Clinical Epigenetics

REVIEW

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Roles and mechanisms of histone methylation in vascular aging and related diseases

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Abstract

The global aging trend has posed significant challenges, rendering healthcare for older adults a crucial focus in medical research. Among the numerous health concerns related to aging, vascular aging and dysfunction are important risk factors and underlying causes of age-related diseases. Histone methylation and demethylation, which are involved in gene expression and cellular senescence, are closely associated with the occurrence and development of vascular aging. Consequently, this review aimed to identify the role of histone methylation in the pathogenesis of vascular aging and its potential for treating age-related vascular diseases and provided new insights into therapeutic strategies targeting the vascular system.

Keywords Histone methylation, Vascular diseases, Aging, Cellular senescence

Introduction

Aging represents a major risk factor for fatal chronic diseases, including cardiovascular disease, cancer, and neurodegenerative disease [1]. Cardiovascular disease ranks among the leading global causes of mortality [2]. With aging, arteries experience wall thickening, lumen narrowing, and pathological remodeling, which give rise to age-related vascular diseases, such as hypertension, atherosclerosis, arterial aneurysms, and cerebrovascular disease [3–6]. Improving vascular health by counteracting age-related signals promotes healthy aging and extends lifespans [7].

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Epigenetic alteration is a hallmark of cardiovascular aging, and histone modifications play a critical role in regulating cellular processes, such as proliferation, differentiation, and apoptosis [8]. Changes in histone acetylation and their contribution to cellular senescence have been investigated; however, the role of methylation has not been comprehensively reviewed [9].

Histone methylation is a reversible epigenetic modification catalyzed by histone methyltransferases (HMTs). It mainly occurs on lysine and arginine residues of H3 and H4 histones and is removed by histone demethylases (HDMs) [10]. Unlike other modifications, histone methylation is recognized by distinct domain types and occurs slowly, which indicates its importance and epigenetic stability [11, 12]. Accumulating evidence suggests that histone methylation is pivotal to vascular aging and related diseases [13–16]. Consequently, this review aimed to elucidate the roles of various HMTs and HDMs in these processes. Our focus was primarily on hypertension, atherosclerosis, neointimal hyperplasia, pulmonary hypertension (PH), aortic diseases, diabetic vascular diseases and ischemic stroke. A comprehensive literature search

was conducted to examine the relationship between histone methylation sites or enzymes and these diseases. We also explored the potential therapeutic applications of inhibitors targeting these sites and enzymes in the management of age-related vascular diseases.

Histone modification and methylation

Epigenetic modifications are heritable modifications that cause changes in gene expression independent of DNA sequence alterations and regulate gene transcriptional activity [17]. In eukaryotic cells, chromosomes are tightly packaged into the chromatin, with nucleosomes as the basic units. Each nucleosome consists of 146 bp of DNA wrapped around an octamer composed of core histones H3, H4, H2A, and H2B [18]. Therefore, modifications of these histones are crucial for activating or repressing gene transcription by precisely regulating the activities of gene promoters and enhancers [19]. Moreover, a growing body of evidence suggests that the dysregulation of epigenetic regulators of histone modifications is a predisposing factor for vascular aging and related diseases [9, 20].

Methylation is an important histone modification during individual development and stem cell differentiation [21]. By adding a methyl group to lysine or arginine residues in histone tails, histone methylation alters the chromatin structure to activate or silence gene expression [22, 23]. Lysine methylation is catalyzed by HMTs, resulting in monomethylation (me1), dimethylation (me2), or trimethylation (me3) [24]. At promoter sites, active methylated H3K4, H3K36, and H3K79 are enriched, creating an open chromatin structure that activates transcription. In contrast, methylation of H3K9, H3K27, and H4K20 leads to a compact chromatin structure that represses transcription. Differently, arginine methylation is catalyzed by protein arginine methyltransferases (PRMTs) [25]. (Fig. 1).

From vascular development and maturation to senescence, histone methylation is consistently involved throughout the process. Vasculogenesis and angiogenesis are importantly controlled by histone methylation regulators. Knockout of Setd2 (a H3K36-specific methyltransferase) in mice results in embryonic lethality with severe defects in blood vessel development [26]. Likewise, the disruptor of telomeric silencing 1-like (DOT1L), a H3K79-specific methyltransferase, maintains vascular integrity and function during embryonic development and postnatal life [27, 28]. Other HMTs and HDMs also have an effect on vascular development [29, 30].

The amount of research on histone methylation contributing to vascular aging and related diseases far exceeds that contributing to vascular development [31]. Table 1 comprehensively lists HMTs, HDMs, and PRMTs family members involved in the regulation of vascular aging and related conditions.

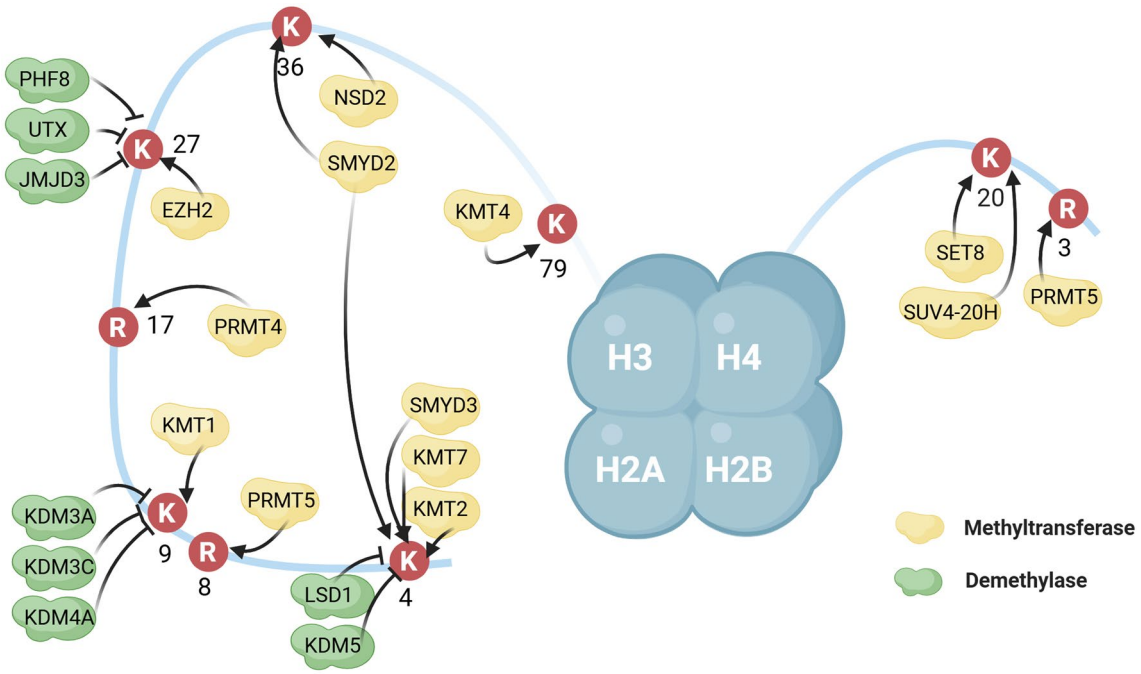

Fig. 1 Activators or inhibitors of histone methylation in this review

Table 1 Histone methylases, demethylases, and their synonyms mentioned in this paper

Subclass	Residue	HMTs and HDMs involved in vascular diseases	Synonym	Type of vascular diseases	Reference
Lysine methyltransferases (KMTs)					
KMT1	H3K9	SUV39H1	KMT1A	Diabetic vascular diseases	[16, 95, 103, 111, 112, 137]
		G9a	KMT1C	Pulmonary arterial hypertension	
		SETDB2	KMT1F	Abdominal aortic aneurysm	
KMT2	H3K4	MLL2	KMT2B	Atherosclerosis	[60, 62, 69, 100, 101, 136]
		MLL3	KMT2C	Diabetic vascular diseases	
		SET1A	KMT2F	Abdominal aortic aneurysm	
		ASH2	ASH2L	Atherosclerosis	
KMT3	H3K4 H3K36	SMYD2	KMT3C	Neointimal hyperplasia; Hypertension	[13, 14, 26, 77–79, 96, 122]
		SMYD3	KMT3E	Neointimal hyperplasia; Hypertension	
		NSD2	KMT3G	Pulmonary arterial hypertension	
KMT4	H3K79	DOT1L	KMT4	Atherosclerosis	[74, 75, 90, 91, 121, 138]
KMT5	H4K20	SET8	KMT5A	Diabetic vascular diseases	[52, 53, 57, 110, 139]
		SUV420H	KMT5B-C	Pulmonary arterial hypertension; Cardiac aging	
KMT6	H3K27	EZH2	KMT6A	Atherosclerosis; Hypertension; Aortic diseases; Stroke	[63, 72, 86, 87, 104–106, 128, 140–143]
KMT7	H3K4	SET7	SETD7	Diabetic vascular diseases	[64–66, 136]
Lysine demethylases (KDMs)					
KDM1	H3K4	LSD1	KDM1A	Atherosclerosis; Diabetic vascular diseases	[64, 70, 136]
KDM2	H3K36	–	KDM2A	Atherosclerosis	36,552,592
KDM3	H3K9	JMJD1A	KDM3A	Abdominal aortic aneurysm; Diabetic vascular diseases	[55, 97, 101, 102, 113, 144]
		JMJD1C	KDM3C	Pulmonary arterial hypertension	
KDM4	H3K9	JMJD2A	KDM4A	Abdominal aortic aneurysm	[100]
KDM5	H3K4	KDM5A	JARID1A	Hypertension	[71, 85]
KDM6	H3K27	UTX	KDM6A	Hypertension	[43–46, 81, 82, 145]
		JMJD3	KDM6B	Atherosclerosis; Hypertension	
Protein arginine methyltransferases (PRMTs)					
PRMT I	H3R17	PRMT4	CARM1	Atherosclerosis; Diabetic vascular diseases	[146]
PRMT II	H3R8 H4R3	PRMT5	–	Neointimal hyperplasia	[37]

Histone methylation-mediated hallmarks in vascular aging

Cellular senescence is characterized by irreversible growth arrest, which directly contributes to endothelial cell (EC) dysfunction, phenotypic transition of vascular smooth muscle cell (VSMC), and macrophage activation[32]. Ultimately, these changes lead to vascular dysfunction and age-related diseases[5]. During this process, telomere attrition occurs along with the increased expression of senescence markers, such as p53, p21, p16, reactive oxygen species (ROS), and genes associated with the senescence-associated secretory phenotype (SASP) [33]. (Fig. 2).

Endothelial dysfunction and vascular remodeling

Vascular cell senescence, which is associated with vascular cell phenotypic transformation and dysfunction, can be localized in almost all age-related vascular diseases. In particular, histone methylation of genes related to cardiovascular diseases is often altered in ECs and VSMCs. Here, the major role of arginine methylation and its modifying enzymes is described, while common lysine methylation modifications are detailed elsewhere.

Type I PRMTs are responsible for the formation of asymmetric dimethylarginine (ADMA). When proteins containing methylarginine are hydrolyzed, ADMA is released into the cytoplasm, inhibiting NOS activity,

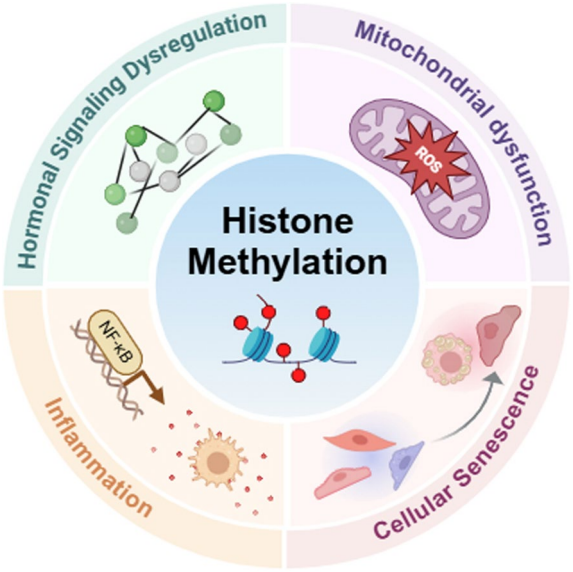

Fig. 2 Histone methylation modulates vascular aging hallmarks. The scheme compiles the four hallmarks of cardiovascular aging proposed in this work: hormonal signaling dysregulation, mitochondrial dysfunction, cellular senescence, and inflammation

which affects vascular EC function and increases the risk of cardiovascular diseases [34]. Plasma ADMA concentrations are elevated in patients with renal failure, coronary artery disease, hypertension, and diabetes mellitus. Notably, acute ADMA injections induce significant vascular dysfunction in humans, whereas chronic ADMA injections promote the development of atherosclerosis in mice [35].

The key Type II PRMT, PRMT5, catalyzes the formation of monomethylation (MMA) and symmetric dimethylarginine (SDMA) and plays diverse biological roles [36]. It is abundantly expressed in human atherosclerotic lesions and in mouse carotid arteries after balloon injury [37]. Overexpression of PRMT5 results in H3R8me2 and H4R3me2, which in turn attenuates acetylation of H3K9 and H4, limits the enrichment of myocardin and serum response factor (SRF) to CArG boxes, and subsequently inhibits VSMC differentiation. PRMT5 also affects VSMC phenotypic transformation by modifying non-histone methylation [38].

Renin–angiotensin–aldosterone system dysfunction

Angiotensin II is widely involved in the pathogenesis of vascular diseases by mediating DNA damage and accelerating cellular senescence in vascular cells [39, 40]. If not promptly repaired, damaged DNA accumulates in senescent cells. Tumor suppressors such as p53, p21, and p16 play crucial roles in this process by regulating the cell cycle and promoting apoptosis [41, 42].

In ECs, angiotensin II mediates the upregulation of SET and MYND domain-containing protein (SMYD) 2 and SMYD3. This upregulation enhances the methylation of H3K4 and activates p21 genes, leading to vascular aging [13, 14]. Besides, angiotensin II perfusion induces the upregulation of Jumonji domain-containing-3 (JMJD3) and the deletion of H3K27me3 in the aorta, thereby promoting the expression of Na^+-K^+-$2Cl^-$ cotransporter (NKCC) [43, 44]. Paradoxically, in the kidney, aging downregulates JMJD3 expression and conditional knockout of ubiquitously transcribed tetratricopeptide repeat X chromosome (UTX) increases the levels of H3K27me3, which upregulates blood pressure and NKCC through diminished ERK signaling and increased WNK signaling [45, 46].

Mitochondrial dysfunction and oxidative stress

Mitochondrial dysfunction is characterized by mitochondrial membrane permeability alteration, ROS overproduction and development of oxidative stress [47]. Interestingly, studies have found that slight mitochondrial dysfunction during early developmental stages can delay senescence by plant homeodomain finger protein 8 (PHF8) and JMJD3 [48]. However, more severe mitochondrial dysfunction, or dysfunction occurring later in life, tends to have detrimental effects on lifespan. Furthermore, the relationship between the opening of the mitochondrial permeability transition pore and PHF8-mediated histone methylation may offer valuable insights into how mitochondrial pathways influence stress-induced longevity and disease development [49].

ROS affects cell survival leading to apoptosis and oxidative stress, inducing cellular senescence and contributing to vascular aging [50]. The nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway is crucial for fighting oxidative stress by binding to kelch-like ech-associated protein 1 (Keap1) in the cytoplasm [51]. When oxidative stress occurs, Nrf2 dissociates from Keap1 and accumulates in the nucleus. Subsequently, Nrf2 interacts with antioxidant response elements, which helps protect mitochondrial function and reduce ROS production. Overexpressing SET8 can attenuate Keap1 promoter activity to inhibit hyperglycemia-mediated ROS accumulation [52, 53].

Hypoxia-inducible transcription factor-1α (HIF-1α) modulates histone methylation markers, including activating marks such as H3K4me2/3 and repressing marks like H3K9me2/3 and H3K27me3 [54]. High glucose combined with HIF-1α expression enhances EC inflammatory injury independent of the nuclear factor kappa B (NFκB) pathway. Therefore, reducing HIF-1α expression suppresses the expression of IL-6 and monocyte chemoattractant protein 1 (MCP-1) through JMJD1A [55].

Moreover, inhibiting the expression of PRMT5 attenuates the protein stability of HIF-1α and the VEGF signaling pathway [56]. Some other signaling pathways, like TGF-β signaling, are also involved in the senescence caused by oxidative stress in vascular diseases [57].

Nuclear factor kappa B-p65 pathway and senescent-associated secretory phenotype

The NFκB-p65 pathway is a critical signaling mechanism that regulates various cellular processes, including inflammation, immune response, and proliferation [58]. Vascular senescence also activates the NFκB-p65 pathway, resulting in numerous upregulated SASP components, including cytokines such as IL-6 and IL-8, chemokines, and MMPs. Furthermore, SASP factors can activate NFκB-p65, creating positive feedback loops that amplify the inflammatory response [59]. This interactive relationship is vital for the progression of vascular aging and related diseases.

In vascular endothelium, H3K4me2/3 interacts with myocardin-related transcription factor A (MRTF-A) and ASH2 (a crucial component of histone H3K4 methyltransferase complexes) through the NFκB pathway, leading to atherosclerosis [60, 61]. Lin et al. have demonstrated that MRTF-A amplifies inducible nitric oxide synthase (iNOS) activity in macrophages by recruiting ASH2 [62]. Furthermore, in VSMCs exposed to TNF-α, downregulating smooth muscle 22α enhances NFκB activity and the expression of proinflammatory molecules through EZH2-mediated H3K27me3 at its promoter region [63].

Additionally, hyperglycemia can persistently activate NFκB-p65 gene expression by influencing some common methylation modification sites, such as H3K4, H3K9, and their modifying enzymes [64]. SET7 recruitment and H3K4me1 cause NFκB to be overactive, leading to the subsequent transcription of Cyclooxygenase-2, iNOS, and proinflammatory genes that affect vascular inflammation [65, 66].

Advances in histone methylation in aging-related vascular diseases

Vascular aging and dysfunction are common features in almost all vascular risk factors and related diseases, such as atherosclerosis, neointimal hyperplasia, hypertension, PH, aortic diseases, diabetic vascular diseases, and cerebrovascular disease (Fig. 3).

Atherosclerosis

Atherosclerosis is a chronic and progressive inflammatory disease characterized by pathological changes in the walls of large and medium-sized arteries [67]. The exact cause of atherosclerosis remains unclear; however, several factors are closely related to the occurrence and progression of atherosclerosis, including obesity, hypertension, diabetes, elevated low-density lipoprotein levels and decreased high-density lipoprotein levels,

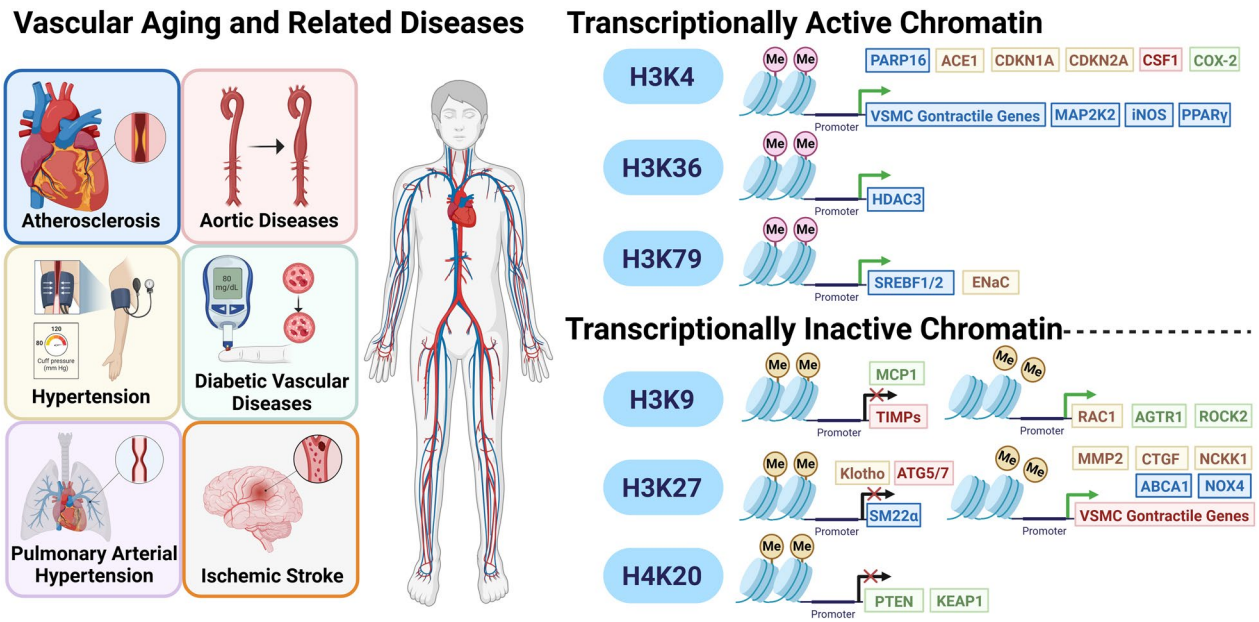

Fig. 3 Regulation of the histone methylation of associated genes during vascular aging and related disease development. Vascular aging and related vascular diseases, particularly hypertension, atherosclerosis, and diabetic vascular diseases, occur simultaneously and create a vicious cycle. Due to their similarities and simultaneous occurrence, they may share the same histone methylation patterns

respectively. Moreover, vascular aging significantly contributes to atherosclerotic cardiovascular diseases [68].

Histone methylation is pivotal to the pathological progression of atherosclerosis. Specifically, the H3K4 methylation is increased in atherosclerotic plaques, while the methylation of H3K9 and H3K27 is reduced in VSMCs and inflammatory cells [69]. This might be associated with enhanced gene expression that promotes inflammation and lipid deposition.

In macrophages within carotid atherosclerotic lesions, lnc_000048 promotes MAP2K2 transcription by attenuating LSD1 activity, which leads to the accumulation of H3K4me2, and ultimately induces downstream inflammatory factors [70]. Due to variations in the cells and molecules of interest in research, the increase in H3K4 methylation leads to different phenotypes. Inhibiting KDM5 activity increases H3K4me3 and significantly reduces EC proliferation, migration, and tube formation in the vascular tissues of patients with cardiovascular disease [71].

The histone methyltransferase EZH2 is elevated in atherosclerotic plaque tissues and silences gene expression by mediating H3K27me3. Knockdown of growth arrest-specific 5 potentially promotes the reverse transport of cholesterol and ultimately prevents the progression of atherosclerosis by reducing EZH2-mediated transcriptional inhibition of ATP-binding cassette transporter A1 (ABCA1), a protein capable of regulating lipid efflux [72]. Additionally, EZH2 also regulates the expression of DNA methyltransferase 1 and subsequently promotes DNA methylation of the *Abca1* promoter, resulting in silencing of the *Abca1* gene [73].

During the development of atherosclerosis, DOT1L expression is upregulated. It-induced H3K79me2 can increase expression of cytosolic C–C motif chemokine ligand 5 and C-X-C motif chemokine 10, which promotes phenotypic transition of VSMCs [74]. DOT1L also directly regulates macrophage function by controlling the expression of lipid biosynthesis genes, such as sterol regulatory element binding protein (SREBP) 1/2. Inhibition of DOT1L results in macrophage hyperactivation and reduced atherosclerotic plaque stability associated with disrupted SREBP pathways [75].

Neointimal hyperplasia

In patients with atherosclerosis, VSMCs contribute to vessel-wall inflammation, lipoprotein retention, and the formation of a fibrous cap that stabilizes plaque. These responses increase upon injury and lead to in-stent restenosis, bypass-graft occlusion, and transplant vasculopathy [76]. Although VSMCs in the arterial intima-media do not proliferate, injury or other stimuli can cause mid-membrane VSMCs to migrate to the intima, proliferate, and secrete extracellular matrix, resulting in neointimal hyperplasia [76].

Methylation of H3K4 in the CArG box region of VSMC contractile genes is crucial for maintaining the VSMC contractile phenotype and function [14, 68]. Recent evidence suggests that the inhibition of the VSMCs phenotypic switch, proliferation, and migration by SMYD2 is myocardin-dependent. Mechanistically, SMYD2 increases the levels of H3K4me1/3 in the CArG regions of the VSMCs marker gene promoters, enhancing the enrichment of SRF/myocardin complexes, preventing the VSMC phenotypic switch, and inhibiting neointima formation after vascular injury [77]. Another member of the SMYD family, SMYD3, also promotes VSMC proliferation and migration [78]. Poly(ADP-Ribose) Polymerase Family Member 16 is a potential target gene of SMYD3 [79].

The expression of KLF4, a member of the KLF family of zinc-finger transcription factors, decreases during VSMC senescence induced by Angiotensin II [80]. When recruited by KLF4, JMJD3 reduces H3K27me3 in the enhancers and promoters of epithelial and pluripotency genes [81]. Furthermore, JMJD3 also mediates VSMC proliferation and migration by altering NOX4 expression [82]. Therefore, downregulating JMJD3 enhances endothelial neovascularization.

Hypertension

Hypertension, influenced by genetic factors, aging, and lifestyle habits, is a major risk factor for cardiovascular disease [83]. Aging and pathology-induced declines in arterial compliance significantly affect the systolic components of hypertension [84].

The renin–angiotensin–aldosterone system has been associated the development of hypertension and multi-organ damage. In the two-kidney and one-clip hypertension mouse model, SMYD2 and SMYD3 were involved in the upregulation of senescence markers [13, 14]. Additionally, angiotensin-converting enzyme 1 (ACE1) is upregulated in the hearts and kidneys of spontaneously hypersensitive rats. Valsartan treatment significantly promotes the binding of KDM5A to the *Ace1* promoter region and downregulates H3K4me3 and ACE1 expression [85].

Although EZH2 expression is elevated in atherosclerotic plaques, it decreases with age and is associated with increased vascular sclerosis in mice and humans [86]. In response to angiotensin II stimulation in the aorta, aging enhances the activity of aldosterone and its mineralocorticoid receptor (MR) [87]. The MR increase in human aortic VSMCs inhibits EZH2 expression, thereby reducing H3K27 methylation. This results in MR recruitment and H3K27ac deposition at the promoter of stiffness

genes, such as connective tissue growth factor, MMP2, and Integrin α5, thus promoting vascular aging [86, 87].

Long-term blood pressure management requires the maintenance of sodium homeostasis, a process affected by aging, and renal sodium processing [88]. Blood pressure sensitivity to salt is characterized by blood pressure changes corresponding to salt intake [89]. The interaction between DOT1a and Af9 induces H3K79 hypermethylation and inhibits the renal epithelial sodium channel (ENaC) gene, thereby maintaining normal blood pressure. The disruption of interaction between DOT1a and Af9 induces H3K79 hypomethylation, leading to the activation of the renal epithelial sodium channel (ENaC) gene, and consequent hypertension [90]. Conversely, Af17 directly inhibits DOT1a-mediated H3K79 methylation at the ENaC promoter, activating ENaC [91].

Pulmonary arterial hypertension

PH is a fatal disease characterized by pathological remodeling of the pulmonary arteries due to the excessive growth of pulmonary arterial smooth muscle cells (PASMCs) [92]. In patients with idiopathic PH, there are increased cellular senescence and DNA damage markers in the lungs. Chronic exposure to hypoxia also increases cell senescence [93].

Euchromatic histone–lysine N-methyltransferase 2 (G9a) and its partner G9a-like protein (GLP), which belong to the KMT1 family, methylate H3K9 and contribute to the pro-survival and pro-proliferative phenotypes of PH-PASMCs [94, 95]. Additionally, silencing NSD2 significantly reduces H3K36me2 in the pulmonary arteries, and inhibits autophagy, thus alleviating pulmonary artery wall and right ventricular thickening [96]. Inhibiting G9a/GLP and NSD2 protects against elevated pulmonary artery pressure and right ventricular dysfunction by inhibiting autophagy.

Another important aspect of PH is increased glycolysis caused by hypoxia. JMJD1C promotes glycolysis through activating STAT3 signaling, which in turn promotes PASMC proliferation and pulmonary vascular remodeling. Silencing JMJD1C reduces the glycolytic enzymes, Hexokinase 2, Phosphoglycerate kinase 1, and Lactate dehydrogenase A, as well as excessive lactate accumulation in the lungs of mice exposed to hypoxia [97].

Aortic diseases

Abdominal aortic aneurysm (AAA) is a degenerative disease associated with aging, predominantly affecting men aged > 55 and women aged > 70 years, respectively [98]. In patients with AAA, ECs, VSMCs, and macrophages develop signs of cellular senescence, such as shortened telomeres and oxidative DNA damage [99].

The core component of the mammalian chromatin-remodeling complex, Brahma-Related Gene 1 (BRG1), has been shown to interact with and regulate transcription through its crosstalk with SET1A, JMJD1A, and JMJD2A [100, 101]. These interactions create an active chromatin conformation that promotes colony-stimulating factor 1 transcription and macrophage recruitment and sustains vascular inflammation [101, 102]. Notably, the AAA phenotype in *Brg1*-knockout mice is reduced [102]. Furthermore, recent single-cell RNA sequencing analyses of human AAA tissues have revealed upregulated SETDB2 in macrophages compared with controls. Targeting JAK/STAT3 signaling pathway with Tofacitinib reduces SETDB2 expression in aortic macrophages, and decreases MMP activity [103].

Beyond AAA, thoracic aortic aneurysm (TAA) and acute aortic dissection involve medial degeneration with the loss of VSMCs, altered elastic fibers, and inflammation. Aortic stress triggers the transition of VSMCs from a contractile to a proliferative, extracellular matrix-producing, inflammatory phenotype [104]. In VSMCs, the double-stranded DNA stimulator of interferon genes-interferon regulatory factor 3 (IRF3) signaling pathway induces inflammatory gene expression. Here, IRF3 recruits EZH2 to contractile genes, thus inducing repressive H3K27me3 modification and gene suppression [104]. However, EZH2 modulates integrin β3 for downstream molecules and promotes VSMC invasion and calcification, which leads to TAA and aortic coarctation [105]. Furthermore, EZH2 regulates autophagy by controlling autophagosome formation, contributing to its role in aortic diseases [106]. These results provide important insights into the relationship between EZH2 and aortic diseases.

Diabetic vascular diseases

Diabetes mellitus is a risk factor for vascular diseases. The main pathological manifestations of several vascular comorbidities are atherosclerosis in large vessels and impaired endothelial function in microvessels, which seriously affect patient prognosis and treatment [107]. Even when normal blood glucose levels are restored, patients with diabetes often experience ongoing inflammatory and vascular complications due to a hyperglycemia-induced methylation epigenetic markers memory [108, 109] (Fig. 4).

Notably, in patients or rats with diabetes, SET8 is decreased and Forkhead box protein O1 (FOXO1) expression is increased. Enriching H4K20me1 and FOXO1 in the phosphatase and tensin homolog (PTEN) promoter region upregulates PTEN expression, induces p65 phosphorylation and adhesion molecule expression, and triggers endothelial inflammation [110]. Thus, SET8

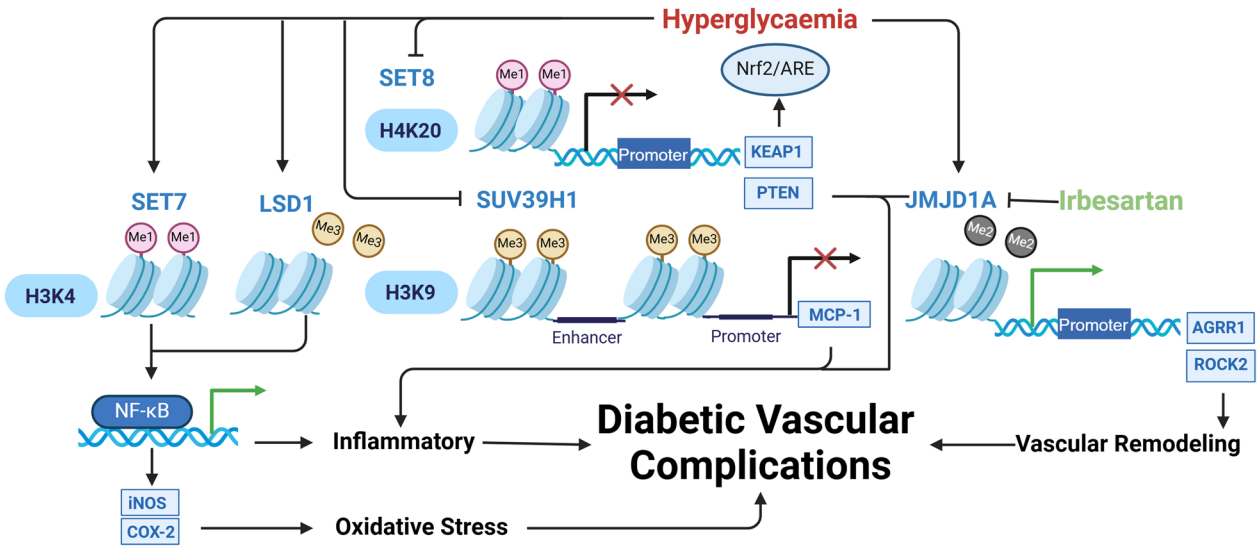

Fig. 4 Relationship between histone methylation and hyperglycemia

seems to protect against endothelial damage induced by elevated glucose and hyperglycemic memory.

The histone–lysine N-methyltransferase SUV39H1, which belongs to KMT1 and methylates H3K9 [94]. Reduced SUV39H1 and H3K9me3 levels in VSMCs of mice with diabetes induce the activity of IL-6 and MCP-1 genes. Similar patterns have been found in human VSMCs, indicating that H3K9me3 and SUV39H1 generally protect against inflammation [111]. Likewise, lower SUV39H1 levels in ECs under oxidative stress promote cell migration, tube formation, and MMP activity, thereby contributing to vascular complications [112]. Additionally, reduced levels of JMJD1A protein are associated with increased H3K9me2 levels on the Rho-associated protein kinase 2 and angiotensin II receptor type 1 promoter, which is accompanied by the development of vascular remodeling and neointimal hyperplasia under diabetic conditions [113].

Ischemic stroke

Cerebral small vessel disease (CSVD) refers to a range of clinical, imaging, and pathological syndromes caused by various factors affecting small blood vessels in the brain, including arteries, arterioles, capillaries, venules, and small veins. Older adults constitute a high-risk group for CSVD, being more prone to lesions such as cerebral microvessel stenosis, occlusion, or hemorrhage, which subsequently impair brain function. Recently, Su et al. have reviewed the role of histone methylation and related HMT inhibitors in the pathogenesis of ischemic stroke [6]. The methylations of H3K4, H3K9, and H3K27 are primarily involved in the development and prognosis of ischemic stroke. Apart from what is mentioned in the article, the latest finding suggests that EZH2-mediated H3K27me3 instigated the regulation of apoptosis, brain infarction and delayed ischemic changes of neurons via epigenetic upregulation of PI3K/AKT/mTOR signaling pathway in ischemic stroke[114].

Combined modulation of histone methylation and acetylation in vascular aging

Compared to methylation, histone acetylation has garnered more clinical attention in the fields of cardiovascular diseases and aging. Reviews have systematically elaborated on the impact of acetyltransferases and deacetylases on cardiovascular diseases [9]. Particularly, the Sirtuin (SIRT) family of acetylases plays a pivotal role in this context. Several anti-aging drugs targeting this family, including Resveratrol, Quercetin SRT2104, and MDL-800/811 are currently under clinical trial [115–118].

There is a crosstalk between SIRT family and methylation in vascular aging and related diseases. The regulation of EZH2 protein level by SIRT1 affects the repressive effects of EZH2 on the target gene expression [119]. For instance, Shu et al. have found that upregulation of EZH2 inhibits the anti-inflammatory function of SIRT1, whereas SIRT1 can remove the H3K27me3 of SM-22α by deacetylating EZH2, thereby increasing the expression of SM-22α and exerting an anti-inflammatory effect [63]. Alternatively, although inhibition of EZH2 or activation of SIRT1 elicits individual atheroprotective effects, target genes for EZH2 and SIRT1 overlap [120]. According to Karnewar et al., the longevity effects mediated by SIRT1 are partially achieved through the

DOT1L-mediated enhancement of H3K79me3. Furthermore, H3K79 methylation significantly regulates age-related vascular dysfunction through interaction with SIRT3 [121].

Besides the SIRT family, additional acetylation enzymes are associated with methylation in vascular biology [122]. Considering an interconnection between the effects these epigenetic enzymes evoke during vascular aging and related diseases; it might suggest therapeutic synergy when interventions at the level of methylation and acetylation are combined.

Emerging therapeutic approaches targeting histone methylation in patients with vascular aging

Histone methylation is crucial for regulating gene expression and cellular functions. Obviously, the intervention of HMT and HDM can reduce the activation signal of related pathways, reduce inflammatory cytokines, lower oxidative stress levels, and improve vascular aging. Therefore, targeting these enzymes with methylase and demethylase inhibitors could be an effective strategy for treating vascular aging and related diseases.

Several inhibitors of HMTs or HDMs such as LSD1, EZH2, and JMJD3 have been approved or in clinical trials in the field of oncology. A few preclinical studies have shown that several inhibitors against tumors are also effective on vascular diseases (Table 2). For instance, the use of the JMJD3 inhibitor GSKJ4 ameliorates AAA and neointima formation after vascular injury [44, 82].

Blockers of LSD1 are presently under evaluation in clinical trials for the treatment of diseases [123]. Inhibitors of LSD1 expression significantly alleviate atherosclerosis and neointimal formation [124, 125]. In particular, tranylcypromine has been shown to increase the risk of hypertension with use, because of its off-target effects [126, 127].

The relationship between EZH2 expression and vascular aging is complex. As previously mentioned, EZH2 expression in vascular vessels decreases with age, which leads to vascular sclerosis, but it increases in atherosclerotic plaques and aortic aneurysm tissues. Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) reduce the severity of atherosclerosis by modulating EZH2 actions and lowering lipid levels [128]. Tazemetostat, the first EZH2 inhibitor approved by the United States Food and Drug Administration for cancer treatment, has highlighted the therapeutic potential of targeting EZH2 [129]. In hyperlipidemic mice, Tazemetostat slows progression of atherosclerosis and drastically improves plaque phenotype [130]. Other inhibitors like EPZ005687, GSK126 and GSK343 also ameliorate age-related vascular diseases [131–134]. However, the reduced levels of H3K27me and EZH2 in aging blood vessels lead to stiffness, indicating that the EZH2 inhibitors used in cancer treatment have a negative impact on the vascular system [86, 87]. Therefore, it is crucial to monitor indicators such as pulse wave velocity when using these drugs. Collectively, more attention should be paid to the clinical application of these inhibitors.

Some frequently used drugs of cardiovascular diseases target histone methylation. For instance, Valsartan significantly increases the binding of KDM5A protein to the *Ace1* promoter region. This interaction reduces H3K4me3 levels in the heart and kidney, decreases blood pressure, and alleviates target organ damage [85]. Metformin, a 5′-adenosine monophosphate-activated protein kinase activator, increases H3K79me3 levels through the SIRT1-DOT1L axis. This process enhances SIRT3 expression and mitochondrial function, thereby delaying endothelial cellular senescence and vascular aging. Thus, long-term metformin administration is beneficial for retarding vascular aging [121].

Table 2 Overview of HMTs or HDMs inhibitors involved in vascular diseases

Target	Drugs	Phase	Diseases	Status	Effects on vascular system	References
LSD1	Tranylcypromine	Phase I/II	Acute myeloid leukemia	Completed	Causes high blood pressure	[126, 127, 147]
	ORY-1001	Phase I	Acute myeloid leukemia	Completed	Alleviates neointimal hyperplasia	[124, 148]
	GSK2879552	Phase I	Small cell lung cancer	Completed	Reduces the extent of atherosclerotic lesions	[125, 149]
EZH2	Tazemetostat	Phase II	Lymphoma	Completed	Slows atherosclerotic plaque progression Protects against ischemic brain injury	[114, 129, 130, 150]
	Astemizole	Preclinical	–	–	Aggravates atherosclerosis	[151, 152]
	EPZ005687	Preclinical	–	–	Ameliorates pulmonary hypertension	[131]
	GSK126	Preclinical	–	–	Alleviates atherosclerosis Causes vascular stiffening	[86, 134]
	GSK343	Preclinical	–	–	Improves aortic performance Reduces neointimal formation	[132, 133]
JMJD3	GSKJ4	Preclinical	–	–	Ameliorates AAA and neointima formation	[44, 82]

In addition to many pharmaceutical drugs, several natural agents can also alleviate vascular aging by influencing histone methylation. Phenethyl isothiocyanate, a major component of watercress and other cruciferous vegetables, reduces H3K9 acetylation and H3K4me2 levels, leading to decreased hepatic lipid accumulation and aortic atherosclerosis [135]. Another promising natural compound is puerarin, the main isoflavone glycoside in the roots of *Pueraria lobata*, which significantly inhibits the hyperglycemia-induced upregulation of H3K4me2/3 on the *MCP-1* promoter, thus alleviating diabetic vascular complications [136].

The study of histone methylation in aging and vascular diseases is still in its early stages, especially when compared to the more established research on histone acetylation and DNA methylation. Most clinical trials aimed at modulating histone methylation for therapeutic purposes focus on oncology, with limited research directed toward vascular diseases. A key challenge in this field is that the off-target effects of certain drugs may lead to cardiovascular side effects, such as hypertension and atherosclerosis aggravation. Another challenge is the lack of understanding regarding how histone methylation interacts with other modifications in the context of vascular aging and related diseases. Gaining deeper insights into these interactions is crucial for developing targeted therapies.

Vascular aging is a pivotal factor in the function of organs and systems in the body. However, the effects of histone methylation can vary significantly across different vascular cell types, and some modifications may even have opposing effects within the same tissue. Additionally, while animal and cell models offer valuable insights into the pathological processes underlying age-related vascular diseases, they do not fully replicate human conditions, limiting the applicability of the results. For this reason, clinical applications still require more comprehensive studies to examine potential side effects, identify targeted selective inhibitors, and evaluate their safety and efficacy in human patients.

Despite these challenges, continued research into the mechanisms of HMT and HDM inhibitors, in conjunction with both in vitro and in vivo models, holds great promise. Further exploration in this area is essential to advancing the development of effective and safe histone modification-based treatments for vascular aging and related diseases.

Conclusion and future perspectives

Histone methylation is common and essential for the regulation of gene expression and is involved in vascular aging and the development and prognosis of vascular diseases through epigenetics. Future investigations should focus on elucidating the direct and deeper association between specific histone methylation and age-related vascular diseases, the crosstalk between histone methylation and other histone modifications in vascular aging, and assessing the impact of therapeutic targets of HMTs and HDMs on human cardiovascular system in clinical trial. These insights are pivotal for the development of targeted therapies, which will lead to breakthroughs in the treatment and prevention of vascular aging and related diseases.

Abbreviations

AAA	Abdominal aortic aneurysm
ABCA1	ATP-binding cassette transporter A1
ADMA	Asymmetric dimethylarginine
BRG1	Brahma-Related Gene 1
CSVD	Cerebral small vessel disease
DOT1L	Disruptor of telomeric silencing 1-like protein
EC	Endothelial cell
ENaC	Epithelial sodium channel
FOXO1	Forkhead box protein O1
GLP	G9a-like protein
HDAC3	Histone deacetylase 3
HDMs	Histone demethylases
HMTs	Histone methyltransferases
iNOS	Inducible nitric oxide synthase
IRF3	Interferon genes-interferon regulatory factor 3
JMJD	Jumonji domain-containing protein
Keap1	Kelch-like ech-associated protein 1
MCP-1	Monocyte chemoattractant protein 1
MMA	Monomethylation
MR	Mineralocorticoid receptor
MRTF-A	Myocardin-related transcription factor A
NFκB	Nuclear factor kappa B
Nrf2	Nuclear factor erythroid 2-related factor 2
PH	Pulmonary hypertension
PRMTs	Protein arginine methyltransferases
PTEN	Phosphatase and tensin homolog
ROS	Reactive oxygen species
SASP	Senescence-associated secretory phenotype
SDMA	Symmetric dimethylarginine
SMYD	SET and MYND domain-containing protein
SREBP	Sterol regulatory element binding protein
SRF	Serum response factor
TAA	Thoracic aortic aneurysm
UTX	Ubiquitously transcribed tetratricopeptide repeat X chromosome
VSMC	Vascular smooth muscle cell

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Availability of data and materials

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Declarations

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