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REVIEW

The Regulatory Network of Transcription Factors in Macrophage Polarization

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Abstract: Macrophage polarization, a dynamic process crucial for immune responses and tissue homeostasis, is tightly regulated by transcription factors. Understanding the transcriptional regulation of macrophage polarization holds significant therapeutic implications for various diseases, including cancer, autoimmune disorders, and metabolic syndromes. Studies have shown that transcription factors, including signal transducer and activator of transcription (STAT), nuclear transcription factor-κB (NF-κB), peroxisome proliferator-activated receptors (PPARs), interferon regulatory factors (IRFs), BTB and CNC homology (BACH), CCAAT-enhancer binding proteins (C/EBPs), kruppel-like factors (KLFs), Cellular Myc (c-Myc), the SNAIL family, v-Maf Musculoaponeurotic Fibrosarcoma Oncogene Homolog (Maf), and hypoxia-inducible factor alpha (HIFα), are highly involved in shaping macrophage polarization. Targeting transcription factors involved in macrophage polarization may provide promising avenues for immunomodulatory therapies aimed at restoring immune homeostasis and combating pathological conditions characterized by dysregulated macrophage activation. Here, we review the intricate transcriptional networks that govern macrophage polarization, highlighting the pivotal role of transcription factors in orchestrating these processes.

Keywords: macrophages, transcription factor, macrophage polarization, inflammation

Introduction

Macrophages are vital components of the immune system, playing key roles in development, scavenging, inflammation, and pathogen defense by directly removing foreign agents and coordinating the stages of inflammation and tissue repair.[1–3] In response to various environmental cues (eg, microbial products, harmful organisms, apoptotic cells, insult-related debris, and activated lymphocytes) or under different pathophysiological conditions, macrophages can adopt a variety of functional phenotypes through tightly regulated phenotypic polarization.[4,5] Two well-established polarized phenotypes are commonly known as classically activated macrophages (M1 macrophages) and alternatively activated macrophages (M2 macrophages). Bacterial lipopolysaccharide (LPS), tumor necrosis factor-α (TNF-α), and interferon-gamma (IFN-γ)-induced M1 macrophage activation is characterized by a robust capacity for antigen presentation, elevated production of interleukin-12 (IL-12), IL-23, and toxic intermediates such as nitric oxide and reactive oxygen species (ROS), which together drive a polarized type I immune response. Thus, M1 macrophages are widely regarded as powerful effector cells that effectively kill microorganisms and tumor cells while producing substantial amounts of proinflammatory cytokines. In contrast, various signals (eg, IL-4, IL-10, IL-13, glucocorticoids, and immunoglobulin complexes/Toll-like receptor (TLR) ligands) induce distinct M2 functional polarization, which can attenuate inflammatory responses, induce adaptive T-helper 2 immunity, scavenge debris, and promote angiogenesis, tissue repair and remodeling. Macrophage polarization significantly influences disease outcomes. In infectious diseases, M1 polarization enhances pathogen clearance, but excessive activation can lead to chronic inflammation. Conversely, M2 macrophages resolve inflammation and promote tissue repair, but their functions can also support tumor progression and metastasis in cancer. The polarization state of macrophages directly affects their ability to recognize, phagocytose and kill pathogens in

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infectious diseases, while also influencing the degree and duration of inflammation in rheumatoid arthritis, inflammatory bowel disease, and other diseases. The polarization status of macrophages is closely associated with tumor growth, metastasis, and treatment response, impacting the prognosis and treatment response of many diseases and serving as a key factor in prognosis and therapy.[6–8] As transcription factors play pivotal roles in orchestrating the fate and biological functions of all cells, many transcription factors are closely involved in mastering the dynamic polarization of macrophages in response to environmental cues, which has been widely studied (Figure 1). An in-depth understanding of the regulatory network of transcription factors underlying macrophage polarization would greatly help us to develop novel therapeutic approaches for inflammation-related diseases. Here, we review the current understanding of how transcription factor-mediated regulation of macrophage polarization occurs in physiological and pathological contexts. The transcription factors discussed in the present review include STAT, NF-κB, PPARs, IRFs, BACH, C/EBPs, KLFs, c-Myc, the SNAIL family, Maf, HIFα, and others.

The STAT Family

STAT family members are pivotal transcription factors that regulate macrophage polarization and key macrophage functions such as inflammation, tissue repair, and tumor progression (Figure 2). STATs shape macrophage phenotypes in response to cytokines and growth factors by activating diverse signaling pathways, critically impacting the functional programming of tumor-associated macrophages (TAMs).[9] STAT1 is a critical mediator of M1 macrophage polarization driven by IFN-γ, forming homodimers that bind to cis elements known as IFN-γ-activated sequences in the promoters of genes such as nitric oxide synthase 2 (NOS2), the major histocompatibility complex (MHC) class II transactivator and IL-12, crucial for M1's proinflammatory responses and pathogen defense. In vivo, this can be driven by IFN-γ derived from T cells or innate lymphocyte-like natural killer cells, playing a critical role in defending against intracellular pathogens, such as viruses, *Listeria monocytogenes*, and *Mycobacterium tuberculosis*.[10] Conversely, STAT6 serves as the key transcription factor in the polarization of M2 macrophages mediated by IL-4 or IL-13. STAT6 initiates the transcription of genes characteristic of M2 polarization, such as chitinase-like molecule 3(YM1/Chi3l3), resistance-like

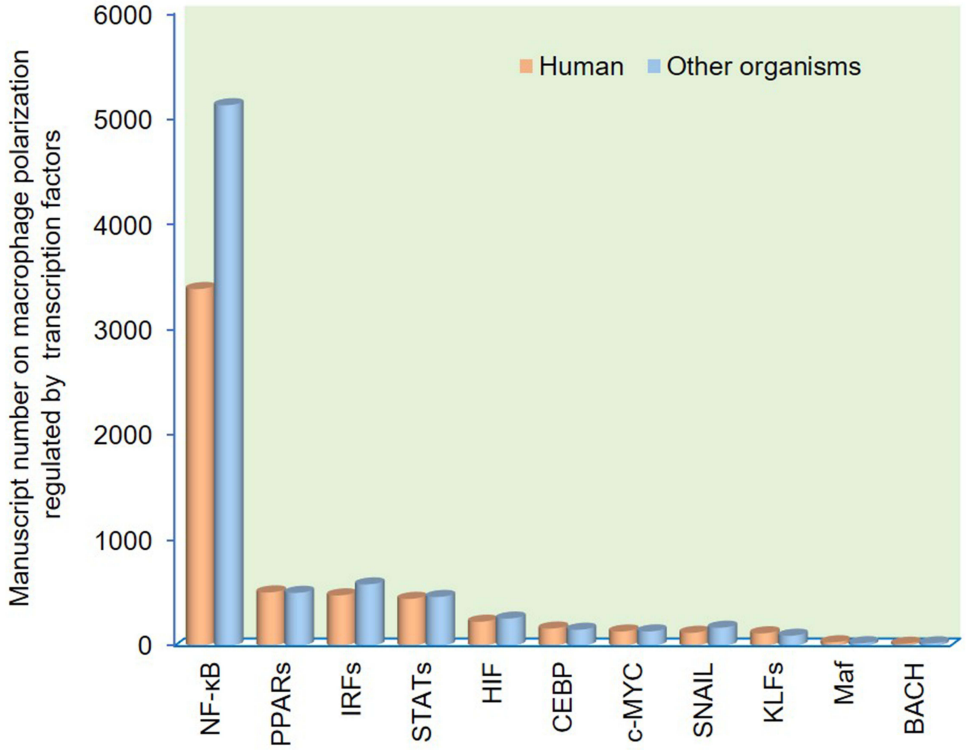

Figure 1 Transcription factors associated with macrophage polarization as reported up to 2024. For the transcription factors associated with macrophage polarization and summarized in the present review, the number of studies conducted in humans (Orange bars) and in all other organisms (blue bars) according to PubMed is shown.

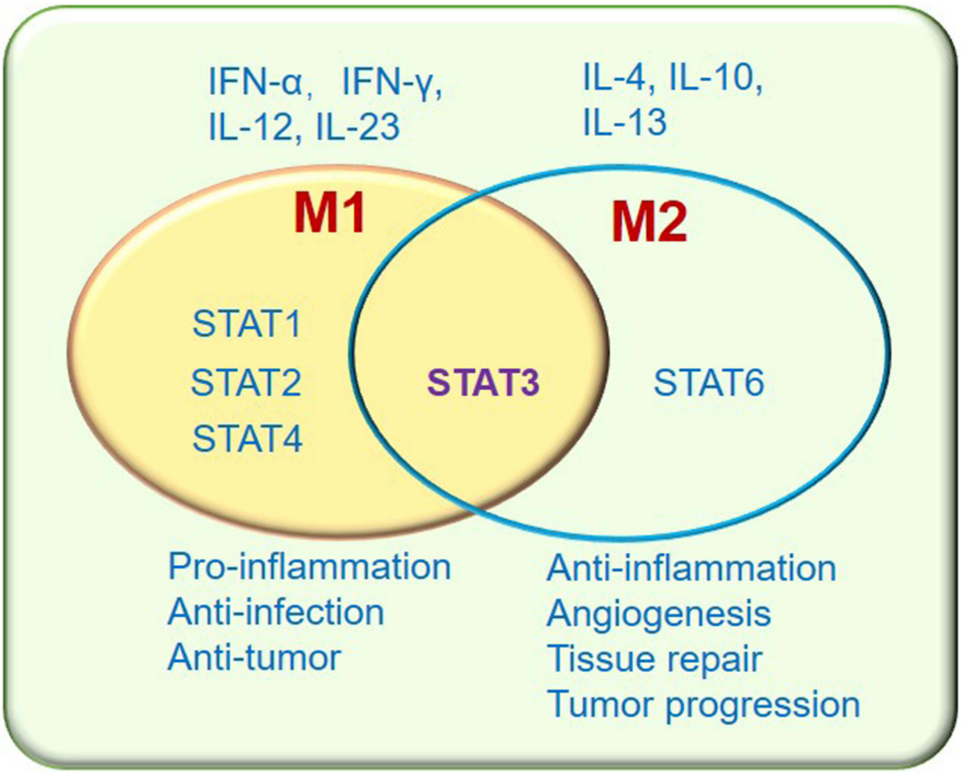

Figure 2 Effect of STATs on macrophage polarization. STAT family members play crucial roles as transcription factors that orchestrate M1/M2 macrophage polarization across diverse contexts. STAT1, STAT2, and STAT4 are responsible for driving M1 polarization in response to stimuli such as IFN-α, IFN-γ, IL-12, and IL-23 and play key roles in regulating inflammation, antitumor responses, and infection immunity. Conversely, STAT6 primarily regulates M2 activation induced by IL-4, IL-10, and IL-13, facilitating anti-inflammatory processes, angiogenesis, tissue repair, and tumor progression. Notably, STAT3 has regulatory effects on both M1 and M2 polarization, depending on the specific stimulus.

α (Retnlα/Fizz1) and mannose receptor C type 1(Mrc1), which support tissue repair, immune regulation, and macrophage polarization toward the TAM phenotype, contributing to tumor progression and tissue remodeling. Besides, IL-4-activated STAT6 mediates transcriptional repression in alternative macrophage polarization by inhibiting p300 and RNA polymerase II binding, reducing enhancer RNA expression, and overlapping with the NF-κB p65 cistrome, leading to reduced inflammatory responses.[11,12] STAT3 is activated by various cytokines, including IL-6 and IL-10, and has a context-dependent role in macrophage polarization, supporting both proinflammatory M1 and anti-inflammatory M2 responses. In the presence of IL-6, STAT3 activation can lead to the expression of genes involved in inflammation, while IL-10-induced STAT3 activation promotes angiogenesis, tumor progression and tissue repair functions. This dual role allows STAT3 to finely tune the immune response according to the specific needs of the tissue environment, making it a promising target for altering the M1/M2 ratio and effectively controlling disease progression.[13,14] STAT2 primarily mediates IFN-α/β signaling, which is essential for antiviral defenses. STAT2 activation contributes to the antiviral state and supports the expression of certain M1-related genes, but its direct role in macrophage polarization is less prominent.[15] STAT4, which is activated by IL-12 and IL-23, plays a significant role in driving Th1 responses and promoting M1 macrophage polarization.[16] STAT5a and STAT5b play a role in macrophage survival and proliferation, but few studies have investigated macrophage polarization.[17] Overall, STAT family members play distinct and overlapping roles in regulating macrophage plasticity, each contributing to the complexity and specificity of the immune response.

NF-κB

NF-κB plays a crucial role as a transcriptional regulator in the M1 macrophage polarization induced by TLR4. The activation of NF-κB begins with the phosphorylation of inhibitor of kappa B (IκB) in response to microenvironmental stimuli such as LPS. Following IκB phosphorylation and subsequent degradation, NF-κB translocates to the nucleus, where it binds to specific

DNA sequences and regulates the expression of proinflammatory cytokines.[18,19] NF-κB has two subunits: p65/p50, which promotes a proinflammatory M1 response, and p50/p50, which is associated with an anti-inflammatory M2 response (Figure 3). When NF-κB is activated in the p65/p50 form, the production of proinflammatory cytokines significantly increases, resulting in an M1 phenotype. However, p50 lacks a transactivation domain. When the p50/p50 homodimer binds to specific DNA sequences in various promoters, it does not activate transcription and blocks the access of heterodimers such as p65/p50, thereby inhibiting the production of proinflammatory cytokines and resolving inflammation.[20–22] Subsequent studies have shown that p50 also plays a crucial role in directly promoting IL-10 transcription. Upon LPS stimulation, the NF-κB binding site on the IL-10 proximal promoter facilitates p50 homodimerization and interaction with the transcriptional coactivator cAMP responsive element-binding protein (CREB), resulting in transcriptional activation.[23] In addition, upon activation of IL-10R, IL-10 subsequently induces STAT3 activation, p50/p50 dimer formation and M2 polarization.[22,24] Consistently, p50-deficient mice also exhibit heightened M1-driven inflammation and impaired ability to initiate M2-polarized inflammatory responses in allergic and helminth-driven conditions. Importantly, when macrophages are exposed long-term to microbial components, such as bacterial LPS, they can also induce a shift in the macrophage phenotype and produce M2-type cytokines via p50/p50, highlighting a mechanism that regulates macrophage plasticity and facilitates rapid responses to infections and changes in the microenvironment.[21,24,25] In the tumor microenvironment, upon activation by IL-1, IL-1R recruits the adaptor protein myeloid differentiation primary response gene 88 (MyD88), which in turn activates the IκB kinase complex, leading to NF-κB activation. This pathway is essential for sustaining the immunosuppressive phenotype of TAMs, which is marked by elevated levels of IL-10, TNF-α, and arginase 1 (Arg1), along with reduced levels of IL-12, MHC II, and NOS2 in ovarian cancer.[26] Conversely, IL-10 from TAMs inhibits IL-12 production by preventing NF-κB activation, thereby promoting tumor survival, but this effect is reversed by blocking IL-10, which restores IL-12 production in a fibrosarcoma mouse model.[27] In liver cancer, NF-κB inhibitor JSH-23 regulates macrophage polarization by inhibiting NF-κB in M1-like TAMs, reducing cell proliferation and promoting apoptosis.[28] Similarly, BAY-11-7082 in Guillain-Barré syndrome reduces M1 macrophages and pro-inflammatory cytokines, alleviating clinical symptoms.[29] Therefore, NF-κB activation may have differential effects on

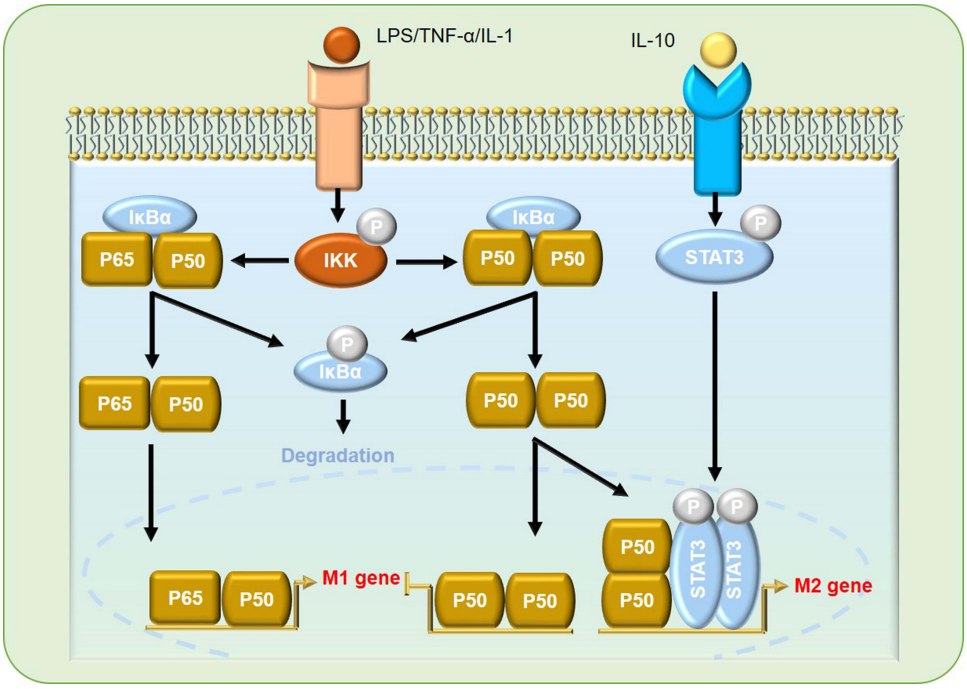

Figure 3 Regulatory roles of NF-κB in macrophage polarization. NF-κB influences macrophage polarization in a two-subunit composition. When stimulated by LPS, TNFα or IL-1, NF-κB is activated in the p65/p50 form, leading to IκBα degradation and increased production of proinflammatory cytokines, resulting in an M1 phenotype. Conversely, activation of the p50/p50 form, in association with phosphorylated STAT3 induced by IL-10, inhibits the p65/p50 form and increases the production of anti-inflammatory cytokines, leading to an M2 phenotype.

these distinct populations of macrophage and play complex roles in macrophage polarization, which provide a therapeutic strategy for cancer and immune-mediated diseases.

The Nuclear Receptor PPARs

PPARs are structurally conserved members of the ligand-activated nuclear hormone receptor superfamily and include PPARα, PPARδ, and PPARγ. Research has demonstrated that PPARs transcriptionally regulate macrophage activation in various health and disease states, including obesity, insulin resistance, cardiovascular disease, liver fibrosis, nonalcoholic fatty liver disease and Chagas disease[30–41] (Table 1). PPARγ, which is highly expressed in adipose tissue and macrophages, is a key regulator of lipid uptake and adipogenesis. PPARγ activation suppresses M1 markers such as NOS2, IL-1β, TNFα, IL-6, and monocyte chemotactic protein 1 through ligand-responsive interference with the STAT-1, AP-1 and NF-κB pathways.[42,43] PPARγ expression levels are positively associated with M2 marker expression (IL-10, Mrc1, and alternative macrophage activation-

Table 1 Summary of PPAR's Roles in Macrophage Polarization

PPAR Isoform	Intervene	Disease	Macrophage Phenotype	Cell Types	Reference
PPARγ	GW1929	Nonalcoholic fatty liver disease	M1↓	RAW264.7	[32,35]
	Sch B	Liver inflammation and fibrosis	M1↓	RAW264.7	[33]
	Docosahexaenoic acid	Acute inflammation	M1↓	RAW264.7	[36]
	IL-4	Muscle regeneration of injury	M2↑	Immortalized macrophages	[47]
	Rosiglitazone	Glutamine metabolism	M2↑	Peritoneal macrophage	[37]
	Rosiglitazone	Wound healing in type 2 diabetes	M2↑	PBMC and BMDMs	[38]
	Thiazolidinediones	Insulin resistance	M2↑, M1↓	Kupffer and BMDMs	[39]
	PPARγ KO	Lung fibrotic	M2↓	Alveolar macrophages and BMDMs	[48,51]
	PPARγ KO	Non-alcoholic steatohepatitis	M1↑	BMDMs	[42]
PPARα	WY14643	Trypanosoma cruzi infection	M1↓, M2↑	Peritoneal macrophages	[31]
	Fenofibrate	Diabetic nephropathy	M1↓	Renal macrophages	[52]
	Fibrates	Cholesterol homeostasis	M1↓	PBMC	[40]
	Bezafibrate	Cardiovascular disease	M1↓	Peritoneal macrophages, THP-1, RAW 264.7	[41]
	PPARα KO	Acute Ischemic Stroke	M2↑	BV-2 and Primary microglia	[53]
PPARδ	GW501516	Diabetic osteoporosis	M1↓, M2↑	BMDMs	[34]
	PPARδ KO	Insulin Sensitivity	M1↑	BMDMs	[57]
	PPARδ KO	Insulin Resistance	M2↓	BMDMs and Kupffer cells	[58]

Notes: ↑: Represents activation of M1 or M2 macrophage polarization. ↓: Represents inhibition of M1 or M2 macrophage polarization.

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associated CC chemokine 1) in human carotid atherosclerotic lesions.[44] PPARγ transcriptional activity is induced by IL-4, IL-13, insulin and the C peptide through PI3-kinase and primes macrophages for M2-induced tissue repair. Additionally, PPARγ also binds to DNA and recruits P300 and RAD21, creating a permissive chromatin environment that promotes STAT6 and RNA polymerase II binding. This enables transcriptional memory and robust gene expression upon IL-4 re-stimulation, regulating extracellular matrix remodeling during muscle regeneration in a mouse injury model.[44–47] Macrophages lacking PPARγ are resistant to M2 polarization, which promotes insulin insensitivity and anti-inflammatory effects and leads to increased pulmonary collagen deposition following influenza infection.[48–51] PPARα plays a key role in fatty acid oxidation and energy metabolism. Upon activation, PPARα enhances transcriptional activity, promoting M2 macrophage polarization and increasing the expression of M2 marker genes such as Arg1, YM1, Mrc1, and transforming growth factor-β (TGF-β), while simultaneously inhibiting the expression of NOS2 and proinflammatory cytokines in murine macrophages. After stroke, microglia/macrophages shift from the neuroprotective M2 phenotype to the neurotoxic M1 phenotype, influencing brain injury and repair. The protective role of PPARα in acute ischemic stroke was confirmed in PPARα-deficient mice, where PPARα activation promoted M2 polarization of microglia/macrophages, thereby enhancing neuronal survival and improving recovery.[31,52,53] PPARδ is expressed ubiquitously and is involved in lipid metabolism, insulin resistance, wound healing, and inflammation.[54–56] PPARδ expression in macrophages is driven by STAT6 binding to its promoter, induced by Th2 cytokines IL-13 and IL-4 produced by adipocytes, facilitating alternative activation. The ablation of PPARδ prevents macrophages from transitioning to the M2 phenotype, leading to inflammation and metabolic dysregulation in adipocytes reducing the expression of glucose transporter 4 and hindering insulin-stimulated glucose uptake. Myeloid-specific PPARδ-deficient mice on a high-fat diet also showed elevated M1 markers and reduced M2 markers in white adipose tissue and liver, leading to a decrease in insulin sensitivity. Additionally, transferring PPARδ-deficient bone marrow into wild-type mice inhibited the alternative activation of macrophages, causing hepatic dysfunction and systemic insulin resistance.[57,58] Overall, PPARs are crucial regulators of macrophage polarization, influencing the immune response and inflammation through their transcriptional activities. Modulating PPAR function offers promising therapeutic potential for managing conditions such as cardiovascular diseases, insulin resistance, obesity, and infectious diseases by restoring the balance between proinflammatory and anti-inflammatory macrophage activities.

IRFs

IRFs, originally identified as regulators of type I interferon expression and signaling, are also recognized as crucial mediators involved in macrophage polarization. The IRF family comprises nine members (IRF1-9) that regulate both the development and activation of immune cells.[59] Among the IRF family members, only seven (IRF1-5 and IRF-8,9) are involved in the differentiation and polarization of macrophages. Notably, IRF1, IRF5, IRF8 and IRF9 play crucial roles in the proinflammatory polarization of macrophages, whereas IRF3 and IRF4 are key contributors to M2 macrophage polarization[60–66] (Figure 4). IRF4, which is induced by IL-4 via jumonji domain-containing protein 3(JMJD3), is crucial for the M2 macrophage response to helminth infection. Both IRF4 and the histone demethylase JMJD3 play crucial roles in IL-4-induced M2 macrophage polarization by binding to specific promoter regions of M2-specific genes, including CD206, Arg1, Fizz1, and YM1.[67] Furthermore, IL-4 modulates a subset of M2 phenotype-associated genes, including MHC-II genes, Class II transactivator genes, IL-1R antagonist gene, and cytochrome P450 1B1 genes, which are disrupted in IRF4-deficient macrophages.[68] Additionally, the protein levels of IRF4, together with those of STAT3 and phosphorylated STAT3, were found to be elevated in IL-6-induced monocyte-derived M2 macrophages in vitro.[69] Interestingly, the competition between IRF4 and IRF5 for binding to the middle region of MyD88 plays a crucial role in determining macrophage polarization toward either the M1 or M2 phenotype.[70] IRF5 is central to macrophage polarization toward the proinflammatory M1 phenotype, mediating TLR-dependent induction of key inflammatory cytokines, including TNF, IL-6, and IL-12.[71] When IRF5 is co-expressed with IκB kinase β, a kinase responsible for phosphorylating and activating IRF5, it drives the polarization of TAMs toward the M1 phenotype, effectively suppressing tumor development in models of advanced-stage ovarian cancer, metastatic melanoma, and glioblastoma.[72] IRF9 lacks known transcriptional activity independently and is recognized primarily as a subunit of interferon-stimulated gene factor 3 or as a complex with STAT1 or STAT2.[73] Studies have demonstrated that IRF9 deficiency provides significant protection against colon inflammation induced by dextran sodium sulfate. Besides, IRF9 promotes the progression of rheumatoid arthritis by regulating macrophage polarization through the proteasome 20S alpha 5 signaling pathway. IRF9 and proteasome subunit alpha 5 were significantly elevated in RA patients, M1/M2 ratio was also

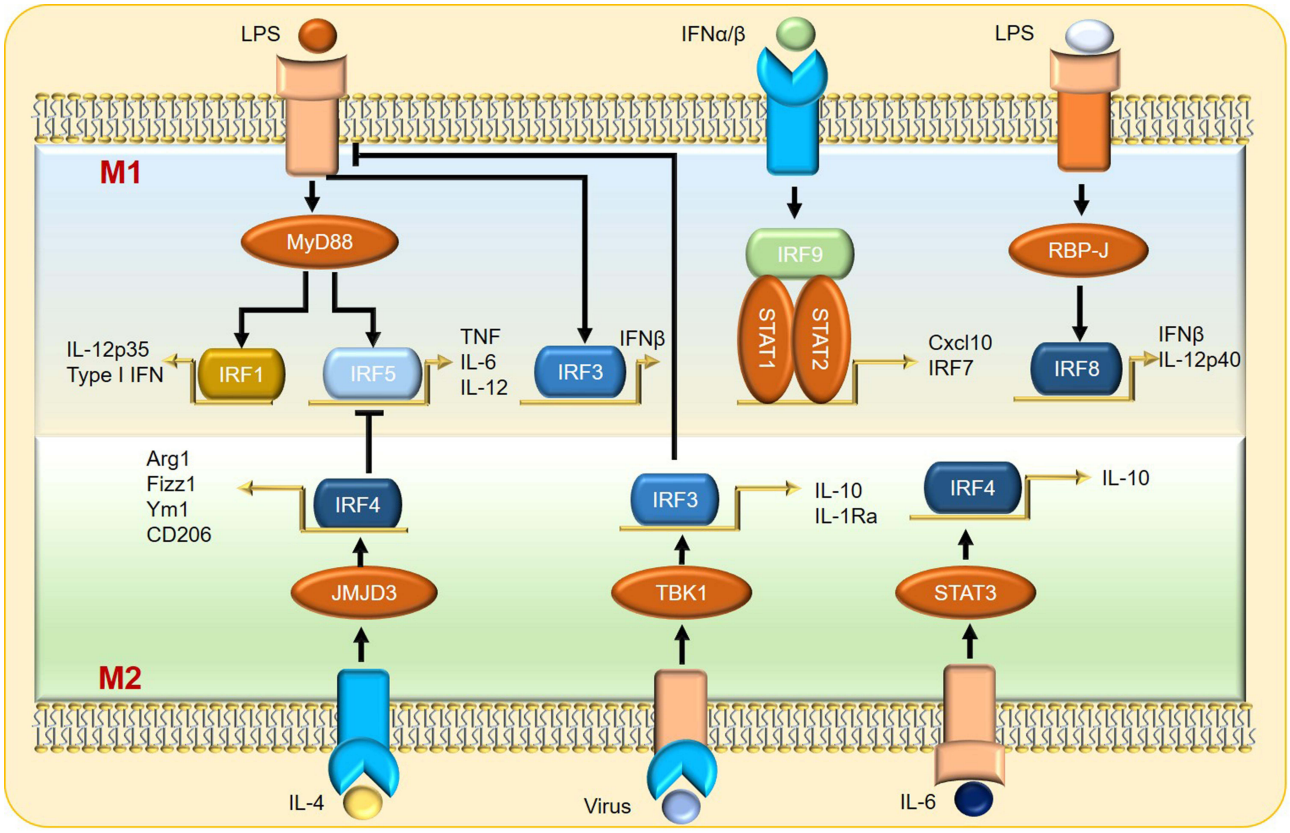

Figure 4 Overview of the roles of IRFs in macrophage polarization. IRFs implicated in M1 and M2 macrophage polarization are indicated. Among the IRF family members, IRF1, IRF3 and IRF5 are activated by LPS, driving M1 polarization. IRF9 and IRF8 also play roles in inducing the M1 phenotype via the IFNα/β and Notch-1 signaling pathways, respectively. Conversely, IRF3 and IRF4 regulate M2 activation induced by IL-4, IL-6, and IL-10.

increased. Knockdown of IRF9 in RAW264.7 cells suppresses proteasome 20S alpha 5 expression, reduces the M1/M2 ratio, and decreases the secretion of pro-inflammatory factors. IRF9 is also involved in regulating type I interferon signaling and contributes to the promotion of M1 macrophage polarization.[74–76] Overall, IRFs represent critical regulators of macrophage polarization, influencing the balance between proinflammatory and anti-inflammatory responses in health and diseases. Further elucidating the specific roles and mechanisms of IRFs in macrophage polarization will pave the way for novel therapeutic strategies aimed at restoring immune homeostasis.

BACH Proteins

BACH proteins, including BACH1 and BACH2, are transcriptional repressors belonging to the basic region leucine zipper (bZIP) transcription factor family and play widespread roles in governing the development and function of both the innate and adaptive immune systems.[77] BACH1 has an important function in inflammatory macrophage differentiation.[78] BACH1-deficient mice have a lifespan comparable to that of wild-type mice but they show resistance to inflammation by upregulating the expression of heme oxygenase-1 across multiple scenarios, including spinal cord injury, ischemia/reperfusion myocardial injury, hypoxic lung injury, LPS-induced hepatic injury, atherosclerosis and colitis triggered by 2,4,6-trinitrobenzene sulfonic acid.[79–86] Peritoneal macrophages derived from BACH1-deficient animals exhibited elevated levels of genes linked to M2 macrophage differentiation, such as Arg1, CD206, Fizz1, and YM1, due to the release of transcriptional activity inhibition. Additionally, BACH1-deficient mice show partial resistance to the onset of experimental autoimmune encephalomyelitis due to a reduced antigen-presentation capacity, which results from decreased proportions of macrophages and dendritic cells that express MHC-II.[86] Similarly, BACH2-deficient alveolar macrophages display defects in phagocytosis and cholesterol handling, and further studies have identified altered gene expression related to chemotaxis, lipid metabolism, and alternative M2 macrophage activation, including increased

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levels of YM1, Arg1, and the M2 regulator IRF4. These changes lead to impaired lipid processing and the accumulation of surfactant proteins, contributing to the development of pulmonary alveolar proteinosis. In addition, BACH2-deficient peritoneal macrophages also exhibit increased YM1 expression upon stimulation with IL-4.[87] Overall, accumulating evidence suggests that BACH factors are involved in macrophage polarization. Further work is needed to understand the precise functions of BACH factors in human immunity and the modification of immune function in patients with allergies, chronic infections, autoimmune diseases, and cancer.

C/EBPs

C/EBPs are a family of bZIP transcription factors that play vital roles in myeloid development and macrophage activation.[88] C/EBPα is known primarily for its role in the differentiation of myeloid cells. It facilitates the development of monocytes and macrophages from hematopoietic progenitors. In macrophages, C/EBPα is associated with the promotion of anti-inflammatory and homeostatic functions. Macrophage-specific deficiency of C/EBPα protects against high-fat-induced inflammation in skeletal muscle. Moreover, C/EBPα-deficient macrophages exhibit a blunted response to cytokine-induced expression of both M1 and M2 macrophage markers, indicating that C/EBPα regulates both M1 and M2 polarization.[89] Previous studies have indicated that the transcription factors C/EBPβ and C/EBPδ are involved in TLR-induced M1 activation through MyD88 and L-1R-associated kinase 4. In macrophages deficient in MyD88 or IL-1R-associated kinase 4, the expression of C/EBPβ and C/EBPδ is diminished following LPS treatment. Furthermore, the absence of both C/EBPβ and C/EBPδ leads to impaired induction of proinflammatory cytokines in response to several TLR ligands.[90] Conversely, another study demonstrated that C/EBPβ interacts with STAT factors specifically regulates M2-associated genes involved in tissue repair, such as Arg1, IL-10, and Msr1, when its expression is transcriptionally activated by the CREB binding protein, another transcription factor from the bZIP family.[91,92] Importantly, although CREB is essential for LPS-induced expression of C/EBPβ, only M2-associated genes were suppressed in the mutant mice, while M1-associated genes, such as NOS2 and IL-12, remained unaffected, suggesting that the M2 program seems to be specifically sensitive to C/EBPβ levels.[92,93] Additionally, C/EBPβ also regulates arginine metabolism by activating Arg1 expression in macrophages via STAT6 and C/EBPβ binding sites in response to IL-4, which may provide a foundation for developing strategies to modulate arginase expression in Th2 cytokine-predominant diseases.[94] However, the role of C/EBPs in regulating macrophage polarization and the molecular mechanisms involved in atherosclerosis, autoimmune diseases, and cancer remains unclear. Therefore, more studies, such as the development of relevant in vivo and in vitro pathological models, single-cell transcriptomic analysis of clinical samples, and gene editing, are needed to reveal the roles of C/EBPs in the cross-linking networks that modulate macrophage function in various disease contexts.

KLFs

KLFs are a subfamily of zinc-finger transcription factors involved in macrophage polarization in response to various stimuli.[95,96] KLF4 plays a crucial role in M2 macrophage polarization and enhances the expression of genes associated with tissue repair, immune regulation, and resolution of inflammation. KLF4 cross-talk with STAT6 signaling impairs NF-κB activity by sequestering essential coactivators, p300 and p300/CBP-associated factors, leading to the induction of M2-related genetic reprogramming and effectively preventing M1 polarization. KLF4-deficient macrophages exhibit impaired expression of typical M2 markers after IL-4 or IL-13 stimulation in vitro. Additionally, these macrophages exhibit increased proinflammatory gene expression, enhanced bactericidal activity, and altered metabolic responses.[97] IL-4 induces STAT6 phosphorylation, which promotes KLF4 gene expression. In turn, KLF4 cooperates with STAT6 to enhance the M2 gene profile through the activation of monocyte chemotactic protein-induced protein expression and the upregulation of Arg1 and Fizz1 expression.[98] Furthermore, KLF4 deficiency in macrophages infiltrating the kidney enhances M1 polarization, exacerbating glomerular matrix deposition and tubular epithelial damage in a murine model of chronic kidney disease.[99] However, other studies have shown that KLF4 is significantly induced in macrophages by pro-inflammatory stimuli such as IFN-γ, LPS, or TNF-α, while its expression is decreased by TGF-β. Overexpression of KLF4 enhances M1 polarization by activating STAT1 and inducing iNOS, which leads to increased production of inflammatory cytokines and tissue damage. This effect is further amplified when KLF4 is overexpressed in the presence of IFN-γ and LPS.[100,101] A potential explanation for KLF4's dual role in promoting both M1 and M2 polarization may lie in the use of different cell types across studies. The studies showing KLF4

promoting M1 polarization often utilized immortalized cell lines (eg, J774a, THP-1, RAW264.7), while those demonstrating its role in M2 polarization typically used primary macrophage cell lines. Additionally, variations in LPS concentration (ranging from 10 ng/mL to 1000 ng/mL) and its source (eg, E. coli, *Porphyromonas gingivalis*, and *Salmonella enterica*) could also account for the divergent results observed. Recent research has shown that KLF14 also regulates glycolysis and immune function in macrophages. KLF14 expression is elevated in septic patients, and its deletion results in significantly higher mortality in lethal models of murine endotoxemia and sepsis via the transcription of hexokinase 2(HK2) to promote glycolysis and the release of inflammatory cytokines.[102] KLF6 is another crucial member of the KLF family that significantly influences macrophage polarization. KLF6 expression is strongly induced by LPS and IFN-γ and is essential for LPS- and IFN-γ-induced macrophage polarization to the M1-like phenotype, working in concert with NF-κB signaling. It suppresses anti-inflammatory gene expression by downregulating PPARγ in macrophages, both in vitro and in KLF6-deficient mice.[103] KLF6 overexpression elevates inducible HIF-1α expression in macrophages, whereas KLF6 deficiency reduces it.[104] Notably, overexpressing oxygen-stable HIF-1α in KLF6-deficient macrophages restores proinflammatory and glycolytic gene expression, enabling a coordinated inflammatory and hypoxic gene program for an effective immune response[104] (Figure 5).

c-Myc

The c-Myc transcription factor is crucial for regulating M2 and TAM activation.[105] c-Myc expression is primarily limited to the M2 phenotype and is nearly undetectable in M0 and M1 macrophages in human cells. The study demonstrated that c-Myc expression is induced in human M2-like macrophages in response to various stimuli, including IL-4, IL-10, IL-13, and TGF-β. However, murine M0 macrophages express small but detectable levels of c-Myc.[105,106] c-Myc expression has been observed in certain types of human TAMs in vivo, which exhibit an M2-like macrophage activation status. Studies with mouse bone marrow-derived macrophages (BMDMs) cultured in conditioned medium from Hepa1-6 cell have indicated that Wnt/β-catenin signaling mediates M2 macrophage polarization through c-Myc-mediated expression of mannose receptor (MR), Arg1, and YM1, which supports the progression of hepatocellular carcinoma.[107] In addition, in a coculture model of human monocytes and hepatocellular carcinoma cells, IL-12 inhibited the transcriptional activity of STAT3 and the expression of

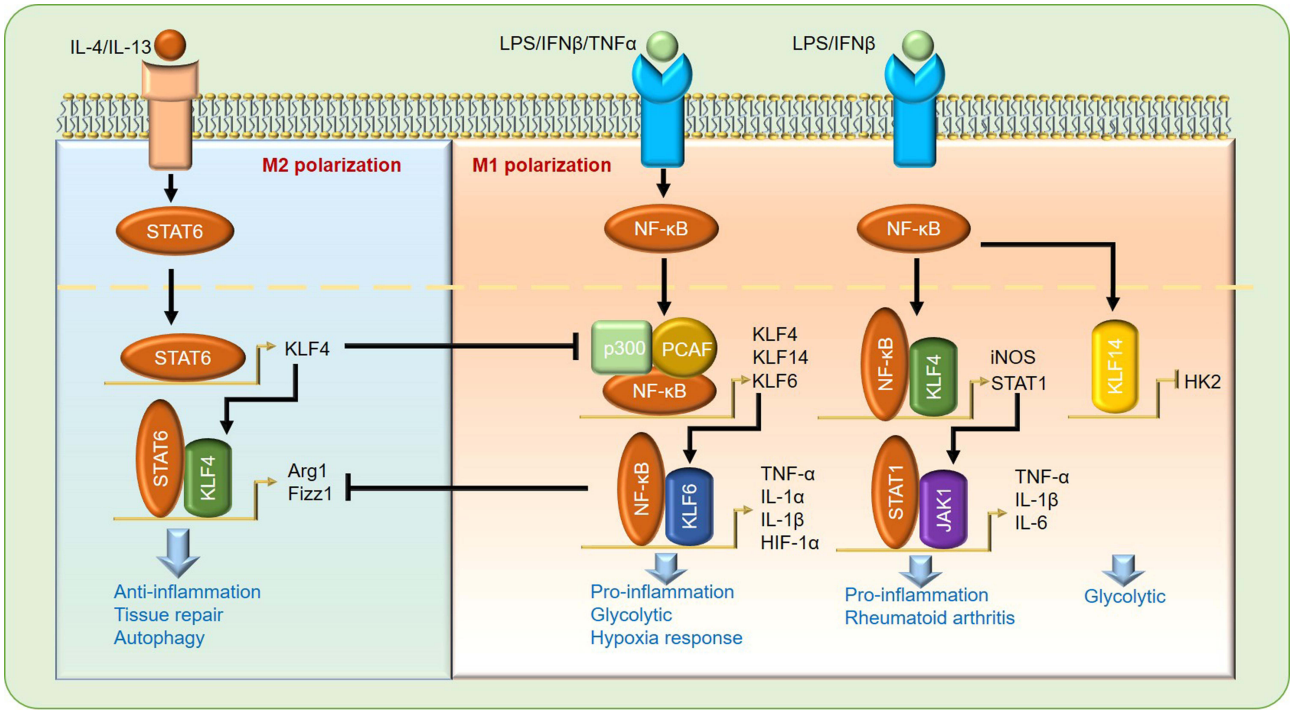

Figure 5 Regulatory roles of KLF4 KLF6 and KLF14 in macrophage polarization. The increase in KLF4 expression, which is mediated by STAT6 transcription in response to IL-4/IL-13, regulates M2 macrophage polarization and suppresses LPS- and IFN-γ-induced M1 gene expression in macrophages. Conversely, KLF4/KLF6 is prominently induced and activated by LPS and IFN-γ and is required for the LPS- and IFN-γ-induced M1-like phenotype and suppresses M2 macrophage polarization in cooperation with NF-κB signaling. KLF14 is also induced by LPS, leading to the suppression of HK2 expression and inhibition of glycolysis.

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c-Myc in monocytes, promoting M1 polarization, affecting T cell infiltration and suppressing hepatocellular carcinoma growth.[108] Furthermore, the inhibition or deletion of c-Myc reduces the expression of pro-angiogenic molecules (eg, vascular endothelial growth factor (VEGF), matrix metalloproteinase 9, and HIF-1α) and diminishes tumor growth [109] Besides, c-Myc serves as a transcriptional activator by binding to enhancer box sequences in the promoter regions of its target genes. It directly induces the expression of key M2-associated genes, including arachidonate 15-lipoxygenase, Mrc1, scavenger receptor class B member 1, STAT6, and PPARγ, thereby driving M2 macrophage polarization. In response to IL-4, STAT6 and PPARγ further enhance M2 activation by directly binding to the promoters of M2 target genes, such as CD209 and CD36.[105,109] Thus, c-Myc is a critical regulator of macrophage polarization, particularly in promoting the M2 phenotype and supporting tumor progression (Figure 6). Its inhibition or deletion in macrophages suppresses protumor gene expression and reduces tumor growth, making it a potential therapeutic target for modulating macrophage activity in cancer. In addition, future research could explore the potential of overexpressing c-Myc in M0 or M1 macrophages to induce M2 polarization, offering a promising strategy for the treatment of autoimmune and inflammatory diseases.

SNAIL Family

The transcription factor SNAIL may play a regulatory role in macrophage polarization. In human THP-1 macrophages, SNAIL expression induced by TGF-β, through the transcriptional activation of PI3K/AKT and Smad2/3 signaling pathways, drives M2-like macrophage polarization. SNAIL overexpression promotes M2-like differentiation by reducing the expression of proinflammatory cytokines and enhancing the expression of M2-specific markers. Conversely, SNAIL knockdown favors M1 polarization by increasing proinflammatory cytokine production and blocking TGF-β-induced M2 polarization.[110] Moreover, Jagged1-mediated myeloid Notch1 signaling regulates NOD-like receptor family pyrin domain containing 3(NLRP3) function and promotes the activation of heat shock transcription factor 1, which subsequently induces the expression of SNAIL. Furthermore, SNAIL increases thioredoxin-1 expression and reduces thioredoxin-interacting protein, NLRP3/caspase-1, and ROS production, which in turn suppresses NLRP3 function and hepatocellular apoptosis, resulting in the reduction of ischemia/reperfusion-induced liver injury. Ablation of myeloid SNAIL expression significantly increased apoptotic signals regulating kinase 1 activation by transcriptionally regulates the thioredoxin 1/ thioredoxin-interacting protein and thioredoxin 1/ apoptosis signal-regulating kinase 1 complexes,

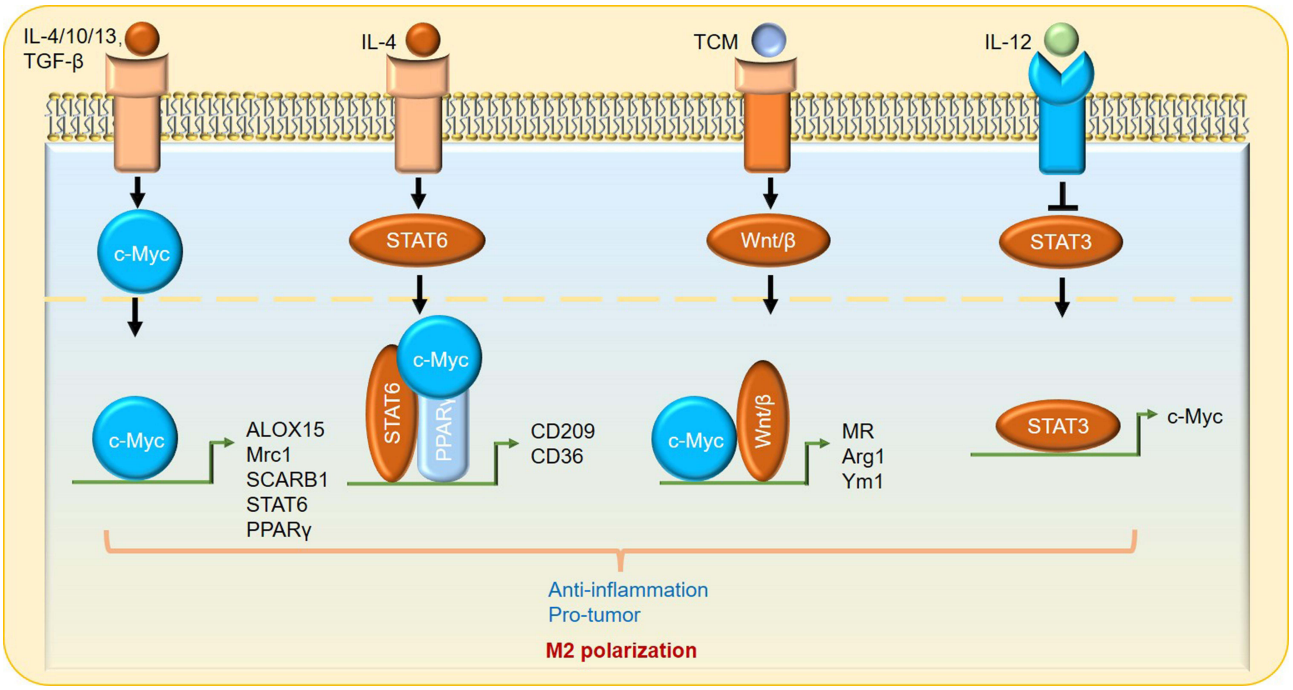


Figure 6 Macrophage polarization is regulated by c-Myc. C-Myc, which is prominently induced and activated by IL-4, tumor-conditioned medium (TCM), and IL-12, is essential for M2 macrophage polarization and functions in cooperation with the STAT3/6 and Wnt/β-catenin signaling pathways.

leading to enhanced NLRP3 inflammasome activation and ROS-induced hepatocellular apoptosis in a mouse model of ischemia/reperfusion-induced liver injury.[111,112] Studies have shown that SNAIL also regulates M1 polarization. In the cecal ligation and puncture-induced sepsis models, high glucose and LPS stimulation promoted M1 macrophage polarization and reduced miR-3061 levels, which were associated with increased SNAIL expression in RAW264.7 cells. Furthermore, overexpression of miR-3061 inhibited SNAIL expression, thereby suppressing M1 macrophage polarization and the production of inflammatory cytokines, which ultimately exacerbated sepsis-induced intestinal injury.[113] However, there are few reports on the direct involvement of SNAIL in regulating macrophage polarization in TAMs. Instead, SNAIL influences macrophage polarization indirectly through its abnormal expression in tumor cells.[114–118] Overall, additional research is required to fully understand the mechanisms through which SNAIL directly regulates macrophage polarization in TAMs. Furthermore, there is a need to develop effective strategies, such as small-molecule inhibitors, cell therapies, or gene editing, to modulate its activity in different disease contexts.

Maf

The Maf transcription factor family consists of several members, including MafA, MafB, c-Maf, Neuroretina Leucine zipper protein 11, MafF12, MafG13, and MafK. Among them, MafB and c-Maf are recognized as significant factors that regulate macrophage differentiation and polarization in both mouse and human models.[119–121] In BMDMs from adult wild-type mice, MafB expression is stimulated by IL-10 or IL-4/IL-13, while it is suppressed by LPS or granulocyte-macrophage colony-stimulating factor (GM-CSF).[120] Immunostaining analysis revealed strong MafB expression in $CD204^+$ and $CD68^+$ TAMs at stage 3 of human lung cancer. Furthermore, in MafB-GFP knock-in heterozygous mice with Lewis lung carcinoma, $MafB^+$ macrophages significantly expressed protumor factors such as IL-10, Arg1 and TNFα.[119] Additionally, increased MafB expression in TAMs was noted in a murine model of breast cancer.[122] These findings suggest that MafB expression can be a potential marker of TAMs in malignant tumor. In human primary macrophages, IL-10-induced MafB activated the STAT3 signaling pathway, increasing the levels of the matrix metalloproteinase 9 and IL-7R genes, which help resolve inflammation and restore tissue integrity.[123] Consistently, wound healing was significantly delayed in MafB-deficient mice, as MafB deficiency downregulated the expression of C-C motif chemokine ligand 12, C-C motif chemokine ligand 2, and Arg1, leading to reduced macrophage recruitment and impaired tissue repair.[124] Conversely, c-Maf expression is stimulated by IL-10 and suppressed by IL-4 in combination with IL-13 or GM-CSF in BMDMs.[120] However, recent research has shown that M2 macrophages induced by IL-4 and IL-13 also express high levels of c-Maf, which directly transcriptionally induces the expression of colony-stimulating factor 1 receptor, thereby regulating the expression of M2-related genes (IL-12, IL-6, IL-10, IL-1β, Arg1, TGF-β, VEGF, IRF4, and the chemokine C-C-motif receptor 2).[125] In human non-small cell lung carcinoma, TAMs express c-Maf, which facilitates M2-mediated T-cell suppression and tumor progression by regulating M2-related genes in vivo. Knockout of c-Maf in macrophages diminished the suppression of effector T cells, decreased the expression of CD206, and increased MHC-II levels. Consequently, the absence of c-Maf in myeloid cells results in delayed tumor growth compared with that in mice with c-Maf–competent myeloid cells.[125,126] Additionally, c-Maf acts as a key regulator of the transcriptional program in perivascular macrophages. Compared to wild-type mice, high-fat diet-fed mice with c-Maf-deficient macrophages demonstrated improved metabolic outcomes, including reduced weight gain, enhanced glucose tolerance, and a decreased inflammatory cell profile in white adipose tissue.[127] Overall, MafB and c-Maf are pivotal transcription factors, with both loss-of-function and gain-of-function studies demonstrating their roles in promoting M2 macrophage polarization and regulating TAMs. These findings highlight their potential as therapeutic targets, with approaches such as small molecule inhibitors, gene editing, and cell therapy showing promise in cancer and metabolic diseases. However, the widespread expression of MafB and c-Maf in various cell types, as well as the unique immunogenicity associated with macrophages, must also be carefully considered to ensure the safety and efficacy in therapeutic applications.

HIFα

HIFα, which includes the isoforms HIF-1α and HIF-2α, is a master transcriptional regulator of the cellular response to hypoxia and plays a crucial role in macrophage polarization[128,129] (Figure 7). Notably, HIFα stabilization in macrophages can occur in an oxygen-independent manner. In the presence of different pathogens, the activation of HIF-1α expression has been observed in macrophages cultured under normoxic conditions.[130] LPS/IFNγ rapidly induces HIF-1α expression in macrophages,

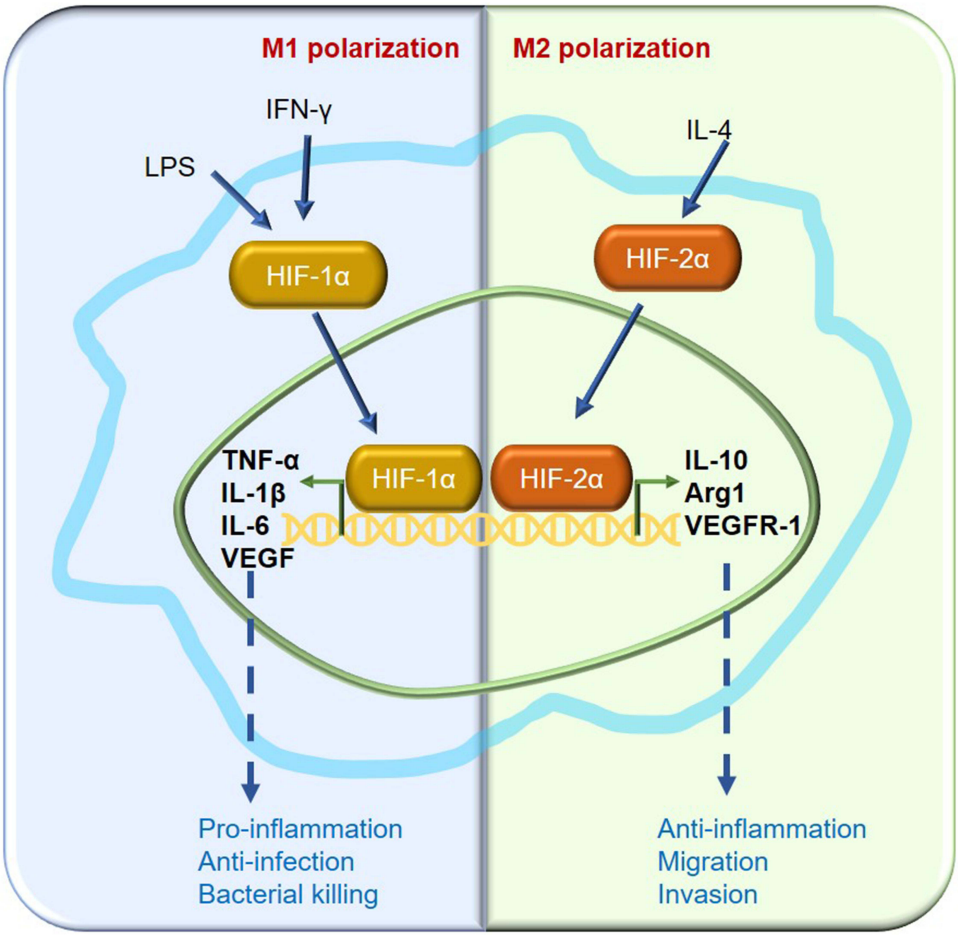


Figure 7 Different regulatory roles of HIF1α and HIF2α in macrophage polarization. HIF-1α, which is prominently induced and activated by LPS and IFN-γ, is responsible for driving M1 polarization and plays key roles in inflammation, infection resistance, and bacterial killing. Conversely, HIF-2α prominently regulates M2 polarization induced by IL-4, facilitating anti-inflammatory effects, migration, and invasion.

thereby promoting NOS production independently of hypoxia. In contrast, HIF-2α mRNA responds more slowly to IL-4/IL-13, which induces Arg1 expression via the JAK/STAT6 pathway. However, IFNγ and LPS can suppress IL-4/STAT6 signaling by inducing suppressor of cytokine signaling proteins, which ultimately inhibits HIF-2α synthesis. Under low IFNγ conditions, HIF-2α promotes the expression of arginase 1, thereby reducing NO production. In contrast, under high IFNγ conditions, HIF-2α levels decrease, leading to the activation of iNOS, which produces NO.[131,132] Furthermore, the overexpression of HIF-1α in macrophages increases the expression of M1 markers, whereas HIF-2α promotes M2 polarization through the expression of markers such as Arg1.[132,133] Despite these roles, deletion of myeloid HIF-1α or HIF-2α does not affect macrophage polarization or function during skeletal muscle regeneration induced by sterile tissue damage.[134] However, HIF-1α deficiency attenuates pro-inflammatory pathways and impairs M1 macrophage polarization in stenotic artery macrophages. Interestingly, myeloid cell-specific knockout of HIF-1α and HIF-2α has been shown to alleviates sepsis, reducing proinflammatory cytokine production and improving survival in LPS-induced endotoxemia models.[135–137] These observations underscore the plasticity of macrophages and their context-dependent roles in inflammation and repair. Loss of HIF-1α in myeloid cells downregulates iNOS and Arg1 expression, relieving T-cell proliferation suppression, which significantly reduces tumor mass and inhibits tumor progression.[138] Similarly, in a murine colitis-associated colorectal cancer model, the loss of HIF-2α also reduced tumor burden and progression by impairing macrophage migration and invasion through the downregulation of macrophage colony-stimulating factor receptor and C-X-C chemokine receptor type 4 expression.[139] LPS-induced HIF-1α stabilization leads to M1 polarization, highlighting the role of HIF-1α in inflammatory responses to bacteria and viruses. HIF-1α increases following *Mycobacterium tuberculosis* infection, increasing IL-1β production and reducing bacillary survival. In addition,

HIF-1α is an essential mediator of IFN-γ-dependent control of *Mycobacterium tuberculosis* infection, and RNA sequencing revealed that almost half of all genes inducible by IFN-γ are regulated in HIF-1α–deficient macrophages during infection.[140,141] In H1N1 virus-infected macrophages, the levels of HIF-1α mRNA and protein actually remain constant, yet its transcriptional activity increases, resulting in elevated TNF-α and IL-6 production, reduced IL-10, and heightened inflammation.[142] HIF-1α promotes VEGF induction in macrophages in response to GM-CSF and low oxygen levels, whereas HIF-2α, dependent on JAK2/STAT5 signaling, induces soluble VEGF receptor 1 to neutralize VEGF as oxygen levels decrease. This indicates that HIF-1α and HIF-2α may have opposing roles in regulating VEGF signaling across different oxygen concentrations.[143–145] In general, these studies indicate that the functions of HIF-1α and HIF-2α in macrophage polarization are complex, sometimes overlapping and dependent on the pathophysiological context. Although many small molecule inhibitors targeting HIF-1α and HIF-2α, such as PX-478 and PT2385, are currently used in cancer therapy, the widespread expression of these factors across various cell types makes it important to focus on identifying macrophage-specific inhibitors and drug strategies as a key direction for future research. Furthermore, gene editing-based cell therapy represents a promising targeted strategy to precisely modulate HIF-1α and HIF-2α activity in macrophages, potentially enhancing targeting specificity while minimizing side effects.

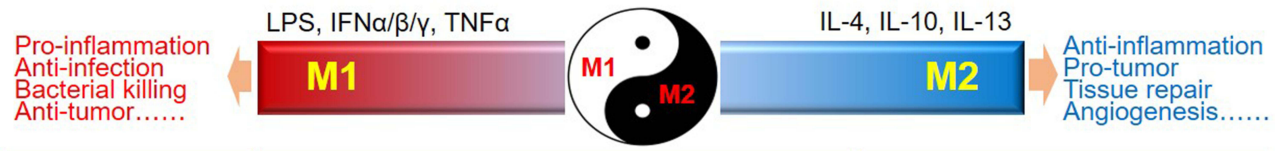
Other Transcription Factors

In addition, an increasing number of studies have revealed a broader correlation between transcription factors and macrophage polarization. Zinc fingers and homeobox 2 (zhx2) play important roles in B-cell differentiation, NK cell maturation and macrophage survival.[146–148] It is also highly expressed in LPS-stimulated macrophages, where it promotes glycolysis and inflammatory responses during sepsis by binding to the promoter and enhancing the transcription of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3, a rate-limiting enzyme in glycolysis.[149] Furthermore, zhx2 regulates macrophage polarization in inflammatory environments and tumor microenvironments by associating with NF-κB (p65) and binding to the IRF1 promoter, which leads to the induction of IRF1 transcription in macrophages. Deletion of zhx2 in myeloid cells suppresses LPS-driven proinflammatory polarization while promoting anti-inflammatory and protumor phenotypes induced by IL-4 and the tumor microenvironment in liver tumor models.[150] Myocyte enhancer factor 2C (MEF2C) is essential for bone, neuronal, cardiac, and skeletal muscle development.[151] MEF2C binding sites were the most significantly enriched motifs identified in a ChIP-seq analysis in *M. tuberculosis*-infected macrophages, suggesting their role in macrophage responses to infection. Indeed, MEF2C promotes M1 macrophage polarization by controlling the expression of cytokines characteristic of macrophage lineages, and myeloid-specific Mef2c-knockout mice display diminished IL-12 production and weakened Th1 responses, resulting in increased susceptibility to *Listeria monocytogenes* infection but protection against dextran sulfate sodium salt-induced inflammatory bowel disease.[152,153] Activating transcription factor 3 (ATF3) belongs to the mammalian ATF/CREB family of transcription factors and responds to various physiological and pathological processes.[154] In macrophages, ATF3 acts as a significant negative regulator of proinflammatory cytokines. Upon the activation by TLRs, ATF3 expression is rapidly induced, which subsequently recruits histone Deacetylase 1 to the ATF3/p65 complex, facilitating the deacetylation of p65 and thereby suppressing the inflammatory gene expression triggered by TLR signaling.[155,156] Moreover, ATF3 is induced in both mouse and human immune cells in response to IFN-α and IFN-β. It acts as a transcriptional repressor by directly binding to the Ifnb1 promoter, playing a critical role in a negative feedback loop that regulates IFN-β expression. This regulation is achieved through modulation of both basal and inducible IFN-β levels, as well as influencing the expression of IFN-γ and downstream genes regulated by IFN signaling pathways [157] Furthermore, ATF3 overexpression enhances macrophage migration and promotes the expression of markers associated with the M2 phenotype while inhibiting markers of the M1 phenotype by upregulating tenascin through the Wnt/β-catenin signaling pathway.[158,159] Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor pivotal in the cellular defense against oxidative stress.[160] Increasing evidence underscores the significant role of Nrf2 in shaping the distinct metabolic and inflammatory profiles of M1 and M2 macrophages.[161] Nrf2 has been shown to negatively regulate M1 macrophage polarization while promoting M2 macrophage polarization through redox control via the upregulation of heme oxygenase-1 and glutathione S-transferase expression.[162,163] In response to immunological stresses, such as those induced by bacterial products and tumor growth, the NF-κB(p50)–CSF-R1–C3aR axis activates Nrf2, leading to the upregulation of heme oxygenase-1 expression in TAMs. This process promotes immunosuppression, angiogenesis, and epithelial-mesenchymal transition, which together enhance metastasis formation.

Accordingly, in vivo treatment of mice bearing fibrosarcoma with brusatol, a selective Nrf2 inhibitor, significantly reduced lung metastasis formation [164] Impaired wound healing is one of the major complications of diabetes, treatment with the Nrf2 activator dimethyl fumarate markedly improved wound healing in streptozocin-induced diabetic rats by boosting antioxidant enzyme expression and reducing pro-inflammatory cytokines, while the Nrf2 inhibitor ML385 replicated diabetic effects, highlighting Nrf2 activation as a potential therapeutic strategy for diabetic wound healing.[165] Moreover, Nrf2 activation by diethyl maleate suppresses inflammation by preventing RNA Pol II recruitment to the IL-6 and IL-1β gene loci without affecting p65 recruitment. This anti-inflammatory mechanism is independent of the Nrf2-binding motif and ROS levels. Additionally, Nrf2 activation plays a pivotal role in regulating macrophage polarization by suppressing M1 polarization while simultaneously enhancing the expression of M2 markers, through its interaction with several key signaling pathways, such as TGF-β/SMAD, TLR/NF-κB, JAK/STAT, Notch, PI3K/AKT, NLRP3, and MAPK. Together, these pathways create a complex network that not only drives macrophage polarization but also highlights potential therapeutic targets for addressing osteoarthritis.[166,167]

Conclusions and Future Directions

Transcription factors play pivotal roles in regulating macrophage polarization, which determines the functional phenotypes of immune responses. To achieve a comprehensive understanding of how macrophage polarization is regulated by transcription factors, we summarize the properties and roles of these transcription factors in determining macrophage phenotypes, as shown in Figure 8. Under physiological or pathological conditions, LPS, IFNα/β/γ, or TNFα activate STAT1/2/4, NF-κB (p65/50), IRF1/5/8/9, CEBPδ, KLF6, HIF-1α, Zhx2 and MEF2C to promote M1 macrophage polarization. Conversely, IL-4, IL-10, and IL-13, or tumor-conditioned medium, mediate STAT6, PPARα/γ/δ, IRF4, HIF-2α, NF-κB (p50/50), MafB, c-Maf, c-Myc, ATF3 and Nrf2 transcriptional activities, promoting macrophage M2 polarization. Notably, STAT3, CEBPα/β, KLF4, and SNAIL induce macrophage polarization toward the M1 or M2 phenotype in various settings, underscoring the complexity, plasticity and context dependence of macrophage polarization. Furthermore, PPARα/γ/δ, KLF4/14, NF-κB (p50/50), IRF3/4, STAT6, ATF3 and Nrf2 also inhibited M1 phenotype differentiation in the presence of IL-4, IL-6 or IL-10, whereas BACH1/2, KLF6 and NF-κB (p65/50) inhibited M2 polarization under the stimulation of LPS, IFNβ or TNFα via autocrine and paracrine mechanisms. Besides, the interactions between transcription factors and their cascading effects responding to different stimuli, such as direct interactions (eg, NF-κB with KLF4/6 and STAT1/3), competitive binding (eg, IRF4 and IRF5 competing for the middle region of MyD88), epigenetic inhibition (eg, STAT6 or Nrf2 binding to RNA polymerase II to suppress NF-κB and RNA polymerase II initiation), and cascading effects (eg, NF-κB inducing KLF4/6/14 expression, which then binds to induce M1 polarization), further highlighting the intricate regulation, cross-linking and environmental sensitivity involved in macrophage polarization. Understanding the intricate transcriptional regulatory networks governing macrophage polarization holds great promise for therapeutic interventions in inflammatory diseases. Recent advancements in single-cell RNA sequencing and genome editing technologies have offered unprecedented insights into the transcriptional landscape of macrophage polarization. For instance, a single-cell RNA sequencing map of human macrophage specification dynamics from postconceptional weeks 4–26 across 19 tissues identified a population of microglia-like cells in the skin, testis, and heart, which resemble central nervous system microglia in transcriptome, protein expression, and morphology. Additionally, a pan-cancer analysis of single myeloid cells from 210 patients across 15 cancer types reveals tissue-specific gene expression profiles in pro-angiogenic TAMs, such as secreted phosphoprotein 1(SPP1)+ in breast cancer and VCAN+ in melanoma.[168,169] Integrating multi-omics data and computational modeling enables the identification of key transcription factors and their target genes involved in polarization dynamics. For example, integrating time-course proteomics, phosphoproteomics, and transcriptomics revealed metabolic shifts in M1/M2 polarization, highlighting PPARγ-induced retinoic acid and mitogen-activated protein kinase signaling as key regulators of M2 polarization. Additionally, single-cell RNA sequencing and spatial imaging identified prognostically relevant macrophage subpopulations in CRC, such as IL4I1+ macrophages in high-cell-turnover regions (favorable prognosis) and SPP1+ macrophages in hypoxic tumor areas (poor prognosis), providing potential therapeutic insights.[170–173] By deciphering the molecular mechanisms that govern macrophage polarization, researchers aim to manipulate transcription factor activities to direct macrophages toward desirable phenotypes. This could be achieved through emerging immunotherapeutic approaches, such as small molecules, nucleic acid-based products, gene editing, and



Transcription factor	M1	M2
NF-κB (p65/50)	Promoting	Inhibiting
KLF6	Promoting	Inhibiting
SNAIL	Promoting	Promoting
STAT3	Promoting	Promoting
CEBPα/β	Promoting	Promoting
KLF4	Promoting/Inhibiting	Promoting
PPAR α /γ/δ	Inhibiting	Promoting
NF-κB(p50/50)	Inhibiting	Promoting
IRF4	Inhibiting	Promoting
ATF3	Inhibiting	Promoting
Nrf2	Inhibiting	Promoting
STAT6	Inhibiting	Promoting

Transcription factor	M1
HIF-1α	Promoting
Zhx2	Promoting
MEF2C	Promoting
IRF1/5/8/9	Promoting
CEBPδ	Promoting
STAT1 /2/4	Promoting
KLF14	Inhibiting
IRF3	Inhibiting

Transcription factor	M2
HIF-2α	Promoting
MafB	Promoting
c-Maf	Promoting
c-Myc	Promoting
BACH1/2	Inhibiting

Figure 8 Transcription factors governing macrophage polarization. Overview of the transcription factors that mediate the regulation of M1 and M2 macrophage polarization, which impacts inflammation, tissue damage, metabolism, infection, tumors, and other processes in various contexts.

cell therapy, ultimately leading to novel therapeutic strategies for inflammatory disorders, infectious diseases, and cancers.[174,175] In the future, exploiting transcriptional regulation to fine-tune macrophage polarization holds immense potential for personalized medicine and targeted immunotherapy, particularly in enhancing both efficacy and safety. However, further research is certainly needed to elucidate the context-specific roles of transcription factors in macrophage polarization and their immunotherapy implications for pathogenesis, which is essential to translate these findings into clinical applications, ultimately improving patient outcomes.

Abbreviations

ALOX15, Arachidonate 15-Lipoxygenase; ATF3, Activating transcription factor 3; Arg1, Arginase 1; BACH, BTB and CNC homology; BMDM, Bone marrow derived macrophage; bZIP, belonging to the basic region leucine zipper; C/EBP, CCAAT-enhancer binding protein; Chi3l3, Chitinase-like molecule 3; c-Myc, Cellular Myc; CREB, cAMP responsive element-binding protein; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; HK2, Hexokinase 2; HIF-1α, Hypoxia-inducible factor alpha; IκB, inhibitor of kappa B; IFN, Interferon-gamma; IL-12, Interleukin-12; IRF, Interferon

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regulatory factor; JMJD3, Jumonji domain-containing protein 3; KLF, Kruppel-like factor; LPS, Lipopolysaccharide; Maf, v-Maf Musculoaponeurotic Fibrosarcoma Oncogene Homolog; MEF2C, Myocyte enhancer factor 2C; MHC, Major histocompatibility complex; Mrc1, Mannose receptor C type 1; MR, Mannose receptor; MyD88, myeloid differentiation primary response gene 88; NF-Kb, Nuclear transcription factor-κB; NOS2, Nitric oxide synthase 2; Nrf2, Nuclear factor erythroid 2-related factor 2; PPAR, Peroxisome proliferator-activated receptor; PCAF, p300/CBP-associated factor; RBP-J, Recombination Signal Binding Protein for Immunoglobulin kappa J region; Retnlα, Resistance-like α; SCARB1, Scavenger Receptor Class B Member 1; SPP1, secreted phosphoprotein 1; STAT, Signal transducer and activator of transcription; TAM, Tumor-associated macrophages; TBK1, TANK-binding kinase 1; TGF-β, Transforming growth factor-β; TLR, Toll-like receptors; TNF-α, Tumor necrosis factor-α; VEGF, Vascular endothelial growth factor; zhx2, Zinc-fingers and homeoboxes 2.

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Disclosure

The authors declare no competing interests.

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