Cellular Signalling 26 (2014) 521–527

Contents lists available at ScienceDirect

Cellular Signalling

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

Review

Histone deacetylases in cardiac fibrosis: Current perspectives for therapy

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ARTICLE INFO

Article history:
Received 12 November 2013
Received in revised form 30 November 2013
Accepted 30 November 2013
Available online 7 December 2013

Keywords:
Histone deacetylase
Cardiac fibrosis
Epigenetic
Histone deacetylation
Fibroblast
Proliferation

ABSTRACT

Cardiac fibrosis is an important pathological feature of cardiac remodeling in heart diseases. The molecular mechanisms of cardiac fibrosis are unknown. Histone deacetylases (HDACs) are enzymes that balance the acetylation activities of histone acetyltransferases on chromatin remodeling and play essential roles in regulating gene transcription. In recent years, the role of HDACs in cardiac fibrosis initiation and progression, as well as the therapeutic effects of HDAC inhibitors, has been well studied. Moreover, numerous studies indicated that HDAC activity is associated with the development and progression of cardiac fibrosis. In this review, the innovative aspects of HDACs are discussed, with respect to biogenesis, their role in cardiac fibrosis. Furthermore, the potential applications of HDAC inhibitors in the treatment of cardiac fibrosis associated with fibroblast activation and proliferation.

Contents

1. Introduction

Cardiac fibrosis is a major factor in the progression of myocardial infarction and heart failure [1,2]. Cardiac fibrosis is characterized by the excessive deposition of collagens and extracellular matrix (ECM) proteins that lead to impaired organ function [3–5]. Fibroblasts are the predominant cell type responsible for the homeostatic maintenance of tissue ECM, healing after injury [6–8]. Myofibroblasts are characterized by increased protein synthesis, including collagens, other ECM proteins, certain cytokines and α-smooth muscle actin (α-SMA), a contractile protein and marker of profibrogenic cardiac fibroblasts (CFs) activation [9,10]. Recent investigations have shown that the expression of distinct HDACs is strongly correlated to the genesis, progression and treatment of cardiac fibrosis [11].

Histone acetylation/deacetylation of the N-terminal tail is crucial in modulating gene expression [12,13]. The balance between the acetylated/deacetylated states of histones is mediated by two different sets of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs) [14,15]. Histone acetylation plays an important

Abbreviations: HDACs, Histone deacetylases; ECM, Extracellular matrix; α-SMA, α-smooth muscle actin; HATs, Histone acetyltransferases; TGF-β1, Transforming growth factor β1; PDGF, Platelet-derived growth factor; FGF, Fibroblast growth factor; TIMPs, Tissue inhibitors of matrix metalloproteinases; MEF2, Myocyte enhancer factor-2; IGF-IIR/Man-6-P, IGF-II/mannose 6-phosphate receptor; NRVMs, Neonatal rat ventricular myocytes; PKD1, Protein kinase D1.

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http://dx.doi.org/10.1016/j.cellsig.2013.11.037

role in regulation of transcription in eukaryotic cells by promoting a more relaxed chromatin structure necessary for transcriptional activation [16,17]. Histone deacetylases (HDACs) remove acetyl groups and suppress gene expression [18,19]. HDACs are a family of enzymes that remove acetyl groups from a ε-*N*-acetyl lysine amino acid on a histone and restore the positive charge to lysine residues [20,21]. HDAC proteins are also referred to as lysine deacetylases to more precisely describe their function rather than their targets, since they can catalyze deacetylation of many nonhistone proteins in addition to histones [22].

The present paper was designed to discuss the role of HDACs as novel molecular tools in the progression of cardiac fibrosis, as well as discuss the potential applications of HDAC inhibitors in treatment of cardiac fibrosis and fibroblast activation.

2. HDAC classes and HDAC inhibitors

HDACs catalyze removal of acetyl groups from ε-amino groups of lysine residues in a variety of proteins [23,24]. HDACs have been studied mainly in the context of chromatin, where they serve an epigenetic function by deacetylating nucleosomal histones and altering the electrostatic properties of chromatin in a manner that leads to gene repression [25]. However, it is now clear that HDACs deacetylate many nonhistone proteins, and thus the enzymes also are called lysine deacetylases (KDACs) [26].

To date, 18 mammalian HDAC proteins have been identified, and they are divided into four classes based on similarity to yeast orthologs [27]. Class I, II, and IV enzymes depend on zinc for catalytic activity and contain a highly conserved deacetylase domain [28,29]. The remaining class III HDAC enzymes, which are NAD^+-dependent, are called the sirtuins [30]. Class III HDACs (SirT1-7) to yeast Sir2 [31]. Enzymes in classes I, II and IV share a zinc-dependent catalytic mechanism [32], these classes will form the focus of this review. Class I is comprised of HDACs 1, 2, 3, and 8 [33]. Class II is subdivided into class IIa, containing HDACs 4, 5, 7, and 9, and class IIb, which contains HDACs 6 and 10 [34]. HDAC 11 is the sole member of class IV because its catalytic domain resembles the actives sites of both class I and class II enzymes [35]. Recent studies have shown that HDACs are critically involved in tissue fibrosis in the heart (Fig. 1).

What is more, HDAC inhibitors selectively alter gene transcription through chromatin remodeling and by changing the protein structure of transcription factor complexes [18,36]. HDAC inhibitors generally consist of three domains: a linker region, a capping group and a metal moiety [37]. There are four major chemotypes of HDAC inhibitors currently in clinical development: hydroxamic acids, short-chain fatty acids, cyclic tetrapeptides and benzamides [38,39]. All inhibitors share a common pharmacophore pattern consisting of a zinc-binding domain, a linker domain that mimics the substrate and occupies the active site channel, a connecting unit, and a capping unit that contacts the surface of the enzyme [39].

3. General features of histone acetylation/deacetylation

Acetylation of histone and nonhistone proteins provides a key mechanism for controlling signaling and gene expression in heart [40]. Genomic DNA within the nuclei of eukaryotic cells is highly compacted with histone and nonhistone proteins in a dynamic polymer called chromatin [41]. The basic unit of chromatin is the nucleosome, which comprises 146 base pairs of DNA wrapped around a histone octamer that consists of 2 copies each of histones H2A, H2B, H3, and H4 [42]. Residues within histone tails are subject to diverse posttranslational modifications, including phosphorylation, acetylation, and methylation, which together establish a “histone code” that governs the higher-order

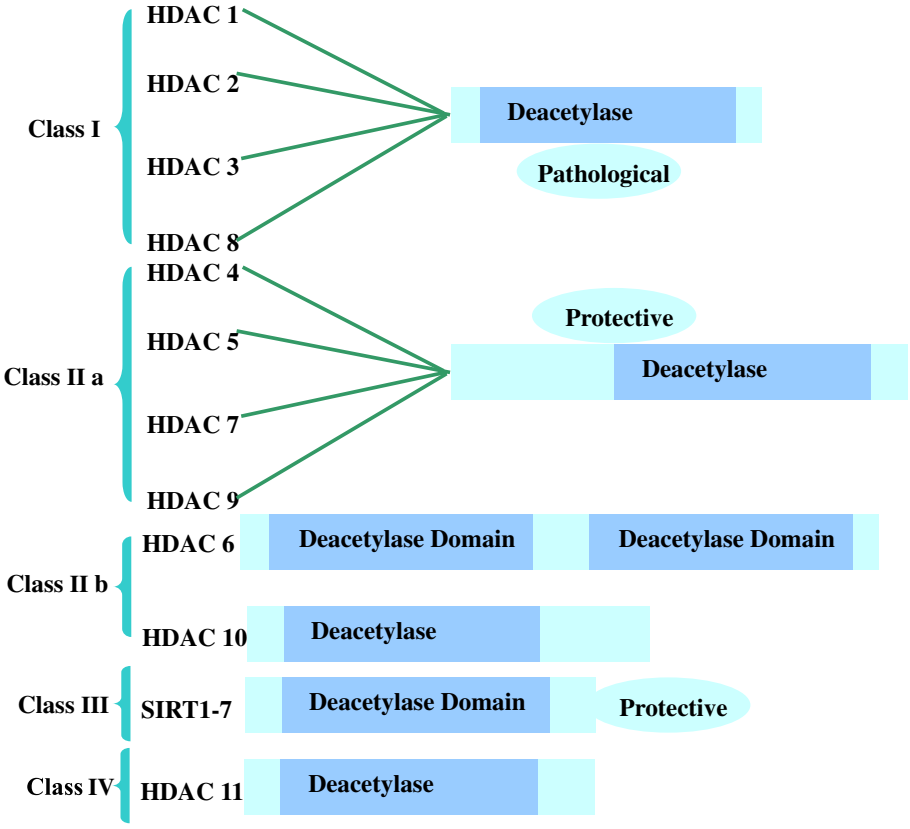

Fig. 1. Regulation of lysine acetylation by histone deacetylases. Histone acetyltransferases (HATs) transfer acetyl groups from acetyl-CoA to ε-amines of lysine residues on a variety of proteins, and HDACs catalyze removal of these groups. HDACs are categorized into class I, class II, class IV and sirtuins classes. Class II HDACs are further divided into two subclasses, IIa and IIb. Current data based on genetic and pharmacological investigations suggests that class I HDACs promote pathological cardiac remodeling while class IIa HDACs are protective. There is nothing known about the functions of class IIb and class IV HDACs in the heart.