Journal of Molecular and Cellular Cardiology 83 (2015) 14–20

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review article

Non-sirtuin histone deacetylases in the control of cardiac aging

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ARTICLE INFO

Article history:
Received 22 November 2014
Received in revised form 19 February 2015
Accepted 10 March 2015
Available online 16 March 2015

Keywords:
Histone deacetylase
Heart failure
Aging

ABSTRACT

Histone deacetylases (HDACs) catalyze the removal of acetyl-groups from lysine residues within nucelosomal histone tails and thousands of non-histone proteins. The 18 mammalian HDACs are grouped into four classes. Classes I, II and IV HDACs employ zinc as a co-factor for catalytic activity, while class III HDACs (also known as sirtuins) require NAD + for enzymatic function. Small molecule inhibitors of zinc-dependent HDACs are efficacious in multiple pre-clinical models of pressure overload and ischemic cardiomyopathy, reducing pathological hypertrophy and fibrosis, and improving contractile function. Emerging data have revealed numerous mechanisms by which HDAC inhibitors benefit the heart, including suppression of oxidative stress and inflammation, inhibition of MAP kinase signaling, and enhancement of cardiac protein aggregate clearance and autophagic flux. Here, we summarize recent findings with zinc-dependent HDACs and HDAC inhibitors in the heart, focusing on newly described functions for distinct HDAC isoforms (e.g. HDAC2, HDAC3 and HDAC6). Potential for pharmacological HDAC inhibition as a means of treating age-related cardiac dysfunction is also discussed. This article is part of a Special Issue entitled: CV Aging

Contents

1. Introduction

Acetylation of nucleosomal histone tails provides a critical mechanism for epigenetic control of gene expression. Additionally, proteomic studies have revealed that thousands of non-histone proteins are also subject to reversible lysine acetylation [1,2], further highlighting the biological significance of this post-translational modification. Acetyl groups are transferred to lysine residues by histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs), which are often referred to as "writers" and "erasers", respectively. Lysine acetylation also creates binding sites for bromodomain-containing "reader" proteins such as bromodomain and extraterminal (BET) proteins. Although HATs, HDACs and acetyl-lysine readers have all been shown to contribute to the pathogenesis of heart failure, this review specifically focuses on HDACs.

The 18 mammalian HDACs are encoded by distinct genes and are grouped into four classes 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. 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 [3]. Coordination of a zinc ion in the

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http://dx.doi.org/10.1016/j.yjmcc.2015.03.010
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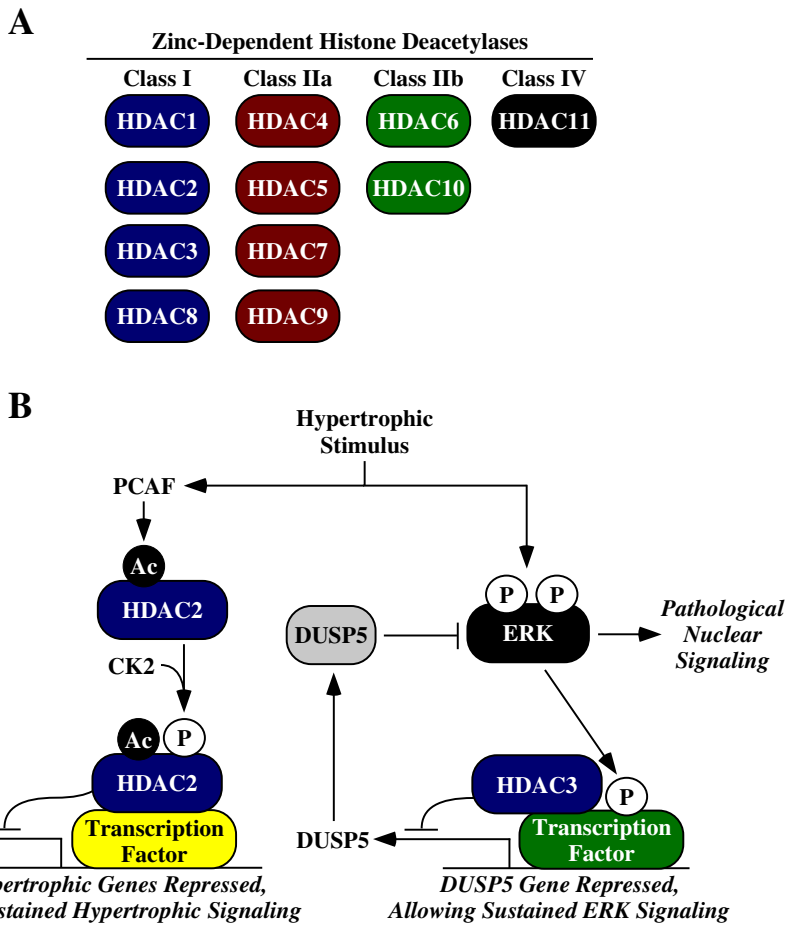

Fig. 1. Zinc-dependent HDACs and cardiac aging. (A) Zinc-dependent HDACs fall into three classes, with class II being subdivided into IIa and IIb. Class III HDACs (sirtuins), which are NAD+-dependent, are not shown. (B) In response to hypertrophic stimuli, HDAC2 is acetylated by p300/CBP-associated factor (PCAF), which primes the protein for phosphorylation by casein kinase 2 (CK2). Acetylated and phosphorylated HDAC2 is more active, and thus has increased capacity to repress anti-hypertrophic gene expression. Hypertrophic signals also lead to HDAC3-mediated repression of the gene encoding dual-specificity phosphatase 5 (DUSP5). In HDAC inhibitor-treated cardiomyocytes, DUSP5 expression increases, creating a negative feedback loop that blocks pro-hypertrophic ERK signaling in the nucleus.

catalytic domains of classes I, II and IV HDACs is required for catalysis (Fig. 1A). In contrast, class III HDACs (sirtuins) utilize nicotinamide adenine dinucleotide (NAD+) as a co-factor for catalytic activity. Class III HDACs are most commonly associated with aging (decreased activity and expression is thought to contribute to aging), and these HDACs clearly serve important roles in the heart. However, class III HDACs will not be discussed further in this review, since they are not inhibited by the small molecule HDAC inhibitors that were used in the pre-clinical models of heart failure described below.

2. HDAC inhibitors in heart failure models

Positive effects of pan- and isoform-selective HDAC inhibitors in rodent models of heart failure have been reviewed extensively [4,5]. Importantly, HDAC inhibition is capable of regressing established cardiac hypertrophy and systolic dysfunction in mice subjected to aortic constriction [6,7]. Recently, a major advance in the field was provided by the discovery that SAHA (vorinostat), an FDA-approved pan-HDAC inhibitor, was efficacious in a rabbit model of cardiac ischemia-reperfusion (I/R) injury [8]. Delivery of SAHA before or during reperfusion resulted in a 40% decrease in infarct size and preservation of systolic function of the heart. Efficacy of SAHA in this model appeared to be due to enhancement of autophagic flux in the infarct border zone. It is thought that autophagy serves to protect cardiomyocytes during ischemia by resupplying energy, and by destroying damaged mitochondria [9]. This proof-of-concept study in a large animal model sets the stage for a clinical trial in humans to assess effects of HDAC inhibition on pathological cardiac remodeling post-myocardial infarction. Such a trial would be the first assessment of an HDAC inhibitor for a cardiovascular indication.

It will be interesting to determine whether isoform-selective HDAC inhibitors are efficacious in the rabbit I/R model. A recent evaluation of HDAC inhibitors in an ex vivo model of rat cardiac I/R injury demonstrated that MS-275, a class I HDAC (HDAC1, -2, -3)-selective inhibitor, preserved cardiac function and reduced infarct size [10]. These results suggest that class I HDAC activity contributes to ischemic cardiac damage.

Fibrosis is a hallmark of the aging heart, and pan-HDAC inhibitors have clearly been shown to reduce excess extracellular matrix (ECM) deposition in multiple models of cardiac disease [11]. We discovered that a small molecule inhibitor of class I HDACs, MGCD0103, blocks angiotensin II-mediated cardiac fibrosis [12]. A follow-up study with the same compound showed that class I HDAC inhibition reduces cardiac fibrosis and improves ventricular function in a chronic coronary artery ligation model in rats [13].

Multiple mechanisms account for class I HDAC inhibitor-mediated suppression of cardiac fibrosis. First, class I HDAC inhibition blocks cardiac fibroblasts in the G_0/G_1 phase of the cell cycle by preventing retinoblastoma (Rb) phosphorylation, which is required to stimulate downstream expression of target genes that drive the G_1-to-S transition. Specifically, class I HDAC inhibitor treatment of cardiac fibroblasts results in upregulation of expression of p15 and p57, which are endogenous suppressors of the kinases that target Rb, cyclin-dependent kinases [12]. Through