Received: 12 March 2021 | Revised: 14 April 2021 | Accepted: 14 April 2021

DOI: 10.1002/agm2.12151

REVIEW ARTICLE

Aging Medicine Open Access WILEY

The mechanisms of vascular aging

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 31571829

Abstract

Vascular senescence is one of the hotspots in current research. With global average life expectancy increasing, delaying or reducing aging and age-related diseases has become a pressing issue for improving quality of life. Vascular senescence is an independent risk factor for age-related cardiovascular diseases (CVD) and results in the deterioration of CVD. Nevertheless, the underlying mechanisms of the vascular senescence have not been expressly illustrated. In this review, we attempt to summarize the recent literature in the field and discuss the major mechanisms involved in vascular senescence. We also underline key molecular aspects of aging-associated vascular dysfunction in the attempt to highlight potential innovative therapeutic targets to delay the onset of age-related diseases.

KEYWORDS
mechanisms, senescence, vascular aging

1 | INTRODUCTION

Aging is an irreversible and inevitable physiological process.[1] The proportion of aged population is increasing in the world. According to the World Population Prospects, by 2050, it has been estimated that the number of people aged 65 or over will almost double from 2019% to 16%; and the proportion of persons aged 80 years or over is predicted to triple.[2] The demographic change has enormous influence on society. Cardiovascular disease is a primary cause of death worldwide,[3] leading to a public health burden for patients and society. It is well known that mortality from heart disease and stroke increases exponentially with age, accounting for more than 40% of all deaths in patients aged 65–74 and nearly 60% of all deaths in patients aged over 85.[4]

Vascular aging is an independent risk factor for morbidity and mortality of age-related diseases, particularly cardiovascular diseases (CVDs) such as hypertension and atherosclerosis.[5,6] Vascular aging is characterized by vascular stiffening, intimal and medial thickening, increased luminal diameter, reorganization of the extracellular matrix, and endothelial dysfunction.[7] The theories for the mechanisms of vascular aging include inflammation, mitochondrial dysfunction, oxidative stress, telomere attrition, epigenetics, and autophagy. Understanding the underlying mechanisms of vascular aging holds possibility for developing new therapeutic strategies and clinical diagnostic methods. This review will discuss the molecular alterations of aging vessels and their associated age-related diseases, especially in cardiovascular vessel-related diseases.

2 | INFLAMMATION

Inflammaging occurs during physiological aging in the absence of an overt infection, which describes the low-grade, chronic systemic inflammation.[8] Inflammaging plays a role in all age-related diseases such as CVDs, which affect the mortality and morbidity of elderly people.[9] The activation of immune cells such as macrophages/monocytes and the endothelial cell dysfunction participates in vascular low-grade inflammatory processes.[10,11]

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The activated nuclear factor-kappa B (NF-κB) signaling pathway and immune cells are involved in the inflammatory processes, which occur in vascular aging. The occurrence of inflammatory phenotype is attributed to NF-κB activation, resulting in the overexpression of inflammation-related genes including pro-inflammatory cytokines (eg, interleukin-1β [IL-1β], tumor necrosis factor-α [TNFα] and interleukin-6 [IL-6]) and cellular adhesion molecules (eg, vascular adhesion molecule-1 [VCAM-1], intercellular adhesion molecule-1 [ICAM-1], inducible nitric oxide synthase [iNOS], monocyte chemo-attractant protein-1 [MCP-1] and cyclooxygenase-2 [COX-2]), thus conferring the endothelial dysfunction, which is also related to atherosclerotic pathogenesis. The renin/angiotensin system (RAS) is involved in normal vascular function and takes part in pathogenesis, playing an important role in vascular biology. The activity and expression of the angiotensin-converting enzyme-1 (ACE-1) obviously increase during aging.[12,13] Ang II originating from Ang I by ACE is involved in the vascular remodeling process that acts via angiotensin II type 1 receptor (AT1R) and type 2 (AT2R).[14,15] Ang II is involved in the inflammatory process, which increases the activation of inflammatory factors by activating nuclear transcription factor-kappa B (NF-κB) through AT1R and AT2R during vascular aging.[16,17] When activated, NF-κB translocates to the nucleus and then upregulates the expression of inflammatory cytokines, resulting in vascular injury and atherosclerosis.[18] Growing research shows that inhibiting vascular inflammation is the principal factor for the prevention and treatment of aging-related vascular diseases.[19] The previous research showed that the Milk Fat Globule epidermal growth factor 8 (MFG-E8) plays a significant role in aging vascular.[20] The synthesis of anti-inflammatory modulators including IL-10 and transforming growth factor β (TGF-β) was decreased after MFG-E8 was deficiency.[21,22] Furthermore, MFG-E8 also led to the defective clearance of apoptotic cells and then upregulated the expression of pro-inflammatory cytokines such as IL-10 and TNF-α.[23]

Growing research has identified that hypoxia-inducible factor-1α (HIF-1α) has an important effect on the aging-related process, particularly regulating cardiovascular aging. Vascular endothelial growth factor (VEGF), which is regulated by HIF-1, is a significant regulator for angiogenesis and a vital player of vascular aging.[24] The activity of HIF-1 decreases during aging and then downregulates the expression of VEGF and results in the impairment of angiogenesis.[25] It is reported that HIF is involved in decreasing the secretions of erythropoietin (EPO) among elderly patients[26] and old animals.[27] In fact, HIF-1α also regulated the expression of aging-related genes including p16, p53 in ECs.[28] The research found that HIF-1α is involved in regulating vascular inflammation in macrophages by limiting excessive vascular remodeling; nevertheless, the specific mechanism was still unknown.[29] In conclusion, HIF-1α may be a potential therapeutic target in vascular diseases, particularly in vascular aging. Klotho was first discovered by Kuro-o et al. and then found to be involved in aging, which represents the anti-aging protein.[30] The Klotho protein has anti-inflammatory and vascular-protective effects. It has been found that Klotho protein could suppress the expression of cellular adhesion molecules through attenuating the activation of NF-κB and the phosphorylation of IkappaB[31] (Figure 1).

3 | MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS

Mitochondria play a significant role in regulating intracellular processes including immune response,[32] cell proliferation,[33] apoptosis,[34] migration,[35] and gene expression.[36] Meanwhile, mitochondria are involved in controlling the cellular metabolism by synthesizing the crucial metabolites of proteins and nucleotides as well as producing adenosine 5-triphosphate (ATP), whereas mitochondria generate the reactive oxygen species (mtROS) that account for 90% of total ROS, by oxidative phosphorylation.[37] The observed increase in mitochondrial ROS during aging is considered to be the cause and result of cellular senescence.[38] Oxidative stress attributed to an imbalance between the alleviating activation of antioxidant enzymes (eg, manganese Mn-SOD, copper/zinc-superoxide dismutase [Cu/Zn-SOD], extracellular SOD) and overproduction of ROS (eg, superoxide [O2-] and hydrogen peroxide [H_2O_2]) from pro-oxidative enzymes (eg, nicotinamide adenine dinucleotide phosphate [NADPH] oxidase, xanthine oxidase, uncoupled eNOS or enzymes of mitochondrial respiration), which is the dominating cause to the progression of vascular senescence.[39] Redox homeostasis is a principal process of protecting cells and organisms from oxidative stress, including a balance between a ROS production and concomitant antioxidant defenses.[40] This balance is a significant role of physiological processes that ensure the maintenance of healthy cellular function, especially the cardiovascular system.[41] The massive production of ROS will activate the protein kinase C (PKC) β2 subunit, up-regulate the expression of adhesion molecules such as ICAM-1, MCP-1, VCAM-1, and then induce the adhesion of monocytes and endothelial cells in the vascular intima and promote atherosclerosis.[42] Another important regulatory gene in the process of oxidative stress is an adaptor protein $p66^{Shc}$, which is encoded by Shc gene in the cardiovascular

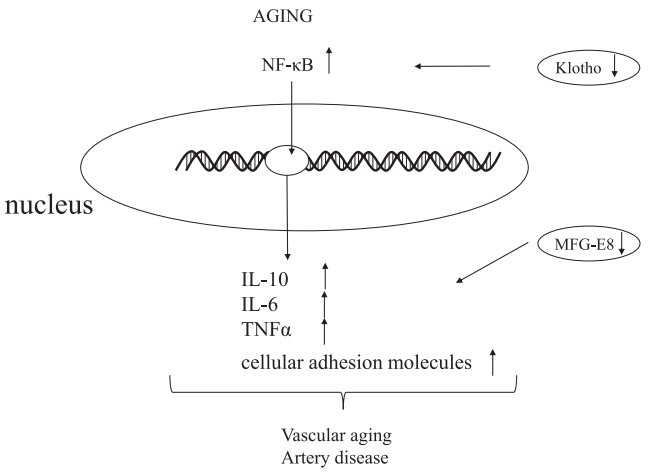

FIGURE 1 Inflammation signaling pathway underlying vascular aging

system that can transmit tyrosine protein kinase signaling pathway. Studies have found that this gene can act as an upstream regulator to activate its downstream NADPH oxidase and thus became the key regulator to control the production of superoxide reactants. Studies have found that downregulating this gene could reduce the metabolic level of oxidative products in tissues and reduce the degree of damage caused by oxidative stress.[43]

Recent studies demonstrated that the decreasing of mitochondrial biogenesis and the upregulating of mtROS results in reducing the efficiency of electron transport chain via downregulating nuclear factor (erythroid-derived-2)-related factor 2 (Nrf-2)-induced antioxidant pathways[44] and activating $p66^{Shc}$-mediated oxidative stress pathway[45] in the aged. The PGC-1 family including transcriptional co-activators (PRC, PGC-1α, PGC-1β) is involved in regulating the function of many transcription factors related to mitochondrial biogenesis and function and is comprised of nuclear factor (erythroid-derived-2)-related factor 2 (Nrf-2).[46] PGC-1α also regulates the expression of antioxidant enzymes including SOD and glutathione peroxidase 1 (Gpx-1).[47,48] Xiong et al.[49] found that PGC-1α activity is inhibited by Ang II through upregulating its phosphorylation in serine 570 by Akt, which is significant for the uniting of the acetyltransferase general control non-represses 5 (GCN5) and the acetylation and inhibition of PGC1α. Ang II reduces the PGC-1α activity by downregulating the binding of transcription factor Fox1 and the catalase promotor and then decreasing the expression of antioxidant enzymes and increasing the ROS levels.[50] Silence information regulator 2-like 1 (Sirt1), which is a conservative longevity gene from yeast to human and a member of the NAD-dependent sirtuin family of histone deacetylases, could upregulate the expression of antioxidant enzymes (eg, catalase, MnSOD and eNOS) through deacetylating and activating FoxO transcription factors[51] and PGC1α.[52] Although downregulation of either Sirt1, FoxO1, or PGC1α by siRNA attributes to senescence of VSMCs without Ang II, genetic silencing of PGC1α could induce vascular senescence of mice.[53] In addition, the research also showed that FoxO1 increases its transcription by binding to the Sirt1 promotor.[54] Sirt1 also protects the heart from oxidative stress attributing to increasing expression of catalase by FoxO1a. In addition, studies showed that supplementation with mononuclear nucleotide nicotinamide (NMN), referred to as NAD^+ intermediate, could regulate Sirt1 and alleviates endothelial function in senescent vessels.[55] Therefore, the regulatory molecules mentioned above may be the therapeutic targets that are beneficial in alleviating vascular senescence and atherosclerosis (Figure 2).

4 | TELOMERE ATTRITION

Telomeres are present at the end of the chromosomes, which are tandem repeats of TTAGGG and are guanine-rich and protect chromosome from degradation, recombination and fusion. The maintenance of telomere length is regulated by a reverse transcription catalytic submit (TERT) and telomerase RNA component (TERC) as well as the protein complex Shelterin that it could protect the chromosome ends.[56] As is well known, telomere attrition could cause DNA damage response, which may result in apoptosis,[57] inflammation,[58] or cellular senescence.[59] Telomic-repeat binding factor 2 (TRF2) is a significant telomere binding protein that maintains the t-loop structure. The study demonstrated that overexpression of TRF2 could alleviate senescence in VSMCs and decrease DNA damage in vitro. In summary, telomeres within the vasculature could be the sites of alleviating vascular senescence.

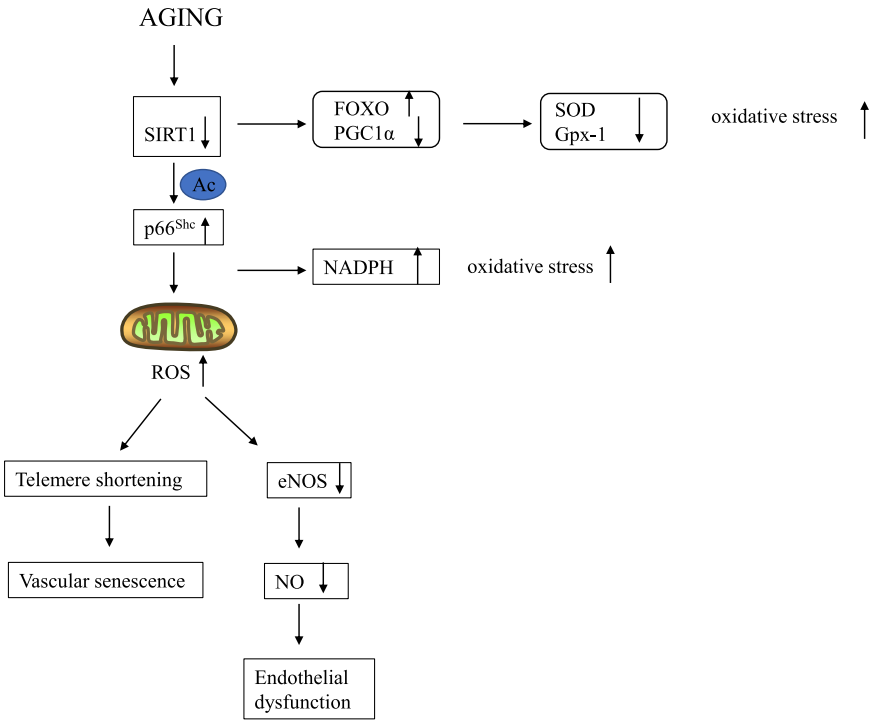

FIGURE 2 Mitochondrial dysfunction and oxidative stress signaling pathway underlying vascular aging

5 | EPIGENETICS

Emerging evidence demonstrated that epigenetics has an important effect on vascular aging, which refers to the heritable changes of gene expression without alterations to the coding sequence of DNA. The mechanism of changes is involved in DNA methylation patterns, non-coding RNAs, posttranslational modification of histone, and chromatin remodeling. In this review, we emphasize the possible intervention targets for alleviating vascular senescence in terms of histone modification and DNA methylation.

5.1 | Histone modifications

Nucleosome is the unit of eukaryotic chromation, which consists of core regions (H2A, H2B, H3, and H4) and DNA. Histone modifications are characterized as being involved in gene transcription by altering histone protein's mutual effect with DNA and then influence gene expression, stability, and replication.[60,61] The mechanisms of histone modifications are comprised of ubiquitination, acetylation, methylation, and phosphorylation. Meanwhile, the enzymes of regulating histone modification consist of histone acetyltransterase (HATs), histone deacetylase (HDACs), and histone methyltransferase, and these enzymes have significant effect on development of vascular aging.[62] NAD-dependent deacetylase sirtuin-1 (SIRT1) plays a significant role in vascular senescence and specific mechanisms are described above. It's worth mentioning that SIRT1 has an effect on deacetylation of histone H3 at lysine 16 (H4K16) and that this process alleviates endothelial cells and vascular senescence.[63] Inhibiting the histone deacetylases (HDAC) upregulates the expression of TNF-α and activates the NF-κB signaling pathway.[64] Other members of the HDAC family such as HDAC4 regulate Ang II-induced autophagy by activating the FoxO3a deacetylation and then is involved in vascular inflammation.[65] H3K4 methylation could accelerate gene activation and H3K9 and H3K27 methylation conversely suppress gene activation. Moreover, the modification of methylation on histone lysine is involved in vascular senescence. Research demonstrated that histone demethylase Jumonji domain-containing protein 3 (JMJD3) plays a vital role in vascular remodeling[66] and regulates inflammatory response.[67] Set and MYND domain containing-3 (Smyd3) could catalyze demethylation and trimethylation of H3K4. Yang et al found that Smyd3 increases the expression in Ang II-induced endothelial cell senescence.[61] Moreover, the accumulation of Smyd3 resulted in senescence-related phenotypes in ECs. In addition, inhibiting Smyd3 decreased senescence-related phenotypes in vitro and in vivo. Smyd3 (with H3K4 methyltransferase activity), which accumulated with aging, was echoed by upregulated H3K4me3 level at p21 promoter. Therefore, Smyd3 may be a promising target to ameliorating vascular senescence. Other studies showed that H3K4me3 and H3K27me3 associate with lifespan extension. It has been reported that H3K4 methylation is also involved in angiogenesis and regulates the longevity-related genes including Mixed lineage leukemia (MLL) 1/2, MLL3/4, SET1A/B, and SET7.[68] In addition, SET7 is involved in controlling the expression of longevity genes.[69]

5.2 | DNA methylation

DNA methylation refers to adding a methyl group to the 5th carbon atom of cytosine, which is involved in epigenetic mechanisms. CpG islands are a GC-rich region and feature the short interspersed DNA sequences.[70] As is well known, the DNA methylation is regulated by a family of DNA methyltransferases, including DNMT1, DNMT3a, and DNMT3b.[70] In summary, the abnormal DNA methylation emerges in aged cells and accelerates the process of age-related diseases. DNA methylation, oxidative stress, and vascular senescence have a close relationship in blood vessels. The endothelial nitric oxide synthase (eNOS) generating the vasoactive molecule nitric oxide (NO) is regulated by methylation status. The research showed that hypermethylation in the eNOS promoter region decreases the expression of eNOS and downregulates the level of NO when in the pathological situations.[71] $p66^{Shc}$ is also regulated by methylation status, which is protein related to endothelial dysfunction. $p66^{Shc}$ has plenty of methylation sites involved in the hydrogen peroxide (H_2O_2)-associated signaling pathway. In summary, the regulation of methylation modification is a significant method to control the expression of vascular senescence–related protein.

6 | AUTOPHAGY

It is becoming more evident that autophagy occurs in age-related diseases; however, its mechanism is not clear. The studies found that autophagy has a relationship with vascular senescence, including a degradative process of providing energy and nutrients, and a crucial regulator of organellar homeostasis, particularly mitochondrial. The studies have founded that the autophagy-related gene LC3-II knockout in mice results in pulmonary hypertension.[18] In addition, mice are susceptible to vascular remodeling, increased apoptosis, and decreased vascular re-endothelialization after the knockout of autophagy-related gene beclin1.[72] Furthermore, specific deletion of autophagy-related gene ATG7 in smooth muscle cells could accelerate atherosclerotic plaque formation and intimal hyperplasia.[73] Study by Pulakat et al reported that the senescent mice intervened by autophagy-enhancing agent could be alleviated by NO-mediated vasodilatation.[74] The study also suggested that autophagy is impaired in senescent endothelial cells, which leads to endothelial dysfunction.[75] Nevertheless, studies found that excessive autophagy can injure cells. The 3-methyladenine (autophagy inhibitor, 3-MA) inhibits autophagy and moderates vascular endothelial cell injury.

7 | CONCLUSION

The purpose of this review is to explore the specific mechanisms of vascular senescence. In conclusion, targeting the crucial process of vascular senescence could prevent/alleviate the vascular pathologies and some senescence-associated diseases instead of regarding a single disease as the target. In recent years, plenty of potential drugs

or interventions have targeted the aging process. Furthermore, these interventions are applied to treatment of the age-associated vascular diseases.

ACKNOWLEDGEMENTS

The authors thank many investigators for their precious instructions.

CONFLICTS OF INTEREST

Nothing to disclose.

AUTHOR CONTRIBUTIONS

Mao Yongjun and Hu Song directed the article writing. Wang Shan prepared and revised the manuscript.

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How to cite this article: Wang S, Hu S, Mao Y. The mechanisms of vascular aging. *Aging Med*. 2021;4:153–158. https://doi.org/10.1002/agm2.12151