INTRODUCTION

Aging is an irreversible and inevitable physiological process. 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. The demographic change has enormous influence on society. Cardiovascular disease is a primary cause of death worldwide, 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. Vascular aging is an independent risk factor for morbidity and mortality of age-related diseases, particularly cardiovascular diseases (CVDs) such as hypertension and atherosclerosis. Vascular aging is characterized by vascular stiffening, intimal and medial thickening, increased luminal diameter, reorganization of the extracellular matrix, and endothelial dysfunction. 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.

INFLAMMATION

Inflammaging occurs during physiological aging in the absence of an overt infection, which describes the low-grade, chronic systemic inflammation. Inflammaging plays a role in all age-related diseases such as CVDs, which affect the mortality and morbidity of elderly people. The activation of immune cells such as macrophages/monocytes and the endothelial cell dysfunction participates in vascular low-grade inflammatory processes.
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, which is also related to atherosclerotic pathogenesis. Angiotensin-converting enzyme-1 (ACE-1) obviously increase during aging.12,13 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 [H2O2]) 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) ε2 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 p66Shc, which is encoded by Shc gene in the cardiovascular system.

![FIGURE 1](image)

**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 pathways44 and activating p66Shc-mediated oxidative stress pathway45 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 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 deacetylation and activating FoxO transcription factors51 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 promoter.54 Sirt1 also protects the heart from oxidative stress attributing to increasing expression of catalase by FoxO1a. In addition, studies showed that supplementation with mononucleuric 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 Telomeric-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.60-63 The mechanisms of histone modifications are comprised of ubiquitination, acetylation, methylation, and phosphorylation. Meanwhile, the enzymes of regulating histone modification consist of histone acetyltransferase (HATs), histone deacetylase (HDACs), and histone methyltransferase, and these enzymes have significant effect on development of vascular aging.64 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.65 Inhibiting the histone deacetylases (HDAC) upregulates the expression of TNF-α and activates the NF-kB signaling pathway.66 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.66 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 remodeling66 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.68 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 p66Shc is also regulated by methylation status, which is protein related to endothelial dysfunction. p66Shc has plenty of methylation sites involved in the hydrogen peroxide (H2O2)-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 found 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/ameliorate 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.

ACKNOWLEDGMENTS

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.

ORCID

Shan Wang  
https://orcid.org/0000-0002-6560-5786

REFERENCES

1. Jamil A, Habil S. Delaying vascular aging: a new prospect in medi-cine. EXCLI J. 2019;18:1092-1093.
2. Magenta A, Lorde R, Syed SB, Capogrossi MC, Puca A, Madeddu P. Molecular therapies delaying cardiovascular aging: disease- or health-oriented approaches. Vasc Biol. 2020;2(1):R45-R58.
3. Xiao L, Liu Y, Wang N. New paradigms in inflammatory signal-ing in vascular endothelial cells. J Genet Genomics. 2014;41(9):485-495.
4. Donato AJ, Morgan RG, Walker AE, Lesniewski LA. Cellular and molecular biology of aging endothelial cells. J Mol Cell Cardiol. 2015;89(Pt B):122-135.
5. Lakatta EG. Arterial and cardiac aging: major shareholders in cardio-vascular disease enterprises: part III: cellular and molecular clues to heart and arterial aging. Circulation. 2003;107(3):490-497.
6. Liu Y, Bloom SI, Donato AJ. The role of senescence, telomere dysfunction and shelterin in vascular aging. Microcirculation, 2019;26(2):e12487.
7. Minniti C, Boscaglia A, Andreassi MG. The molecular biomarkers of senescence induced by angiotensin II, A potential therapy via seno-lytics and senomorphics. Int J Mol Sci. 2020;21(18).
8. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med. 2010;2(7):247-257.
9. Jin J, Liu Y, Huang L, Tan H. Advances in epigenetic regulation of vascular aging. Rev Cardiovasc Med. 2019;20(1):19-25.
10. Xu H, Du S, Fang B, et al. VSMC-specific EP4 deletion exacerbates angiotensin II-induced aortic dissection by increasing vascular inflammation and blood pressure. Proc Natl Acad Sci USA. 2019;116(17):8457-8462.
11. Tan J, Liu J, Du W, et al. Lactadherin deficiency leads to apoptotic cell accumulation and accelerated atherosclerosis in mice. Circulation. 2007;115(16):2168-2177.
12. Mukundan L, Odegaard JI, Morel CR, et al. PPAR-delta senses and orchestrates clearance of apoptotic cells to promote tolerance. Nat Med. 2009;15(11):1266-1272.
13. Aziz M, Jacob A, Matsuda A, Wang P. Review: milk fat globule-EGF factor 8 expression, function and plausible signal transduction in resolving inflammation. Apoptosis. 2011;16(11):1077-1086.
14. Ait-Oufella H, Kinugawa K, Zoll J, et al. Lactadherin deficiency leads to apoptotic cell accumulation and accelerated atherosclerosis in mice. Circulation. 2007;115(16):2168-2177.
15. Liu Y, Bloom SI, Donato AJ. The role of senescence, telomere dysfunction and shelterin in vascular aging. Circulation. 2007;115(16):2168-2177.
16. Kroemer G, Galluzzi L, Brenner C. Mitochondrial membrane perme -ability in vascular smooth muscle senescence induced by angiotensin II, A potential therapy via senolytics and senomorphics. Int J Mol Sci. 2020;21(18).
17. Wang M, Jiang L, Monticone RE, Lakatta EG. Proinflammation: the molecular basis of vascular disease. EMBO Mol Med. 2014;6:251-270.
18. Jin J, Liu Y, Huang L, Tan H. Advances in epigenetic regulation of vascular aging. Rev Cardiovasc Med. 2019;20(1):19-25.
19. Xu H, Du S, Fang B, et al. VSMC-specific EP4 deletion exacerbates angiotensin II-induced aortic dissection by increasing vascular inflammation and blood pressure. Proc Natl Acad Sci USA. 2019;116(17):8457-8462.
20. Ni YQ, Zhan JK, Liu YS. Roles and mechanisms of MFG-E8 in vascular aging-related diseases. Aging Res Rev. 2020;64:101176.
21. Ait-Oufella H, Kinugawa K, Zoll J, et al. Lactadherin deficiency leads to apoptotic cell accumulation and accelerated atherosclerosis in mice. Circulation. 2007;115(16):2168-2177.
22. Mukundan L, Odegaard JI, Morel CR, et al. PPAR-delta senses and orchestrates clearance of apoptotic cells to promote tolerance. Nat Med. 2009;15(11):1266-1272.
23. Aziz M, Jacob A, Matsuda A, Wang P. Review: milk fat globule-EGF factor 8 expression, function and plausible signal transduction in resolving inflammation. Apoptosis. 2011;16(11):1077-1086.
24. Ait-Oufella H, Kinugawa K, Zoll J, et al. Lactadherin deficiency leads to apo-
25. Liu Y, Bloom SI, Donato AJ. The role of senescence, telomere dysfunction and shelterin in vascular aging. Circulation. 2007;115(16):2168-2177.
26. Maccio A, Madeddu C. Management of anemia in inflammation of the elderly. Anemia. 2012;2012:1-20.
27. He Y, Yu S, Hu J, Cui Y, Liu P. Changes in the Anatomic and Microscopic Structure and the Expression of HIF-1alpha and VEGF of the Yak Heart with Aging and Hypoxia. PLoS ONE. 2016;11(2):e0149947.
28. Ait-Oufella H, Kinugawa K, Zoll J, et al. Lactadherin deficiency leads to apo-
29. Nakayama T, Kurobe H, Sugawara N, et al. Role of macrophage-derived hypoxia-inducible factor (HIF)-1alpha as a mediator of vascular remodelling. Cardiovasc Res. 2013;99(4):705-715.
30. Lim K, Halim A, Lu TS, Ashworth A, Chong I. Klotho: a major share-
31. Maekawa Y, Ishikawa K, Yasuda O, et al. Klotho suppresses TNF-alpha-induced expression of adhesion molecules in the endothelium and attenuates NF-kappaB activation. Endocrine. 2009;35(3):341-346.
32. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in endothelial senescence. Aging Med. 2013;4(1):709-721.
33. Xiao L, Liu Y, Wang N. New paradigms in inflammatory signaling in vascular endothelial cells. Am J Physiol Heart Circ Physiol. 2014;306(H3):H317-325.
34. Basso N, Cini R, Pietrelli A, Ferder L, Terragno NA, Inserra F. Protective effect of long-term angiotensin II inhibition. Am J Physiol Heart Circ Physiol. 2007;293(3):H1321-1358.
35. Wang M, Takagi G, Asai K, et al. Aging increases aortic MMP-2 activity and angiostatin II in nonhuman primates. Hypertension. 2003;41(6):1308-1316.
36. Wang M, Jiang L, Monticone RE, Lakatta EG. Proinflammation: the key to arterial aging. Trends Endocrinol Metab. 2014;25(2):72-79.
37. Stegbauer J, Coffman TM. New insights into angiotensin receptor actions: from blood pressure to aging. Curr Opin Nephrol Hypertens. 2011;20(1):84-88.
38. Okuno K, Cicalese S, Elliott KJ, Kawai T, Hashimoto T, Eguchi S. Targeting molecular mechanisms of vascular smooth muscle senescence induced by angiotensin II, A potential therapy via senolytics and senomorphics. Int J Mol Sci. 2020;21(18).
39. Wang M, Jiang L, Monticone RE, Lakatta EG. Proinflammation: the key to arterial aging. Trends Endocrinol Metab. 2014;25(2):72-79.
40. Stegbauer J, Coffman TM. New insights into angiotensin receptor actions: from blood pressure to aging. Curr Opin Nephrol Hypertens. 2011;20(1):84-88.
38. van der Rijt S, Molenaars M, McIntyre RL, Janssens GE, Houtkooij RH. Integrating the hallmarks of aging throughout the tree of life: a focus on mitochondrial dysfunction. *Front Cell Dev Biol*. 2020;8:594416.

39. Salazar G. NADPH oxidases and mitochondria in vascular senescence. *Int J Mol Sci*. 2018;19(5):1327.

40. Dabla PK, Sinha NJCHR. Oxidative stress and antioxidants in hypertension—a current. *Review*. 2015;11(2):132-142.

41. Sack MN, Fyhrquist FY, Saijonmaa OJ, Fuster V, Kovacic JC. Basic biology of oxidative stress and the cardiovascular system: part 1 of a 3-part series. *J Am Coll Cardiol*. 2017;70(2):196-211.

42. Reiner Z, Tedeschi-Reiner E. New information on the pathophysiology of atherosclerosis. *Lijec Vjesn*. 2001;121(1-2):26.

43. Paneni F, Cosentino FJCVP. p66 Shc as the engine of vascular aging. *Arterioscler Thromb Vasc Biol*. 2006;26(1):397-408.

44. Ungvari Z, Bailey-Downs L, Sosnowska D, et al. Vascular oxidative stress: a 3-part series. *Curr Atheroscler Rep*. 2017;19(5):1327.

45. Kong D, Zhan Y, Liu Z, et al. SIRT1-mediated ERbeta suppression of reactive oxygen damage checkpoint kinase Chk2 triggers replicative senescence. *EMBO J*. 2004;23(13):2554-2563.

46. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. *Nat Rev Genet*. 2016;17(8):487-500.

47. Yang D, Wei G, Long F, et al. Histone methyltransferase Smyd3 is a new regulator for vascular senescence. *Aging Cell*. 2020;19(9):e13212.

48. Shao Y, Chernaya V, Johnson C, et al. Metabolic diseases downregulate the majority of histone modification enzymes, making a few upregulated enzymes novel therapeutic targets—"Sand Out and Gold Stays". *J Cardiovas Trans Res*. 2016;9(1):1-18.

49. Wan YZ, Gao P, Zhou S, et al. SIRT1-mediated epigenetic downregulation of plasminogen activator inhibitor-1 prevents vascular endothelial replicative senescence. *Aging Cell*. 2014;13(5):890-899.

50. Jin Z, Henagan TM, Zhanguo G, Jianping YJE. Inhibition of glycogenesis by histone deacetylase 3 contributes to lipodystrophy in mice with adipose tissue inflammation. *Endocrinology*. 2011;5:1829-1838.

51. Yang D, Xiao C, Long F, et al. HDAC4 regulates vascular inflammation via activation of autophagy. *Cardiovasc Res*. 2018;114(7):1016-1028.

52. Luo X, Yang D, Wu W, et al. Critical role of histone demethylase Junonji domain-containing protein 3 in the regulation of neoantimia formation following vascular injury. *Cardiovasc Res*. 2018;114(14):1894-1906.

53. Liu S, Wang X, Pan L, et al. Endogenous hydrogen sulfide regulates histone demethylase JMJD3-mediated inflammatory response in LPS-stimulated macrophages and in a mouse model of LPS-induced septic shock. *Biochem Pharmacol*. 2018;2017:153-162.

54. Ernst P, Vakoc CR. WRAD: enabling of the SET1-family of H3K4 histone methyltransferases. *Brief Funct Genomics*. 2012;11(3):217-226.

55. Paneni F, Volpe M, Luscher TF, Cosentino F. SIRT1, p66(Shc), and Set7/9 in vascular hyperglycemic memory: bringing all the strands together. *Diabetes*. 2013;62(6):1800-1807.

56. Ding Q, Shao C, Rose P, Zhu YZ. Epigenetics and vascular senescence-potential new therapeutic targets? *Front Pharmacol*. 2020;11:53395.

57. Chan Y, Fish JE, D‘abreo C, et al. The cell-specific expression of endothelial nitric-oxide synthase: a role for DNA methylation. *J Biol Chem*. 2004;279(33):35087-35100.

58. Lv XF, Zhang YJ, Liu X, et al. TMEM16A ameliorates vascular remodeling by suppressing autophagy via inhibiting Bcl-2-p62 complex formation. *Theranostics*. 2020;10(9):3980-3993.

59. Grootaert MO, da Costa Martins PA, Bitsch N, et al. Defective autophagy in vascular smooth muscle cells accelerates senescence and promotes neoantimia formation and atherogenesis. *Autophagy*. 2015;11(11):2014-2032.

60. Pulakat L, Chen HH. Pro-senesence and anti-senesence mechanisms of cardiovascular aging: cardiac miRNA regulation of longevity drug-induced autophagy. *Front Pharmacol*. 2020;11:774.

61. Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csiszar A. Mechanisms of vascular aging. *Circ Res*. 2018;123(7):849-867.

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](https://doi.org/10.1002/agm2.12151)