Histone Deacetylases and Cardiometabolic Diseases

Kan Hui Yiew, Tapan K. Chatterjee, David Y. Hui, Neal L. Weintraub

Abstract—Cardiometabolic disease, emerging as a worldwide epidemic, is a combination of metabolic derangements leading to type 2 diabetes mellitus and cardiovascular disease. Genetic and environmental factors are linked through epigenetic mechanisms to the pathogenesis of cardiometabolic disease. Post-translational modifications of histone tails, including acetylation and deacetylation, epigenetically alter chromatin structure and dictate cell-specific gene expression patterns. The histone deacetylase family comprises 18 members that regulate gene expression by altering the acetylation status of nucleosomal histones and by functioning as nuclear transcriptional corepressors. Histone deacetylases regulate key aspects of metabolism, inflammation, and vascular function pertinent to cardiometabolic disease in a cell- and tissue-specific manner. Histone deacetylases also likely play a role in the metabolic memory of diabetes mellitus, an important clinical aspect of the disease. Understanding the molecular, cellular, and physiological functions of histone deacetylases in cardiometabolic disease is expected to provide insight into disease pathogenesis, risk factor control, and therapeutic development.

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Key Words: cardiovascular ■ histone deacetylases ■ inflammation ■ metabolic disease ■ sirtuins

Epigenetic processes influence gene expression and regulation without altering the information encoded by the primary DNA sequence. In the 1960s, Alfrey et al4 discovered that chemical modification of histones influenced chromatin structure and RNA synthesis in eukaryotic cells, thus laying the foundation for modern epigenetics research. Subsequently, proteins that possess intrinsic histone acetyltransferase and deacetylase activities were identified,2,3 followed by enzymes involved in histone methylation, ubiquitination, and sumoylation.3 Reversible modification of histone proteins is a fundamental mechanism of gene regulation in cell differentiation, organogenesis, growth, aging, etc.

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Histone deacetylases (HDACs) are a class of enzymes that remove acetyl groups from an ε-N-acetyl lysine amino acid on histone or nonhistone proteins. Deacetylation of histones promotes a closed chromatin structure, thereby impairing access of transcription factors to their regulatory sites and silencing gene expression. Some HDACs are multifunctional proteins that can also suppress gene expression by functioning as nuclear transcriptional corepressors, independent of their deacetylase activity.5,6 To date, 18 evolutionary conserved mammalian HDACs have been identified and are grouped into 4 classes based on their phylogenetic conservation.7 HDACs exhibit a wide variety of functional activities and cellular and tissue distribution (Table I in the online-only Data Supplement). Numerous studies describing HDAC protein regulation, structure, and functions pertinent to cardiovascular and metabolic diseases have been summarized in recent publications.5-12 This review will highlight cellular mechanisms of HDAC action, in vivo data in animal models of cardiometabolic disease, and studies linking HDACs to cardiometabolic disease in humans.

There is a strong interplay between metabolic disease, inflammation, and cardiovascular risk factors. Metabolic syndrome is a proinflammatory state that is tightly linked to C-reactive protein levels in humans,13 and vascular inflammation plays a role in all stages of atherosclerosis.14 Dyslipidemia, hypertension, and insulin resistance, major components of metabolic syndrome, are powerful cardiovascular disease risk factors.15,16 Data from the longitudinal Framingham heart study suggest that hypertension and glucose intolerance are interrelated phenomena that predispose to the development of premature atherosclerotic disease.17 Additionally, growing evidence suggests that insulin resistance predisposes to heart failure.19 A better understanding of the molecular mechanisms whereby HDACs regulate the interplay between metabolic disease, inflammation, and cardiovascular risk factors could lead to novel therapeutic approaches for cardiometabolic disease.

Potential Role of HDACs in Metabolic Disease

Class I and II HDACs have been reported to regulate a variety of metabolic processes, including differentiation of pancreatic...
The liver has emerged as an important target of HDACs’ metabolic effects. Liver-specific HDAC3 and SIRT6 have been shown to regulate hepatic lipid synthesis, glycolysis, and fatty acid oxidation. Mice lacking SIRT1 specifically in the liver displayed impaired mTORC2/Akt signaling, resulting in oxidative damage, insulin resistance, and hyperglycemia. Hepatic SIRT1 deficiency also impaired PPARα signaling and decreased fatty acid β-oxidation, resulting in hepatic steatosis, hepatic inflammation, and endoplasmic reticulum stress in high-fat–fed mice. Conversely, loss of hepatic class Ila HDACs (HDAC4, -5, -7) was metabolically protective because it lowered fasting blood glucose levels and improved glucose tolerance in diabetic mouse models.

Skeletal muscle, which is responsible for >30% of resting metabolic rate and 80% of whole-body glucose uptake, is also emerging as a target of HDACs. Skeletal muscle is composed of heterogeneous myofibers with characteristic metabolic properties. Class II HDACs have been shown to suppress the formation of type I myofibers, which stimulate insulin-mediated glucose uptake and protect against glucose intolerance, through the repression of MEF2 (myocyte enhancer factor-2) activity. Overexpression of HDAC5 was reported to suppress skeletal muscle glucose uptake by repressing GLUT4 gene expression. Conversely, deletion of SIRT3 in skeletal muscle perturbed mitochondrial function and promoted oxidative stress and insulin resistance.

Mounting evidence suggests that both peripheral and central mechanisms act in concert to maintain energy balance. The hypothalamic/pituitary axis is essential to the central control of whole-body metabolism. Delivery of a SIRT1 activator, resveratrol, into the central nervous system was shown to attenuate hyperglycemia and hyperinsulinemia in diabetic and DIO mice. SIRT1 in pro-opiomelanocortin neurons was reported to be required for leptin’s central functions and for energy expenditure adaptations to DIO. Furthermore, SIRT1 was found to act on steroidogenic factor 1 neurons to protect against the development of DIO and hyperglycemia via promoting energy expenditure and skeletal muscle insulin sensitivity.

The concept of metabolic memory was proposed by Nathan et al in relation to their clinical findings that the benefits of tight glycemic control on micro- and macrovascular complications in diabetic patients might not be immediately obvious but become more evident with time. Consistently, metabolic memory has been demonstrated in experimental models; transient hyperglycemia resulted in persistent epigenetic changes leading to aberrant antioxidant and inflammatory gene expressions in vascular smooth muscle cell (VSMC) and endothelial cells during subsequent normoglycemia. With regard to HDACs, SIRT1 was shown to mediate high glucose–induced cellular metabolic memory via the liver kinase B1/AMPK/ROS pathway.

**HDACs and Inflammation**

Inflammation is a pivotal factor that underlies both cardiovascular and metabolic diseases, and HDACs have been implicated in regulating both the innate and adaptive immune systems. HDAC3, HDAC4, and HDAC9 have been associated

with proinflammatory responses in macrophages and monocytes. HDAC3 was reported to promote inflammatory gene expression in lipopolysaccharide-stimulated macrophages and HDAC4 to contribute to tumor necrosis factor-α–induced monocyte adhesion to VSMCs.\textsuperscript{51} HDAC9 was reported to induce inflammatory gene expression in macrophages and prevent polarization to anti-inflammatory M2 phenotype.\textsuperscript{52} With regards to adaptive immunity, HDAC7 and HDAC2 have been reported to maintain B cell and CD4\textsuperscript{+} T cell identity, respectively.\textsuperscript{53,54} Interestingly, HDAC9 and HDAC3 were shown to control CD4\textsuperscript{+} Foxp3\textsuperscript{+} T regulatory cell development and function.\textsuperscript{55,56} HDAC9-deficient mice exhibited enhanced expression of Foxp3, a master regulator of T regulatory differentiation,\textsuperscript{55} whereas deletion of HDAC3 disrupted T regulatory cell development and function, restored interleukin (IL)-2 production, and upregulated proinflammatory IL-6.\textsuperscript{56} The pan-HDAC inhibitor SAHA (vorinistat) enhanced oxidized low-density lipoprotein–induced interleukin-8 and monocyte-chemoattractant protein-1 expression in human vascular endothelial cells.\textsuperscript{57} However, vorinistat is remarkably effective at preventing allogeneic transplant rejection; allogeneic hematopoietic cell transplant patients treated with vorinostat have increased T regulatory cell numbers with greater suppressive function and reduced plasma levels of proinflammatory cytokines, such as IL-1β, tumor necrosis factor-α, IL-6, and IL-8.\textsuperscript{58} Thus, pan HDAC inhibition produces complex effects on the immune system that can potentially modulate pro- and anti-inflammatory pathways in the context of specific diseases.

**Potential Role of HDACs in Cardiovascular Diseases**

The link between HDACs and cardiovascular disease is less well developed compared with metabolic disease. However, the body of data is growing dramatically, and evidence of link to human cardiovascular disease is also emerging. HDACs clearly have the potential to regulate many aspects of cardiovascular disease, including inflammation, as discussed earlier.

HDACs are fundamentally important in cardiac development and regulate hypertrophy, fibrosis, ischemia/reperfusion injury, and other aspects of cardiac function.\textsuperscript{59,60} HDAC inhibitors have shown promise in experimental studies for their ability to prevent heart failure.\textsuperscript{51} As is the case for metabolic disease and inflammation, the mechanisms whereby HDACs modulate cardiac function are complex. For example, HDACs were recently identified as part of a chromatin repressor complex that inhibits transcription of a long noncoding RNA, which in turn protects the heart against pathological hypertrophy.\textsuperscript{52} It is tempting to speculate that HDACs could play a particularly important role in cardiomyopathy associated with metabolic diseases, such as uncontrolled diabetes mellitus,\textsuperscript{63} but in vivo experimental data are lacking.

Modulation of inflammation by HDACs has important implications for both cardiac and vascular diseases. For example, in spontaneously hypertensive rats, HDAC inhibition (valproic acid) led to reduced left ventricular expression of IL-1β and tumor necrosis factor-α, attenuation of cardiac hypertrophy and fibrosis, and improved cardiac function.\textsuperscript{64} Conversely, SIRT1 has been reported to protect against atherosclerosis in part through its anti-inflammatory effects. Its expression in endothelial cells and macrophages was reported to diminish foam cell formation and vascular reactive oxygen species and promote ABCA1-driven reverse cholesterol transport.\textsuperscript{65,66}

Moreover, SIRT1 expression in VSMC protected against DNA damage, medial degeneration, and atherosclerosis.\textsuperscript{67} In diabetic patients, incretin therapy was associated with SIRT6 induction, reduced inflammation and oxidative stress, and a more stable plaque phenotype.\textsuperscript{58} Interestingly, mice treated with the HDAC inhibitor trichostatin A showed a significant and dose-dependent improvement in high-density lipoprotein cholesterol levels and reduced serum glucose, triglycerides, and total cholesterol, suggesting favorable metabolic effects with regard to the pathogenesis of vascular disease.\textsuperscript{69}

A recent genome-wide association study identified HDAC9 to be associated with large vessel ischemic stroke\textsuperscript{70} and atherosclerosis.\textsuperscript{71} Elevated expression of HDAC9 was also noted in human atherosclerotic plaques. A polymorphism in the intergenic region between HDAC9 and TWIST1/FERD3L...
in humans was associated with selectively increased HDAC9 expression and an increased incidence of atherosclerosis.72 In animal models, HDAC9 gene deficiency was shown to be atheroprotective, favorably modulating inflammatory and lipid homeostatic gene expression while polarizing macrophages toward a protective M2 phenotype.52

Experimental studies have established the relevance of HDACs in hypertension and neointima formation. SIRT1 in VSMC was shown to protect against angiotensin II–induced vascular remodeling, oxidative stress, inflammation, and hypertension in mice.73 Conversely, in isolated mesenteric arteries, trichostatin A reversed angiotensin II–induced contraction and increased endothelium-dependent relaxation stimulated by acetylcholine in spontaneously hypertensive rats.31 HDAC4 has been implicated in hypertension through its effects on VSMC51; HDAC4 gene silencing inhibited tumor necrosis factor–induced monocyte adhesion, vascular cell adhesion protein 1 expression, transcriptional activity of NF-κB, and oxidative stress in VSMC.51 Additionally, HDAC4 has been suggested to control neointima hyperplasia by promoting the activation of p38 mitogen–activated protein kinase/heat shock protein 27 signaling and inducing VSMC proliferation and migration.74 In contrast, HDAC7 (unspliced isoform) was shown to suppress VSMC proliferation and neointima formation by preventing β-catenin nuclear translocation and activity.75 Class I/II HDAC inhibition increased neointimal thickening in a murine model of postangioplasty restenosis,76 whereas class Ila HDAC inhibition prevented neointimal hyperplasia in a murine carotid ligation model.74 These conflicting results may reflect the diverse functions of HDACs and nonspecificity of HDAC inhibitors.

Perspective/Future Research

Recent scientific advances have improved our understanding of HDAC function and its potential role in cardiometabolic disease (Figure). Several issues remain to be resolved, however. Most contemporary HDAC inhibitors lack selectivity toward individual HDACs and have limited efficacy against class II HDACs. Nonselectively inhibiting HDACs could yield adverse effects given their broad contributions to cell differentiation, development, and tissue homeostasis. Furthermore, HDACs may produce divergent, cell-specific actions. For instance, endothelial HDAC3 is atheroprotective in response to exposure to disturbed flow, whereas myeloid HDAC3 prevents collagen deposition and induction of a stable plaque phenotype.77,78 Selectively targeting HDAC isoforms in a tissue-specific manner may thus be beneficial but would require identification of tissue-specific mechanisms whereby HDACs function (ie, histone deacetylase enzymatic activity, transcriptional repression, and interactions with other epigenetic regulatory mechanisms). Subsequently, designing inhibitors to target key HDAC functional domains (rather than full-length protein function) could enhance selectivity and minimize unwanted side effects. Also, designing inhibitors against key HDACs (such as HDAC9), which produce consistent cell-specific actions in metabolic and vascular tissues, is a compelling approach.

Further studies are needed to understand the interplay between histone post-translational modifications, DNA methylation, and noncoding RNAs and the consequence of their dysregulation in disease phenotype. Additionally, more work is required to dissect the mechanisms of cellular and trans-generational epigenetic memory. Advancing such studies will likely refine our knowledge of the role of HDACs in cardiometabolic disease and their potential as therapeutic targets.

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Disclosures

None.

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Significance
Cardiometabolic disease, emerging as a worldwide epidemic, is a combination of metabolic derangements leading to type 2 diabetes mellitus and cardiovascular disease. These derangements are generally long lasting and resistant to conventional therapies. Histone deacetylases are a class of enzymes that alter chromatin structure and epigenetically reprogram gene expression, thereby influencing key metabolic pathways, such as differentiation and function of pancreatic islet cells, adipocytes, hepatocytes, and skeletal muscle. Histone deacetylases also play complex roles in regulating the immune and cardiovascular systems. Increasing evidence suggests that histone deacetylases are centrally positioned to regulate the interplay between metabolic disease, inflammation, and cardiovascular risk factors. Understanding the molecular, cellular, and physiological functions of histone deacetylases in cardiometabolic disease is expected to provide insight into disease pathogenesis, risk factor control, and therapeutic development.

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<th>Subcellular localization</th>
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<th>CV-relevant tissue</th>
<th>Immune/Nervous system</th>
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Supplementary table 1. Characterizing histone deacetylases activity, subcellular localization, and expression in cardiovascular and metabolically-relevant tissues (partial list). Abbreviations: CV, cardiovascular; Ref, references.
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