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The role of interferon regulatory factors in atherosclerosis

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Cardiovascular diseases (CVDs) remain a leading cause of global morbidity and mortality, largely driven by the progression of atherosclerotic plaques. In atherosclerosis (AS), transcription factors and epigenetic mechanisms play pivotal roles in regulating gene expression. Interferon regulatory factors (IRFs), a family of transcription factors initially identified for their role in coordinating interferon (IFN) responses, are now recognized as critical modulators of innate and adaptive immunity. Emerging evidences highlights their involvement in inflammation, lipid metabolism, cell differentiation, cell proliferation, and programmed cell death during AS pathogenesis. This review synthesizes current knowledge on the roles and regulatory mechanisms of IRFs in AS, offering novel insights and potential therapeutic targets for AS management.

1 Introduction

Cardiovascular diseases (CVDs) remain a leading cause of global morbidity and mortality, which projected to account for 23.6 million annual deaths by 2030 (1). Atherosclerosis (AS) serves as the primary pathological basis for most CVD-related fatalities. It is a chronic inflammatory disorder characterized by endothelial dysfunction, lipid accumulation, and immune cell infiltration. During early atherogenesis, specific plasma lipoproteins, including low-density lipoprotein (LDL), lipoprotein(a), and triglyceride-rich lipoprotein remnants may undergo modifications within the arterial intima. This process initiates an inflammatory cascade that drives monocyte recruitment and their subsequent differentiation into macrophages. Within this microenvironment, macrophages phagocytose modified lipoprotein particles, forming foam cells that progressively accumulate lipids, cholesterol esters, and cellular debris. Concurrently, vascular smooth muscle cells (VSMCs) migrate to the intima, proliferate, and contribute to plaque calcification (2). These events are tightly regulated by transcriptional and epigenetic mechanisms, with transcription factors such as Interferon regulatory factors (IRFs) emerging as key players in AS progression (3).

The IRFs are a family of transcription factors that are highly conserved across species. Originally identified as regulators of IFN signaling, IRFs (IRF1–IRF9) have expanded roles in immune responses, lipid metabolism, and cellular stress. They are extensively involved in diverse biological processes, including cytokine signaling, pathogen response, cell cycle regulation, cell differentiation, apoptosis, and hematopoietic development (4–9). Emerging evidence highlights their role in AS-related processes, including endothelial activation, macrophage polarization, and VSMC dysfunction (3, 10–12). However, the specific roles

and mechanisms haven't yet to be fully elucidated. This review comprehensively examines the contributions of IRF family members to AS pathogenesis, emphasizing their potential as therapeutic targets.

2 Interferon regulatory factors: structure and function

The mammalian IRF family comprises nine members (IRF1-IRF9), each containing a conserved N-terminal DNA-binding domain (DBD) and a C-terminal IRF-association domain (IAD) (Figure 1) (13, 14). While the DBD facilitates recognition of IFN-stimulated response elements (ISREs), the IAD mediates interactions with cofactors, enabling diverse regulatory functions (Table 1) (15, 16). Key signaling pathways, such as Toll-like receptor (TLR) and cytosolic DNA-sensing cascades (e.g., cGAS-STING), converge on IRFs to modulate inflammatory and metabolic responses (17).

IRF activation progresses through five core phases: (1) signal perception, (2) post-translational modifications (PTMs), (3) dimerization, (4) nuclear translocation, and (5) transcriptional regulation. Crucially, PTMs serve as the initiating molecular switch, with phosphorylation, acetylation, ubiquitination, and SUMOylation being principal modifications that dynamically regulate IRF functional states (17). Subsequently, homo- or hetero-dimerization constitutes an essential activation prerequisite, enabling conformational changes required for nuclear trafficking (18). Latent cytoplasmic IRFs undergo stimulus-dependent nuclear translocation upon PRR activation.

These receptors—including TLRs, NLRs, RLRs, and DNA sensors—detect PAMPs/DAMPs to trigger IRF-mediated IFN/pro-inflammatory responses, demonstrating dual roles in AS pathogenesis (protective vs. pathogenic) (19–21). The TLR pathway bifurcates into TRIF- and MyD88-dependent arms, with IRF members exhibiting selective or combinatorial pathway activation to drive context-specific transcriptional programs (17).

2.1 Key IRF family members

IRF1: a pleiotropic transcription factor predominantly localized within the nuclear compartment. Its expression undergoes significant upregulation following viral infection or immune stimulation, mediated through critical signaling pathways IFN (Interferon), NF-κB(Nuclear Factor kappa B), TBK-1(TANK-Binding Kinase 1), and IKK-ε(Inhibitor of Nuclear Factor Kappa-B Kinase Subunit ε). This transcription factor plays a pivotal role in orchestrating the development, differentiation, and functional regulation of key immune cell populations, particularly B lymphocytes, T helper 1 (Th1) cells, and dendritic cells (DCs). Additionally, IRF1 exerts critical cytostatic and pro-apoptotic effects across diverse mammalian cell types. Mechanistically, these activities involve modulation of oxidative stress responses and participation in regulated cell death pathways, including ferroptosis (14, 22–24).

IRF2: a competing factor engages in cis-regulatory element occupation, directly antagonizing IRF1-mediated transcriptional activity by binding to shared DNA recognition motifs. This molecular interference suppresses the expression of
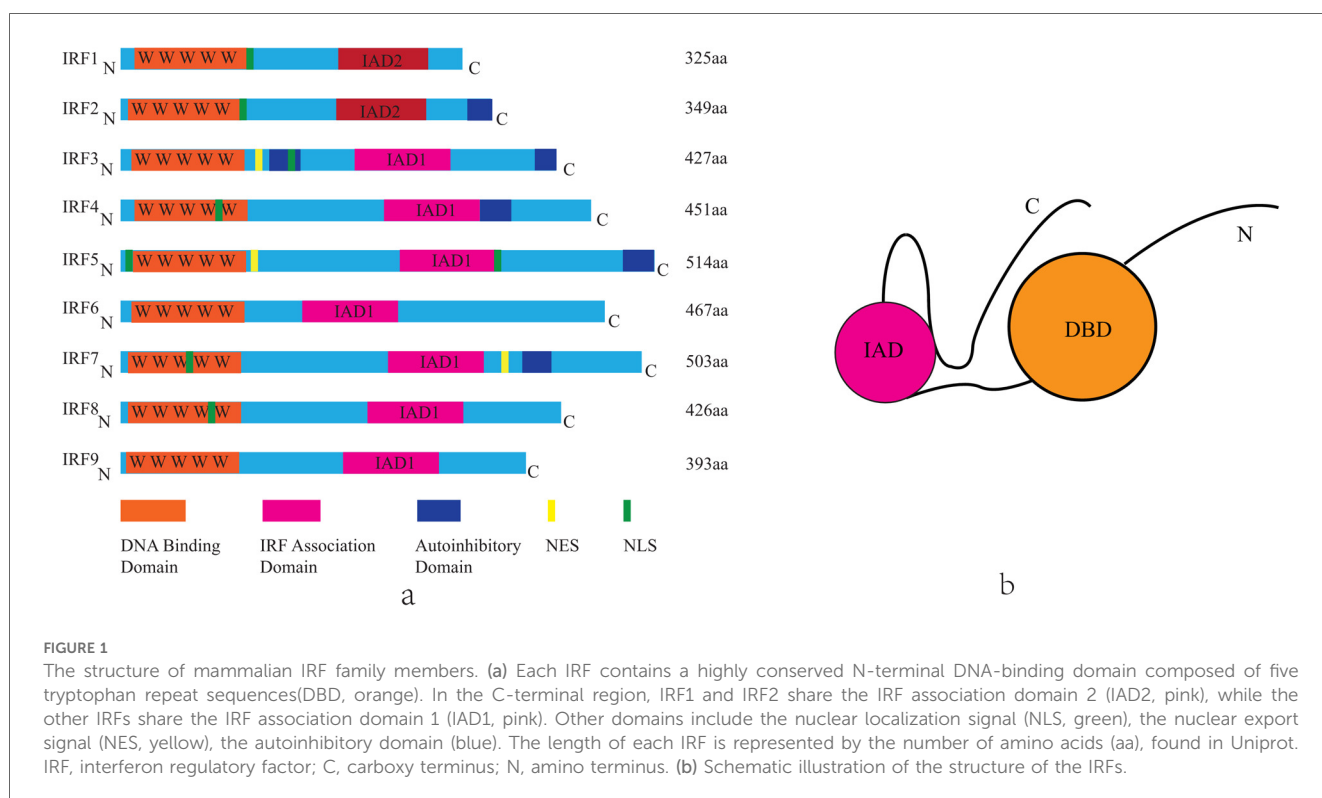
FIGURE 1
The structure of mammalian IRF family members. (a) Each IRF contains a highly conserved N-terminal DNA-binding domain composed of five tryptophan repeat sequences(DBD, orange). In the C-terminal region, IRF1 and IRF2 share the IRF association domain 2 (IAD2, pink), while the other IRFs share the IRF association domain 1 (IAD1, pink). Other domains include the nuclear localization signal (NLS, green), the nuclear export signal (NES, yellow), the autoinhibitory domain (blue). The length of each IRF is represented by the number of amino acids (aa), found in Uniprot. IRF, interferon regulatory factor; C, carboxy terminus; N, amino terminus. (b) Schematic illustration of the structure of the IRFs.

TABLE 1 Classification of IRF family.

IRFs member	Main functions	References
IRF1	Orchestrates innate immune responses and antiviral defense; modulates immune cell differentiation, apoptosis, and anti-proliferative activity across hematopoietic lineages.	(14, 22–24)
IRF2	Regulates immune cell maturation and transcriptional activation/repression in hematopoietic development.	(25)
IRF3	Key mediator of innate antiviral signaling; initiates type I interferon production via pathogen-sensing pathways.	(26, 27)
IRF4	Modulates oncogenic processes and lipid homeostasis in adipocytes; fine-tunes adaptive immune responses.	(28–32)
IRF5	Central driver of autoimmune pathogenesis; regulates pro-inflammatory cytokine production and macrophage polarization.	(34–40)
IRF6	Governs epithelial differentiation and morphogenesis; critical for epidermal and craniofacial development.	(42, 43)
IRF7	Master regulator of type I interferon amplification; essential for antiviral innate immunity and dendritic cell activation.	(44, 45)
IRF8	Controls myeloid/lymphoid cell differentiation; regulates antigen presentation and inflammasome activation.	(46–48)
IRF9	Mediates interferon signaling; emerging roles in metabolic regulation (hepatic steatosis, insulin resistance).	(49, 50)

IRF1-dependent pro-inflammatory genes, while simultaneously fine-tuning transcriptional programs critical for immune cell ontogeny and functional maturation including lineage commitment, antigen presentation capacity, and effector molecule production. Such competitive regulation establishes a dynamic equilibrium between inflammatory activation and homeostatic restraint, ensuring balanced immune responses while preventing pathological hyperinflammation (25).

IRF3: primarily resides in the cytoplasm in an inactive state, serving as an essential component of the innate immune defense system. This transcription factor demonstrates remarkable sensitivity in detecting viral components and plays a pivotal role in initiating antiviral responses to prevent pathogenic infections. Furthermore, recent studies have revealed IRF3's significant involvement in cardiovascular pathophysiology, where it functions as a negative regulator of pathological cardiac remodeling. Mechanistically, IRF3 binds to Extracellular Signal-Regulated Kinase(ERK) 2 through protein-protein interaction, leading to subsequent suppression of ERK 1/2 signaling activity (26, 27). This regulatory mechanism not only highlights IRF3's dual functionality in both immune regulation and cardiac homeostasis but also provides potential therapeutic targets for CVDs.

IRF4: initially characterized as a lymphocyte-specific nuclear factor and discovered to exhibit conserved cardiac expression in both human and animal models (28). Distinct from other IRF family members, IRF4 demonstrates unique activation

mechanisms, primarily responding to mitogenic stimuli such as antigen receptor signaling, lipopolysaccharide (LPS) stimulation, and CD40 receptor engagement rather than canonical interferon-mediated pathways (29, 30). Beyond its established role as an oncogenic transcription factor that modulates upstream signaling cascades and protein-DNA interactions, IRF4 paradoxically serves dual functions in metabolic regulation. It acts as a master transcriptional regulator of lipid homeostasis in adipocytes and functions as an anti-inflammatory mediator in diet-induced obesity, positioning it at the intersection of metabolic inflammation and energy balance (31, 32).

IRF5: predominantly expressed in immune cells such as monocytes, macrophages, B lymphocytes, and DCs. Its dysregulation is strongly implicated in the pathogenesis of autoimmune disorders including systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and rheumatoid arthritis (RA) (33). his transcription factor plays a pivotal role in inflammatory responses through its synergistic interaction with the NF-κB p65 subunit RelA, co-activating inflammatory gene networks and driving the production of key pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-12, and tumor necrosis factor-alpha (TNF-α) (34–36). Emerging genetic evidence further underscores the clinical significance of IRF5 polymorphisms, which have been associated with both susceptibility to and protection against AS. Notably, the high degree of genetic variation in IRF5 correlates with pathological changes in carotid intima-media thickness (cIMT) and demonstrates a strong association with coronary artery disease (CAD) development in SLE patients (37–40).

IRF6: critically regulates epidermal development and differentiation (41). Emerging evidence further suggests its potential involvement in the pathogenesis and metabolic reprogramming of pancreatic ductal adenocarcinoma and gliomas (42, 43).

IRF7: a key regulatory component in type I/III IFN-mediated signaling cascades. It shares significant structural homology with IRF3 while exhibiting distinct functional specialization. Notably, it serves multifaceted roles in antiviral defense mechanisms and innate immune responses (44). Emerging evidence implicates IRF7 in modulating obesity-associated adipose tissue inflammation (45).

IRF8: originally characterized as being selectively expressed in immune system lineages (lymphoid and myeloid cells). It serves as a master regulator of immune cell development and maturation (14). Additionally, IRF8 acts as a potent inducer of macrophage differentiation from bone marrow progenitor cells. Genome-wide association studies have revealed significant correlations between IRF8 genetic variants and CAD manifestations, particularly through three key phenotypic markers: carotid plaque formation, augmented carotid intima-media thickness, and systemic leukocytosis. These clinical observations collectively establish its potential role as a biomarker for subclinical AS risk (46–48).

IRF9: a critical downstream effector of type I IFN signaling through its integration into the STAT1-STAT2 heterotrimeric complex, collectively forming the interferon-stimulated gene

factor 3 (ISGF3) transcriptional machinery. While its canonical role in IFN response pathways is well-established, its specific regulatory mechanisms governing immune cell ontogeny remain underexplored (49). Notably, IRF9 interacts with peroxisome proliferator activating receptor alpha (PPARα) and forms a metabolic-regulatory axis that co-activates PPARα-responsive genes. This interaction manifests therapeutic potential by ameliorating pathological processes including inflammatory responses, hepatic lipid accumulation, and insulin resistance (50).

3 IRFs and as

Current observations highlight a significant role for IRFs in murine models of atherosclerosis AS. In apolipoprotein E-deficient (ApoE$^{-/-}$) mice, IRF1 promotes a proinflammatory M1 macrophage phenotype, exacerbates atherosclerotic burden (51), facilitates foam cell formation and increases plaque instability (3). Conversely, ablation of IRF3 expression enhances plaque stability, characterized by thicker fibrous caps, increased collagen deposition and smooth muscle cell (SMC) content, alongside reduced macrophage infiltration (10, 52). Similar to IRF1, IRF5 can also promotes macrophage polarization towards a pro-atherogenic state and foam cell formation (53–55). Notably, IRF7 plays a non-redundant role in AS pathogenesis specifically in diabetic mouse models (56). Furthermore, in chronic myelogenous leukemia-prone mice, IRF8 is implicated in regulating phagocytic function of macrophages (57). Whether these specific roles of IRFs translate identically to humans, beyond *in vitro* and animal studies, remains to be elucidated. The mechanisms by which IRFs contribute to AS are summarized below.

3.1 Inflammatory regulation

The inflammatory cascade permeates all stages of AS, with endothelial cells (ECs) and immune cells coordinating vascular inflammation through IRF-mediated mechanisms. Key IRF members demonstrate cell-type specific pro-atherogenic effects: IRF1/IRF3 modulate cytokine production in ECs and T cells, IRF5/IRF8 drive macrophage polarization, while IRF7 exhibits context-dependent anti-inflammatory properties (Table 2).

3.1.1 IRF 1

Inflammation of damaged ECs leads to endothelial dysfunction, a critical initiating event in atherosclerotic plaque development and progression (58). IRF1 orchestrates endothelial dysfunction through multiple mechanosensitive pathways, though its role in the atherosclerotic microenvironment remains controversial. Previous studies have reported conflicting IRF1-dependent regulation of TNF-induced vascular cell adhesion molecule-1 (VCAM-1) expression (59, 60). Emerging evidence clarifies that IRF1 mediates triglyceride-rich lipoprotein (TGRL)-induced VCAM-1 via the PERK/eIF2α/CHOP signaling

axis, with polyunsaturated fatty acids counteracting this pro-inflammatory pathway in human aortic endothelial cells(HAECs) (61, 62). Shear stress (SS), the frictional force exerted by blood flow on ECs, modulates IRF1 activity through distinct mechanisms (63). Fluid SS regulates IRF1 nuclear translocation via platelet EC adhesion molecule 1 (PECAM-1)-mediated mechanotransduction, involving p38/x-box binding protein 1 (XBP1s) interactions and Phosphoinositide 3-kinase (PI3 K)/ MAPK phosphatase 1 (MKP-1) modulation (64, 65). Conversely, interleukin 33 (IL-33) inhibits VCAM-1 expression through IRF1- ERK 1/2 pathway cross-talk in HAECs (66). Additionally, Ataxin-10 binds cytoplasmic IRF1 to suppress its nuclear translocation and downstream cytokine/chemokine transcription (67). Moreover, IRF1 drives CD40(TNFR5) expression in ECs, promoting adhesion molecules and chemokines essential for leukocyte recruitment (68). By constructing a mouse atherosclerotic model, Wang et al. found in human and mouse primary cells that the IRF1/RIG-I axis mediates 25-hydroxycholesterol-induced IL-8 production in AS, activating NF-κB, AP-1, and NF-IL-6 through MAVS/TAK-1/JNK/ERK1/2 signaling (69). In ApoE$^{-/-}$ mice, IRF1 promotes M1 polarization via TLR2/4-casein kinase 2 (CK2)- RNA polymerase II transcriptional coactivator p15 (SUB1/Sub1, PC4) signaling, enhancing TNF-α/IL-1β production (51). This pro-inflammatory shift exacerbates plaque vulnerability. IRF1-driven IFN-γ/TNF-α production contributes to plaque rupture and acute coronary syndromes (ACS) (70). In rat VSMCs, IRF1 amplifies DC inflammatory responses through MAPK pathway activation (JNK/p38/ERK1/2 phosphorylation), accelerating plaque destabilization (71).

3.1.2 IRF 3

IRF3 demonstrates paradoxical regulatory effects in vascular inflammation through distinct molecular mechanisms (72). Knockdown of EC-specific IRF3 significantly attenuates plaque formation in Western diet-fed ApoE$^{-/-}$ mice, while bone marrow-derived macrophage IRF3 shows no such effect. Mechanistic studies demonstrate that IRF3 specifically binds to the ISRE within the ICAM-1 promoter(P1 site), predominantly suppressing ICAM-1 transcription and moderately inhibiting VCAM-1 expression (10, 52). Paradoxically, while suppressing ICAM-1 transcription through ISRE binding, IRF3 simultaneously promotes inflammatory signaling through four distinct axes.

3.1.2.1 Axis 1: cGAS-STING-PERK activation via oxidized mtDNA

Oxidized mitochondrial DNA triggers cyclic GMP-AMP (cGAMP) synthase (cGAS)-stimulator of IFN genes (STING) signaling, leading to the formation of a transcriptional complex comprising IRF3, NF-κB, and bromodomain protein 4 (BRD4). This complex drives pro-inflammatory genes expression including ICAM-1, through PERK pathway activation in both human and mouse ECs (72).

Table 2 The role of IRFs in inflammtory response.

Irfs	Influenced genes	Involved signal pathway	Effects	References
IRF1	VCAM-1	Activates: PERK-eIF2α-CHOP pathway, PECAM-1-P38-XBPs pathway	Promotes EC inflammation	(61, 62, 65)
		Inhibits: IL-33-ERK1/2 pathway; Ataxin-10		(66, 67)
	CD40	-	Induces adhesion molecules and chemokines expression in ECs	(68)
	RIG-I	MAVS/TAK-1/JNK&ERK1/2 signaling pathway	Stimulates IL-8 secretion in macrophages	(69)
	TNF-α, IL-1β, CCL-2	TLR2/TLR4/SUB1 pathways	Drives macrophage polarization to M1 phenotype	(51)
	IFN-γ, TNF-α, IL-12p70	-	Enhances Th1-mediated pro-inflammatory cytokine production	(70)
	IL-6, IL-12p70, TNF-α	MAPK pathway (JNK/p38/ERK1/2 phosphorylation)	Upregulates inflammatory cytokines and enhances DC maturation	(71)
IRF3		Noncanonical STING-PERK pathway (complex with NF-κB & BRD4)	Mediates EC inflammatory activation	(72)
	IL-6	cGAS-STING DNA-sensing pathway	Promotes VSMC inflammation.	(73)
	IL-6, PPARγ	MyD88-independent TLR4 signaling	Contributes to VSMC inflammatory responses	(75)
	CCL5, Cxcl10	IKK-related kinase/TBK1 pathway	Upregulates RANTES and IP-10 expression	(74)
IRF5	IL-10	TLR7/TLR9 pathway	Attenuates macrophage inflammation in lupus-associated atherosclerosis	(80)
	CD11c, CCL2, CCL4	-	Activates macrophage inflammatory responses	(78, 79)
	TNF-α, IL-6	TRAF6-IKK-IRF5 axis	Drives pro-inflammatory gene expression in M1 macrophages	(54, 55)
IRF7	iNOS, Arg1, IL-10	-	Modulates macrophage inflammatory processes	(56)
IRF8	Lymphoid CD8α+ cDCs	Aortic CD11b–CD103 + cDCs	Regulates dendritic cell subpopulation development	(82)
	Arg1	-	Suppresses macrophage inflammatory activity	(81)

3.1.2.2 Axis 2: cGAS-STING-IRF3-Il6 activation via DNA double-strand breaks

In ApoE$^{-/-}$ mice, DNA damage-induced double-strand breaks (DSBs) activate this axis to amplify pro-inflammatory responses in AS, highlighting its potential as a therapeutic target (73).

3.1.2.3 Axis 3: TBK1/IRF3/CCL5-CXCL10 activation in HCMV-infected VSMCs

Human cytomegalovirus (HCMV) infection in human VSMCs activates a novel IκB kinase (IKK)-related pathway involving TBK1, IRF3, and chemokines CCL5/RANTES and CXCL10/IP-10. This axis contributes to atherosclerotic lesion progression by modulating inflammatory chemokine production (74).

3.1.2.4 Axis 4: TLR4-TRIF-Ip10 pathway modulation

IRF3 mediates C-reactive protein (CRP)-induced NF-κB activation in rat VSMCs via the MyD88-independent TLR4 pathway. This mechanism suppresses peroxisome proliferator-activated receptor γ (PPARγ) expression, a key anti-inflammatory regulator while enhancing IL-6 production. Notably, the PPARγ agonist rosiglitazone reverses PPARγ downregulation and demonstrates novel anti-inflammatory effects through modulation of the TLR4/TRIF/IRF3/IP-10 signaling axis (75, 76).

Recent work by Zeyu Xing et al. reveals that karyopherin subunit alpha 2 (KPNA2) facilitates nuclear translocation of IRF3 and NF-κB p65,.a process regulated by the E3 ubiquitin ligase F-box and WD repeat domain containing 7 (FBXW7) (77). This discovery expands our understanding of post-translational regulation in IRF3-mediated inflammatory responses.

3.1.3 IRF5/7/8

IRF5 is well-established as a driver of pro-inflammatory M1 macrophage polarization. Emerging evidence highlights its paradoxical role in inflammatory regulation. Julia Leipner et al. demonstrated that IRF5 deficiency reduces M1 marker expression *in vitro* and enhances atherosclerotic plaque stability, suggesting its critical role in sustaining vascular inflammation (53). Mechanistically, in ApoE$^{-/-}$ mice, IRF5 promotes M1 polarization via TRAF6-IKK and miR-22-dependent pathways, positioning it as a promising therapeutic target for AS management (54, 55). IRF5 further induces the differentiation of macrophages into the pro-inflammatory CD11c + subset by directly targeting the CD11c gene, thereby amplifying chemokine release (CCL2 and CCL4) to fuel inflammatory cascades (78, 79). Notably, IRF5 exhibits disease-specific functionality. TLR7/9-activated IRF5 elevates IL-10 in systemic lupus erythematosus (SLE) models, contrasting with its pro-inflammatory role in TLR2/4-mediated pathways (80).

In diabetic contexts of mice, IRF7 disrupts macrophage homeostasis by suppressing the anti-inflammatory M2 marker arginase-1 (Arg1) and IL-10 via RAGE signaling, while enhancing pro-inflammatory TNF-α and CCL2 production (56). Conversely, IRF8 cooperates with the Ets family transcription factor PU.1, a downstream effector of liver X receptors (LXRs),

to regulate Arg1 expression, highlighting its role in balancing macrophage functional states (81).

Conventional dendritic cells (cDCs) in atherosclerotic plaques, characterized by the CD11b⁻ CD103⁺ IRF8hi phenotype, originate from DNGR1-expressing precursors. Conditional deletion of IRF8 in CD11c⁺ cells ablates lymphoid-like CD8α^+ cDCs and CD11b-CD103 + cDCs, significantly attenuating AS progression despite hypercholesterolemia. This effect correlates with suppressed T/B cell activation and differentiation under high-fat diet (HFD) conditions, underscoring IRF8's non-redundant role in bridging innate and adaptive immune responses in AS pathogenesis (82).

3.2 Dysregulation of lipid homeostasis

Under physiological conditions, macrophages maintain lipid homeostasis through balanced uptake, efflux, and degradation. Foam cell formation, a hallmark of early AS, is tightly linked to dysregulated lipid metabolism in macrophages (83). Emerging evidence implicates IRF1, IRF3, IRF5, and IRF7 as critical regulators of lipid handling in macrophages, with distinct roles in modulating scavenger receptors, cholesterol transporters, and nuclear receptor signaling (Figure 2).

3.2.1 IRF1

Elevated IRF1 expression correlates with atherosclerotic lesion progression and oxidized LDL (oxLDL)-induced foam cell formation (84). Scavenger receptor AI (SR-AI), which is a direct downstream gene target of IRF1, is primarily responsible for the recognition and uptake of oxLDL (85). Mechanistically, in a mouse atherosclerotic model, IRF1 amplifies lipid uptake in macrophages by upregulating scavenger receptor AI (SR-AI) through the TLR2/4-MyD88 pathway, while IRF1 silencing reverses this opposite effect (3). OxLDL receptor-1 (LOX-1), a transmembrane glycoprotein, is also famous for binding to and internalizing oxLDL (71). In DCs in acute coronary syndrome (ACS) patients, IRF1 overexpression enhances lectin-like LOX-1 expression, promoting oxLDL binding and internalization (71).

3.2.2 IRF3

IRF3 exerts dual regulatory effects on lipid metabolism. ATP-binding cassette transporter A1 (ABCA1) is a key transporter protein for cholesterol efflux in macrophages (86). IRF3 suppresses the transcriptional activity of Liver × Receptor (LXR) at the ABCA1 promoter through TLR3/4 signaling in aortic tissue *in vivo*. This process could reduce cholesterol efflux and favor lipid accumulation (87). Concurrently, IRF3 synergizes with Chlamydia pneumoniae-activated TLR2/4 signaling via MyD88 and TRIF-dependent pathways to drive foam cell formation.
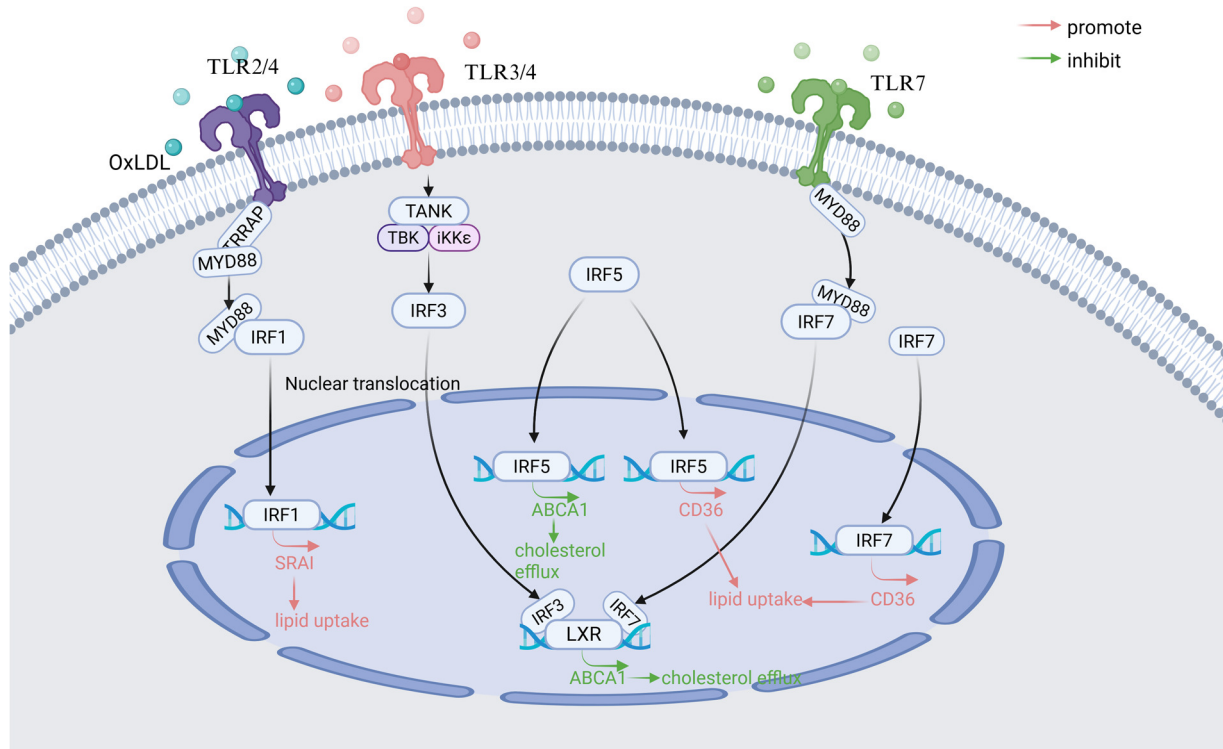

FIGURE 2
Main signaling pathways of IRFs involved in regulating macrophage lipid metabolism in atherosclerosis. TLR, Toll-like receptor; MyD88, Myeloid differentiation primary response 88; TANK, TRAF family member-associated NF-kappa-B activator; TBK-1, TANK-binding kinase 1; LXR, Liver X Receptor; IKK-ε, Inhibitor of nuclear factor kappa-B kinase subunit epsilon; SR-AI, scavenger receptor AI; ABCA1, ATP-binding cassette transporter A1; CD36, Cluster of Differentiation 36. Created in BioRender. Wang, Y. (2025) https://BioRender.com/zmlx50r.

Intriguingly, crosstalk between IRF3 and LXR pathways suggests therapeutic potential for LXR agonists in mitigating AS progression (88).

3.2.3 IRF5

Cluster of Differentiation 36 (CD36) is a class B scavenger receptor primarily responsible for lipid uptake (89). Demonstrated *in vivo* and *in vitro* models, IRF5 promotes foam cells formation by skewing the ABCA1/CD36 ratio toward lipid uptake. This means IRF5 can reduce the expression of ABCA1 and increase the expression of CD36 in macrophages (53). Paradoxically, in SLE, IRF5 improves systemic lipid profiles by lowering very low-density lipoprotein (VLDL) and elevating high-density lipoprotein (HDL) levels, highlighting its context-dependent functionality (80).

3.2.4 IRF7

IRF7 disrupts cholesterol homeostasis through the TLR7-MyD88-ABCA1 axis, suppressing cholesterol efflux in murine macrophages (90). In diabetic mouse bone marrow-derived macrophages (BMDMs), IRF7 downregulation increases cholesterol transporter expression while reducing CD36 levels, implicating that IRF7 is a negative regulator of reverse cholesterol transport (56).

3.3 Regulation of programmed cell death in atherosclerosis

Programmed cell death (e.g., pyroptosis, apoptosis) and efferocytosis, the phagocytic clearance of apoptotic cells, are critical determinants of atherosclerotic plaque stability. Emerging evidence highlights that exacerbated programmed cell death coupled with impaired efferocytosis drives atherosclerotic progression. Key IRF family members regulate these processes through distinct mechanisms (Table 3).

3.3.1 IRF1

Pyroptosis, a caspase-dependent inflammatory cell death mechanism, is critically regulated by IRF1 (91). In HAECs, IRF1 binds promoter regions of Gasdermin D (GSDMD) and CASP1, enhancing their expression to drive NLRP3 inflammasome-mediated pyroptosis. This progress is initiated by RelB/p52-mediated NF-κB activation (11). Similarly, in macrophages, IRF1 modulates Cysteine-aspartic proteases 1 (caspase-1) activation, GSDMD-N cleavage, and IL-1β/IL-18 maturation via ROS-dependent NLRP3-ASC inflammasome. IRF1 overexpression amplifies pyroptotic signaling, whereas its inhibition attenuates inflammatory cell death (92).

Notably, IRF1 further promotes macrophage from patients with CAD pyroptosis by regulating Methyltransferase-like 3 (METTL3)-mediated m6A modification of circular RNA circ_0029589. This interaction suppresses circ_0029589 expression, which normally inhibits caspase-1 p10, GSDMD-N, IL-1β p17, and IL-18 production (93, 94). IRF1 also facilitates

TABLE 3 The role of IRFs in programmed cell death, efferocytosis and vascular smooth muscle cells.

IRFs	Target genes	Functions	References
Programmed cell death and Efferocytosis			
IRF1	GSDMD	Induces EC apoptosis.	(11)
	NLRP3-ASC, caspase-1 p10, IL-1β p17, IL-18	Mediates macrophage pyroptosis activation	(92)
	METTL3	Enhances pyroptotic pathway activation in macrophages	(93, 94)
IRF5	Itgb3, Mfge8	Impairs macrophage efferocytic capacity	(78, 79)
IRF8	CD36	Suppresses macrophage efferocytosis	(57)
Vascular smooth muscle cells: differentiation, proliferation and calcification			
IRF1	CDK	Induces cell cycle arrest in VSMCs at G1 phase	(99)
	NOS2	Mediates VSMC cycle arrest through nitric oxide signaling	(99)
	CCL19	Facilitates VSMC pathological processes:As a potential stimulus for SMC-to-macrophage transdifferentiation.	(101)
IRF8	Unknown	Potential mediator of SMC-to-macrophage transdifferentiation	(12)

NLRP3-ASC recruitment to enhance caspase-1 activation, establishing a feedforward loop of inflammation (93, 94).

3.3.2 IRF5

In human carotid artery and mouse models, IRF5 impairs macrophage efferocytosis by downregulating integrin-β3 (Itgb3) and milk fat globule epidermal growth factor 8 (Mfge8), the key mediators of apoptotic cells, in pro-inflammatory CD11c + macrophages. This defect enlarges the necrotic core and increases plaque rupture susceptibility, underscoring IRF5's role in destabilizing advanced lesions (78, 79).

3.3.3 IRF8

IRF8-deficient macrophages from chronic myelogenous leukemia-prone mice exhibit reduced CD36 expression, impairing efferocytosis of apoptotic polymorphonuclear neutrophilic leukocytes (PMNs) (57). This finding positions IRF8 as a regulator of phagocytic function in inflammatory contexts.

3.4 VSMC plasticity and phenotypic switching in atherosclerosis

VSMCs undergo dynamic phenotypic changes during AS, migrating from the medial layer to the intima, proliferating, and depositing extracellular matrix to shape plaque architecture (95). Emerging evidence highlights the regulatory roles of IRFs in VSMC plasticity, which governs their transition into distinct functional subtypes with divergent roles in AS progression (96) (Table 3).

3.4.1 IRF1

IRF1 exerts antiproliferative and pro-apoptotic effects across vascular cell types (3). In murine neointimal hyperplasia models, IRF1 suppresses coronary artery smooth muscle cell (CASMC) proliferation and migration while inhibiting neointima formation. Mechanistically, IRF1 induces G1-phase cell cycle arrest via two complementary pathways: (1)P21-Dependent CDK Inhibition: IRF1 upregulates the cyclin-dependent kinase (CDK) inhibitor p21, directly or indirectly blocking CDK activity (97, 98); (2)Nitric Oxide (NO)-Mediated Arrest: IRF1 enhances NO production, a known inducer of cell cycle arrest and endothelial function modulator (99).The p21 pathway also inhibits CASMC migration, potentially through interactions with CDK inhibitory proteins (CKIs) of the Cip/Kip family (100). These dual mechanisms provide novel insights into IRF1's role in mitigating VSMC-driven AS pathophysiology.Paradoxically, IRF1 promotes AS progression by upregulating CCL19, a chemokine elevated in AS patient serum. CCL19 enhances VSMC proliferation, migration, inflammatory factor secretion (IL-1α/β, TNF-α, IL-6), and extracellular matrix deposition (collagen III, osteopontin), positioning it as a potential diagnostic biomarker and therapeutic target (101).

3.4.2 IRF8

Single-cell transcriptomic analyses reveal five VSMC subtypes in AS: contractile, fibroblast-like, osteogenic, synthetic, and macrophage-like. Notably, Xue Gong et al. identified IRF8 as a master regulator SMC-to-macrophage transdifferentiation via NF-κB signaling activation in human carotid plaque laden with atherosclerotic core (12). The macrophage-like SMC subtype exhibits a hybrid phenotype co-expressing inflammatory mediators(CCL2, CXCL1-3), matrix-remodeling enzymes(MMP3, MMP9, MMP19) and osteogenic markers(LGALS3, KLF4) (102–105). This transdifferentiation process amplifies plaque instability by promoting matrix degradation, inflammation, and calcification, underscoring IRF8's pathogenic role in advanced AS.

4 Conclusions

IRFs are multifaceted regulators of AS, influencing inflammation, lipid handling, cell death, and VSMC plasticity. While IRF1, IRF3, IRF5, and IRF8 predominantly exacerbate AS, context-dependent roles (e.g., IRF5 in lupus-associated AS) highlight their therapeutic complexity. Future studies must clarify unresolved questions, including functional redundancies among IRFs, tissue-specific effects, and translational potential. Targeting IRF signaling pathways may offer novel strategies for stabilizing atherosclerotic plaques and reducing CVD burden.

Author contributions

YW: Writing – review & editing, Conceptualization, Writing – original draft. TF: Conceptualization, Writing – review & editing. XZ: Conceptualization, Writing – review & editing. NH: Supervision, Conceptualization, Writing – review & editing, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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