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Literature Reviews

Atherosclerosis as Age-Related Disease: The Potential of Sirtuins Treatment

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Abstract: Atherosclerosis, a global health concern, has attracted researchers worldwide due to its severe consequences. The elderly are particularly susceptible to cardiovascular diseases and events, making them a high-risk group. Although gaps in our understanding of atherosclerosis pathogenesis persist, it is evident that oxidative stress, endothelial dysfunction, inflammation, mitochondrial dysfunction, and autophagy impairments are key components of its development. Remarkably, these features are also observed in the aging process, suggesting that atherosclerosis may be an aging-associated disease. However, causality relationships between aging, atherosclerosis, and associated mechanisms continue to be speculative. Additionally, the lack of effective therapeutic options for both atherosclerosis and aging poses a significant challenge. Sirtuins hold promise as potential agents in addressing this challenge. This review aims to consolidate evidence on the association between atherosclerosis and vascular aging through mitochondrial dysfunction and discusses the potential role of sirtuins as therapeutic options for atherosclerosis.

Keywords: Atherosclerosis, Cardiovascular Disease, Sirtuins, Aging, CVD

Introduction

Atherosclerosis in Scope of Aging

Atherosclerosis is a complex process involving multiple mechanisms. It begins with endothelial dysfunction, where the inner lining of blood vessels loses its ability to regulate vessel size effectively. The damaged endothelium attracts LDL cholesterol, which accumulates and gets trapped in the artery walls.

As the LDL particles build up, they undergo modifications and are taken up by immune cells called macrophages, forming foam cells.

These foam cells, along with other cells and molecules, contribute to fatty streaks and plaque formation.

The plaque formation triggers an inflammatory response, leading to chronic inflammation in the artery walls. Smooth muscle cells migrate to the affected area, proliferate, and contribute to plaque growth.

Over time, the plaque may undergo changes, including the deposition of calcium and the formation of a fibrous cap. However, factors like increased inflammation can weaken the fibrous cap, making it more susceptible to rupture.

If the fibrous cap ruptures, the plaque's contents are exposed to the bloodstream, resulting in the formation of a blood clot or thrombus. The clot can partially or completely block the artery, leading to disrupted blood flow and severe consequences such as heart attacks or strokes.

It's important to remember that atherosclerosis is influenced by various risk factors like smoking, high blood pressure, high cholesterol, diabetes, obesity, and a sedentary lifestyle. These factors contribute to the development and progression of atherosclerosis.

Cardiac Dysfunction in the Elderly

Elderly individuals commonly experience functional changes in the heart, including diastolic and systolic

dysfunction, as well as electrical dysfunction leading to arrhythmias. These alterations contribute to an increased prevalence of heart failure, atrial fibrillation, and other cardiovascular diseases (Rodgers *et al*., 2019). The elevated occurrence of cardiovascular diseases in this population can be attributed to factors such as heightened oxidative stress, inflammation, apoptosis, and overall myocardial degeneration (Senoner and Dichtl, 2019). Inflammatory factors and other mediators facilitate cardiac remodeling, resulting in significant Extracellular Matrix (ECM) remodeling that disrupts ECM turnover (is part of healthy tissue maintenance, where old proteins are degraded and new proteins formed). Enhanced collagen deposition, hypertrophy, and fibrosis contribute to structural changes and cardiac dysfunction in the elderly (Lu *et al*., 2011). Notably, fibrosis caused by metabolic disorders has been linked to the progression of atrial fibrillation in elderly patients (Pellman and Sheikh, 2015).

The regulation of Matrix Metalloproteinase (MMP) and Tissue Metalloproteinase suppressor (TIMP) levels plays a crucial role in collagen deposition and hypertrophy in the heart. MMPs degrade ECM, including collagen, while TIMPs inhibit MMP activity.

In aging, there's an increase in collagen deposition and hypertrophy.

This is often associated with an imbalance in the regulation of MMPs and TIMPs, leading to an up-regulation of MMPs and/or a down-regulation of TIMPs.

When MMPs are up-regulated or TIMPs are down-regulated, the ECM remodeling process becomes dysregulated. Excessive activity of MMPs and insufficient inhibition by TIMPs result in an increased degradation of collagen in the ECM. This leads to a disruption in ECM turnover, creating an environment favoring collagen deposition. The accumulation of collagen contributes to hypertrophy, involving an increase in cardiac muscle mass and changes in the structure of the heart.

Therefore, in the context of aging and cardiac dysfunction, the elevated expression of MMPs and decreased expression of TIMPs promote collagen deposition and hypertrophy.

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction refers to the impairment or malfunctioning of mitochondria, the organelles responsible for energy production within cells (Rodgers *et al*., 2019). This dysfunction can lead to an imbalance in the production and elimination of Reactive Oxygen Species (ROS), resulting in oxidative stress (Senoner and Dichtl, 2019). Oxidative stress happens with a ROS surplus and the body's antioxidant defenses can't neutralize them (Senoner and Dichtl, 2019). Age-related mitochondrial dysfunction is a major ROS producer (Lu *et al*., 2011).

As mitochondria age, their capacity to produce energy efficiently declines, leading to an accumulation of ROS. This process is further influenced by environmental factors such as exposure to pollutants, radiation, and certain medications (Pellman and Sheikh, 2015).

Excessive ROS can damage cells, causing DNA mutations and lipid peroxidation (Lu *et al*., 2011).

Lipid peroxidation, where ROS harm cellular lipids, is vital in age-related oxidative stress (Izzo *et al*., 2021). PUFAs are highly susceptible to lipid peroxidation due to their high unsaturation.

The peroxidation of lipids produces reactive aldehydes and other toxic byproducts that further contribute to cellular damage and inflammation (Izzo *et al*., 2021; Görlach *et al*., 2015; Eisner *et al*., 2017; Tan *et al*., 2018).

Chronic low-grade inflammation induced by omega-6-enriched diets can also exacerbate oxidative stress and mitochondrial dysfunction (Görlach *et al*., 2015). A diet high in omega-6 fatty acids, commonly found in processed foods and vegetable oils, can disrupt the delicate balance between omega-6 and omega-3 fatty acids. This imbalance promotes inflammation and oxidative stress within cells, further compromising mitochondrial function (Kain *et al*., 2018).

It is important to note that age-associated oxidative stress, in combination with mitochondrial dysfunction, plays a significant role in the progression of several chronic diseases, including cardiovascular diseases, neurodegenerative disorders, and metabolic disorders such as diabetes (Eisner *et al*., 2017).

Vascular Aging and Susceptibility to Atherogenesis

The atherosclerotic disease manifests differently in older individuals compared to younger ones, indicating the influence of various factors on the vascular system. Vascular aging is a critical factor in the susceptibility to atherogenesis among the elderly (Cheng *et al*., 2014). It is important to note that vascular aging and the development of atherosclerosis are distinct, as autopsy studies reveal that some older individuals have minimal or negligible coronary plaque burden despite their age (Head *et al*., 2017). However, the molecular factors and vascular changes associated with aging increase the vulnerability of aging arteries to atherogenesis (Izzo *et al*., 2018). Figure 1 illustrates the complex relationship between vascular aging, atherogenesis, and the potential role of sirtuins as a treatment strategy. Exploring sirtuin biology and its therapeutic potential may uncover innovative approaches to combat atherosclerosis and alleviate the negative effects of vascular aging.

Vascular Aging

Pre/Atherosclerotic Vascular Mitochondrial Dysfunction

Even before the onset of the atherosclerotic process, aging affects the vascular system (Rodgers *et al*., 2019). It is characterized by remodeling of the arterial wall,

endothelial cell dysfunction, collagen deposition, fibrosis, and stiffer vessels (Senoner and Dichtl, 2019). Vascular Smooth Muscle Cells (VSMCs) become more proliferative and demonstrate excessive formation of Reactive Oxygen Species (ROS) and oxidative damage (Jaminon *et al*., 2019). Aging also leads to a disturbed antioxidant ability of endothelial cells, indirectly related to the complexity of the nuclear factor-erythroid-2-related factor 2 signaling (Jaminon *et al*., 2019). These consequences can stimulate hypertension, a key risk factor for Cardiovascular Disease (CVD) (Abdulle *et al*., 2018).

Most studies on vascular aging were conducted on normolipidemic rodent models (Bryda, 2013). They show that mitochondrial dysfunction, a distinctive feature of aging, stimulates vascular aging before atherogenesis (Schuh *et al*., 2014). Mitochondrial dysfunction progresses in the aorta of normolipidemic mice with age, indicated by a decrease in Oxygen Consumption Rate (OCR) at 11 months and a further decline at 18 months (Schuh *et al*., 2014). This is accompanied by mitochondrial DNA (mtDNA) damage, which characterizes the instability of the mitochondrial genome (Schuh *et al*., 2014). Reduced expression of mtDNA helicase Twinkle leads to vascular aging delay, decreased aortic flexibility, and increased stiffness (Tyrrell and Goldstein, 2021) in transgenic mice with elevated Twinkle levels.

Thus, mitochondrial dysfunction plays a key role in aging, particularly in vascular aging (LaRocca *et al*., 2014).

Twinkle, a protein crucial for maintaining mitochondrial DNA stability and function, has been studied in transgenic mice (Tyrrell and Goldstein, 2021). Increasing Twinkle expression enhances mitochondrial function and mitigates the negative effects of aging on the vasculature (Tyrrell and Goldstein, 2021). The decreased progression of vascular aging in these transgenic mice suggests that targeting and improving mitochondrial function, such as through increased Twinkle expression, reduces Reactive Oxygen Species (ROS) production and counteracts oxidative stress in smooth muscle cells (Tyrrell and Goldstein, 2021). Preserving mitochondrial function and reducing dysfunction could help counteract the aging process, especially in vascular aging (Tyrrell and Goldstein, 2021).

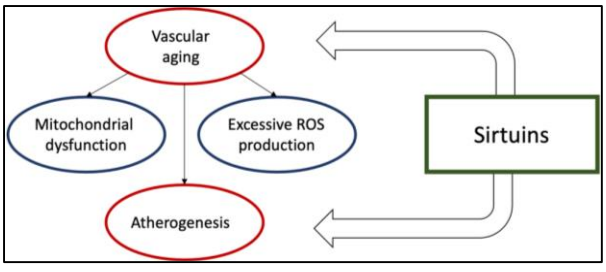

Fig. 1: The simplified scheme of the cause-effect relationship of vascular aging and atherogenesis. Sirtuins are indicated as a potential treatment for atherosclerosis and vascular aging

In conclusion, transgenic mouse studies with increased Twinkle expression provide strong evidence for the role of mitochondrial dysfunction in aging, specifically in vascular aging (Tyrrell and Goldstein, 2021). Improving mitochondrial function attenuates the negative effects of aging on blood vessels, emphasizing the significance of mitochondrial health in combating aging-related changes. Experimental data support the idea that mitochondrial dysfunction and mtDNA instability contribute to vascular aging (LaRocca *et al*., 2014).

Vascular Mitochondrial Dysfunction During Atherogenesis

Atherosclerotic plaques in humans indicate mitochondrial DNA (mtDNA) damage and decreased mitochondrial function. Specifically, areas of the fibrous cap and the nucleus of the plaque show a lower Oxygen Consumption Rate (OCR) compared to the brachial region of the plaque or unaffected areas of the aorta (Yu *et al*., 2017). This finding suggests impaired mitochondrial function and energy metabolism in these regions, highlighting the significance of mitochondrial dysfunction in atherosclerosis and vascular aging.

The ApoE gene encodes apolipoprotein E, involved in lipid metabolism. The ApoE4 variant increases the risk of cardiovascular diseases, including atherosclerosis. Absence or deficiency of ApoE is associated with increased mtDNA damage, as mitochondria are prone to oxidative stress caused by Reactive Oxygen Species (ROS) generated during cellular respiration. ApoE protein possesses antioxidant properties, protecting mitochondria from oxidative damage. Without ApoE, heightened oxidative stress leads to elevated mtDNA damage, impacting mitochondrial function and contributing to vascular aging and atherogenesis.

Twinkle, a DNA helicase enzyme, plays a crucial role in mtDNA replication and maintenance. It unwinds double-stranded mtDNA during replication and helps maintain mtDNA stability. Increasing Twinkle expression in transgenic mice aims to improve mitochondrial function, preserve mtDNA integrity, and counteract the effects of mitochondrial dysfunction on aging processes, including atherosclerosis and vascular aging. Studies in Apoe−/−mice on a standard diet plan showed high damage to vascular mtDNA but not nuclear DNA with aging (Shuo *et al*., 2020). Similarly, atherosclerotic plaques in humans and Apoe−/−mice on a high-fat diet contain lower levels of mitochondrial complex I and complex II compared to undamaged areas of the aorta (Zhang *et al*., 2016).

Apoe−/−mice with twinkle overexpression display reduced necrotic nucleus area in plaques (Yu *et al*., 2017). The connection between mitochondrial dysfunction and ROS is complex. Low ROS levels aid adaptability and

survival, while high levels contribute to age-related cardiovascular disease. Mitochondrial enzymatic pathways disruption or ROS-absorbing enzyme deficiency can affect atherosclerosis development in mice (Senoner and Dichtl, 2019). Mitochondrial dysfunction and mtDNA damage occur in vascular smooth muscle cells and monocytes, correlating with atherosclerotic burden in humans, although changes in ROS levels are not evident (Wang and Tabas, 2014).

Clinical trials on antioxidants in atherosclerotic cardiovascular disease patients show inconsistent positive outcomes. Mitochondrial dysfunction occurs in chronic hyperlipidemia and atherogenesis, promoting atherosclerosis development (Suárez-Rivero *et al*., 2021).

Sirtuins

Sirtuins (SIRT1-7) are NAD + dependent cellular deacetylases, sensing nutrients and metabolism. They play roles in metabolic processes, including inflammation, gluconeogenesis, insulin sensitivity, and the RAAS system (Li, 2013). Studies by Lagouge *et al*. (2006); Baur *et al*. (2012) showed that SIRT1 activation during resveratrol treatment improved metabolic profiles in mice. Over the past two decades, research has highlighted sirtuins' importance in combating aging. Animal studies with sirtuin overexpression, activators, or NAD + precursors have shown improved organ function and lifespan (Bonkowski and Sinclair, 2016; Rizki *et al*., 2011; Moroz *et al*., 2014; Banerjee *et al*., 2012; Whitaker *et al*., 2013; Schmeisser *et al*., 2013).

Data obtained from yeast, worms, fruit flies, and mice showed that sirtuin knockout shortens life expectancy, while genetically modified sirtuin overexpression increases life expectancy. The same is true for sirtuin activators. The seven mammalian sirtuins differ in location and function. SIRT1, SIRT6, and SIRT7 are in the nucleus (Giblin *et al*., 2014) and regulate transcription, energy metabolism, DNA repair, and inflammation. SIRT2 is cytosolic, while SIRT3, SIRT4, and SIRT5 are mitochondrial (Lu *et al*., 2011), interacting with non-histone proteins. Nuclear sirtuins can target non-histone proteins like p53, NF-κB, and PARP1 (Bosch-Presegue and Vaquero, 2014).

The biological activity of sirtuins can be controlled by numerous other upstream factors. This happens at several levels, including transcription, translation, post-translational modifications, protein-protein interactions, and natural compounds or molecules. Sirtuin expression varies based on energy status, being linked to metabolism as a protein family (Zhang *et al*., 2020). For example, Nemoto *et al*. showed that acute nutrient deficiency in mammalian cells at once increased the expression of SIRT1 (Nemoto *et al*., 2004). Posttranslational modifications of phosphorylation can also affect the sirtuin activity. Several kinds of Sirtuin-Activating Compounds (STAC) were discovered and created, including natural compounds (e.g., resveratrol) and synthetic STACs (e.g., SRT1720, SRT2104) (Grabowska *et al*., 2017). Because sirtuins are NAD + dependent enzymes, an alternative method of activating sirtuins is the use of NAD + accelerators (e.g., nicotinamide riboside).

Recent studies highlight the critical role of sirtuins in aging and age-related diseases, including atherosclerosis (Imai and Guarente, 2014). Among them, mitochondrial sirtuins include SIRT3, SIRT4, and SIRT5, while nuclear sirtuins encompass SIRT6 and SIRT7 (Singh *et al*., 2018).

In addition to their general deacetylase activity, every member of the SIRT family has its bonus activity, which is summarized in Table 1.

Table 1: Sirtuins and their main characteristics

Sirtuin	Localization	Additional Activity	Effect on atherosclerosis	Effect on aging	References
SIRT1	Nucleus, mitochondria	Deacetylation Deacylation	lower levels of plasma LDL, cholesterol and atherosclerotic plaques	suppresses cell aging	Gorenne *et al*. (2013)
SIRT2	cytosol	Demyristoylation Deacetylation Deacylation	stabilizes the atherosclerotic plaque, controls lipid metabolism and gluconeogenesis	age-dependent accumulation of isoform 3 of SIRT2 in the CNS	Zhang *et al*. (2018)
SIRT3	mitochondria	Deacetylation decrotonylation	Suppresses oxidative stress	Prevents aging and cancerogenesis	Sun *et al*. (2018)
SIRT4	mitochondria	ADP-ribosylation Delipoylation Deacetylation Deacylation	Prevents inflammation	Prevents inflammation	Kida and Goligorsky (2016)
SIRT5	Mitochondria, cytosol	Desuccinylation Demalonylation Deacetylation	protects the cell from oxidative stress	protects the cell from oxidative stress	Toulassi *et al*. (2021)
SIRT6	Nucleus	Deacetylation ADP-ribosylation Demyristoylation	lowers the level of LDL in plasma	stabilizes the genome to avoids premature cell aging	Li *et al*. (2021)
SIRT7	Nucleus	Deacetylation Desuccinylation	SIRT7 suppresses the development of atherosclerosis	deficiency and accelerates senescence	Ma *et al*. (2019)

Research has indicated that intermittent fasting, which involves cycles of fasting and eating within specific time windows, can activate sirtuins in different tissues and organisms. Intermittent fasting has been associated with an increase in the expression of SIRT1, the most well-known sirtuin member.

SIRT1 is associated with various health benefits, including improved insulin sensitivity, enhanced cellular survival, and protection against age-related diseases (Cheng *et al*., 2014; Koltai *et al*., 2017). One study published in Cell Metabolism in 2017 showed that intermittent fasting in mice increased the expression of SIRT3, another sirtuin isoform, in the liver. SIRT3 is known for its involvement in mitochondrial function and cellular energy metabolism (Mattson *et al*., 2017).

Another study published in Circulation Research in 2014 examined the effects of intermittent fasting in humans. The researchers found that intermittent fasting resulted in increased SIRT1 expression and activity, as well as improvements in various metabolic markers like insulin sensitivity and lipid profiles (Michán *et al*., 2010).

While these studies provide promising insights into the potential benefits of intermittent fasting on sirtuin production, it's important to note that further research is still needed to fully understand the mechanisms and long-term effects. Nonetheless, intermittent fasting has gained attention as a potential strategy to enhance sirtuin activity and promote overall health.

Mitochondrial sirtuins are vital for mitochondrial dynamics, oxidative stress, and various metabolic processes like fatty acid oxidation, glucose metabolism, ketone metabolism, and amino acid metabolism. Overall, sirtuins are crucial for regulating aging and life expectancy.

They also regulate cardiometabolic diseases like cardiac hypertrophy, ischemic heart damage, endothelial dysfunction, and drug cardio-toxicity and lipotoxicity (Kaeberlein *et al*., 1999).

Sirtuins in Ageing and Ageing-Related Diseases

In 1999, it was found that sirtuins have anti-aging properties (Kaeberlein *et al*., 1999). Due to the overexpression of sirtuins, the lifespan of yeast increases by 70%. This is the consequence of the prevention of recombination between rDNA repeats. The ability of sirtuins to increase life expectancy was also revealed in *Drosophila melanogaster* and *Caenorhabditis elegans*. The aging process involves cellular changes, leading to impaired function as cells age. DNA damage is a primary factor, but insufficient repair mechanisms leave cells vulnerable (Satoh *et al*., 2013). Aging is also marked by tissue inflammation and oxidative stress. Sirtuins help slow cell aging and extend lifespan, with SIRT1 and SIRT6 shown to inhibit cell aging in various cell types exposed to oxidative stress (Han *et al*., 2022). Despite the data that the presence of these sirtuins stimulates the premature aging of similar phenotypes in endothelial cells, it was also reported that their overexpression inhibits aging in these cells. Subsequently, this indicates their importance in maintaining cellular aging. As a rule, sirtuins mediate these effects, excluding the possibility of telomere shortening and thereby favoring the rehabilitation of DNA damage and the preservation of the normal state of chromatin condensation (Grabowska *et al*., 2017).

Nuclear sirtuins, including SIRT1, SIRT6, and SIRT7, regulate gene expression by stabilizing chromatin structure. They influence stem cell self-renewal and aging and interact with pathways affecting lifespan, like insulin/IGF-1, AMPK, and FOXO (Lee *et al*., 2019).

Nowadays, the only effective way to increase life expectancy without genetic or pharmacological interventions is Caloric Restriction (CR). Caloric restriction increases life expectancy and resists aging-related diseases in various species, such as rodents, fish, fruit flies, worms, and yeast. There is more and more information about the benefits of the fight against human aging. According to a recent study, caloric restriction was found to decelerate aging and metabolism and prevent aging-related diseases. The potential mechanism is the reduction of systemic oxidative stress by 15% in people who adhere to a lower calorie intake for more than 2 years (Santos *et al*., 2016). Therefore, CR appears to be a promising method of containing changes related to human aging. Sirtuins are extremely important in the phenotypic changes associated with CR. It was reported that the level of all sirtuins, except SIRT4, elevates as a result of caloric restriction (Duan, 2013).

Also, sirtuins target substrates similar to those affected by caloric restriction. In healthy people, SIRT1 is Caloric restriction and exercise induces an increase in lifespan. In human fibroblast cells, this increase requires higher NAD + levels and activation of SIRT1 (Nogueiras *et al*., 2012). In mice on a high-fat diet, a loss of SIRT1 was proven. The same effect was observed in obese people. There is also information that when SIRT1 is turned off, the CR diet does not increase life expectancy (Madeo *et al*., 2019).

The importance of SIRT1 in Caloric Restriction (CR) mediated health benefits is emphasized. Other sirtuins (SIRT3, SIRT5) also play a role in modifying the health span through CR (Houtkooper *et al*., 2012). Sirtuins significantly impact the cardiovascular system, influencing vascular biology and atherogenesis. Reduced SIRT1 expression in human VSMCs with aging correlates with diminished vascular repair potential, decreased stress response, and accelerated aging. It is reported that in mice, the inhibition of SIRT1 in VSMCs creates prerequisites for the development of

atherosclerosis. SIRT1 reduces hypertrophy in vascular smooth muscle cells triggered by angiotensin II, promoting atherosclerosis (Grabowska *et al*., 2017). Endothelial cells play a vital role in vascular homeostasis, with SIRT1 highly expressed and contributing to various physiological functions. SIRT1 dysfunction results in endothelial dysfunction (D'Onofrio *et al*., 2018). Increased SIRT1 expression is associated with endothelial progenitor cell differentiation into endothelial cells. Sirtuin regulation and functions were also studied in the central nervous system, revealing unique spatial and temporal expression patterns in the rat brain across all developmental stages. A reduction in SIRT1 activity in the cerebellum refers to a reduction in motor function caused by aging. To maintain the circadian rhythm, which is disrupted in rats during aging, the interaction between the SIRT1 genes and the biological clock is vital. Sirtuins are recognized for their neuroprotective effects in various neurodegenerative conditions like Alzheimer's, Parkinson's, and Huntington's diseases (Fujita and Yamashita, 2018).

SIRTs: A Chemotherapeutic Target for Atherosclerosis?

SIRT1

SIRT1 is an important protein for endothelial function. It helps reduce inflammation and cell aging by controlling genetic and biochemical factors, including deacetylating p53. The association of p53 with sirtuins is important for several pathways involved in the development and progression of atherosclerosis.

One essential aspect is the regulation of inflammation. Atherosclerosis involves chronic inflammation within blood vessels. P53, together with SIRT1, inhibits inflammation by deacetylating and suppressing the activity of Nuclear Factor Kappa B (NF-κB), a transcription factor that promotes inflammation. This combined action helps reduce plaque formation.

Another significant aspect is the control of cellular senescence. Cellular senescence contributes to atherosclerosis. P53, along with SIRT1 and SIRT6, works to suppress cellular senescence, preventing the accumulation of senescent cells in plaques. P53 activation induces cell cycle arrest or apoptosis in senescent cells, while SIRT1 and SIRT6 regulate specific genes involved in senescence.

P53 and sirtuins manage oxidative stress and DNA repair, crucial for vascular health. SIRT1 and SIRT6 regulate antioxidant defenses, reducing oxidative stress and aiding DNA repair. P53 controls cell survival or apoptosis in severe DNA damage scenarios. Their collaboration preserves genomic integrity and minimizes oxidative stress effects.

Sirtuins, especially SIRT1, deacetylate p53, enhancing its stability and transcription factor function. This regulates the cell cycle, DNA repair, and apoptosis, crucial in atherosclerosis by combating inflammation and DNA damage and reducing plaque formation.

SIRT1 can prevent impaired apoptosis and cell death during oxidative stress or DNA damage, which can be oncogenic. However, studies on mice show that SIRT1 can also inhibit tumors (Man *et al*., 2019). When DNA is damaged, SIRT1 moves to the site and suppresses the transcription of damaged genes to protect the genome. SIRT1 suppresses FOXO3a acetylation, preventing oxidative stress and apoptosis. SRT3025, a SIRT1 activator, reduces LDL and atherosclerotic plaques in mice. SIRT1 boosts eNOS activity, promoting vasodilation and antioxidant effects. SIRT1 activation enhances autophagy, reducing inflammation and atherosclerosis.

SIRT2

SIRT2 has been found to play a key role in stabilizing atherosclerotic plaques, controlling lipid metabolism, and preventing obesity and metabolic diseases that are linked to atherosclerosis (Takeda-Watanabe *et al*., 2012). Studies have shown that SIRT2 stabilizes plaques by preventing macrophages from polarizing to the M1 phenotype. It also enhances lipolysis during fasting by activating FOXO1 and inhibiting PPARϒ (Zhang *et al*., 2018). Additionally, SIRT2 controls gluconeogenesis during fasting periods by stabilizing PEPCK1 through deacetylation (Wang and Tong, 2009).

SIRT3

SIRT3 in mitochondria prevents oxidative stress, critical for atherosclerosis. Knockdown leads to increased reactive oxygen species and cell death. Despite high superoxide dismutase and catalase levels, SIRT3 controls oxidative stress. It also regulates fat oxidation and ketogenesis during calorie restriction, reducing metabolic syndrome and atherosclerosis risk (Zhang *et al*., 2017; Weir *et al*., 2013).

SIRT6

SIRT6 maintains genome stability, regulates LDL cholesterol metabolism, and responds to inflammatory stress. It prevents premature cell aging by deacetylating H3K9 and suppressing Pcsk9, reducing LDL levels and preventing atherosclerosis. By inhibiting NF-kb activity, SIRT6 has anti-inflammatory and anti-aging effects, deacetylating histone H3K9 to reduce inflammation and prevent atherosclerosis (Shi *et al*., 2017; Sasaki *et al*., 2020; Tao *et al*., 2013).

Other Sirtuins

SIRT4 and SIRT3 are mitochondrial. SIRT4 prevents endothelial cell inflammation by inhibiting NF-kb translocation and reducing cytokine expression (Kawahara *et al*., 2009). SIRT7 in the nucleus is vital for

cellular survival and heart hypertrophy, inhibiting atherosclerosis development via Wnt/β-catenin signaling (Tao *et al*., 2015; Ford *et al*., 2006). SIRT5's role in atherosclerosis is unclear, but it may deacetylate CPS1, an enzyme in the urea cycle (Singh *et al*., 2018; Zheng *et al*., 2018).

Discussion

The findings and insights presented in this review shed light on the intricate mechanisms underlying vascular aging, atherosclerosis, and mitochondrial dysfunction. By exploring the novel perspectives of mitochondrial DNA stability, sirtuins, and oxidative stress, we unravel new possibilities for therapeutic interventions in addressing these age-associated cardiovascular conditions.

One significant novelty unveiled in this review is the impact of mitochondrial dysfunction on vascular aging. Mitochondrial dysfunction contributes to endothelial cell dysfunction, collagen deposition, fibrosis, and smooth muscle cell proliferation, leading to vessel stiffness and compromised vascular health. The link between vascular aging and mitochondrial dysfunction reveals an exciting avenue for further research and therapeutic development.

Intriguingly, sirtuins emerge as potential therapeutic targets in combating vascular aging and atherosclerosis. The diverse functions of sirtuins, particularly SIRT1 to SIRT7, unveil their active involvement in regulating cellular processes, including metabolism, inflammation, and oxidative stress response. Manipulating these sirtuins could potentially restore or enhance mitochondrial function, offer protection against oxidative stress and ultimately delay or mitigate the progression of age-related vascular diseases.

One specific protein, Twinkle, presents a novel therapeutic possibility. By maintaining mitochondrial DNA stability, Twinkle plays a critical role in preserving mitochondrial function. Targeting Twinkle or leveraging its protective effects may hold promise in protecting mitochondria from age-related damage and preventing the downstream consequences on vascular health.

Furthermore, the interplay of mitochondrial dysfunction and atherosclerotic plaque formation adds another layer of novelty to this review. The disrupted mitochondrial function and energy metabolism within specific regions of atherosclerotic plaques contribute to reduced oxygen consumption rates and mitochondrial DNA damage. Unraveling these connections paves the way for potential interventions that address the underlying mitochondrial dysfunction in atherosclerosis and hinder plaque progression.

However, despite the valuable insights presented in this review, it is important to acknowledge some limitations.

Firstly, the majority of the evidence discussed in this review comes from preclinical studies and experimental models. While these studies provide essential mechanistic insights, caution should be exercised when extrapolating the findings to human patients. Further translational and clinical research is needed to validate the therapeutic potential of targeting mitochondrial dysfunction and sirtuins in the context of vascular aging and atherosclerosis.

Secondly, the complexity of the interplay between mitochondrial dysfunction, oxidative stress, and age-related cardiovascular conditions necessitates a comprehensive understanding of the underlying mechanisms. The intricate nature of these processes makes it challenging to isolate specific molecular targets and develop precise therapeutic interventions. Future studies should aim to dissect these intricate mechanisms to identify more effective therapeutic strategies.

Lastly, the review focused primarily on the role of mitochondrial dysfunction and sirtuins in vascular aging and atherosclerosis. However, it is important to consider that these conditions are multifactorial and involve various pathophysiological processes beyond mitochondrial dysfunction. Exploring the broader landscape of molecular pathways and cellular interactions involved in vascular aging and atherosclerosis will provide a more complete understanding of these complex conditions and may uncover additional therapeutic targets.

In conclusion, while this review provides valuable insights into the novel therapeutic strategies for vascular aging and atherosclerosis, it is essential to acknowledge the limitations of the current understanding. Future research should address these limitations by conducting translational studies, elucidating the intricate mechanisms, and considering the multifactorial nature of these age-associated cardiovascular conditions. By overcoming these challenges, we can advance towards the development of effective therapeutic interventions that preserve cardiovascular health and improve patient outcomes.

Conclusion

In the course of writing this review, we examined various materials regarding the relationship of atherosclerosis with aging. We paid special attention to the mechanisms that cause this relationship, among which we singled out mitochondrial dysfunction. Separately, we considered sirtuins as potential therapeutic targets in the treatment of atherosclerosis.

It is safe to say that atherosclerosis and vascular aging have much in common. This primarily applies to inflammation, oxidative stress, and mitochondrial impairments. Based on the available data, we are inclined to assume the following, albeit a simplified version, of causal relationships. These processes are consequences of the aging of the vascular system and, in turn, favor the

development of atherosclerosis. However, we cannot write off the fact that although older people are more vulnerable to atherosclerosis and other cardiovascular diseases, atherosclerosis can also develop in young people. This unequivocally points to a more complex nature of the relationship between atherosclerosis and aging, which can be clarified only by further fundamental research.

As for sirtuins, their role in aging and its prevention has been shown in numerous studies. Based on the assumption of the relationship of atherosclerosis with aging, it is logical to assume that sirtuins will also have an effect on the prevention of atherosclerosis. This is also supported by several studies that show different roles for members of the sirtuin family. We believe that our proposed simplified model of the relationship between vascular aging, mitochondrial dysfunction, atherosclerosis, and sirtuins is fair and its refinement will be of great benefit. Our findings are consistent with the suggestions of (Donato *et al*., 2018) who proposed that arterial dysfunction is linked to arterial aging, but the underlying pathways need to be evaluated (Nakagawa *et al*., 2009). The same position was stated by Csiszar *et al*. (2019) who were investigating the implication of NAD + deficiency in age-related vascular dysfunction (Donato *et al*., 2018).

Considering the future prospects, it seems quite clear for now. STACs have proven their efficiency in the treatment and prevention of a variety of age-associated conditions in model animals and humans. Synthetic STACs appear to be efficient, but their bioavailability is far from perfect, which is a limitation of their use. Now, there are more specific and soluble compounds, such as resveratrol, are available, so STACs are on the scene again. Thus, further investigation and clinical tests of such compounds seem to be profitable. Also, NAD + increasing compounds demonstrate the potential as calorie restriction mimetics to treat numerous age-related conditions and possibly extend lifespan. Despite the numerous studies that revealed some important properties and effects of sirtuins, many features still need to be evaluated. The most intriguing question that needs to be answered is whether STACs can be approved as a drug to treat aging, age-related, and/or cardiovascular diseases in humans. With the elderly population increasing worldwide and healthcare costs threatening the global economy, the answer to that question cannot come soon enough.

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Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

Conflicts of Interest

The authors declare no conflict of interest.

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