**How autophagy and mitophagy affect plaque stability in atherosclerosis**

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**Abstract:**

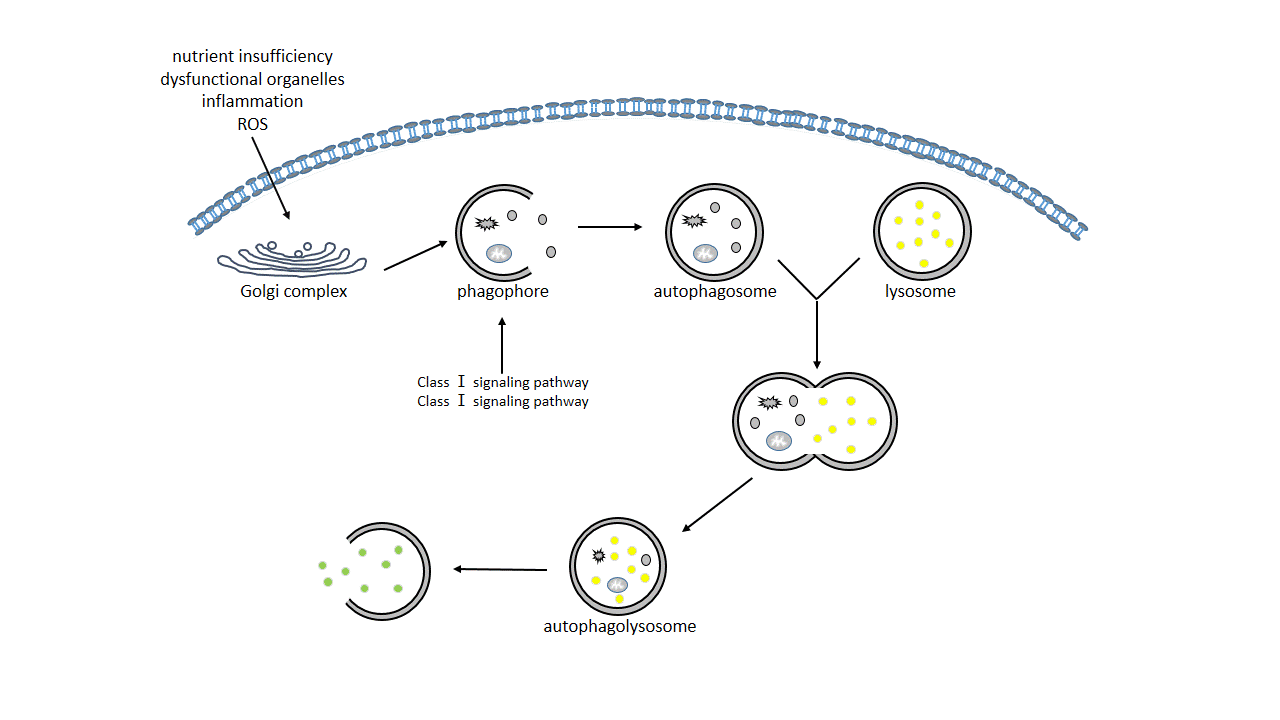
Atherosclerosis is a complex chronic inflammatory disease and a leading cause of death worldwide, and unstable plaque is one of the main features of advanced atherosclerosis. Plaque rupture and thrombus formation are the most fatal complications of atherosclerosis. Therefore, it is important to elucidate the mechanism underlying the formation of unstable plaques in order to prevent atherosclerosis-related complications. Autophagy is an important self-renewal process that degrades harmful cellular components and dysfunctional organelles via lysosomes to maintain cellular homeostasis and normal function. Previous studies have shown that autophagy plays a pivotal role in reducing inflammatory responses, oxidative stress, and the number of apoptotic cells, thereby improving cholesterol efflux from macrophages in atherosclerosis. Activating autophagy can significantly inhibit the development of atherosclerotic plaque and maintain plaque stability, as shown in various experimental models, including animal studies. Autophagy exerts a protective effect during early atherosclerosis but becomes dysregulated during advanced atherosclerosis. Therefore, appropriate activation of autophagy can inhibit atherosclerosis progression and prevent its complications. In this review article, we summarize the mechanisms of autophagy in -, as well as the effect of mitophagy on atherosclerotic plaque stability.

**Keywords:** atherosclerosis; plaque stability; autophagy; mitophagy; macrophage; vascular smooth muscle cell

**1. Introduction**

As an inflammatory disease, atherosclerosis can occur in almost all arteries and is characterized by plaque formation [1,2]. Through the course of disease development, plaque stability plays a paramount role in the occurrence of atherosclerotic complications: stable atherosclerotic plaques contain a thick fibrous cap covering the necrotic core, a small necrotic core, and a few macrophages; during advanced atherosclerosis, where a violent inflammatory response causes cell death, stable plaques can turn into unstable plaques that contain a thin fibrous cap, a large necrotic core, few vascular smooth muscle cells (VSMCs), and a large number of macrophages, and the rupture of unstable plaques can cause several fatal complications, such as stroke, acute myocardial infarction, or sudden death [3]. To prevent these fatal complications, new therapeutic options must be identified by elucidating the mechanisms underlying plaque instability and rupture.

Autophagy is a highly conserved biological process that degrades harmful components and organelles, such as dysfunctional mitochondria and misfolded proteins [4]. Based on the binding mode of harmful cell components and lysosomes, autophagy can be classified as macroautophagy, microautophagy, and molecular chaperone-mediated autophagy [5]. In this study, we focused on autophagy (also known as macroautophagy). Autophagy begins with the formation of the phagosome, an isolation membrane enclosing toxic cellular components and dysfunctional organelles (see **figure 1**). These phagosomes gradually elongate to form a cup-shaped structure, finally forming double lipid membrane vesicles called autophagosomes [6]. Subsequently, autophagosomes and lysosomes fuse to form autophagosomal lysosomes, and lysosomal hydrolases decompose the toxic substances within [7]. To date, two crucial signaling pathways of autophagy have been identified: the PI3K-mTOR-related signaling pathway and the PI3K-Beclin1-related signaling pathway [8,9]. Basic autophagy can maintain cell homeostasis and function [10]. Autophagy can be activated by environmental stress-related signals, such as dysfunctional organelles, inflammation, and [oxidative](javascript:;) [stress](javascript:;), and it facilitates nutrient recycling, energy generation, and maintenance of cellular viability [11].



**Figure 1:** Schematic diagram of the autophagy process. Induced by nutrient insufficiency, inflammation, or oxidative stress, bilayer lipid membranes from the endoplasmic reticulum or Golgi complex form cup-shaped phagophores. The phagophore digests damaged organelles and harmful components to form the autophagosome. The autophagolysosome is formed by the integration of the autophagosome and lysosome. Two crucial signaling pathways of autophagy have been found: the PI3K-mTOR-related signaling pathway and the PI3K-Beclin1-related signaling pathway.

Endothelial cells (EC), VSMCs, and macrophages are the three most important cell types involved in the development of atherosclerosis, and all of them can express autophagy markers [12]. In addition, autophagy has been observed in the main cells in human atherosclerotic plaque using transmission electron microscopy [13,14]. Recent studies have shown that autophagy plays a critical role in attenuating atherosclerosis and maintaining plaque stability, suggesting that autophagy may be a useful target for the treatment of atherosclerosis [15,16]. In atherosclerosis, autophagy exerts similar effects in endothelial cells, macrophages, and VSMCs, although using different mechanisms. Next, we will focus on the mechanism of dysfunctional autophagy in these three cell types and the effect of mitophagy on plaque stability.

**2. Mechanism of autophagy effect on plaque stability in endothelial cells**

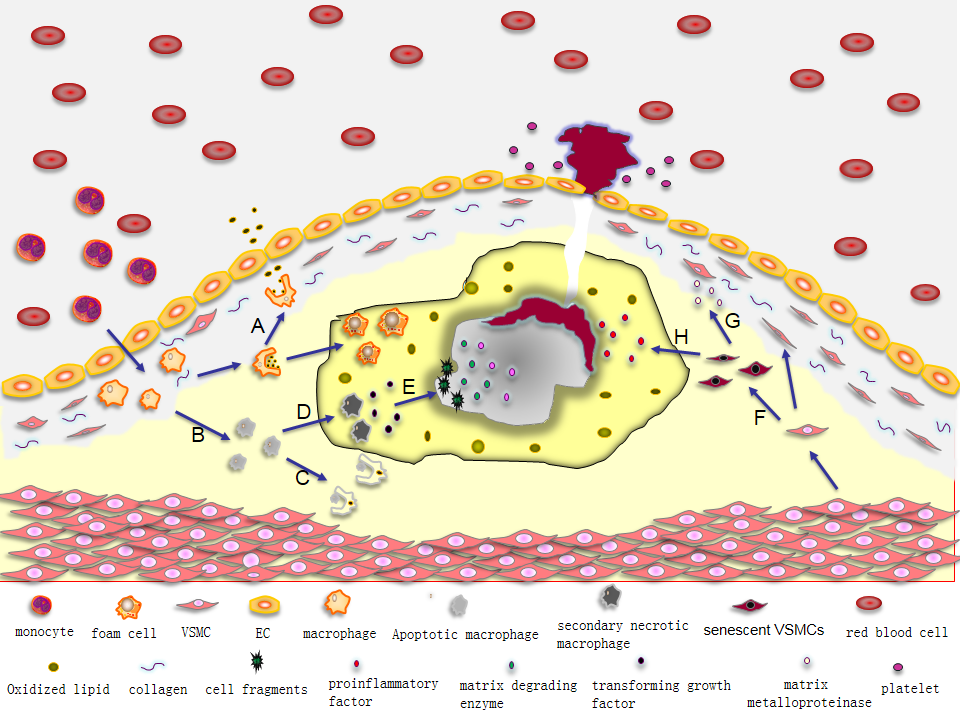
Endothelial cells, located in the innermost layer of the atherosclerotic plaque, are in direct contact with blood and control material exchange and communication between blood and vessel walls [17,18]. Endothelial cells regulate vascular tension, anticoagulation, and inflammation [19]. In atherosclerosis, defective autophagy in endothelial cells affects plaque stability by affecting thrombus formation, endothelial function, and apoptosis; for example, tissue factor (TF), expressed in the necrotic core of atherosclerotic plaques, is the main promoter of the extrinsic pathway that causes thrombus formation when the plaque ruptures. TF activates the coagulation cascade when it comes in contact with the activating factor VIIa, finally producing thrombin, which plays a pivotal role in platelet activation and fibrin formation [20]. Yau et al. [21] provided evidence that the deletion of *ATG7*, a key autophagy-specific mediator in endothelial cells, attenuates the expression of TF in human umbilical vein endothelial cells induced by tumor necrosis factor-α. Moreover, deletion of the key autophagy-related gene *ATG7* in mouse endothelial cells resulted in dysfunctional thrombosis. In addition, stents coated with rapamycin (an autophagy activator) are more likely to cause in-stent thrombosis in patients receiving percutaneous coronary stent interventional therapy [22,23]. However, there is no clear clinical evidence that reducing endothelial autophagy can inhibit thrombosis in atherosclerosis.

Blood flow exerts frictional and shear stress on the vascular walls, which influence atherosclerosis development and plaque stability via dynamic interactions with endothelial cells. In addition, atherosclerotic plaque can change blood flow patterns by causing abnormal flow and turbulence, which affect endothelial repair, vasodilation, and endothelial nitric oxide synthase (eNOS) production [24,25]. Guo et al. [26] demonstrated that when endothelial autophagy is upregulated, eNOS expression is increased, and endothelin-1 expression is inhibited, thereby maintaining normal vascular wall tension and plaque stability. Endothelin-1 is a natural counterpart of the vasodilator nitric oxide (NO) and a specific protein marker of endothelial dysfunction.

Moreover, defective autophagy in endothelial cells can accelerate apoptosis, promote plaque instability and platelet aggregation, and promote thrombus formation and plaque rupture [17,27,28]. Furthermore, apoptotic stimuli, such as tumor necrosis factor-α, oxidized low-density lipoprotein (oxLDL), and ceramide, are more likely to lead to the death of autophagic defective endothelial cells, possibly due to decreased NO levels and increased reactive oxygen species (ROS)-induced damage [29–31]. Evidence suggests that these effects are regulated by the overexpression of lectin-like oxidized LDL (LOX-1), a scavenger receptor that selectively internalizes oxLDL in endothelial cells [32]. LOX-1 expression can be directly regulated by mechanical force, oxLDL, oxidative stress, and angiotensin II, which play a pivotal role in the progression of atherosclerosis [33–35]. Recently, Mollace et al. [36] showed that oxLDL reduces NO production and increases cell death in bovine aortic endothelial cells through overexpression of LOX-1 and attenuation of autophagy.

**Macrophage autophagy modulates plaque stability**

Macrophages play both harmful and beneficial roles in atherosclerosis. During the initial phase of atherosclerosis, the harmful plaque components, such as cytotoxic lipoproteins and apoptotic cells, can be scavenged by macrophages. In addition, macrophages promote tissue repair and plaque stability by increasing extracellular matrix synthesis and VSMC proliferation [37]. In advanced atherosclerosis with disordered homeostasis and gradual autophagy damage, a large number of dysfunctional and apoptotic macrophages, which secrete matrix-degrading enzymes and release ROS (reactive oxygen species)and pro-inflammatory factors, lead to extracellular matrix degradation and necrosis of surrounding cells, resulting in plaque destabilization, plaque rupture, and thrombotic events [38]. Accumulating evidence demonstrates that autophagy can alleviate atherosclerosis and maintain plaque stability by promoting macrophage cholesterol efflux and apoptotic macrophage clearance and reducing macrophage apoptosis (see **figure 2**) [39].



**Figure 2:** Macrophages and vascular smooth muscle cells (VSMCs) influence plaque stability in several ways. (A) Cholesterol efflux from macrophages reduces the accumulation of foam cells; (B) Macrophage apoptosis; (C) Apoptotic macrophages are eliminated; (D) Apoptotic macrophages transform into secondary necrosis cells; (E) Secondary necrotic macrophages secrete pro-inflammatory factors and matrix-degrading enzymes, which promote plaque necrosis and rupture; (F) VSMC senescence; (G) Senescent VSMCs secrete matrix metalloproteinases, which degrade collagen tissues and reduce fibrous cap formation; (H) Senescent VSMCs secrete various pro-inflammatory factors to promote the formation of the necrotic core.

**3. Autophagy increases cholesterol efflux in macrophages**

During the initial stage of atherosclerosis, monocytes in the blood enter the intima of the vessels and differentiate into macrophages. Macrophages form foam cells by internalizing large amounts of modified lipoproteins (such as oxLDL) and lipoproteins [40]. The continuous accumulation and death of foam cells, along with chronic inflammation, promote the formation of atherosclerotic plaques [41,42]. Research has shown that during the initial phase of atherosclerosis, autophagy can promote cholesterol efflux in macrophages and reduce foam cell accumulation, thereby inhibiting plaque formation. This particular type of autophagy is termed “lipophagy [43]”. As atherosclerosis progresses, autophagy in macrophage cells is gradually impaired, characterized by increased number of autophagosomes and decreased number of autophagolysosomes in intermediate and advanced atherosclerosis [44,45]. Liu et al. [44] demonstrated that autophagy in macrophages was impaired gradually as macrophages were incubated with oxLDL for longer periods of time, leading to cell death and decreased cell viability. Recently, Zhai et al. [39] showed that, in the vulnerable plaques induced in New Zealand white rabbits, the level of autophagy in macrophages was upregulated by selectively inhibiting the Akt/mTOR signaling pathway, and plaque rupture incidence, plaque burden, and vulnerability index were also decreased.

**4. Autophagy reduces macrophage apoptosis**

Macrophage apoptosis and necrosis are significant features of advanced atherosclerosis that influence necrosis core formation and unstable plaque formation [37]. There is evidence that dysfunctional autophagy in macrophages can accelerate apoptosis and promote plaque instability in advanced atherosclerosis [46]. For example, Liao et al. [47] demonstrated that deletion of macrophage autophagy-specific mediator *ATG5* increases macrophage apoptosis and necrosis in LDLR−/− mice, leading to the development and rupture of atherosclerotic plaque after 12–16 weeks of consuming a high-fat diet. In addition, *in vitro* experiments showed that activating autophagy can reduce macrophage apoptosis, suggesting that autophagy could alleviate atherosclerosis and promote plaque stability [44]. Evidence supports the notion that deficient autophagy in macrophages promotes apoptosis by enhancing nicotinamide adenine dinucleotide phosphate oxidase-mediated oxidative stress, leading to lower recognition of apoptotic cells by efferocytosis [47]. Furthermore, apoptotic macrophages may reduce collagen synthesis in VSMCs due to reduced transforming growth factor-β secretion, resulting in unstable plaque [48].

**5. Autophagy promotes clearance of apoptotic macrophages and prevents secondary necrosis**

Apoptotic macrophages can be effectively cleared during the early stage of atherosclerosis; however, during the late stage of atherosclerosis, several factors lead to insufficient phagocytic clearance of apoptotic macrophages, resulting in secondary necrosis and pro-inflammatory responses [37]. Schrijvers et al. [49] showed that a large number of apoptotic macrophages are found in human carotid atherosclerosis without being cleared via phagocytosis. Liao X et al. [47] provided evidence that silencing macrophage autophagy mediator *ATG5* in fat-fed LDLR-/- mice could reduce the recognition and clearance of apoptotic macrophages, which may lead to secondary necrosis, thereby promoting atherosclerotic plaque development and necrosis in advanced atherosclerosis. Apoptotic macrophages that have not been cleared develop into secondary necrotic cells, which can promote the occurrence of unstable plaque by inducing inflammation and expanding the necrotic core [50]. These macrophages are also important sources of TFs that promote intraplaque thrombosis [51]. In addition, secondary necrosis of apoptotic macrophages promotes plaque development and necrosis and directly induces the secretion of pro-inflammatory cytokines and the formation of damage-related molecular patterns (DAMPs) [52]. DAMPs can enhance the inflammatory response in the necrotic core, leading to its enlargement and plaque rupture. In addition, in advanced atherosclerosis, macrophages with secretory phenotypes secrete matrix-degrading enzymes that cause thinning of the fibrous cap, plaque rupture, and thrombus formation. Abnormal macrophages also release nitrogen radicals and toxic oxygen, causing the death of surrounding cells [38,53].

**6. Autophagy affects plaque stability in VSMCs**

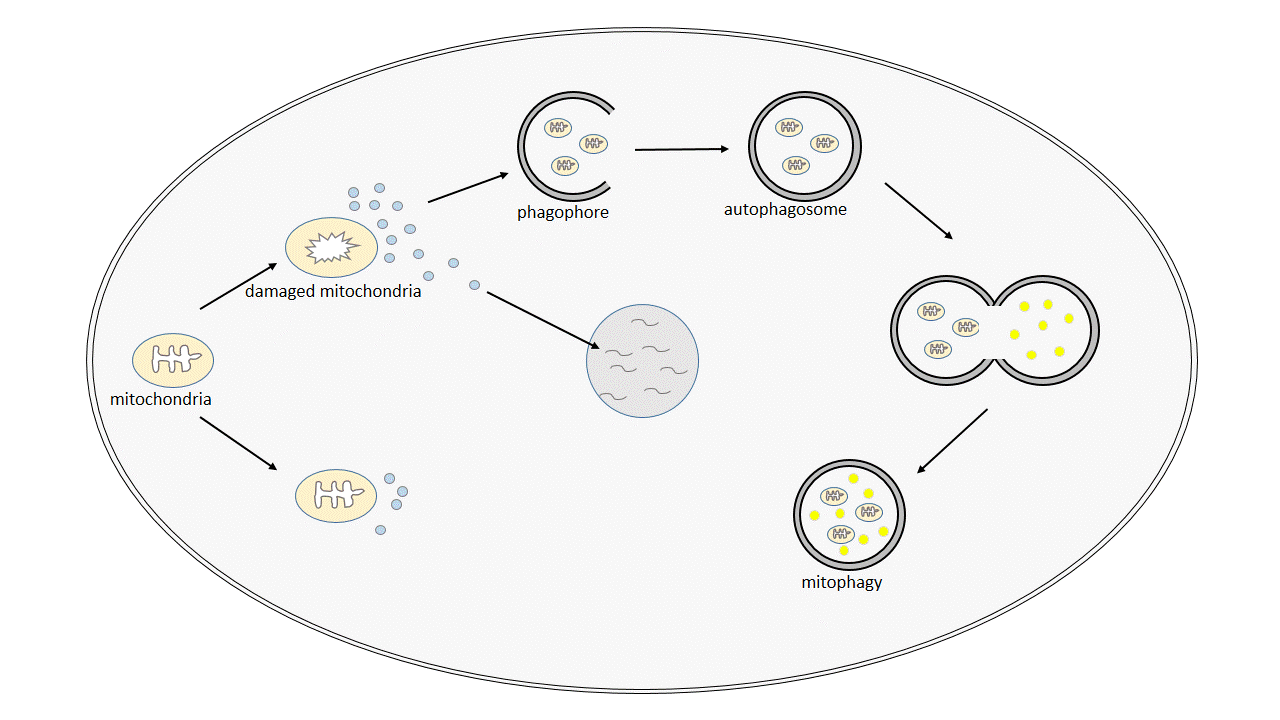
VSMCs can regulate blood pressure, distribute nutrients and oxygen to the surrounding tissues, and exhibit significant plasticity [54]. On one hand, VSMCs can transform from a contractile phenotype to a macrophage-like phenotype, phagocytose lipoproteins or apoptotic cells, and form smooth muscle cell-derived foam cells, thus promoting the progression of atherosclerosis; in contrast, in advanced atherosclerosis, VSMCs transform into a synthetic phenotype, which shows high proliferative and migratory abilities and enhances extracellular matrix production, thereby maintaining plaque stability [55,56]. Therefore, VSMCs are considered to play a pivotal role in increasing plaque stability and preventing plaque rupture and thrombus formation [3,57–59]. Many studies have shown that activation of autophagy in VSMCs can attenuate atherosclerosis by reducing oxidative stress, inhibiting the VSMC phenotypic shift, and inhibiting senescence (see **figure 2**) [10,60,61].

Evidence suggests that the proliferative and self-repairing abilities are impaired in senescent VSMCs, leading to reduced fibrous cap formation [62]. Many senescent VSMCs are found in unstable atherosclerotic plaques, with a marked decrease in proliferative capacity and increased expression of senescence markers, such as senescence-associated β-galactosidase [63]. Recently, Grootaert et al. [64] have shown that the deletion of the smooth muscle cell-specific autophagy-related mediator *ATG7* promotes senescence and ligation-induced neointima formation in a mouse model of atherosclerosis, suggesting that autophagy affects VSMC phenotype and proliferation. Masuyama et al. [65] established a model of carotid tandem stenosis and showed that autophagy-deficient VSMCs increased the risk of atherosclerotic plaque rupture; moreover, ApoE-/- mice with autophagy-deficient VSMCs showed increased intraplaque bleeding, plaque rupture, and thrombosis. Studies have shown that autophagy can inhibit oxidative stress and protein toxic stress by scavenging impaired mitochondria and protein aggregates, thereby negatively regulating cell senescence [66]. Maatinet et al. [67] demonstrated that the autophagy inducer 7-ketocholesterol could effectively reduce senescence in VSMCs, which, in turn, improved plaque stability. The altered secretory activity of senescent VSMCs is referred to as a proinflammatory senescence-associated secretory phenotype, where these cells secrete proinflammatory cytokines, chemokines, growth factors, and proteases, but not anti-inflammatory factors [68]. These findings suggest that senescent VSMCs can aggravate the inflammatory response and matrix degradation in atherosclerotic plaques [69].

Although autophagy is generally considered a protective mechanism against atherosclerosis, excessive activation of autophagy can induce autophagic death of VSMCs, leading to plaque instability [70]. An *in vitro* study showed that a moderate dose of ox-LDL (10–40 μg/mL) induced VSMC proliferation, while higher levels of ox-LDL (more than 60 μg/mL) were more likely to cause cell apoptosis [71]. Luo et al. [72] demonstrated that low doses of rapamycin in an ApoE−/− mouse atherosclerosis model could moderately upregulate autophagy, thereby mitigating the progression of atherosclerosis and maintaining plaque stability, which are associated with the regulation of autophagy and senescence in VSMCs via the mTORC1/ULK1/Atg13 signaling pathway; however, high doses of rapamycin had no additional beneficial effects on atherosclerosis and plaque stability. Furthermore, other cell types, such as macrophages, pancreatic cells, and neurons, are also more vulnerable to damage-mediated cell death in the case of defective or excessive autophagy [47,73].

**7. Effect of mitophagy on plaque stability**

In addition to the non-selective process, by which autophagosomes phagocytose the cytoplasm, they also selectively degrade damaged organelles (e.g., mitochondria and ribosomes). This selective autophagy is referred to as organ-specific autophagy [74,75]. Mitophagy, the selective degradation of damaged mitochondria to inhibit cell death, can occur during specific developmental processes, such as red blood cell maturation, or after pathological mitochondrial damage (see **figure 3**) [76–78]. Selective elimination of dysfunctional mitochondria can reduce the production of pro-apoptotic factors, such as cytochrome C, which can activate cell death pathways [79]. There is evidence that mitophagy can resist oxidative stress, reduce ROS production, and inhibit the apoptosis of VSMCs, thereby alleviating atherosclerosis and maintaining plaque stability [80].



**Figure 3:** Schematic illustration of mitophagy. The excessive accumulation of reactive oxygen species (ROS) during cellular stress can damage mitochondrial components, including mitochondrial DNA, proteins, and lipids, thus aggravating the production of ROS and mitochondrial dysfunction. ROS, especially hydrogen peroxide, hydroxyl radicals, and superoxide anions, can cause a series of DNA changes, such as DNA strand breaks and DNA base changes, which accelerate replicative senescence. Phagophores specifically phagocytose dysfunctional mitochondria and combine with lysosomes to form autophagolysosomes to eliminate harmful mitochondria.

Of all organelles, mitochondria have the most direct effect on cellular energy metabolism and disease phenotypes [81]. The main role of mitochondria is to produce adenosine triphosphate via oxidative respiratory phosphorylation, and they can regulate innate immunity, necrosis, apoptosis, and autophagy [82–84]. The production of ATP through the respiratory chain is accompanied by the formation of ROS as a byproduct. Low levels of ROS can be directly removed by antioxidants or actively stimulate the signal/transcription pathway to maintain an appropriate redox balance; however, excessive accumulation of ROS during stress can damage mitochondrial components, including mitochondrial DNA, proteins, and lipids, thus aggravating ROS production and mitochondrial dysfunction [85]. ROS, especially hydrogen peroxide, hydroxyl radicals, and superoxide anions, can cause a series of DNA changes, such as DNA strand breaks and DNA base changes, thereby triggering DNA damage response pathways. In some types of cells, ROS can cause telomere loss during replication and lead to premature senescence that does not depend on telomere shortening [86,87]. ROS levels are significantly elevated in all types of cells in atherosclerotic lesions, especially in the plaque itself [88]. Matthews et al. [89] have demonstrated that VSMC senescence in plaques is attributed to oxidative DNA damage that accelerates replicative senescence. Replicative senescence and sustained apoptosis of VSMCs lead to reduced fibrous cap formation, commonly observed in advanced atherosclerosis in humans, which may also contribute to plaque rupture through overexpression of adhesion molecules, hemostatic regulatory factors, matrix metalloproteinases, and other proteins [90–92]. Swiader A et al. [80] showed that human VSMCs exposed to oxLDL selectively scavenge damaged mitochondria through autophagy, which can inhibit VSMC apoptosis caused by atherosclerotic stressors. In addition, this process depends on the PTEN-mediated putative kinase 1 (PINK1)/parkin pathway. In addition, oxidative stress is significantly enhanced, and the number of apoptotic cells is significantly increased in the cardiomyocytes of PINK1-deficient mice. Kubli et al. [93,94] demonstrated that parkin-deficient mice were more prone to myocardial infarction, which was primarily due to the dysfunctional mitophagy in cardiomyocytes. Although mitophagy plays a pivotal role in alleviating atherosclerosis and maintaining plaque stability, its related pathways and mechanisms require further study.

**8. Conclusion**

In conclusion, here, we have summarized the progress in research focused on the mechanism of autophagy in three different types of cells and the effects of mitophagy on plaque stability in atherosclerosis. The effect of autophagy on atherosclerosis and plaque stability is similar in different types of cells, but it is executed via different mechanisms. Therefore, revealing the underlying autophagy mechanism of alleviating atherosclerosis and maintaining plaque stability in different types of cells could provide a new basis for treating and preventing atherosclerosis. A growing body of evidence has shown that activating autophagy is an effective method to inhibit plaque growth and maintain plaque stability, but clinical data are still limited. Atherosclerosis is a dynamic pathological process. It is important to identify the critical time points of autophagy activation, as well as the mode and degree of its activation in pathological conditions. Any autophagy regulatory approach targeting only advanced atherosclerosis will not inhibit the development of atherosclerosis, and may aggravate its pathological changes instead. In recent years, several stable and effective animal models of unstable plaques have been established, providing a new basis for elucidating the therapeutic effect of autophagy on unstable plaques.

Abbreviations: vascular smooth muscle cells (VSMCs); endothelial cells (EC); tissue factor (TF); endothelial nitric oxide synthase (eNOS); nitric oxide (NO); oxidized low-density lipoprotein (oxLDL); reactive oxygen species (ROS); lectin-like oxidized LDL (LOX-1); damage-related molecular patterns (DAMPs); PTEN-mediated putative kinase 1 (PINK1)

**Declarations**

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**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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