Review Article

Interferon-Regulatory Factors Determine Macrophage Phenotype Polarization

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The mononuclear phagocyte system regulates tissue homeostasis as well as all phases of tissue injury and repair. To do so changing tissue environments alter the phenotype of tissue macrophages to assure their support for sustaining and amplifying their respective surrounding environment. Interferon-regulatory factors are intracellular signaling elements that determine the maturation and gene transcription of leukocytes. Here we discuss how several among the 9 interferon-regulatory factors contribute to macrophage polarization.

1. Introduction

During development mononuclear phagocyte progenitors populate most tissues where they differentiate into transcriptionally and functionally diverse phenotypes [1–3]; for example, bone marrow, liver, and lung harbor macrophages with an enormous capacity to clear airborne particles, gut-derived pathogens, or cell nuclei expelled from erythroblasts, respectively [4]. In contrast, skin, kidney, and brain host a dense network of dendritic cells [4, 5]. Upon tissue injury M-CSF drives resident mononuclear phagocyte to proliferate [6] or circulating monocytes recruit to the site of injury. It is the local microenvironment that then determines mononuclear phagocyte polarization to distinct phenotypes, which can vary between disorders or between the different stages of a disease process [7]. Several factors mediate mononuclear phagocyte polarization, as being mostly described by in vitro experiments [7, 8]. However, attempts to translate this simplistic model to disease states in vivo often failed to cover all aspects of heterogeneous and changing tissue environments. For example, ischemia-reperfusion injury induces transient sterile inflammation because dying tissue cells release damage-associated molecular patterns (DAMPs) that polarize macrophages toward a classically activated M1-like phenotype [9, 10]. This process is associated with NF-κB and STAT1 pathway activation [2]. Macrophages apoptosis or their phenotype switches towards alternatively activated, M2-like macrophages that produce IL-10 and TGF-β, induce resolution of inflammation, and enforce tissue regeneration [11–15]. Failure of this phenotype switch leads to persistent tissue inflammation, atrophy, and fibrosis [16]. The uptake of neutrophils, epithelium-derived alarmins, and Th2 cytokines IL-4 and IL-13 supports this phenotype switch [11]. As disease processes do not always occur in a serial manner, concomitant proinflammatory and anti-inflammatory macrophages infiltrates often populate organs affected by persistent injury, for example, in slowly progressive lesions of organ transplants [17, 18].

Current data suggest that the family of the interferon-regulatory factors (IRFs) plays an important role in regulating macrophage polarization. IRFs are intracellular proteins that regulate immune cell maturation [19]. Here we provide a summary on IRF biology that is focused on the IRF’s role in macrophage phenotype control and the associated contributions to tissue inflammation and remodeling.
2. The Family of Interferon-Regulatory Factors

The IRFs were discovered in search of transcription factors that bind to the conserved virus response elements within the promoters of type I IFN genes [19]. It was found that both NF-κB and IRF-3 activate IFN-β gene transcription while IFN-α gene expression is entirely based on IRFs [19]. The generation of Irf-deficient mice led to the discovery of additional regulatory roles of the IRFs for cell growth, for immune cell maturation and activation, and for apoptosis. In mammals the IRF gene family consists of nine members: IRF-1, IRF-2, IRF-3, IRF-4, IRF-5, IRF-6, IRF-7, IRF-8/ICSBP, and IRF-9. Their respective IRF proteins share significant homologies at the N-terminal 115 amino acids where they share a conserved tryptophan pentad repeat DNA-binding domain [20]. These include a DNA-binding domain of five tryptophan repeats of which three recognize the GAAA and AANNNGAA sequence motifs, that is, the IFN-stimulated response elements [20]. However, the variable domains at the C-terminus determine the functional specificity of the nine IRFs, their potential to interact with each other via IRF-association domains, and their cell type-specific actions [21] (Figure 1). Accordingly, the IRFs have been subdivided into the “interferonic” IRFs (IRF-2, -3, -7, and -9), the “stress-responsive” IRFs (IRF-1 and -5), the “hematopoietic” IRFs (IRF-4 and -8), and the “morphogenic” IRF-6 [22]. The genetic and biological characteristics of the IRF family members are listed in Table 1.

3. IRFs in Macrophage Polarization

3.1. IRF-1. IRF-1 was first described in 1980s as a 325-amino acid-long nonredundant transcription factor for type I IFNs upon TLR3 ligation [23–25]. IRF-1 is only weakly expressed in resting DCs and macrophages but is induced by IFN-γ up to 8-fold in M1 polarized macrophages [26]. IRF-1 interacts with MyD88 to migrate into the nucleus where it triggers TLR-mediated expression of proinflammatory genes [27,28]. Casein kinase II activates IRF-1 by phosphorylation [29]. The protein complex formed by IRF-1, NF-κB, and Jun that bind to the IFN-β promotor was named “enhanceosome” [28,30–32]. Sumoylation represses the transcriptional activity of IRF-1 [33]. LPS challenge requires IRF-1 to induce TLR3, TLR6, and TLR9 in macrophages [34]. In fact, Irf1-deficient macrophages almost entirely lack inducible nitric oxide synthase (iNOS) production upon LPS and IFN-γ stimulation [35]. This way, IRF-1 contributes to the priming of classically activated, M1-like macrophage polarization in inflammatory tissue environments that involve IFN-γ-producing NKT cells or Th1 T cells [36]. At the same time, IRF-1 suppresses the binding of other transcription factors to the IL-4 promoter, which inhibits alternative macrophage activation [37].
This process supports host defense against intracellular pathogens but also accounts for M1 macrophage-related immunopathology [35, 36, 38]. The latter is particularly evident in sterile inflammation, for example, in ischemia-reperfusion injury [39, 40].

3.2. IRF-2. IRF-2 is 349-amino acid-long and displays considerable sequence homology with IRF-1 [23]. IRF-2 competes with IRF-1 for the same cis-acting recognition sequences in gene promoters [41]. Hence, IRF-2 is a negative regulator of IRF-1-mediated type I IFN and Cox-2 induction [23, 31]. IRF-2 has a more complex role in cytokine regulation as it suppresses LPS-induced TNF expression while augmenting LPS-induced IL-1, IL-6, IL-12, and IFN-γ secretion [42]. Sumoylation increases IRF-2’s ability to inhibit IRF-1 transcriptional activity [43]. LPS challenge regulates TLR3, TLR4, and TLR5 via IRF-2 in macrophages [34]. IRF-2 suppresses caspase-1-mediated programmed cell death by interfering with the transcriptional regulation of caspase-1 and by suppressing STAT1/3 signaling [44]. IRF-2-deficient mice are highly susceptible to Listeria monocytogenes infection, which seems to be related to IRF-2’s role in mediating the IFN-γ-induced oxidative burst that kills the pathogen inside intracellular compartments of macrophages [45]. However, this was iNOS transcription independent. IRF-2 rather regulates iNOS in a posttranscriptional manner [46]. The net effect of IRF-2 on sterile inflammation seems to be immunosuppressive as IRF-2-deficient mice are more susceptible to lymphocytic choriomeningitis virus infection as well as to ischemia-reperfusion injury-related tissue inflammation while that latter was suppressed in mice that overexpress IRF-2 [47]. IRF-2’s negative regulatory effect on type I IFN expression also suppresses inflammatory skin disease involving CD8 T cells [48]. In addition, IRF-2 is needed for the development of splenic and epidermal CD4+ dendritic cells [49].

3.3. IRF-3. IRF-3 was discovered by searching genes with homology sequences with IRF-1 and IRF-2 [50]. This 427-amino acid protein shares a number of characteristics with IRF-7 [51]. Unlike IRF-7, that confers MyD88 signaling, IRF-3 is involved in TRIF-dependent signaling pathways. After binding pathogens, pattern-recognition receptors like TLR-3, TLR-4, or RIG-I recruit TRIF to trigger an IRF-3-mediated induction of type I IFNs [52–55]. Additional cytoplasmic DNA recognition receptors use the STING pathway to activate IRF-3 [56]. The transcriptional activation of the IFN-β gene requires an enhanceosome of 7 additional proteins that create a continuous surface that recognizes the DNA-binding element [57]. Phosphorylation of TLR3’s specific tyrosine residues can initiate two distinct signaling pathways. One activates TBK-1 and the other activates PI3 kinase and Akt for full phosphorylation and activation of IRF-3 [58, 59]. Cytoplasmic IRF-3 is inactive unless phosphoactivation of IRF-3 triggers unfolding of the autoinhibitory elements and exposes the hydrophobic surface to interaction with CREBBP to translocate to the nucleus [60]. By contrast, ubiquitination inactivates IRF-3 [61]. GM-CSF-primed M1-like macrophages display a diminished IRF-3 axis and enhanced activation of MyD88. In contrast, M-CSF stimulated macrophages that develop an M2-like phenotype show defective NF-κB activation and enhanced TRIF-mediated IRF-3 induction upon LPS stimulation [62, 63]. Hence, the IRF-3 axis is rather enabled in M2-like macrophages than in M1-like macrophages. But does IRF-3 also contribute to the development of an alternatively activated macrophage phenotype? One study transduced
IRF-3 into primary human microglia. Stimulation with IFN-γ/IL-1 suppressed proinflammatory mediators like IL-6, TNF-α, or IL-1β, whereas anti-inflammatory mediators including IL-10 were enhanced [64]. Altogether the data suggest that IRF-3 is associated with anti-inflammatory microenvironments and contributes to the polarization toward a M2 macrophage phenotype. However, IRF-3 also induces a number of inflammatory cytokines such as CCL5 and IFN-β [65].

3.4. IRF-4. IRF-4, first described in 1995, is a 450-amino acid-long “hematopoietic” protein with considerable homology with IRF-1 and IRF-2 [66]. IRF-4 contributes to the maturation of multiple myeloid and lymphoid cell types from their lineage-specific progenitors [19, 67]. IRF-4 competes with IRF-5 for binding to the adaptor MyD88 that transmits TLR outside-in signaling to NF-κB and other proinflammatory transcription factors [27]. As IRF-5 is needed for signal transduction the competitive action of IRF-4 for MyD88 binding renders IRF-4 an endogenous TLR signaling antagonist that can suppress M1 macrophage polarization [68]. IL-10 induction needs IRF-4 and IRF-4 overexpression enhances IL-4 and IL-10 secretion [69]. On the contrary, IRF-4−/− mice are more sensitive to LPS-induced sepsis and exhibit higher production of proinflammatory cytokines like TNF and IL-6 [70]. IL-4 induces macrophages to upregulate IRF-4 and contributes to their M2 polarization [71]. Accordingly, IRF-4 deficiency leads to decreased expression of M2 marker genes like Arg1, Ym1, and Fizz1 [72]. In fact, Junonji domain-containing-3 (Jmjd3), a histone 3 Lys27 (3K27) demethylase, regulates the trimethylation at H3K27 of a selected number of genes including IRF-4. This mechanism controls IRF-4 induction and is needed for M2 macrophage polarization, for example, in the host defense during helminth infection [72]. Interestingly, IL-4-induced STAT6 signaling regulates Jmjd3 [73]. Hence, polarization of alternatively activated macrophages through IL-4 seems to be mediated via STAT6-Jmjd3-IRF-4 signaling and reveals an essential role of IRF-4 in macrophage polarization for helminth control.

3.5. IRF-5. IRF-5 is a 504-amino acid-long stress-responsive IRF [22]. IRF-5 is required for TLR-mediated induction of IL-6, TNF, IL-12, and other proinflammatory cytokines [74]. IRF-5 competes with IRF-4 for binding to the signaling adapter MyD88 and the downstream subsequent activation of proinflammatory transcription factors [27]. Its capacity to induce inflammatory cytokines and B cell transcription factors implies its role in host defense and autoimmune disorders [75, 76]. This competitive interaction involves IRF-5 in the polarization into M1 macrophages [68]. In fact, the balance between IRF-4 and IRF-5 seems to be a major determinant of M1 versus M2 macrophage polarization. For example, M-CSF induces IRF-4 in human monocyte-derived macrophages while GM-CSF induces IRF-5, which results in two phenotypically different macrophage phenotypes [77]. M1 macrophages express high levels of IFN-5 where it not only mediates the expression of proinflammatory cytokines but also suppresses the immunoregulatory cytokine IL-10 [68]. IRF-5 itself is regulated by the transcriptional corepressor KAP1/TRIM28 to avoid overshooting secretion of TNF and other mediators that induce immunopathology [78]. KAP1/TRIM28 regulates IRF-5 by recruiting histone deacetylases and methyltransferases that can silence IRF-5-related gene expression [78]. IRF-5-mediated polarization of monocytic phagocytes involves the secretion of various IL-12 family members including IL-12p35 and IL-23p19, which support Th17 T cell immunity, an element of adaptive immunity that contributes to autoimmune disorders [79]. In fact, gain of function mutations in the IRF-5 gene exists that increases TLR- or NOD-mediated secretion of proinflammatory cytokines [80]. Such variants also predispose to autoimmune diseases like systemic lupus erythematosus [81–83], which may be related to these phenomena.

3.6. IRF-6. IRF-6 is a so-called “morphogenic” IRF of 467 amino acid length. IRF-6 has a large structural homology with IRF-5 but does not seem to share its functional properties or contribute to macrophage biology, which is related to the tissue-specific expression of IRF-6. IRF-6 mutations rather predispose to cleft lip or palate and other abnormalities of limb, skin, and craniofacial morphogenesis [84, 85].

3.7. IRF-7. IRF-7, together with IRF-3, is a 503-amino acid central and nonredundant mediator of viral nucleic acid-induced induction of IFN-α [19, 86, 87]. IRF-7 drives the differentiation of monocytes to macrophages but a direct role in macrophage polarization has not been reported.

3.8. IRF-8. IRF-8, also known as interferon consensus sequence-binding protein (ICSBP), is a 393-amino acid-long “hematopoietic” IRF [22]. IRF-8 (like IRF-4) has a dominant role in the maturation and differentiation of monocytes and macrophages from their immature progenitors, while it represses neutrophil production [88–90]. IFN-γ and LPS slow down the intrinsic mobility of IRF8 inside the nucleus to enforce its chromatin interaction for the initiation of transcription [91]. IFN-γ induces IRF-8 and IRF-8 drives to induction of IFN-β, IL-12p40, IL-12p35, and iNOS upon TLR stimulation, that is, M1 macrophage gene profile [92]. In addition, IRF-8 integrates outside-in signaling of Notch receptors and TLRs for the induction of genes that define an M1 macrophage phenotype [93]. IRF-8 selectively modulates TLR4 signaling via IRAK2-dependent activation of MNK1 and elf4E-regulated translation. IRF-8 itself is regulated by small ubiquitin-like modifiers (SUMO) 2/3 at the lysine residue 310. SUMO3-conjugated IRF8 cannot induce IRF-8 target genes [94]. Upon macrophage activation, SUMOylation of IRF-8 is reduced as the deSUMOylating enzyme, sentrin-specific peptidase 1 (SENPI), inactivates SUMOylation-related IRF-8 repression. As such IRF-8 SUMO conjugation/deconjugation represents a previously unrecognized mechanism of macrophage phenotype control.

3.9. IRF-9. IRF-9 is a 424-amino acid-long regulator of type I IFN signaling. It forms a DNA-binding complex with
the STAT1 homodimer, for example, for the induction of CXCL10 [95]. A specific role in macrophage polarization has not been reported.

4. Summary and Perspective

Macrophages contribute to tissue homeostasis and all phases of tissue injury and repair. Tissue environments prime macrophages to distinct phenotypes to assure that their functional properties enforce the surrounding environment, whether this may be inflammation, the resolution of inflammation, tissue repair (fibrosis), or the resolution of extracellular matrix. Members of the IRF family are an integral component of the macrophage polarization process and, hence, regulate the phenotypic plasticity and heterogeneity of tissue macrophages. Research in this area is still in progress, but our present working model refers to IRF-1, IRF-5, and IRF8 as factors driving the proinflammatory, classically activated (M1) macrophage phenotype, while IRF-3 and IRF-4 promote anti-inflammatory, alternatively activated (M2) macrophages (Figure 2). Future work in this area will certainly refine this concept and define additional functions of the IRFs in this context and elucidate additional mechanisms of how changing tissue environments shape immune effector cells to meet the tissue needs in homeostasis and disease.

**Abbreviations**

- CCL: Chemokine ligand
- CCR: Chemokine receptor
- Cox-2: Cyclooxygenase 2
- CREBBP: CREB-binding protein
- DAMP: Danger-associated molecular pattern
- eIF4E: Eukaryotic translation initiation factor 4E
- GM-CSF: Granulocyte-macrophage colony-stimulating factor
- IFN: Interferon
- iNOS: Inducible nitric oxide synthase
- IRF: Interferon-regulatory factor
- JmjD3: Jumonji domain-containing-3
- KAPI: KRAB-associated protein-1
- M-CSF: Macrophage colony-stimulating factor
- MNK1: MAPK signal-integrating kinase 1
- NO: Nitric oxide
- NOD: Nucleotide-binding oligomerization domain-containing protein
- PAMP: Pathogen-associated molecular pattern
- RIG-I: Retinoic acid-inducible gene 1
- SENP1: Sentrin-specific protease 1
- STAT: Signal transducer and activator of transcription
- SUMO: Small ubiquitin-like modifier
- STING: Stimulator of interferon genes
- TGF-β: Transforming growth factor-β
- TLR: Toll-like receptor
- TNF: Tumor necrosis factor
- TRIF: TIR-domain-containing adapter-inducing interferon-β
- TRIM28: Tripartite motif-containing 28.

**Conflict of Interests**

All authors do not have competing interests and do not have a financial relation to profiting companies or commercial products.

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