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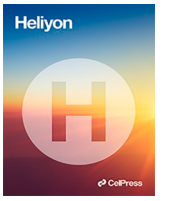

Review article

Caveolin-1 in endothelial cells: A potential therapeutic target for atherosclerosis

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ABSTRACT

Atherosclerosis (AS) is a chronic vascular disease characterized by lipid accumulation and the activation of the inflammatory response; it remains the leading nation-wide cause of death. Early in the progression of AS, stimulation by pro-inflammatory agonists (TNF-α, LPS, and others), oxidized lipoproteins (ox-LDL), and biomechanical stimuli (low shear stress) lead to endothelial cell activation and dysfunction. Consequently, it is crucial to investigate how endothelial cells respond to different stressors and ways to alter endothelial cell activation in AS development, as they are the earliest cells to respond. Caveolin-1 (Cav1) is a 21-24-kDa membrane protein located in caveolae and highly expressed in endothelial cells, which plays a vital role in regulating lipid transport, inflammatory responses, and various cellular signaling pathways and has atherogenic effects. This review summarizes recent studies on the structure and physiological functions of Cav1 and outlines the potential mechanisms it mediates in AS development. Included are the roles of Cav1 in the regulation of endothelial cell autophagy, response to shear stress, modulation of the eNOS/NO axis, and transduction of inflammatory signaling pathways. This review provides a rationale for proposing Cav1 as a novel target for the prevention of AS, as well as new ideas for therapeutic strategies for early AS.

1. Introduction

Atherosclerosis (AS) is the most common form of cardiovascular disease (CVD); it is a chronic inflammatory vascular disorder characterized by lipid-rich plaques in the arterial wall and is a common pathological precursor for many cardiovascular diseases. CVD is clinically prevalent in older adults, and the proportion of older patients has gradually increased with the aging population in many countries [1–3]. However, in recent years, a CVD trend has become apparent for younger age groups; in particular, there has been a progressive increase in the proportion of young women admitted with acute myocardial infarction [4]. Although the incidence of AS has decreased in some countries, it remains the leading cause of death worldwide [5].

The main components of AS are lipid accumulation and inflammatory activation in large arteries; lesions occur mainly in medium or large arteries where they are located preferentially at bifurcations and bends with oscillating shear stress and low shear stress, leading to phenotypic changes in endothelial cells (e.g., inflammation) [6]. Endothelial cell dysfunction (ECD) allows LDL and triglyceride-rich lipoproteins (TGRL) to enter the endothelium and undergo enzymatic and oxidative modifications in the

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subendothelial space; when this occurs, the overlying endothelium is activated to express leukocyte adhesion factor (VCAM-1), which interacts with its cognate ligand very late antigen-4 (VLA4) to promote the rolling and adhesion of blood monocytes and lymphocytes to the endothelium and their migration towards the arterial intima [1].

As the intimal lesion progresses, mononuclear macrophages proliferate beneath the intima and become macrophage-derived foam cells that phagocytose lipids. Proliferating smooth muscle cells (SMCs) secrete collagen to form a layer of fibrous connective tissue called the fibrous cap, which has a stabilizing effect on atherosclerotic plaques; SMCs also secrete matrix metalloproteinases (MMPs) that promote plaque rupture and increase plaque instability [7]. Activation of the subintimal inflammatory cascade (e.g., Toll-like receptor (TLR), NOD-like receptor family pyrin domain containing 3 (NLRP3), and proprotein convertase subtilisin/kexin 9(PCSK9) pathways) due to innate and acquired immune responses combined with excessive cholesterol accumulation triggers foam cell and leukocyte apoptosis and necrosis, resulting in a necrotic core rich in cellular debris and lipids. As leukocyte recruitment continues and inflammation increases, the necrotic core expands reducing luminal blood flow by more than 50% and resulting in angina pectoris. When the fibrous cap of the necrotic core develops a gap or even breaks, coagulation factors contact thrombogenic material in the plaque through the gap to form a thrombus, which can trigger a heart attack; the thrombus can also travel to the brain and cause adverse clinical outcomes, such as stroke [3].

As the earliest cells to respond to AS, the endothelium is a single-cell layer with unique biological properties that separates the blood from its surrounding tissues; these cells are involved in vascular hemodynamics, modulation of cellular permeability, molecular substance transport, and innate immunity regulation and thus play a leading role in the pathogenesis of AS [8]. Resting endothelial cells resist blood leukocyte adhesion, and excessive lipoprotein deposition within the arterial intima can lead to endothelial cell structural damage and functional impairment. Consequently, maintaining endothelial cell homeostasis is essential for delaying the development of early AS.

In 1961, Palade was the first to discover many vesicles under the cell membrane and that they were involved in endothelial cell transport [9]. These very small spherical pit-like depressions in the cell membrane were thought to be intracellular caves (caveolae) [10]. In 1992, after nearly 30 years of research, Karen G. Rothberg used an anti-v-Src tyrosine kinase substrate antibody to identify a 22-kDa molecule that was part of the caveolae envelope in Rous sarcoma virus-transformed chicken embryonic fibroblasts. Rothberg first named this molecule caveolin. There are three known members of the caveolin family, caveolin-1 (Cav1), caveolin-2 (Cav2), and caveolin-3 (Cav3). Of these, Cav1 (also known as VIP21), a 21-24-kDa oligomeric cholesterol-binding membrane protein, was identified as essential for caveolae formation. The core component Cav1 is co-expressed with cavin1 (Cav1 adaptor protein) to form caveolae, which are unique plasma membrane depressions with an inverted omega (Ω) shape and sizes of 50–100 nm.

Since the discovery of caveolae, scientists have been exploring the physiological functions of these particular plasma membrane vesicles; they have been shown to play an important role in cell signaling, lipid regulation, and endocytosis through the construction of $Cav1^{-/-}$ gene-deficient mouse models [11–13]. Whether dependent or independent of caveolae function, Cav1 has been implicated in the pathogenesis of AS. This protein is an important regulatory molecule for many signals, and it can induce endothelial cell

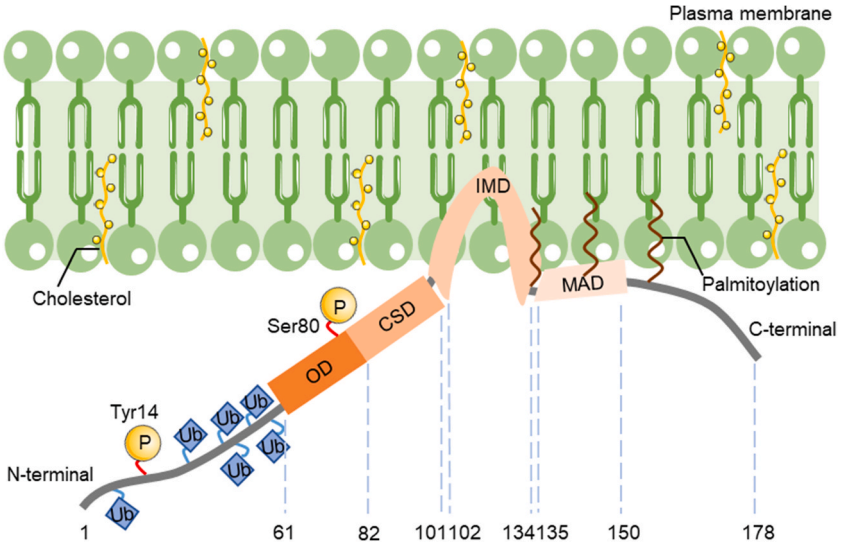

Fig. 1. Schematic representation of Cav1 with membrane topology. Cav1 is a membrane protein of 178aa in length with an IMD (102-134aa) inserted into the plasma membrane, and both the N and C termini are expressed in the cytoplasm to form a unique hairpin loop structure. Cav1 contains six lysine sites (Lys5/26/30/39/47/57) at the N terminus that can be modified for ubiquitination; it is modified by phosphorylation at the tyrosine 14 and serine 80 sites, with three palmitoylation sites (Cys133/143/156) in the C-terminal structural domain and MAD (135-150aa) for membrane insertion. Its OD (61-101aa) is an oligomeric structural domain directing the homo-zwitterionization of Cav1 molecules and hetero-oligomerization of cholesterol, fatty acids, and others. The CSD (82-101aa) is located within the OD structural domain and Cav1 exerts different biological functions by binding to different proteins through the CSD. OD, oligomerization domain; CSD, caveolin scaffolding domain; IMD, intramembrane domain; MAD, membrane attachment domain.

dysfunction through a variety of mechanisms. Lipoprotein uptake and transcytosis are essential components of AS progression. The link between Cav1 action on LDL/ox-LDL transcytosis and endothelial cell dysfunction is a topic of intense research, and Cav1 has been identified as a target of ox-LDL-induced endothelial dysfunction [14]. However, the mechanisms of autophagic regulation of Cav1 in AS and its effects on endothelial function through autophagy have yet to be elucidated, and there is limited agreement on its role as a signaling hub in response to hemodynamic changes and modulation of the inflammatory response. Therefore, this review focuses on the structure and physiological functions of Cav1 and recent developments regarding the regulatory mechanisms it plays in the early stages of AS lesions, particularly in endothelial cell autophagy, hemodynamic regulation, and in pro-inflammatory signaling. These data illustrate that Cav1 could be a target for the early prevention and treatment of AS and provide new ideas for disease treatment.

2. Structure and function of Cav1

2.1. Structure of Cav1

As the first member of the caveolin family to be studied, Cav1 is a 178-amino acid protein that is localized primarily to caveolae membranes; however, Cav1 is also localized to the plasma membrane to form non-caveolar scaffolds, and it has a broad intracellular membrane distribution, including the endoplasmic reticulum and late endosomal/lysosomal membranes, suggesting that Cav1 has functions independent of caveolae [15–19]. Cav1 has two isoforms, the slow-migrating 24-kDa (1–178 aa) Cav-1α and the fast-migrating 21-kDa (32–178 aa) Cav-1β; these isoforms have different N-terminal sequences, but both have identical C-termini, with Cav-1β lacking the N-terminal 31 amino acids so that only Cav-1α can be phosphorylated at tyrosine 14 [20,21].

Cav1 is localized primarily in caveolae on the membrane in its homo-oligomerized structure; for this structure, the N- and C-terminal regions of Cav1 are rich in hydrophilic amino acids and are thus expressed in the cytoplasm [22]. The intramembrane insertion of a 102–134 aa hydrophobic segment allows Cav1 to form a unique hairpin ring structure (Fig. 1). Biotinylation studies have failed to successfully label Cav1, demonstrating that all of its components are not outside the cell membrane and all of its functions should thus be derived from its cytosolic and intracellular parts [23,24]. Cav1 consists of five main components, namely, the N-terminal, the oligomerization domain (OD) at 61–101 aa, which contains the caveolin scaffold domain (CSD) at 82–101 aa, the intramembrane domain (IMD) at 102–134 aa, the membrane attachment domain (MAD) at 135–150 aa and the C-terminal. In these domains, the CSD and MAD bind to the membrane through their high membrane affinity to form the membrane attachment structure of Cav1. However, Cav1 membrane insertion depends on the IMD and the three palmitoylation sites at the C-terminus [24–26]. The N terminus contains two phosphorylation sites at tyrosine 14 and serine 80, as well as six ubiquitination sites (Lys5/26/30/39/47/57), and the C terminus contains three palmitoylation sites (Cys133/143/156) [25].

The CSD directs mainly the homodimerization of Cav1 molecules to form high molecular weight complexes with the same relative stoichiometric ratio or maintain structural stability by heterodimerization with fatty acids and cholesterol [23,25]. In addition, the CSD is a highly conserved sequence responsible for membrane adhesion and mediating protein-protein interactions [15,16,27]. Most proteins that can interact with Cav1 share a common Cav1-binding motifs (CBMs, ΦXXXXΦXXΦ and ΦXΦXXXXΦ, where Φ represents an aromatic amino acid, and X is any nonaromatic amino acid) [24]. Different proteins bind to Cav1 through the CBM (caveolin binding domain) with different physiological effects.

2.2. Overview of the physiological roles of caveolae and Cav1

Caveolae are plasma membrane sensors; each caveola consists of approximately 140–150 Cav1 molecules, and caveolae comprise 30% of the total surface area of capillary endothelial cells. The CSD of Cav1 interacts with a variety of signaling molecules located in caveolae to regulate signaling pathways, including endothelial nitric oxide synthase (eNOS), epidermal growth factor receptor (EGFR), Src family tyrosine kinases, and G proteins [11,25,28,29]. Early, it was demonstrated that Cav1 negatively regulates eNOS by binding to it and that only caveolar Cav1 exerts this negative regulatory effect; correspondingly, the interaction of non-caveolar Cav1 with eNOS markedly lower [30]. Previously, it was shown that Cav1 binding to eNOS leads to reduced NO production, which increases LDL infiltration into the arterial wall, as well as inflammatory factor expression, which in turn exacerbates the atherosclerotic process. However, studies using $Ldlr^{-/-}eNOS^{-/-}$, $Ldlr^{-/-}Cav1^{-/-}$, and $Ldlr^{-/-}Cav1^{-/-}eNOS^{-/-}$ mouse models demonstrate that eNOS deficiency did not significantly affect the atheroprotective effect observed in Cav1-deficient mice, suggesting that the atheroprotective effect of Cav1 deficiency is independent of increased NO [31] and probably acts through natural attenuation of LDL transcytosis and vascular inflammation. Inflammation regulation by Cav1 is bidirectional. Cav1 downregulation in macrophages increases production of the LPS-induced pro-inflammatory cytokines TNF-α and IL-6, yielding anti-inflammatory effects [32], but when phosphorylated at Tyr14, Cav1 can mediate inflammation by interacting with TLR4 [33].

2.2.1. Cav1 and lipid metabolism

Cav1 is also a cholesterol and fatty acid binding protein that is closely associated with membrane lipids and plays an important role in lipid metabolism. Caveolae are specific lipid rafts composed of cholesterol, Cav1, and sphingolipids, and the number of caveolae is proportional to the amount of cholesterol ingested by the body. Cav1 is thought to primarily regulate cholesterol transport and accumulation by cells, and increased cholesterol efflux was found in aortic endothelial cells overexpressing Cav1 due to ATP-binding cassette transporter-1 (ABCA1) expression upregulation [34]. At the same time, Cav1 expression increases triglyceride formation and storage and protects cells from fatty acid-induced toxic effects [35]. A Cav1 knockout mouse model has been developed and has a relatively lean phenotype with altered circulating lipid homeostasis and insulin resistance; in fact, these mice have increased plasma

triglyceride and high-density lipoprotein levels and reduced hepatic very low density lipoprotein secretion levels, as well as weak lipolytic activity [36–38]. The high plasma triglyceride levels may be due to reduced insulin-dependent lipid storage or reduced hepatic cholesterol uptake [13]. Postprandial lipid metabolism status was also altered. For example, plasma free fatty acids (FFAs) decreased during fasting and increased after meals, and circulating plasma FFAs increased further in Cav1 knockout mice after high-fat diet feeding; plasma non-esterified fatty acids were lower in Cav1 knockout mice on a chow diet than control wild-type (WT) mice [38, 39]. These data suggest a role for Cav1 in maintaining lipid homeostasis. Furthermore, Cav1 deficiency reduced LDL uptake by aortic endothelial cells, making it a potential therapeutic target for AS [40–42].

2.2.2. Cav1 and endocytosis

Caveolae are recognized for their role in endocytosis, also known as caveolae-mediated endocytosis (CavME); this process is independent of clathrin-mediated endocytosis (CME), and the endocytic cargo is mainly cholesterol, albumin, neurospherin glycolipids, and integrins [43,44]. Caveolae budding from the plasma membrane form vehicles for endocytosis, and the budding process is dependent on membrane cleavage of the GTPase dynamin [45]. Cav1 endocytosis relies on actin filaments and actin regulatory proteins and is regulated by dynamin 2 (Dyn2). With the help of actin filaments and microtubules, vesicles are formed and then cut off from the membrane by dynamin; after which, the caveolar-like vesicles are transported intracellularly [17]. After the endocytosis of albumin, lipids, thyroxine transporter proteins, and various membrane proteins, the cargo is not usually degraded by lysosomal fusion; instead, the contents are released to the other side of the cell membrane by cellular transport, a process called transcytosis (an endocytic pathway). This property of CavME could provide new options for nanotherapeutic transport and blood-brain barrier crossing [43,46]. Additionally, CavME has been shown to be involved in the infection process of vaccine vectors. Recently, human adenovirus type 26 (HAdV26) infection of cells containing high levels of αvβ3 integrins was revealed to be dependent on Cav1, which is the limiting factor for HAdV26 infection [47]. In addition, Cav1 penetration, with its excess albumin phagocytosis and lipid transcytosis, could be a target to explore for pathological states such as microalbuminuria and subendothelial lipid deposition [48,49].

2.2.3. Cav1 and mechanical sensing

Caveolae are thought to act as mechanosensors and mechanotransducers in the vascular endothelium. Under physiological levels of shear stress, the vasculature of $Cav1^{-/-}$ knockout rats produced only 38% of the vasodilatory response of WT rats, suggesting that caveolae may be mechanosensors transmitting the effects of shear stress. Furthermore, all three vasodilatory pathways (NO, PG, EETs) lost their response to shear stress in the absence of caveolae; shear stimulation failed to induce an increase in intracellular Ca^{2+} in endothelial cells, further demonstrating that shear stress-induced coronary artery dilation is caveolae-dependent [50]. Caveolae form special membrane vesicles that reduce fluid shear stress within them, thereby protecting their internal mechanosensitive receptors from continuous exposure to fluids that diminish endothelial cell responses to stimuli [51]. Caveolae are also thought to act as a surface reserve for the plasma membrane. In this manner, they provide some mechanical function through "caveolae flattening", which rapidly increases the cell surface area allowing dynamic endothelial cell surface area changes to protect the plasma membrane from mechanical stimuli [52]. Recently, it has been shown that Cav1 possesses mechanical adaptability independent of caveolae. Unlike caveolae that 'flatten' under stress, ultrastructural studies have revealed that Cav1 can form invaginated "dolines" of different diameters in the absence of Cavin-1/PTRF, forming Cav1 clusters to offer cellular mechanical protection upon plasma membrane tension [53].

2.2.4. Summary

Cav1 has been implicated in the pathogenesis of many diseases, including cardiovascular diseases (e.g., AS and pulmonary hypertension), metabolic diseases (e.g., diabetes and metabolic syndrome), tumor invasion, and chronic kidney disease, due to its roles in signaling pathway transduction, endocytosis, and lipid metabolism [15,39,54–56]. Recently, Cav1 has also been shown to be negatively associated with ferroptosis. In fact, Cav1 overexpression plays a protective role in ferroptosis-induced diabetes-associated cognitive dysfunction (DACD) [57], while Cav1 inhibits ferroptosis in tumor cells (e.g., head and neck squamous cell carcinoma, HNSCC), leading to poor prognosis [58]. Additionally, Cav1's unique roles in protecting endothelial cells from senescence, bacterial toxins, and tumor radioresistance have recently been demonstrated [59–61].

3. Effect of Cav1 on endothelial cells in AS

3.1. Modulation of endothelial cell autophagy by Cav1

3.1.1. AS and autophagy

Autophagy is a highly conserved cellular recycling mechanism that degrades cytoplasmic components, including damaged organelles, misfolded protein aggregates, lipid droplets, and pathogenic microorganisms, through the lysosomal system [62]. These degraded components are recycled to provide energy during periods of cellular nutrient deprivation and metabolic substrates such as glucose, proteins, and lipids. The process of autophagy, therefore, plays a role in maintaining intracellular homeostasis. Autophagy levels have been shown to progressively decrease with age, while autophagy defects can lead to increased risk of spontaneous cardiovascular disease [63,64].

There are three types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy [63]. The process of autophagy is usually triggered by stress factors, such as energy deprivation and hypoxia [65], and begins with the production of double-membrane phagocytic vesicles. These wrap around to form autophagic vesicles to engulf and sequester cytoplasmic contents

and eventually fuse with lysosomes, where acidic proteases and hydrolases degrade autophagic vesicles to recycle their internal cargo [66,67]. In an ATG5$^{-/-}$ knockout mouse model of autophagy deficiency, increased atherosclerotic plaque formation and premature signs of aging were found [68,69]; these effects were possibly due to the autophagy deficiency. Decreased insulin sensitivity and increased levels of oxidative stress were also evident in this mouse model. Deficiency of the autophagy proteins ATG16L1 and ATG5 is associated with increased inflammatory factor and cell adhesion molecule (e.g., IL-1β and platelet endothelial cell adhesion molecule-1 [PECAM-1]), increased occurrence of abnormal structures at endothelial cell contact sites and increased neutrophil penetration leading to endothelial cell dysfunction [68,70]. ATG14 overexpression promotes the fusion of macrophage autophagic vesicles and lysosomes through increased binding to syntaxin 17; this effect promotes lipid degradation, regulates Treg cell populations, and reduces apoptosis, thereby slowing AS [71]. Ultimately, a moderate level of autophagy is thought to be beneficial in the progression of AS due to its regulation of inflammation and mediation of macrophage cholesterol transport [66,68,71].

Deficiency of other types of autophagy, such as chaperone-mediated, has also recently been shown to increase pro-inflammatory

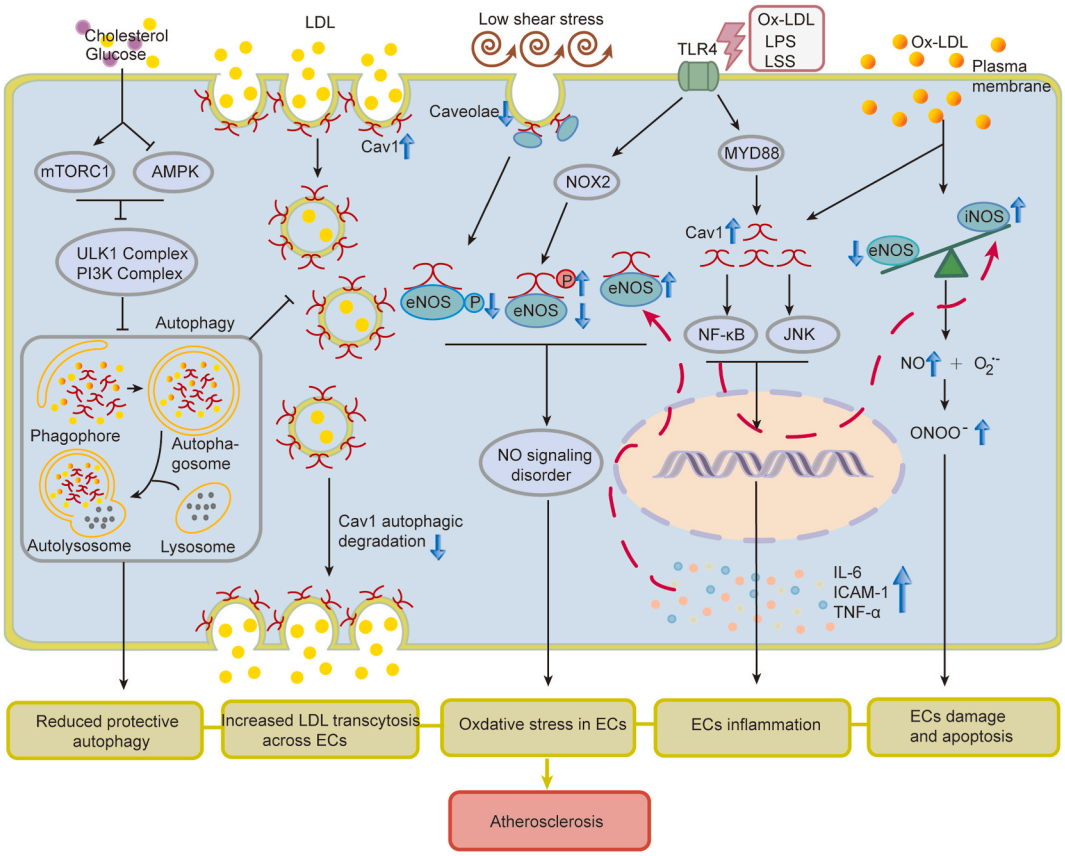

Fig. 2. Mechanism of Cav1 induced endothelial dysfunction leading to AS. The main features of atherosclerosis are lipid accumulation and chronic inflammatory activation. When endothelial cells sense nutrient depletion, they activate mTORC1 signaling and inhibit AMPK signaling, thereby inhibiting the formation of ULK1 and Class III PI3K complexes, preventing the formation of autophagic phagocytic vesicles and thus inhibiting autophagy, resulting in reduced levels of protective intracellular autophagy to degrade excess cholesterol and damaged organelles, and reduced degradation of Cav1 through reduced autophagy, leading to increased LDL transcytosis across the endothelial cells. When endothelial cells respond to shear stress stimulation leading to a decrease in glycocalyx and a decrease in caveolae, the co-localization of caveolae with eNOS-pS1177 is impaired thereby attenuating NO signaling. Activation of TLR4 by LSS and thus NOX2 induces an increase in Cav1 phosphorylation leading to eNOS inactivation, while inflammatory cytokines induce inflammation in endothelial cells upregulating eNOS signaling leading to a massive accumulation of NO leading to a state of oxidative stress in endothelial cells. Activation of the TLR4-MyD88 axis by LPS increases Cav1 expression, promoting the downstream NF-κB inflammatory signaling pathway. At the same time, Cav1 also mediates the activation of the JNK signaling pathway after Ox-LDL treatment, and the increased release of inflammatory cytokines such as IL-6, ICAM-1, and TNF-α leads to an inflammatory state in endothelial cells. Ox-LDL disrupts the balance between eNOS and inflammation-induced iNOS in endothelial cells and increases NO overproduction in response to superoxide anion ($O_2^{\cdot-}$) to produce peroxynitrite ($ONOO^-$); meanwhile, Ox-LDL can activate Cav1 expression through TLR4 signaling to induce NF-κB ectopic entry into the nucleus to regulate iNOS transcription, leading to increased endothelial cell injury and apoptosis. In conclusion, endothelial cell dysplasia induces endothelial cell dysfunction, promoting early atherosclerosis formation. mTORC1: mechanistic target of rapamycin complex 1; AMPK: AMP-activated protein kinase; PI3K: phosphoinositide 3-kinase; ULK1: unc-51 like autophagy activating kinase 1; eNOS: endothelial nitric oxide synthase; iNOS: inducible nitric oxide synthase; TLR4: Toll-like receptor 4; LSS: low shear stress; NOX2: NADPH oxidase 2; MYD88: myeloid differentiation primary response 88; LPS: lipopolysaccharide; JNK: c-Jun N-terminal kinase; ox-LDL: oxidized LDL; IL-6: Interleukin 6; ICAM, intercellular cell adhesion molecule; TNF-α: tumor necrosis factor alpha; NF-κB, nuclear factor kappa-B.

factor levels through NLRP3 inflammasome activation, thereby promoting atherosclerotic inflammatory progression [72]. Although the molecular mechanisms linking autophagy to AS progression are not yet fully elucidated, this evidence suggests that autophagy may be a valuable drug target for treating this disease.

3.1.2. Cav1 and autophagy

Cav1-deficient rats and cell models exhibit increased levels of plasma 8-isoprostane (8-OHdG), reactive oxygen species (ROS), and autophagy in response to redox stress [73,74]. These data tentatively suggest that Cav1 plays an important role in regulating oxidative stress and autophagy in endothelial cells. However, the regulation of autophagy by Cav1 and resulting beneficial system effects remain controversial, with most studies suggesting that Cav1 negatively regulates autophagy [75–77]. For example, it has been reported that Cav1 reduces fibroblast activation by inhibiting P62-mediated autophagy, thereby reducing intestinal fibrosis in patients with Crohn's disease [78]. Upon aflatoxin B1 (AFB1) stimulation, Cav1 inhibits autophagy by regulating the EGFR/PI3K-AKT/mTOR pathway and promotes AFB1-induced oxidative stress and apoptosis in hepatocytes, increasing hepatotoxicity [79]. The mechanism by which Cav1 inhibits autophagy has also not been fully elucidated. Previous studies have indicated that Cav1 deficiency inhibits insulin and lipolytic responses, thereby inducing adipocyte autophagy [80]. This is similar to the mechanism through which starvation induces cellular autophagy. In addition, Cav1 deletion in the tumor microenvironment promotes the infiltration of multiple types of inflammatory cells and oxidative stress-induced autophagy in fibroblasts [81]. A direct competitive interaction between Cav1 and autophagy-associated proteins ATG5 and ATG12 was recently reported. Upon starvation or knockdown of Cav1, Cav1 dissociates from autophagy-related proteins, and the ATG5-ATG12 complex is formed, activating the autophagic process, which becomes a mechanism by which Cav1 inhibits autophagy [82].

In contrast, autophagy-promoting effects of Cav1 have also been reported in the literature [83]. Cav1 activates mitochondrial autophagy via the PINK-1/Parkin pathway and inhibits the Akt/mTOR signaling pathway to activate autophagy to reduce hepatic lipid accumulation [84,85]. Under cellular oxidative stress conditions, Cav1 acts as an anchoring protein to recruit BECN1 and ATG proteins to the mitochondria to initiate autophagy and reduce ischemic cell injury in the brain [86]. Cav1 has different functions in the autophagic process, and its regulation of autophagy may depend on the cell type and differences in cellular loading status. In tumor cells, Cav1 deletion and disruption of the associated lipid rafts act independently of caveolae, activating lysosomal function and autophagy as a survival mechanism for cancer cells in a starved state [87]. Cav1 knockdown inhibits Parkin-mediated mitochondrial autophagy and increases cisplatin-induced mitochondrial damage to maintain chemosensitivity in A549 lung cancer cells [88]. Cav1 phosphorylation can also affect triple-negative breast cancer cell proliferation via interaction with mitofusin 2 and dynamin related protein 1, proteins essential for forming the PINK1/Parkin complex; this prevents the initiation of mitochondrial autophagy [89]. Consequently, the negative regulation of autophagy by Cav1 may be a mechanism to hinder tumor survival in the microenvironment and increase cancer chemoradiotherapy sensitivity [90].

3.1.3. Cav1 and autophagy in AS

LDL particles are approximately 20–30 nm in diameter, much larger than the adjacent intercellular gap in the endothelium (3–6 nm), and the LDL receptor (LDLR)-mediated pathway is downregulated upon high LDL concentrations. Therefore, LDL particle transport in the endothelium is largely LDLR-independent and requires caveolae-mediated transcytosis (Fig. 2) [14,91]. Autophagic regulation of Cav1 can directly affect lipoprotein transcytosis via Cav1 degradation, and Cav1 regulation of autophagy can indirectly affect AS by modulating inflammation and endothelial cell function. Autophagic degradation of Cav1 has currently been demonstrated in a variety of cellular models, such as palmitic acid-induced autophagic degradation of Cav1 in astrocytes, where Cav1 reduction is blocked by the autophagy inhibitor 3-MA or the lysosomal inhibitor CQ and reversed by knockdown of ATG5 and ATG7 [92], A549 induces autophagic degradation of Cav1 under hypoxia [93], and Sirt6 deacetylates Cav1 in human umbilical vein endothelial cells and triggers its autophagic degradation under hyperglycaemic conditions [94].

Some research has revealed that Cav1 and Cavin1 knockdown activates autophagy in endothelial cells. Cav1 on the cell membrane can translocate to the cytoplasm and be degraded by autophagy as an autophagic cargo receptor, reducing the number of caveolae on the cell membrane that mediate LDL transcytosis; consequently, subendothelial lipoprotein retention is reduced, and early atherosclerotic phenotype formation is prevented. Different regions of Cav1 were found to possess different autophagic functions; the caveolin scaffold domain (CSD) of Cav1 interacts with the CBM domain of LC3 to inhibit autophagy, whereas the intramembrane domain (IMD) of Cav1 may interact with LC3 as an autophagic degradation cargo receptor to activate autophagy. When Cav1 mediates LDL transcytosis within the caveolae, the IMD of Cav1 is concealed within the membrane, and therefore Cav1 can only bind to LC3B via its CSD to exert autophagy inhibition. When Cav1 translocates to the cytoplasm, IMD exposure offers the opportunity to bind to LC3B and thus mediate the autophagic degradation of Cav1. During high glucose stimulation, the AMPK-MTOR-PIK3C3 pathway inhibits the autophagic degradation of Cav1 and disrupts the interaction between IMD and LC3B on Cav1, followed by more LC3B binding to CSD on Cav1 leading to autophagy inhibition, further exacerbating the degree of autophagy inhibition and forming a feedback loop to advance the development of early AS [42]. Another study showed that salidroside treatment prevented atherosclerotic plaque formation by activating the AMPK pathway to initiate autophagy, resulting in c-Cbl, p-Src, and Cav1 recruitment to lysosomes for degradation and reduced production of both phosphorylated and non-phosphorylated Cav1, ultimately reducing LDL transcytosis [95]. Consistent with this finding, it has been reported that Sirt6 is a deacetylase that activates endothelial cell autophagy, that the level of sirt6 translocated from the nucleus to the cytoplasm for Cav1 deacetylation was reduced under high glucose treatment, preventing Cav1 from being bound by LC3B in its maintained acetylated state thereby decreasing autophagic degradation, and that Sirt6-mediated Cav1 degradation was not dependent on the ubiquitin-protease vesicle degradation pathway. Ultimately, increased Cav1 levels promote lipoprotein transcytosis and accelerate the atherosclerotic process [94]. Zhang et al. recently used high-fat diet-fed Cav1$^{-/-}$,

Ldlr$^{-/-}$, and Cav1$^{-/-}$ Ldlr$^{-/-}$ mouse models to demonstrate that Cav1 deficiency promoted aortic endothelial cell autophagy and prevented atherosclerotic progression by reducing vascular inflammation and macrophage infiltration in the arterial wall [96]. It has recently been reported that Cav1 and caveolae possessed AS pathogenic effects in NO-independent functions, i.e., the lack of eNOS did not significantly affect the AS-protective effect observed in Cav1-deficient mice, and Cav1 deletion more likely exerted an AS-protective influence by attenuating LDL transport and atherogenic fibronectin deposition in endothelial cells and interfere with flow-mediated endothelial cell inflammation [31]. These studies all demonstrate autophagy's vital role in Cav1 regulation and, thus, in Cav1-mediated lipoprotein endothelial cell transcytosis in the progression of AS.

Negative regulation of autophagy by Cav1 can also indirectly influence the inflammatory process and limit endothelial cell function. Autophagic activation of endothelial cells negatively regulates the expression of cell adhesion molecule PECAM-1 and reduces the occurrence of abnormal structures at endothelial cell contact sites, thereby inhibiting neutrophil infiltration during inflammation and alleviating endothelial cell damage [70]. Low shear stress generated at arterial branch points can inhibit endothelial mitochondrial autophagy via the Cav1/miR-7-5p/Sequestosome 1 (SQSTM1) signaling pathway, leading to impaired mitochondrial function, aggressive ROS production, and endothelial oxidative stress and dysfunction [97]. Mitochondrial autophagy has been shown to exert protective effects on vascular endothelial cells due to timely removal of damaged mitochondria and reduced mtROS production [98,99]. Metabolic diseases such as AS and diabetes mellitus have varying degrees of endothelial dysfunction, so Cav1 regulation of mitochondrial autophagy via PINK1/Parkin has implications for maintaining endothelial cell homeostasis and delaying disease progression.

3.2. Hemodynamic regulation of endothelial cells by Cav1

3.2.1. Cav1 and shear stress

The hemodynamic regulation of the endothelial cells refers primarily to the endothelium response to vascular lumen diameter and tension and vascular blood flow direction, velocity, viscosity, and shear stress. Shear stress is considered one of the key hemodynamic determinants of endothelial function. In fact, it is a potent endothelium-dependent physiological vasodilator signal, primarily involving endothelium-dependent vasodilators, including NO, prostacyclin (PGI2), and endothelium-derived hyperpolarizing factors (EDHFs) [50,100]. Shear stress (SS) refers to the force per unit area generated by the tangential force of blood flow acting on the endothelial surface, and it is generally greater in arteries (10 dyn/cm^2 to 40 dyn/cm^2) than in veins (1 dyn/cm^2 to 6 dyn/cm^2) [52,101]. In arteries, the flow at the arterial trunk is high laminar SS (HSS), a stable laminar flow with anti-atherosclerotic effects due to inhibiting oxidative stress and inflammation in the vessel wall. Its counterpart is low shear stress (LSS), a localized flow with disturbed turbulence (e.g., non-uniform, irregular oscillation) that usually occurs at bifurcations, curves, and stenoses of arteries; LSS is prevalent in AS-prone areas [102]. Endothelial cells can translate hemodynamic forces into intracellular signaling events. As such, hemodynamics can induce different endothelial cell responses to adverse conditions, such as dyslipidemia, hypertension, and diabetes, and induce endothelial-specific sites of atherosclerotic susceptibility [103].

Caveolae have been shown to play an important regulatory role as mechanosensors in the endothelium-dependent dilation of coronary arteries induced by physiological shear stress. Cav1$^{-/-}$ knockout mice exhibit abnormal endothelial function and impaired vasodilator and blunted intracellular Ca^{2+} responses to SS [50]. An in-depth mechanistic study showed that caveolae-transient receptor potential vanilloid 4 (TRPV4)-KCa2.3 (SK3) signaling is also involved in regulating arterial vasodilation via tangential stress, where SS activation of TRPV4 channels induces TRPV4 translocation to caveolae and TRPV4-mediated Ca^{2+} influx into endothelial cells activates SK3 channels, thereby promoting endothelium-derived relaxing factor production [100]. This study further suggests that caveolae are important factors in the regulation of arterial vascular dynamics. Under pathological conditions, on the one hand, SS leads to decreased plasma membrane cholesterol levels that affect downstream signaling, and some studies have shown that LSS leads to decreased caveolae in the glycocalyx and decreased caveolae invagination. The diffuse localization is consistent with this conclusion, suggesting that caveolae exert a mechanosensory effect in response to SS intervention and that SS-induced increases in mitochondrial ATP synthesis induce mitochondrial oxidative phosphorylation, which may be associated with a decrease in caveolae. LSS-induced decreases in caveolae reduce the expression of eNOS-pS1177, the active form of eNOS, disrupting caveolae-eNOS-pS1177 co-localization to attenuate NO signaling (Fig. 2) [104]. Moreover, by activating Erk1/2 phosphorylation, VSMC proliferation and migration are promoted [105]. LSS also induces NADPH oxidase 2 (NOX2) by activating TLR4, which causes Cav1 phosphorylation and thus inactivates eNOS to cause oxidative stress in endothelial cells (Fig. 2) [106]. On the other hand, Cav1 also plays a role in LSS-induced inflammatory signaling. LSS induces pSMAD1/5 signaling by promoting the accumulation and endocytosis of ALK1 and endoglin in early endosomes (EEs) of Cav1-containing cells and the subsequent transcription of inflammatory genes to accelerate AS [107]. Cav1 deletion leads to reductions in SMAD1/5, making it a potentially interesting target for treating early AS. In conclusion, Cav1 regulation in hemodynamics is indeed complex and contradictory. Under physiological shear stress, Cav1 acts as a mechanosensor to maintain vascular dilation and endothelial homeostasis. Under adverse conditions, Cav1 acts as a signaling hub to induce the expression of downstream pro-inflammatory signaling pathways and inhibit NO signaling, leading to endothelial dysfunction; in this way, Cav1 could play a role in promoting AS.

3.2.2. Cav1 and the eNOS/NO system

To maintain normal arterial tone and tangential stress, endothelial cells also produce a variety of bioactive substances, such as the vasodilators NO and endothelial hyperpolarizing factor, as well as the vasoconstrictors angiotensin II, endothelin, and superoxide anion [8]. Among these, NO is a well-known endothelial molecule with vasodilatory effects that plays an important role in regulating vascular endothelial cell survival and angiogenesis. Under physiological conditions, endothelial cells produce basal levels of NO to

regulate vasodilatory tone. However, under pathological conditions, NO production can limit the endothelial cell activation induced by inflammatory factor biomechanical stimulation; NO can also inhibit new endothelium proliferation and monocyte adhesion, regulate platelet thrombosis and fibrinolysis, and limit atherogenic LDL oxidation, thus exerting vasoprotective effects [52,108]. NO is produced mainly by vascular endothelial cells through L-arginine metabolism by endothelial nitric oxide synthase (eNOS), with L-citrulline as a by-product [109]. eNOS has a complex regulatory system. First, eNOS gene transcription is regulated by fluid mechanical forces. When cells are exposed to laminar flow for prolonged periods, eNOS transcription is upregulated, which increases the capacity for EC-dependent NO formation. Second, eNOS is regulated by its membrane localization and is enriched specifically in the caveolae of endothelial cells. Cav1 (in the caveolae) acts as a negative regulatory molecule and binds eNOS through the CSD domain to maintain its inactive conformation, thus reducing NO production [110]. Specifically, in unstimulated endothelial cells, eNOS possesses three acyl anchors due to myristoylation and palmitoylation modifications that target and tightly attach to caveolae microdomains [111]. Cav1 then prevents the calmodulin complex (CaM) from binding to eNOS. This inhibition blocks electron transfer from NADPH to eNOS. When the cell is stimulated by blood flow or acetylcholine (Ach), which triggers the inward flow of Ca^{2+} to bind CaM, eNOS progressively dissociates from Cav1 to bind CaM, and the blocked electron flow from NADPH is restored to release NO [112].

$Cav1^{-/-}$ mouse models exhibit enhanced Ach-induced arterial relaxation and impaired vasoconstrictor responses to phenylephrine (PE). $Cav1^{-/-}$ knockout cells with defective caveolae formation also exhibit higher NO release and 3-fold higher levels of cyclic guanosine monophosphate (cGMP), a downstream component of NO; these models demonstrate the involvement of Cav1 and caveolae in NO pathway regulation [11,12]. The 894T eNOS gene mutation is considered an independent risk factor for carotid AS [113]. Numerous studies have shown that ox-LDL negatively regulates eNOS via Cav1. Furthermore, eNOS interacts with only phosphorylated Cav1, and ox-LDL increases the interaction of p-Cav1 with eNOS, inhibiting its activity to reduce NO release and induce abnormal endothelial cell proliferation, which accelerates AS [114]. Ox-LDL also disrupts the balance between eNOS and inflammation-induced iNOS in endothelial cells. This directly or indirectly inhibits eNOS to reduce structural NO (constitutional NO) production and thus induces excessive iNOS activation; NO then reacts with superoxide anion to produce peroxynitrite, leading to EC damage (Fig. 2). Ox-LDL, on the one hand, reduces eNOS activity by activating Cav1 expression through HMGB1 and subsequent TLR4 signaling. On the other hand, It can also increase TLR4 levels and induce lectin-like oxidized LDL receptor 1 (LOX-1) expression due to positive feedback between TLR4 and LOX-1 [115], so that ox-LDL-induced increases in LOX-1 directly and indirectly through TLR4 promote increased iNOS transcription in nuclear factor kappa-B (NF-κB) heterotopic nuclei. Moreover, Cav1 regulates NF-κB activation, and its knockdown decreases NF-κB p65 activation and nuclear translocation [116,117]. Increased Cav1 activation of the NF-κB pathway further promotes increased iNOS, excessive free radical production leads to eNOS uncoupling, and further inhibition of eNOS function, decreased protective autophagy, and increased endothelial apoptosis, ultimately inducing endothelial dysfunction to promote AS development (Fig. 2) [118]. Cav1 and eNOS single- and double-knockout mouse models have been established and used for carotid artery grafts. Larger plaques were observed in $Cav1^{-/-}$ $eNOS^{-/-}$ mice than in WT mice, and significant de novo intimal hyperplasia was found in $Cav1^{-/-}$ mice after model grafts were performed. These atheroprotective effects were locally cell-mediated and were possibly caused by increased ROS production due to eNOS uncoupling upon Cav1 deletion [108]. Interestingly, excessive NO accumulation is also potentially toxic. Nasoni et al. showed that the oxysterol 3β-hydroxy-5β-hydroxy-B-norcholestane-6β-carboxaldehyde (SEC-B), a cholesterol oxidation product in ox-LDL, induces endothelial eNOS phosphorylation, as well as Cav1 downregulation and eNOS upregulation, resulting in excessive NO production causing endothelial dysfunction. Meanwhile, ox-LDL mediates reactive vasodilatation in the early stages of endothelial dysfunction, which may be one of the mechanisms of increased NO synthesis, and ultimately multiple pathways that induce excessive NO production leading to prolonged endothelial dysfunction with the release of inflammatory factors, ultimately leading to cell death; this again reveals the unique regulatory role of Cav1/eNOS dysregulation in AS [119]. In conclusion, moderate NO levels play a role in maintaining endothelial cell homeostasis and are anti-atherosclerotic; Cav1/eNOS regulation in the early stages of ox-LDL-induced AS development could thus be a promising target for cardiovascular disease prevention.

3.3. Regulation of endothelial cell inflammation by Cav1

Ross first proposed the inflammatory hypothesis of AS and suggested that the earliest lesions occurring prior to its formation were in the endothelium, leading researchers to describe AS as a "chronic inflammatory disease of thrombosis" [120]. Vascular endothelial cells respond to pro-inflammatory agonists (inflammatory cytokines, TNF-α, LPS, and others), ox-LDL, advanced glycosylation end products (AGEs), and biomechanical stimuli (LSS), resulting in their activation and dysfunction [109]. Inflammatory chemostimulatory responses involving the LPS/TLR axis, NLRP3 inflammatory vesicle formation, PCSK9 signaling pathway activation [121], and NF-κB signaling pathway activation constitute an inflammatory signaling cascade response. This induces inflammatory cytokine expression (IL-1β, IL-6, IL-8, IL-12, and VCAM-1) and ROS production, ultimately inducing inflammatory cell recruitment to the vessel wall, and this chronic inflammatory state accompanied by endothelial dysfunction drives the development of AS plaques [122].

Previous substantial evidence supports a negative role of endothelial caveolae and Cav1 in AS. In a $Cav1^{-/-}$ $ApoE^{-/-}$ double knockout mouse model, Cav1 deletion resulted in an approximately 70% reduction in atherosclerotic lesion area compared to $ApoE^{-/-}$ single knockout mice, and the expression of AS-promoting molecules (VCAM-1, CCL-2/MCP-1, and TNF-α) was downregulated; ultimately, leukocyte adhesion was impaired, and endothelial cell oxidative stress levels and lipid dysregulation were significantly reduced [56,123–125]. Endothelial-specific re-expression of Cav1 reversed these protective effects [126]. Cav1 has direct regulatory effects on inflammation in vascular disease. For example, Cav1 deficiency attenuates the pro-AS cytokine inflammatory response induced by oscillatory shear stress (OSS) [31]. In line with this, Cav1 deficiency has been shown to reduce AS and plaque inflammation by reducing leukocyte influx and systemic anti-inflammatory T lymphocytes [125]. In AS induced by PCB29-PQ (a metabolite of the

typical environmental pollutant PCB), Cav1 can act as a scaffold for inflammatory signaling by negatively regulating TGF-β and Cav1 phosphorylation to activate pro-inflammatory ROS [127]. Cav1 activates cellular inflammatory states through various signaling pathways. Cav1 interacts with the TLR signaling pathway axis, and LPS can increase Cav1 expression through activating the TLR4-MyD88 axis to activate downstream NF-κB inflammatory signaling (Fig. 2) [128]. Similarly, dipeptidyl peptidase (DPP)-4, known initially as the catalytic site for the T cell surface marker CD26, is widely expressed in most cells, and CD26 leads to activation of the NF-κβ pathway through direct binding of phosphorylated Cav1. A DPP4 inhibitor (Teneligliptin) has been demonstrated to bind Cav1 competitively with CD26, blocking TLR4/IRAK-4 pathway activation by inhibiting Cav1 phosphorylation to moderate the inflammatory response of macrophages [129]. Cav1 also regulates the TNF-α signaling pathway in endothelial cells; in this manner, NF-κB activation is regulated and induces endothelial cell activation. Cav1 deletion also attenuates the inflammatory response in p-c-Jun N-terminal kinase (JNK)-overexpressing cells treated with ox-LDL. This result demonstrates that the pro-AS effect of Cav1 is partly dependent on JNK signaling pathway activation (Fig. 2) [124]. In particular, treating endothelial cells with oxysterol for 24 h promoted endothelial dysfunction with increased levels of inflammatory cytokines (IL-6, TNF-α, ICAM-1) expression in endothelial cells inducing inflammation, at which time eNOS is upregulated and Cav1 levels are decreased leading to a massive accumulation of NO resulting in oxidative stress (Fig. 2) [119]. Decreased Cav1 expression did not inhibit inflammation. Instead, it became a secondary cause of NO production. This insignificant effect of Cav1 may be due to the massive acute stimulation-induced NO production and the effect of sterols on cell membrane fluidity [8,119]. Thus, Cav1 has multiple roles in AS. In addition to its direct effects on inflammatory signaling, its role as a lipoprotein carrier in the NO-independent transport of LDL to the vessel wall and its dependence on NO for negative eNOS regulation both play an important role in the early progression of inflammation in AS [14,31,130].

Ultimately, the role of Cav1 in regulating inflammation in AS is complex. Although a large body of literature has reported that Cav1 promotes the progression of early AS, Cav1 levels are reportedly significantly lower in arterial plaques than in non-AS vascular specimens, and its levels decrease with plaque progression [125]. Low expression levels of Cav1 are associated with the unstable and labile characteristics of plaques, which are also thought to be stabilizing factors in late AS [131]. These differences may be due to changes in cellular composition during plaque development and the cellular specificity of Cav1, which exhibits a pro-inflammatory phenotype in endothelial cells and smooth muscle cells and anti-inflammatory protective effects in macrophages [132]. Similarly, Cav1 has been reported negatively regulate inflammation, and its overexpression inhibits silica-induced inflammatory cell infiltration and reduces inflammatory factor release. Cav1$^{-/-}$ mouse models exhibit severe silicosis injury and fibrosis, and Cav1 expression is downregulated in LPS-induced acute lung injury due to specific mechanisms involving TLR4-NF-κB inflammatory signaling pathway inhibition and reduced cellular oxidative stress and macrophage M1 differentiation [133–136].

4. Conclusion

Cav1, an abundant concave component of endothelial cell membranes, plays an important regulatory role in the development of

Table 1
Summary of the mechanism of the role of Caveolin-1 in endothelial cells during the progression of atherosclerosis.

Regulation of endothelial cells	Mechanisms performed by Cav1			References
	Main functions	Main mechanisms		
Reduced protective autophagy	Negative regulation of autophagy by Cav1	Direct effects	Cav1 interacts with LC3B and the autophagy-associated proteins ATG5 and ATG12	[42,82,137]
			Cav1 deficiency promotes the activation of cellular autophagy	[75–77]
		Indirect effects	Autophagy inhibition increases the expression of adhesion molecules and increases the occurrence of abnormal structures at endothelial cell contact sites, thereby promoting inflammation	[68,70]
Increased LDL transcytosis across ECs	Reduced autophagic degradation of Cav1		Cav1 mediates lipoprotein uptake and transcytosis	[14,49]
			Decrease in cellular autophagy	[31,56]
			Post-translational modification of Cav1 increases the functionality and stability of Cav1	[94,137]
Oxidative stress and apoptosis in ECs	Dysregulation of the eNOS/NO system	Under low shear stress (LSS)	LSS causes caveolae to localize diffusely to reduce eNOS-pS1177 (the active form of eNOS)	[104]
			Activation of TLR4 by LSS leads to the activation of NOX2 and induction of Cav1 phosphorylation resulting in eNOS inactivation	[106]
		Under Ox-LDL	Ox-LDL increases phosphorylation of Cav1 interacting with eNOS to inhibit NO release	[113]
			Ox-LDL contributes to increased iNOS via Cav1/NF-κB leading to suppression of eNOS function	[117,118]
			Excessive activation of iNOS leads to the reaction of NO with superoxide anion ($O_2^{\bullet-}$) to produce peroxynitrite ($ONOO^-$)	[8,118]
ECs inflammation	Cav1 promotes the activation of inflammatory pathways		Cav1 facilitates SMAD1/5 signaling	[107]
			Cav1 regulates the activation of NF-κB	[116,129,138]
			Cav1 interacts with the TLR signaling pathway axis	[128]
			Cav1 activates the JNK signaling pathway	[124]

ECs: endothelial cells; ATG: autophagy-related; eNOS: endothelial nitric oxide synthase; ox-LDL: oxidized LDL; NOX2: NADPH oxidase 2; NF-κB, nuclear factor kappa-B; TLR: Toll-like receptor; JNK: c-Jun N-terminal kinase.

early atherogenesis (**Table 1**). This review summarizes the structure, and physiological functions of the Cav1 molecule and describes the potential mechanisms and related physiological roles it plays in regulating endothelial cell autophagy, SS response, the eNOS/NO axis, and inflammatory signaling pathways. The specific mechanisms by which Cav1 regulates autophagy and its degradation via this pathway are not yet fully elucidated. However, its regulation of autophagy is divided mainly into two parts: direct regulation of autophagy, which affects lipoprotein catabolism, and regulation of its own autophagic clearance, which indirectly affects sub-endothelial lipoprotein deposition. Furthermore, cellular autophagy is a dynamic process, and whether the autophagy-inhibiting functions of Cav1 in nutrient-rich conditions, including high glucose and lipid levels, occur at the early or late stage of autophagy is poorly reported. More in-depth studies are needed to better understand the mechanisms of AS formation and to identify new targets for intervention. In the meantime, the use of more functionally specific models, such as mouse models of endothelial-specific autophagy deficiency, would be useful to observe the unique role of endothelial autophagy in AS. Regarding the post-translational modifications (PTMs) of Cav1 that are essential for regulating its function, most studies have focused on phosphorylation, ubiquitination, and palmitoylation-related modifications. Less research has been done on the acetylation and sumoylation modifications of Cav1. Future studies are needed to explore in greater depth the effects of Cav1 PTMs on the development of AS due to altered function and metabolic kinetics.

AS development is a complex process in which altered hemodynamics and NO signaling, together with subsequent inflammatory changes, all play integral complementary roles. Most hemodynamic studies have examined caveolar-Cav1, which responds to hemodynamic signals through caveolae function (e.g., caveolae "flattening" in response to changes in the blood flow environment). The function of non-caveolar Cav1 has been less well studied; more in-depth studies are needed to determine whether non-caveolar Cav1 and caveolar-Cav1 function synergistically or independently in endothelial cells in the development of AS. Additionally, while negative regulation of the eNOS/NO axis by Cav1 was previously thought to be a major contributor to inflammation regulation, it has now been shown that Cav1 can directly induce chronic inflammation by transporting lipoproteins into the vascular wall. There, Cav1 acts as a signaling hub. It would be interesting to investigate the mechanisms by which Cav1 directly mediates the increase in inflammation.

A significant amount of research on Cav1 remains at the stage of basic mechanistic research, and its application in the clinical setting is still some distance away. However, a seven-amino acid deletion fragment of CSP (CSP7), a Cav1-derived peptide, was designed to inhibit P53 in alveolar epithelial progenitor type II cells, thereby attenuating apoptosis and the abnormal proliferation and accumulation of fibrotic lung fibroblasts after lung injury, and exerting a moderating effect on idiopathic pulmonary fibrosis. Meanwhile, the administration of CSP7 during the fibrosis phase in three pre-clinical models demonstrated its efficacy in enhancing lung function. It assessedits non-carcinogenicity [139], suggesting that Cav1 has clinical translational potential. Furthermore, a number of drugs that exert anti-AS effects, such as 5,2'-Dibromo-2,4',5'-trihydroxydiphenylmethanone (TDD), exert anti-inflammatory effects precisely by specifically targeting Cav1 and thereby inhibiting LPS-induced vascular inflammation and NF-κB signaling pathways [138]. At the same time, Tiaopi Huxin recipe (TPHXR) may improve endothelium-dependent vasodilation and attenuate vascular system inflammation by increasing eNOS phosphorylation and NO levels in ApoE$^{-/-}$ mice through down-regulation of Cav1 expression [140]. Therefore, the attempt to design peptides and other gene delivery systems (e.g., nanoparticles, exosomes, and others) [141] for Cav1 has an essential role in the clinical translation of Cav1.

In conclusion, our investigation of how Cav1, a lipid carrier on the endothelial cell membrane, responds to hemodynamic signals and regulates lipid transport and the corresponding inflammatory response. This line of questioning is essential to elucidate the pathogenesis of AS and may provide a new therapeutic target for its early prevention and treatment.

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Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

Cav1	caveolin-1
EGFR	epidermal growth factor receptor
eNOS	endothelial nitric oxide synthase

HMGB1	high mobility group box 1
iNOS	inducible nitric oxide synthase
LDLR	LDL receptor
LOX-1	lectin-like oxidized LDL receptor 1
NLRP3	NOD-like receptor family pyrin domain containing 3
ox-LDL	oxidized LDL
PCSK9	proprotein convertase subtilisin/kexin 9
ROS	reactive oxygen species
TGRL	triglyceride-rich lipoproteins
TLR	Toll-like receptor
VLA4	very late antigen-4

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