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Review

The Role and Mechanisms of Histone Acetyltransferases in Arterial Lesions

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Abstract

Cardiovascular and cerebrovascular diseases are among the leading causes of death worldwide. Development of these diseases occurs following pathological structural remodeling and functional changes in the vascular wall. Emerging evidence suggests that histone acetyltransferases (HATs) play a role in the pathological processes of the arterial wall. However, there is currently a lack of comprehensive reviews examining the role of HATs in vascular diseases. The aim of this research is therefore to systematically describe the pathological effects of various risk factors on different layers of cells in the arterial vascular wall. The risk factors include abnormal activation of the renin-angiotensin system, hyperglycemia, high-sodium diets, and intermittent hypoxia. The effects regulated by HATs involve the nuclear factor kappa-B (NF-κB)-NOD-like receptor family pyrin domain containing 3 (NLRP3) and AMP-activated protein kinase (AMPK) pathways, and the mitogen-activated protein kinase (MAPK) and vascular endothelial growth factor receptor 2 (VEGFR2) signaling pathways. We also explore the dual role of HATs in vascular protection and injury. Additionally, this study focuses on the prospects of future therapeutic strategies targeting HATs, including innovative approaches such as HAT inhibitors, epigenetic degraders, non-coding RNA interventions, and epigenetic editing technologies. The aim of this review is to provide a basis for the development of selective subtype HAT inhibitors.

Keywords: histone acetyltransferases; vascular endothelial cells; smooth muscle cells; immune cells; renin-angiotensin system; vascular remodeling; epigenetic therapy

1. Introduction

Cardiovascular and cerebrovascular diseases are among the leading causes of death worldwide. The prevalence of coronary heart disease among adults aged $\geq$18 years in China is 758 per 100,000 population [1]. With a prevalence of up to 20% in China, primary hypertension is one of the most common chronic diseases and a serious threat to public health [2]. Diseases such as cerebrovascular disorders, vasculitides, and aneurysms also pose significant threats to human health. Therefore, it is crucial to further investigate the pathogenesis of vascular diseases and improve current strategies for prevention and intervention.

The arterial vascular wall is primarily composed of three layers: the endothelium, vascular smooth muscle cells (VSMCs), and adventitia. Under the combined effects of long-term environmental factors such as hypertension, hyperglycemia, and genetic factors, each layer of the vascular wall may undergo pathological changes. For example, in the presence of hypertension and hyperglycemia, endothelial cells (ECs) secrete less amounts of important vasodilators, while increasing the expression of adhesion molecules that promote immune cell recruitment and lead to dysfunction of coagulation. VSMCs may shift from a contractile phenotype to a synthetic phenotype, accompanied by cell proliferation and migration, inflammation, and oxidative stress. The adventitia is mainly characterized by infiltration of inflammatory cells and remodeling of the extracellular matrix. Chronic inflammation of the vascular wall is recognized as a fundamental reason for the development of various cardiovascular diseases. Hence, there is an urgent need to find ways to reduce vascular wall inflammation.

Histones are core components of chromatin. Conventional histones consist of two molecules each of H2A, H2B, H3, and H4, forming an octamer that participates in the regulation of DNA expression, folding, and protection. Acetylation is one of the most important modifications of histones. Following the acetylation of histone lysine residues, the chromatin structure becomes more relaxed, facilitating the binding of transcription factors, RNA polymerase, and other transcription-related proteins to DNA, and thereby promoting gene transcription [3]. Histone acetylation is primarily regulated by a balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs can be classified into families such as the MOZ-Ybf2/Sas3-Sas2-TIP60 family (MYST), Gcn5-related N-acetyltransferase family (GNAT), p300/CBP histone acetyltransferase family (p300/CBP), nuclear receptor coactivator family, and general transcription factor family.

These enzymes not only acetylate histone lysine residues, but also participate in the recruitment of transcription factors and RNA polymerase [4,5]. At the same time, HDACs can be divided into four categories, one of which indirectly regulates gene expression by recruiting HATs such as p300 (histone acetyltransferase p300) [6].

Current research indicates that HATs promote pathological processes in various diseases by having pro-inflammatory roles, regulating excessive gene transcription, and affecting metabolism. HATs can directly promote the expression of genes such as nuclear factor kappa-B (NF-κB) and interleukin-6 (IL-6), thereby driving endothelial cell senescence and the onset of inflammatory responses [7]. Moreover, the transcriptional activity of NF-κB is co-regulated by HATs and HDACs. HATs can interact with the p65 subunit of NF-κB, enhancing its transcriptional activity through protein-protein interactions [8]. HDACs, on the other hand, can deacetylate histone 3 at Lysine 9 (Lys9), ultimately reducing the binding of NF-κB-p65 to DNA and alleviating cardiac hypertrophy and oxidative stress by downregulating the transcription of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits [9]. The expression of renin is directly regulated by p300, and its excessive expression worsens the prognosis of cardiovascular diseases [10].

The levels of histone acetylation can influence both systemic and cellular metabolic processes, as well as impact the prognosis of various diseases. For example, several studies have shown that significant increases in histone acetylation levels play a key role in the development and progression of cardiovascular and cerebrovascular diseases. Abnormalities have been observed in the levels and activity of HATs in disease and these may directly drive the pathological processes [11,12]. Although a large number of studies have explored the role of HATs in cardiovascular and cerebrovascular diseases, the related reviews have not been updated in a timely manner. In particular, there have been few systematic summaries of newly discovered mechanisms in recent years. The goal of this paper is therefore to systematically analyze the histone acetylation characteristics of VSMCs, ECs and immune cells in the arterial walls in cardiovascular and cerebrovascular diseases. This will help to elucidate the disease progression mechanisms driven by abnormal HAT activity and expression, as well as the associated molecular pathways. We also discuss the bidirectional regulatory role of HATs in vascular protection and injury, and analyze the potential clinical value of HATs as therapeutic targets.

2. Core Mechanisms of HATs in Vascular Diseases

Abnormal activity and levels of HATs have been linked to damaging effects in several cardiovascular diseases [7,13]. In arterial diseases such as hypertension, atherosclerosis (AS) and vasculitis, long-term inflammation and excessive release of reactive oxygen species (ROS) are considered to be the most important steps in disease progression. Recent studies indicate that HATs play a critical regulatory role in these damaging processes.

NF-κB is a core transcription factor in the inflammatory response. Upon activation, it binds to specific sites in the promoter regions of target genes, regulating the transcription of various inflammatory mediators and promoting their release. Under various pathological conditions, multiple immune cell types in rat models have shown increases in both HATs and NF-κB. In neuroinflammation, microglial cells activate lysine acetyltransferase 2A (KAT2A) via Toll-like receptor 4 (TLR4) signaling in response to stress signals. KAT2A then acetylates the p65 subunit of NF-κB at Lys310, increasing its ability to translocate into the nucleus and activate inflammatory gene transcription, ultimately triggering an inflammatory response [14]. In another study, inhibition of p300 with C646 suppressed the activation of p65 in macrophages [15]. Furthermore, inhibitors of KAT2A and lysine acetyltransferase 8 (KAT8) were shown to reduce NF-κB activation and the binding of NOD-like receptor family pyrin domain containing 3-apoptosis-associated speck-like protein containing a CARD inflammasome (NLRP3-ASC), subsequently decreasing the expression of NLRP3 and pro-inflammatory cytokines such as IL-1 [15,16]. Excessive ROS is a critical factor in causing cellular damage. On one hand, HATs promote the release of ROS by activating NF-κB. KAT8 inhibitors have been shown to significantly reduce ROS release by cells [17]. On the other hand, KAT2A and p300/CBP-associated factor (PCAF) (both GNAT family members) directly regulate mitochondrial function [18].

Pathological conditions such as hyperglycemia, hyperlipidemia, and high salt can directly damage ECs and smooth muscle cells. This causes the release of ROS and inflammatory factors, thereby activating systemic and local vascular immune cells and exacerbating tissue damage. During this process, ROS and NF-κB form a vicious cycle through oxidative stress-inflammation cascades, further aggravating endothelial injury, lipid deposition, inflammatory infiltration, and vascular remodeling. This cycle forms the critical pathological basis for cardiovascular diseases such as AS, hypertension, and diabetic vascular complications. HATs can exacerbate vascular damage by regulating pathways such as MAPK, the renin-angiotensin system, hypoxia-inducible factor-1, vascular endothelial growth factor A (VEGFA), and chemokines.

3. Effects of HATs on ECs, VSMCs, and Vascular Immune Cells

3.1 HATs and ECs

ECs form the first barrier of the blood vessel wall. They also regulate substance exchange, secrete signaling molecules, and maintain the balance between coagulation and anticoagulation. Early dysfunction of ECs is often

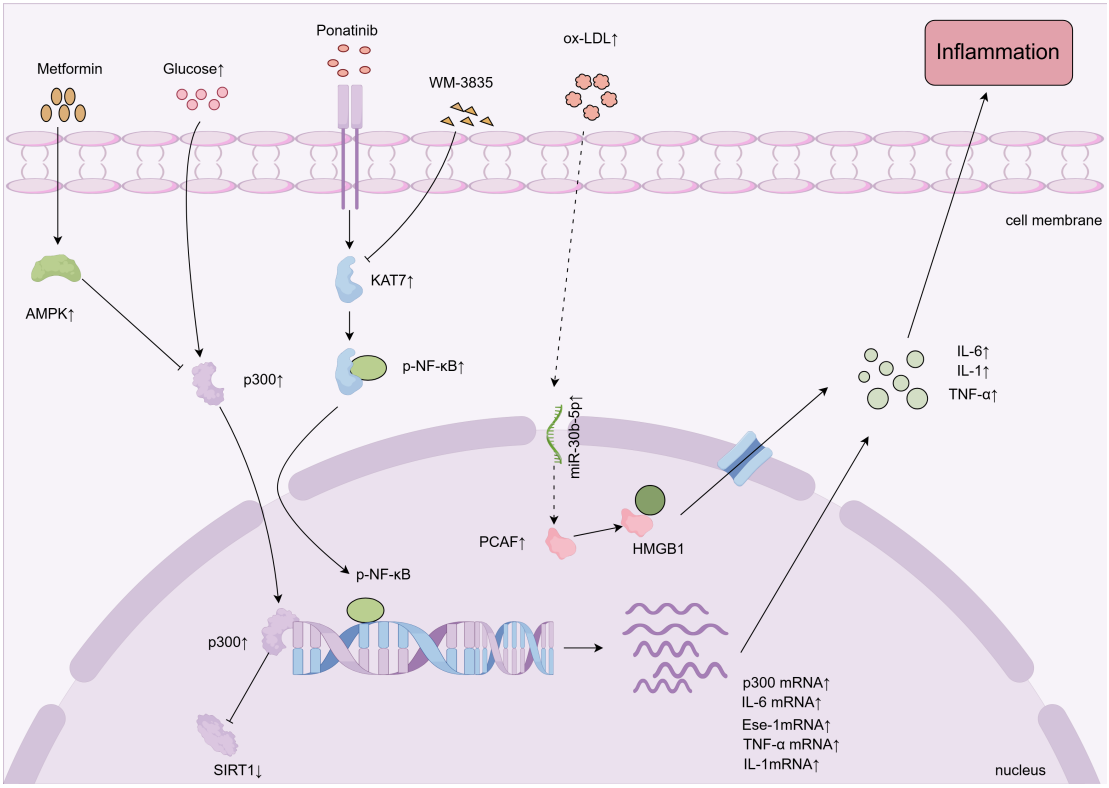

Fig. 1. HATs promote vascular endothelial cell inflammation. High glucose, ponatinib, and ox-LDL promote vascular endothelial inflammation by affecting HATs. HATs, histone acetyltransferases; AMPK, AMP-activated protein kinase; HMGB1, high mobility group box 1; ox-LDL, oxidized low-density lipoprotein; SIRT1, sirtuin 1; IL-6, interleukin-6; IL-1, interleukin-1; TNF-α, tumor necrosis factor-alpha; PCAF, p300/CBP-associated factor; WM-3835, inhibitor of histone acetyltransferase KAT7. This figure was created using Figdraw (Version 2.0, http://www.figdraw.com), Home for Researchers, China.

the starting point for the development of various vascular-related diseases. Long-term exposure to high levels of glucose, lipids, angiotensin, or other harmful substances can significantly increase the production of inflammatory factors and ROS within ECs, which can ultimately lead to abnormal EC proliferation, plaque formation, and even induce the proliferation of VSMCs [19]. It is worth noting that polyphenolic compounds, such as green tea extract, and substances like metformin can effectively alleviate endothelial inflammation. Current evidence suggests that abnormal HATs promote EC injury through regulatory mechanisms involving NF-κB, as well as the vascular endothelial growth factor receptor 2 (VEGFR2), Delta-like ligand-Notch, and AMP-activated protein kinase (AMPK) signaling pathways (Fig. 1).

3.1.1 HATs Involved in the Inflammation and Senescence of Vascular ECs are Induced by Various Pathogenic Factors

Pathogenic factors such as high glucose, AS and smoking can induce EC inflammation and senescence by upregulating HATs. Under high glucose stimulation, the permeability of ECs is significantly increased, accompanied by upregulation of p300 expression levels [20]. Elevated p300 expression further promotes the upregulation of epithelial-specific transcription factor 1 in ECs, which then induces the expression of inflammatory factors such as TNF-α, Macrophage Inflammatory Protein-1β (MIP-1β), MIP-2, and phosphorylated p65 (p-p65), ultimately exacerbating endothelial damage. Inhibition of p300 expression can attenuate the endothelial damage phenotype induced by high glucose [21]. Furthermore, KAT7A was shown to enhance NF-κB activation in a vascular endothelial injury model induced by tyrosine kinase inhibitors [7]. p300 and NAD^+-dependent class III histone deacetylase (SIRT1) also jointly regulate the endothelial inflammation process induced by a high glucose environment. This milieu upregulates p300 expression and decreases SIRT1 levels. siRNA-mediated knockdown of p300 restores SIRT1 mRNA to normal levels, and also reduces the mRNA expression of ET-1 and TGF-β1, as well as the acetylation levels of histone H3 at Lys9/14 (Ac-H3K9/14). On the other hand, overexpression of SIRT1 can effectively improve the high glucose-induced abnormalities of endothelial permeability and excessive collagen Iα deposition [20].

Factors such as aging, AS, palmitic acid, smoking, and angiotensin II (Ang II) can significantly increase the expression levels of p300 and PCAF in vascular ECs, along

with upregulating senescence markers such as p53, p21, and p16 [22–24]. Downregulation of PCAF expression has also been shown to promote the activation of nuclear factor erythroid-2-related factor 2 (Nrf2) in ECs and increase the expression of its downstream anti-aging factors. This ultimately reduces ROS levels in ECs and delays vascular aging [22]. Obesity can also accelerate vascular aging. Research has shown that vascular tissue isolated from the visceral fat arteries of obese individuals exhibits significant ROS-driven endothelial dysfunction, with the expression of acetyltransferase steroid receptor coactivator-1 (SRC-1) being 5.8-fold higher than in normal-weight controls [25]. This finding suggests that SRC-1 may play a key role in obesity-induced endothelial dysfunction, although its specific mechanism requires further investigation.

3.1.2 The Effect of HATs on VEGFA and Delta-Like Ligand-Notch Signaling Pathway

HATs promote the pathological effects induced by VEGFA and the Delta-like ligand-Notch signaling pathway. The expression of VEGFR2 in human umbilical vein ECs is significantly enhanced under stimulation by high concentrations of exogenous VEGFA. When p300 is inhibited, the level of histone H3 lysine 27 acetylation (H3K27Ac) modification at the VEGFR2 promoter region decreases, leading to reduced VEGFR2 expression and a corresponding decrease in angiogenesis [26]. In glioblastoma cells, HAT1 can acetylate hypoxia-inducible factor 2α (HIF2A) and bind to the promoter regions of hypoxia-related target genes such as VEGFA, thereby promoting transcription through histone acetylation modifications and enhancing angiogenesis [27].

HATs are also involved in regulating the Delta-like ligand-Notch signaling pathway. In VEGFA-treated ECs, the HAT p300 specifically binds to the enhancer region of Delta-like ligand 4 [28]. Furthermore, in vascular endothelial inflammation induced by IL-1β, the level of H3K27ac in the enhancer region of inflammation-related genes decreased by 31% following notch homolog 1 (notch1) knockdown [29]. In another experiment, inhibition of p300 activity by imatinib resulted in the downregulation of key Notch pathway proteins, reducing the epithelial-mesenchymal transition potential of breast cancer cells [30].

3.1.3 Non-Coding RNAs Promote Cardiac Lesions and Endothelial Cell Inflammatory Responses by Regulating HAT Levels

Non-coding RNAs (ncRNAs) regulate gene expression at the post-transcriptional level. They also play a critical role in cardiovascular diseases by influencing epigenetic regulators, particularly the activity of HATs. HATs such as p300 and CBP are core enzymes that regulate chromatin accessibility and heart-specific gene expression, and their fine-tuning is closely related to cardiac structural remodeling. Previous studies have found that miRNA-199a is significantly upregulated following myocardial infarction. miRNA-199a targets and inhibits Sirt1, thereby releasing the inhibitory effect of Sirt1 on p300, enhancing p300 acetylation, and activating the Yin-yang 1/soluble Suppression of Tumorigenicity 2 (Yy1/sST2) signaling pathway. This subsequently promotes myocardial hypertrophy and fibrosis. Notably, antimiR-199a can reverse this pathological process by antagonizing the action of miRNA-199a [31]. Animal experiments also showed that miR-330-3p targets the 3′-UTR of CBP in porcine cardiac valve interstitial cells, decreasing its expression. This weakens the acetylation modifications mediated by CBP, leading to upregulation of pro-calcification factors such as bone morphogenetic protein 2 (BMP2) and runt-related transcription factor 2 (RUNX2), which then exacerbate valve fibrosis and calcification [32]. These findings suggest that ncRNAs regulate the expression and activity of HATs, thereby altering histone acetylation levels and acting as a bridge in pathological processes such as myocardial remodeling, fibrosis and valve calcification, and driving the progression of cardiovascular diseases.

ncRNAs also promote inflammatory responses in vascular ECs by regulating the activity of HATs. Studies have shown that ox-LDL induces the upregulation of miR-30b-5p, which subsequently activates the UBE2D2/PCAF pathway. Activated PCAF acetylates high mobility group box 1 protein (HMGB1), leading to the dissociation of acetylated HMGB1 from SIRT1. This dissociation facilitates the migration of HMGB1 from the nucleus to the cytoplasm and its release into the extracellular space, which then induces expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), enhancing endothelial inflammation [33].

3.1.4 Epigallocatechin Gallate and Other Compounds Protect Vascular ECs by Inhibiting HATs

Epigallocatechin gallate (EGCG) is a polyphenolic compound extracted from green tea and known for its significant antioxidant and anti-inflammatory properties. In a polychlorinated biphenyl-induced vascular endothelial injury model, EGCG was found to significantly reduce the binding of NF-κB-regulated genes (including IL-6, CRP, ICAM-1, VCAM-1, and IL-1α/β) to the promoter regions of p65 and p300. This in turn decreased H3 acetylation levels, and ultimately suppressed the expression of inflammatory genes [34]. The activation of AMPK in vascular ECs leads to important anti-inflammatory effects. AMPK can be activated by 5-aminoimidazole-4-carboxamide-1-β-D-ribonucleoside (AICAR) or metformin. Activated AMPK has been found to reduce the acetylation level of Lys221 in the NF-κB p65 subunit through atypical protein kinase C (PKC)-mediated phosphorylation at the Ser89 site of p300, thereby inhibiting the adhesion of monocytes to ECs and reducing EC inflammation [35]. Furthermore, the transcrip-

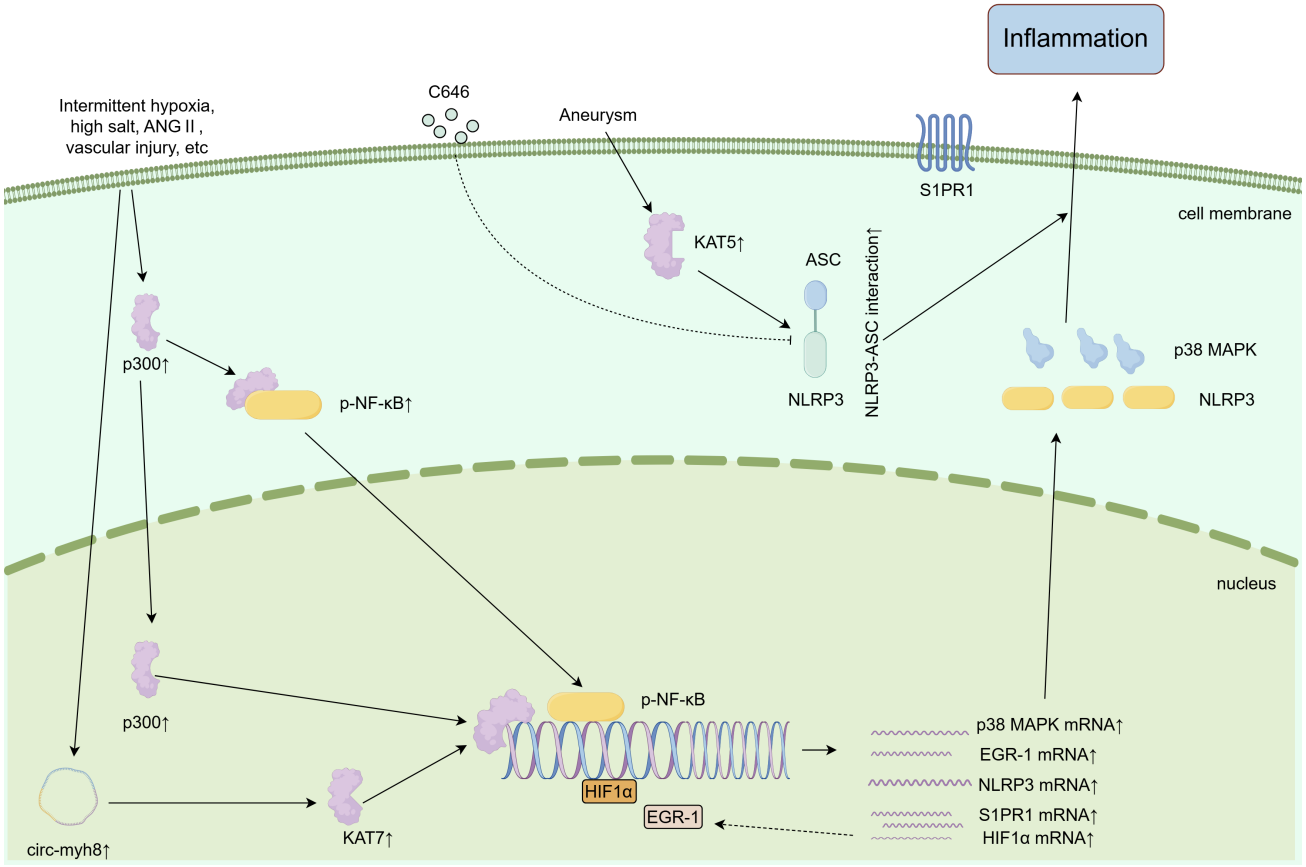

Fig. 2. HATs promote vascular smooth muscle cell inflammation. Multiple pathological factors promote vascular smooth muscle inflammation and injury through HATs. ASC, apoptosis-associated speck-like protein containing a CARD; NLRP3, NOD-like receptor family pyrin domain containing 3; C646, inhibitor of histone acetyltransferase p300. This figure was created using Figdraw (Version 2.0, http://www.figdraw.com), Home for Researchers, China.

tion factor Kruppel-like factor 2 (KLF2) exerts multiple biological effects (including anti-inflammatory and anti-thrombotic effects) and maintains normal vasodilation by regulating the expression of various endothelial genes [36]. Recent studies indicate that KLF2 expression is closely related to histone acetylation modifications, although the precise regulatory mechanisms between KLF2 and various HATs await further investigation.

3.2 HATs and VSMCs

The inflammation, abnormal proliferation, and migration of VSMCs are known to exacerbate the progression of diseases such as hypertension, AS, and vascular restenosis. Recent studies suggest that excessive modification through histone acetylation can promote the pathological changes observed in VSMCs. Various pathological factors, including intermittent hypoxia, Ang II hyperglycemic environments, and vascular physical injury can exacerbate pathological changes in VSMCs by enhancing the activity of HATs, leading to vascular dysfunction (Fig. 2).

3.2.1 HATs Promote Vascular Smooth Muscle Injury by Enhancing the Expression of Hypoxia-Inducible Factor-1, NF-κB, and NLRP3

Hypoxia-inducible factor-1 (HIF-1) and NLRP3 can promote vascular smooth muscle injury under pathological conditions. Intermittent hypoxia refers to repeated cycles of hypoxia and reoxygenation. In experimental animals and patients, this can lead to symptoms such as activation of the sympathetic nervous system and increased blood pressure. Moreover, the expression and activity of p300, HIF-1, and ROS in the adrenal medulla of rats increase significantly under conditions of intermittent hypoxia. Inhibition of p300 can effectively lower blood pressure and reduce the secretion of norepinephrine in rats [37]. In another experiment, the expression of circ-myh8 was observed to increase significantly in the pulmonary arteries of hypoxic mice. Circ-myh8 recruits KAT7 to the HIF1α promoter, enhancing acetylation of histone H4K5, which ultimately promotes the proliferation of pulmonary arterial smooth muscle. Inhibition of KAT7 reduced the mRNA and protein expression of HIF1α induced by circ-myh8 [38]. Expression

of p300 was significantly increased in the vascular smooth muscle of spontaneously hypertensive rats, while binding to the NLRP3 promoter region was enhanced. Inhibition of p300 significantly attenuated NLRP3 inflammasome activation and vascular remodeling in these rats [39].

3.2.2 HATs Promote Ang II-Induced Vascular Inflammation and Injury

Ang II is considered to be one of the key hormones responsible for the development of cardiovascular diseases, making it a major target for treatment. Renin is essential for the synthesis of Ang II. In As4.1 cells, cAMP activates protein kinase A (PKA), which promotes the recruitment of p300 and H3K27 acetylation, thereby increasing transcription of the renin gene [10]. In another study of obesity-associated hypertension, the increase in p300 upregulated the expression of angiotensin-converting enzyme 1 (ACE1) in renal tubular epithelial cells [40]. HATs significantly enhance Ang II-induced vascular inflammation and injury. When VSMCs are damaged, histone acetylation levels in the nucleus increase significantly [41,42]. Following intervention with Ang II, p300 increases the acetylation of histone H3 lysines (K9/14) in the IL-6 promoter region, thereby upregulating IL-6 expression. Inhibition of p300/CBP function through the use of mutant variants suppressed Ang II-induced IL-6 expression [43,44]. Additionally, under conditions of IL-1β stimulation, p300 was enriched at the early growth response gene 1 (EGR-1) promoter region in VSMCs, effectively activating the EGR-1 promoter and inducing the expression of EGR-1 [45]. EGR-1 is an important transcription factor that promotes the proliferation of VSMCs. Ang II can also induce the expression of fibrotic factors by activating the Janus kinase 2-signal transducer and activator of transcription 3 pathway (JAK2-STAT3). p300 amplifies this effect by enhancing acetylation and phosphorylation of STAT3, leading to increased expression of fibronectin, collagen IV, and other fibrotic markers [46].

Ang II can regulate histone acetylation levels in the promoter regions of several key proteins in VSMCs through both direct and indirect mechanisms, thus affecting cell functions such as inflammation, proliferation, and migration. These key proteins include the sphingosine-1-phosphate receptor 1 (S1PR1), EGR-1, and sodium channels [42,45,47,48]. Ang II upregulates the expression of S1PR1, for example, which then increases the proliferation of VSMCs. This process is accompanied by increased histone H3 acetylation levels in the S1PR1 promoter region [48]. Additionally, Ang II activates its own type 1 receptor, which then activates an Akt-dependent signaling pathway to specifically phosphorylate Ser570 of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α). This phosphorylation modification prompts KAT2A to acetylate PGC-1α, thereby suppressing its activity. The result is reduced catalase expression, increased intracellular ROS levels, and ultimately the induction of VSMC hypertrophy [49].

3.2.3 High Glucose and High Salt Promote Vascular Smooth Muscle Cell Proliferation and Remodeling by Regulating PCAF Activity

Abnormal microenvironmental conditions, such as high glucose and high salt, can promote pathological changes in VSMCs by regulating PCAF activity. These environmental factors have been shown to induce increased histone acetylation levels in the nucleus, particularly the acetylation of H3K9 [50,51]. In a high-glucose environment, rat VSMCs and human aortic smooth muscle cells both exhibit increased PCAF activity and expression levels. PCAF then promotes excessive production of ROS within VSMCs, leading to upregulation of synthetic markers (such as collagen type I, osteopontin) and NLRP3 expression, and promoting the abnormal proliferation and migration of VSMCs. Specific PCAF inhibitors can effectively reduce histone acetylation levels and suppress ROS production, thereby mitigating oxidative stress damage to VSMCs [52,53]. In a high-sodium environment, VSMCs also exhibit significant phenotypic changes, such as decreased expression of contractile markers, and increased expression of synthetic markers and PCAF. Similarly, the inhibition of PCAF activity can promote the transition of VSMCs to a contractile phenotype with reduced NLRP3 expression, thus exerting protective effects [51].

3.2.4 PCAF Exacerbates Smooth Muscle Cell Proliferation and Remodeling Following Vascular Injury

Vascular injury, such as stent interventions or balloon damage, can lead to the proliferation, migration, and inflammation of VSMCs, ultimately resulting in stenosis and thrombosis within the vessel lumen. In a rat carotid artery model with repeated balloon injury, researchers observed a significant increase in histone acetylation levels in the transcriptional regions of inflammation-related genes such as Cebpd, suggesting that HATs may promote the expression of inflammatory genes [41]. In another study, researchers injured the left common carotid artery in Sprague-Dawley rats (SD rats). By inhibiting PCAF expression, a significant reduction in the ratio of intimal to medial area was observed, confirming that PCAF promotes pathological remodeling following vascular injury [54].

Further investigation of signaling pathways revealed the levels of phosphorylated p38 mitogen-activated protein kinase (p-p38 MAPK) and phosphorylated serine/threonine protein kinase AKT (p-AKT) were elevated in lipopolysaccharide (LPS)-induced VSMCs. Upon inhibition of PCAF, the expression of both p-p38 MAPK and p-AKT decreased significantly, while the proliferation of VSMCs was inhibited. This suggests that PCAF may affect the proliferation of VMSCs by regulating the p38 MAPK and AKT signaling pathways [55]. Additionally, the inhibition of PCAF

in PCAF-induced smooth muscle inflammation reduced the secretion of monocyte chemoattractant protein-1 (CCL2) in the vascular intima, leading to a 54.8% decrease in the number of macrophages in the intima. *In vitro* experiments further confirmed that downregulation of PCAF resulted in the inhibition of LPS-induced VSMC proliferation and migration, as well as nuclear translocation of NF-κB p65 [56,57].

Using a mouse femoral artery injury model, the proliferation and migration abilities of VSMCs were found to be regulated by an interaction between staphylococcal nuclease domain-containing protein 1 (SND1) and serum response factor (SRF). Specifically, SND1, as a co-activator of SRF, recruits PCAF to the promoter region of proliferation and migration-related genes rich in CC(A/T)$_6$GG (CArG) motifs. By catalyzing histone acetylation modifications, PCAF alters the chromatin structure, thus increasing the binding of SRF to the CArG motif and subsequently activating the transcription of downstream genes. This process ultimately promotes VSMC proliferation and migration, and drives the repair and remodeling process after vascular injury [58].

3.2.5 The Effect of Non-Coding RNAs and Histone Methyltransferases on HATs

Non-coding RNAs can exacerbate vascular smooth muscle damage by regulating HATs. The circular RNA circ-myh8 has been shown to bind to and recruit the HAT KAT7, which targets acetylation of histone 4 lysine 5 (H4K5) in the promoter region of HIF1α, thereby upregulating its transcription. The increased expression of HIF1α subsequently drives proliferation and cell cycle progression of pulmonary artery smooth muscle cells, ultimately exacerbating pulmonary vascular remodeling and the development of pulmonary arterial hypertension (PAH) [38]. Another study found that under conditions of PAH, KAT7 cooperates with circ-myh8 to increase the H3K27ac modification at the FOS-like 2 (*FOSL2*) gene super-enhancer. This drives the transcription of PANoptosis-related genes, thereby intensifying pulmonary vascular remodeling [59].

Histone acetylation and methylation have reciprocal regulatory effects. For example, PCAF acetylates ubiquitin-like with PHD and ring finger domains 1 (UHRF1), a key regulator of DNA methylation maintenance, thereby interfering with its binding to hemimethylated DNA and disrupting the maintenance of genomic methylation [60]. Additionally, CBP/p300 upregulates H3K27ac levels, which has the effects of promoting ten-eleven translocation 2 (TET2) demethylation, inhibiting DNA Methyltransferases (DNMTs) from binding to the promoter, reducing the methylation of genes like RUNX2, and activating transcription to accelerate vascular calcification [61]. Similarly, methyltransferases can also methylate certain sites on HATs [62]. In diabetic cardiac microvascular disease, the demethylase Alkylation Repair Homolog (AlkB) homolog 5 can reduce the level of m6A methylation in KAT2A mRNA, leading to upregulation of KAT2A. By increasing acetylation levels of the transferrin receptor (Trfc) and heme oxygenase 1 (Hmox1) promoters, KAT2A promotes ferroptosis, thereby exacerbating microvascular disease [63]. Therefore, we hypothesize that the interaction between histone acetylation and DNA methylation may promote arterial damage.

3.3 HATs and Vascular Immune Cells

Various immune cells, including T cells, B cells, dendritic cells and macrophages, have been shown to participate in chronic inflammatory processes within the vasculature and are thus considered potential therapeutic targets for various arterial diseases [64]. Recent studies have found that histone acetylation can promote the release of pro-inflammatory cytokines by certain immune cells, thereby enhancing the inflammatory response. For instance, LPS and high glucose can induce acetylation modifications of H3K27, H3K9, and H3K14 in the chromatin of monocyte-macrophages, promoting their conversion to the M1 pro-inflammatory phenotype. This transformation leads to the secretion of more pro-inflammatory cytokines, further exacerbating the inflammatory response. Inhibition of p300 can suppress expression of the pro-inflammatory marker inducible nitric oxide synthase (iNOS) [65,66]. Additionally, HATs and HDACs also jointly regulate the activity of T cells and B cells [67–69].

The vascular pathological tissues and peripheral blood of patients with AS and abdominal aortic aneurysm show elevated chromatin acetylation levels in the monocyte-macrophage system and in T cells [70–72]. Moreover, the protein levels of p300, KAT1, H3K27ac, and NADPH oxidase 5 (Nox5) were also elevated in atherosclerotic tissues. Immunohistochemistry and immunofluorescence staining experiments indicated these proteins co-localized in CD45$^+$/CD68$^+$ immune cells and lipid deposition regions within atherosclerotic plaques. *In vitro* experiments showed the levels of KAT1, H3K27ac, H3K9ac and Nox5 increased significantly in cultured human macrophages under LPS stimulation, with both p300 and KAT1 recruited to active transcriptional regions of the Nox5 gene promoter. In addition, HAT inhibitors reduced Nox5 mRNA and protein expression in LPS-stimulated macrophages, thereby decreasing ROS production and inflammatory responses [70].

The interaction between HATs and certain non-coding RNAs not only regulates the prognosis of some cardiac diseases, but also promotes macrophage activation during coronary AS, thereby exacerbating the progression of the disease. In this pathological process, oxidized low-density lipoprotein (ox-LDL) can induce the upregulation of miR-21-5p (a non-coding RNA), which then activates P300. Activated P300 subsequently catalyzes the acetylation of HMGB1, causing it to migrate from the nucleus to the cytoplasm and be secreted into the extracellular microenviron-

ment. Here, it induces macrophages to polarize into the M1 phenotype, thus driving the development of AS [73]. Related studies have also shown that miR-486 binds directly to the 3' untranslated region of KAT1 mRNA, inhibiting its post-transcriptional expression. This reduces its regulation of the downstream target ATP-binding cassette transporter A1 (ABCA1), impeding cholesterol efflux in macrophages and promoting cholesterol accumulation, which ultimately worsens AS [74].

PCAF also participates in the recruitment of inflammatory cells. Intervention with PCAF siRNA, or the PCAF inhibitor garcinol, can significantly reduce the secretion of CCL2 in the vascular intima, leading to a 54.8% reduction in the number of macrophages in the intima [56]. Studies have also found that PCAF knockout attenuates the VSMC-induced increase in leukocytes and inflammatory response [75]. Lastly, the atherogenic phospholipid phosphatidylcholine promotes AS by upregulating the activity of HATs and increasing the H3K14ac modification of chromatin, thereby upregulating the expression of tat-interactive protein (TIP) genes in human aortic ECs. This activation triggers trained immunity pathways, initiating sustained chronic inflammation [76]. The above findings suggest the HAT system exacerbates vascular injury by regulating the activation of immune cells and the production of inflammatory factors.

3.4 Core Mechanisms of HATs in Vascular Inflammation

In chronic damage conditions such as hypertension, hyperglycemia and hypoxia, the HAT levels in the vascular wall increase, and histone acetylation in the nucleus is significantly elevated. At the same time, abnormal expression of HATs exacerbates inflammation, senescence, and damage in the vascular wall, forming a positive feedback loop. This bidirectional interaction between inflammation and HAT activity is an important mechanism for the persistence and amplification of the inflammatory response.

The NF-κB-NLRP3 pathway is involved in inflammation of the entire vascular wall. During vascular wall injury, HATs acetylate p65, thus increasing the activity of NF-κB. Additionally, HATs strengthen the binding at various gene promoter regions, such as VEGFR2, IL-1, IL-6, Nox5, and NLRP3, which loosen the chromatin structure and promote transcription. Recent studies have shown that KAT7 and CBP can also recruit RNA polymerase to specific gene sites, promoting the initiation of transcription [59,77]. HATs can further influence inflammation by affecting the binding of NLRP3 to its adaptor protein (ASC). In osteoarthritis, KAT7 has a positive regulatory effect on the TLR4/NF-κB/NLRP3 pathway [78].

The MAPK pathway also promotes vascular inflammatory responses, immune cell regeneration, release of inflammatory mediators, and vascular remodeling. Following LPS induction of VSMCs, the expression of p-p38 MAPK and p-AKT increases. Downregulation of PCAF significantly inhibits the phosphorylation of both proteins, thus reducing VSMC proliferation. Mechanistically, VEGFR2, a key receptor in the MAPK pathway, is transcriptionally regulated by p300. Additionally, researchers have found that KAT7 increases the transcription of MRAS (a small GTPase from the RAS superfamily) by acetylating histone H3 at Lys14, which then activates the MAPK/ERK pathway and promotes colorectal cancer progression [79].

AMPK is a key energy metabolism-regulating kinase that is generally considered to play a protective role in vascular wall inflammation. The AMPK/SIRT1/mTOR pathway is the main pathway through which AMPK exerts its anti-inflammatory effects. AMPK can also inhibit inflammation by suppressing HATs. Furthermore, AMPK can activate SIRT1 and directly phosphorylate p300, thereby downregulating p300 activity [80]. In diseases like hypertension and AS, the levels of HATs and NF-κB are significantly elevated in vascular ECs, smooth muscle cells, and immune cells. Following AMPK intervention, the levels of HATs/NF-κB in these cells are reduced, alleviating vascular inflammation.

4. The Dual Role of HATs in Vascular Protection and Damage

HATs primarily amplify inflammation and promote damage in vascular wall lesions. However, under certain conditions, HATs can also play a protective role in the vasculature. For example, KAT3A promotes the expression of miR-322 by stabilizing the HIF-1α complex, inhibiting cell apoptosis and inflammation, and alleviating ischemia-reperfusion injury in rats [81]. In the ApoE3*Leiden mouse model, the absence of PCAF leads to an increase in atherosclerotic lesions in the aortic sinus by reducing the number of systemic FoxP3$^+$ regulatory T cells (Tregs) [82]. Another study found that inhibiting p300 expression aggravated pulmonary hypertension and promoted the proliferation of VSMCs [83]. These results suggest that HATs have a dual regulatory role in arterial diseases. There may be several reasons behind this dual effect. Firstly, HATs regulate essential cell processes such as proliferation and inflammation during normal cellular metabolism [84,85]. When HATs are completely knocked out in certain cells, this can disrupt basic cellular functions, leading to an increase in the atherosclerotic area and impaired blood flow recovery. Secondly, recent research on HATs has led to the discovery of more family members, each with unique functions. For example, although p300 and CBP share similar structure and function, they can have different effects on VSMCs. Mice with p300 knockout (p300iKO) had significantly worse intimal hyperplasia and increased VSMC proliferation compared to controls, whereas CBP knockout (CBPiKO) mice were unaffected by intimal hyperplasia [86]. Moreover, HATs and HDACs jointly regulate downstream genes and proteins. Sirt6 (HDAC III) directly interacts with KAT2A

Table 1. Inhibitory/promotional effects of HAT inhibitors on pathological processes in cardiovascular diseases.

HAT inhibitor	HATs	Target cell	Inhibitory/Promotional pathological effects
A-485	p300/CBP	Human aortic SMCs	Ferroptosis [93]
Curcumin	p300/CBP	Rat VSMCs	Smooth muscle cell inflammation [39]
WM-3835	KAT7	Rat mesenteric artery ECs	EC senescence and inflammation [7]
EGCG	p300/CBP	Human ECs	EC inflammation [34]
CPTH2	KAT2A	Human macrophages	Oxidative stress [70]
C646	p300/CBP	Human macrophages	Oxidative stress [70]
Garcinol	PCAF	White blood cells	Intimal leukocyte recruitment [56]
Anserine	p300/CBP	Mouse cardiomyocytes	Myocardial hypertrophy [94]
Andrographolide	p300/CBP	Mouse valve interstitial cells	Aortic valve calcification [95]
Anacardic acid	p300/CBP	Mouse cardiomyocytes	Myocardial hypertrophy [96]
Metformin	p300/CBP	Rat cardiomyocytes	Myocardial hypertrophy [12]
Curcumin	p300/CBP	Human atrial fibroblasts	Atrial fibroblast senescence [97]
Anacardic acid	PCAF	Mouse cardiomyocytes	Myocardial hypertrophy [98]
L002	p300/CBP	Cardiac fibroblasts	Myocardial hypertrophy [99]
Pentamidine	KAT5	Mouse cardiomyocytes	Myocardial infarction area [92]
CTK7A	p300/CBP	pheochromocytoma-12 cells	Oxidative stress [37]

to enhance its acetylation activity on PGC-1α. This modification turns PGC-1α into a "high acetylation state", which in turn inhibits hepatic gluconeogenesis. When Sirt6 is depleted, KAT2A activity is reduced, thereby exacerbating hyperglycemia [87]. Finally, the function of downstream proteins or genes determines the effects of HATs. For example, after a cerebrovascular accident, elevated PCAF activity promotes p53 acetylation, which then induces neuronal apoptosis. In contrast, overexpression of HDAC6 deacetylates p53, inhibiting its pro-apoptotic function and delaying tissue repair. Therefore, increasing PCAF activity, inhibiting HDAC6, and promoting p53 acetylation at Lys320 may provide therapeutic benefits for stroke recovery [88].

5. Therapeutic Potential of Targeting HATs

HATs regulate inflammation-related pathways, promote oxidative stress responses, and accelerate vascular cell aging (e.g., by affecting the p53/p21 signaling axis), thereby contributing to the formation of atherosclerotic plaques, vascular remodeling, and other pathological processes. Given the multifaceted regulatory roles of HATs in the core pathological mechanisms of arterial diseases, the targeting of HATs has become a promising therapeutic strategy in the cardiovascular field, drawing widespread interest from researchers.

Several commonly used clinical drugs, including metformin, curcumin, melatonin, and green tea extracts, have shown significant potential for HAT inhibition. Among them, metformin has shown clear supporting evidence of cardiovascular protective effects. *In vitro* experiments have confirmed this is primarily mediated by activating the AMPK signaling pathway, which in turn inhibits p300 acetyltransferase activity [89]. Clinical trials showed that oral curcumin significantly lowers plasma BNP levels in patients with hypertensive heart disease [90]. Similarly, the cardiovascular protective effects of natural bioactive substances such as curcumin, melatonin, tea polyphenols, garcinol, and urushiol are closely related to their molecular mechanisms involving inhibition of p300 and PCAF [22,34,53,91]. Table 1 (Ref. [7,12,34,37,39,56,70,92–99]) summarizes the most important findings to date of research on HAT inhibitors in relation to cardiovascular diseases. Intraperitoneal injection of CTK7A, a p300 inhibitor, effectively lowers blood pressure in rats and reduces norepinephrine secretion [37]. Pentamidine, an inhibitor of acetyltransferase Kat5, mitigates damage from myocardial infarction [92]. WM-3835, a KAT7 inhibitor, significantly improves hypertension and endothelial damage induced by punatayin in SD rats [7]. The p300 inhibitor A-485 and the imidazole ketone erastin induced ferroptosis in human aortic smooth muscle cells [93]. C646, a specific p300 inhibitor, and CPTH2, a KAT2A inhibitor, reduced macrophage activation to varying degrees following LPS-induced activation [70]. In terms of clinical translation, significant progress has been made in the development of targeted drugs for histone acetylation modifications. Notably, the histone deacetylase inhibitor (HDACi) CS1 has entered phase II clinical trials for PAH [100], while several other HDACis have been approved for the clinical treatment of malignant tumors.

Despite the current intense research into the clinical application of HAT inhibitors, several major issues have limited the progress in this field. For example, HATs are key enzymes that catalyze histone acetylation ('writing'). However, the 'reading' mechanism, which relies on bromodomain proteins recognizing acetylation modifications, and the details of its coordination with the 'writing' process remain unclear [101]. This makes it difficult to precisely in-

tervene in the activity of HATs, or to target specific gene loci during transcription. Single-cell epigenomics techniques (such as scChIP-seq, CoBATCH) have enabled high-throughput analysis at the single-cell level by optimizing cell isolation and library preparation processes, thereby refining epigenetic research. Secondly, HAT inhibitors lack subtype selectivity, and their broad target range results in many side effects [102]. Compared to traditional HAT inhibitors, epigenetic degraders offer higher selectivity and low-dose catalysis, making them a promising alternative to HAT inhibitors [102].

In addition to HAT inhibitors and epigenetic degraders, non-coding RNAs and epigenetic editing technologies are also key areas of research. Non-coding RNAs target KATs through direct binding or competitive binding. They play a critical role in the development of cardiovascular diseases, thus providing new directions for disease diagnosis and treatment. For example, miR-185-5p binds to the 3′UTR of KAT7 to suppress its expression, while lncRNA ADAMTS9-AS1 competes with miR-185-5p to upregulate KAT7, inhibiting myocardial cell hypertrophy [103]. Circmyh8 recruits KAT7 to the HIF1α promoter region, triggering histone acetylation and promoting the development of PAH [38]. Additionally, miR-134-5p regulates KAT7, affecting the acetylation of histones and other antioxidant enzymes, and reducing ROS levels in rat cardiac fibroblasts [104]. Recent breakthroughs in epigenetic editing technologies, especially CRISPR-derived tools, offer significant potential for the precise targeting of specific genes to achieve long-term silencing in cell and animal models. Unlike traditional gene editing, this technology does not directly alter the DNA sequence. Instead, it targets modifications to DNA chemical markers, such as DNA methylation or histone acetylation, to dynamically regulate gene activity without affecting the coding information. For example, regulation of the key cholesterol metabolism gene PCSK9, which is highly expressed in hepatocytes, has significant therapeutic value for hypercholesterolemia. Studies in mice have shown that a single intravenous injection of lipid nanoparticles encapsulating the editing mRNA can reduce circulating levels of PCSK9 protein by nearly 50%, and maintain this reduction for almost a year. More importantly, under extreme conditions that simulate liver regeneration (to mimic liver injury repair), the silencing of PCSK9 and the accompanying epigenetic suppression markers remained sustained. This work is the first confirmation that artificially established epigenetic states have genetic stability across cell divisions [105].

Although drug developments that specifically target HATs are still in the preclinical stage, an accumulating body of basic research evidence suggests that HATs could become a novel molecular target for cardiovascular disease intervention. This view is gaining increasing recognition and attention among researchers.

6. Conclusions

Currently, HATs are primarily considered to promote vascular pathological changes. This review mostly discusses the pro-inflammatory mechanisms of HATs, including their enhanced activity, upregulated expression, and increased acetylation levels of chromatin histones, all of which contribute to vascular wall damage. We systematically explore several common pathological factors, including hyperglycemia, high salt, intermittent hypoxia, and activation of the renin-angiotensin system, and delve into their potential molecular mechanisms, such as the Nfkb-NLRP3 pathway, MAPK signaling pathway, AMPK pathway, and VEGFR2 signaling pathway. Additionally, this review discusses the dual role of HATs in vascular homeostasis, both as a protective agent for blood vessels, as well as a participant in the vascular injury process. We also explore the potential clinical applications of HATs, with a focus on innovative and targeted intervention strategies for HATs.

In recent years, multiple studies have demonstrated that HATs promote the expression of inflammatory mediators, such as IL-6 and IL-1, by influencing the promoter regions of these factors. Notably, as histone acetylation levels increase, there is a tendency for upregulation of various inflammation-related genes, cell proliferation proteins, and chemokines, suggesting there may be a complex network of interactions between these proteins and HATs that warrants further investigation. Although the functional regulation of HATs in the vascular system is starting to be revealed, significant gaps remain in our understanding of the epigenetic mechanisms underlying HATs. Further elucidation of the epigenetic regulatory networks mediated by HATs will help to identify new drug targets and provide theoretical support for screening specific HAT inhibitors. This should eventually lead to new directions for the targeted prevention and treatment of vascular-related diseases.

In conclusion, HATs are significantly implicated in vascular pathological changes. Their unique regulatory mechanisms and therapeutic potential open new pathways for the treatment of vascular diseases, while expanding knowledge in this field.

Author Contributions

WL, JD, YJ and QJ conceived the study topic and the manuscript design. WL, JD, and YJ contributed to figure preparation and making the table. All authors performed the literature search and manuscript writing and made substantial contributions to the interpretation of the literature. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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