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REVIEW ARTICLE

New insights into the suppression of inflammation and lipid accumulation by *JAZF1*

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TAK1

Abstract Atherosclerosis is one of the leading causes of disease and death worldwide. The identification of new therapeutic targets and agents is critical. *JAZF1* is expressed in many tissues and is found at particularly high levels in adipose tissue (AT). *JAZF1* suppresses inflammation (including *IL-1β*, *IL-4*, *IL-6*, *IL-8*, *IL-10*, *TNFα*, *IFN-γ*, *IAR-20*, *COL3A1*, *laminin*, and *MCP-1*) by reducing *NF-κB* pathway activation and AT immune cell infiltration. *JAZF1* reduces lipid accumulation by regulating the liver X receptor response element (*LXRE*) of the *SREBP-1c* promoter, the *cAMP*-response element (*CRE*) of *HMGCR*, and the *TR4* axis. *LXRE* and *CRE* sites are present in many cytokine and lipid metabolism gene promoters, which suggests that *JAZF1* regulates these genes through these sites. *NF-κB* is the center of the *JAZF1*-mediated inhibition of the inflammatory response. *JAZF1* suppresses *NF-κB* expression by suppressing *TAK1* expression. Interestingly, *TAK1* inhibition also decreases lipid accumulation. A dual-targeting strategy of *NF-κB* and *TAK1* could inhibit both inflammation and lipid accumulation. Dual-target compounds (including prodrugs) 1–5 exhibit nanomolar inhibition by targeting *NF-κB* and *TAK1*, *EGFR*, or *COX-2*. However, the *NF-κB* suppressing activity of these compounds is relatively

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low (IC_{50} > 300 nM). Compounds 6—14 suppress *NF-κB* expression with IC_{50} values ranging from 1.8 nM to 38.6 nM. HS-276 is a highly selective, orally bioavailable *TAK1* inhibitor. Combined structural modifications of compounds using a prodrug strategy may enhance *NF-κB* inhibition. This review focused on the role and mechanism of *JAZF1* in inflammation and lipid accumulation for the identification of new anti-atherosclerotic targets.
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Introduction

Atherosclerosis is a common risk factor for the occurrence and development of many diseases, such as coronary heart disease (CHD), and a key problem threatening the health and life expectancy of the elderly population.[1,2] Atherosclerosis, which is characterized by the formation of fat-laden plaques in large and medium-sized vessels, has been identified as a chronic inflammatory disease of the artery wall. Atherosclerosis occurs during foam cell generation. Oxidative stress and intracellular reactive oxygen species (ROS) production cause vascular aging and induce LDL to oxidize and form ox-LDL. Previous studies from our laboratory and others have demonstrated that the uncontrolled uptake of ox-LDL by lectin-like oxidized low-density-lipoprotein receptor-1 (*LOX-1*), class A1 scavenger receptor (*SR-A1*), and cluster of differentiation 36 (*CD36*), and the impaired cholesterol efflux by ATP-binding cassette transporter A1 (*ABCA1*) and *ABCG1* result in cholesterol accumulation and subsequently trigger macrophages and VSMCs to become foam cells.[3—7] Lipid accumulation in macrophages could induce *NLRP3* inflammasome activation. Ox-LDL could activate the *NLRP3* inflammasomes (*IL-1β* and *IL-18*) in atherosclerosis by binding to the *CD36—TLR4—TLR6* signaling complex. Ox-LDL also triggers inflammatory responses, such as interleukin-6 (*IL-6*), *IL-7*, *IL-1β*, and *IL-15*, to accelerate atherosclerosis development.[8] Therefore, controlling lipid metabolism dysfunction and the inflammatory response is an essential measure for preventing atherosclerosis.

Juxtaposed with another zinc finger gene 1 (*JAZF1*, also named *Tip27* and *ZNF802*) is a cysteine—histidine structured zinc finger protein. This gene encodes a 27-kDa nuclear protein containing 3 putative zinc finger motifs. *JAZF1* is the corepressor of orphan nuclear receptor *TR4* (also named *NR2C2*), which is a member of the nuclear orphan receptor family. Recent studies have demonstrated that *JAZF1* plays an important role in atherosclerosis progression.[9] To our knowledge, *JAZF1* is expressed in a variety of tissues in humans and mice and is most highly expressed in adipose tissue (AT).[10] However, *JAZF1* is a relatively new gene with many unknown functions and mechanisms. The main aims of this review are to describe the role and mechanism of *JAZF1* in immune and inflammatory responses and lipid metabolism and to discuss its contributions to atherosclerosis and its potential role in atherosclerosis treatment.

Role of *JAZF1* in atherosclerosis

Many studies have shown that *JAZF1* is associated with atherosclerosis. *JAZF1* is downregulated in atherosclerosis development in prediabetes patients.[11] The rs864745 single nucleotide polymorphism (SNP) of *JAZF1* is associated with atherosclerosis, which suggests that *JAZF1* may be a potential biomarker.[12] Indeed, *JAZF1* has been patented by several companies and scientists as a biomarker for a variety of diseases, including atherosclerosis (US20190078093A1 and WO2015073531A1), diabetes (EP2215266B1 and US20160138103A1), aging (US20140079836A1), lupus (JP2016095330A), and cancer (US20140357516A1, US20180045727A1, and EP3179393B1). In addition, *JAZF1* also suppresses atherosclerosis development. The downregulation of *JAZF1* expression leads to dysfunction in lipid metabolism and the inflammatory response.[13,14] *JAZF1* overexpression by an adenoviral plasmid containing *JAZF1* reduces the entire aorta's *en face* plaque area and the aortic sinus's cross-sectional plaque area in $apoE^{-/-}$ mice by increasing *JAZF1* expression in various tissues, including the liver and AT. *JAZF1* reduces the blood TC (29%) and LDL-C (30%) levels and the hepatic TC levels (65%) in $apoE^{-/-}$ mice. However, *JAZF1* does not change the TG levels in the blood or hepatic tissue in $apoE^{-/-}$ mice, which suggests that *JAZF1* mainly regulates cholesterol metabolism.[15] *JAZF1* overexpression in transgenic *JAZF1* mice also reduces the risk of atherosclerosis by increasing *JAZF1* expression in various tissues, including the heart, liver, lung, testis, spleen, kidney, and pancreas.[16] These transgenic mice show low inflammatory reaction, body weight, and abdominal fat, low levels of plasma parameters (including TG, TC, LDL-C, glucose, FBG, ALT, and AST), and low hepatic lipid accumulation (TG and TC).[13,14] However, these mice also exhibit heart failure symptoms (such as high blood pressure, cardiomyocyte apoptosis, absence of ventricular contractions, and mitochondrial defects) and enhanced expression of proapoptotic genes, including *caspase-8/9*, *Bim*, *Apaf1*, and *Aifm1*, which suggests that *JAZF1* overexpression may have many side effects.[16]

Many studies have shown that aging, hepatic steatosis, obesity, and type 2 diabetes mellitus (T2DM) are risk factors for atherosclerosis.[17,18] The expression of *JAZF1* is gradually downregulated in aging mice. *JAZF1* overexpression steadily decreases the serum TG, TC, and LDL-C levels in aging mice.[16] *JAZF1* ameliorates aging and hepatic steatosis. The role of *JAZF1* in obesity and T2DM has been

reviewed.[19] Overall, *JAZF1* inhibits atherosclerosis development by suppressing the inflammatory response and lipid metabolism dysfunction.

New insights into the mechanism of *JAZF1* in suppressing inflammation and lipid accumulation

Systemic immune and inflammatory responses of JAZF1 involving reducing NF-κB expression

The inflammatory response could induce atherosclerosis. *JAZF1* reduces the levels of the inflammatory markers, including *IL-4*, *IL-6*, *IL-10*, interferon γ (*IFN-γ*), tumor necrosis factor-α (*TNFα*), fibrotic gene collagen type III alpha 1 (*COL3A1*) and *Lamin*, in mice.[13] *JAZF1* decreases the inflammatory state under high-fat diet (HFD) conditions. JAZF1 inhibits the expression of proinflammatory cytokines (such as *TNFα*, *MCP-1*, *IAR-20*, and *IL-8*) by reducing the NF-κB pathway *in vitro* and *in vivo*.[14,20,21] Thus, the NF-κB pathway plays key roles in suppressing the inflammatory response mediated by *JAZF1*.

Immune responses also regulate atherosclerosis development.[22] *JAZF1* suppresses chronic inflammation by inhibiting mouse peritoneal macrophage differentiation toward the *CD11c*$^+$ M phenotype. In addition, *JAZF1* suppresses chronic inflammation by increasing the number of Tregs and restrictive T cells and the secretion of *IL-10* and *IL-4*. *JAZF1* also reduces the number of *CD4*$^+$ T cells, active T cells, and memory T cells and the secretion of *IL-1β*, *TNF-α*, and *IL-6* in mice.[23–25] Overall, *JAZF1* suppresses atherosclerosis development by regulating immune and inflammatory responses and cytokines (including *IL-1β*, *IL-4*, *IL-6*, *IL-8*, *IL-10*, *TNFα*, *IFN-γ*, *IAR-20*, *COL3A1*, *laminin*, *MCP-1*, *CD4*$^+$ T cells, active T cells, memory T cells, *CD11c*$^+$ macrophages, and *CD206*$^+$ macrophages) by reducing the activation of the NF-κB pathway.

Interestingly, the *JAZF1*-induced reduction in gene expression depends on the *LXR*-responsive element *(LXRE*) and the *cAMP*-response element (*CRE*) site in the gene promoter.[13] The promoter of *IFN-γ* contains *LXRE* and *CRE* sites,[26,27] which suggests that *JAZF1* reduces *IFN-γ* expression by regulating *LXRE* and *CRE* in the *IFN-γ* promoter. The promoters of many cytokines, including *IL-1β*,[28] *IL-4*,[29] *IL-6*,[30] *IL-8*,[31] *IL-10*,[32] *TNFα*,[33] and *IL-17*,[34,35] contain a *CRE* site, which suggests that *JAZF1* reduces the expression of these cytokines by regulating the *CRE* in the promoters of the genes encoding these cytokines (Fig. 1).

Immune and inflammatory responses of JAZF1 involving the regulation of at macrophages and T cells

AT macrophages

AT is a connective tissue that is extensively found in the body and contains adipocytes, fibroblasts, vascular endothelial cells, adipocyte stem/progenitor cells, stromal cells, autonomic nerves, numerous immune cells (including mast cells, eosinophils, leukocytes, T cells, B cells, and macrophages), collagen and elastic fibers, nerve bundles, and vasa vasorum.[36,37] Macrophages play various roles at all stages of atherosclerosis development by secreting proinflammatory and anti-inflammatory cytokines. The subtypes of AT macrophages include M1 macrophages, M2 macrophages, oxidized macrophages (Mox macrophages), and metabolically activated macrophages (MMe macrophages). M1 macrophages are induced by proinflammatory cytokines and secrete proinflammatory factors, including *CD80*, *CD86*, *CD16/32*, *CD11c*, *IL-1β*, *IL-6*, *IL-12*, and *TNFα*, whereas M2 macrophages inhibit inflammation and repair tissue by overexpressing anti-inflammatory and tissue

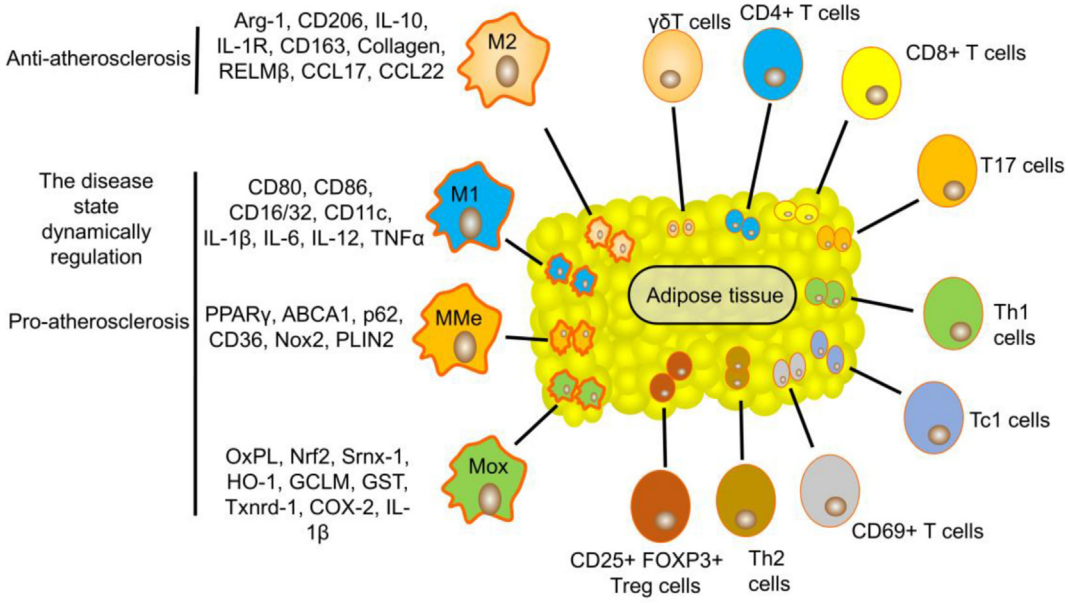


Figure 1 Role of AT macrophages, T cells, and their markers or cytokine profiles in atherosclerosis.

repair factors, including arginase-1 (*Arg-1*), *CD206*, *IL-10*, *IL-1* receptor (*IL-1R*), *CD163*, resistin-like molecule β (*RELMβ*), *CCL17* and *CCL22*.[38] In general, M2 macrophages tend to transform into M1 macrophages in AT. AT contributes to atherosclerosis development by increasing the number of M1 macrophages and releasing proinflammatory factors. Mox macrophages account for 30% of plaque macrophages, and M1 and M2 subsets comprise 40% and 20% of the remaining population, respectively. The molecules oxidized phospholipid (*Ox-PL*), NF-E2-related factor 2 (*Nrf2*), sulfiredoxin-1 (*Srnx-1*), heme oxygenase-1 (*HO-1*), glutamate-cysteine ligase modifier subunit (*GCLM*), glutathione S-transferase (*GST*), and thioredoxin reductase-1 (*Txnrd-1*) are markers of the Mox cell surface. Mox cells are a proatherogenic subset based on their production of proinflammatory cytokines (*COX-2* and *IL-1β*). Genes, including peroxisome proliferator-activated receptor γ (*PPARγ*), *ABCA1*, *p62*, *CD36*, *NADPH* oxidase-2 (*Nox2*), and Perilipin 2 (*PLIN2*), are markers of MMe cells. Under basal conditions, MMe cells in AT could balance the progression of inflammation. *CD36*-mediated cholesterol uptake is in balance with *ABCA1*-mediated cholesterol efflux in MMe cells. However, the state of MMe cells in AT is dynamically regulated by disease states, which can promote a proinflammatory response and cholesterol accumulation and potentially lead to atherosclerosis development.[39,40] Therefore, Mox and MMe cells are the proatherogenic subsets in AT (Fig. 2).

As mentioned previously, *JAZF1* is most highly expressed in *AT*. Importantly, in mouse AT, *JAZF1* overexpression decreases the number of total AT macrophages (ATMs) and *CD11c*$^+$ ATMs and proinflammatory cytokine secretion (including *TNFα* and *IL-1β*) and increases the number of *CD206*$^+$ ATMs.[24,25] *JAZF1* deficiency increases the *CD68*-positive macrophage and monocyte numbers in mouse AT.[10] *CD206* is a marker of anti-inflammatory M2 ATMs, whereas *CD11c*, *TNFα*, and *IL-1β* are markers of proinflammatory M1 ATMs, which suggests that *JAZF1* suppresses inflammation and atherosclerosis development by promoting M1 macrophage transformation into M2 macrophages in AT.

AT T cells

AT T cells are also associated with atherosclerosis, including γδ T cell, *CD4*$^+$ T cell, *CD8*$^+$ T cell, *CD69*$^+$ T cell, T cytotoxic 1 (Tc1) cell, Th17 cell, Th1 cell, Th2 cell, and *CD25*$^+$*FOXP3*$^+$ Treg cell (Fig. 2).[41] *CD4*$^+$ T cells are involved in the initial stage of AT inflammation during the progression of atherosclerosis. Th1, Tc1, and T17 cells are proatherogenic cells that release pro-inflammatory factors, including *IFN-γ*, *TNFα*, and *IL-17*. Treg and Th2 cells are atheroprotective cells that release *IL-10*. An HFD promotes lipid accumulation and chronic inflammation in mouse AT by recruiting immune cells (such as *CD4*$^+$ T cell, *CD8*$^+$ T cell, *CD69*$^+$ T cell, and *CD44*$^+$ T cell) and promoting the production of pro-inflammatory cytokines (such as *IFN-γ* and *IL-17*), which leads to atherosclerosis development.[42–44] The Th1:Th2 balance in AT is highly associated with systemic inflammation and atherosclerosis development. Overall, AT T cells are extensively involved in the development of atherosclerosis.

JAZF1 also regulates the AT T-cell numbers *in vivo*. Specifically, *JAZF1* increases the number of total T cells and *CD25*$^+$*FOXP3*$^+$ Treg cells but decreases the number of total *CD4*$^+$ T cells, *CD69*$^+$ active T cells, and *CD44*$^+$ memory T cells in the AT of mice. *JAZF1* decreases the *IFN-γ* and *IL-17* levels but increases the *IL-4* levels in AT *CD4*$^+$ T cells. Notably, ATMs promote AT *CD4*$^+$ T-cell activation by releasing *MHCII*, *CD86*, and *CD40*. *JAZF1* decreases *CD4*$^+$ T-cell activation by reducing ATM *MHCII*, *CD86*, and *CD40* secretion, which suggests that *JAZF1* regulates T-cell subtype differentiation by regulating ATM cytokine secretion.[24,25] Overall, *JAZF1* suppresses AT inflammation and atherosclerosis development by limiting the macrophage and T-cell populations and their antigen presentation functions.

Lipid metabolism of JAZF1 involving binding to LXREs and serving as a corepressor of TR4

Binding to LXREs

Lipid metabolism dysfunction induces atherosclerosis. Many genes, including acetyl—coenzyme A carboxylase (*ACC*),

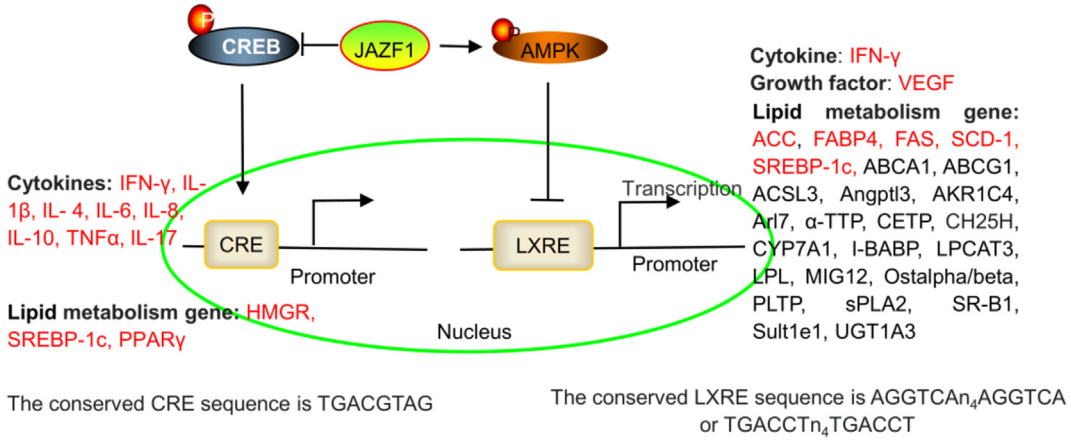


Figure 2 *JAZF1* regulates many cytokines and lipid metabolism genes by regulating the *LXRE* and *CRE* sites of the gene promoter. The *JAZF1*-mediated regulation of *SREBP-1c* and *HMGCR* expression via *LXRE* and *CRE* sites has been investigated. *JAZF1* also regulates *IFN-γ*, *IL-1β*, *IL-4*, *IL-6*, *IL-8*, *IL-10*, *TNFα*, *IL-17*, *VEGF*, *SCD-1*, *FAS*, *ACC*, and *FABP4* expression (red). However, the regulatory mechanisms have not been investigated.

adipose triglyceride lipase (*ATGL*), CCAAT/enhancer binding protein α (*C/EBP*α), fatty acid synthetase (*FAS*), fatty acid binding protein 4 (*FABP4*), stearoyl CoA desaturase-1 (*SCD-1*), sterol regulatory element—binding protein 1c (*SREBP-1c*) and hormone-sensitive lipase (*HSL*), play key roles in lipid metabolism. *ACC* and *FAS* are master enzymes in lipid synthesis that are linked to the development of atherosclerosis.[45,46] *ATGL* is the rate-limiting enzyme that catalyzes the first step of the breakdown of TGs into glycerol and fatty acids.[47] *C/EBP*α plays an important role in lipogenesis, VLDL secretion, and lipolysis.[48] *FABP4* is a lipid chaperone that binds fatty acid precursors. *FABP4* also promotes macrophage foaming and inflammation by enhancing *IL-1*β and *MMP-9* secretion and *CD36* expression, which suggests that *FABP4* plays a key role in lipid uptake and the inflammatory response.[49,50] *SCD-1* and *SREBP-1c* have been shown to be the principal regulatory transcription factors for lipid synthesis.[51,52] *HSL* is the key rate-limiting enzyme that catalyzes AT lipolysis.[53]

JAZF1 suppresses lipid accumulation and decreases the droplet size by reducing *ACC*, *FAS*, *SCD-1*, and *SREBP-1c* expression and increasing *HSL* and *ATGL* expression *in vitro* and *in vivo*.[54—56] *JAZF1* deficiency in *JAZF1*$^{+/-}$ and *JAZF1*$^{-/-}$ mice decrease lipid accumulation by decreasing *FABP4* and *C/EBP*α expression.[10] Thus, *JAZF1* decreases lipid accumulation by regulating *ACC*, *FAS*, *SCD-1*, *SREBP-1c*, *HSL*, *ATGL*, *FABP4*, and *C/EBP*α expression.

LXREs are necessary for *SREBP-1c* promoter activities. Interestingly, *JAZF1* inhibits *SREBP-1c* transcription by increasing *AMPK* phosphorylation and binding to *LXREs* in the *SREBP-1c* promoter, which suggests that *LXREs* play a key role in *JAZF1*-mediated gene expression.[13] *JAZF1* also regulates *SCD-1*, *FAS*, *ACC*, and *FABP4* expression.[10,19,57] However, the mechanism is unclear. Interestingly, the promoters of *ACC*,[58] *FAS*,[59,60] *FABP4*,[61] and *SCD-1*[62] also contain *LXREs*. Other lipid metabolism genes also contain *LXREs*, including *ABCA1*,[63,64] *ABCG1*,[65,66] long-chain acyl-CoA synthetases 3 (*ACSL3*),[67] angiopoietin-like protein 3 (*Angptl3*),[68] 3alpha-hydroxysteroid dehydrogenase (*AKR1C4*),[69] ADP ribosylation factor like GTPase 4C (*Arl4c*, also named *Arl7*),[70] α-tocopherol transfer protein (α-*TTP*),[71] cholesteryl ester transfer protein (*CETP*),[72] cholesterol 25-hydroxylase (*CH25H*),[73] cholesterol 7-alpha-hydroxylase (*CYP7A1*),[74] ileal bile acid-binding protein (*I-BABP*),[75] lysophosphatidylcholine acyltransferase 3 (*LPCAT3*),[76] lipoprotein lipase (*LPL*),[77] midline-1-interacting G12-like protein (*MIG12*),[78] organic solute transporter alpha/beta (*Ostalpha/beta*),[79] phospholipid transfer protein (*PLTP*),[80] group IIA secretory phospholipase A2 (*sPLA2*),[81] *SR-BI*,[82] sulfotransferase family 1E (*Sult1e1*),[83] and UDP-glucuronosyltransferase 1A3 (*UGT1A3*).[84] Because *JAZF1* regulates *SREBP-1c* expression via *LXREs*, we hypothesized that *JAZF1* could regulate lipid metabolism by binding to the *LXREs* of these genes (Fig. 1). However, further studies are needed.

Serving as a corepressor of TR4

JAZF1 is a corepressor of *TR4*, which inhibits *PPAR*$\alpha/\beta/\delta$ expression by competitively binding to *PPREs*. *PPAR*$\alpha/\beta/\delta$ promote the transcription and activation of *visfatin* by binding to the *PPRE* of the *visfatin* promoter region.[85] *JAZF1* promotes *visfatin* promoter activity by upregulating *PPAR*$\alpha/\beta/\delta$ expression in adipocytes. Interestingly, *visfatin* promotes TG accumulation. However, *JAZF1* inhibits lipid accumulation in adipocytes. Indeed, *JAZF1* also inhibits *PPAR*γ expression, which is mainly expressed in AT and is an essential regulatory factor associated with lipid accumulation.[86,87] This finding suggests that *PPAR*γ plays a key role in JAZF1-mediated reductions in lipid accumulation. However, *JAZF1* deficiency decreases *PPAR*γ expression in *JAZF1*$^{+/-}$ and *JAZF1*$^{-/-}$ mice, which suggests that *JAZF1* may increase *PPAR*γ expression.[10] The effect of *JAZF1* on *PPAR*γ may be cell-specific, and more studies are needed to confirm the effect of *JAZF1* on *PPAR*γ.

HMGCR is the key rate-limiting enzyme of cholesterol synthesis.[86] *JAZF1* reduces the serum cholesterol levels and hepatic cholesterol synthesis by inhibiting *HMGCR* expression.[15] The *HMGCR* promoter has a *CRE* site (TGACGTAG), which is necessary for *CREB* activities. *JAZF1* suppresses *CREB* activation by decreasing the phosphorylation of *CREB* at the Ser133 site. Furthermore, *JAZF1* decreases *HMGCR* expression by suppressing the phosphorylation of *CREB*.[15] *TR4* promotes the phosphorylation of *CREB*. *TR4* also directly promotes lipid accumulation by activating the Fatty acid transport protein 1 (*FATP1*) and *CD36* promoters, which suggests that *FATP1* and *CD36* are target genes of *TR4*.[88,89] As mentioned previously, *PPARs* are also target genes of *TR4*. *JAZF1* is a corepressor of *TR4*, which suggests that *JAZF1* regulates lipid accumulation by regulating the *TR4-PPAR*, *TR4-CREB-HMGCR*, *TR4-FATP1*, and *TR4-CD36* axes. In addition, the promoters of *SREBP-1c*[90] and *PPAR*γ[91] also contain a *CRE* site, which suggests that *JAZF1* regulates the expression of these genes by regulating the *TR4-CREB* pathway. Overall, *JAZF1* suppresses lipid accumulation by regulating the expression of *ACC*, *ATGL*, *C/EBP*α, *FAS*, *FABP4*, *HMGCR*, *HSL*, *PPAR*$\alpha/\beta/\delta/\gamma$, *SCD-1*, *SREBP-1c*, and *visfatin*, and this regulation mainly depends on *LXREs* and *TR4*.

Development of a dual-target compound targeting *NF-*κ*B* and *TAK1* (downstream of *JAZF1*)

The antiatherosclerotic therapeutic strategies targeting *NF-*κ*B* were reviewed in 2012.[92] However, the activity of these drugs (such as aspirin and tepoxalin) in suppressing *NF-*κ*B* is low. As mentioned previously, *NF-*κ*B* is the center of the *JAZF1*-mediated inhibition of the inflammatory response. Transforming growth factor β (*TGF-*β)-activated kinase 1 (*TAK1*, also named *MAP3K7*) is a pivotal kinase upstream of *NF-*κ*B*. *JAZF1* suppresses *NF-*κ*B* expression by inhibiting *TAK1* expression.[93] Interestingly, *TAK1* inhibition also decreases lipid accumulation.[94] A positive feedback regulation exists between proinflammatory *NF-*κ*B* signaling and lipid accumulation.[95] The design strategy of *NF-*κ*B* and *JAZF1* or *TAK1* dual-target compounds could inhibit both inflammation and lipid accumulation. There are no dual-target *JAZF1* and *NF-*κ*B* compounds because *JAZF1* is a relatively new target, but dual-target *TAK1* and *NF-*κ*B* compounds exist. Indeed, many dual compounds target *NF-*κ*B* (Table 1). For example, the dual-target compounds 1—5 exhibit nanomolar inhibition by targeting *NF-*κ*B* and *TAK1*, *EGFR*, or *COX-2*.[96—98] However, the activity of these

Table 1 Structure and activities of compounds targeting *NF-κB*.

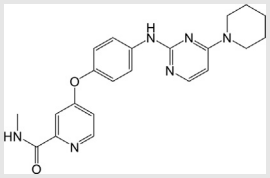
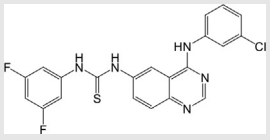
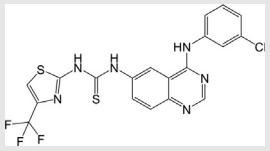
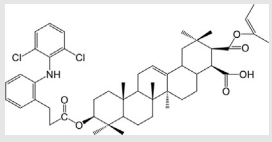
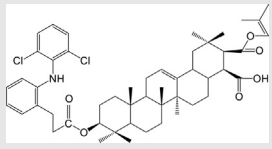
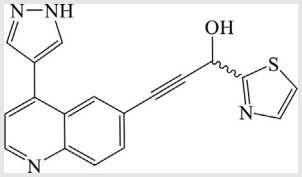
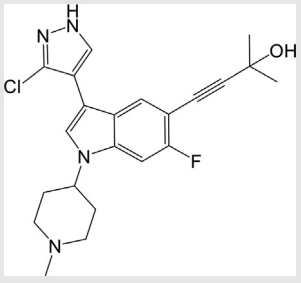
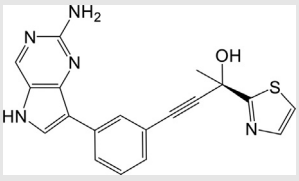
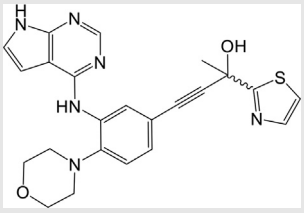
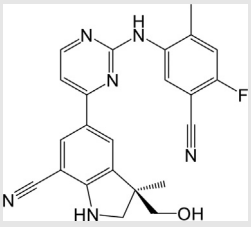
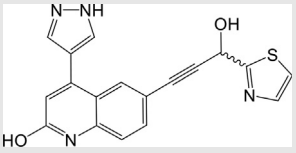
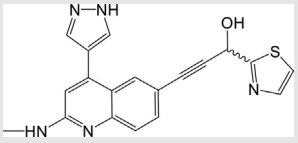
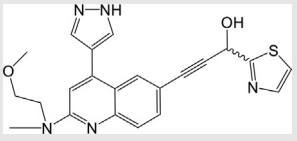
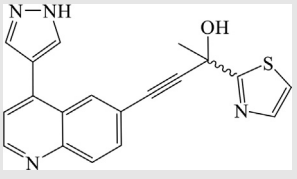
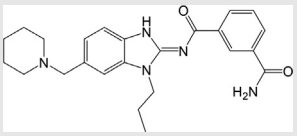
Number	Structure	Activity	Reference
Compound 1		*NF-κB* IC_{50}: 840 nM; *TAK1* IC_{50}: 580 nM	[96]
Compound 2		*NF-κB* IC_{50}: 300 nM; *EGFR* IC_{50}: 60.1 nM	[97]
Compound 3		*NF-κB* IC_{50}: 600 nM; *EGFR* IC_{50}: 137 nM	[97]
Compound 4 (Prodrug)		*NF-κB* IC_{50}: 620 nM; *COX-2* IC_{50}: 680 nM	[98]
Compound 5 (Prodrug)		*NF-κB* IC_{50}: 890 nM; *COX-2* IC_{50}: 840 nM	[98]
Compound 6		*NF-κB* IC_{50}: 4.9 nM	[99]
Compound 7		*NF-κB* IC_{50}: 21 nM	[99]

Table 1 (*continued*)

Number	Structure	Activity	Reference
Compound 8		*NF-κB* IC_{50}: 9.1 nM	[99]
Compound 9		*NF-κB* IC_{50}: 9.87 nM	[99]
Compound 10		*NF-κB* IC_{50}: 1.8 nM	[99]
Compound 11		*NF-κB* IC_{50}: 38.6 nM	[99]
Compound 12		*NF-κB* IC_{50}: 26 nM	[99]
Compound 13		*NF-κB* IC_{50}: 5.2 nM	[99]
Compound 14		*NF-κB* IC_{50}: 22.1 nM	[99]

(*continued on next page*)

Table 1 (*continued*)

Number	Structure	Activity	Reference
HS-276		*TAK1* IC_{50}: 2.5 nM	100

compounds in suppressing *NF-κB* is relatively low ($IC_{50} > 300$ nM). Interestingly, compounds 6—14 suppress *NF-κB* expression with IC_{50} values ranging from 1.8 nM to 38.6 nM.[99] Compounds 3—4 are prodrugs that target *NF-κB* and *COX-2*. Combined structural modification using a prodrug strategy may enhance the inhibition of *NF-κB*. However, many studies are needed. In addition, many *TAK1* inhibitors have been developed, but their clinical advancement has been limited by a lack of oral bioavailability. *HS-276* is a highly selective orally bioavailable *TAK1*

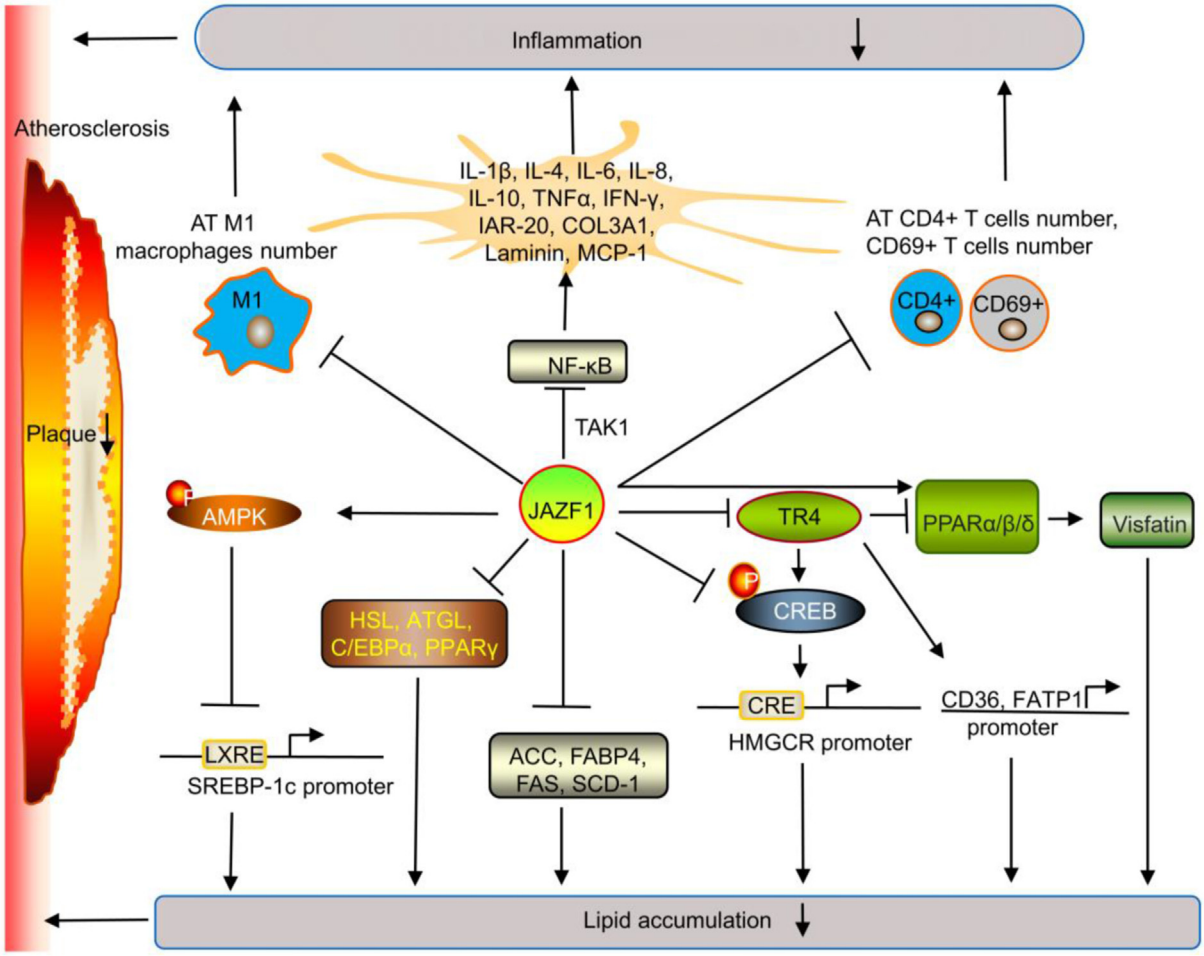


Figure 3 Potential mechanism of *JAZF1* in atherosclerosis. *JAZF1* suppresses inflammation by reducing the *NF-κB*-mediated secretion of cytokines (including *IL-1β*, *IL-4*, *IL-6*, *IL-8*, *IL-10*, *TNFα*, *IFN-γ*, *IAR-20*, *COL3A1*, *laminin*, and *MCP-1*) via the *JNK*, *MAPK*, and *TAK1* pathways and reducing the AT cell numbers (including M1 macrophages, $CD4^+$, and $CD69^+$). *JAZF1* suppresses lipid accumulation by suppressing *SREBP-1c* transcription through increasing *AMPK* phosphorylation and binding to *LXREs* in the *SREBP-1c* promoter, suppressing *HMGCR* transcription by decreasing *CREB* phosphorylation and binding to *CRE* in the *HMGCR* promoter, and suppressing *ACC*, *FAS*, *SCD-1*, *HSL*, *ATGL*, *FABP4*, and *C/EBPα* expression. *JAZF1* may also suppress the *TR4-FATP1* and *TR4-CD36* axes to reduce lipid accumulation. *JAZF1* promotes visfatin expression and accumulation by regulating the *TR4-PPARα/β/δ* axis. However, this effectiveness is reduced. *JAZF1* generally reduces lipid accumulation.

Table 2 Main physiological functions of genes containing *LXRE* and *CRE* sites.

Gene	Function	References
ABCA1	Cholesterol efflux	63,64
ABCG1	Cholesterol efflux	65,66
ACC	Fatty acid synthesis	58
ACSL3	Fatty acid metabolism	67
Angptl3	Triglyceride metabolism	68
AKR1C4	Bile acid biosynthesis, steroid and hormone metabolism	69
Arl7	Cholesterol efflux	70
α-TTP	Vitamin E regulatory protein	71
CETP	Cholesterol metabolism and transportation	72
CH25H	25-Hydroxycholesterol synthesis	73
CYP7A1	Conversion of cholesterol to bile acids	74
FABP4	Fatty acid metabolism and adipocyte differentiation	75
FAS	Fatty acid synthesis	59,60
I-BABP	Enterohepatic circulation of bile acids	75
IFN-γ	Immune and inflammatory responses	26,27
IL-1β	Immune and inflammatory responses	28
IL-4	Immune and inflammatory responses	29
IL-6	Immune and inflammatory responses	30
IL-8	Immune and inflammatory responses	31
IL-10	Immune and inflammatory responses	32
IL-17	Immune and inflammatory responses	34,35
LPCAT3	Phospholipid metabolism	76
LPL	Hydrolysis of circulating triglyceride-rich lipoproteins	77
MIG12	Fatty acid synthesis and TG accumulation	78
Ostalpha/beta	Bile acid absorption	79
PLTP	Phospholipid metabolism	80
PPARγ	Lipid metabolism	91
SCD-1	Monounsaturated fatty acid synthesis	62
sPLA2	Phospholipid metabolism	81
SR-BI	Cholesterol uptake and efflux	82
SREBP-1c	Lipid synthesis	13,90
Sult1e1	Sulfation and inactivation of estrogen	83
TNFα	Immune and inflammatory responses	33
UGT1A3	Bile acid glucuronidation	84
VEGF	Angiogenesis	106

inhibitor (IC_{50} = 2.5 nM). *HS-276* suppresses the levels of proinflammatory cytokines, such as *TNFα*, *IL-6*, and *IL-1β*.[100] However, the role of *HS-276* in *NF-κB* has not been investigated.

Future directions and challenges

Atherosclerosis is the presumed cause of 40% of all deaths and the leading cause of death in elderly populations. Patients who are actively being treated with statins still have a residual cardiovascular risk even when LDL-C is controlled or decreases below 70 mg/dL.[101] Therefore, the identification of new therapeutic targets and the development of new antiatherosclerotic agents are critical. *JAZF1* reduces atherosclerosis development by reducing immune and inflammatory responses and lipid metabolism dysfunction (Fig. 3). Thus, *JAZF1* may be a new target for the prevention and treatment of atherosclerosis. However, there remain many problems to be investigated. (i) *JAZF1* is most highly expressed in AT. *JAZF1* also suppresses atherosclerosis development by reducing AT inflammation via limiting the macrophage and T-cell populations and their antigen presentation functions. However, strategies for targeting *JAZF1* expression in AT need to be investigated. (ii) *LXRE* and *CRE* sites are present in many cytokine and lipid metabolism gene promoters (Table 2). *JAZF1* may regulate the expression of these genes by regulating *LXRE* and *CRE* sites. However, only *SREBP-1c* and *HMGCR* have been investigated. (iii) *JAZF1* is a corepressor of *TR4*. The *TR4-FATP1* and *TR4-CD36* axes reduce lipid accumulation, but the role of *JAZF1* in these axes has not been investigated. (iv) *JAZF1* SNPs are associated with T2DM and insulin resistance (IR)-related diseases in humans.[102] The rs864745 SNP of *JAZF1* is associated with atherosclerosis. However, the role of other *JAZF1* SNPs in atherosclerosis has not been investigated. (v) The noncoding RNA *circPTK2* can promote lipolysis and decrease adipogenesis by regulating the *miR-182-5p-JAZF1* axis and may be used as a diagnostic marker of cachexia.[103] However, the role and mechanism of *circPTK2* in atherosclerosis have not been investigated. (vi) *miR-19b-3p* is transferred by macrophage-derived extracellular vesicles (M-EVs) into VSMCs and then promotes VSMC migration and proliferation to induce atherosclerosis development by targeting *JAZF1*, which suggests that *JAZF1* is expressed in M-EVs and is a target gene of *miR-19b-3p*.[104] However, the roles of *JAZF1* in M-EVs in AT, lipid metabolism, and immune and inflammatory responses have not been investigated. (vii) *JAZF1-AS1*, which is a long noncoding RNA, is located upstream of *JAZF1* in overlapping head-to-head gene pairs. *JAZF1-AS1* promotes *JAZF1* expression by forming double-stranded RNAs. However, *JAZF1* does not affect *JAZF1-AS1*.[105] The role and mechanism of *JAZF1-AS1* in atherosclerosis have not been investigated. (viii) *JAZF1*-overexpressing transgenic mice exhibit reduced atherosclerosis risk factors and atherosclerosis development. However, these mice also show heart failure symptoms. The safety of *JAZF1* overexpression *in vivo* requires extensive evaluation. (viiii) *JAZF1* exerts antiatherosclerotic effects *in vitro* and in animal studies. However, human studies are relatively lacking, and an evaluation of the effects on humans is needed. We thus

hope that more scientists will focus on the potential roles of *JAZF1* in AT and atherosclerosis and identify new therapeutic targets for this disease.

Author contributions

WC and YZ participated in writing-original draft, supervision, and resources. YY, MZ, and WH participated in formal analysis, and investigation. NL and DX participated in conceptualization, writing-review & editing, project administration, and funding acquisition. All authors read and approved the final version of the manuscript.

Conflict of interests

The authors declare that they have no competing interests.

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Abbreviations

ABCA1 ATP-binding cassette transporter A1
ACC acetyl—coenzyme A carboxylase
ACSL3 long-chain acyl-CoA synthetases 3
AKR1C4 3alpha-hydroxysteroid dehydrogenase
Angptl3 angiopoietin-like protein 3
Arl4c ADP ribosylation factor-like GTPase 4C
aP2 adipocyte fatty acid-binding protein
Arg-1 arginase-1
AT adipose tissue
ATGL adipose triglyceride lipase
ATM adipose tissue macrophage
CD206 mannose receptor
CETP cholesteryl ester transfer protein
CHD coronary heart disease
CH25H cholesterol 25-hydroxylase
COL3A1 fibrotic gene collagen type III alpha 1
CRE cAMP responsive element
CYP7A1 cholesterol 7-alpha-hydroxylase
C/EBPα CCAAT/enhancer-binding protein α
FABP4 fatty acid-binding protein 4
FAs fatty acids
FAS fatty acid synthetase
FATP1 fatty acid transport protein 1
GCLM glutamate-cysteine ligase modifier subunit
GST glutathione S-transferase
HFD high-fat diet
HO-1 heme oxygenase-1
HSL hormone-sensitive lipase
IFN-γ interferon γ
IL-1R IL-1 receptor
IL-6 interleukin-6
I-BABP ileal bile acid-binding protein
JAZF1 juxtapose with another zinc finger gene 1
LPCAT3 lysophosphatidylcholine acyltransferase 3
LPL lipoprotein lipase
LXREs liver X receptor response elements
MCP-1 monocyte chemotactic protein 1
MIG12 midline-1-interacting G12-like protein
MMe metabolically activated macrophage
Mox oxidized macrophage
Nox2 NADPH oxidase-2
Nrf2 NF-E2-related factor 2
NR2C2 nuclear receptor subfamily 2, group C, member 2
Ostalpha/beta organic solute transporter alpha/beta
Ox-PL oxidized phospholipid
PLIN2 perilipin 2
PLTP phospholipid transfer protein
RELMβ collagen, resistin-like molecule β
ROS reactive oxygen species
SCD-1 stearoyl CoA desaturase-1
SNP single nucleotide polymorphism
sPLA2 group IIA secretory phospholipase A2
SREBP-1c sterol regulatory element-binding protein 1c
Srnx-1 sulfiredoxin-1
Sult1e1 sulfotransferase family 1E
TAK1 transforming growth factor β-activated kinase 1
Tc1 T cytotoxic 1
TNF-α tumor necrosis factor-α
TR4 testicular orphan nuclear receptor-4
Txnrd-1 thioredoxin reductase-1
T2DM type 2 diabetes mellitus
UGT1A3 UDP-glucuronosyltransferase 1A3
VEGF vascular endothelial growth factor
α-TTP α-tocopherol transfer protein

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