition stress. Consistent with this, mice lacking IRF7 show improved hepatic insulin sensitivity and attenuated hepatic steatosis on an HFD [9]. These mice also exhibit less macrophage infiltration into multiple organs and are protected from local and systemic inflammation. In contrast to IRF7, we have shown that IRF3 and IRF9 play a protective role in HFD-induced obesity [10,11]. Mice with IRF9 or IRF3 deficiency show significant increases in chronic HFD-induced hepatic insulin resistance, steatosis, and inflammation; in contrast, the hepatic overexpression of IRF9 or IRF3 preserves glucose and lipid homeostasis and attenuates inflammation. Mechanistically, IRF9 interacts with peroxisome proliferator-activated receptor alpha (PPAR-α), a master regulator of fatty acid (FA) oxidation in the liver, to activate PPAR-α target genes, whereas IRF3 interacts with the kinase domain of IKKβ in the cytoplasm and inhibits IKKβ/NF-κB downstream signaling. IRF9 is primarily localized in the nucleus, and by promoting PPARα transactivation, it accelerates lipid catabolism and mitigates hepatic steatosis, suggesting a key role for IRF9 in metabolic functions that is independent of its role in immunity [10]. In contrast to IRF9, IRF3 is primarily expressed in the cytoplasm and is phosphorylated and translocated into the nucleus upon recognition of PAMPs, as discussed above. Therefore, in the absence of pathogen infection, IRF3 interferes with IKKβ/NF-κB signaling in the cytoplasm of hepatocytes, thereby alleviating inflammation and insulin resistance [11].

Additionally, IRF3 can contribute to early alcoholic liver disease (ALD) independent of inflammation or type I interferons [12]. Ethanol induces ER stress and triggers the association of IRF3 with STING, which is an ER adaptor associated with cytosolic DNA signaling, as discussed above. This association is followed by the subsequent phosphorylation of IRF3. Activated IRF3 associates with the proapoptotic molecule Bax (B-cell lymphoma 2 [Bcl2]-associated X protein) and contributes to hepatocyte apoptosis [12].

Taken together, these studies indicate that IRFs are involved in the normal differentiation of adipocytes and the pathogenesis of metabolic diseases by targeting different aspects of nutrition overload, insulin resistance, and apoptosis in manners that are dependent on or independent of inflammation.

4.2. IRFs in cardiovascular diseases

As with metabolism, it is now recognized that low-grade inflammation plays a role in cardiovascular disease. The participation of the immune response in mechanisms that contribute to inflammation in cardiovascular disease has been reported in patients with atherosclerosis and hypertension [121].

IRF8 has been reported to be involved in the pathogenesis of atherosclerosis [13]. Apolipoprotein E-deficient mice reconstituted with $IRF8^{-/-}$or $IRF8^{-/-}$apolipoprotein E-deficient bone marrow display exacerbated atherosclerotic lesion formation compared with controls. Following the demonstration that mice lacking IRF8 spontaneously develop a chronic myelogenous leukemia-like phenotype, the authors suggested that the expansion of polymorphonuclear neutrophilic leukocytes (PMNLs) contributes to accelerated atherosclerosis [13]. Arginase 1 (Arg1) expression is inversely correlated with atherosclerosis progression, and IRF8 has also been reported to regulate the expression of macrophage Arg1 in cooperation with PU.1 downstream of liver X receptors (LXRs) [126]. Additionally, SNPs located in the IRF8 gene are strongly associated with coronary heart disease in SLE [127].

However, we must also determine whether IRFs affect cardiovascular disease indirectly via infiltrating inflammatory cells and/or directly in a cell-autonomous fashion [128]. Recently, we showed that IRF8 also plays a crucial role in modulating smooth muscle cell (SMC) phenotype switching and neointima formation in response to vascular injury [19]. Serum response factor (SRF) and its co-activator myocardin affect the expression of SMC-specific genes by binding to CArG elements, while IRF8 represses these genes by regulating serum response factor (SRF) transactivation in a myocardin-dependent manner, revealing a role for IRF8 that is independent of immunity [19]. In contrast to IRF8, IRF3 inhibits vascular smooth muscle cell (VSMC) proliferation and neointima formation after vascular injury. IRF3 directly binds to and serves as a co-activator of PPARγ, a negative regulator of SMC proliferation, resulting in decreased proliferation cell nuclear antigen expression and suppressed proliferation [20].

Cardiac hypertrophy and pathological remodeling are hallmarks of cardiomyopathy that are associated with many pathological stressors. By employing both transgenic and knockout mouse models, we recently found that IRF3 [14], IRF7 [16], IRF8 [21], and IRF9 [17] protect against aortic banding (AB)-induced cardiac hypertrophy, whereas IRF4 [15] and IRF1 [18] promote this condition. Importantly, the expression of these IRFs changes in accordance with their protective or antagonistic roles during cardiac hypertrophy, indicating that IRFs can be regulated in response to a broad spectrum of pathological stressors, perhaps in an interferon-independent manner. Molecularly, IRF8 directly interacts with NFATc1, a well-established hypertrophic transcription factor, to prevent NFATc1 translocation and thus inhibit the hypertrophic response [21]. By directly interacting with ERK2 and IKKβ, respectively, IRF3 and IRF7 interfere with the ERK1/2 and NF-κB signaling pathways, both of which play important roles in the development of pathological cardiac hypertrophy and heart failure [14,16]. Similar to IRF8, IRF9 competes with p300 for binding to the transcription activation domain of myocardin, thereby suppressing its transcriptional activity [17]. Lastly, IRF4 and IRF1 bind to the promoters and activate the expression of cAMP response element-binding protein (CREB) and inducible nitric oxide synthase (iNOS) at the transcriptional level, respectively [15,18]. Because several IRF members (IRF3, IRF7, IRF8, and IRF9) have inhibitory effects on cardiac hypertrophy, they may be mobilized as part of a coordinated compensatory response to pathological stresses in the heart by targeting different but complementary pathways in hypertrophy, including those involving extracellular signal-regulated kinase, NF-κB, and myocardin [128]. Thus, beyond their roles in

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inflammation, IRFs regulate pathological cardiac hypertrophy by interacting with either related signaling pathway components or transcription factors.

Taken together, these findings clearly indicate that the IRF family members are potentially important new players in cardiac gene regulation during the onset of pathological hypertrophy and remodeling [128]. We infer that other members of the IRF family may also be involved in these processes, and we are currently investigating their roles in heart, vascular, and ischemia/reperfusion diseases.

4.3. IRFs in neurological diseases

IRFs have recently been shown to be involved in neurological diseases, which are disorders of the central and peripheral nervous systems. Multiple sclerosis (MS) is an inflammatory disease of the CNS that involves demyelination and neuronal injury [129]. Microglia, which are CNS-resident APCs, are activated in EAE, a mouse model of MS, and play a role in disease progression. IRF8 has been reported to play a key role in microglial activation during EAE by promoting αvβ8 integrin expression in APCs and activating TGF-β signaling, leading to Th17 cell differentiation [23]. IRF8 also stimulates IL-12 p40 and IL-23 production but inhibits IL-27, which in turn increases the intra-CNS amplification of Th1 and Th17 cells, finally activating microglia and exacerbating neuroinflammation [23]. In agreement with this observation, although microglia are present in the CNS of $Irf8^{-/-}$ mice, they express reduced levels of Iba1 and other microglial markers and are deficient in IL-12p40 induction in vitro [130,131]. Moreover, IRF8 is important for transforming quiescent microglia to a reactive phenotype after peripheral nerve injury, such that they produce pro-inflammatory cytokines [132]. Thus, IRF8 contributes to the pathogenesis of MS by activating integrin-mediated TGF-β signaling and promoting neuroinflammation.

Stroke is the most severe and devastating neurological disease globally, and ischemic stroke is the predominant stroke type. We have previously shown that IRF4 is a mediator of protection against ischemia/reperfusion (IR)-induced neuronal death [24]. Neuron-specific IRF4 transgenic mice exhibit reduced infarct lesions; however, this effect is reversed in IRF knockout mice. IRF4 directly activates SRF, which is crucial for salvaging neurons during stroke, and the protective role of SRF has been further shown by the complete reversal of the SRF deficiency phenotype in IRF4 transgenic mice. Thus, the IRF4-SRF axis is critical for neuronal survival in the setting of ischemic stroke [24]. Similar to IRF4, IRF8 is also strongly protective during ischemic stroke. IRF8 knockout mice exhibit aggravated apoptosis, inflammation, and oxidative injury in the ischemic brain, eventually leading to poorer stroke outcomes, whereas neuron-specific IRF8 transgenic mice show marked inhibition of apoptosis and improved stroke outcomes [22].

Thus, the roles of IRFs in neuroinflammation appear to be dependent on their effects on immune activation, whereas the contributions of IRFs to IR-induced injury are dependent on their regulation in apoptosis.

5. IRFs are stress sensors

As we have described above, IRFs are located at the crossroads between immunity and metabolism and their related diseases. Vertebrates have evolved immune systems to face constant challenge by infective pathogens. Upon recognition of PAMPs, PRRs initiate a series of signaling programs that execute the first line of host defense responses. Currently, support is growing for the hypothesis that the pathogen-sensing pathway and the nutrient-sensing pathway (i.e., immunity and metabolism) are deeply integrated and evolutionarily conserved [120]. Many metabolic diseases, such as obesity and type 2 diabetes, are associated with chronic low-grade inflammation. With this perspective, overnutrition can be regarded as a metabolic stress that transforms the delicate balance between immune and metabolic responses into a pathological relationship. Similarly, cardiac hypertrophy can be an adaptive response of myocytes to exercise or a maladaptive response of myocytes to pathophysiological stress, such as hypertension, while stroke is an acute ischemic stress for neurons. IRFs respond to these stresses in various ways, including altering their levels of expression, post-translational modifications, cellular localization, interactions with protein partners, and DNA binding, all of which can be dependent on or independent of their effects on immunity. For example, IRF7 expression is strongly induced by type I IFN signaling [1] but is downregulated in experimental models of hypertrophy [16]. In RLR signaling, IRF3 is phosphorylated in the auto-inhibitory region, leading to its dimerization and nuclear translocation [133]. During B-cell development, differing concentrations of IRF4 regulate mutually antagonistic GC and PC programs by binding to different composite DNA motifs with their respective partners [100]. Thus, in response to diverse stresses, IRFs integrate upstream signaling information and convert it to the activation or repression of a set of target genes by altering their own state; dysregulation of these programs leads to various diseases. Therefore, similar to the DNA damage sensor of p53 and the starvation sensor of FoxO [134], we propose that IRFs are stress sensors, in some cases acting beyond their originally defined roles in immune cell regulation (Fig. 3).

6. Perspective

IRFs integrate and process stimulus-specific signals to orchestrate cellular responses during the constant challenge of various stresses. Although critical and versatile roles for the IRF family have been revealed, it is likely that our understanding of IRF function is currently in its infancy. Many questions remain regarding how the IRF-mediated signaling pathways interact with each other, how the tissue- and developmental stage-specific regulation and target gene specificity of IRFs are determined, and how IRFs themselves are regulated. IRFs are mediators of different signaling pathways that interconnect in a variety of ways, and the mechanisms by which IRFs coordinate such crosstalk require further elucidation [26]. At the chromatin level, it remains unclear how the specificity of IRF binding throughout the genome is determined in concert with other transcription factors, chromatin structure regulators, and other cofactors in different cell types, developmental stages, and disease models. Due to the rapid development of high-throughput technologies, such as ChIP-Seq, RNA-Seq, and microarrays, we are now beginning to understand the function of IRFs from a whole-genome perspective. It is clear that the regulation of IRF expression levels is one mechanism of regulating transcriptional responses, as some IRFs can be induced or repressed in certain pathophysiological conditions. However, the upstream regulators of IRFs and the mechanisms by which external signals are ultimately transmitted to alter IRF states, such as their expression levels and cellular localization patterns, remain to be fully determined. Although it is known that IRFs can be modified by phosphorylation [135], SUMOylation [78], ubiquitylation [136], and acetylation [137], the question of whether other IRF modifications exist and whether these modifications can influence the function of IRFs (e.g., their interactions with other partners or DNA sequences) awaits further study. Consistent with the essential roles of IRFs in stress responses, they are involved in several diseases, as mentioned above. IRFs differentially participate in these diseases, and multiple IRFs can contribute to the progress of a single disease, such as cardiac hypertrophy. Additionally, IRFs exhibit high levels of homology. Thus, it must be determined whether crosstalk between IRFs exists. Interestingly, a recent study has shown that a SNP within an IRF4 intron affects skin pigmentation in humans, thus affecting the risk of cutaneous malignancies [138]. This observation suggests that the functions of IRFs are significantly broader than previously thought. Thus, it is possible that IRFs are also involved in the progression of other diseases, such as acute lung injury, fibrosis, Alzheimer's disease, and Huntington's disease; if so, IRFs may prove to be an attractive therapeutic target for the treatment of these diseases.

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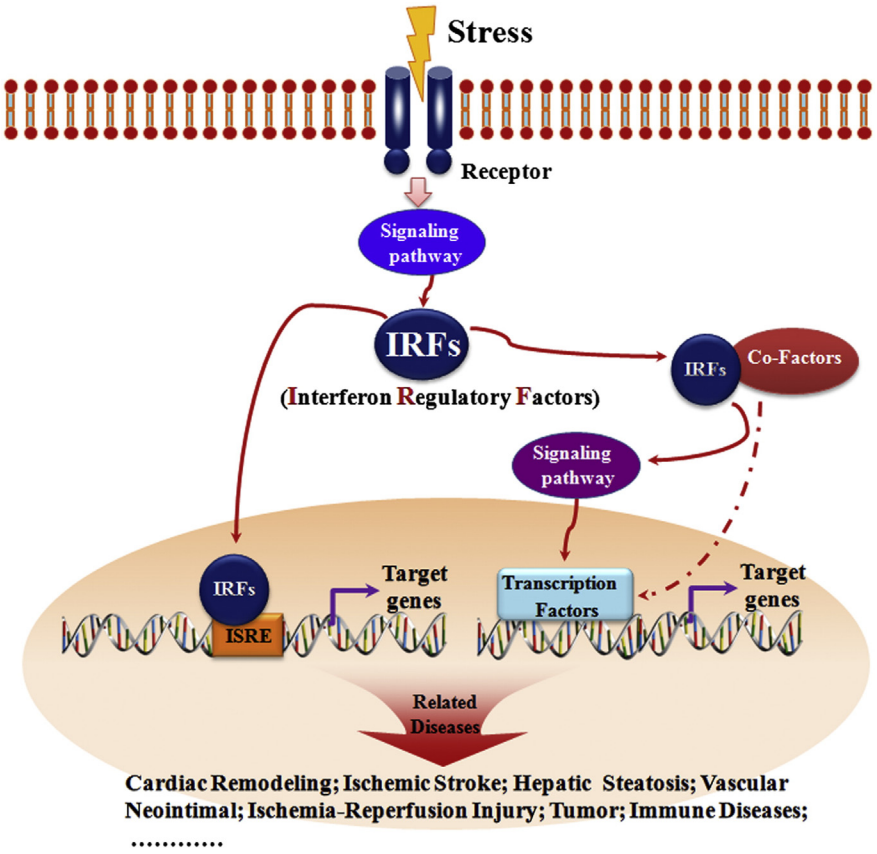

Fig. 3. IRFs are stress sensors. In response to diverse pathophysiological stresses, such as overnutrition, vascular injury, hypertension and cerebral ischaemia, IRFs integrate upstream signaling information and convert it to the activation or repression of a set of target genes by changing their own state, including altering their levels of expression, post-translational modifications, cellular localization, interactions with protein partners, and DNA binding; dysregulation of these programs leads to various diseases, such as cardiac remodeling, ischemic stroke, hepatic steatosis, vascular neointimal, ischemia-reperfusion Injury, etc.

Disclosures

The authors declare no competing financial interests.

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