# Activating transcription factors: Orchestrators of macrophage biology in pathological settings (Review)

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**Abstract.** Macrophages, an essential component of the innate immune system, exhibit remarkable plasticity and functional heterogeneity governed by the intricate transcriptional regulatory networks. Activating transcription factors (ATFs) have recently been recognized to modulate multiple signaling pathways, including the MAPK cascades, endoplasmic reticulum stress response and NF-κB signaling, thereby regulating macrophage biological processes such as inflammatory response, glucose-lipid metabolism, cellular stress adaptation, autophagy-apoptosis balance and senescence. By integrating stress signals and metabolic cues, ATF family members construct a sophisticated regulatory network implicated in the pathogenesis of infectious and inflammatory diseases, metabolic disorders, malignancies and neurodegenerative diseases. Therefore, targeted modulations of ATFs or their associated pathways are considered to be capable of precisely regulating macrophage anti-inflammatory function, metabolic activity and tissue repair capacity in disease settings. Recent technological advances, such as specific targeted delivery systems and gene-editing strategies, offer promising avenues for the spatiotemporal ATF-targeting interventions in macrophages, which is critical for improving therapeutic efficacy and safety. The present review systematically summarized recent advances in the understanding of ATF-mediated regulation of macrophage development, survival, migration, phagocytosis, activation/cytokine secretion, along with polarization and metabolic reprogramming. It also elucidated the pathophysiological implications of these regulatory mechanisms and critically evaluated the clinical feasibility of ATF-targeted therapeutic interventions.

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*Abbreviations:* ATFs, activating transcription factors; ATM, adipose tissue macrophage; AD, Alzheimer's disease; bZIP, basic leucine zipper; CRE, cAMP response element; C/EBP, CCAAT/enhancer-binding protein; ER, endoplasmic reticulum; gMac, gut-resident macrophages; HSCs, hematopoietic stem cells; HO-1, heme oxygenase-1; IRI, ischemia-reperfusion injury; LPS, lipopolysaccharide; LXR, liver X receptor; M-CSF, macrophage colony-stimulating factor; NO, nitric oxide; oxLDL, oxidized low-density lipoprotein; PGN, peptidoglycan; PAS, placental accreta spectrum; PROTAC, proteolysis-targeting chimera; RTECs, renal tubular epithelial cells; SMCs, smooth muscle cells; SIRS, systemic inflammatory response syndrome; TLR, Toll-like receptor; UPR, unfolded protein response

*Key words:* activating transcription factors, macrophage, metabolic disorders, chronic inflammation, cytokines, targeted therapy

## Contents



## 1. Introduction

As a sentinel of the immune system, macrophages are characterized by the robust phagocytic capacity to play a pivotal

role in pathogen clearance and tissue homeostasis (1). Based on their developmental origins, macrophages are categorized into hematopoietic monocyte-derived macrophages and embryonic-derived tissue-resident macrophages (2). Hematopoietic-derived macrophages originate from $CD34^+$ hematopoietic stem cells (HSCs) in the bone marrow, progressing through granulocyte-monocyte progenitors and monocytic stages, before entering systemic circulation (3). Under specific microenvironmental signals, such as inflammatory mediators and chemokines, circulating monocytes are recruited to tissues and subsequently differentiate into functionally specialized macrophages. By contrast, embryonic-derived tissue-resident macrophages originate from yolk sac precursors during organogenesis (4-9), including microglia in the central nervous system (10), Kupffer cells in the liver (11) and Langerhans cells in the skin (12). These developmentally distinct populations differ fundamentally from their hematopoietic counterparts in both ontogeny and functional specialization (2,6,8,13-16).

Macrophages exhibit extraordinary plasticity and functional heterogeneity, dynamically adapting their polarization states in response to microenvironmental stimuli (17). The classical paradigm classifies macrophages into pro-inflammatory M1 and anti-inflammatory/reparative M2 phenotypes (18-20). M1 macrophages, activated by interferon (IFN)-γ and lipopolysaccharide (LPS) (21,22), amplify inflammatory responses and resist pathogenic infection through the production of IL-1β, IL-6, IL-12, TNF-α and chemokines (23-26). While being critical for pathogen containment, sustained M1 activation leads to chronic inflammation and tissue destruction. Conversely, M2 macrophages polarized by IL-4/IL-13 secrete immunosuppressive cytokines (such as IL-10 and TGF-β) to alleviate inflammation and promote tissue regeneration through growth factor-mediated extracellular matrix remodeling and angiogenesis (27). However, their immunosuppressive function may facilitate tumor progression by establishing pro-tumorigenic microenvironments. Importantly, the M1/M2 classification is considered an oversimplification of macrophage functional spectrum. Under pathophysiological conditions, macrophages exhibit a continuous spectrum of polarization from M1 to M2 phenotypes, rather than discrete binary states (28-31). Tissue macrophages frequently exhibit hybrid phenotypes with overlapping M1-M2 characteristics, reflecting their capacity to adapt to dynamic microenvironmental changes. To further clarify this conceptual framework, it is essential to distinguish between the processes of macrophage activation and polarization. Macrophage activation refers to the early process by which macrophages sense external stimuli through receptor-mediated signaling pathways, initiating intracellular cascades that endow them with enhanced responsiveness and effector potential. Macrophage activation represents a transition from resting state to functionally poised state. By contrast, macrophage polarization, dictated by specific cytokine milieu and environmental cues, denotes a more specialized process in which activated macrophages differentiate along a continuous spectrum into distinct functional phenotypes (32,33). Therefore, activation represents the initiation of macrophage responsiveness, whereas polarization describes the directional specification that follows.

Through coordinated phagocytosis, antigen presentation, cytokine secretion and crosstalk with immune and non-immune cells, macrophages play a central role in regulating inflammatory responses, host defense and tissue homeostasis. Dysregulated macrophage function underlies numerous pathologies. For instance, macrophages take up lipids from the blood to transform into foam cells, thereby promoting plaque formation and atherosclerotic progression (34-39). Obesity-associated metabolic disorders are featured by the macrophage-mediated chronic low-grade inflammation, which triggers the development of insulin resistance and type 2 diabetes (40-47). In certain cases, M2 macrophages may promote tumor cell growth, metastasis, invasion and drug resistance by secreting immunosuppressive factors and enhancing tumor angiogenesis through cytokines (such as VEGF) (48-52). As highly plastic innate immune cells derived from myeloid precursors, the differentiation of macrophage is orchestrated by the macrophage colony-stimulating factor (M-CSF, also known as CSF1) (53-55). This process is fundamentally governed by the transcription factor purine-rich U-box binding protein 1, which drives macrophage lineage differentiation through transcriptional activation of the M-CSF receptor CSF1R (56-58). NF-κB and STAT1 pathways drive classical M1 polarization (59,60), while alternative M2 polarization is mediated by JAK1/3-STAT6 signaling and nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) (61-65). Collectively, these observations underscore that macrophage differentiation, activation and polarization are governed by intricate transcriptional networks. Among these, the activating transcription factors (ATFs) have emerged as pivotal integrators of immune and metabolic cues, orchestrating macrophage responses under diverse physiological and pathological conditions. The current review sought to summarize the recent findings on how activated ATFs regulate macrophage development, survival, migration, phagocytosis, activation, cytokine secretion, polarization and their involvement in immune, metabolic, cardiovascular, neurological disorders and cancer, with a particular emphasis on their therapeutic potential (Fig. 1).

## 2. ATFs are pivotal signaling hubs

The ATF family, comprising seven members (ATF1-7), was initially characterized in 1987, as a group of transcriptional factors involved in the regulation of gene expression across diverse biological contexts (66). All ATF members share a highly conserved basic leucine zipper (bZIP) domain comprising a basic region responsible for DNA binding and a leucine zipper structure that mediates dimerization (67,68). ATFs are activated by upstream signals and exert transcriptional activities by forming either homodimers or heterodimers with other bZIP transcription factors such as AP-1 or C/EBP family members. ATF1 commonly forms heterodimers with cAMP response element-binding protein (CREB) or cAMP response element modulator (CREM) family members to bind to DNA and regulate target gene transcription (69-72). ATF2 dimerizes with c-Jun to form a canonical AP-1 complex (73,74), while its structurally related homolog ATF7 could interact with ATF2 to generate functional heterodimers (75-77). ATF3 cooperates with bZIP proteins including c-Jun, JunB, or C/EBP to

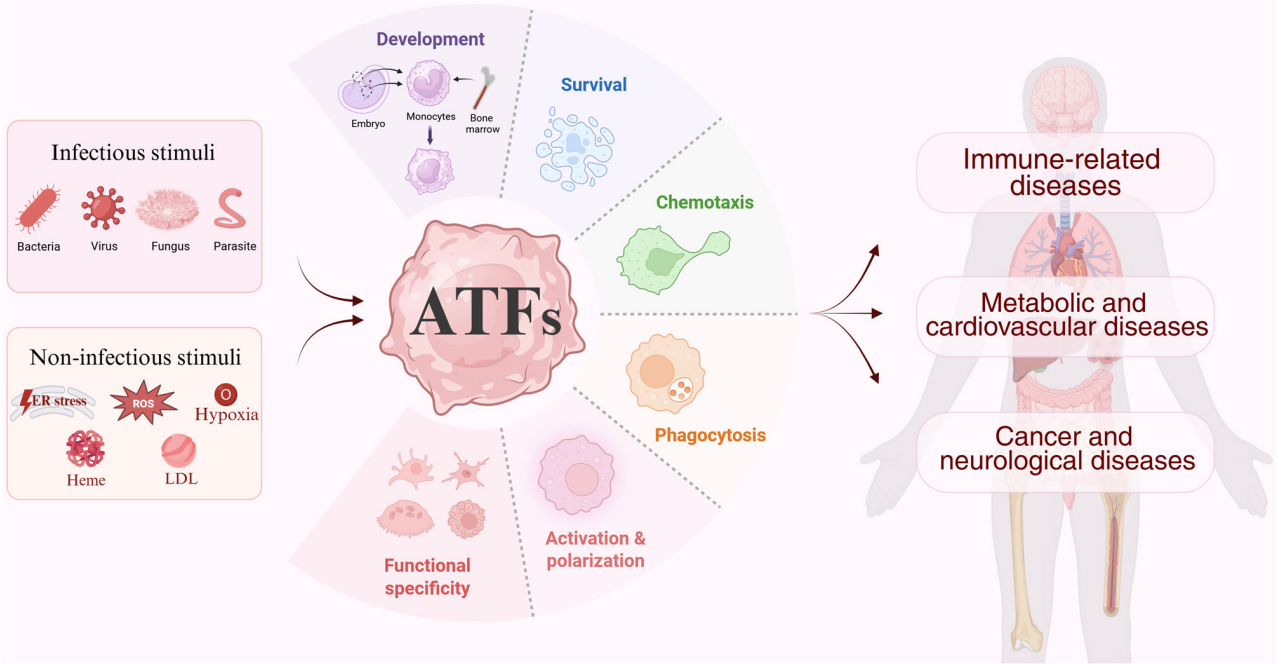


Figure 1. ATFs as orchestrators of macrophage biology in pathological settings. ATFs can be triggered by infectious stimuli (such as bacteria, viruses, fungi and parasites) or non-infectious challenges (including ER stress, oxidative stress, hypoxia, heme and LDL). Upon activation, ATFs orchestrate macrophage development, survival, migration, phagocytosis, activation, cytokine production and polarization, thereby linking macrophage responses to immune, metabolic, cardiovascular, neurological diseases and cancer with important therapeutic implications. ATFs, activating transcription factors; ER, endoplasmic reticulum; LDL, low-density lipoprotein.

regulate responsive genes (78,79). ATF4 integrates stress and metabolic signals through heterodimerization with members of the C/EBP family or with nuclear factor erythroid 2-related factor 2 (NRF2) to coordinate adaptive transcriptional programs (80-82). Similarly, ATF5 forms functional heterodimers with C/EBPγ (83). ATF6, however, undergoes a unique activation process. At steady state, ATF6 resides in the endoplasmic reticulum (ER) membrane as a monomer, dimer, or oligomer. Upon the challenge of ER stress, ATF6 translocates into the Golgi apparatus, where it is cleaved by S1P/S2P proteases to release its N-terminal fragment (50 kDa) that enters the nucleus. The nuclear p50 ATF6 forms homodimers or heterodimers with its homolog ATF6β (84) and both of them can associate with nuclear transcription factor Y (NF-Y) to form transcriptional complexes (85). In addition, ATF6 has been shown to heterodimerize with XBP1s, thereby broadening its target gene repertoire (86).

The specific dimerization partners of each ATF member largely determine its DNA-binding specificity and transcriptional outcomes. Accordingly, ATF1 and ATF5 predominantly recognize canonical CRE sequences (70,87), whereas the binding preferences of ATF2, ATF3 and ATF7 are largely determined by their dimerization partners (88-91). Once they form homodimers or heterodimers with the CREB family members, they preferentially bind to the CRE consensus sequence. By contrast, heterodimerization with AP-1 family proteins, such as c-Jun, redirects their binding toward AP-1 sites (74,78,92-94). Moreover, ATF3 and ATF4 can recognize C/EBP-ATF response elements (CARE), to composite motifs containing both CCAAT-box and CRE characteristics (95). Under stress conditions, the C/EBPγ-ATF4 heterodimer constitutes the predominant form to bind to the CARE motifs (81), whereas ATF4 can also form a complex with C/EBPβ to regulate differentiation-related gene expression (80). When ATF4 forms heterodimers with NRF2, the complex can recognize both antioxidant response elements (AREs) and ATF/CRE motifs, thereby synergistically activating antioxidant and detoxifying gene transcription (96). Likewise, ATF6α/ATF6β heterodimers, as well as ATF6α homodimers, associate with NF-Y to recognize ER stress response elements, which comprise a 5'-CCAAT-3' core, a GC-rich spacer and a terminal 5'-CCACG-3' motif (97-101). Within this composite motif, the CCAAT box serves as the NF-Y binding site, whereas ATF6 recognizes and binds to the terminal CCACG half-site to initiate transcription of target genes (85,102). Notably, CRE sequences vary among genes, often exhibiting one or two base substitutions and even half-CRE sites (such as TGACG or CGTCA) can be recognized by ATFs, suggesting that while the core CRE motif is evolutionarily conserved, a certain degree of sequence flexibility is tolerated (103).

The activation and function of the ATF family are governed by multi-layered regulatory mechanisms operating across epigenetic, transcriptional and post-translational dimensions. Epigenetic control involves DNA methylation (such as ATF3 silencing through promoter hypermethylation) (104), dynamic histone modifications and mRNA m6A modifications. Transcriptionally, factors, such as SP1/MYC and p53, modulate ATF activity *via* promoter binding (104). Post-translationally, numerous ATFs are activated through phosphorylation (PKA or MAPK) (105), while others undergo regulated proteolysis (such as cleavage of ATF6) or ubiquitin-mediated turnover (106), all of which influence their stability, localization and activity. Specifically, under stress conditions, JNK/p38 MAPK phosphorylates ATF2 to enhance its transcriptional activity (107),

while ER stress activates ATF4 and ATF6 *via* the unfolded protein response (UPR) to restore proteostasis (106,108). Moreover, ATFs could also be regulated by signals such as IL-6, LPS or growth factors (109-111), thereby integrating immune and metabolic cues into coordinated transcriptional responses. Once activated, ATFs execute their transcriptional regulatory functions primarily through the recruitment of a wide range of transcriptional cofactors and chromatin-modifying complexes that sculpt gene expression programs. Among them, ATF family members recruit diverse histone-modifying enzymes and chromatin-remodeling complexes to mediate epigenetic regulation. For example, phosphorylated ATF1 recruits the histone acetyltransferase CBP/p300 to enhance local H3/H4 acetylation and chromatin accessibility (112,113). Similarly, following LPS stimulation, ATF2 recruits histone deacetylase 1 (HDAC1) to remove repressive acetylation marks, thereby facilitating target gene transcription (114). However, activated ATF3 recruits HDAC1 onto promoters of proinflammatory genes to erase permissive acetylation marks and repress gene transcription, implying the complex nature of ATF-related epigenetic regulation (115,116). Upon the insult of ER stress, ATF6α recruits the mediator complex together with multiple histone acetyltransferase assemblies, including SAGA and ATAC, to promoters such as HSPA5, to increase local histone acetylation level (117,118). ATF7 persistently recruits the histone H3K9 methyltransferase G9a in resting macrophages to deposit the repressive H3K9me2 mark, which silences the transcription of innate immune genes and maintain the quiescent state (119). Moreover, ATF6α recruits arginine methyltransferases such as PRMT1, to methylate histone arginine residues at target genes, by which it remodels chromatin architecture and regulates stress-responsive gene expression (120). Moreover, some ATF members can directly or indirectly recruit ATP-dependent chromatin-remodeling complexes, altering nucleosome positioning and conformation to reorganize the chromatin landscape (112).

ATFs play a crucial role in various biological processes. For instance, ATF family members regulate antioxidant gene expression during ER stress and oxidative stress responses, serving as a critical regulator in stress adaptation (121-123). In glucose and lipid metabolism, ATF proteins modulate the expression of multiple metabolic genes to maintain glucose and lipid homeostasis (111,124). Furthermore, ATF members participate in immune responses by regulating inflammatory cascades and immune evasion (125-128), the balance between autophagy and apoptosis (129) and the process of cell senescence (126). Notably, perturbation of ATF signaling networks demonstrates strong association with tumor (130), metabolic disorders (121), neurodegenerative diseases (121) and immune-related diseases (124,131). Such dynamic nature warrants ATFs as a crucial hub for developing targeted therapeutic strategies.

## 3. ATFs in macrophage development and survival

ATFs exert multidimensional regulatory effect on macrophage development and functional homeostasis through regulating the proliferation, differentiation and metabolic pathways. During macrophage development, ATF4 serves as a master regulator to govern monocytes differentiation to gut-resident macrophages (gMac). In septic models, ATF4 depletion in $Ly6C^+$ monocyte precursors (P1 cells) disrupts gMac (P4 cell) differentiation coupled with aberrant proliferation and increased apoptosis of P1 cells, leading to exacerbated intestinal barrier dysfunction (132). ATF2 orchestrates monocyte differentiation through modulating the expression of phosphatase PPM1A by binding to its promoter (133). In atherosclerosis, the accumulation of macrophages is markedly reduced in plaques of mice overexpressing ATF3. ATF3 overexpression suppresses the PI3K/AKT signaling pathway, by which it downregulates the expression of matrix metalloproteinases (MMP-2/MMP-9) and reduces macrophage-mediated extracellular matrix degradation, coupled with plaque stabilization (134). Notably, the anti-proliferative effect of ATF3 persists throughout the macrophage lifespan by suppressing cell cycle genes (*Mem2* and *Cdk2*) and inhibiting the Clec4e-Csf1 axis (135,136).

Regarding macrophage senescence and cell death, ATF4 is identified as the core responder to hypoxic stress and it rapidly accumulates in macrophage nuclei within 1-h of hypoxic challenge to activate adaptive gene networks to sustain cell viability (137). ATF3 exhibits anti-senescence properties in *Pseudomonas aeruginosa* infection models. Macrophages deficient in *ATF3* exhibit elevated ROS levels and accelerated senescence, while ectopic ATF3 overexpression partially reverses these phenotypes (138). Additionally, in LPS-stimulated microglia, ATF2 exacerbates inflammatory pyroptosis by upregulating IL-1β, NLRP3 and key pyroptotic effector molecules such as GSDMDC1 and Caspase-1 (139).

## 4. ATFs in macrophage chemotaxis and phagocytosis

ATF family members essentially regulate macrophage chemotaxis and phagocytosis by modulating chemokine expression and cytoskeletal remodeling. LPS induces phosphorylation of ATF2 in alveolar epithelial cells, which subsequently upregulates macrophage inflammatory protein-2 (MIP-2) to promote macrophage recruitment (140). Additionally, LPS enhances macrophage chemotactic capacity *via* ATF3, which binds to the CRE/AP-1 motif within the promoter of Regulated upon Activation, Normal T-cell Expressed and Secreted (*RANTES*) (141). Notably, ATF3 also regulates macrophage migration through other mechanisms. Transwell assays suggest that ATF3-overexpressing macrophages exhibit markedly enhanced migration under MCP-1 treatment (142,143). Mechanistically, ATF3 suppresses gelsolin expression and F-actin de-polymerization to promote cytoskeleton reorganization (144). On the other hand, ATF3 activates the Wnt/β-catenin signaling pathway to upregulate extracellular matrix protein tenascin C, which subsequently reinforces macrophage migration (142). These findings elucidate the molecular basis by which ATF family members, ATF3 in particular, integrate chemokine networks and cytoskeletal dynamics to precisely orchestrate macrophage migration.

Phagocytosis is another biological process relevant to cytoskeleton remodeling (145). ATF3 directly binds to the AP-1 motif within the promoter of *Slc11a1*, a gene that is critical for phagolysosomal iron transport and function, to downregulate SLC11A1 expression (146). Such inhibitory effect markedly impairs macrophage phagocytotic capacity, as evidenced by the enhanced uptake of fluorescent microspheres in

ATF3-knockout models (138). In cyclophosphamide-induced immunosuppressive model, ATF3 further reduces macrophage phagocytosis of tumor cells by repressing antimicrobial peptide genes, such as *Camp*, *Lcn2* and *Ltf* (147). Notably, ATF3 also influences lipid metabolism by upregulating the expression of scavenger receptor class B type 1 to promote macrophage reversing cholesterol transport (RCT), thereby preventing foam cell formation (148). By contrast, ATF2 enhances oxidized low-density lipoprotein (oxLDL) uptake and lipid accumulation by directly binding to the *Cd36* promoter (-100 nt site) to drive its transcription (149). During *Mycobacterium tuberculosis* (Mtb) infection, overexpression of ATF2 enhances macrophage phagocytic capacity for pathogen clearance (133). Additionally, ATF1 coordinates the separation of iron and lipid metabolism during the response to heme-derived products, by regulating the expression of heme oxygenase-1 (HO-1), liver X receptor (LXR) and Spi-C transcription factor (SPIC). ATF1 deficiency disrupts phagolysosomal homeostasis, which impairs post-phagocytic processing (150). Further studies revealed that ATF1 and ATF2 exert synergistic effects on pathogen recognition. The two factors are involved in the O-acetylation of the cell wall component glycolipid in Mtb and *Mycobacterium abscessus* (*M. abscessus*), altering the molecular patterns on the pathogen surface and affecting macrophage phagocytotic efficiency (151). In fungal infection models, upon macrophage uptake of *Mucor circinelloides*, ATF1 and ATF2 are activated to regulate a series of gene networks, including Chi1 and Aqp1, thus enhancing fungal survival within the phagosome. This process supports fungal persistence and germination during phagocytosis (152).

## 5. ATFs in macrophage activation and cytokine secretion

Macrophage activation and cytokine secretion are orchestrated by ATFs that integrate microbial, metabolic and stress-derived signals, into coordinated transcriptional programs. ATF1, ATF5 and ATF6 predominantly act as pro-inflammatory drivers, while ATF3 and ATF7 serve as negative feedback regulators. Intriguingly, ATF2 and ATF4 exhibit context-dependent dual functions, capable of both amplifying and restraining inflammatory responses depending on the microenvironmental cues. The upstream stimuli, signaling connections and differential impacts on cytokine expression are summarized in Fig. 2 and Table I, which together outline the overall regulatory network and highlight the synergistic and antagonistic interactions among ATF members. The dynamic equilibrium among these ATF subsets ultimately determines the intensity and persistence of macrophage activation and cytokine production.

*Pro-inflammatory ATFs (ATF1, ATF5 and ATF6): Amplifiers of microbial and stress-induced cytokine programs*. ATF family members regulate macrophage pro-inflammatory activation through multiple pathways. ATF1, activated *via* sensing bacterial peptidoglycan (PGN), drives pro-inflammatory cytokine transcription either in its phosphorylated form or as a dimer with CREB (153). ATF5 directly amplifies inflammatory responses by upregulating TNF-α, IL-1β and IL-6 expression (154). ATF6, a key regulatory factor in ER stress (155), is essential for initiating the UPR triggered by pattern recognition receptors such as nucleotide-binding oligomerization domain-containing protein 2 (NOD2) (106). Upon the challenge of oxLDL, ATF6 dissociates from the ER membrane, moves into the Golgi apparatus, where it is cleaved into its active form (p50-ATF6), which subsequently translocates into the nucleus to regulate target genes, such as GRP78 and XBP-1 (156). Activated ATF6 stimulates the expression of genes involved in cholesterol biosynthesis, but represses the genes associated with cholesterol efflux (*Abca1, Abcg1, Lxrα*), to drive cholesterol accumulation (157). ATF6 directly binds to the *Tnf-α* promoter to enhance its transcriptional activity, thereby activating the NF-κB and TNF signaling pathways and driving macrophages to secrete pro-inflammatory cytokines, such as TNFα, IL-1β and IL-6 (156). In liver Kupffer cells, ATF6 also mediates the pro-inflammatory enhancement of TLR4 response and cytokine production (158). Markedly, ubiquitination at K152 residue of ATF6 is essential for its antimicrobial function. Mutations at this site (ATF6-K152A) exhibit defective bacterial uptake, coupled with reduced ROS generation, diminished LC3II/ATG5 expression and impaired intracellular pathogen clearance (159). Together, these findings establish ATF1, ATF5 and ATF6 as central mediators that translate microbial and metabolic stress into potent inflammatory cytokine programs.

*Anti-inflammatory ATFs (ATF3 and ATF7): Epigenetic and transcriptional brakes restraining macrophage activation*. In sharp contrast, ATF3 and ATF7 largely hinder the activation of macrophages. Under physiological condition, ATF7 acts as an epigenetic repressor by recruiting histone H3K9 dimethyltransferase G9a to the promoters of activation-related genes (such as *Cxcl2*, *Ccl3*, *Stat1*, *Myo10*, *Nfkb2* and *Tap1*), thereby maintaining macrophage at the resting state. However, LPS stimulation induces p38-dependent phosphorylation of ATF7, prompting ATF7 dissociation from chromatin, which leads to a significant reduction of H3K9me2 levels at target genes and the unleashing of transcriptional repression. Such epigenetic change persists for weeks, which sustains low H3K9me2 levels and high transcriptional activity to confer long-term immune memory (119). Similarly, ATF3 functions as an essential effector in curbing excessive macrophage activation. First, ATF3 inhibits the phosphorylation of JNK, ERK and p38 MAPK, thereby reducing the production of TNF-α, IL-6, IL-1β and IL-12β induced by LPS, ROS, or *Mycoplasma pneumoniae* infection (125,138,160-162). Second, NRF2 binds to the antioxidant response elements (ARE1) within the *Atf3* promoter to initiate *Atf3* transcription (161). Activated ATF3 then recruits HDAC1 to pro-inflammatory gene promoters (143,163), thereby reducing H3/H4 histone acetylation (138,164) and counteracting Rel/NF-κB transcriptional activity (115,164,165). This epigenetic pathway is further reinforced in Clec4e-mediated response, in which ATF3 inhibits the downstream NF-κB/JNK pathway and reduces TNF-α and CCL2 secretion (136). Moreover, ATF3 also promotes GDF15 expression to foster the adaptation of macrophages to metabolic stress (125). Collectively, by counteracting the effects of ATF1, 2, 4, 5 and 6, ATF3 and ATF7 serve as critical rheostats in maintaining macrophage homeostasis.

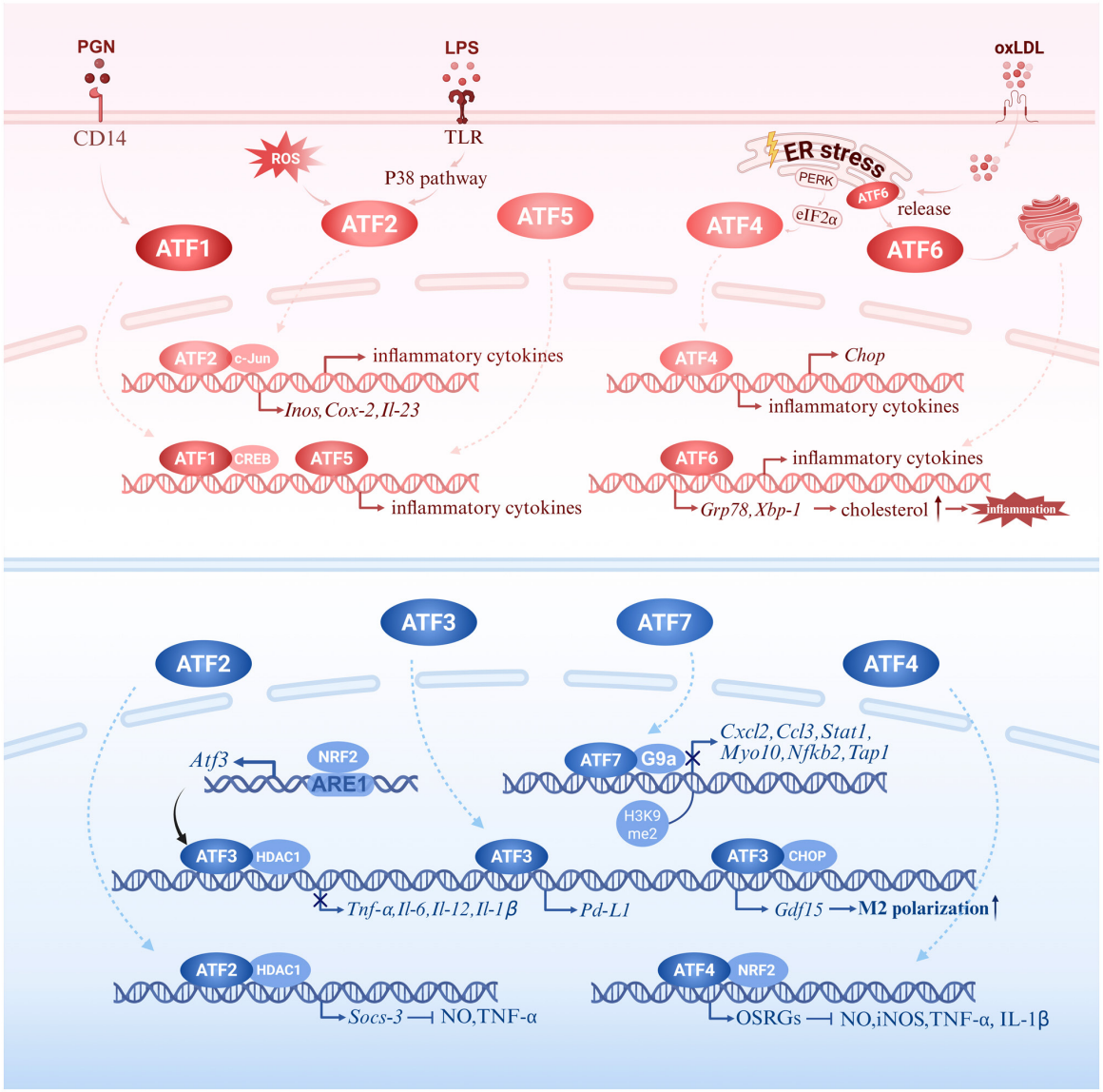


Figure 2. ATF family members in macrophage activation and polarization. Macrophages sense bacterial PGN to activate ATF1, which drives pro-inflammatory cytokine expression either in its phosphorylated form or through dimerization with CREB. ATF5 directly amplifies inflammatory responses by upregulating the expression of TNF-α, IL-1β and IL-6. ATF2, activated via the LPS-TLR-p38MAPK pathway or reactive oxygen species (ROS), also promotes pro-inflammatory cytokine expression. The ATF2/c-Jun heterodimer synergistically enhances the production of inflammatory mediators NO and PGE2 by promoting the transcription of a series of pro-inflammatory genes (such as *Inos* and *Cox-2*) and facilitates Il-23 transcription, concurrently induces *Socs-3* transcription to restrain TLR4-mediated inflammation, demonstrating its dual regulatory nature. ATF4 is activated through the PERK-eIF2α pathway and activated ATF4 persistently induces *Chop* expression and the production of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6), establishing a vicious cycle of inflammation and apoptosis. Furthermore, ATF4 can form heterodimers with NRF2 to cooperatively regulate transcription of OSRGs. Activated ATF6 modulates target genes including *Grp78* and *Xbp-1*, driving cholesterol accumulation that subsequently elevates cellular inflammation. NRF2 binds to the ARE1 within the *Atf3* promoter to initiate *Atf3* transcription. Activated ATF3 recruits HDAC1 onto pro-inflammatory genes, by which it suppresses NF-κB activity and reduces pro-inflammatory factor production. Additionally, ATF3 promotes the expression of PD-L1 and GDF15, driving macrophage polarization towards the M2 phenotype. Under physiological conditions, ATF7 maintains macrophage quiescence by recruiting the H3K9 di-methyltransferase G9a to the promoters of activation-associated genes. ATFs, activating transcription factors; PGN, peptidoglycan; CREB, cAMP response element-binding protein; LPS, lipopolysaccharide; TLR, toll-like receptor; NRF2, nuclear factor erythroid 2-related factor 2; OSRGs, oxidative stress response genes; ARE, antioxidant response element; HDAC1, histone deacetylase 1; PD-L1, programmed death-ligand 1; H3K9, histone H3 lysine 9; GDF15, growth differentiation factor 15.

*Dual regulators with context-dependent functions (ATF2 and ATF4): Integrators of inflammatory and metabolic stress signals*. ATF2 and ATF4 display dual regulatory activities that depend on the nature, strength and duration of environmental stimuli. As a key regulator in Toll-like receptor (TLR) signaling, ATF2 undergoes p38 MAPK-dependent phosphorylation at Thr71 (107,166), through which it promotes the expression of pro-inflammatory mediators, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), TNF-α, IL-6 and IL-1β (167-172). This process is further amplified by the formation of AP-1 complex with c-JUN, which enhances the production of nitric oxide (NO) and prostaglandin $E_2$ ($PGE_2$) (173). Notably, ATF2 is highly expressed in M1 macrophages within the white adipose tissue from obese mice, where its phosphorylation is induced by ROS and LPS (139) and sustains the pro-inflammatory phenotype by suppressing the expression of anti-inflammatory ATF3 (174). Furthermore, ATF2 forms heterodimers with

Table I. Distinct regulatory roles of ATF family members in macrophage activation and cytokine secretion.

| ATF member | Function | Upstream and downstream signals/pathways | Effects on macrophage activation and cytokine secretion | (Refs.) |
|---|---|---|---|---|
| ATF1 | Pro-inflammatory | PGN→CD14→ERK1/2/ JNK→ATF1 →ATF1/CREB dimer→TNF-α/IL-1β/ IL-6 | TNF-α, IL-1β, IL-6↑ | (153) |
| ATF2 | Pro-inflammatory | LPS→p38 MAPK→ATF2→ATF2-c-JUN (AP-1 complex) | iNOS, COX-2, TNF-α, IL-6, IL-1β↑ NO and $PGE_2$ production↑ | (107,153,166-172) |
| | | ROS, LPS→p-STAT3→BATF2↓→ATF2-c-JUN→IL-23 | IL-23↑ | (174) |
| | Anti-inflammatory | LPS→ MyD88-TRAF6-ASK1/TAK1-MKK3/6- p38δ signaling pathway→ATF2→ATF2-HDAC1 complex→SOCS-3 | TNF-α, NO↓ | (118) |
| ATF3 | Anti-inflammatory | LPS, ROS, MP→ATF3→JNK, ERK, p38 MAPK↓→TNF-α, IL-6, IL-1β, IL-12β↓ | TNF-α, IL-6, IL-1β, IL-12β↓ | (125,138,160-162) |
| | | NRF2→ATF3→HDAC1→N F-κB/ JNK↓ | TNF-α, CCL2↓ | (115,136,143,161, 163-165) |
| | | MNV infection→CHOP-ATF3→GDF15→NF-κB↓ | TNF-α, IL-6, GM-CSF, COX-2↓ | (125) |
| ATF4 | Pro-inflammatory | ER stress→PERK-/ eIF2α→ATF4→CHOP/ STAT3 →IL-6, IL-8, IL-23, TNF-α, IL-1β↑ | IL-6, IL-8, IL-23, TNF-α, IL-1β↑ | (175,176) |
| | | HFD/LPS/PA→PERK-eIF2α→ATF4→PDIA3→ RhoA-YAP→IL-1β, IL-6, TNF-α, IFN-γ, CCL2, CCL7 | IL-1β, IL-6, TNF-α, IFN-γ↑ CCL2, CCL7↑ | (177) |
| | Anti-inflammatory | Leishmania infection→PERK-eIF2α→ ATF4→ATF4-NRF2 complex→HO-1→NO, iNOS | NO, iNOS↓ TNF-α, IL-1β↓ | (82) |
| ATF5 | Pro-inflammatory | LPS→ASGR1→NF-κB(p65/IKBα) →ATF5→CD68/CD86/F4/80/ TNF-α/IL-1β/IL-6 | CD68/CD86/F4/80↑ TNF-α, IL-1β, IL-6↑ | (154) |
| ATF6 | Pro-inflammatory | NOD2→RNF186→ATF6→ PERK/IRE1α→UPR transcriptional program→MAPK, NF-κB→TNF-α/ IL-1β/IL-6 | TNF-α, IL-1β, IL-6↑ | (106) |
| | | oxLDL/ER stress→PI3K/AKT↓→ ATF6→GRP78/XBP-1 →LXRα-ABCA1/ABCG1↓ | Cholesterol accumulation | (157) |
| | | ER stress→ATF6 p50→TNF-α→NF-κB →IL-6, IL-1β | TNF-α, IL-1β, IL-6↑ | (156) |
| | | ER stress→ATF6→AKT→ NF-κB→TNF-α, IL-6, IL-1α, IL-1β↑IL-10↓ | TNF-α, IL-6, IL-1α, IL-1β↑IL-10↓ Kupffer cell activation | (158,159) |
| ATF7 | Anti-inflammatory | ATF7→recruit G9a to the promoters of activation-related genes | Cxcl2, Ccl3, Stat1, Myo10, Nfkb2, | (119) |

Table I. Continued.

| ATF member | Function | Upstream and downstream signals/pathways | Effects on macrophage activation and cytokine secretion | (Refs.) |
|---|---|---|---|---|
| | | | Tap1↓ maintain macrophage at the resting state | |

ATF, activating transcription factor; PGN, peptidoglycan; ERK1/2, extracellular signal-regulated kinase 1/2; JNK, c-Jun N-terminal kinase; CREB, cAMP response element-binding protein; TNF-α, tumor necrosis factor alpha; IL-1β, interleukin 1 beta; IL-6, interleukin 6; LPS, lipopolysaccharide; p38 MAPK, p38 mitogen-activated protein kinase; c-JUN, Jun proto-oncogene; AP-1, activator protein 1; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; NO, nitric oxide; $PGE_2$, prostaglandin $E_2$; ROS, reactive oxygen species; p-STAT3, phosphorylated signal transducer and activator of transcription 3; BATF2, basic leucine zipper ATF-like transcription factor 2; IL-23, interleukin 23; MyD88, myeloid differentiation primary response protein 88; TRAF6, TNF receptor-associated factor 6; ASK1, apoptosis signal-regulating kinase 1; TAK1, TGF-beta activated kinase 1; MKK3/6, mitogen-activated protein kinase kinase 3/6; HDAC1, histone deacetylase 1; SOCS-3, suppressor of cytokine signaling 3; MP, mycoplasma pneumoniae; IL-12β, interleukin 12 beta; NRF2, nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; CCL2, C-C motif chemokine ligand 2; MNV, murine norovirus; CHOP, C/EBP homologous protein; GDF15, growth differentiation factor 15; GM-CSF, granulocyte-macrophage colony-stimulating factor; ER stress, endoplasmic reticulum stress; PERK, protein kinase R-like endoplasmic reticulum kinase; eIF2α, eukaryotic translation initiation factor 2 alpha; STAT3, signal transducer and activator of transcription 3; IL-8, interleukin 8; HFD, high-fat diet; PA, palmitic acid; PDIA3, protein disulfide-isomerase A3; RhoA, Ras homolog family member A; YAP, Yes-associated protein 1; IFN-γ, interferon gamma; CCL7, C-C motif chemokine ligand 7; HO-1, heme oxygenase 1; ASGR1, asialoglycoprotein receptor 1; IKBα, inhibitor of nuclear factor kappa-B alpha; NOD2, nucleotide-binding oligomerization domain-containing protein 2; RNF186, ring finger protein 186; IRE1α, inositol-requiring enzyme 1 alpha; UPR, unfolded protein response; MAPK, mitogen-activated protein kinase; oxLDL, oxidized low-density lipoprotein; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; GRP78, glucose-regulated protein 78; XBP-1, X-box binding protein 1; LXRα, liver X receptor alpha; ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; IL-1α, interleukin 1 alpha; IL-10, interleukin 10; G9a, euchromatic histone lysine methyltransferase 2; Cxcl2, C-X-C motif chemokine ligand 2; Ccl3, C-C motif chemokine ligand 3; Stat1, signal transducer and activator of transcription 1; Myo10, myosin X; Nfkb2, nuclear factor kappa B subunit 2; Tap1, transporter associated with antigen processing 1.

HDAC1 to induce *Socs-3* transcription to negatively regulate TLR4-mediated inflammation (118), demonstrating its dual regulatory nature. Under metabolic stress, such as cholesterol accumulation, ATF4 is activated *via* the protein kinase R-like ER kinase (PERK)-eukaryotic translation initiation factor 2 alpha (eIF2α) pathway. During transient stress, ATF4 promotes macrophage survival, whereas persistent stress induces the expression of C/EBP homologous protein (CHOP), triggering macrophage apoptosis along with the release of inflammatory mediators (175,176). In obese microenvironments, ATF4 acts as a metabolic stress sensor, transcriptionally upregulating protein disulfide isomerase a3 (PDIA3) to drive TNF-α, IL-6 and chemokine (C-C motif) ligand 2 (CCL2) production, thereby intensifying adipose tissue inflammation (177). The dual regulatory role of ATF4 is further reflected in its ability to influence antioxidant defenses. Knockdown of ATF4 reduces NRF2 activity and HO-1 expression, leading to attenuated antioxidant defenses and increased NO production (82). Overall, ATF2 and ATF4 act as context-dependent signal integrators that fine-tune macrophage activation, coordinating inflammatory, oxidative and metabolic pathways to define the amplitude and persistence of cytokine responses.

## 6. ATFs in macrophage polarization and phenotypic plasticity

ATFs exert multidimensional roles in macrophage polarization via metabolic reprogramming and signal transduction. ATF1 drives macrophage polarization toward the antioxidant 'Mhem' phenotype through coordinated regulation of iron and lipid metabolism. This involves the induction of HO-1, which promotes the degradation of heme into iron and antioxidant metabolites (biliverdin and bilirubin) to help mitigate oxidative stress. Furthermore, ATF1 activates liver X receptor-β (LXR-β) to augment the expression of cholesterol efflux proteins ABCA1 and ApoE, by which it reduces lipid accumulation and prevents foam cell formation (178). Phosphorylated ATF1 further improves macrophage adaptation to intraplaque hemorrhage, thus maintaining the homeostasis under dural iron-lipid stress (178). ATF2 deficiency (THP-ΔATF2) induces abnormal macrophage morphology, whereas ATF2 overexpression (THP-ATF2) triggers a rounded, flattened morphology resembling M1 macrophages, along with elevated expression of MHC class II, IL-1β and interferon-γ-induced protein 10 (133). Mechanistically, ATF2 drives M1 polarization by enhancing glycolytic flux. Metabolomic profiling confirmed that those ATF2-overexpressing macrophages recapitulate the classical M1 metabolic signatures (139).

ATF3 also plays a pivotal role in macrophage polarization. Overexpression of ATF3 suppresses the differentiation of M1 (pro-inflammatory) macrophage, as evidenced by the decreased expression of M1 markers such as TNF-α and CD11c in adipose tissues, thereby attenuating local inflammation (179). In atherosclerotic lesions, ATF3 mediated inhibition of M1 polarization reduces inflammatory responses and lowers

the risk of plaque rupture. In tumor microenvironments, cyclophosphamide (CTX)-induced pro-tumor macrophage traits are reversed in ATF3-knockout mice, shifting macrophages toward anti-tumor phenotypes (147). ATF3 also enhances M2 (anti-inflammatory) macrophage program through indirect pathways. ATF3 suppresses the Nrf2/ARE signaling pathway, leading to the death of renal tubular epithelial cells (RTECs). The resulting apoptotic RTECs release miR-1306-5p-containing exosomes, which in turn inhibit M1 activation while enhance M2 polarization (180). In placental accreta spectrum (PAS) lesions, upregulated ATF3 facilitates M2 macrophage polarization by enhancing the expression of PD-L1, which interacts with PD-1 to strengthen the immunosuppressive microenvironment (181). Conversely, during receptor activator of nuclear factor-κB ligand (RANKL)-induced osteoclastogenesis, ATF3 overexpression promotes osteoclast formation and activity. ATF3 directly binds to the promoters of key transcription factors *c-Fos* and *NFATc1*, to drive macrophage-to-osteoclast differentiation. However, as a pro-inflammatory ATF member, ATF4 could otherwise promote M2 program (122,182). Upon hypoxic insult, ATF4 upregulates the expression of M-CSF in hemangioma stem cells (HemSCs), to facilitate M2 macrophage polarization (183). ATF4 also activates RANKL signaling by promoting NFATc1 expression, synergistically regulating the differentiation of osteoclasts (184,185). Furthermore, ATF4 drives the transition of vascular smooth muscle cells (SMCs) into foam cells, as evidenced by the upregulation of macrophage markers such as *Cd68* and *Lgals3* (186).

## 7. ATFs in macrophage-associated diseases

Under various pathological conditions, macrophages exhibit disease-specific functional plasticity. Emerging evidence indicates that members of the ATF family in macrophages display distinct and highly disease-specific activation patterns rather than a uniform stress response. Overall, ATF1, ATF2, ATF4, ATF5 and ATF6 are persistently upregulated in most inflammatory, metabolic and stress-related diseases, acting primarily as transcriptional activators that drive pro-inflammatory programs or adaptive stress responses. By contrast, ATF3 and ATF7 are predominantly induced as negative feedback regulators to restrain excessive inflammation or mediate innate immune memory. Importantly, the direction and magnitude of these expression changes are strongly context-dependent. For instance, ATF1 is markedly upregulated during sepsis and atherosclerosis but suppressed in tissue hemorrhage (150,153,178). In addition, ATF3 is rapidly induced during the early hyperinflammatory phase of sepsis to attenuate cytokine storm, whereas its sustained overexpression at later stage contributes to immunosuppression (142,161,162,187). Furthermore, ATF4 is downregulated during early acute sepsis, but is elevated under chronic metabolic stress (132,177,182,186). These observations suggest that ATF activation is finely orchestrated by disease-specific microenvironments through the selective engagement of distinct upstream signaling pathways. A detailed summary of ATF expression dynamics in various diseases and their pathophysiological consequences, along with related signaling pathways, is presented in Table II.

*Immune-related diseases*. In infectious and immune-related diseases, macrophages situate at the first line of defense (1,188). During the early inflammatory phase, they rapidly recognize and phagocytose pathogens, release pro-inflammatory cytokines and recruit other immune cells to the infection sites, thereby amplifying host defense (189-191). However, excessive or prolonged activation can lead to systemic inflammatory syndromes, such as sepsis and cause secondary tissue injury (191,192). As inflammation resolves, macrophages adopt a reparative phenotype that clears apoptotic cells and produces anti-inflammatory mediators to promote tissue repair (193). Moreover, macrophages can acquire innate immune memory, known as trained immunity, which enables them to respond more effectively to secondary challenges through enhanced cytokine production and antimicrobial activity (194). By contrast, excessive suppression of macrophage activation impairs pathogen clearance and increases vulnerability to secondary infections, thereby disturbing immune homeostasis (195,196). In chronic inflammatory conditions, persistent low-grade activation or failure to transition into a reparative state drive sustained cytokine production, tissue remodeling and fibrosis, all of which predispose to disease progression (197). During bacterial infection, ATF3 exhibits pathogen-specific regulatory effect. Specifically, ATF3 enhances macrophage clearance of *Staphylococcus aureus* by directly binding to the promoters of antimicrobial peptide genes, such as Reg3β and S100A8/9, to bolster host defense (198). Conversely, during *Pseudomonas aeruginosa* or uropathogenic *E. coli* infection, ATF3 attenuates host resistance by downregulating pro-inflammatory factors (TNF-α and IL-6) and upregulating IL-10 (138). Following *Leishmania* infection, ATF3 expression reaches the highest after 1-h of infection, which establishes an anti-inflammatory environment in favor of parasite survival (163). ATF4 enhances macrophage antioxidant capacity by promoting HO-1 expression to limit NO production, thus creating an environment conducive to *Leishmania amazonensis* survival (82). By contrast, ATF7 contributes to innate immune memory by modulating STAT1/NF-κB-dependent inflammatory networks (such as CXCL9/10), thus enhancing macrophage-mediated responses against bacteria and fungi (119). In antiviral immunity, ATF2 activates the p38 MAPK/ATF2/AP-1 axis to promote the secretion of interferon-stimulated genes and IFN-β, thereby enhancing the resistance to *vesicular stomatitis virus*, *Newcastle disease virus* and *herpes simplex virus* (105). However, ATF3 may compromise *murine norovirus* clearance by suppressing type I interferon expression or impairing Mx1 activity (125). During *Aspergillus fumigatus* infection, ATF4 is upregulated *via* the TLR4/LOX-1/MAPK pathway, which modulates corneal macrophage barrier function and disease severity (199).

In acute inflammatory diseases, ATFs exhibit a dynamic and balanced role. Hyperactivation of ATF1 induces excessive pro-inflammatory cytokine release from macrophages, contributing to systemic inflammatory response syndrome (SIRS) or septic shock (153). ATF3 plays a complex part at different septic stages. In LPS-induced septic models, ATF3 reduces TNF-α, IL-6 and IL-1β levels in plasma, potentially mitigating early-stage hyperinflammation (162,187). Additionally, ATF3 promotes macrophage polarization towards the M2

Table II. Pathophtsiological roles of ATF family members across diverse diseases.

| ATF molecule | Disease | ATF expression | Specific roles in macrophages | Functional outcomes | Upstream pathway | Target gene | (Refs.) |
|---|---|---|---|---|---|---|---|
| ATF1 | SIRS/Sepsis | Up | Promotes pro-inflammatory cytokine secretion | Enhances inflammatory responses | PGN→CD14→ ERK1/2/JNK→ ATF1 | *Tnf, Il1b, Il6, Ccl4, Selp* | (153) |
| | Osteoporosis | Up | Promotes osteoclast differentiation and maturation | Enhances bone resorption and progression of osteoporosis | RANKL→ATF1 | miR-214-5p | (217) |
| | Atherosclerosis | Up | Induces Mhem phenotype, enhance cholesterol efflux and iron chelation, prevent foam cell formation | Stabilizes plaques | Heme→ATF1 | *Hmox1, Nr1h2* | (150,178) |
| | Tissue hemorrhage | Down | Impairs iron and lipid metabolism | Delays hematoma clearance and aggravates oxidative stress | Heme→AMPK →ATF1 | *Hmox1, Nr1h3/ Nr1h2, Apoe, Abca1, Igf1, Socs1, Spic* | (150) |
| ATF2 | Viral infection (VSV, NDV, HSV, etc.) | Up | Enhances type I interferon response | Resists viral infection and improves survival rate | NaCl↑→p38 MAPK→ATF2 | *Ifnb1* | (105) |
| | Acute lung injury | Up | Promotes macrophage recruitment | Exacerbates pulmonary inflammation | LPS→MAPK (ERK/JNK/p38) →ATF2/c-Jun | *Cxcl2* | (140) |
| | Chronic inflammation | Up | Promotes inflammatory cytokine expression | Aggravates chronic inflammation | LPS→TLR4→ p38 MAPK→ ATF-2 | *Nos2, Ptgs2* | (107) |
| | Autoimmune diseases (MS, IBD, RA) | Up | Promotes IL-23 secretion | Induces pathogenic Th17 cell expansion and triggers disease development | TMEV→ TLR3/TLR7→ JNK MAPK→ ATF-2 | *Il23a* | (201) |
| | Obesity/Metabolic syndrome | Up | Enhances M1 polarization, suppress ATF3 expression | Aggravates white adipose tissue inflammation and insulin resistance | LPS/FFA→ TLR4→ JNK/p38/ERK →ATF2 | *Socs3, Atf3* | (173) |
| | Atherosclerosis | Up | Accelerates lipid uptake and foam cell formation | Exacerbates plaque progression | Thrombin→ PAR1→Gα12 →Pyk2→Gab1 →PKCθ→ ATF2 | *Cd36* | (149) |
| | Neurodegenerative diseases (AD, PD, MS) | Up | Promotes microglial pyroptosis | Amplifies neuroinflammation and aggravates brain injury | LPS→ PKM2(pY105) ↑→ATF2 | *Nos2, Il1b, Il18, Nlrp3, Gsdmd* | (139) |

Table II. Continued.

| ATF molecule | Disease | ATF expression | Specific roles in macrophages | Functional outcomes | Upstream pathway | Target gene | (Refs.) |
|---|---|---|---|---|---|---|---|
| ATF3 | Staphylococcus aureus infection | Up | Enhances antimicrobial peptide and proinflammatory cytokines expression | Promotes inflammatory responses and tissue damage in fungal keratitis | TLR4/LOX-1→ ERK1/2-JNK-MAPK→ATF4 | *Il1b*, *Il6* | (198) |
| | MNV infection | Up | Inhibits inflammatory responses and induce immune tolerance | Impairs viral clearance | MNV→GCN2 →eIF2α→ ATF4/CHOP/ ATF3; MNV→ JNK2→ATF2→ ATF3 | *Gdf15*, *Tnf*, *Il6*, *Il12b*, *Chac1*, *Ppp1r15a*, *Trib3*, *Bcl2l11* | (125) |
| | Pseudomonas aeruginosa/ uropathogenic E. coli (UPEC infection) | Up | Suppresses proinflammatory cytokine expression | Prevents infection-induced immunosenescence | PAO1→ROS→ ATF3 | *Tnf*, *Il6*, *Il10* | (138) |
| | Leishmania infection | Up | Creates anti-inflammatory environment favoring parasite survival | Facilitates persistent pathogen infection | ROS→NRF2→ ATF3 | *Tnf*, *Il12b*, *Hdac1* | (163) |
| | Sepsis | Up | Inhibits proinflammatory cytokine secretion | Early stage: mitigates hyperinflammation and promote tissue repair SAIS stage: leads to secondary infection | ROS→GSH→ NRF2→ATF3; LPS→AMPK→ ATF3 | *Mcp1*, *Nos2*, *Cd16*, *Cd163*, *Mrc1*, *Arg1*, *Pparg*, *Tnc*, *Il6*, *Tnf*, *Il12b*, *Il1b* | (142,161, 162,187) |
| | Acute kidney injury | Up | Suppresses inflammatory cytokine expression and NF-κB activity | Alleviates I/R-induced renal injury | TLR4-NF-κB→ ATF3 | *Il6*, *Il12b*, *Tnf*, *Ifng*, *Cebpd*, *Sele* , *Cdkn1a* | (165) |
| | Renal ischemia-reperfusion injury | Up | Promotes RTEC apoptosis and exosome release, induce M2 polarization | Accelerates renal fibrosis | IRI→ROS/ oxidative stress→ATF3 | *Nrf2*, *Hmox1*, *Ptgs2*, *Tfrc*, miR-1306-5p | (180) |
| | Alcoholic liver disease | Up | Inhibits TNF-α expression, induce LPS/TLR4 tolerance, impair macrophage migration | Induces a systemic immune hyporesponsive state and impair host defense against infection | Ethanol→ HDAC1→ATF3 | *Tnf*, *Il6*, *Il1b*, *Ccl2* | (143) |
| | Rheumatoid arthritis | Up | Enhances osteoclast differentiation | Enhances bone resorption and decrease bone mass | RANKL→$Ca^{2+}$ →CaMKII/ CaMKIV-CREB→ATF3 | *Nfatc1*, *Acp5*, *Oscar* | (249) |

Table II. Continued.

| ATF molecule | Disease | ATF expression | Specific roles in macrophages | Functional outcomes | Upstream pathway | Target gene | (Refs.) |
|---|---|---|---|---|---|---|---|
| | Endotoxemia/ nflammation-related metabolic disorders | Up | Suppresses TLR4-induced inflammatory cytokine expression, alleviate macrophage activation and cytokine storm | Reduces obesity-related inflammation and improve insulin resistance | Berberine→ AMPK→ATF3 | *Tnf, Il6, Il1b* | (162) |
| | Atherosclerosis | Up | Suppresses inflammatory cytokine expression | Promotes vascular endothelial repair and re-endothelialization | HDL→ATF3, synergistically enhanced by TLR ligands (CpG, Pam3CSK4) | *Il6*, *Il12b*, *Tnf*, *Ch25h* | (148,208) |
| | | Up | Inhibits inflammatory signaling and cell proliferation | Maintains plaque stability and alleviate inflammation | Necrosis/TDB→ Clec4e→Syk→ ER stress (CHOP, IRE1α)→ATF3 | *Clec4e*, *Tnf*, *Ccl2*, *Csf1* | (136) |
| | | Up | Inhibits macrophage apoptosis and inflammatory mediator release | Stabilizes plaque structure | PI3K→AKT→ ATF3 | *Mmp2*, *Mmp9* | (134) |
| | Breast cancer | Up | Promotes expansion of myeloid progenitors and TAM formation | Serves as an early biomarker for malignancy | Breast tumor-derived factors/ ATP→ NLRP3→IL-1β →ATF3 | Not reported | (213) |
| | Placenta accreta spectrum | Up | Expands CD14+ immunosuppressive macrophages | Promotes trophoblast immune evasion and deep invasion into the uterine myometrium | Fibronectin/ ITGβ1→ MAPK→PI3K/ AKT→ATF3 | *Mmp2, Mmp9, Cd274 and Cd44* | (181) |
| ATF4 | Fungal keratitis | Up | Enhances inflammatory response | Exacerbates corneal barrier destruction | TLR4/LOX-1/ MAPK→ATF4 | *Il6*, *Il23a*, *Ddit3*, *Hspa5*, *Ern1* | (199) |
| | *Leishmania amazonensis* Infection | Up | Alleviates ER stress and oxidative stress | Creates favorable environment for parasite survival and promote infection progression | TLR4→PERK →eIF2α-P→ ATF4 | *Hmox1*, *Nfe2l2*, *Nos2* | (82) |
| | Sepsis | Down | Promotes Ly6C$^{hi}$ monocyte differentiation into intestinal resident macrophages | Promotes bacterial translocation across gut barrier, exacerbate systemic inflammation | TGF-βR→ATF4 | Not reported | (132) |

Table II. Continued.

| ATF molecule | Disease | ATF expression | Specific roles in macrophages | Functional outcomes | Upstream pathway | Target gene | (Refs.) |
|---|---|---|---|---|---|---|---|
| | Colitis | Up | Induces CHOP expression, amplify inflammatory cytokine release | Aggravates intestinal inflammation and epithelial damage | LPS/DSS→BIP →PERK→ eIF2α-P→ATF4 | *Ddit3* | (176) |
| | Osteoporosis | Up | Enhances osteoclast differentiation | Promotes inflammatory bone resorption | RANKL→ RANK→ TRAF6→NF-κB →ATF4 | *Nfatc1, Ctsk, Acp5, Dcstamp, Atp6v0d2* | (184) |
| | Type 2 diabetes mellitus/ metabolic syndrome | Up | Promotes proinflammatory cytokine expression | Enhances ATM-mediated chronic adipose tissue inflammation, impair metabolic homeostasis | PKR/PERK→ eIF2α-P→ATF4 | *Il6, Pdia3* | (177,182) |
| | Atherosclerosis | Up | Induces SMC transdifferentiation, foam cell formation | Promotes necrotic core expansion | PERK→ eIF2α-P→ATF4 | *Klf4, Cd68, Lgals3, Abca1, Ddit3, Grp78, Grp94, Edem, Fn1, Spp1, Timp1, Lcn2, Bgn, Dcn, Prg4* | (186) |
| | Infantile hemangioma | Up | Promotes M2 polarization | Aggravates lesion formation | Hypoxia→ HIF-1α→ATF4 | *Csf1* | (183) |
| | AD | Up | Drives microglial shift toward neurotoxic phenotype, secrete toxic lipids (such as long-chain phospholipids, sphingolipids, sterol esters, glycerides) | Promotes neuronal synaptic loss, Tau protein propagation and cognitive decline | PERK→ eIF2α-P→ATF4 | *Asns, Aldh18a1, Mthfd2, Fasn, Sqstm1, Wfs1, Canx, Vldlr, Slc6a6* | (216) |
| ATF5 | Sepsis-associated liver injury | Up | Enhances infiltration of inflammatory macrophages (CD45+CD11b +Ly6C+) and pro-inflammatory cytokine release | Induces hepatocyte necrosis and tissue damage | ASGR1→ NF-κB→ATF5 | Not reported | (154) |
| ATF6 | ALI/IBD/RA | Up | Activates ERS pathway and amplify inflammation | Promotes disease progression | p90RSK→ MAGI1→ATF6 | *Xbp1, Eif2ak3, Tnfsf15* | (106,155, 157,200) |

Table II. Continued.

| ATF molecule | Disease | ATF expression | Specific roles in macrophages | Functional outcomes | Upstream pathway | Target gene | (Refs.) |
|---|---|---|---|---|---|---|---|
| | Acute liver injury | Up | Promotes macrophage activation and pro-fibrotic cytokine release | Activates HSCs and drive fibrosis | ER stress→ ATF6 | *Il1a*, *Il1b*, *Il6*, *Tnf* | (159) |
| | Hepatic ischemia-reperfusion injury | Up | Enhances pro-inflammatory response and cytokine secretion | Exacerbates hepatic inflammatory injury | Ischemia→ER stress→ATF6 | *Chop*, *Grp78*, *Xbp1*, *Tnf*, *Il6*, *Il10* | (158) |
| | Corticotomy-assisted orthodontic tooth movement | Up | Promotes osteoclast activation | Drives proinflammatory bone remodeling, accelerating tooth movement and bone resorption | Corticotomy→ ER stress→BiP →ATF6 | *Tnf* | (156) |
| | Atherosclerosis | Up | Promotes cholesterol accumulation and foam cell formation | Promotes plaque formation | oxLDL→ER stress→ATF6 | *Grp78*, *Xbp1*, *Abca1*, *Abcg1*, *Lxrα* | (157) |
| | Autoimmune encephalomyelitis | Up | Promotes inflammation | Triggers demyelination | ER stress→ ATF6α | *Hspa5*, *Hsp90b1*, *Nos2*, *Ccl2*, *Ccl8* | (202) |
| ATF7 | Bacterial/fungal infections | Up | Enhances innate immune memory | Boosts antimicrobial response | LPS→TLR4→ p38 MAPK→ ATF7 | *Ccl3*, *Cxcl2*, *Stat1*, *Nfkb2*, *Tap1*, *Myo10*, *Cxcl9*, *Cxcl10*, *Nos2* | (119) |

ATF, activating transcription factor; SIRS, systemic inflammatory response syndrome; PGN, peptidoglycan; ERK1/2, extracellular signal-regulated kinase 1/2; JNK, c-Jun N-terminal kinase; RANKL, receptor activator of NF-κB ligand; AMPK, AMP-activated protein kinase; VSV, vesicular stomatitis virus; NDV, Newcastle disease virus; HSV, herpes simplex virus; MAPK, mitogen-activated protein kinase; LPS, lipopolysaccharide; ERK, extracellular signal-regulated kinase; TLR4, toll-like receptor 4; MS, multiple sclerosis; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; TMEV, Theiler's murine encephalomyelitis virus; TLR, toll-like receptor; FFA, free fatty acid; PAR1, protease-activated receptor 1; PKCθ, protein kinase C theta; AD, Alzheimer's disease; PD, Parkinson's disease; PKM2, pyruvate kinase M2; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; GCN2, general control nonderepressible 2; CHOP, C/EBP homologous protein; MNV, murine norovirus; UPEC, uropathogenic Escherichia coli; PAO1, Pseudomonas aeruginosa strain PAO1; ROS, reactive oxygen species; NRF2, nuclear factor erythroid 2-related factor 2; SAIS, sepsis-associated immunosuppressive state; GSH, glutathione; AKI, acute kidney injury; NF-κB, nuclear factor kappa-B; IRI, ischemia-reperfusion injury; RTEC, renal tubular epithelial cell; TNF, tumor necrosis factor; HDAC1, histone deacetylase 1; CREB, cAMP response element-binding protein; HDL, high-density lipoprotein; TLR, toll-like receptor; TDB, trehalose-6,6-dibehenate; ER, endoplasmic reticulum; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; TAM, tumor-associated macrophage; NLRP3, NOD-like receptor family pyrin domain containing 3; PAS, placenta accreta spectrum; PERK, protein kinase R-like endoplasmic reticulum kinase; TGF-βR, transforming growth factor-β receptor; DSS, dextran sulfate sodium; BIP, binding immunoglobulin protein; TRAF6, TNF receptor-associated factor 6; ATM, adipose tissue macrophage; PKR, protein kinase R; SMC, smooth muscle cell; HIF-1α, hypoxia-inducible factor-1 alpha; ASGR1, asialoglycoprotein receptor 1; ALI, acute lung injury; ERS, endoplasmic reticulum stress; MAGI1, membrane-associated guanylate kinase inverted 1.

phenotype, enhances the expression of anti-inflammatory factors such as Arg-1 and PPARγ, but suppresses M1 markers (such as iNOS and TNF-α), thereby alleviating inflammatory responses and facilitating tissue repair (142). However, during

the sepsis-associated immunosuppression phase, persistent ATF3 overexpression impairs immune responses and increases susceptibility to secondary infections (161). During septic progression, reduced ATF4 expression in P1 cells leads to diminished gMacs, which promotes bacterial translocation across the epithelial barrier and worsens systemic inflammation (132). ATF5 contributes to sepsis-associated liver injury by promoting the accumulation of inflammatory macrophages ($CD45^+$ $CD11b^+$ $Ly6C^+$) through an NF-κB-dependent pathway, leading to the release of inflammatory cytokines (154). Excessive activation of ATF1 is also associated with the progression of SIRS and sepsis by enhancing macrophage cytokine secretion (153).

In chronic inflammatory diseases, ATF family members influence macrophage polarization and amplify inflammatory signaling, contributing to disease pathology. In LPS-induced acute lung injury, ATF2 exacerbates pulmonary inflammation by upregulating MIP-2 to further recruit macrophages (140), while ATF6 intensifies macrophage activation and cytokine release *via* ER stress signaling (200). ATF2 activation also amplifies TLR signaling cascades and exacerbating chronic inflammation (107,170). Moreover, upon LPS stimulation, ATF2 promotes IL-23 secretion in macrophages, which then induces pathogenic Th17 cell expansion in autoimmune disorders, such as multiple sclerosis, inflammatory bowel disease and rheumatoid arthritis (201). In organ-specific inflammatory injuries, ATF3 exhibits bidirectional regulatory properties. ATF3 attenuates renal ischemia-reperfusion injury (IRI) by inhibiting TLR4/NF-κB pathway (165). However, IRI-induced ATF3 overexpression in RTECs exacerbates ferroptosis and promotes the release of exosomes carrying miR-1306-5p. These exosomes, upon uptake by macrophages, drive M2 polarization and accelerate interstitial fibrosis (180). In alcohol-induced immunosuppression, ATF3 upregulation leads to enhanced Kupffer cell tolerance to LPS and reduced TNF-α production, impairing pathogen clearance and exacerbating alcoholic liver disease (143). In dextran sulfate sodium (DSS)-induced colitis, activation of the ATF4-CHOP pathway drives excessive release of inflammatory cytokines, intensifying intestinal inflammation and epithelial damage (176). It was also noted that ATF6 deficiency impairs macrophage antibacterial responses, worsening intestinal inflammation (106). During hepatic ischemia-reperfusion injury, ATF6 aggravates tissue damage by enhancing NF-κB activation and suppressing the anti-inflammatory Akt-GSK3β signaling pathway in Kupffer cells (158). However, during early acute liver injury, ATF6 activation *via* ER stress promotes IL-1α production, activating HSCs and driving liver fibrosis (159). ATF6 deficiency in microglia attenuates inflammation in autoimmune encephalomyelitis by promoting NF-κB p65 degradation (202).

*Metabolic and cardiovascular diseases*. In metabolic disorders, adipose tissue macrophages produce pro-inflammatory cytokines including TNF-α, IL-6 and IL-1β to impair insulin signaling and disrupt adipocyte homeostasis, thereby contributing to insulin resistance and metabolic syndrome (203-207). ATF4 exacerbates chronic inflammation in adipose tissue, driving the progression of metabolic syndrome and type 2 diabetes mellitus (177,182). By contrast, ATF3 mitigates obesity-associated inflammation by suppressing TLR4-mediated macrophage activation. Therefore, mice deficient in *ATF3* exhibit aggravated obesity-related inflammation and insulin resistance, underscoring its protective role in maintaining metabolic homeostasis (162). Conversely, ATF2 activation intensifies macrophage M1 program within adipose tissue by perpetuating an 'inflammation-hypoxia-ROS' vicious cycle, worsening insulin resistance and metabolic syndrome (173). Additionally, ATF2 aggravates inflammation and metabolic disturbances in white adipose tissue by suppressing ATF3 expression, further enhancing M1 program (139).

In atherosclerosis, macrophages take up OxLDL to form foam cells and orchestrate inflammatory and reparative responses within vascular lesions, thereby playing a pivotal role in plaque formation and progression (28,34,36). ATFs influence disease progression by regulating macrophage lipid metabolism and plaque stability. ATF3 exerts an atheroprotective effect through multiple mechanisms. ATF3 suppresses cholesterol 25-hydroxylase to reduce oxidized cholesterol accumulation and promotes macrophage RCT, thereby limiting foam cell formation (148,208). Furthermore, ATF3 stabilizes plaque structure by inhibiting macrophage apoptosis and the release of inflammatory mediators, lowering the risk of myocardial infarction and stroke (134). ATF3 deficiency impairs ABCA1-mediated cholesterol efflux, aggravating oxLDL-induced lipid deposition (136). Moreover, ATF1 induces Mhem macrophage polarization and activates the HO-1/LXR-β pathway to enhance cholesterol efflux and iron chelation, thereby delaying plaque progression and rupture (150,178). By contrast, ATF6 activation positively correlates with the severity of atherosclerotic lesion and accelerates plaque development by facilitating cholesterol accumulation (157). ATF4 drives necrotic core expansion and plaque destabilization *via* switching an SMC phenotype ('transdifferentiated SMCs' which express both macrophage and fibroblast markers) and inducing CHOP-dependent cell apoptosis (186). As a downstream effector of PKCθ signaling, ATF2 upregulates CD36 to accelerate foam cell formation and plaque progression. PKCθ-deficient mice exhibit blunted ATF2 activation, along with reduced CD36 levels and markedly smaller plaque areas (149). Moreover, ATF1 deficiency impairs the segregation of iron and lipid within macrophages, resulting in their colocalization, which disrupts iron metabolic homeostasis, delays hematoma clearance following tissue hemorrhage and exacerbates oxidative stress-related damage (150). Collectively, ATFs spatiotemporally modulate macrophage inflammatory state, thus influencing the pathological progression of metabolic and cardiovascular diseases.

*Cancer and neurological diseases*. Macrophages are major immune infiltrates that regulate angiogenesis, immune suppression, antigen presentation and metastatic dissemination in the tumor microenvironment (1,209). In bone lesions, macrophages further contribute to osteoclast differentiation and tumor-induced bone destruction (210-212). ATF4 regulates tumor-associated macrophage polarization and promotes the differentiation of monocyte-macrophage precursors into osteoclasts to enhance bone resorption. In parallel, ATF4 exacerbates inflammation through the NF-κB signaling axis, further accelerating cancer-associated bone destruction (184).

Unlike ATF4, ATF3 exhibits functional heterogeneity in tumor immunomodulation. Tumor-derived IL-1β upregulates ATF3 in bone marrow hematopoietic stem cells, driving myeloid precursor expansion and increasing peripheral $CD11b^+$ myeloid cells, including TAMs, tumor-associated macrophages. In a breast cancer model, ATF3 deficiency inhibits monocyte-macrophage differentiation, while its overexpression serves as an early biomarker distinguishing malignant lesions (213). Furthermore, ATF3 activates immune checkpoint pathways to amplify $CD14^+$ immunosuppressive macrophages in PAS lesions, exacerbating pathological progression (181).

In neurological diseases, macrophages and microglia not only phagocytose neuronal debris but also release neuroregulatory substances and inflammatory mediators, thereby modulating neuronal survival and degeneration (214,215). ATF2 promotes neuroinflammatory cascades in multiple sclerosis, Alzheimer's disease (AD) and Parkinson's disease by promoting pyroptosis in macrophages and microglia (139). Additionally, ATF4 is the core transcription factor for AD microglial cells to integrate stress response, by inducing them to enter the neurotoxic state and mediating neurodegeneration through lipid secretion (216). Furthermore, ATF4 synergizes with HIF-1α under hypoxic conditions in infantile hemangioma (IH) proliferative phases, driving M2 macrophage infiltration to fuel lesion expansion (183).

## 8. Targeting ATFs in macrophages could be a potential therapeutic strategy

Targeting ATFs in macrophages offers a promising therapeutic strategy, as these key transcription factors orchestrate diverse macrophage functional states, thereby enabling precise modulation of disease processes (Table III). Currently, therapeutic strategies targeting ATFs can be broadly divided into three categories: Direct intervention, which employs small-molecule agonists or inhibitors and gene-editing approaches to directly modulate ATF expression or activity; indirect modulation, which targets upstream signaling pathways or downstream effector molecules to influence ATF-dependent regulatory networks; and emerging innovative techniques, including proteolysis-targeting chimera (PROTAC)-mediated protein degradation, peptide or peptidomimetic modulators and molecular glue technologies, which offer more efficient and specific manipulation of ATF functions.

*Direct intervention*. Blocking the function of ATFs through small inhibitors, short interference (si)RNA, or gene-editing technologies offers a strategic approach to precisely control disease states driven by macrophages. Targeted inhibition of ATF1 reduces osteoclastogenesis by suppressing the miR-214-5p/ITGA7 axis, suggesting a novel direction for osteoporosis treatment (217). The traditional herbal medicine, HangAmDan-B (HAD-B), reduces LPS-induced NO and $PGE_2$ production in macrophages by blocking ATF2 phosphorylation, consequently limiting tumor-promoting activity of TAMs in gastric and colorectal cancers (166). Ginsenoside Rc markedly reduces LPS-induced TNF-α release by suppressing the p38/ATF2 pathway, presenting a candidate strategy for rheumatoid arthritis and other inflammatory diseases (168). Moreover, the traditional compound formula Qingfei Paidu Decoction and its active component wogonoside, inhibit ATF2 phosphorylation and enhance its ubiquitin-mediated degradation, curbing macrophage-mediated inflammation and showing potential as adjunct therapies for coronavirus pneumonia and colitis (169). Moreover, extracts from *Vaccinium oldhamii* stems reduce ATF2 nuclear accumulation, which blocks MAPK signaling pathway activation and limits macrophage-driven osteoclast differentiation to mitigate bone resorption (218). Exosomes derived from adipose-derived stem cells (ADSCs) or mesenchymal stem cells attenuate ATF2 expression, resulting in reduced NF-κB activation, decreased ROS generation and diminished macrophage infiltration, thereby mitigating vascular dysfunction (219). Similarly, perfluorocarbon (PFC) could reduce inflammatory cell infiltration and alleviate acute lung injury by decreasing ATF2 activity in macrophages (140). The dynamic modulation of ATF3 requires consideration of disease progression. During the early hyperinflammatory phase of sepsis, induction of ATF3 expression in macrophages may counteract cytokine storms, while its inhibition during the immunosuppressive phase may help mitigate secondary infection risk (138). ATF4 suppression also requires meticulous evaluation due to its dualistic effect. The application of small-molecule inhibitors or siRNA-mediated knockdown of ATF4 has been shown to attenuate M-CSF secretion and limit M2 macrophage infiltration (183), which in turn impedes the progression of infantile hemangioma while simultaneously counteracts the pro-tumorigenic properties of TAMs (122). Inhibiting ATF4 can also mitigate *Leishmania* infection (82), though excessive inhibition might compromise the antifungal defense. Therefore, therapies targeting ATF4 must balance the anti-inflammatory outcomes with host immune protection (199). Naringenin, a flavanone compound found in grapefruits and other citrus fruits, could reduce ATF6 nuclear translocation and activity, by which it decreases the expression of ER stress markers while enhances the expression of cholesterol efflux genes (ABCA1, ABCG1 and LXRα). This action promotes macrophage cholesterol efflux, reducing atherosclerotic plaque formation (157). Furthermore, siRNA-mediated ATF6 knockdown alleviates macrophage-driven inflammation and fibrosis, highlighting its potential for treating chronic inflammatory disorders (159).

By contrast, activating or overexpressing ATFs through gene-editing technologies (such as adenoviral vectors) and small-molecule agonists offer an approach to enhance anti-inflammatory, anti-infectious and tissue-repairing functions of macrophages. Developing small-molecule drugs or gene therapies to enhance ATF1 activity presents a potential intervention for atherosclerosis by inducing the protective macrophage subset (178). ATF2 activation inhibits viral replication, with its agonists serving as potential therapeutics for chronic viral infections (167). High-salt diets have also been proposed as a strategy to enhance antiviral immunity *via* ATF2-mediated pathways in macrophages (105). Targeted activation or overexpression of ATF3 exhibited a promising therapeutic potential in inflammatory diseases, infections and metabolic disorders. Gene-editing technologies, such as lentiviral and adenoviral deliveries (Ad/ATF3) of ATF3, alleviate excessive inflammation following *Mycoplasma pneumoniae* infection (160), protect renal tubular cells from

Table III. Therapeutic strategies targeting the ATF family members.

| ATF Molecule | Drug/therapeutic Strategy | Intervention Type | Applicable disease | Regulatory effect | Mechanism of action | (Refs.) |
|---|---|---|---|---|---|---|
| ATF1 | Anti-CD14 monoclonal antibody (MY4) | Antibody drug | Sepsis | Inhibition | Inhibits PGN-induced ATF1 activation, reduce excessive inflammatory response | (153) |
| | Ad-ATF1 | Gene therapy | Atherosclerosis | Overexpression | Upregulates HO-1 and LXR-β expression, induce protective macrophage subsets | (178) |
| ATF2 | HangAmDan-B (HAD-B) | Natural compound (Traditional Chinese Medicine Formula) | Gastric cancer, colorectal cancer | Inhibition | Blocks ATF2 phosphorylation, reduce NO and PGE2 production, diminish TAMs' pro-tumor activity | (166) |
| | Ginsenoside Rc | Natural compound | Rheumatoid arthritis | Inhibition | Inhibits p38/ATF2 pathway, reduce TNF-α release | (168) |
| | Qingfei Paidu decoction (QFPDD) | Natural compound (Traditional Chinese Medicine Formula) | COVID-19, Colitis | Inhibition | Suppresses ATF2 phosphorylation and enhances ubiquitin-mediated degradation, inhibit macrophage inflammation | (169) |
| | *Vaccinium oldhamii* Stem extract (VOS) | Natural compound | Chronic inflammatory diseases, Osteoporosis | Inhibition | Inhibits MAPK/ATF2 pathway activation, reduce IL-18, IL-6, TNF-α expression, limits macrophage-driven osteoclast differentiation | (218) |
| | ADSCs/MSCs exosomes | Extracellular vesicles | Vasculitis, atherosclerotic vascular dysfunction | Inhibition | Reduces ATF2 expression, suppresses NF-κB activation and ROS generation, alleviates macrophage infiltration | (219) |
| | Perfluorocarbon (PFC) | Small-molecule inhibitor | Acute lung injury | Inhibition | Inhibits ATF2 activity, reduce inflammatory cell infiltration | (140) |
| | High-salt diet | Dietary intervention | Viral infection | Activation | Enhances ATF2-mediated p38 MAPK/ATF2/AP-1 axis, promote antiviral gene expression | (105) |
| | SB203580 (p38 MAPK inhibitor) | Small-molecule inhibitor | Inflammatory diseases | Inhibition | Inhibits p38 MAPK/ATF2 pathway, attenuates inflammatory response | (166) |
| | SP600125 (JNK inhibitor) | Small-molecule inhibitor | Inflammatory diseases | Inhibition | Blocks JNK/ATF2 pathway, reduces pro-inflammatory cytokine release | (166) |
| | SCH79797 (PAR1 antagonist) | Small-molecule inhibitor | Atherosclerosis | Inhibition | Inhibits PKCθ/ATF2 pathway, improves insulin sensitivity | (149) |

Table III. Continued.

| ATF Molecule | Drug/therapeutic Strategy | Intervention Type | Applicable disease | Regulatory effect | Mechanism of action | (Refs.) |
|---|---|---|---|---|---|---|
| | BFNM, Javamide-II | Novel compounds | Inflammatory diseases | Inhibition | Suppresses p38 MAPK/ATF2 pathway, reduces inflammatory mediator production | (107,170) |
| ATF3 | Ad-ATF3/Lv-ATF3 | Gene therapy | Mycoplasma pneumonia, renal injury, atherosclerosis | Overexpression | Suppresses hyperinflammation (such as TLR4/NF-κB pathway), reduces pro-inflammatory cytokine release | (134,138, 160,164, 165) |
| | Berberine | Natural compound | Metabolic disorders | Activation | Inhibits LPS-induced pro-inflammatory cytokine production | (162) |
| | Metformin | Small-molecule drug | Type 2 diabetes mellitus (T2DM), obesity | Activation | Suppresses inflammation via AMPK/ATF3 pathway, improves insulin resistance | (187) |
| | NRF2 inhibitor (trigonelline hydrochloride; Trigi) | Small-molecule inhibitor | Parasitic infections | Inhibition | Reduces ATF3 expression by inhibiting NRF2, decreases parasite burden in liver/spleen | (163) |
| | AMPK agonist (AICAR) | Small-molecule agonist | Metabolic disorders | Activation | Activates AMPK to induce ATF3 expression, suppress inflammatory signaling | (162) |
| ATF4 | Gene Delivery (ATF4 Overexpression) | Gene therapy | Sepsis-associated intestinal injury | Overexpression | Restores monocyte differentiation into gut-resident macrophages (gMacs), enhances intestinal barrier function | (132) |
| | PERK inhibitor (ISRIB) | Small-molecule inhibitor | Atherosclerosis | Inhibition | Inhibits PERK-eIF2α-ATF4 pathway, reduces foam cell formation and plaque burden | (186) |
| | Limonin | Natural compound | Colitis | Inhibition | Blocks PERK-ATF4-CHOP axis, decreases inflammatory cytokine release | (176) |
| | FTY720 | Small-molecule drug | Inflammatory bone disease | Inhibition | Upregulates HDAC4 to suppress ATF4 expression, reduce osteoclast activity | (184) |
| ATF5 | NF-κB inhibitor (DHMEQ) | Small-molecule inhibitor | Sepsis-associated liver injury | Inhibition | Inhibits ATF5-mediated pro-inflammatory macrophage differentiation | (154) |
| ATF6 | Naringenin | Natural compound | Atherosclerosis | Inhibition | Inhibits ATF6 nuclear translocation, promote cholesterol efflux | (157) |
| | siRNA-ATF6 | RNA interference | Chronic inflammatory diseases | Knockdown | Silences ATF6 and alleviate macrophage-mediated inflammation and fibrosis | (200) |

ATF, activating transcription factor; PGN, peptidoglycan; Ad, adenoviral vector; HO-1, heme oxygenase-1; LXR-β, liver X receptor beta; HAD-B, HangAmDan-B; NO, nitric oxide; PGE2, prostaglandin E2; TAMs, tumor-associated macrophages; RA, rheumatoid arthritis; p38, p38 mitogen-activated protein kinase; TNF-α, tumour necrosis factor alpha; QFPDD, Qingfei Paidu decoction; COVID-19, coronavirus disease 2019; VOS, Vaccinium oldhamii stem extract; MAPK, mitogen-activated protein kinase; IL-18, interleukin-18; IL-6, interleukin-6; ADSCs, adipose-derived stem cells; MSCs, mesenchymal stem cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ROS, reactive oxygen species; PFC, perfluorocarbon; AP-1, activator protein 1; JNK, c-Jun N-terminal kinase; PAR1, protease-activated receptor 1; PKCθ, protein kinase C theta; T2DM, type 2 diabetes mellitus; AMPK, AMP-activated protein kinase; NRF2, nuclear factor erythroid 2-related factor 2; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; gMacs, gut-resident macrophages; PERK, protein kinase RNA-like endoplasmic reticulum kinase; ISRIB, integrated stress response inhibitor; eIF2α, eukaryotic translation initiation factor 2 alpha; CHOP, C/EBP homologous protein; HDAC4, histone deacetylase 4.

inflammatory damage (165) and reduce the risk of atherosclerosis development (134). ATF3 overexpression further diminishes LPS-induced pro-inflammatory cytokine release, thus improving the outcomes in chronic inflammatory diseases (138,164). In bacterial infections, enhancing ATF3 activity optimizes immune responses and promotes macrophage activation, migration and bactericidal activity, coupled with increased host clearance of *Staphylococcus aureus* (144). Across multiple disease models, berberine and metformin have been demonstrated to enhance ATF3 expression (162,220) and attenuates LPS-induced production of pro-inflammatory cytokines from macrophages (164). In particular, metformin exerts its anti-inflammatory effects by engaging the AMPK/ATF3 signaling axis, through which it potently manages inflammation associated with type 2 diabetes and obesity (187). ATF4 may represent a novel strategy for treating sepsis-related intestinal injury (142). Enhancing ATF4 expression through pharmacological or gene therapies help the restoration of monocyte differentiation into gMacs, thereby strengthening intestinal barrier function, reducing bacterial translocation and mitigating sepsis-induced inflammatory damage (132). In type 2 diabetes, upregulating ATF4 can improve insulin resistance by promoting M2 macrophage polarization (182). Targeting ATF7-mediated epigenetic modifications offers a strategy to refine vaccine adjuvant efficacy, by promoting macrophage activation and memory formation, ultimately advancing the development of more durable and effective vaccine-induced protection (119).

However, the clinical translation of strategies that directly targeting ATFs faces multiple inherent challenges. The first obstacle lies in the intrinsic 'undruggability' of these transcription factors. The interaction surfaces of ATFs with DNA or partner proteins are typically broad and shallow, lacking well-defined pockets that allow high-affinity binding of small molecules, thereby rendering the development of conventional inhibitors or agonists extremely difficult. Second, substantial structural similarity exists among ATF family members, particularly within their DNA-binding domains. As a result, small molecules targeting ATFs may suffer from poor subtype selectivity, potentially leading to off-target toxicity. Therefore, developing compounds capable of precisely distinguishing individual ATF isoforms or specific ATF homo- and heterodimers remains a formidable challenge, which warrants further intensive investigations (221).

*Indirect modulation*. Given the challenges associated with direct targeting, indirect modulation of upstream signaling pathways or downstream effector molecules have emerged as an attractive alternative strategy. Studies show that PERK inhibitors (such as integrated stress response inhibitor (ISRIB)) suppress the PERK-eIF2α-ATF4 pathway, thereby reducing foam cell formation and alleviating atherosclerotic plaque burden (186). The small molecule Limonin blocks the PERK-ATF4-CHOP axis to attenuate inflammatory cytokine release (186). Moreover, drugs, such as FTY720, modulate ATF4 expression *via* histone deacetylase 4 (HDAC4), thus reducing osteoclastic activity in inflammatory bone diseases (184). For ATF2, multiple upstream intervention strategies have been explored, including p38 MAPK inhibitors (SB203580) and JNK inhibitors (SP600125), which reduce inflammation by suppressing ATF2 phosphorylation (166). Additionally, PAR1 antagonists (such as SCH79797) or PKCθ inhibitors decrease ATF2 activation to improve insulin sensitivity (149). Novel compounds, such as bis(5-methyl)2-furylmethane and Javamide-II, reduce inflammatory mediator production by suppressing the p38 MAPK/ATF2 pathway. Particularly, Javamide-II manifests lower systemic toxicity compared with BFNM due to its selective inhibition of specific inflammatory cytokines without affecting TNF-α or IL-1β (107,170). For ATF1, anti-CD14 monoclonal antibodies (MY4) showed potential as an adjunctive therapy for sepsis by inhibiting PGN-induced ATF1 activation (153). Similarly, AMPK agonists (such as AICAR) induce ATF3 expression and offer therapeutic benefits for metabolic disorders (162). Conversely, the NRF2 inhibitor, trigonelline hydrochloride, markedly reduces parasitic loads in the liver and spleen by diminishing ATF3 expression (163). Additionally, NF-κB inhibitors [such as dehydroxy-methylepoxy-quinomicin (DHMEQ)] alleviate sepsis-associated liver damage by inhibiting ATF5-mediated pro-inflammatory macrophage differentiation (154).

Nevertheless, indirect modulation strategies also present substantial limitations. The fundamental drawback of such approaches lies in their lack of specificity. Upstream kinases or signaling pathways targeted by these interventions are often ubiquitously expressed across multiple cell types, leading to severe off-target effects and systemic toxicity. Second, the high redundancy of intracellular signaling networks frequently triggers compensatory activation of alternative pathways, thereby diminishing therapeutic efficacy or even resulting in treatment failure. Moreover, the regulatory effects of pathway-level interventions tend to attenuate along the signaling cascade and are highly dependent on the disease microenvironment, rendering the ultimate modulation of specific ATFs indirect and unpredictable. Finally, this relatively 'coarse-grained' mode of regulation is insufficient to precisely govern the bidirectional functions of ATF members or their heterodimeric interactions, limiting its ability to achieve fine-tuned control over their specific physiological and pathological activities.

*Emerging innovative techniques*. To overcome the aforementioned obstacles, researchers have explored intervention strategies such as PROTACs and molecular glues, aiming to target traditionally 'undruggable' molecules through novel mechanisms of action. The advent of PROTAC technology has provided a new avenue for addressing such targets (222-225). A PROTAC molecule contains two functional domains, one binds to the target protein and the other recruits an E3 ubiquitin ligase, thereby tagging the target for selective proteasomal degradation (226,227). Although no highly potent small-molecule ligands have yet been reported for ATF proteins, researchers are creatively adapting the PROTAC concept for transcription factor degradation. One proposed generalizable strategy involves using DNA fragments recognized by transcription factors as targeting elements, which are linked to E3 ligase ligands to induce ubiquitination and subsequent degradation of transcription factor-DNA complexes (228). For example, the antioxidant response factor NRF2, a bZIP transcription factor that heterodimerizes with small Maf proteins to bind to the AREs, can be targeted by a chimeric molecule termed 'ARE-PROTAC', which successfully induced simultaneous

degradation of the NRF2-MafG complex and synergistically suppressed Nrf2 signaling (229). This design suggests that DNA-binding factors, such as ATF/CREB, DNA mimetics or DNA-derived small molecules, could serve as decoy binding modules to achieve targeted degradation *via* the PROTAC mechanism. Unlike conventional inhibitors that merely block protein activity, this approach eliminates the target protein itself, offering more complete and durable inhibition while potentially alleviating feedback activation caused by persistent protein accumulation. Nevertheless, applying this technology to ATF targeting remains challenging. It requires the discovery of small, high-affinity ligands specific for ATF proteins and the relatively large molecular weight of PROTACs limits their intracellular delivery, especially into macrophages. To address this issue, recent studies have explored macrophage-targeted nanocarrier systems utilizing surface receptors such as citrate or scavenger receptors, enabling PROTAC accumulation and selective degradation at the inflammatory or tumor sites (230,231).

Building on this concept, molecular glues have emerged as another promising and simplified strategy for targeted protein degradation. Molecular glues are typically single small molecules that 'glue' the target protein and an E3 ubiquitin ligase, thereby promoting their interaction and inducing target degradation (232). Unlike PROTACs, molecular glues do not require a linker and can directly induce contact between transcription factors and E3 ligases, offering a simpler architecture and easier optimization. The classic example is lenalidomide, which remodels the substrate-binding surface of the CRBN E3 ligase, enabling selective recognition and degradation of the transcription factors IKZF1 and IKZF3 (233). This mechanism holds particular interest for targeting ATF family members. First, molecular glues generally have much smaller molecular weights than PROTACs, conferring superior membrane permeability and drug-like properties, thereby facilitating macrophage penetration. Second, their activity does not depend on identifying traditional ligand-binding pockets, which is advantageous for transcription factors lacking well-defined active sites. Nevertheless, challenges remain, including the difficulty of identifying suitable adaptor molecules and the dependency on specific E3 ligases, which may restrict the target spectrum.

In addition, peptide mimetics and interfering peptides offer new avenues for disrupting transcription factor activity. Researchers have developed a dominant-negative form of ATF5 (dn-ATF5) by deleting its N-terminal activation domain while retaining the bZIP dimerization and DNA-binding regions and further conjugated it to an HIV-TAT sequence to generate a cell-permeable synthetic peptide (CP-dn-ATF5) (234,235). This peptide can get into the nucleus and compete with endogenous ATF5 for partner proteins or DNA-binding sites, thereby blocking its transcriptional activity. The advantages of peptide-based therapies lie in their high specificity and flexible design. With advances in peptide drug modification techniques, such as cyclization, D-amino acid substitution and nanocarrier encapsulation, peptide-based ATF inhibitors are expected to become an important complement to small-molecule strategies.

Of note, enhancing the spatiotemporal specificity of ATF-targeting interventions is critical for improving therapeutic efficacy and safety. Advanced delivery systems are under development to achieve tissue- or cell-specific targeting, ensuring that drugs could be selectively delivered into macrophages in affected tissues (236). Encouragingly, advances in nanocarrier and bioengineering technologies now enable the precise delivery of therapeutic agents to macrophages, allowing for selective modulation of ATF-associated pathways without affecting other cell types. For instance, in atherosclerosis models, macrophage-targeted nanoparticles have been utilized to deliver drugs directly to macrophages within the plaques (237). These nanoparticles substantially improved the pharmacokinetic profiles of the encapsulated drugs, enhancing their accumulation at the lesion site and promoting the therapeutic efficacy. Similarly, in viral pneumonia models, lipid nanoparticles conjugated with macrophage-specific antibodies (such as anti-F4/80) have been used to deliver siRNA to lung macrophages, effectively silenced upstream inflammatory molecules such as TAK1 (238). These findings underscore the feasibility of macrophage-targeted delivery for therapeutic interventions and highlight the substantial potential of integrating delivery technologies into ATF-targeted therapies. Therefore, innovative targeted technologies coupled with advanced delivery systems, might overcome the barrier of ATFs-targeted therapies and accelerate their clinical translation.

## 9. Conclusions and perspectives

By integrating mechanistic insights and disease-specific evidence, this review delineated how ATFs orchestrate macrophage development, survival, migration, phagocytosis, activation, cytokine secretion and polarization and how these regulatory axes converge to shape macrophage-driven pathology in infectious, inflammatory, metabolic, oncologic and neurodegenerative settings. Through transcriptional control of macrophage-expressed genes across diverse tissues and organs, ATFs are not only implicated in the initiation and progression of multiple disorders but also emerged as nodal regulators integrating pathophysiological signals with immune and metabolic reprogramming (Fig. 3). Of note, ATFs exhibit complex context-dependent versatility in macrophage-mediated immune responses. Mechanistically, the effector outcomes of ATFs largely hinge on the variety of stimuli and upstream signaling pathways in macrophages. For instance, TLR2 activation by Gram-positive bacteria induces moderate inflammation, during which ATF3 promotes antimicrobial gene expression, whereas LPS-TLR4 signaling from Gram-negative bacteria elicits strong NF-κB and IRF3 activation that rapidly induces ATF3 as a negative feedback regulator to suppress excessive cytokine production (115,144,161,239-242). In addition, the intensity and duration of stimulation further shape ATF activity. During early sepsis, ATF3 alleviates hyperinflammation and promotes tissue recovery, whereas its sustained overexpression contributes to late-phase immunosuppression and secondary infections (142,161,162,187). Transient stress activates ATF4 *via* the PERK-eIF2α pathway, upregulating adaptive and survival-related genes to enhance macrophage resilience; however, prolonged stress leads to persistent ATF4-CHOP signaling, promoting apoptosis and pro-inflammatory

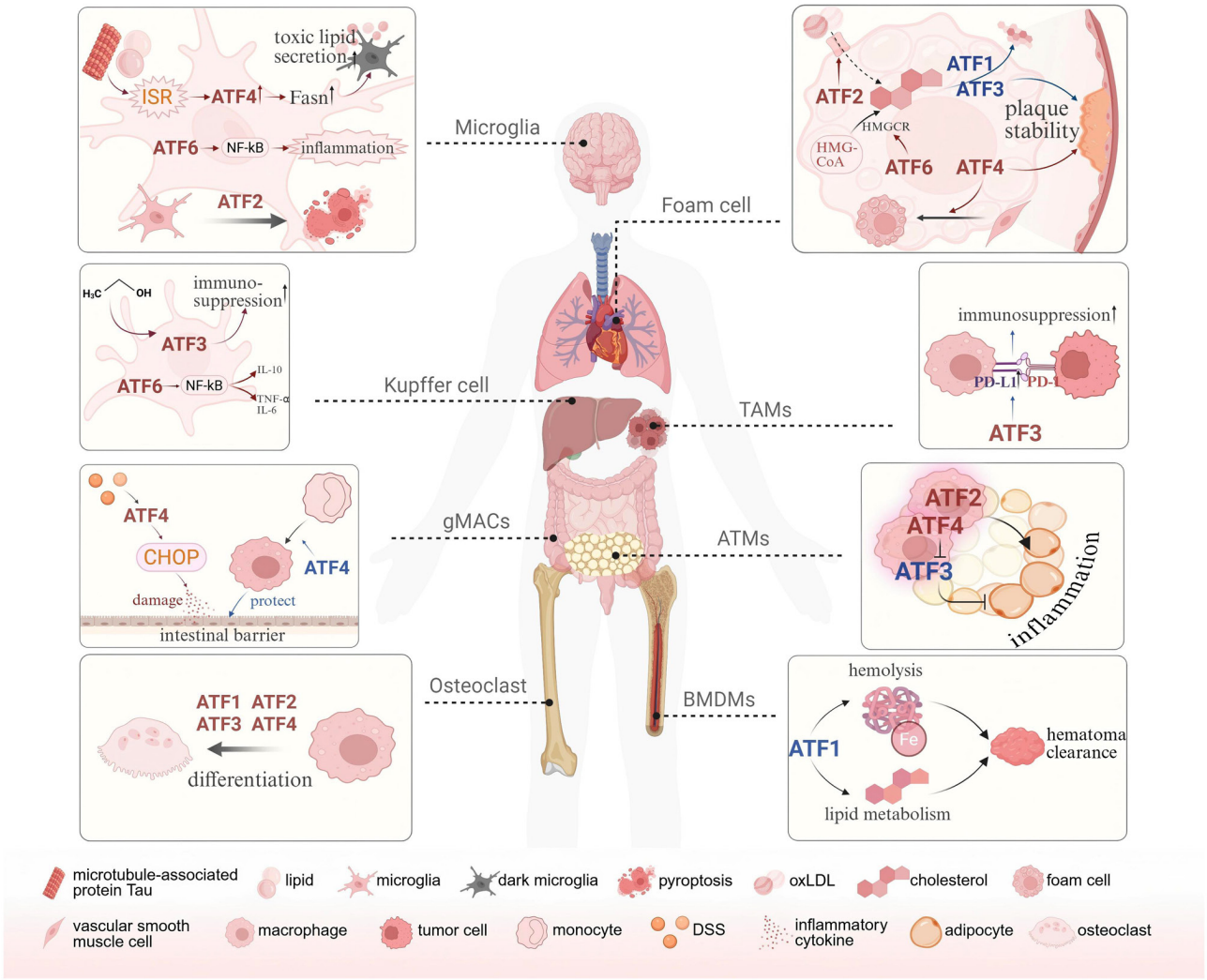


Figure 3. ATF family members regulate the function of tissue-adapted macrophages. ATF4 serves as the core transcription factor for AD-associated microglia to integrate stress responses and mediate neurodegeneration. ATF6 exacerbates inflammation by promoting the activation NF-κB pathway. ATF2 accelerates inflammatory pyroptosis following LPS stimulation. In foam cells, ATF2 upregulates CD36 to accelerate foam cell formation and atherosclerotic plaque progression. ATF6 promotes cholesterol synthesis through 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) activation. ATF4 drives the phenotypic transition of VSMCs into foam cells and reduces plaque stability via CHOP-mediated apoptosis. Conversely, ATF1 and ATF3 enhance macrophage cholesterol efflux, thereby inhibiting foam cell formation and promoting plaque stabilization. In Kupffer cells, ATF3 upregulation exacerbates alcohol-induced immunosuppression, while ATF6 bolsters pro-inflammatory TLR4 signaling and cytokine production. In TAMs, upregulated ATF3 facilitates M2 polarization by enhancing PD-L1 expression, which interacts with PD-1 to reinforce the immunosuppressive tumor microenvironment. Under physiological conditions, ATF4 promotes differentiation of $Ly6C^+$ gMacs, thereby maintaining intestinal barrier integrity. In DSS-induced colitis, activation of the ATF4-CHOP pathway drives excessive pro-inflammatory cytokine release, exacerbating intestinal inflammation and epithelial damage. In ATMs, ATF2 and ATF4 exacerbate adipose inflammation, while ATF4 also suppresses ATF3 functionality. Notably, ATF3 itself exerts anti-inflammatory effect on adipose tissue. ATF1, ATF2, ATF3 and ATF4 collectively promote osteoclast differentiation through distinct molecular pathways. In BMDMs, ATF1 regulates heme and lipid metabolism, with its upregulation enhances the efficiency of hematoma clearance. ISR, integrated stress response; ATF, activating transcription factor; AD, Alzheimer's disease; LPS, lipopolysaccharide; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; VSMCs, vascular smooth muscle cells; CHOP, C/EBP homologous protein; TLR, Toll-like receptor; TAMs, tumor-associated macrophages; Fasn, fatty acid synthase; HMG CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; gMACs, gut macrophages; DSS, dextran sulfate sodium; ATMs, adipose tissue macrophages; BMDMs, bone marrow-derived macrophages; oxLDL, oxidized low-density lipoprotein.

mediator release (175,176). Similarly, ATF6 activation under acute ER stress (such as triggered by pattern-recognition receptors) induces chaperone and autophagy programs that facilitate pathogen clearance (106,155,159). By contrast, during chronic metabolic stress, such as obesity or hyperlipidemia, sustained ATF6 activation increases cholesterol biosynthesis, suppresses cholesterol efflux, promotes foam cell formation and amplifies inflammatory responses (156,157). In addition, as bZIP transcription factors, ATF family members exert highly context-dependent effects determined by their interacting partners and chromatin accessibility. Microenvironmental factors, such as oxidative stress, metabolic stress and ER stress, not only regulate ATF activation levels but also influence their combination with c-Jun, CHOP, C/EBP, or HDAC1, thereby switching their transcriptional output between activation and repression. Upon inflammatory stimulation, ATF2 forms an AP-1 complex with c-Jun to transcribe *Inos* and *Cox-2* expression, promoting NO and

$PGE_2$ production (156,168-173), while during inflammatory resolution stage, ATF2 recruits HDAC1 to transcribe *Socs3* and suppresses excessive TLR4 signaling (162). ATF3 similarly shifts its binding preference. Under mild stimulation, ATF3 partners with c-Jun or CHOP to activate antimicrobial and metabolic genes, but under strong LPS-TLR4 signaling, ATF3 recruits HDAC1 to repress NF-κB target genes (115,138,143,163-165). The functional direction of ATF4 also depends on its binding partners. ATF4-NRF2 heterodimers drive adaptive metabolism and cell survival (82), while heterodimers formed with CHOP mediate inflammation and cell apoptosis (175,176). Likewise, ATF6 enhances cytoprotective UPR genes such as *Grp78* and *Xbp1* during acute stress, but under chronic lipotoxicity, it preferentially targets inflammatory and lipid metabolic genes to amplify macrophage inflammation (156). Moreover, changes in chromatin accessibility under infection or metabolic stress might reshape cis-element exposure, determining the preferential binding sites of ATFs and their downstream transcriptional outcomes. Collectively, these mechanisms highlight ATFs as crucial 'rheostats' that balance inflammatory signaling, metabolic adaptation and stress responses in macrophages. However, this functional duality also underscores the caution in therapeutic targeting: suppressing ATFs in pathogenic conditions must not compromise their protective roles and activating them to resolve inflammation should avoid inducing immunosuppression. A deeper understanding of the context-dependent mechanisms of ATF signaling is be essentially required.

It is noteworthy that alternative splicing may represent another critical but insufficiently investigated layer of ATF modulation. Except for ATF4, most ATF family members possess alternatively spliced isoforms, although their roles in macrophages remain largely unknown. Distinct ATF1 isoforms differ in DNA-binding affinity and subnuclear localization (243), whereas multiple ATF2 variants, including the human isoforms ATF2-sm and ATF2 (SV5) as well as the murine variant Atf2(Δ8,9) (244-246), exhibit reduced transcriptional activity and may alter gene expression by modifying nuclear-cytoplasmic trafficking or by interfering with canonical ATF2/AP-1 dimerization. Moreover, a truncated ATF3 isoform (ΔZip) lacking the leucine-zipper domain antagonizes the transcriptional repressive function mediated by full-length ATF3 (247), while cytoplasmic ATF7-4 acts as a molecular 'decoy' to sequester upstream kinases responsible for ATF7/ATF2 phosphorylation (77). These findings suggest that alternative splicing may establish negative-feedback circuits and intermolecular counter-regulatory balances responsible for the precise modulation of ATF function. Although their implications in macrophages remain to be defined, exploring ATF splicing isoforms represents an important direction for elucidating the dynamic regulatory mechanisms by which ATFs regulate immune homeostasis and stress responses.

The central involvement of ATFs in macrophage-driven pathologies positions them as promising therapeutic targets and biomarkers. On the one hand, ATF expression dynamics serve as diagnostic or prognostic indicators. Rapid ATF3 upregulation (8-fold within 24 h) in silicosis macrophages is an early diagnostic biomarker for silicosis detection (248). Additionally, due to its plaque-stabilizing effects on atherosclerosis, ATF3 expression aids in the identification of high-risk patients and guides personalized treatments (134). On the other hand, single-target interventions may be limited by compensatory mechanisms, necessitating the need for multi-target synergistic approaches for the regulation of macrophage functionality. Lastly, ATF-targeting strategies such as siRNA interference, gene editing, or more advanced protein degradation technologies such as PROTACs, all face common challenges related to *in vivo* delivery efficiency, tissue and cell specificity, immunogenicity and the durability of their effects. Although these interventions have shown remarkable efficacy in preclinical models, extensive studies are still required to validate their safety, efficacy and controllability in complex physiological settings and to further optimize targeted delivery systems to facilitate clinical translation.

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**Availability of data and materials**

Not applicable.

**Authors' contributions**

YCL conceived the study, wrote the manuscript and prepared the figures. JWZ, QJC and XTL curated data and collected references. SJR and FS organized the tables. SWL, CLY and CYW reviewed and revised the manuscript. Data authentication is not applicable. All authors approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

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**Competing interests**

The authors declare that they have no competing interests.

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