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Mechanisms of Transcription Factor Acetylation and Consequences in Hearts

Devi Thiagarajan[1], **Srinivasan Vedantham**[2], **Radha Ananthakrishnan**[1], **Ann Marie Schmidt**[1], and **Ravichandran Ramasamy**[1,*]

[1]Diabetes Research Program, Division of Endocrinology, Department of Medicine, NYU Langone Medical Center, New York, New York 10016

[2]SASTRA University, Thanjavur, India

Abstract

Acetylation of proteins as a post-translational modification is gaining rapid acceptance as a cellular control mechanism on par with other protein modification mechanisms such as phosphorylation and ubiquitination. Through genetic manipulations and evolving proteomic technologies, identification and consequences of transcription factor acetylation is beginning to emerge. In this review, we summarize the field and discuss newly unfolding mechanisms and consequences of transcription factor acetylation in normal and stressed hearts.

Introduction

Global acetylation of proteins has been observed in many human diseases. [1, 2]. Increased acetylation of key enzymes/proteins and transcription factors have been observed in diabetes associated accelerated atherosclerosis [3], hypertension [4, 5], diabetic cardiomyopathy [6], coronary artery disease (CAD) [7], arrhythmia [8], pulmonary arterial hypertension (PAH) [9, 10], and heart failure [11]. In the sections to follow we will review the mechanisms of transcription factor acetylation and its consequences in the heart.

Overview of Acetylation

With several thousand proteins non-nuclear proteins now identified as being K-acetylated [12, 13], this protein post-translational modification is gaining rapid acceptance as a cellular control mechanism on par with other protein modification mechanisms such as phosphorylation and ubiquitination [14]. Proteomic studies and bioinformatic analysis revealed acetylation of metabolic enzymes and transcription factors in various cell types [12, 15–17]. Acetylation of nucleosomal histone tails provides a critical mechanism for epigenetic control of gene expression. Acetyl groups are transferred to lysine residues by

*To whom correspondence should be addressed: Ravichandran Ramasamy, PhD., Division of Endocrinology, Department of Medicine, NYU Langone Medical Center, 550 First Avenue, New York, New York 10016, (tel) 212-263-9475, ramasr02@nyumc.org.

histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs). Lysine acetylation also creates binding sites for bromodomain-containing proteins such as bromodomain and extraterminal (BET) proteins. HDAC proteins are grouped into four classes based on function and DNA sequence similarity. Mammalian HDACs are encoded by distinct genes and are classified on the basis of similarity to yeast transcriptional repressors. Class I HDACs (HDACs 1, 2, 3 and 8) are related to yeast RPD3, class II HDACs (HDACs 4, 5, 6, 9 and 10) to yeast HDA1, and class III HDACs (SirT1–7) to yeast Sir2 (Figure 1). Class II HDACs are further divided into two subclasses, IIa (HDACs 4, 5, 7 and 9) and IIb (HDACs 6 and 10). HDAC11 falls into a fourth class [18] (Figure 1). While zinc ion is required for catalysis in classes I, II and IV HDACs, class III HDACs (sirtuins) require nicotinamide adenine dinucleotide (NAD+) as a co-factor for catalytic activity. So far, seven sirtuin family proteins (SIRT1–7) have been identified as mammalian SIR2 orthologs[19]. Figure 1 shows the subcellular compartment for each of the HDACs.

Classical studies by Allfrey et al. using radiolabeled acetate identified that histones in nuclei can be acetylated and that these acetylated histones were less inhibitory for RNA polymerase [20]. Several decades later histone HATs and HDACs were cloned and linked to the regulation of gene expression on chromatinized templates [21, 22]. Our current understanding is that there are several acetyl-CoA dependent HATs and HDACs that function to regulate all DNA-templated processes primarily by reversible acetylation of histone lysine residues [23–25] and that site-specific acetylation is sufficient to alter nucleosome dynamics and chromatin folding [26, 27]. In addition, acetylated lysines on histones can function as ‘epitopes’ for the recruitment of acetyl-lysine binding domains (e.g., bromodomains) that are contained within large protein complexes such as histone acetyltransferases, methyltransferases, transcriptional coactivators, and ATP-dependent chromatin-remodelers [28]. The acetylation of p53 and tubulin were early examples that protein acetylation extends beyond histone proteins [29, 30]. The observation that several deacetylases were localized outside the nucleus spurred further interest in exploring protein acetylation as a broader phenomenon [31]. Shortly studies thereafter showed that acetylation renders the acetyl-CoA synthetases inactive, while deacetylation restores full of these acetyl-CoA synthetases [32–34]. It should be noted that studies have shown contradicting outcome on the effect of increased acetylation on fatty acid β oxidation and glycolytic enzymes [35–38]. An accompanying review article by Fukushima and Lopaschuk specifically discusses the impact of acetylation on fatty acid metabolism in the heart [39].

Collectively, these results demonstrated the existence of functionally-relevant non-histone targets, which lead to the use of unbiased acetyl-proteomic discovery methods to identify and characterize other acetylation events. Immunoprecipitation with an antibody against acetyl-lysine followed by liquid chromatography coupled mass spectrometry (LC-MS) was the method of choice. These acetylation studies lead to discovery of high abundant metabolic proteins. With the advances in proteomics methodology, subsequent studies indicated that the acetylation is widespread, including acetylation of transcription factors. In the section to follow, we will briefly provide an overview of HDACs in the heart prior to review acetylation of transcription factors.

Histone acetyltransferases

HATs are divided into two types (Figure 1), nuclear (type A HATs) and cytoplasmic (type B HATs). Type A HATs are localized in the nuclear and are involved in the regulation of gene expression through acetylation of histones. They contain a bromodomain, which helps them recognize and bind to acetylated lysine residues on histone substrates. The nuclear Type A HATs, transcription related, are further subclassified into five families: (1) General Control Nonderepressible (GNAT) related acetyltransferases family represented by GCN5, p300/CREB-binding protein (CBP) associated factor (PCAF), and Elongator complex protein 3 (ELP3); (2) p300/CBP family represented by p300 and CBP; (3) MYST family of histone acetyl transferases (MOZ, YBF2/SAS3, SAS2, and TIP60 protein) family, which consists of MYST1 (HMOF, males absent on the first), MYST2 (HBO1, histone acetyltransferase binding to ORC), MYST3 (MOZ, monocytic leukemia zinc finger), MYST4 (MORF, monocytic leukemia zinc finger protein-related factor), and TIP60 (tat interacting protein 60 kDa); (4) basal TF family; TFIIIC (Transcription Factor IIIC), TAF1, and (5) nuclear receptor cofactors (NRCF) family, steroid receptor coactivator (SRC), ACTR/NCOA3 (nuclear receptor coactivator 3).

Type B HATs, localized in the cytoplasm, are responsible for acetylating newly synthesized histones prior to their assembly into nucleosomes. Type B HATs, lack a bromodomain, recognize newly synthesized unacetylated core histones. HAT1, HAT2 [40], Rtt109 [41], HatB3.1 [42], and HAT4 [43] are the Type B HATs that have been studied so far.

Among the HATs in muscle, the p300 and the closely related coactivator, CREB-binding protein (CBP), play critical roles in physiological and pathological growth of cardiac myocytes. The p300 knockout mice die between days 9 and 11.5 of gestation. In addition, these mice show reduced expression of muscle structural proteins such as β-myosin heavy chain (MHC) and α-actinin, as well as cardiac structural defects and reduced trabeculation [44]. Further, a gene knock-in study demonstrated the importance of the HAT domain of p300 in heart formation [45]. Emerging studies have linked GCN5 to metabolic changes in hearts from high fat diet fed mice [38] and neonatal mice [46].

Histone deacetylases

HATs and HDACs play an important role in regulating cardiac hypertrophy [47–50]. The activity of NAD^+-dependent class III HDACs (Sirtuins) are prominent in the heart and vasculature [49–57]. Sirtuins deacetylate both histones and nonhistone targets in mice and humans [53–57]. Mice deficient in SIRT1 exhibit developmental abnormalities in the heart and only infrequently survive postnatally [57–59]. Sirtuins favor longevity and cell survival and uniquely couple with the cellular metabolic state [57, 59]. Subcellular localization studies initially identified SIRT1 as a nuclear protein [60]. In the heart, the nuclear and cytoplasmic localization of SIRT1 was found to be regulated during development and stress conditions [61, 62]. Impaired nucleocytoplasmic shuttling and increased cytoplasmic SIRT1 during ischemic stress was observed in aged hearts [62]. Studies performed with a cardiac-specific SIRT1 transgenic mouse model showed that SIRT1 exhibits hormesis [63], i.e depending on the magnitude of SIRT1 expression, it can be either beneficial or harmful. Sadoshima and coworkers have shown that moderate SIRT1 overexpression (2.5- to 7.5-fold)

protects against the age-dependent increase in cardiac hypertrophy and in I/R [63–65]. SIRT3 inhibits apoptosis by deacetylating Ku70 to sequester Bcl2-associated X protein away from mitochondria [66]. SIRT4, SIRT5, SIRT6, and SIRT7 also exhibit antiapoptotic effects in the heart [67–70]. Hearts from mice deficient in SIRT3 are not protected from ischemia-reperfusion injury [71]. Interestingly, ischemia-reperfsuion injury did not alter the patterns or levels of increased protein acetylation in adult SIRT3−/− compared to adult non-transgenic littermate hearts [71]. Mice with cardiomyocyte specific deletion of SIRT3 exhibited increased vulnerability to hypertrophy when subjected to transaortic constriction [72]. Importantly, SIRT3 deletion lead to increased acetylation of cyclophilin D at lysine 166 and impaired miotochondrial permeability pore opening [72]. Although SIRT5 and SIRT7 protects from inflammatory cardiomyopathy [70], their roles in protecting hearts from ischemia-reperfusion injury remain to be investigated.

Among the class I HDACs, HDAC 2 and 3 are well studied in the heart. Studies have shown that HDAC2 promotes cardiac hypertrophy [73], in part by undergoing acetylation by p300/CBP associated factor [74]. Cardiac-specific deletion of HDAC3 in mice leads to cardiac hypertrophy and excessive myocardial lipid accumulation [75]. The catalytic activity HDAC8, was shown to be elevated in hypertension-induced cardiac hypertrophy [76]. However, the function of HDAC8 in the heart remains unknown. Among Class II HDACs, HDAC6 is well studied in the heart. HDAC6 contributes to structural and functional remodeling of atrial myocytes [77], and its activity is elevated in multiple models of cardiac hypertrophy [78, 79]. HDAC10, as well as the lone class IV HDAC, HDAC11, remain poorly characterized, in part due to the inability to monitor their catalytic activity [80]. In the next section we will review mechanisms and consequences of transcription factor acetylation the heart.

Direct acetylation of transcription factors in heart

Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α)

Peroxisome proliferator-activated receptor γ coactivator 1α(PGC-1α) was originally identified as a transcriptional coactivator of the nuclear receptor PPARγ [81]. Subsequent studies have established that PGC-1α interacts with several other transcription factors, including PPARα, glucocorticoid receptor (GR), hepatic nuclear factor 4α (HNF-4α), estrogen receptor related α (ERRα) and FOXO1 [82–84]. By binding and modulating the activity of these different transcription factors, PGC-1α regulates expression of several genes involved in metabolic pathways, such as fatty acid oxidation, gluconeogenesis, glycolysis and fatty acid synthesis. Several studies have shown that acetylation of PGC-1α represses its ability to function as a transcriptional coactivator [38, 85–87]. Alrob et al [38] demonstrated increased acetylation of PGC-1α along with increased GCN5 acetyltransferase activity in the hearts of obese high fat diet fed mice. They showed that SIRT1, a key activator of PGC-1α, [38], expression was unchanged in hearts from high fat diet fed mice and low fat diet fed mice. Interestingly, they observed significant increases in SIRT6 expression in hearts of high fat diet fed mice. Since SIRT6 can deacetylate and activate GCN5 to increase PGC-1α acetylation [88], they opined that their data in high fat diet fed mice hearts were consistent with GCN5 acetyltransferase as a key regulator of PGC-1α

acetylation [89]. Unexpectedly, they showed that increased PGC-1α expression and PGC-1α acetylation was dissociated from the regulation of fatty acid oxidation in the high fat diet fed mice hearts [38].

Recent studies by Fukushima et al showed that acetylation of PGC-1α significantly decreases post-birth and was linked to increases in PPARα but not with the protein levels related to mitochondrial biogenesis [46]. Furthermore, they showed an age-dependent increase in (a) the overall acetylation of cardiac proteins along with an increase in mitochondrial acetyltransferase, GCN5L1, and (b) acetylation of the fatty acid β-oxidative enzymes β-HAD and LCAD along with increased fatty acid oxidation rates. Biphasic changes in SIRT1, SIRT6, and GCN5L1 suggests a complex mechanism regulating PGC-1α acetylation, PPARα, and fatty acid metabolism in neonatal and young hearts. Comprehensive transcriptional and metabolic changes driven PGC-1α acetylation in hearts under various pathological conditions are under active investigation.

Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFκB)

A growing appreciation for NF-κB as a central mediator of various cardiac pathologies has led to the notion that complete inhibition of this pathway will be beneficial in the setting of stress and heart disease [90–93]. In addition to phosphorylation, NF-κB subunits are subject to additional posttranslational modifications. Acetylation has emerged as a significant component of NF-κB signaling linked to the regulation of subunit DNA binding, IκB binding and transactivation potential [94–97]. To date, three NF-κB family members, p50, p65 and p52, have been identified as targets of histone acetylases such as p300/CBP and PCAF [95, 98–103]. Of the three, p65 has been most extensively studied. K122, 123, 218, 218, 221, and 310 have been identified as the key acetylation sites on p65 [104].

Histone lysine acetylation has been associated with induction of gene expression by proinflammatory agents in endothelial cells and vascular smooth muscle cells [105–110]. A complex of NF-kB and cAMP response element-binding protein with HATs including p300/CBP, steroid receptor co-activator-1, and pCAF was required for increased expression of inflammatory genes [105–109, 111]. Increased histone lysine acetylation and increased NF-kB driven gene induction was observed in monocytes obtained from T1D and T2D patients [112, 113].

Resveratrol a known activator of SIRT-1 was found to attenuate cardiac hypertrophy and oxidative stress in Sprague Dawley (SD) rats fed with fructose. These fructose fed rats had increased NOX activity, ROS production, increased activity of NFkB along with acetylation of p65 subunit of NFkB and Histone 3 (H3). Resveratrol improved SIRT-1 actvity, deacetylated NFkB and H3 and decreased ROS, thereby preventing diabetes induced cardiac hypertrophy [114]. Acetylation of NFkB in the lysine 310 position and acetylation of H3 in lysine 9 position in the NFkB binding region has been observed [115, 116]. Functional consequences of NFkB acetylation in hearts are under active investigation.

Early Growth Response-1 (Egr1)

The hypoxia responsive transcription factor Egr-1 [117], is increased in models of cardiac pathology. Expression of Egr-1 has been previously linked to several aspects of

cardiovascular pathology including intimal thickening following acute vascular injury [118], cardiac hypertrophy [119], atherosclerosis [120] and angiogenesis [121]. Doxorubicin induced cardiomyopathy is also mediated by Egr-1 [122] and targeting Egr-1 reduces the pathological effects of acute myocardial infarction in rats [123]. Our studies have reported a novel mechanism linking glucose metabolism to acetylation of Egr-1, leading to proinflammatory and prothrombotic responses in diabetic atherosclerosis [3]. The acetylation was indicated to occur at the consensus KDKK region in the Egr-1 protein [124]. We generated mutants of the Egr-1 in which the "K" was mutated to "A." In vitro acetylation of the mutant and WT Egr-1 (KDKK) using p300 showed acetylation in the WT Egr-1 and the single mutant (ADKK) but not in the double (ADAK) or triple (ADAA) mutants of Egr-1. We established that glucose flux via polyol pathway reduced NAD+/NADH ratio, leading to reduction in NAD+ dependent SIRT1 activity in endothelial cells. As a consequence of SIRT1 activity reduction, we observed increased acetylation of Egr-1 in endothelial cells from mice models of diabetic atherosclerosis. In cardiomyocytes Egr1 acetylation has been linked to calcium regulation. Kaesneci et al [117] showed that in H9c2 cells calsequestrin (CSQ) expression was reduced in Egr-1-expressing cells. Using in vivo and in vitro chromatin immunoprecipitation they showed Egr-1 binding to the CSQ2 promoter. Inhibition of protein acetylation reduced CSQ expression, thus indicating that protein acetylation is important in CSQ repression [117]. Furthermore, they linked reduction in CSQ protein with abnormal calcium dynamics. Taken together, these studies set the stage for detailed investigations to address in vivo acetylation driven mechanisms of Egr1 acetylation and its cardiovascular consequences in normal and stressed hearts.

Hypoxia-Inducible Factor 1α (HIF 1α)

The transcription factor HIF-1 has an essential role in the maintenance of oxygen homeostasis in mammalian organisms [125–129]. HIF-1 exists as an α/β heterodimer, the activation of which depends on stabilization of an oxygen-dependent degradation domain of the α subunit by the ubiquitin-proteasome pathway [130, 131]. Reduced O_2 availability in tissue leads to increased activity of HIF-1, which coordinates adaptive responses through the transcriptional activation of hundreds of target genes [132]. *Hif1a*$^{-/-}$ mouse embryos, which are homozygous for a knockout allele at the locus encoding HIF-1α, die with cardiac malformations and vascular regression [133].

Lysine acetylation regulates HIF-1 protein stability and function by distinct mechanisms. p300, a component of the HIF-1 transcriptional complex, positively regulates the transactivation of HIF-1. Studies by Geng et al [134] show that p300 increases HIF-1α protein acetylation and stability. They showed that (a) p300 specifically acetylates HIF1α at Lys-709, which increases the protein stability and decreases polyubiquitination in both normoxia and hypoxia, and (b). HDAC1 disrupted HIF1α-p300 interaction. Studies using K709A mutant expressing cancer cells showed that this mutant was transcriptionally more active and less sensitive to hypoxia-induced growth arrest than the cells containing the HIF1α wild-type. These data demonstrated that HIF1α-p300 interaction stabilizes HIF1α via Lys-709 acetylation.

Another mechanism of HIF 1α stabilization was demonstrated by Joo et al [135]. In their studies, it was shown that SIRT1 stabilized HIF-1α via direct binding and deacetylation during hypoxia. SIRT1 depletion or inactivation led to reduced hypoxic HIF-1α accumulation, accompanied by an increase in HIF-1α acetylation. Yoon et al [136] showed that HIF-1α K674 and HIF-2α K741 are acetylated by PCAF and CBP, respectively, but are deacetylated commonly by SIRT1. In this study, SIRT1-mediated accumulation of HIF-1α protein led to increased expression of HIF-1α target genes, including VEGF, GLUT1 and MMP2, and ultimate promotion of cancer cell invasion [135]. These findings imply that hypoxic HIF-1α stabilization requires SIRT1 activation.

While the above two studies in cancer cell showed, contrasting findings on HIF-1α stabilization was published by Lim et al [137]. Authors showed that SIRT1 inactivated HIF-1α by blocking p300 recruitment and consequently repressed HIF-1 target genes. In this study HIF-1α was acetylated at Lys674, SIRT1 binding to HIF-1α lead to deacetylation of this lysine residue. During hypoxia, SIRT1 was downregulated, which which allowed the acetylation and activation of HIF-1α [137]. Transcriptional activity of HIF-1α is largely determined by transactivating domain C-TAD. Studies by Lando et al has shown that C-TAD recruits p300/CBP to facilitate transcription, and that this C-TAD is inhibited by FIH in normoxia [138]. Based on the studies of Lando et al, Lim et al speculated that the acetylation of HIF-1α at Lys674 leads to derepression of C-TAD and increased transcriptional activity both in cells and in vivo.

These contrasting findings have led to comprehensive investigations on the impact of specific lysine reidue (Lys 674, Lys 709) acetylation on transcriptional activation in normoxic and hypoxic cells and tissue including hearts.

Signal Transducer and Activator of Transcription (STATs)

The STAT family contains seven members, STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6 [139, 140], all of which are expressed in the heart. Murine studies showed that STAT3 deletion is embryonically lethal [139, 140]. Hearts from mice with a cardiac-specific knockout of STAT3 have larger infarcts after I/R, increased apoptosis, and increased mortality [141]. Furthrmore, deletion of STAT3 in cardiomyocytes renders hearts more susceptible to inflammatory damage [142]. STAT3 is a pleiotropic transcription factor that is activated by the phosphorylation of tyrosine 705 in response to many cytokines and growth factors. Unphosphorylated STAT3 (U-STAT3) is also a potent transcription factor. Dasgupta et al [143] showed using mass spectroscopic analysis that U-STAT3 is acetylated on Lys-685, and the integrity of Lys-685 is required for the expression of most U-STAT3-dependent genes. They found only a minor role for Lys-685 in gene expression induced in response to tyrosine-phosphorylated STAT3. Importantly, they showed using cellular and molecular approaches that U-STAT3 plays an important role in angiotensin II-induced gene expression and in the consequent development of cardiac hypertrophy. While the role of p300 in acetylating U-STAT3 was demonstrated in this study, specific deacetylases that ensure deacetylation of U-STAT3 remains to be determined.

Forkhead box proteins (FoxOs)

FoxO proteins are a family of transcription factors whose activity can be modulated by phosphorylation, acetylation, ubiquitination, and glycosylation. Acetylation sites of human FoxOs have been characterized and are well described in comprehensive review articles [144, 145]. Briefly, the acetylation sites for each of the human FoxOs are as follows: FoxO1a (K245, K265, K248, K262, K274, K294, K559), FoxO3a (K203, K242, K245, K259, K271, K290, K569), FoxO4 (K186, K189, K215, K237, K407), and FoxO6 (K173, K176, K190, K202, K229). Reversible lysine acetylation is accomplished by the action of histone acetyltransferases and deacetylases: CBP, p300 and p300/CBP-associated factor (PCAF) acetylate FoxOs, using acetyl-CoA as co-substrate, whereas enzymes of the sirtuin family (SIRT1, SIRT2 in some instances) catalyze deacetylation of FoxOs [56, 57, 146–150]. Acetylation sites in human FoxO proteins surround a consensus site for Akt-induced serine phosphorylation within the nuclear localization signal (NLS) motif [145]. This NLS motif is well conserved in all human FoxOs. Acetylation has been shown to result in both stimulation and inhibition of the transcriptional activity of FoxOs, depending on the examined FoxO isoforms and their binding partners such as other transcription factors and transcriptional co-activators, the FoxO target genes and the cell types used in the studies [56, 57, 87, 146–152]. The molecular mechanisms underlying those discrepancies are currently being addressed.

Hariharan et al [153] investigated the role of FoxOs and its posttranslational modification in mediating starvation-induced autophagy in heart. Starvation in cardiomyocytes was induced by glucose deprivation They showed that starvation increased autophagic flux and upregulation of SIRT1 and FoxO1 in cardiomyocytes and that both SIRT1 and FoxO1 were required for starvation induced autophagy. They showed that starvation increased deacetylation of FoxO1, and SIRT1 was essential for deacetylation of FoxO1. Delving into mechanisms they overexpressed FoxO1(3A/LXXAA), a mutant FoxO1 which cannot interact with SIRT1or p300, and observed increased acetylation of FoxO1 and inhibition of starvation induced autophagy. Furthermore, their studies revealed that FoxO1 driven expression of Rab7, is a key component mediating FoxO1-induced increases in autophagic flux. In vivo studies in mice with cardiac-specific overexpression of FoxO1(3A/LXXAA) and those with cardiac-specific homozygous deletion of FoxO1 (c-FoxO1(−/−))showed that cardiac function was reduced and autophagy was inhibited in these hearts [153]. This study linked SIRT1-mediated deacetylation of FoxO1 and upregulation of Rab7 in hearts to autophagic flux.

Sin et al [154] investigated the effects of long-term treatment of SIRT1 activator resveratrol on cardiac function and FoxO1-associated pro-apoptotic signaling in senescent mice. They observed that aging significantly reduced the deacetylase activity and that this reduction was accompanied by increased acetylation of the FoxO1 transcription factor and transactivation of its target, pro-apoptotic Bim. Furthermore, their data showed thatresveratrol restored SIRT1 activity and suppressed elevations of Foxo1 acetylation, Bim and pro-apoptotic signaling in the aged heart. This study linked SIRT1 activity and FoxO1 acetylation to pro-apoptotic signaling in the aged heart.

FoxO1 nuclear localization has been shown to essential for regulating pyruvate dehydrogenase kinase-4 (PDK4) in the rat cardiomyocytes [155]. Puthanveetil et al showed that dexamethasone increased nuclear FoxO1, as well as SIRT1-FoxO1 interaction, decreased FoxO1 acetylation with consequent increases in PDK4 expression in cardiomyocytes. Importantly, this study linked FoxO1 acetylation changes to increased glucose oxidation in cardiomyocytes.

Taken together these studies indicate acetylation of FoxOs and consequent regulation of autophagy, glucose metabolism, and apoptosis in hearts.

GATA binding protein 4 (GATA4)

GATA4 is a critical transcription factor for proper mammalian cardiac development and essential for survival of the embryo. Bnip3 is a hypoxia-regulated member of the Bcl-2 family of proteins that is implicated in apoptosis, programmed necrosis, autophagy and mitophagy. Bnip3 is induced in the heart by ischemia and pressure-overload, and may contribute to cardiomyopathy and heart failure. Studies by Thompson et al [156], showed novel activity of Bnip3 that is independent of mitochondrial function and programmed cell death. Using cultured cardiomyocytes and transgenic mice overexpressing Bnip3 in the heart, they demonstrated novel activity of Bnip3 that involves binding and activation of p300-acetyltransferase with downstream effects on transcription and histone acetylation. Importantly, cell culture date revealed that Bnip3 bound and activated the acetyltransferase p300 driving increased acetylation of histones and the transcription factor GATA4. Morphological changes conferred by Bnip3 overexpression were significantly blocked by curcumin treatment or knockdown of GATA4. In their studies, mice overexpressing Bnip3 mice exhibited age-dependent ventricular dilation and dilated cardiomyopathy. Inhibition of p300 with curcumin partially prevented cardiac dysfunction in the Bnip3 transgenic mice. The results suggest that GATA4 acetylation by Bnip3 regulates cardiac gene expression and function.

Nuclear factor erythroid 2-related factor (Nrf2)

The transcription factor Nrf2, an oxidative stress response modifier, induces transcription of a variety of genes via binding to the antioxidant response element (ARE) in target gene promoters [157–159]. Nrf2-dependent induction of cytoprotective proteins enable cells to combat oxidative stress [157–160] Nrf2 possesses six highly conserved domains called Nrf2-ECH homology (Neh) domains. Acetylation of Neh domains in Nrf2 was thought to regulate its transcriptional activity. Mutational analysis of the Neh1 domain led Sun *et al* [161] to conclude that acetylation-dependent modulation of the transcriptional activity of Nrf2 is, in part, due to the lysyl residues in the Neh1 domain. Mutating all the 18 lysine residues in Neh1 domain led to a 40–45% decrease in Nrf2-induced transcription [162], suggesting that other Neh domains may harbor acetylation sites that may also contribute to reductions in Nrf2 activity. In this regard, studies by Kawai et al [163] showed that acetylation/deacetylation plays a crucial role in nucleocytoplasmic shuttling of Nrf2 and that acetylatable lysine residues in its Neh3 domain participate in modulating its transcriptional activity. Their studies in K562 cells and HepG2 cells revealed that the Neh3 domain modulates the transcriptional activity of Nrf2 through acetylation-dependent regulation that

can be ascribed to Lys^{591} and Lys^{588} located in that domain. Using molecular and pharmacological strategies they showed that SIRT1 deacetylated Nrf2 and blocked Nrf2 driven gene transcription. In mice models of stroke, HDAC inhibition using trichostatin A activated Nrf2 and upregulated proteins downstream of Nrf2, including HO1, NAD(P)H:quinone oxidoreductase 1, and glutamate-cysteine ligase catalytic subunit [164]. Since trichostatin A does not inhibit NAD+ dependent SIRT activity, it appears that regulation of Nrf2 deacetylation in brain may be driven by non-NAD+ dependent HDACs. Mechanisms and consequences of Nrf2 acetylation in normal and stressed hearts are under active investigation.

In the next section we will review how indirect actions of acetylation can impact transcription factors in the heart.

Indirect actions of acetylation on transcription factors

Transforming growth factor β (TGF-β)

Tissue fibrosis is a major cause of organ dysfunction during chronic diseases and aging. A critical step in this process is TGF-β1-mediated transformation of fibroblasts into myofibroblasts, a cell capable of synthesizing extracellular matrix. Studies by Sunderesan et al [165] demonstrate that SIRT3 controls transformation of fibroblasts into myofibroblasts by suppressing the pro-fibrotic TGF-β1 signaling. They showed SIRT3 deficiency caused induction of TGFβ1 expression and hyper-acetylation of GSK3β at K15 residue. This hyperacetylation negatively regulated GSK3β activity to phosphorylate the substrates, Smad3 and β-catenin. Consequently, reduced phosphorylation led to stabilization and activation of these transcription factors regulating profibrotic genes. Data from rescue studies utilizing overexpression of SIRT3 reveled deacetylation and activation of GSK3β, and consequent attenuation of TGFβ1 signaling and tissue fibrosis.

Myocardin

Myocardin belongs to the SAF-A/B, Acinus, PIAS (SAP) domain family of transcription factors and is specifically expressed in cardiac and smooth muscle. Myocardin functions as a transcriptional coactivator of SRF and is sufficient and necessary for smooth muscle gene expression. Myocardin has been shown to induce the acetylation of nucleosomal histones surrounding SRF-binding sites in the control regions of cardiac and smooth muscle genes through recruiting chromatin-modifying enzyme p300 [166]. Cao et al [167] showed that myocardin is a direct target for p300-mediated acetylation and that p300 acetylates lysine residues at the N terminus myocardin. Importantly, they showed that interaction between p300 and myocardin, mediated by the C terminus of myocardin, is required for the acetylation. Myocardin acetylation by p300 (a) enhanced the association of myocardin and SRF as well as the formation of the myocardin-SRF-CArG box ternary complex, (b) decreased the binding of histone deacetylase 5 (HDAC5) to myocardin, and (c) activated smooth muscle gene expression [167].

Krüppel-like factor (KLF)

Krüppel-like factor KLF5, a member of the Sp/KLF family of zinc finger factors and a key regulator of cardiovascular remodeling. KLF5, is regulated positively by the acetylase p300 and negatively by the oncogenic regulator SET through coupled interaction and regulation of acetylation, [168]. Nagai and his researchers [169] have shown that the deacetylase HDAC1 can negatively regulate KLF5 through direct interaction. Using gThey showed that KLF5 interaction with HDAC1 inhibits the DNA binding activity of KLF5 and suppresses KLF5-dependent promoter activation. Overexpression of HDAC1 suppressed KLF5-dependent activation of its endogenous downstream gene, platelet-derived growth factor-A chain gene. They also showed that HDAC1 binding to the first zinc finger of KLF5, inhibits binding of p300 to KLF5. Other studies have demonstrated in non-cancerous epithelial cells, KLF5 converts from pro-proliferative to anti-proliferative activity upon acetylation [170–172]. KLF5 acetylation alters its transcriptional complex and the expression of genes such as p15 and MYC [Ref A–C]. Li et al showed that, in prostate cancer cell lines, KLF5 inhibited the proliferation, and the inhibition was dependent on KLF5 acetylation [173]. KLF5 suppressed tumor growth in an acetylation-dependent manner in Nude mice. Using RNA-Seq studies they determined that multiple molecules, including RELA, p53, CREB1, MYC, JUN, ER, AR and SP1, mediate the opposing functions of acetylated KLF5 and unacetylated KLF5. Their results indicated a novel acetylation driven mechanism that controls how KLF5 can be both pro- and anti-tumorigenic. Taken together, these studies indicate multiple mechanisms by transcriptional activity of KLF5 cn be altered in multiple cell types.

While all these studies highlight indirect mechanisms by which acetylation influences transcription factors in the heart. In the next section we will review novel and emerging mechanisms impacting HDACs in the heart.

Novel mechanisms impacting HDAC function

HDAC3 degradation

HATs and HDACs form large activator and repressor complexes, resulting in transcriptional gene regulation [174, 175]. HDAC3 is recruited to the SMRT (silencing mediator of retinoid and thyroid receptor) complex, where it interacts with the DAD (deacetylase activation domain) domain of either NCOR1 (nuclear corepressor 1) or SMRT (nuclear corepressor 2; [176]). HDAC3 synthesis is an ongoing process, and this protein is degraded if unbound to the corepressors. The HDAC3-corepressor complex represses several nuclear receptors including thyroid receptor (TR), retinoic acid receptor (RAR), vitamin D receptor (VDR), androgen receptor, glucocorticoid, receptor (GR), and others [177–180].

In our recent study [181], we showed that the interaction of polyol pathway enzyme aldose reductase (AR) with the nuclear corepressors, NCOR1 and SMRT, could lead to HDAC3 degradration (Figure 2). HDAC3, a class I enzyme exists as a multiprotein complex including HDAC3, nuclear corepressors and cofactors. HDAC3 binds to the deacetylation domain (DAD) of either silencing mediator of retinoic and thyroid receptor (SMRT) or nuclear corepressor 1 (NCOR1) [176, 182]. Molecular, cellular, and in vivo studies revealed that AR interaction with the DAD domain of nuclear corepressors drives HDAC3

degradation, consequently leading to the expression of nuclear corepressor's cofactors including *Gps2*, *Tblr1*, PPARγ activation and lipid accumulation in the hearts [181]. Our studies demonstrated that regulating the levels of nuclear corepressors or its cofactors could also result in changes of HDACs and consequently transcription.

HDAC3-NCOR complexes take place mostly in the cytoplasm [183]. The HDAC3-corepressor complex represses several nuclear receptors like TR, RXR, RAR, VDR, GR, PXR (pregnane X receptor), and LXR [177–179, 184]. In our study, though we have shown low HDAC3-corepressor complex formation, derepression is specific to PPARg and RARB, altering lipid and retinoid metabolism. Our study revealed a key role for AR as a dissociation factor of the HDAC3-corepressor complex via interaction with the DAD domain, thereby derepressing target gene expression, mimicking the liganded PPARg and RAR state.

Interclass cross talk between HDACs

Histone deacetylases (HDACs) are closely involved in cardiac reprogramming. Although the functional roles of class I and class IIa HDACs are well established, the significance of interclass crosstalk in the development of cardiac hypertrophy is evolving. Recently, Eom et al [74] reported a novel post-translational activation mechanism of HDAC2 that involves acetylation of HDAC2 mediated by p300/CBP-associated factor/HDAC5. They showed that the enzymatic activity of Hdac2 was positively correlated with its acetylation status. p300/CBP-associated factor bound to Hdac2 and induced acetylation. The HDAC2 K75 residue was responsible for hypertrophic stress-induced acetylation. The acetylation-resistant Hdac2 K75R showed a significant decrease in phosphorylation on S394, which led to the loss of intrinsic activity (Figure 3). Hdac5, one of class IIa HDACs, directly deacetylated Hdac2 (Figure 3). Acetylation of Hdac2 was increased in Hdac5-null mice. When an acetylation-mimicking mutant of Hdac2 was infected into cardiomyocytes, the antihypertrophic effect of either nuclear tethering of Hdac5 with leptomycin B or Hdac5 overexpression was reduced. Taken together, these data indicated a novel mechanism by which the balance of HDAC2 acetylation is regulated by p300/CBP-associated factor and HDAC5 in the development of cardiac hypertrophy.

Therapeutic Opportunities to modulate acetylation in hearts

Sirtuins are attractive targets for therapeutic interventions in several diseases, including cancer, inflammation, metabolic disorder, and cardiovascular disease. Chemical compounds such as flavones, stilbenes, and anthocyanidins, can directly stimulate SIRT1 activity by an allosteric mechanism [185]. Natural product resveratrol (3,5,4=-trihydroxystilbene), is a well-known potent activator of SIRT1 [185]. Recently, several clinical trials on SIRT1 activators have been reported. Longevinex, a modified form of resveratrol, has been shown to improve endothelial function in patients with metabolic syndrome [186]. SRT2104, a SIRT1 activator, was demonstrated to improve lipid profiles in otherwise healthy cigarette smokers [187]. SRT2104 was also associated with improvement in lipid profiles in a phase-II, randomized, placebo-controlled, double-blind, multidose study of subjects with type 2 diabetes [188].

Preclinical studies using HDAC inhibitors demonstrated protection in cardiac hypertrophy [189, 190]. Recently, a study demonstrated that SAHA (vorinostat), an FDA-approved pan-HDAC inhibitor for cancer, was efficacious in a rabbit model of cardiac ischemia-reperfusion injury [191]. This proof-of-concept study has set the stage for a clinical trial in humans to assess effects of HDAC inhibitor SAHA on pathological cardiac remodeling post-myocardial infarction. Entinostat, a novel and selective Class I HDAC inhibitor, has been shown to be efficacious in the rat model of ischemia reperfusion injury [192]. Further characterization of these molecules and determining the optimal dose and timing for application to humans will help in advancing clinical use of HDAC inhibitors and sirtuin activators as therapeutic interventions for cardiovascular diseases. Taken together, these considerations highlight examples of the diverse efforts to target acetylation impacting HDACs for protection of the hearts.

Challenges and limitations in determining acetylation stoichiometry and its functional implications

In a recent review Baeza et al [193] discussed in depth the challenges in quantitation and establishing stoichiometry of acetylation in proteins. In the case of transcription factors, low abundance and complexities involved in isolation makes mass spectrometric studies challenging. Nevertheless, as discussed in the earlier sections, studies have identified specific acetylation sites for some of the transcription factors. Most challenging aspect is identifying number of acetylation sites and it impact on transcription factor activity. Acetylation studies for high abundant proteins/enzymes have shown that (a) single acetylation site can directly control enzymatic activity (an example is acetyl-CoA synthetase 2 (AceCS2) [32, 33] and (b) acetylation in multiple sites affect enzymatic activity (examples include ACAT1, HMGCS2 and SOD2) [194–198]. Advances in mass spectrometric techniques and the use of Knockin strategies to generate cells expressing single and multiple site acetylation resistant mutant transcription factors will help address the impact of site specific acetylation on transcription factor activity.

Conclusions

Lysine acetylation has emerged as a major posttranslational modification in the regulation of transcription in cardiovascular cells. Given the wide range of regulatory mechanisms it impacts, acetylation regulation of transcription factors seems poised to only grow in significance as we continue to discover its functions and mechanisms. Comprehensive proteomics, cellular, molecular, and in vivo (including generation of knockin mice) strategies will help delineate mechanisms and consequences of transcription factor acetylation in mediating cardiovascular disease. Intensive research efforts are underway to uncover the potential of inhibiting acetylation as a therapeutic target in cardiovascular diseases.

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Highlights

- Transcription factor acetylation in hearts
- HDACs and HATs in transcription factor acetylation
- Novel mechanisms impacting HDAC function

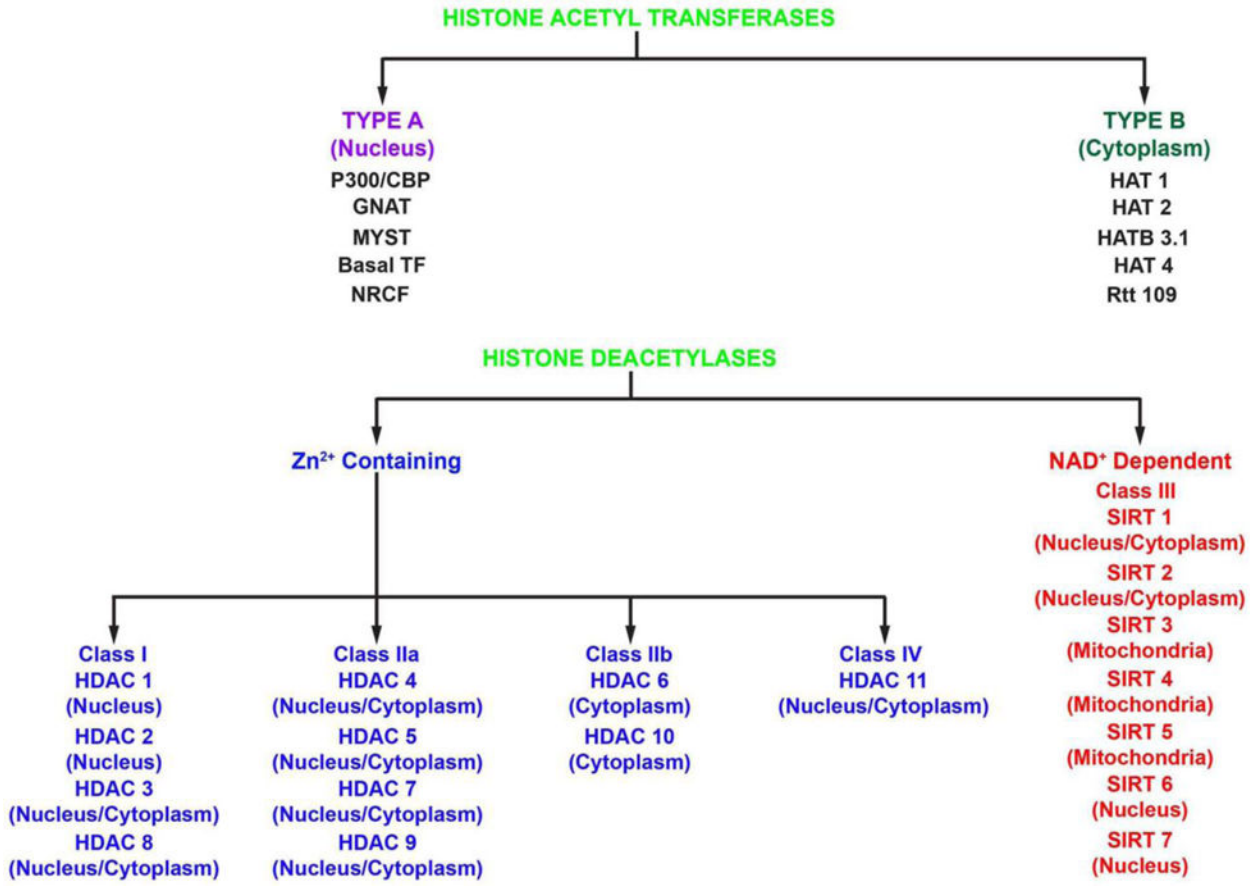

Figure 1.

Figure 1 illustrates the various histone acetyltransferases (top) and Zinc dependent and NAD + dependent histone deacetylases and their subcellular localization in cells (bottom).

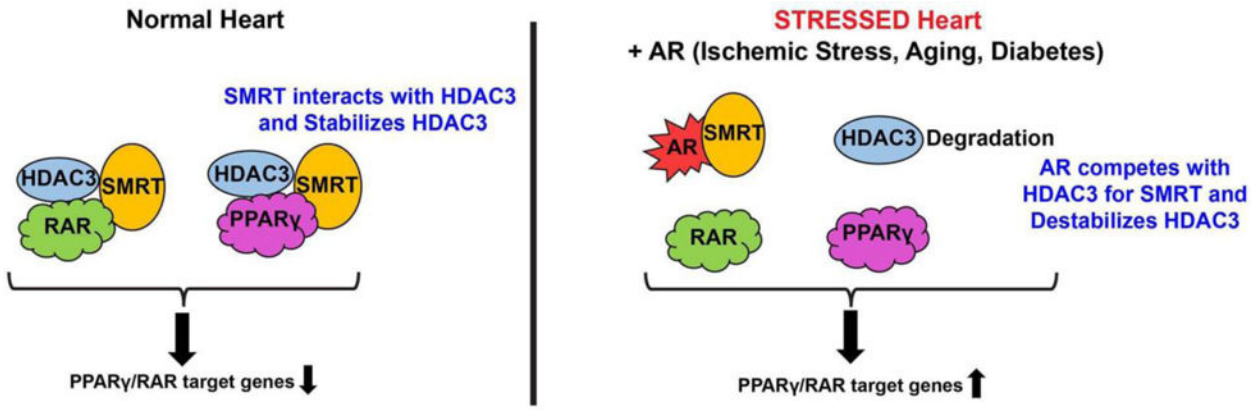

Figure 2.

Figure 2 depicts an emerging mechanism of HDAC3 regulation in cells. This mechanism scheme adapted from [181] shows that polyol pathway enzyme aldose reductase (AR) competes with HDAC3 for corepressor complex binding leading to HDAC3 degradation and derepression of the PPARg and RAR pathways.

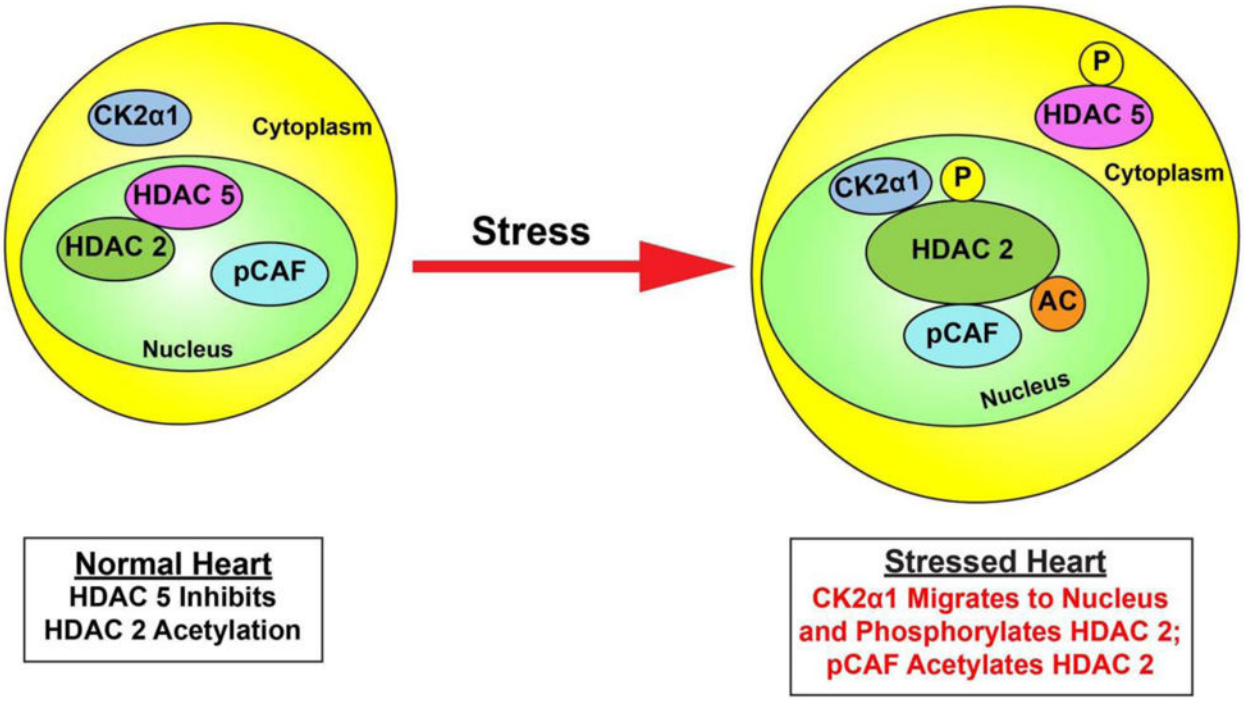

Figure 3.

Figure 3 adapted from [74] depicts post-translational activation mechanism of HDAC2 that involves acetylation of HDAC2 mediated by p300/CBP-associated factor/HDAC5. Cardiac stress induces phosphorylation of HDAC5 and subsequent export to the cytoplasm. Casein kinase 2α1 (CK2α1) phosphorylates HDAC2, and p300/CBP-associated factor (pCAF) binds to HDAC2 and induces acetylation. “P’ indicates phosphorylation, “Ac” indicates acetylation.