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Readers, writers and erasers: Chromatin as the Whiteboard of Heart Disease

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Abstract

Dynamic packaging of DNA into strings of nucleosomes is a major mechanism whereby eukaryotic cells regulate gene expression. Intricate control of nucleosomal structure and assembly governs access of RNA polymerase II to DNA and consequent RNA synthesis. As part of this, post-translational modifications of histone proteins are central to the regulation of chromatin structure, playing vital roles in regulating the activation and repression of gene transcription. In the heart, dynamic homeostasis of histone modification – driven by the actions of modifiers and recruitment of downstream effectors – is a fundamental regulator of the transcriptional reprogramming that occurs in the setting of disease-related stress. Here, we examine the growing evidence for histone modification as a key mechanism governing pathological growth and remodeling of the myocardium.

Keywords

epigenetics; chromatin; remodeling

Introduction

Eukaryotic DNA is packaged, protected, and regulated by a histone protein core, around which the DNA is wrapped. This structure, termed chromatin, can be condensed and “closed”, a state associated with relative transcriptional repression. Conversely, chromatin can be “open”, a state which allows proteins governing transcription to access the DNA and effect RNA synthesis.

Regulation of chromatin in its various active states is controlled significantly through post-translational modifications (PTMs) of the core histone proteins. Primarily targeting amino acids within the N-terminal tails of these proteins, a wide range of PTMs occurs, including phosphorylation, acetylation, methylation, ubiquitination, SUMOylation, and

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Conflicts of Interest

We declare no conflicts of interest.

GlcNAcylation. Regulation of chromatin by reversible incorporation of phosphate, acetyl groups, or methyl groups within histone tails is the best understood.[1]

Governance of chromatin structure through histone PTMs has emerged as a key driver of transcriptional responses in numerous cells. Likewise, histone writers, erasers, and readers – the protein machinery that adds, removes or recognizes these PTMs – have become central figures in our understanding of physiological responses in many cell types (Figure 1).

Writers, enzymes that add PTMs to histones, are divided into classes based on the specific PTM they effect. Similarly, erasers, enzymes which remove specific PTMs from histone substrates, are divided into PTM-specific classes. Finally, readers are dedicated protein factors that recognize either specific post-translational marks on histones or a combination of marks and histone variants to direct a particular transcriptional outcome (Table).

Writers: histone acetyltransferases (HATs)

The relationship between acetylation of histones and transcription of DNA was initially proposed in the 1960's.[2] However, it wasn't until 1996 that the first direct link between these two events was described with the identification of histone acetyltransferase activity from a *Tetrahymena thermophilia* orthologue of the yeast transcription factor Gcn5.[3] Identification of a number of other HATs followed, including TFIID subunit $TAF_{II}250$ and p300/CBP.[4–6] Mammalian cells were then found to have two distinct GCN5 homologs: PCAF and GCN5L. Dozens of HATs have been identified since, comprising roughly 5 different families, the two largest being the GNATs (Gcn5-N-acyltransferases) and MYST families, followed by the SRC (steroid receptor coactivator) family and the highly conserved ATF-2 and aforementioned $TAF_{II}250$ families.[7] Whereas there is little sequence homology among the families, structural similarity in the core enzymatic region exists, indicative of a mechanistic requirement of interaction with the cofactor Acetyl-CoA.[8] In general, HATs function as components within a diverse set of multiprotein complexes that target to promoters and enhancers to regulate transcriptional responses.

Histone methyltransferases

A link between histone methylation and DNA transcription was first described in 1999, but unlike histone acetylation, it was quickly followed by the identification of specific histone methyltransferases.[9, 10] SUV39h1, the first one identified, is now known to be part of the SET family of methyltransferases, mammalian homologs of the Drosophila suppressor of variegation 3–9.[10] A number of SET domain and non-SET domain-containing methyltransferases were subsequently identified with specificity in both protein complex interactions and sites of histone methylation.[11] Like histone acetylation, histone methylation occurs on multiple lysine residues, although with the potential for addition of one, two, or three methyl groups. Unlike histone acetylation, histone methylation can be linked to either repression or activation of transcription depending on the context and extent of methylation.[12] Modifications associated with active transcription include di- or tri-methylation of H3K4 (H3K4me2, H3K4me3) and mono-methylation of H3K9 (H3K9me1). However di- and tri-methylation of H3K9 (H3K9me2, H3K9me3), as well as H3K27 (H3K27me2, H3K27me3), are repressive marks.

Erasers

Histone deacetylases (HDACs)—The search for HDACs, proteins capable of removing acetyl groups from histones, was an active focus of a number of groups in the 1970's. Even so, it wasn't until about the same time that HATs were being linked to transcription that HDAC1 was identified in mammalian cells as a homolog of the yeast transcriptional regulator Rpd3.[13] Since that time, 18 mammalian HDACs have been identified and categorized into four major classes. HDACs 1, 2, 3 and 8 make up the class I HDACs. HDACs 4, 5, 7 and 9 belong to class IIa, with HDACs 6 and 10 termed class IIb. The sirtuins (SirT1-7) make up class III, with HDAC11 the sole class IV HDAC.[14] Identification of specific small molecule inhibitors of HDAC activity has yielded an important tool for understanding the biology of HDAC activity and emerged as a potential therapeutic strategy for treatment of disease, including cancer, immune disorders, and heart disease.[14–16]

Histone demethylases—The discovery in 2004 of LSD1 as an enzyme that specifically demethylates histone H3 lysine 4 was followed by identification of a number of demethylases playing regulatory roles in transcription. These include the Jumonji C family, JHMD1, JMJD3, and JMJD2D, each of which targets specific methyllysine groups.[11, 17] Much as with HDACs, small molecule inhibitors of demethylase activity are being developed for use as potential therapeutics to modulate DNA transcription in disease.[18]

Readers

Just as histone PTMs are accomplished by "writers" and "erasers", their actions to govern DNA transcription are mediated by "readers." Identification of these proteins was originally driven by use of modified histone peptides to identify proteins that recognize histone PTMs.[19] This way, a number of domains have been identified that have high affinity for sites of histone methylation (e.g. PhD [plant homeodomain], chromo [chromatin organization modifier], Tudor, MBT [Malignant Brain Tumor]) or acetylation (e.g. Bromo).[19]

These domains are located within the chromatin modifying proteins themselves, but are also found in chromatin remodelers and adaptor proteins that respond to the histone PTMs. For example, the chromatin remodeler complex SWI/SNF (switching defective/sucrose non-fermenting) is dependent on the presence of bromodomain-containing subunits for full binding and remodeling activity.[20, 21] Similarly, the BET (bromodomain and extraterminal domain) family of adaptor proteins (Brd2, Brd3, Brd4, and Brdt) employs the bromodomain to target to the modified histone and regulate transcription through interactions with the transcriptional machinery.[22] These domains may also recognize PTM's on non-histone proteins, such as transcription factors. Small molecules that disrupt the binding of these BET domains to histone PTMs are emerging as promising therapeutics in a variety of disease conditions.[22]

Histone PTMs and cardiac development

Changes in chromatin structure play critical roles in the differentiation of cells and the intricate orchestration of embryonic development.[23] Thus, it is not surprising that loss of

many of these modulators of chromatin structure elicit defects in cardiac development. Chromatin remodelers, such as the SWI/SNF subunits Brg1, Baf250, Baf180, and Baf60c are required for heart development, and loss of function in these subunits leads to embryonic lethality.[24–27] Changes in expression and composition of these remodeling complexes occur at specific times during cardiac development, resulting in altered gene expression.[27] Brg1, which functions within a complex that includes an HDAC (primarily HDAC2) and PARP, governs two parallel pathways to independently control myocardial growth and differentiation. Silencing of Brg1 within the myocardium results in suppression of proliferation (which can be rescued by BMP10) and premature differentiation.[26]

The requirement for Brg1 to maintain myocytes in an embryonic state is best characterized through its role in α/β-myosin heavy chain (MHC) switching. Brg1, as part of the BAF/HDAC/PARP complex, inhibits the expression of α-MHC and activates β-MHC expression in embryonic cells. Brg1 expression is significantly reduced in the adult cardiomyocyte, facilitating the switch to α-MHC expression.[26]

Histone acetylation is also critical to cardiovascular development. The HAT activity of p300 plays a role in co-activation of GATA4-dependent transcription, and genetic ablation of p300 or mutation of the HAT domain elicit defects in atrial and ventricular septum formation.[28, 29] And just as acetylation is important, deacetylation is critical as well. Global deletion of HDAC1 or HDAC3 results in embryonic death at E9.5, and global silencing of HDAC2 results in morphological abnormalities in the neonatal heart and death within 24 hours of birth.[30, 31] Cardiomyocyte-restricted silencing of HDAC1 or HDAC2 individually, however, has no effect on cardiac development.[31] Additionally, combinatorial deletion of both of these class I HDACs in cardiac myocytes is associated with normal cardiac morphology at birth; however, these animals rapidly develop heart failure by P14, marked by lethality and dysregulation of genes involved in calcium handling and contraction.[31]

In contrast, loss of HDAC3 in cardiac myocytes has no immediate effect on development or function, but rather triggers cardiac hypertrophy from dysregulation of the metabolic program.[30] The class II HDACs, HDAC5 and HDAC9, are functionally redundant in myocardial development with the combinatorial, double mutant manifesting incomplete penetrance of cardiac developmental defects that result in embryonic and perinatal lethality after E15.5.[32] The class III HDAC, Sirt1, is similarly required for normal cardiac development, with septal and valve defects leading to lethality at birth observed in mutants.[33]

Finally, methylation also plays a role in cardiac development. The histone methyltransferase, SMYD1, is required for expression of a number of genes involved in myocardial growth and expression[34], which may be due in part to its interaction with HDACs. Loss of SMYD1 triggers cardiac enlargement resulting in embryonic lethality.[34] WHSC1 (Wolf–Hirschhorn syndrome candidate 1) is a histone methyltransferase that associates with Nkx2.5 to govern cardiovascular development.[35] Jarid2, Jmjd, and UTX, enzymes within the Jumonji family of histone demethylases, also function in cardiac development, with Jarid2 involved in the formation of the trabeculated region of the developing myocardium, and Jmjd3 and UTX required for cardiovascular

differentiation.[36, 3738] De-methylation of H3K27 by UTX appears to act as a signal to recruit Brg1 to cardiomyocyte-specific enhancers, thereby activating the cardiac development program.[38]

Histone PTM's and cardiac hypertrophy

Stress to the heart caused by myocardial injury, hypertension, or neurohumoral activation typically triggers a hypertrophic growth response, which in the short term may be adaptive.[39, 40] If the disease-related stress is not relieved, however, the heart undergoes irreversible decompensation that results in dilation of the ventricle, perturbations in contractile performance, and clinical heart failure. Many signaling pathways are involved in the development of cardiac hypertrophy, with altered intracellular Ca^{2+} homeostasis a central trigger.[41] These multiple pathways funnel into a limited number of molecular responses, resulting in alterations in gene expression that trigger changes in cardiac structure, energy substrate utilization, and cell survival.

A key marker of pathological hypertrophy is the down-regulation of α-MHC and concurrent up-regulation of β-MHC, a reversing of the switch from fetal to adult myosin heavy chain expression seen at birth. The Brg1-Hdac-Parp chromatin remodeling complex, required for this switch, is activated during pathological stress, and loss of activity of this complex results in a diminished hypertrophic response.[26] Interestingly, control of Brg1 activity occurs, in part, through expression of a cluster of long non-coding RNAs (*Mhrt* RNAs) that bind directly to Brg1 and decrease the helicase activity of the complex.[42] *Mhrt* expression is abundant only in the adult cardiomyocyte and decreases in the setting of pathological stress.[42] Inhibition of *Mhrt* expression is dependent on Brg1-Hdac-Parp complex activity, suggesting a feedback mechanism in which each complex tamps down the activity of the other. Transgenic expression in cardiomyocytes of *Mhrt779* (the most abundant of these *Mhrt* RNAs) during pressure overload stress is protective and leads to a phenotype that is similar to that observed in Brg1 knockout mice.[42]

While Brg1-HDAC-Parp activity is clearly required for a robust hypertrophic response to pressure overload, the role of MHC class switching in this response is less clear. While even small shifts in isoform expression can alter cardiac output, class switching in mice in the absence of other stimuli does not result in hypertrophic growth.[43, 44] Additionally, although increased β-MHC expression is associated with human heart failure, the beta isoform is the predominant MHC class in healthy human hearts.[45] These facts leave open the possibility that other targets of Brg1 may impact hypertrophic growth.

The role of HDACs in pathological cardiac hypertrophy is arguably the most extensively studied context of chromatin modification in the heart. Initial work focused on class II HDACs, which are abundant in the myocardium. A number of biochemical and *in vivo* studies revealed that class II HDACs act as signal-responsive repressors of cardiac hypertrophy, in part through interaction with MEF2 (myocyte enhancer factor-2).[32, 46]

MEF2 proteins act as transcriptional switches that interact with a diverse set of cofactors to respond to specific intracellular signals to either activate or repress transcription.[47] Mammals harbor four MEF2-encoding genes (*Mef2a-d*) that can form heterodimers, with

MEF2A and MEF2D expression being highest in adult heart.[48] Mice silenced for *Mef2a* manifest perinatal lethality and cardiac abnormalities.[49] In contrast, *Mef2d*-null mice develop normally but manifest a blunted growth response to hypertrophic stress.[50] MEF2 proteins are activated during cardiac stress, and forced expression of MEF2d in the heart is sufficient to induce a hypertrophic response.[50]

Class II HDACs interact directly with MEF2 to repress its transcriptional activity.[51] Hypertrophic stress results in the phosphorylation of these HDACs and dissociation of the MEF2/HDAC complex.[46] Mice lacking either HDAC9 or HDAC5 develop spontaneous cardiac hypertrophy as they age and elicit an exaggerated hypertrophic response to afterload stress.[32, 46] Interestingly, these same mutant strains have a normal response to β-adrenergic stimulation, suggesting a difference in either the triggered pathway or extent of hypertrophic pressure under these two conditions.[32]

While class II HDACs appear to repress cardiac hypertrophy through multiple targets, the catalytic domain is, in part, dispensable for this activity.[32] This may be due to the recruitment of other HDAC proteins to the transcriptional complex or through displacement of other activating factors, such as HATs.[32]

While loss of class II HDACs promotes cardiac hypertrophy, broad inhibition of the activities of both class I and class II HDACs using small molecule inhibitors, such as trichostatin A (TSA), represses hypertrophic growth in response to either pressure overload or β-adrenergic stimuli.[52–54] This blunting of hypertrophy is also observed with HDAC inhibitors specific to class I isoforms.[54, 55] Furthermore, treatment of mice with HDAC inhibitors after the onset of hypertrophy leads to regression of pathological growth even when the hypertrophic stress is still present.[54, 56] Thus, class I HDAC activity appears dominant to class II in the balance of hypertrophic growth. The observation that in some complexes the role of the class II HDAC may not rely on catalytic activity may in part explain this differential effect.[57] Additionally, there appears to be cross talk in the regulation of class I and class II HDACs with respect to their roles in hypertrophy. A recent report suggests a model in which pCAF (p300/CBP-associated factor) activates HDAC2 by direct acetylation, and HDAC5 inhibits HDAC2 by removing that acetyl moiety.[58]

Over-expression of HDAC2 alone in cardiac myocytes is sufficient to drive hypertrophic growth.[59] However, class I HDACs appear to be functionally redundant in their ability to regulate hypertrophy, as cardiomyocyte-specific loss of either HDAC1 or HDAC2 has no impact on the response to hypertrophic stimuli.[31] However, this has yet to be tested directly in adult mice. In contrast, cardiomyocyte-specific silencing of HDAC3 provokes abnormalities in myocardial energy metabolism leading to cardiac hypertrophy and failure.[30, 60] Indeed, there are likely multiple pathways regulated by the activity of any given HDAC isoform, as well as redundant activities.

A complete picture of the mechanism of HDAC inhibition in blunting hypertrophy has yet to emerge. It is likely that HDAC inhibition targets a variety of pathways. HDAC2 has been shown to repress expression of the phosphatidylinositol-3,4,5-trisphosphate (PIP3) phosphatase Inpp5f, resulting in activation of the phosphatidylinositol-3-kinase- (PI3K-)

Akt-Gsk3β cascade.[59] Additionally, HDAC inhibition suppresses the maladaptive, disease-promoting autophagy observed under hypertrophic growth conditions.[56, 61] HDAC inhibition also blunts increases in cellular protein synthesis by mechanisms that remain unclear.[52] The recent finding that HDAC inhibitors can also stimulate cardiac protein SUMOylation in the absence of *de novo* gene transcription or protein synthesis suggests that in addition to their role in histone acetylation, acetylation of other protein targets may play a role in the regulation of hypertrophy.[62]

Acetyltransferases would seem to be the natural antagonist to combat the hypertrophy-promoting tendencies of HDAC activity. However, both p300 and pCAF induce hypertrophy, presumably by activating pro-growth genes.[58, 63] Hypertrophic stress, or forced expression of p300, results in increased acetylation of Gata-4 and expression of Gata-4-dependent hypertrophy genes. As mentioned earlier, p300/pCAF can also activate HDAC2 by direct acetylation.[58] Regardless, one would anticipate that specific HATs, yet to be identified, may be important in opposing the activity of class I HDACs. However, given that these are highly regulated, multiprotein complexes with multiple partners and targets, this expectation may be naive.

The role of readers of these hypertrophic stress-induced changes in histone acetylation is just emerging. BET proteins act to increase the occupancy of transcriptional complexes that promote chromatin remodeling, transcriptional initiation, and elongation.[64] Hypertrophic stimulation triggers an increase in steady-state levels of BRD4 protein and enhanced association with target genes.[65, 66] Knockdown of BRD4 in neonatal rat ventricular myocytes (NRVMs) is sufficient to inhibit PE-induced hypertrophy.[65] Interestingly, the control of BRD4 abundance appears not to be transcriptional.[65] Chromatin immunoprecipitation studies in TAC-treated hearts suggest a model in which BRD4, through a known interaction with the transcriptional elongation factor p-TEFb, promotes transcriptional pause release in response to pathologic stress.[65]

The selective bromodomain inhibitor JQ1 inhibits both PE-induced hypertrophy *in vitro* and pressure overload-induced cardiac hypertrophy *in vivo*.[65] JQ1-mediated suppression affects a wide range of pathways involved in cardiac hypertrophy and failure, including cytoskeletal remodeling, cell growth signals, and pro-inflammatory signaling.[65] However, despite these broad effects, JQ1 impacts only a subset of the genes up-regulated in response to hypertrophic stimuli. Specifically, JQ1 inhibition correlated strongly with calcineurin-NFAT, NFκB, and GATA4 gene signatures, but not with c-myc or E2F-regulated genes.[65] Presently, it is unclear the extent to which the protective phenotype of JQ1 treatment is due specifically to blocking BRD4 activity. Conditional alleles for the BRD4 gene will allow this question to be addressed directly.

Changes in histone methylation within cardiac myocytes are observed in heart subjected to hypertrophic stress.[67, 68] These include both activating (H3K9ac, H3K27ac, H3K4me3, H3K79me2) and repressive (H3K9me2, H3K9me3, H3K27me3) modifications.[67] The histone methyltransferase, Ezh2, plays a critical role in repressing the hypertrophic gene program in adult cardiomyocytes by maintaining H3K4me3 modifications.[69] H3K79 methylation is catalyzed by the methyltransferase Dot1L. Cardiomyocyte-specific loss of

Dot1L results in decreased dystrophin expression and leads to a dilated cardiomyopathic phenotype that can be partially rescued with adenoviral delivery of the minidystrophin gene.[70] Increased H3K79 methylation by Dot1L may be important for increased expression of dystrophin in the setting of pressure overload, serving to help maintain cardiac structure and function during hypertrophic growth.[71, 72]

The flip side of the coin is the JmjC domain-containing proteins. JMD2a is part of a family of lysine trimethyl-specific histone demethylases that target H3K9me3.[73] By relieving repressive histone modifications, JMJD proteins can activate transcription through interaction with specific transcription factors, such as the androgen receptor or serum response factor.[74, 75] This epigenetic control of histone methylation is critical to the cardiomyocyte transcriptional response to hypertrophic stress. Cardiomyocyte-specific silencing of *Jmjd2a* attenuates the myocardial response to pressure overload-induced hypertrophy.[75] Conversely, transgenic expression of JMJD2A in the heart leads to an exaggerated hypertrophic response.[75] This appears to occur in part through up-regulation of four-and-a-half LIM domains-1 gene expression.[75]

Alterations in histone methylation in the ANF and BNP promoter regions are also associated with cardiac stress, with JMJD1A and JMJD2A both bound to the promoter region of ANF.[76] In NRVMs, simultaneous siRNA targeting of both of these demethylases results in decreased expression of both ANF and BNP and increased abundance of H3K9me2 and H3K9me3 in the promoter regions.[76] These changes in histone methylation are correlated with the nuclear export of HDAC4 under conditions of increased hemodynamic load.[76] The class II HDAC, HDAC4, is found within a complex harboring the histone methyltransferase SUV39H.[76] This complex is disrupted under stress conditions by CaMKII∂B-induced phosphorylation and nuclear export of HDAC4.[76] CaMKII-mediated phosphorylation of HDAC4 in NRVMs results in hypertrophic growth through de-repression of HDAC target genes.[77] Once again, these data are consistent with a model in which the dynamic balance of histone acetylation/deacetylation and methylation/demethylation on promoters is regulated through interdependency of these enzymes in both complex formation and activity.

Recent studies have demonstrated that CaMKII activation under conditions of hypertrophic stress leads to hyperphosphorylation of Ser-10 on H3 at a number of hypertrophic gene loci.[78, 79] Similar changes have been reported in patients with heart failure.[78] Silencing of nuclear CaMKII reduces H3 Ser-10 phosphorylation, a PTM which is required for normal Mef2-dependent transcription.[79] The chaperone protein 14-3-3 acts as a reader in this situation, binding to phosphorylated H3 to stimulate transcriptional elongation of hypertrophic response genes by RNA Pol II.[78] Thus, in addition to the established roles of acetylation and methylation signals, histone phosphorylation plays a role in cardiac stress.

The reader/eraser paradox

Given that inhibition of readers (e.g. BET inhibitors, such as JQ1) blunts hypertrophy, it seems paradoxical that HDAC inhibitors, which would increase acetylation on histones and presumably BRD4 association with chromatin, decrease expression of hypertrophic genes. Conversely, increased HDAC activity, which would presumably promote BRD4

dissociation, increases the hypertrophic response.[59] The answer to this conundrum may lie in recognizing that this biology is highly dynamic, not static. Both HATs and HDACs are targeted to transcribed regions of active genes, with the HATs activating and the HDACs resetting transcription.[80] The binding of BRD4 to chromatin, the initiation of transcription, and transcript elongation appear to require differential contact with combinations of acetylated histone lysines and an exchange of Brd4-interacting partners.[81] In this way, HDAC-dependent release of BRD4 from chromatin after cell stress has been proposed as a requirement for proper pTEFb recruitment, with HDAC inhibitors blocking BRD4-dependent transcriptional elongation.[82]

Histone PTMs and cardiac ischemia

Hearts affected by ischemic cardiomyopathy manifest a remodeling response that includes increases in fibrosis and a cellular hypertrophic response that is offset in part by cardiomyocyte death. Not surprisingly, then, many of the chromatin changes associated with the pro-hypertrophic transcriptional response are observed in failing ischemic hearts.[67, 68] However, in the acute stages of ischemic cardiomyopathy, as well as during reperfusion injury, specific pathways are likely activated to limit the extent of cell death emerging from the changing oxygen environment. Interestingly, HDAC inhibitors are capable of protecting the ischemic heart from both of these insults, by limiting the extent of cell death at reperfusion and by reducing fibrosis and cardiomyocyte hypertrophy in both the border and remote zones of the infarcted heart.[83–85]

Treatment of Wistar rats with a daily dose of the HDAC inhibitor valproic acid (VPA) or tributyrin beginning one day after ischemic injury preserved ventricular performance, reduced fibrosis, and blunted hypertrophy in the infarcted heart.[83] These results are likely a combination of cardiomyocyte-specific and nonspecific events. Class I-specific HDAC inhibitors can act directly on fibroblasts to inhibit cell cycle progression and block fibrocyte maturation, in part through the inhibition of ERK signaling.[86] Additionally, HDAC inhibition has been shown to target the inflammatory cascade that accompanies heart failure.[87]

Perhaps the most impressive findings reported to date are the impact of HDAC inhibitors on limiting reperfusion injury. A single dose of an HDAC inhibitor administered at the time of reperfusion reduces the size of a myocardial infarct by nearly 50%.[84, 85] Remarkably, this effect can occur even if the dose is delivered 45 minutes after reperfusion.[84] This suggests that the effect of HDAC inhibition treatment is not on the trigger of reperfusion injury, but rather acts on the cell death/survival pathways activated by reperfusion. The mechanism of this protection is likely multifaceted; early studies suggested that it is mediated by HDAC4 and involved reduction in hypoxia-inducible factor-1a protein levels[84].

Our group has demonstrated a role for induction of autophagy by HDAC inhibition in limiting myocardial reperfusion injury.[85] We and others have shown that autophagic flux is repressed in cardiomyocytes during reperfusion.[85, 88, 89] Short-term treatment with HDAC inhibitors restores this flux, conferring cardioprotection. This effect is in contrast to the inhibition of autophagy that occurs with long-term HDAC inhibitor treatment of hearts

under hypertrophic stress.[56, 85] The mechanism whereby HDACs modulate autophagy is unclear but similar activating and inhibiting effects of HDAC activity on autophagy are observed in a variety of cancer cell lines.[90] Given the myriad pathways and cell types that HDACs modulate, it is not surprising that the impact of HDAC inhibition in mitigating ischemic injury is also being examined in the rescue of stroke-related injury.[91]

Alteration of histone methylation may also protect against I/R injury. In a model of murine diabetes, adenoviral delivery of SUV39h1 to the heart resulted in a significant decrease in infarct size after only four hours of reperfusion.[92] While the interaction of SUV39h1 with HDAC4 is unknown under these specific conditions, one possibility is that over-expression of SUV39h1 compensates for the loss of HDAC4 interaction, leading to repression of HDAC4-regulated promoters.[76, 84]

Class III HDACs are also cardioprotective. Activation of sirtuin activity is believed to be part of the basis for the beneficial effects of resveratrol in heart failure.[93] Whereas Sirt1 and Sirt3 are well established as HDACs, their non-histone protein deacetylation activities in the nucleus (Sirt1) and in mitochondria (Sirt3) are the most studied.[94] Given the direct link between sirtuin activity and the energetic and redox states of the cell, it is not surprising that sirtuins play a role in the regulation of reactive oxygen species, a key driver of reperfusion injury.[94] Preconditioning the heart by activation of Sirt1 can be protective against ischemia, and Sirt1 activation is believed to help preserve mitochondrial abundance and energy production in models of heart failure.[95] However, transgenic expression of Sirt1 in cardiomyocytes, even at low levels, triggers a decrease in cardiac function, presumably due to dysregulation of mitochondrial function.[96] Thus, the balance and timing of Sirt1 activity is clearly important.

Conclusion and perspective

Complexity in the regulation of epigenetic changes within disease-stressed heart, and their role in the underlying pathophysiology, is daunting. However, the potential of small molecules to impact the architecture of chromatin and alter the transcriptional response to stress is promising. Indeed, translation to the clinic may be in the offing. Vorinostat, a pan-HDAC inhibitor currently approved for treatment of cutaneous T cell lymphoma, has been shown to limit cardiac reperfusion injury in mice and rabbits.[85] Delivered as a single dose at the time of reperfusion, infarct size is significantly blunted, a finding which is arguably closest to being tested in clinical trials. As we unveil more specifics regarding the interplay of these histone PTM pathways and the sensitivity of target genes to changes in histone PTM homeostasis, we move closer to the objective of clinically meaningful targeting of pathological cardiac remodeling.

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Nonstandard Abbreviations and Acronyms

PTMs	post-translational modifications
HAT	histone acetyltransferase
HDAC	histone deacetylase
H3K4me3	H3-lysine-4 tri-methylation
H3K4me2	H3-lysine-4 di-methylation
H3K9me1	H3-lysine-mono-methylation
H3K9me2	H3-lysine-9 di-methylation
H3K9me3	H3-lysine-9 tri-methylation
H3K27me2	H3-lysine-27 di-methylation
H3K27me3	H3-lysine-27 tri-methylation

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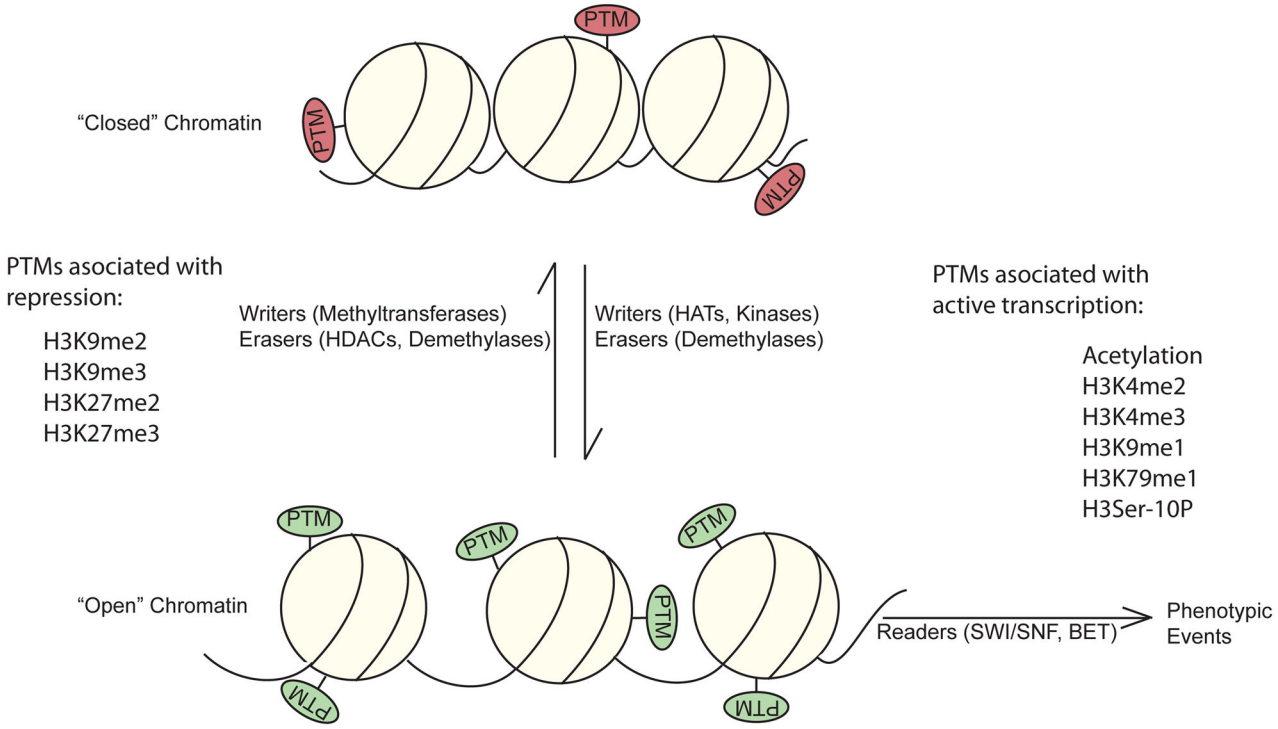

Figure 1.

Post-translational modification (PTM) of histones can act to induce (green) or repress (red) the transition of chromatin to an open state. Coupled with the action of histone PTM "readers", these changes culminate in an increase or repression of the transcription of target genes.

Table 1

Histone modifiers and effectors active in the myocardium and their involvement in cardiac physiology.

Writers:	**Cardiac Involvement:**
HATS	
p300/pCAF	Development[28, 29]; Hypertrophy [58, 63]
HMTs	
SMYD1	Development[34]
WHSC1	Development[35]
Ezh2	Hypertrophy[69]
SUV39h	Hypertrophy[76]; I/R [92]
DOT1L	Hypertrophy[70]
CaMKII	Hypertrophy[78, 79]
Erasers:	
HDAC Class 1	Hypertrophy[31, 52–56]; I/R [83–85]
HDAC1	
HDAC2	Hypertrophy[59]
HDAC3	Hypertrophy[30, 60]
HDAC Class II	Development[32]; Hypertrophy[32, 46]
HDAC4	I/R[84]
HDAC5	
HDAC9	
HDMs	
Jarid2	Development[36]
Jmjd1	Hypertrophy[76]
Jmjd2	Hypertrophy[75, 76]
Jmjd3	Development[37]
UTX	Development[38]
Readers:	
SWI/SNF	
Brg1	Development[26]; Hypertrophy[26, 42]
Baf60	Development[24]
Baf180	Development[25]
Baf250	Development[27]
BETs	Hypertrophy[65, 66]
Brd4	
14-3-3	Hypertrophy[78]