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Posttranslational modifications of histone deacetylases: Implications for cardiovascular diseases

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ABSTRACT

Posttranslational modification (PTM) is a term that implies dynamic modification of proteins after their translation. PTM is involved not only in homeostasis but also in pathologic conditions related to diverse diseases. Histone deacetylases (HDACs), which are known as transcriptional regulators, are one example of posttranslational modifiers with diverse roles in human pathophysiology, including cardiovascular diseases. In experimental models, HDAC inhibitors are beneficial in supraventricular arrhythmia, myocardial infarction, cardiac remodeling, hypertension, and fibrosis. In addition, HDACs are closely related to other vascular diseases such as neointima formation, atherosclerosis, and vascular calcification. Currently, HDACs are classified into four different classes. The class IIa HDACs work as transcriptional regulators mainly by direct association with other transcription factors to their target binding elements in a phosphorylation-dependent manner. Class I HDACs, by contrast, have much greater enzymatic activity than the class II HDACs and target various non-histone proteins as well as the histone-core complex. Class I HDACs undergo PTMs such as phosphorylation, sumoylation, and S-nitrosylation. Considering the growing evidence for the role of HDACs in cardiovascular diseases, the PTMs of the HDACs themselves as well as HDAC-mediated PTM of their targets should be considered for future potential therapeutic targets. In this review, we discuss 1) the roles of each HDAC in specific cardiovascular diseases and 2) the PTM of HDACs, 3) and the implications of such modifications for cardiovascular diseases.

Contents

Abbreviations: CaMK, Ca^{2+}/calmodulin-dependent protein kinase; CK2, Casein kinase 2; COPD, Chronic obstructive pulmonary disease; CTCL, Cutaneous T cell lymphoma; CVD, Cardiovascular diseases; Cys, Cysteine; Hif-1, Hypoxia-inducible factor-1; HAT, Histone acetyltransferase; HDAC, Histone deacetylase; HDACi, Histone deacetylase inhibitors; I/R, Ischemia–reperfusion; KLF, Krüppel-like factor; LDLR, Low-density lipoprotein receptor; Lys, Lysine; MEF, Myocyte enhancer factor; MI, Myocardial infarction; MITR, MEF-2 interacting transcription repressor; NAD, Nicotinamide adenine dinucleotide; PKA, Protein kinase A; PKC, Protein kinase C; PKD, Protein kinase D; PTM, Posttranslational modification; SAHA, Suberoylanilide hydroxamic acid; SCFA, Short chain fatty acid; Ser, Serine; siRNA, Small interfering RNA; SUMO, Small ubiquitin-like modifier; TSA, Trichostatin A; VEGF, Vascular endothelial growth factor; VPA, Valproic acid.

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1. Introduction

1.1. Cardiovascular diseases

Since the 1970s, cardiovascular disease (CVD) has been a leading cause of death throughout the world (Hunter & Reddy, 2013). Although great efforts have been made by physicians, researchers, and even primary care practitioners to reduce the mortality due to CVD, the disease is still a major cause of death in developed countries. In large part because of unbalanced, high-fat diets, the median age of patients with CVD has been decreasing (McGill et al., 2008). "Cardiovascular disease" is a term indicating medical problems in the heart, the blood vessels, or both. Sometimes CVD indicates "heart disease" in a limited sense; usually, however, vascular problems in the brain or kidney or other peripheral arterial disease is also included. The most common CVDs are hypertension and atherosclerosis (Ross, 1999). Even in healthy individuals, aging followed by morphological and physiological changes affects cardiovascular structures and function, which subsequently leads to a high risk of CVD. Therefore, risk-factor-reducing efforts such as consuming a balanced healthy diet, getting adequate amounts of exercise, increasing lean body mass, and stopping smoking are strongly recommended to reduce the development of CVD (McGill et al., 2008). Besides a preventive approach, therapeutic interventions to halt disease progress or to recover a healthy state are necessary as well, and such interventions require a fundamental understanding of disease development and progress. Considering that most CVD-related pathologic events are caused by malfunction of normal proteins, PTMs that might result in those abnormal behaviors should be extensively studied. Thus, understanding the PTMs associated with CVD may offer opportunities for the development of ideal therapeutics with maximal efficacy and minimal unwanted effects.

1.2. Posttranslational modifications

Proteins are not stable but are dynamically modified by other proteins, such as kinases, acetyltransferases, methyltransferases, ubiquitinylases, and carboxylases. These changes are finely balanced by opposing enzymes such as phosphatases, deacetylases, demethylases, deubiquitinylases, and decarboxylases. These dynamic changes are called PTMs and are closely linked to diverse cellular functions and human diseases. For example, when ligands occupy their binding sites in receptors, receptor tyrosine kinases phosphorylate target molecules and an extracellular signal is delivered to cytoplasmic or nuclear targets (Hubbard & Till, 2000). Phosphorylation is an essential modification in the regulation of enzyme activation (Stambolic & Woodgett, 1994; Dimmeler et al., 1999), DNA-binding capacity (Beg et al., 1993), formation of complexes (Maudsley et al., 2000), and cell cycle regulation (Serrano et al., 1993).

Besides phosphorylation, ubiquitination is an important modification that has been intensively investigated recently. Ubiquitin is a small protein with a molecular mass of just 8.5 kDa. It has 7 lysine residues in its structure. *Ubiquitination* indicates the covalent binding of ubiquitin to a substrate. This process generally involves binding of glycine 76 at the C-terminus of ubiquitin to a lysine of the substrate. *Polyubiquitination* refers to additional ligation of ubiquitin to another ubiquitin that has already been conjugated with a protein, which implies that ubiquitin works as a substrate for further ubiquitination. Two lysines of ubiquitin are involved in polyubiquitination: Lys-48 and Lys-63. Lys-48-linked polyubiquitination is associated with protein degradation and recycling by proteolysis (Glickman & Ciechanover, 2002), whereas Lys-63-linked polyubiquitination is atypical and is involved in other processes such as inflammation, DNA repair, and endocytic trafficking (Miranda & Sorkin, 2007). In contrast to polyubiquitination, monoubiquitination, which is also frequently observed, has quite different biological functions. Although monoubiquitination is sometimes regarded as a beginning step of polyubiquitination, most monoubiquitination solely affects cellular events such as endocytosis, trafficking, and signal transduction such as phosphorylation (Miranda & Sorkin, 2007). Small ubiquitin-like modifier (SUMO) proteins are analogous to ubiquitin, and the characteristics of SUMO modification, which is termed *sumoylation*, resemble those of monoubiquitination (Melchior, 2000).

Likewise, protein acetylation, an alternate well-known PTM, has a unique biological function. Perhaps one of the best documented targets of acetylation involves histone H3 and H4 proteins; acetylation of the histone tail is closely associated with transcriptional activation. The positive charge of the histone core is neutralized by adding an acetyl moiety, which thereby loosens the tight interaction between the negative charge of the phosphate group in DNA and the histone tail (de Ruijter et al., 2003). The nucleosome is then opened to the transcriptional machinery, which initiates gene expression. Non-histone proteins are also susceptible to acetylation, which affects enzyme activity (Santos-Rosa et al., 2003), protein–protein interaction (Levy et al., 2004), DNA recruitment (Gu & Roeder, 1997), and transcriptional activity (Evans et al., 2007).

It is noteworthy that each PTM can affect other modifications; indeed, we can easily find multiple modifications at different residues in a single molecule or even at a single residue, which seems like "competition" between the various modifications. For example, acetylation, methylation, and ubiquitination commonly occur at a lysine residue, and these modifications sometimes regulate the target protein function in a competitive manner. Histone H3 Lys-9 is a target site for both acetylation and methylation, and trimethylated Lys-9 is found in constitutively repressed genes (Barski et al., 2007). In contrast, acetylation on this residue activates gene expression (Koch et al., 2007). Following the removal of the methyl group by specific demethylases, histone acetyltransferase (HAT) enzyme acetylates H3 Lys-9. By contrast, after the acetyl moiety is removed by histone deacetylase (HDAC), the remaining unmodified lysine residue is subject to mono-, di-, and tri-methyl modification (Guillemette et al., 2011). Indeed, growing evidence suggests that HDAC works in conjunction with histone methyltransferase (Wysocka et al., 2003). Similarly, acetylation increases protein stability by competition with polyubiquitination (Li et al., 2002). Furthermore, PTM-associated PTMs such as acetylation-dependent phosphorylation (Park et al., 2003), phosphorylation-dependent acetylation (Corre et al., 2009), or phosphorylation-dependent ubiquitination (Koepp et al., 2001; Lin et al., 2002) are also reported.

Protein acetylation is finely regulated by two different groups of enzymes: HATs and HDACs. At least 18 different HDACs in mammals have been discovered, which are categorized into four classes. HDAC1, 2, 3, and 8 are members of the class I HDACs; HDAC4, 5, 6, 7, 9, and 10 are class II HDACs; the sirtuin family members, Sirt1, Sirt2, Sirt3, Sirt4, Sirt5, Sirt6, and Sirt7, are class III HDACs; and HDAC11 is the only class IV HDAC. Class I, II, and IV HDACs contain and require zinc ion for their enzyme activity (Minucci & Pelicci, 2006); however, class III HDACs are NAD^+-dependent (Blander & Guarente, 2004). Like the HATs, HDACs also have non-histone substrates (Chen et al., 2002; Hubbert et al., 2002; Ito et al., 2002; Watamoto et al., 2003; Ito et al., 2006). Thus, it has been suggested that *lysine deacetylase*, or KDAC, would be more appropriate nomenclature because histone is not the only substrate and these non-histone targets have more diverse biological functions than transcriptional regulation (Choudhary et al., 2009). In the present review, we discuss the roles and PTMs of the class I and class II HDACs and their mechanisms of regulation in association with CVD.

2. Histone deacetylases in cardiovascular disease

2.1. Histone deacetylases

The criterion applied to divide the class I and class II HDACs is based on the homology of each HDAC to yeast HDACs (Blander & Guarente, 2004). Class II HDACs consist of 1) a large N terminus regulatory region,