J Lipid Atheroscler. 2023 May;12(2):132-151
https://doi.org/10.12997/jla.2023.12.2.132
pISSN 2287-2892·eISSN 2288-2561

JLA Journal of Lipid and Atherosclerosis

Review

Check for updates

Unbalanced Redox With Autophagy in Cardiovascular Disease

Se-Jin Jeong [1], **Goo Taeg Oh** [2]

[1]Cardiovascular Division, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA
[2]Immune and Vascular Cell Network Research Center, National Creative Initiatives, Department of Life Sciences, Ewha Womans University, Seoul, Korea

OPEN ACCESS

Received: Sep 29, 2022
Revised: Mar 27, 2023
Accepted: Apr 13, 2023
Published online: May 16, 2023

Correspondence to
Goo Taeg Oh
Immune and Vascular Cell Network Research Center, National Creative Initiatives, Department of Life Science, Ewha Womans University, 52 Ewhayeodae-gil, Seodaemun-gu, Seoul 03760, Korea.
Email: gootaeg@ewha.ac.kr

ORCID iDs
Se-Jin Jeong
https://orcid.org/0000-0002-6375-5334
Goo Taeg Oh
https://orcid.org/0000-0002-1104-1698

Funding
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (No. 2020R1A3B2079811 and No. 2021M3E5E7023628) and the Korean Society of Lipid and Atherosclerosis (KSOLA2021-01-001).

Conflict of Interest
The authors have no conflicts of interest to declare.

ABSTRACT

Precise redox balance is essential for the optimum health and physiological function of the human body. Furthermore, an unbalanced redox state is widely believed to be part of numerous diseases, ultimately resulting in death. In this review, we discuss the relationship between redox balance and cardiovascular disease (CVD). In various animal models, excessive oxidative stress has been associated with increased atherosclerotic plaque formation, which is linked to the inflammation status of several cell types. However, various antioxidants can defend against reactive oxidative stress, which is associated with an increased risk of CVD and mortality. The different cardiovascular effects of these antioxidants are presumably due to alterations in the multiple pathways that have been mechanistically linked to accelerated atherosclerotic plaque formation, macrophage activation, and endothelial dysfunction in animal models of CVD, as well as in *in vitro* cell culture systems. Autophagy is a regulated cell survival mechanism that removes dysfunctional or damaged cellular organelles and recycles the nutrients for the generation of energy. Furthermore, in response to atherogenic stress, such as the generation of reactive oxygen species, oxidized lipids, and inflammatory signaling between cells, autophagy protects against plaque formation. In this review, we characterize the broad spectrum of oxidative stress that influences CVD, summarize the role of autophagy in the content of redox balance-associated pathways in atherosclerosis, and discuss potential therapeutic approaches to target CVD by stimulating autophagy.

Keywords: Cardiovascular disease; Inflammation; Oxidative stress; Antioxidants; Autophagy

INTRODUCTION

Reactive oxygen species (ROS) are undesirable byproducts of the cellular respiration system.[1-4] However, cellular respiration-based energy metabolism is an essential process to produce adenosine triphosphate (ATP) for the continuous maintenance of essential cellular functions, such as cellular signaling and protein synthesis. Electron transport through the mitochondrial respiratory chain leaks approximately 1%–2% of electrons, generating superoxide (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH\cdot$).[5,6] To protect the cell against ROS, cells have an equally ubiquitous antioxidant defense system, which is thought to be important for the balance of the intracellular redox environment.[7] Superoxide dismutase

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

Conceptualization: Jeong SJ, Oh GT; Data curation: Jeong SJ; Formal analysis: Jeong SJ; Funding acquisition: Oh GT; Investigation: Oh GT; Supervision: Oh GT; Writing - original draft: Jeong SJ; Writing - review & editing: Jeong SJ, Oh GT.

(SOD) converts O^{2-} into H_2O_2, which is then reduced to water by several cellular enzymes. Peroxiredoxins (Prdx), glutathione peroxidase (Gpx), catalase, and thioredoxin reductase (Trx) are important cellular reductases in eukaryotic cells.[8-10]

The results from numerous studies have demonstrated that a relationship exists between ROS and the incidence and mortality of various diseases, presumably because high oxidative stress results in increased inflammation and contributes to the increased occurrence of apoptosis.[11-14] Inflammation and apoptosis are major risk factors for cardiovascular disease (CVD), whereby activated endothelial cells initiate the recruitment of macrophages to the arterial walls and are associated with several abnormalities involved in the pathogenesis of CVD, including dyslipidemia and hypertension.[15] Thus, the removal of oxidative stress and management of the redox balance form the cornerstone of the prevention and treatment of CVD.

Autophagy is a catabolic pathway for the degradation or recycling of cytoplasmic organelles and aggregated proteins using the lysosomal apparatus.[16,17] Autophagy is highly inducible and triggered by environmental stresses such as oxidative stress by ROS.[18-20] Oxidative stress not only involves the induction of autophagy, but can also serve as an intracellular signaling regulator by reversibly oxidizing the essential signaling components. Recent reports have revealed that acquired defects in autophagy exacerbate atherosclerosis, suggesting that autophagy exerts an anti-atherogenic function.

The oxidative stress associated with antioxidant dysfunction has adverse consequences on cardiovascular health because it is associated with an increased risk of atherogenesis. Numerous studies involving *in vivo* models and *in vitro* cell culture models have demonstrated a direct mechanistic link between the dysfunction of antioxidants and their related signaling pathways and atherosclerosis. In the following sections, we review the current evidence relating to oxidative stress and atherosclerotic risk and explore potential cellular and molecular mechanisms connecting autophagy with atherosclerosis.

ATHEROSCLEROSIS

Atherosclerosis is a gradually progressive disease characterized by the formation of lipid- and inflammatory component-rich plaques, resulting in the thickening of the arterial walls and narrowing of the arterial lumen,[21,22] and it is considered the major cause of CVD. Research on atherosclerosis has provided insights into the relationship between plasma lipid abnormalities and inflammation on the arterial wall, including both vascular wall resident and immune cells. One of the most transformative paradigms in atherosclerosis research has been the discovery of the role of inflammation.[23,24] For most of the 1900s, atherosclerosis was viewed as a hyperlipidemic disease, but in the late 1990s, the role of inflammation in atherosclerosis was identified. These initial findings gave rise to the field of immunometabolism, which is the study of how immune cells respond to and regulate hyperlipidemic states.

Atherosclerosis is initiated by endothelial dysfunction from lipids within the blood.[25] Endothelial cells form a monolayer on the arterial luminal surface because activated endothelial cells release several surface adhesion molecules, inducing the recruitment and adhesion of immune cells, especially monocytes.[26] One of the unique characteristics of endothelial cells is that they can sense vascular flow dynamics. In straight and normal

laminar flow regions, endothelial cells produce few adhesion molecules, whereas in the curvatured and shear flow regions, the amount of surface adhesion molecules is greatly increased. Monocytes are the first immune cells that respond to the adhesion molecules on the endothelial cells and they continuously infiltrate into arterial intima lesions, which are a major area of plaque formation.[27,28] After infiltration, monocytes differentiate into macrophages and respond to various signaling pathways, including the formation of foam cells by the uptake of modified lipoproteins and the secretion of many kinds of chemokines, cytokines, and proteases. Smooth muscle cells are another important mediator in atherogenesis.[29,30] Although most smooth muscle cells in the arterial wall are located in the medial layer, in the late stage of atherogenesis, smooth muscle cells proliferate from the media, migrate into the intimal area, and secrete extracellular matrix proteins to create a fibrous cap that stabilizes the plaque. However, the migrated smooth muscle cells also take up modified lipoproteins, contributing to foam cell formation and further plaque complexity. The pathological process of atherosclerosis is summarized in **Fig. 1**.

Several studies have evaluated the relationship between each cell type and the risk of atherosclerosis. The key cellular features and results from some of the most comprehensive studies are reviewed in the following sections.

1. Oxidized lipids and atherosclerosis

Oxidative stress during atherogenesis can generate various oxidized lipids, including oxidized cholesterol.[31,32] Macrophages are the cells that contribute the most during early atherogenesis through the uptake of oxidized low-density lipoprotein (oxLDL) via scavenger receptors, including scavenger receptor A (SR-A), scavenger receptor BI (SR-BI), CD36, and CD68, and this uptake promotes cellular cholesterol accumulation in the arterial wall. The increase in oxLDL-related macrophage scavenger receptors has also been implicated in the progression of atherosclerosis. Peritoneal macrophages from mice supplemented with oxLDL revealed elevated expression of the scavenger receptors CD36 and SR-A1, which are key mediators of cholesterol metabolism.[33,34] Numerous *in vivo* studies have implicated both CD36 and SR-A1 in early foam cell formation, altered low-density lipoprotein (LDL) uptake, and atherosclerotic plaque progression, complexity, and necrosis.[34-39]

Recent studies have shown that oxidized lipids not only induced the formation of lipid-enriched foam cells and their accumulation in plaques, but also enhanced vascular inflammation and gave rise to autoimmune reactions in the vascular walls.[40-42] *In vitro* studies have revealed that oxidative stress is a major stressor of the vasculature, which is associated with chronic inflammatory conditions and increases with aging.[43,44] Another important oxLDL-mediated effect on atherosclerosis involves smooth muscle cell proliferation within the vasculature.[45,46]

2. Mitochondrial dysfunction in atherosclerosis

Recent studies have demonstrated that mitochondrial damage or dysfunction mediated the activation of oxidative stress, which is pro-atherogenic, by inhibiting mitochondria-dependent metabolism.[47-50] Mitochondria are essential double membrane-bound subcellular organelles that play a central role in various metabolic process, including the synthesis of ATP through oxidative phosphorylation, and prevents various metabolic diseases by controlling apoptosis. Thus, defects due to mitochondrial dysfunction or impairment disrupt metabolic homeostasis and result in excessive ROS production, which leads to serious metabolic diseases.[51-53] Moreover, damaged mitochondria correlate with a rapid rise in mitochondrial DNA (mtDNA) damage and, consequently, elevated apoptosis.[54,55] Increased mtDNA damage

https://doi.org/10.12997/jla.2023.12.2.132

JLA Journal of Lipid and Atherosclerosis

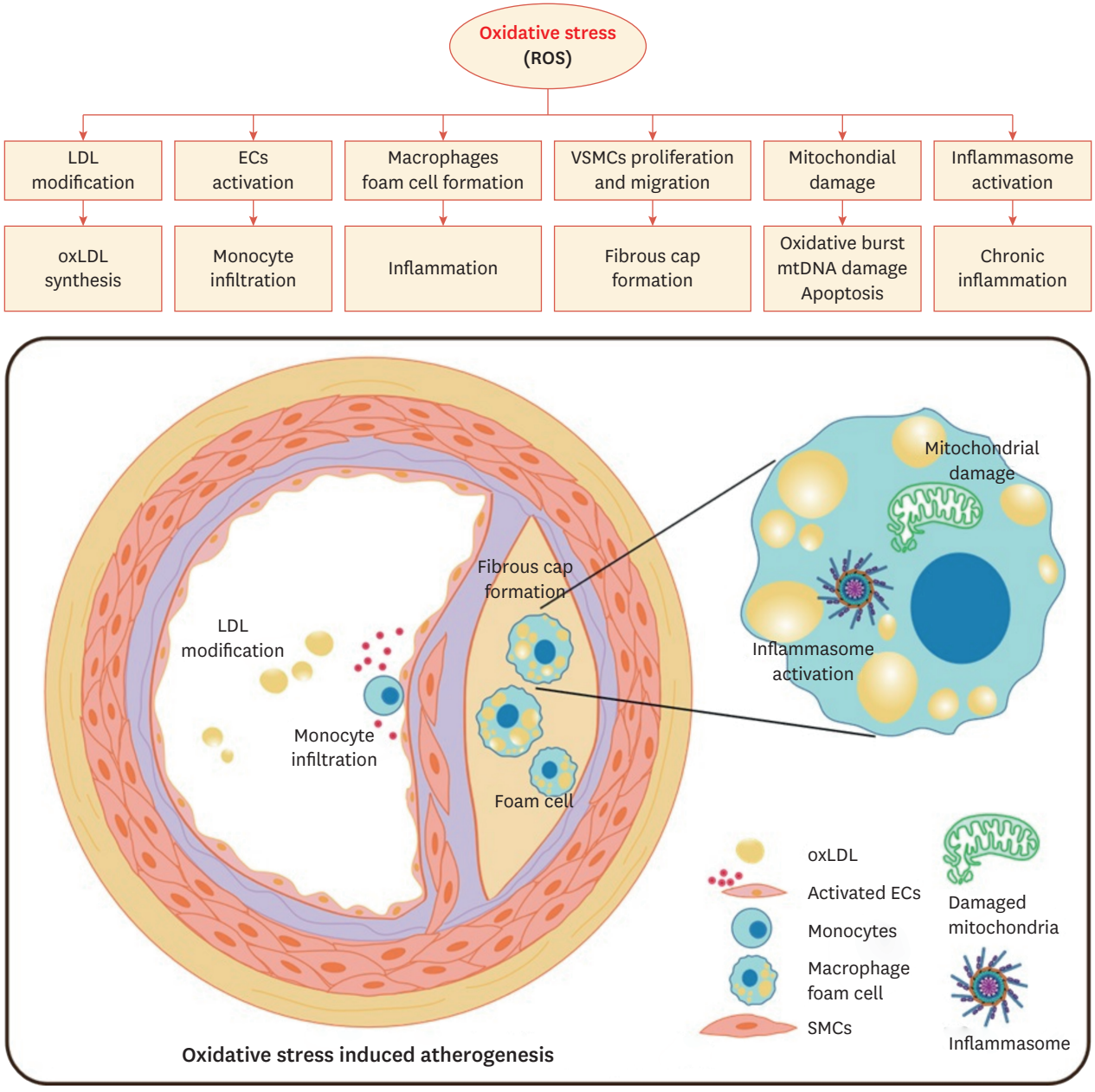

Fig. 1. Schematic overview of the role of oxidative stress in atherosclerosis.
Atherosclerosis is the progressive narrowing of the arteries due to plaque formation and is considered the major cause of cardiovascular disease. Oxidative stress is a major stressor that affects the development of atherosclerosis, including lipid oxidation, endothelial activation, macrophage foam cell formation, and inflammation. ROS, reactive oxygen species; LDL, low-density lipoprotein; EC, endothelial cell; VSMC, vascular smooth muscle cell; oxLDL, oxidized low-density lipoprotein; mtDNA, mitochondrial DNA; SMC, smooth muscle cell.

results in manganese SOD2 deficiency, which inhibits mitochondrial function, leading to accelerated atherosclerosis. This ultimately induces mitochondria-dependent apoptosis and secondary necrotic core expansion in the endothelial cells.[56,57] Endothelial and vascular smooth muscle cell (VSMC) accumulation, along with oxidative stress, elevates mtDNA damage, alters gene expression, and induces mitochondrial dysfunction; these changes are associated with atherosclerotic plaque formation, further supporting an oxidative stress-dependent mechanism for atherogenesis.[48,58,59]

https://doi.org/10.12997/jla.2023.12.2.132

3. Inflammation in atherogenesis

In light of evidence reported in the literature, the involvement of inflammation has become increasingly accepted as a requirement for atherosclerotic plaque progression.[22,60-63] As mentioned above, oxidative stress-induced lipid modification is an important factor in the initiation of atherogenesis, and oxidative stress also leads to inflammation during atherogenesis.[45,64,65] Multiple observational studies have suggested that a lack of antioxidant protection is associated with inflammatory cytokines and chemokine secretion in both animal and human disease models.[66-68] Inflammation within the atherosclerotic plaque induces ROS production, which further activates the oxidative stress-inflammation feedback loop.[69]

Inflammasomes are induced by lipoprotein-derived lipids in macrophages and vascular wall cells and have recently been highlighted as an important mediator of atherosclerosis.[70-72] The most well-studied inflammasome is NLR family pyrin domain containing 3 (NLRP3). The NLRP3 inflammasome is potentially activated through 2 steps. The first step is priming, which is induced by the recognition of pathogen-associated molecular patterns, such as bacterial lipopolysaccharide or an endogenous danger-associated molecular pattern. The activation of the NLRP3 inflammasome results in the proteolytic activation and secretion of 2 proinflammatory cytokines, interleukin (IL)-1β and IL-18.[73] Because atherosclerotic plaques are filled with various potential danger signals for the activation of the NLRP3 inflammasome, including oxLDL, cholesterol crystals, and double-strand DNA, it subsequently binds the macrophage CD36 with the Toll-like receptor complex, leading to the priming and activation of the NLRP3 inflammasome.[74-76] The cholesterol crystals in the atherosclerotic plaque can activate the NLRP3 inflammasome, and an NLRP3 component deficiency, such as in an LDL receptor-deficient or apolipoprotein E (ApoE)-deficient mouse model, reduces atherosclerosis.[71,77-79] Recent studies have shown that human atherosclerotic lesions have increased expression of the NLRP3 inflammasome.[80-82]

OXIDATIVE STRESS

Oxidative stress is defined as an imbalance between the production of ROS and the antioxidant capacity of the cell. Several studies on the atherogenic effect of oxidative stress have relied on various animal models, including rodents (rats and mice) and human participants. In almost all studies, high oxidative stress induced by ROS has been found to be associated with advanced atherosclerotic plaque formation. Among the several types of ROS, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) and mitochondrial electron chain reactions are closely associated with atherosclerosis (**Fig. 2**). Recent studies conducted both *in vivo* and *in vitro,* in cell culture systems, have provided insights into the molecular/signaling pathways involved in the adverse effect of oxidative stress on arterial disease.

In the following sections, we review the critical mechanisms causally linking oxidative stress to cardiovascular risk. These data provide insights into the potential mechanisms that help explain the risks associated with different types of oxidative stress on the various aspects of atherosclerosis.

1. NOX

Several primary ROS-producing systems have been elucidated depending on the type of oxidative stress. Among the several ROS-producing systems, including xanthine oxidase, uncoupled endothelial nitric oxide synthase, enzymes of the mitochondrial respiratory

https://doi.org/10.12997/jla.2023.12.2.132

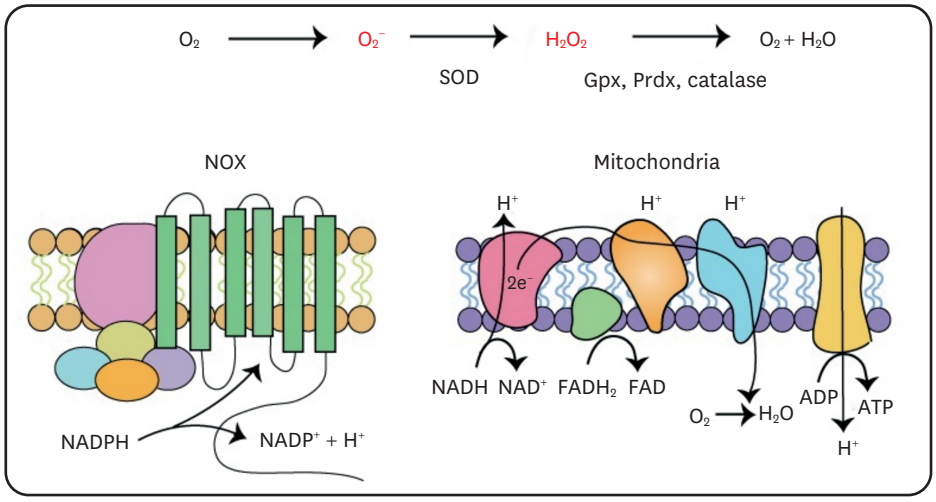

Fig. 2. NOX and mitochondria proton transport are major sources of ROS.
NOX and mitochondrial proton transport are major sources of ROS. Because ROS control is crucial for survival, organelles have various antioxidant enzymes to scavenge ROS.
NOX, nicotinamide adenine dinucleotide phosphate oxidase; ROS, reactive oxygen species; SOD, superoxide dismutase; Gpx, glutathione peroxidase; Prdx, peroxiredoxins; NADPH, nicotinamide adenine dinucleotide phosphate; NADH, nicotinamide adenine dinucleotide (NAD^+) hydrogen (H); NAD^+, nicotinamide adenine dinucleotide; $FADH_2$, dihydroflavine-adenine dinucleotide; FAD, flavin adenine dinucleotide; ADP, adenosine diphosphate; ATP, adenosine triphosphate.

chain, and NOX,[83-85] there is increasing evidence regarding membrane-bound NOX as the major source of superoxide generation. In cultured vascular wall cells, NOX with O^{2-} and H_2O_2 production are increased by several agonists that are associated with pathogenesis, such as angiotensin II (Ang II), thrombin, platelet-derived growth factor, and tumor necrosis factor-α in a time-dependent manner.[86-89] The pro-atherogenic effect of NOX has been demonstrated in both animals and humans, with a deficiency of NOX correlating with mitigated atherosclerotic plaque progression. Knockdown of the p47phox gene, which is a cytosolic component of the NOX complex, resulted in lower levels of aortic O_2^- production and reduced the lesion size in ApoE-deficient mice. NOX2, a specific NOX isoform, is critical for atherogenesis. Higher expression of NOX2 was observed in aortic endothelial cells and macrophages of ApoE-deficient mice, with increased production of aortic O_2^-.[90] In addition, NOX2 deficiency was associated with decreased vascular ROS production, increased NO bioavailability, and substantially mitigated early lesion development.

Further support for NOX-induced oxidative stress in atherosclerosis comes from human studies, which showed a significant positive association of NOX-derived oxidative stress with human atherosclerotic plaques. Similar results were obtained in a mice study where O_2^- production increased with p22phox, a critical component of NOX, and oxidative modification of LDL increased, which was related to atherosclerotic coronary artery disease (CAD).[91] The conclusion of these studies was that O_2^- generation by NOX resulted in foam cell formation and apoptosis, which may be a risk factor for the development of plaque stability and atherogenesis. Similar results were observed in experiments with human intimal smooth muscle and endothelial cells.[92,93]

2. Mitochondrial ROS

As mentioned above, mitochondria are essential cell organelles that provide energy via oxidative phosphorylation and are a potential cellular source of ROS production. Results from

https://doi.org/10.12997/jla.2023.12.2.132

the majority of the reviewed studies suggest that the increased generation of mitochondrial ROS and mitochondrial dysfunction increase the risk for CAD.[51,94-97] Among several targets that are damaged by the increased production of ROS in the mitochondria, mtDNA is the most sensitive to ROS generation as it lacks the protection of a histone-like structure, has an impaired DNA damage-repair system, and shows reduced mtRNA transcription.

Recent studies have directly addressed the relationship between mtDNA damage and the risk of atherosclerosis, as many other studies have focused on exploring atherogenesis with regard to mtDNA damage. The outcomes of human studies have shown mtDNA damage in the aortas of patients with atherosclerosis. Moreover, animal studies have found that mtDNA was increased in macrophages in atherosclerotic plaques of atherosclerosis model mice, such as ApoE- or LDL receptor-deficient mice, and mitochondrial oxidative stress was associated with atherosclerosis.[98,99] Interestingly, mitochondrial dysfunction resulting from manganese SOD2 deficiency was associated with increased mtDNA damage even in the early stages and accelerated atherosclerosis formation in ApoE-deficient mice. The overexpression of catalase, an important antioxidant enzyme, effectively suppressed mitochondrial oxidative stress, which was associated with several downstream effects, including the reduction of atherosclerosis and macrophage inflammation by decreasing the activation of the nuclear factor-κB (NF-κB) pathway.

Mitochondrial ROS have been shown to induce NLRP3 inflammasome-dependent lysosomal damage and inflammasome activation.[74,82,100-102] Damaged mitochondria subsequently bind to NLRP3 to form an inflammasome complex, which triggers NLRP3 inflammasome activation, and this process inhibits autophagy/mitophagy with the release of IL-1β from macrophages. Research on autophagy gene-deficient mice demonstrated that mtDNA release induced by the accumulation of ROS-damaged mitochondria resulted in the activation of the NLRP3 inflammasome.[103,104] Thus, multiple mechanisms may be involved in the mitochondrial ROS-mediated initiation and progression of atherosclerosis.

3. Antioxidants

As mentioned above, to maintain the balance of proper ROS levels, cells have several antioxidant enzymes, including SOD, Prdx, Gpx, and Trx. Many studies over the past few decades have provided substantial evidence that intracellular dysfunction or deficiency of these enzymes induces numerous diseases and mortality due to the ROS imbalance.[105-107] Because increased oxidative stress has been considered as a major cause of CVD, the delicate regulation of ROS by antioxidant enzymes is essential for maintaining cardiovascular health.

AUTOPHAGY AND OXIDATIVE STRESS IN CVD

Autophagy is a highly conserved cellular degradation system for the elimination of unwanted, damaged organelles or aggregated proteins by fusion with lysosomes to protect the cell from environmental stress, such as nutrient depletion or oxidative stress. Autophagy activation has been considered as a survival defense mechanism against cellular damage, and its potential to provide essential amino acids for protein synthesis has been highlighted. Autophagy has recently been considered as a possible connecter between oxidative stress and cardiovascular pathology. Not only is the activation of autophagy a defense against extracellular or intracellular stress, but it also inversely induces autophagic cell death by destroying important cellular organelles, such as mitochondria and the endoplasmic reticulum (ER), when excessively activated.

https://doi.org/10.12997/jla.2023.12.2.132

Here we explore the growing evidence for the role of autophagy in the etiology of CVD, particularly its correlation with the previously described factors that are associated with CVD and enhance its pathogenesis.

1. Evidence that autophagy regulates atherosclerosis

The observed evidence indicates the essential role of autophagy in the development of CVD; in particular, both autophagy and atherosclerosis are closely related to cholesterol metabolism and vascular inflammation. Interestingly, the current understanding of autophagy is that it plays an essential role in the regulation of lipid metabolism. Autophagy delivers lipids from lipid droplets to lysosomes, where they can be hydrolyzed by the lysosomal acid lipase for cholesterol efflux from macrophage foam cells, thereby inhibiting atherogenesis.[108,111] Indeed, wild-type p53-induced phosphatase 1 (Wip1) deficiency induced the suppression of foam cell formation by controlling the autophagy-dependent cholesterol efflux from macrophages.[112,113] In addition, the suppression of autophagy via the silencing of autophagy protein 5 (ATG5), a major component of autophagy initiation, or treatment with autophagy inhibitor 3-methyladenine significantly suppressed cholesterol efflux from macrophages by attenuating autophagy activation.[114] Moreover, observations of ATG5-deficient macrophages demonstrated that autophagy became dysfunctional in atherogenesis, and its deficiency promoted atherosclerosis through macrophage foam cell formation and inflammasome hyperactivation through oxidative stress.[108,115] Additionally, ATG16L1, an essential protein for the early stage of autophagy, has been found to be abundantly expressed in phagocytic cells associated with foam cell formation and could contribute to atherogenesis and the development of plaque vulnerability.[116] Existing studies have focused on oxidative stress and lipid metabolism, both of which cause and increase the incidence of cardiovascular-related atherosclerosis.[117] Prdx is an antioxidant enzyme that is highly dependent on H_2O_2 which is a major ROS in atherosclerosis. Excessive oxidative stress from Prdx1-deficient macrophages enhanced the autophagic dysfunction of lipid metabolism in atherosclerosis.[118]

However, results from studies on the cells of the vascular wall suggest that excessive autophagy increases the risk of cell death.[119] Macrophage-specific ATG5 deficiency promotes oxidative stress, which activates NF-κB in macrophages and inflammation hyperactivation, thus enhancing plaque necrosis.[120] Macrophage apoptosis is considered a promising therapeutic approach for plaque stabilization, and these results suggest that intact autophagy stabilizes atherosclerotic plaques by suppressing macrophage inflammation. Recent evidence has suggested that the phagocytosis of macrophages that are dying via autophagy results in inflammasome activation and inflammatory factor release. Similar to Prdx1 deficiency, atherosclerosis was accelerated in Prdx2-deficient mice by enhancing inflammation through the NF-κB signaling pathway, including p65, c-Jun, c-Jun N-terminal kinases, and p38 mitogen-activated protein kinase.[121] Although this paper did not elucidate the autophagy function in context, the possible autophagy function in oxidative stress-mediated atherogenesis could not be excluded.

Further evidence of the relationship between autophagy and oxidative stress has been found in endothelial cells. It has been shown that oxidative stress initiates autophagy activation in human endothelial cells.[122] Recent findings indicate that autophagy in endothelial cells is a key regulator of the maintenance of redox and inflammation balance in endothelial cell responses to shear stress.[123,124] However, similar to macrophages, excessive autophagy can induce the autophagic death of endothelial cells, and inefficient autophagy contributes to the development of atherosclerosis with inflammation, apoptosis, and senescent

https://doi.org/10.12997/jla.2023.12.2.132

phenotypes.[44,125-127] These findings reveal that autophagy not only plays a protective role in maintaining endothelial cell function, but may also be a key inducer of atherogenesis when excessively activated or dysfunctional.

Recent evidence has elucidated that smooth muscle cells are crucial cells during atherogenesis and could be regulated by autophagy.[128-130] As mentioned above, autophagy is activated by cellular stress, especially oxidative stress or oxLDL, in atherogenesis. Mitophagy of smooth muscle cells plays a protective role in VSMCs against apoptosis induced by oxLDL through the removal of damaged mitochondria and promotes cell survival during atherogenesis.[131] However, high levels of oxLDL augment autophagy, and excessive autophagy activation in smooth muscle cells causes autophagic cell death of the smooth muscle cells on the fibrous cap, which may lead to plaque destabilization. VSMCs of ATG7 knockout mice showed accelerated atherosclerotic plaque formation with enhanced plaque cell death, an increased number of infiltrating macrophages, fibrous cap thickening, and increased collagen content.[132] To summarize, autophagy can protect against cell damage and cellular death or it can activate atherogenesis in various atherosclerosis-related cell types, depending on the extent of autophagy activation through oxidative stress.

2. Evidence that autophagy regulates aortic aneurysm

Aortic aneurysm is the second deadliest aortic disease, and it can be induced by a chronic inflammatory disease, such as atherosclerosis. Although the development of aortic aneurysm has been thoroughly elucidated, the precise mechanism by which cellular and molecular factors induce the pathogenesis of aortic aneurysm remains unclear.

A few studies have explored the possible relationship between the role of autophagy and the pathogenesis of abdominal aortic aneurysm. Similar to atherosclerosis, NADPH is upregulated in human abdominal aortic aneurysm samples. However, NOX deficiency enhanced macrophage inflammation through the secretion of IL-1β and matrix metalloproteinase-9, thereby disrupting the tissue-remodeling function in a mouse abdominal aortic aneurysm model.[133] Additionally, Prdx2-deficient mice also showed an increase in oxidative stress and the inflammatory response, as well as accelerated abdominal aortic aneurysm progression.[134] In both studies, a possible association was observed between autophagy activation in the context of oxidative stress in conjunction with macrophage inflammation activation in mouse models of abdominal aortic aneurysm.

Direct evidence has been adduced from a VSMC autophagy-associated aortic aneurysm model.[135,136] The VSMC phenotype changed, showing functional differentiation towards phagocytic-like phenotypes during aortic aneurysm formation. Moreover, the role of autophagy in aortic aneurysm was identified as critical for the preservation of vessel integrity through the limitation of VSMC death and endoplasmic reticulum stress-dependent inflammation in ATG5-deficient mice. Similar to mice, human aortic aneurysm samples showed increased expression of autophagy and ER stress markers in VSMCs. Deficiency in another important autophagy initiation marker, ATG7, also led to significantly increased aortic aneurysm formation compared to the control. This supports the critical role of autophagy in VSMCs, because ATG7 deficiency increased the frequency of aortic aneurysm formation and rupture.[137-139] Although few studies have investigated the link between oxidative stress-induced autophagy and thoracic aortic aneurysm,[140,141] a recent study in mice and humans provided potential mechanisms that explain the risk of aortic aneurysm induced by oxidative stress with autophagy.

https://doi.org/10.12997/jla.2023.12.2.132

3. Evidence that autophagy regulates myocardial infarction

The role of autophagy has recently been investigated in myocardial infarction. The final stage of chronic CVD is heart failure, which is induced by myocardial infarction under ischemic stress or ischemia/reperfusion injury and is associated with increased mortality.[142]

Clinical studies involving patients with CAD or acute myocardial infarction showing upregulated autophagy have suggested the relevance of autophagy because of hypoxia/ischemia in myocardial infarction.[80,143,144] Research has clarified that the autophagy function is required not only to maintain cardiac function, but also to remove damaged mitochondria to protect the cell against hypoxic/ischemic stress.[145] Studies have shown that mitophagy is readily detected in ischemic/reperfusion models to protect cells from mitochondrial abnormalities.[125,146] Moreover, results from mice deficient in autophagy-related genes, including *Ulk1*, *Atg7*, *Atg13*, beclin-1, and damage-regulated autophagy modulator 2, have shown significant increases in the pathology of cardiomyocytes.[147-152]

Interestingly, the excessive activation of autophagy induces severe cardiac damage in response to reoxygenation following a hypoxic/ischemic injury.[153] Reperfusion after ischemia triggers an increase in autophagosome abundance compared to hypoxic/ischemic injuries, suggesting severe induced autophagy dysfunction or impaired autophagic flux.[154] Moreover, ischemia/reperfusion injuries impair autophagosome clearance through a ROS-induced reduction in lysosomal-associated membrane protein-2 and beclin-1 induction, resulting in cardiomyocyte death.[154-156] In addition, autophagy-targeting drugs have been developed, supporting the relationship between autophagy and myocardial infarction.[157-161] Taken together, these previous studies demonstrated that autophagy activation is precisely regulated at each stage of ischemia/reperfusion and is important for enhancing cell survival in ischemic injuries to protect against cardiomyocyte death from reperfusion injuries.

4. Evidence that autophagy regulates hypertension

Lastly, an increasing amount of evidence indicates that autophagy plays a role in the pathophysiological process of ocular hypertension.[162,163] Hypertension is a systemic disease characterized by persistently elevated blood pressure during the systolic phase (over 130 mmHg) and/or diastolic phase (over 80 mmHg) in systemic circulation and is associated with mortality.[164] Since 1990, the number of people with hypertension worldwide has doubled.[165] Although there is a strong correlation between CVD mortality and hypertension, hypertension provokes few notable symptoms; therefore, the recommendation for initial hypertension treatment to prevent CVD is easily overlooked.

Several studies have demonstrated that excessive and dysfunctional autophagy can cause cell death and senesce in an autophagy machinery depletion model.[166,167] In addition, the inhibition of autophagy or silencing of the gene coding for LC3-II in sympathetic premotor neurons resulted in antihypertension in spontaneously hypertensive rats.[168] Moreover, an autophagy inhibitor, 3-methyladenine, significantly reduced blood pressure and arterial wall thickness, leading to improved vascular relaxation in Ang II-treated mice.[169] Although several studies have suggested that autophagy is associated with the pathogenesis of hypertension, a deeper understanding of the pathological mechanism of autophagy involved in hypertension is required for hypertension prevention and treatment.

https://doi.org/10.12997/jla.2023.12.2.132

JLA Journal of Lipid and Atherosclerosis

CONCLUSIONS AND FUTURE PERSPECTIVES

Oxidative stress occurs abundantly throughout all organisms, and antioxidants play a crucial role in maintaining the redox balance and cellular homeostasis. As discussed in this review, autophagy is positively associated with high oxidative stress, and its dysfunction can induce atherogenesis or abdominal aortic aneurysm, which is one of the most frequently occurring pathologies of the arterial wall (**Fig. 3**). Although little is known regarding the expression and function of autophagy in CVD risk, recent studies have suggested that autophagy is a strong therapeutic candidate to prevent and treat numerous diseases, including CVD. Further mechanistically-oriented clinical trials are required to definitively assess the effects of autophagy on CVD risk and various roles of autophagy in the prevention and treatment of CVD by maintaining redox balance.

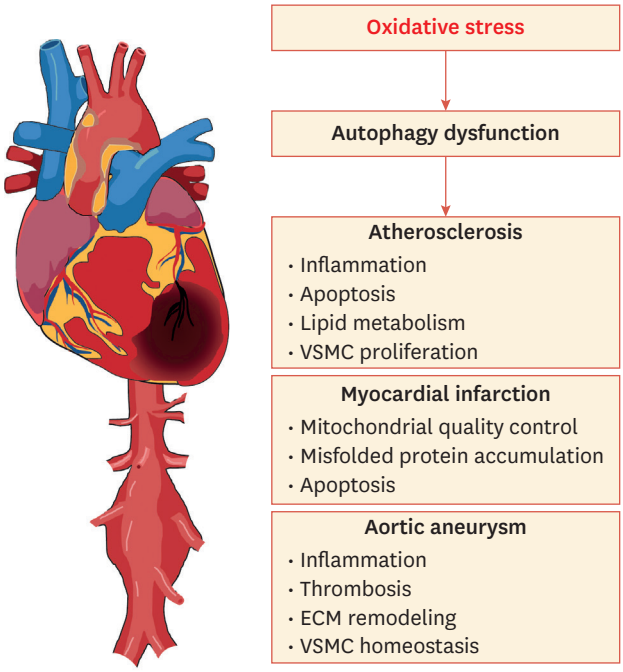

Fig. 3. Effects of impaired autophagy and potential mechanisms affecting CVD.
Excessive oxidative stress impairs autophagy and could affect CVD through these pathogenetic mechanisms.
CVD, cardiovascular disease; VSMC, vascular smooth muscle cell; ECM, extracellular matrix.

REFERENCES

1. Khosravi M, Poursaleh A, Ghasempour G, Farhad S, Najafi M. The effects of oxidative stress on the development of atherosclerosis. Biol Chem 2019;400:711-732.
PUBMED | CROSSREF
2. Hopkins BL, Neumann CA. Redoxins as gatekeepers of the transcriptional oxidative stress response. Redox Biol 2019;21:101104.
PUBMED | CROSSREF
3. Seifried HE, Anderson DE, Fisher EI, Milner JA. A review of the interaction among dietary antioxidants and reactive oxygen species. J Nutr Biochem 2007;18:567-579.
PUBMED | CROSSREF
4. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nat Rev Mol Cell Biol 2020;21:363-383.
PUBMED | CROSSREF

https://doi.org/10.12997/jla.2023.12.2.132

5. Kamata H, Hirata H. Redox regulation of cellular signalling. Cell Signal 1999;11:1-14.
PUBMED | CROSSREF
6. Yang S, Lian G. ROS and diseases: role in metabolism and energy supply. Mol Cell Biochem 2020;467:1-12.
PUBMED | CROSSREF
7. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J 2012;5:9-19.
PUBMED | CROSSREF
8. Rhee SG, Bae YS, Lee SR, Kwon J. Hydrogen peroxide: a key messenger that modulates protein phosphorylation through cysteine oxidation. Sci STKE 2000;2000:pe1.
PUBMED | CROSSREF
9. Arthur JR. The glutathione peroxidases. Cell Mol Life Sci 2000;57:1825-1835.
PUBMED | CROSSREF
10. Biaglow JE, Miller RA. The thioredoxin reductase/thioredoxin system: novel redox targets for cancer therapy. Cancer Biol Ther 2005;4:6-13.
PUBMED | CROSSREF
11. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44-84.
PUBMED | CROSSREF
12. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol 2019.11:45-63.
PUBMED
13. Ranneh Y, Ali F, Akim AM, Hamid HA, Khazaai H, Fadel A. Crosstalk between reactive oxygen species and pro-inflammatory markers in developing various chronic diseases: a review. Appl Biol Chem 2017;60:327-338.
CROSSREF
14. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med 2010;49:1603-1616.
PUBMED | CROSSREF
15. Sikand G, Severson T. Top 10 dietary strategies for atherosclerotic cardiovascular risk reduction. Am J Prev Cardiol 2020;4:100106.
PUBMED | CROSSREF
16. He C, Bassik MC, Moresi V, Sun K, Wei Y, Zou Z, et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. Nature 2012;481:511-515.
PUBMED | CROSSREF
17. Ohsumi Y. Historical landmarks of autophagy research. Cell Res 2014;24:9-23.
PUBMED | CROSSREF
18. Perrotta I, Carito V, Russo E, Tripepi S, Aquila S, Donato G. Macrophage autophagy and oxidative stress: an ultrastructural and immunoelectron microscopical study. Oxid Med Cell Longev 2011;2011:282739.
PUBMED | CROSSREF
19. Scherz-Shouval R, Elazar Z. Regulation of autophagy by ROS: physiology and pathology. Trends Biochem Sci 2011;36:30-38.
PUBMED | CROSSREF
20. Zhang Y, Morgan MJ, Chen K, Choksi S, Liu ZG. Induction of autophagy is essential for monocyte-macrophage differentiation. Blood 2012;119:2895-2905.
PUBMED | CROSSREF
21. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. Cell 2011;145:341-355.
PUBMED | CROSSREF
22. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature 2011;473:317-325.
PUBMED | CROSSREF
23. Andreou DE, Andreadou I. Atherosclerosis: an inflammatory disease. Pharmakeftiki 2009;22:83-96.
24. Hansson GK, Hermansson A. The immune system in atherosclerosis. Nat Immunol 2011;12:204-212.
PUBMED | CROSSREF
25. Song P, Fang Z, Wang H, Cai Y, Rahimi K, Zhu Y, et al. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. Lancet Glob Health 2020;8:e721-e729.
PUBMED | CROSSREF
26. Milutinović A, Šuput D, Zorc-Pleskovič R. Pathogenesis of atherosclerosis in the tunica intima, media, and adventitia of coronary arteries: an updated review. Bosn J Basic Med Sci 2020;20:21-30.
PUBMED | CROSSREF

27. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: process, indicators, risk factors and new hopes. Int J Prev Med 2014;5:927-946.
PUBMED

28. Yang S, Yuan HQ, Hao YM, Ren Z, Qu SL, Liu LS, et al. Macrophage polarization in atherosclerosis. Clin Chim Acta 2020;501:142-146.
PUBMED | CROSSREF

29. Sorokin V, Vickneson K, Kofidis T, Woo CC, Lin XY, Foo R, et al. Role of vascular smooth muscle cell plasticity and interactions in vessel wall inflammation. Front Immunol 2020;11:599415.
PUBMED | CROSSREF

30. Doran AC, Meller N, McNamara CA. Role of smooth muscle cells in the initiation and early progression of atherosclerosis. Arterioscler Thromb Vasc Biol 2008;28:812-819.
PUBMED | CROSSREF

31. Khatana C, Saini NK, Chakrabarti S, Saini V, Sharma A, Saini RV, et al. Mechanistic insights into the oxidized low-density lipoprotein-induced atherosclerosis. Oxid Med Cell Longev 2020;2020:5245308.
PUBMED | CROSSREF

32. Su LJ, Zhang JH, Gomez H, Murugan R, Hong X, Xu D, et al. Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis. Oxid Med Cell Longev 2019;2019:5080843.
PUBMED | CROSSREF

33. Podrez EA, Febbraio M, Sheibani N, Schmitt D, Silverstein RL, Hajjar DP, et al. Macrophage scavenger receptor CD36 is the major receptor for LDL modified by monocyte-generated reactive nitrogen species. J Clin Invest 2000;105:1095-1108.
PUBMED | CROSSREF

34. Kunjathoor VV, Febbraio M, Podrez EA, Moore KJ, Andersson L, Koehn S, et al. Scavenger receptors class A-I/II and CD36 are the principal receptors responsible for the uptake of modified low density lipoprotein leading to lipid loading in macrophages. J Biol Chem 2002;277:49982-49988.
PUBMED | CROSSREF

35. Febbraio M, Podrez EA, Smith JD, Hajjar DP, Hazen SL, Hoff HF, et al. Targeted disruption of the class B scavenger receptor CD36 protects against atherosclerotic lesion development in mice. J Clin Invest 2000;105:1049-1056.
PUBMED | CROSSREF

36. Janabi M, Yamashita S, Hirano K, Sakai N, Hiraoka H, Matsumoto K, et al. Oxidized LDL-induced NF-kappa B activation and subsequent expression of proinflammatory genes are defective in monocyte-derived macrophages from CD36-deficient patients. Arterioscler Thromb Vasc Biol 2000;20:1953-1960.
PUBMED | CROSSREF

37. Park YM, Febbraio M, Silverstein RL. CD36 modulates migration of mouse and human macrophages in response to oxidized LDL and may contribute to macrophage trapping in the arterial intima. J Clin Invest 2009;119:136-145.
PUBMED | CROSSREF

38. Moore KJ, Kunjathoor VV, Koehn SL, Manning JJ, Tseng AA, Silver JM, et al. Loss of receptor-mediated lipid uptake via scavenger receptor A or CD36 pathways does not ameliorate atherosclerosis in hyperlipidemic mice. J Clin Invest 2005;115:2192-2201.
PUBMED | CROSSREF

39. Maxeiner H, Husemann J, Thomas CA, Loike JD, El Khoury J, Silverstein SC. Complementary roles for scavenger receptor A and CD36 of human monocyte-derived macrophages in adhesion to surfaces coated with oxidized low-density lipoproteins and in secretion of H_2O_2. J Exp Med 1998;188:2257-2265.
PUBMED | CROSSREF

40. Allen RM, Michell DL, Cavnar AB, Zhu W, Makhijani N, Contreras DM, et al. LDL delivery of microbial small RNAs drives atherosclerosis through macrophage TLR8. Nat Cell Biol 2022;24:1701-1713.
PUBMED | CROSSREF

41. Cokic I, Chan SF, Guan X, Nair AR, Yang HJ, Liu T, et al. Intramyocardial hemorrhage drives fatty degeneration of infarcted myocardium. Nat Commun 2022;13:6394.
PUBMED | CROSSREF

42. Morris G, Gevezova M, Sarafian V, Maes M. Redox regulation of the immune response. Cell Mol Immunol 2022;19:1079-1101.
PUBMED | CROSSREF

43. Khan SY, Awad EM, Oszwald A, Mayr M, Yin X, Waltenberger B, et al. Premature senescence of endothelial cells upon chronic exposure to TNFα can be prevented by N-acetyl cysteine and plumericin. Sci Rep 2017;7:39501.
PUBMED | CROSSREF

44. Ting KK, Coleman P, Zhao Y, Vadas MA, Gamble JR. The aging endothelium. Vasc Biol 2021;3:R35-R47.
PUBMED | CROSSREF

45. Lozhkin A, Vendrov AE, Pan H, Wickline SA, Madamanchi NR, Runge MS. NADPH oxidase 4 regulates vascular inflammation in aging and atherosclerosis. J Mol Cell Cardiol 2017;102:10-21.
PUBMED | CROSSREF

46. Chahine MN, Dibrov E, Blackwood DP, Pierce GN. Oxidized LDL enhances stretch-induced smooth muscle cell proliferation through alterations in nuclear protein import. Can J Physiol Pharmacol 2012;90:1559-1568.
PUBMED | CROSSREF

47. Peng W, Cai G, Xia Y, Chen J, Wu P, Wang Z, et al. Mitochondrial dysfunction in atherosclerosis. DNA Cell Biol 2019;38:597-606.
PUBMED | CROSSREF

48. Liu CS, Kuo CL, Cheng WL, Huang CS, Lee CF, Wei YH. Alteration of the copy number of mitochondrial DNA in leukocytes of patients with hyperlipidemia. Ann N Y Acad Sci 2005;1042:70-75.
PUBMED | CROSSREF

49. Esposito LA, Melov S, Panov A, Cottrell BA, Wallace DC. Mitochondrial disease in mouse results in increased oxidative stress. Proc Natl Acad Sci U S A 1999;96:4820-4825.
PUBMED | CROSSREF

50. Chan DC. Mitochondrial dynamics and its involvement in disease. Annu Rev Pathol 2020;15:235-259.
PUBMED | CROSSREF

51. Madamanchi NR, Runge MS. Mitochondrial dysfunction in atherosclerosis. Circ Res 2007;100:460-473.
PUBMED | CROSSREF

52. Kinscherf R, Deigner HP, Usinger C, Pill J, Wagner M, Kamencic H, et al. Induction of mitochondrial manganese superoxide dismutase in macrophages by oxidized LDL: its relevance in atherosclerosis of humans and heritable hyperlipidemic rabbits. FASEB J 1997;11:1317-1328.
PUBMED | CROSSREF

53. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 2000;404:787-790.
PUBMED | CROSSREF

54. Wilson FH, Hariri A, Farhi A, Zhao H, Petersen KF, Toka HR, et al. A cluster of metabolic defects caused by mutation in a mitochondrial tRNA. Science 2004;306:1190-1194.
PUBMED | CROSSREF

55. Quan Y, Xin Y, Tian G, Zhou J, Liu X. Mitochondrial ROS-modulated mtDNA: a potential target for cardiac aging. Oxid Med Cell Longev 2020;2020:9423593.
PUBMED | CROSSREF

56. Ballinger SW, Patterson C, Knight-Lozano CA, Burow DL, Conklin CA, Hu Z, et al. Mitochondrial integrity and function in atherogenesis. Circulation 2002;106:544-549.
PUBMED | CROSSREF

57. Harrison CM, Pompilius M, Pinkerton KE, Ballinger SW. Mitochondrial oxidative stress significantly influences atherogenic risk and cytokine-induced oxidant production. Environ Health Perspect 2011;119:676-681.
PUBMED | CROSSREF

58. Ballinger SW, Patterson C, Yan CN, Doan R, Burow DL, Young CG, et al. Hydrogen peroxide- and peroxynitrite-induced mitochondrial DNA damage and dysfunction in vascular endothelial and smooth muscle cells. Circ Res 2000;86:960-966.
PUBMED | CROSSREF

59. Piantadosi CA. Mitochondrial DNA, oxidants, and innate immunity. Free Radic Biol Med 2020;152:455-461.
PUBMED | CROSSREF

60. Cannizzo B, Quesada I, Militello R, Amaya C, Miatello R, Cruzado M, et al. Tempol attenuates atherosclerosis associated with metabolic syndrome via decreased vascular inflammation and NADPH-2 oxidase expression. Free Radic Res 2014;48:526-533.
PUBMED | CROSSREF

61. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-1143.
PUBMED | CROSSREF

62. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol 2006;6:508-519.
PUBMED | CROSSREF

63. Lu N, Cheng W, Liu D, Liu G, Cui C, Feng C, et al. NLRP3-mediated inflammation in atherosclerosis and associated therapeutics. Front Cell Dev Biol 2022;10:823387.
PUBMED | CROSSREF

64. Kim YW, West XZ, Byzova TV. Inflammation and oxidative stress in angiogenesis and vascular disease. J Mol Med (Berl) 2013;91:323-328.
PUBMED | CROSSREF

65. Kong P, Cui ZY, Huang XF, Zhang DD, Guo RJ, Han M. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. Signal Transduct Target Ther 2022;7:131.
PUBMED | CROSSREF

66. Hopps E, Noto D, Caimi G, Averna MR. A novel component of the metabolic syndrome: the oxidative stress. Nutr Metab Cardiovasc Dis 2010;20:72-77.
PUBMED | CROSSREF

67. Iyer A, Fairlie DP, Prins JB, Hammock BD, Brown L. Inflammatory lipid mediators in adipocyte function and obesity. Nat Rev Endocrinol 2010;6:71-82.
PUBMED | CROSSREF

68. Leopold JA, Loscalzo J. Oxidative risk for atherothrombotic cardiovascular disease. Free Radic Biol Med 2009;47:1673-1706.
PUBMED | CROSSREF

69. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative stress and inflammation: what polyphenols can do for us? Oxid Med Cell Longev 2016;2016:7432797.
PUBMED | CROSSREF

70. Sharma A, Tate M, Mathew G, Vince JE, Ritchie RH, de Haan JB. Oxidative stress and NLRP3-inflammasome activity as significant drivers of diabetic cardiovascular complications: therapeutic implications. Front Physiol 2018;9:114.
PUBMED | CROSSREF

71. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010;464:1357-1361.
PUBMED | CROSSREF

72. Zheng D, Liwinski T, Elinav E. Inflammasome activation and regulation: toward a better understanding of complex mechanisms. Cell Discov 2020;6:36.
PUBMED | CROSSREF

73. Wang Z, Zhang S, Xiao Y, Zhang W, Wu S, Qin T, et al. NLRP3 inflammasome and inflammatory diseases. Oxid Med Cell Longev 2020;2020:4063562.
PUBMED | CROSSREF

74. Heid ME, Keyel PA, Kamga C, Shiva S, Watkins SC, Salter RD. Mitochondrial reactive oxygen species induces NLRP3-dependent lysosomal damage and inflammasome activation. J Immunol 2013;191:5230-5238.
PUBMED | CROSSREF

75. Zhang H, Fu R, Guo C, Huang Y, Wang H, Wang S, et al. Anti-dsDNA antibodies bind to TLR4 and activate NLRP3 inflammasome in lupus monocytes/macrophages. J Transl Med 2016;14:156.
PUBMED | CROSSREF

76. Yang Y, Wang H, Kouadir M, Song H, Shi F. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. Cell Death Dis 2019;10:128.
PUBMED | CROSSREF

77. Wang R, Wang Y, Mu N, Lou X, Li W, Chen Y, et al. Activation of NLRP3 inflammasomes contributes to hyperhomocysteinemia-aggravated inflammation and atherosclerosis in ApoE-deficient mice. Lab Invest 2017;97:922-934.
PUBMED | CROSSREF

78. Zhang X, Misra SK, Moitra P, Zhang X, Jeong SJ, Stitham J, et al. Use of acidic nanoparticles to rescue macrophage lysosomal dysfunction in atherosclerosis. Autophagy 2023;19:886-903.
PUBMED | CROSSREF

79. Liu S, Tao J, Duan F, Li H, Tan H. HHcy induces pyroptosis and atherosclerosis via the lipid raft-mediated NOX-ROS-NLRP3 inflammasome pathway in ApoE$^{-/-}$ mice. Cells 2022;11:2438.
PUBMED | CROSSREF

80. Bullón P, Cano-García FJ, Alcocer-Gómez E, Varela-López A, Roman-Malo L, Ruiz-Salmerón RJ, et al. Could NLRP3-inflammasome be a cardiovascular risk biomarker in acute myocardial infarction patients? Antioxid Redox Signal 2017;27:269-275.
PUBMED | CROSSREF

81. Sokolova M, Sahraoui A, Høyem M, Øgaard J, Lien E, Aukrust P, et al. NLRP3 inflammasome mediates oxidative stress-induced pancreatic islet dysfunction. Am J Physiol Endocrinol Metab 2018;315:E912-E923.
PUBMED | CROSSREF

82. Yu JW, Lee MS. Mitochondria and the NLRP3 inflammasome: physiological and pathological relevance. Arch Pharm Res 2016;39:1503-1518.
PUBMED | CROSSREF

83. Brandes RP, Kreuzer J. Vascular NADPH oxidases: molecular mechanisms of activation. Cardiovasc Res 2005;65:16-27.
PUBMED | CROSSREF

84. Förstermann U, Xia N, Li H. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. Circ Res 2017;120:713-735.
PUBMED | CROSSREF

85. Li H, Horke S, Förstermann U. Vascular oxidative stress, nitric oxide and atherosclerosis. Atherosclerosis 2014;237:208-219.
PUBMED | CROSSREF

86. Patterson C, Ruef J, Madamanchi NR, Barry-Lane P, Hu Z, Horaist C, et al. Stimulation of a vascular smooth muscle cell NAD(P)H oxidase by thrombin. Evidence that p47(phox) may participate in forming this oxidase *in vitro* and *in vivo*. J Biol Chem 1999;274:19814-19822.
PUBMED | CROSSREF

87. Ushio-Fukai M, Zafari AM, Fukui T, Ishizaka N, Griendling KK. p22phox is a critical component of the superoxide-generating NADH/NADPH oxidase system and regulates angiotensin II-induced hypertrophy in vascular smooth muscle cells. J Biol Chem 1996;271:23317-23321.
PUBMED | CROSSREF

88. Hilenski LL, Griendling KK. Vascular smooth muscle. In: Creager MA, Beckman JA, Loscalzo J, editors. Vascular medicine: a companion to Braunwald's heart disease. 2nd ed. Philadelphia (PA): Saunders; 2013. p.25-42.

89. Park JM, Do VQ, Seo YS, Kim HJ, Nam JH, Yin MZ, et al. NADPH oxidase 1 mediates acute blood pressure response to angiotensin II by contributing to calcium influx in vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 2022;42:e117-e130.
PUBMED | CROSSREF

90. Judkins CP, Diep H, Broughton BR, Mast AE, Hooker EU, Miller AA, et al. Direct evidence of a role for Nox2 in superoxide production, reduced nitric oxide bioavailability, and early atherosclerotic plaque formation in ApoE$^{-/-}$ mice. Am J Physiol Heart Circ Physiol 2010;298:H24-H32.
PUBMED | CROSSREF

91. Azumi H, Inoue N, Ohashi Y, Terashima M, Mori T, Fujita H, et al. Superoxide generation in directional coronary atherectomy specimens of patients with angina pectoris: important role of NAD(P)H oxidase. Arterioscler Thromb Vasc Biol 2002;22:1838-1844.
PUBMED | CROSSREF

92. Kalinina N, Agrotis A, Tararak E, Antropova Y, Kanellakis P, Ilyinskaya O, et al. Cytochrome b558-dependent NAD(P)H oxidase-phox units in smooth muscle and macrophages of atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2002;22:2037-2043.
PUBMED | CROSSREF

93. Pandey AK, Waldeck-Weiermair M, Wells QS, Xiao W, Yadav S, Eroglu E, et al. Expression of CD70 modulates nitric oxide and redox status in endothelial cells. Arterioscler Thromb Vasc Biol 2022;42:1169-1185.
PUBMED | CROSSREF

94. Sobenin IA, Sazonova MA, Postnov AY, Salonen JT, Bobryshev YV, Orekhov AN. Association of mitochondrial genetic variation with carotid atherosclerosis. PLoS One 2013;8:e68070.
PUBMED | CROSSREF

95. Li X, Fang P, Li Y, Kuo YM, Andrews AJ, Nanayakkara G, et al. Mitochondrial reactive oxygen species mediate lysophosphatidylcholine-induced endothelial cell activation. Arterioscler Thromb Vasc Biol 2016;36:1090-1100.
PUBMED | CROSSREF

96. Song M, Chen Y, Gong G, Murphy E, Rabinovitch PS, Dorn GW 2nd. Super-suppression of mitochondrial reactive oxygen species signaling impairs compensatory autophagy in primary mitophagic cardiomyopathy. Circ Res 2014;115:348-353.
PUBMED | CROSSREF

97. Ming XF, Rajapakse AG, Yepuri G, Xiong Y, Carvas JM, Ruffieux J, et al. Arginase II promotes macrophage inflammatory responses through mitochondrial reactive oxygen species, contributing to insulin resistance and atherogenesis. J Am Heart Assoc 2012;1:e000992.
PUBMED | CROSSREF

98. Wang Y, Wang GZ, Rabinovitch PS, Tabas I. Macrophage mitochondrial oxidative stress promotes atherosclerosis and nuclear factor-κB-mediated inflammation in macrophages. Circ Res 2014;114:421-433.
PUBMED | CROSSREF

99. Li J, Huynh L, Cornwell WD, Tang MS, Simborio H, Huang J, et al. Electronic cigarettes induce mitochondrial DNA damage and trigger TLR9 (Toll-like receptor 9)-mediated atherosclerosis. Arterioscler Thromb Vasc Biol 2021;41:839-853.
PUBMED | CROSSREF

100. Hou Y, Wang Q, Han B, Chen Y, Qiao X, Wang L. CD36 promotes NLRP3 inflammasome activation via the mtROS pathway in renal tubular epithelial cells of diabetic kidneys. Cell Death Dis 2021;12:523.
PUBMED | CROSSREF

101. Chen ML, Zhu XH, Ran L, Lang HD, Yi L, Mi MT. Trimethylamine-N-oxide induces vascular inflammation by activating the NLRP3 inflammasome through the SIRT3-SOD2-mtROS signaling pathway. J Am Heart Assoc 2017;6:e006347.
PUBMED | CROSSREF

102. Usui F, Shirasuna K, Kimura H, Tatsumi K, Kawashima A, Karasawa T, et al. Inflammasome activation by mitochondrial oxidative stress in macrophages leads to the development of angiotensin II-induced aortic aneurysm. Arterioscler Thromb Vasc Biol 2015;35:127-136.
PUBMED | CROSSREF

103. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 2011;12:222-230.
PUBMED | CROSSREF

104. Nakashima Y, Gotoh K, Mizuguchi S, Setoyama D, Takata Y, Kanno T, et al. Attenuating effect of *Chlorella* extract on NLRP3 inflammasome activation by mitochondrial reactive oxygen species. Front Nutr 2021;8:763492.
PUBMED | CROSSREF

105. Taniyama Y, Griendling KK. Reactive oxygen species in the vasculature: molecular and cellular mechanisms. Hypertension 2003;42:1075-1081.
PUBMED | CROSSREF

106. Cervantes Gracia K, Llanas-Cornejo D, Husi H. CVD and oxidative stress. J Clin Med 2017;6:22.
PUBMED | CROSSREF

107. Choi MH, Lee IK, Kim GW, Kim BU, Han YH, Yu DY, et al. Regulation of PDGF signalling and vascular remodelling by peroxiredoxin II. Nature 2005;435:347-353.
PUBMED | CROSSREF

108. Ouimet M, Franklin V, Mak E, Liao X, Tabas I, Marcel YL. Autophagy regulates cholesterol efflux from macrophage foam cells via lysosomal acid lipase. Cell Metab 2011;13:655-667.
PUBMED | CROSSREF

109. Liao X, Sluimer JC, Wang Y, Subramanian M, Brown K, Pattison JS, et al. Macrophage autophagy plays a protective role in advanced atherosclerosis. Cell Metab 2012;15:545-553.
PUBMED | CROSSREF

110. Jeong SJ, Lee MN, Oh GT. The role of macrophage lipophagy in reverse cholesterol transport. Endocrinol Metab (Seoul) 2017;32:41-46.
PUBMED | CROSSREF

111. Emanuel R, Sergin I, Bhattacharya S, Turner J, Epelman S, Settembre C, et al. Induction of lysosomal biogenesis in atherosclerotic macrophages can rescue lipid-induced lysosomal dysfunction and downstream sequelae. Arterioscler Thromb Vasc Biol 2014;34:1942-1952.
PUBMED | CROSSREF

112. Le Guezennec X, Brichkina A, Huang YF, Kostromina E, Han W, Bulavin DV. Wip1-dependent regulation of autophagy, obesity, and atherosclerosis. Cell Metab 2012;16:68-80.
PUBMED | CROSSREF

113. Shreeram S, Demidov ON, Hee WK, Yamaguchi H, Onishi N, Kek C, et al. Wip1 phosphatase modulates ATM-dependent signaling pathways. Mol Cell 2006;23:757-764.
PUBMED | CROSSREF

114. Han XB, Li HX, Jiang YQ, Wang H, Li XS, Kou JY, et al. Upconversion nanoparticle-mediated photodynamic therapy induces autophagy and cholesterol efflux of macrophage-derived foam cells via ROS generation. Cell Death Dis 2017;8:e2864.
PUBMED | CROSSREF

115. Razani B, Feng C, Coleman T, Emanuel R, Wen H, Hwang S, et al. Autophagy links inflammasomes to atherosclerotic progression. Cell Metab 2012;15:534-544.
PUBMED | CROSSREF

116. Magné J, Gustafsson P, Jin H, Maegdefessel L, Hultenby K, Wernerson A, et al. ATG16L1 expression in carotid atherosclerotic plaques is associated with plaque vulnerability. Arterioscler Thromb Vasc Biol 2015;35:1226-1235.
PUBMED | CROSSREF

117. Wang Y, Ding WX, Li T. Cholesterol and bile acid-mediated regulation of autophagy in fatty liver diseases and atherosclerosis. Biochim Biophys Acta Mol Cell Biol Lipids 2018;1863:726-733.
PUBMED | CROSSREF

118. Jeong SJ, Kim S, Park JG, Jung IH, Lee MN, Jeon S, et al. Prdx1 (peroxiredoxin 1) deficiency reduces cholesterol efflux via impaired macrophage lipophagic flux. Autophagy 2018;14:120-133.
PUBMED | CROSSREF

119. Shan R, Liu N, Yan Y, Liu B. Apoptosis, autophagy and atherosclerosis: relationships and the role of Hsp27. Pharmacol Res 2021;166:105169.
PUBMED | CROSSREF

120. Tabas I. Macrophage death and defective inflammation resolution in atherosclerosis. Nat Rev Immunol 2010;10:36-46.
PUBMED | CROSSREF

121. Park JG, Yoo JY, Jeong SJ, Choi JH, Lee MR, Lee MN, et al. Peroxiredoxin 2 deficiency exacerbates atherosclerosis in apolipoprotein E-deficient mice. Circ Res 2011;109:739-749.
PUBMED | CROSSREF

122. Shen W, Tian C, Chen H, Yang Y, Zhu D, Gao P, et al. Oxidative stress mediates chemerin-induced autophagy in endothelial cells. Free Radic Biol Med 2013;55:73-82.
PUBMED | CROSSREF

123. Liu W, Song H, Xu J, Guo Y, Zhang C, Yao Y, et al. Low shear stress inhibits endothelial mitophagy via caveolin-1/miR-7-5p/SQSTM1 signaling pathway. Atherosclerosis 2022;356:9-17.
PUBMED | CROSSREF

124. Bharath LP, Mueller R, Li Y, Ruan T, Kunz D, Goodrich R, et al. Impairment of autophagy in endothelial cells prevents shear-stress-induced increases in nitric oxide bioavailability. Can J Physiol Pharmacol 2014;92:605-612.
PUBMED | CROSSREF

125. Tahrir FG, Langford D, Amini S, Mohseni Ahooyi T, Khalili K. Mitochondrial quality control in cardiac cells: mechanisms and role in cardiac cell injury and disease. J Cell Physiol 2019;234:8122-8133.
PUBMED | CROSSREF

126. Wang Y, Song X, Li Z, Liu N, Yan Y, Li T, et al. MicroRNA-103 protects coronary artery endothelial cells against h_2o_2-induced oxidative stress via BNIP3-mediated end-stage autophagy and antipyroptosis pathways. Oxid Med Cell Longev 2020;2020:8351342.
PUBMED | CROSSREF

127. Takagaki Y, Lee SM, Dongqing Z, Kitada M, Kanasaki K, Koya D. Endothelial autophagy deficiency induces IL6 - dependent endothelial mesenchymal transition and organ fibrosis. Autophagy 2020;16:1905-1914.
PUBMED | CROSSREF

128. Hu M, Jia F, Huang WP, Li X, Hu DF, Wang J, et al. Substrate stiffness differentially impacts autophagy of endothelial cells and smooth muscle cells. Bioact Mater 2020;6:1413-1422.
PUBMED | CROSSREF

129. Zhao Q, Li J, Ko WH, Kwan YW, Jiang L, Sun L, et al. TRPM2 promotes autophagic degradation in vascular smooth muscle cells. Sci Rep 2020;10:20719.
PUBMED | CROSSREF

130. Qiao L, Ma J, Zhang Z, Sui W, Zhai C, Xu D, et al. Deficient chaperone-mediated autophagy promotes inflammation and atherosclerosis. Circ Res 2021;129:1141-1157.
PUBMED | CROSSREF

131. Nahapetyan H, Swiader A, Faccini J, D'Angelo R, Mucher E, Elbaz M, et al. Mitophagy acts as a safeguard mechanism against human vascular smooth muscle cell apoptosis induced by atherogenic lipids. Atherosclerosis 2016;252:e200.
CROSSREF

132. Grootaert MO, da Costa Martins PA, Bitsch N, Pintelon I, De Meyer GR, Martinet W, et al. Defective autophagy in vascular smooth muscle cells accelerates senescence and promotes neointima formation and atherogenesis. Autophagy 2015;11:2014-2032.
PUBMED | CROSSREF

133. Kigawa Y, Miyazaki T, Lei XF, Nakamachi T, Oguchi T, Kim-Kaneyama JR, et al. NADPH oxidase deficiency exacerbates angiotensin II-induced abdominal aortic aneurysms in mice. Arterioscler Thromb Vasc Biol 2014;34:2413-2420.
PUBMED | CROSSREF

134. Jeong SJ, Cho MJ, Ko NY, Kim S, Jung IH, Min JK, et al. Deficiency of peroxiredoxin 2 exacerbates angiotensin II-induced abdominal aortic aneurysm. Exp Mol Med 2020;52:1587-1601.
PUBMED | CROSSREF

135. Kubota Y, Folsom AR, Ballantyne CM, Tang W. Lipoprotein(a) and abdominal aortic aneurysm risk: the Atherosclerosis Risk in Communities study. Atherosclerosis 2018;268:63-67.
PUBMED | CROSSREF

136. Li R, Yi X, Wei X, Huo B, Guo X, Cheng C, et al. EZH2 inhibits autophagic cell death of aortic vascular smooth muscle cells to affect aortic dissection. Cell Death Dis 2018;9:180.
PUBMED | CROSSREF

137. Osonoi Y, Mita T, Azuma K, Nakajima K, Masuyama A, Goto H, et al. Defective autophagy in vascular smooth muscle cells enhances cell death and atherosclerosis. Autophagy 2018;14:1991-2006.
PUBMED | CROSSREF

138. Guo J, Wang Z, Xue M, Mi L, Zhao M, Ma C, et al. Metformin protects against abdominal aortic aneurysm by Atg7-induced autophagy. Adv Clin Exp Med 2022;31:59-69.
PUBMED | CROSSREF

139. Mochida A, Mita T, Azuma K, Osonoi Y, Masuyama A, Nakajima K, et al. Defective autophagy in vascular smooth muscle cells enhances the healing of abdominal aortic aneurysm. Physiol Rep 2021;9:e15000.
PUBMED | CROSSREF

140. Wang Y, Zhao ZM, Zhang GX, Yang F, Yan Y, Liu SX, et al. Dynamic autophagic activity affected the development of thoracic aortic dissection by regulating functional properties of smooth muscle cells. Biochem Biophys Res Commun 2016;479:358-364.
PUBMED | CROSSREF

141. Irace FG, Cammisotto V, Valenti V, Forte M, Schirone L, Bartimoccia S, et al. Role of oxidative stress and autophagy in thoracic aortic aneurysms. JACC Basic Transl Sci 2021;6:719-730.
PUBMED | CROSSREF

142. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics-2021 update: a report from the American Heart Association. Circulation 2021;143:e254-e743.
PUBMED | CROSSREF

143. Xie H, Zha E, Zhang Y. Identification of featured metabolism-related genes in patients with acute myocardial infarction. Dis Markers 2020;2020:8880004.
PUBMED | CROSSREF

144. Yan F, Cheng X, Zhao M, Gong S, Han Y, Ding L, et al. Loss of Wip1 aggravates brain injury after ischaemia/reperfusion by overactivating microglia. Stroke Vasc Neurol 2021;6:344-351.
PUBMED | CROSSREF

145. Zuo W, Zhang S, Xia CY, Guo XF, He WB, Chen NH. Mitochondria autophagy is induced after hypoxic/ischemic stress in a Drp1 dependent manner: the role of inhibition of Drp1 in ischemic brain damage. Neuropharmacology 2014;86:103-115.
PUBMED | CROSSREF

146. Huang J, Li R, Wang C. The role of mitochondrial quality control in cardiac ischemia/reperfusion injury. Oxid Med Cell Longev 2021;2021:5543452.
PUBMED | CROSSREF

147. Kamada Y, Funakoshi T, Shintani T, Nagano K, Ohsumi M, Ohsumi Y. Tor-mediated induction of autophagy via an Apg1 protein kinase complex. J Cell Biol 2000;150:1507-1513.
PUBMED | CROSSREF

148. Matsui Y, Takagi H, Qu X, Abdellatif M, Sakoda H, Asano T, et al. Distinct roles of autophagy in the heart during ischemia and reperfusion: roles of AMP-activated protein kinase and Beclin 1 in mediating autophagy. Circ Res 2007;100:914-922.
PUBMED | CROSSREF

149. Pattison JS, Osinska H, Robbins J. Atg7 induces basal autophagy and rescues autophagic deficiency in CryABR120G cardiomyocytes. Circ Res 2011;109:151-160.
PUBMED | CROSSREF

150. Kaizuka T, Mizushima N. Atg13 is essential for autophagy and cardiac development in mice. Mol Cell Biol 2015;36:585-595.
PUBMED | CROSSREF

151. Salo PP, Vaara S, Kettunen J, Pirinen M, Sarin AP, Huikuri H, et al. Genetic variants on chromosome 1p13.3 are associated with non-ST elevation myocardial infarction and the expression of DRAM2 in the Finnish population. PLoS One 2015;10:e0140576.
PUBMED | CROSSREF

152. Song E, Da Eira D, Jani S, Sepa-Kishi D, Vu V, Hunter H, et al. Cardiac autophagy deficiency attenuates ANP production and disrupts myocardial-adipose cross talk, leading to increased fat accumulation and metabolic dysfunction. Diabetes 2021;70:51-61.
PUBMED | CROSSREF

153. Xiao C, Wang K, Xu Y, Hu H, Zhang N, Wang Y, et al. Transplanted mesenchymal stem cells reduce autophagic flux in infarcted hearts via the exosomal transfer of miR-125b. Circ Res 2018;123:564-578.
PUBMED | CROSSREF

154. Ma X, Liu H, Foyil SR, Godar RJ, Weinheimer CJ, Hill JA, et al. Impaired autophagosome clearance contributes to cardiomyocyte death in ischemia/reperfusion injury. Circulation 2012;125:3170-3181.
PUBMED | CROSSREF

155. Qian J, Ren X, Wang X, Zhang P, Jones WK, Molkentin JD, et al. Blockade of Hsp20 phosphorylation exacerbates cardiac ischemia/reperfusion injury by suppressed autophagy and increased cell death. Circ Res 2009;105:1223-1231.
PUBMED | CROSSREF

156. Chen W, Lv L, Nong Z, Chen X, Pan X, Chen C. Hyperbaric oxygen protects against myocardial ischemia-reperfusion injury through inhibiting mitochondria dysfunction and autophagy. Mol Med Rep 2020;22:4254-4264.
PUBMED | CROSSREF

157. Wu D, Zhang K, Hu P. The role of autophagy in acute myocardial infarction. Front Pharmacol 2019;10:551.
PUBMED | CROSSREF

158. Sciarretta S, Yee D, Nagarajan N, Bianchi F, Saito T, Valenti V, et al. Trehalose-induced activation of autophagy improves cardiac remodeling after myocardial infarction. J Am Coll Cardiol 2018;71:1999-2010.
PUBMED | CROSSREF

159. Kanamori H, Takemura G, Goto K, Maruyama R, Tsujimoto A, Ogino A, et al. The role of autophagy emerging in postinfarction cardiac remodelling. Cardiovasc Res 2011;91:330-339.
PUBMED | CROSSREF

160. Kanamori H, Takemura G, Goto K, Maruyama R, Ono K, Nagao K, et al. Autophagy limits acute myocardial infarction induced by permanent coronary artery occlusion. Am J Physiol Heart Circ Physiol 2011;300:H2261-H2271.
PUBMED | CROSSREF

161. Maejima Y, Kyoi S, Zhai P, Liu T, Li H, Ivessa A, et al. Mst1 inhibits autophagy by promoting the interaction between Beclin1 and Bcl-2. Nat Med 2013;19:1478-1488.
PUBMED | CROSSREF

162. Koch JC, Lingor P. The role of autophagy in axonal degeneration of the optic nerve. Exp Eye Res 2016;144:81-89.
PUBMED | CROSSREF

163. Liton PB. The autophagic lysosomal system in outflow pathway physiology and pathophysiology. Exp Eye Res 2016;144:29-37.
PUBMED | CROSSREF

164. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med 2001;345:479-486.
PUBMED | CROSSREF

165. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021;398:957-980.
PUBMED | CROSSREF

166. Zhu H, Tannous P, Johnstone JL, Kong Y, Shelton JM, Richardson JA, et al. Cardiac autophagy is a maladaptive response to hemodynamic stress. J Clin Invest 2007;117:1782-1793.
PUBMED | CROSSREF

167. Nakai A, Yamaguchi O, Takeda T, Higuchi Y, Hikoso S, Taniike M, et al. The role of autophagy in cardiomyocytes in the basal state and in response to hemodynamic stress. Nat Med 2007;13:619-624.
PUBMED | CROSSREF

168. Chao YM, Lai MD, Chan JY. Redox-sensitive endoplasmic reticulum stress and autophagy at rostral ventrolateral medulla contribute to hypertension in spontaneously hypertensive rats. Hypertension 2013;61:1270-1280.
PUBMED | CROSSREF

169. Kwon Y, Haam CE, Byeon S, Choi SK, Lee YH. Effects of 3-methyladenine, an autophagy inhibitor, on the elevated blood pressure and arterial dysfunction of angiotensin II-induced hypertensive mice. Biomed Pharmacother 2022;154:113588.
PUBMED | CROSSREF