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Review

Histone deacetylases in hearing loss: Current perspectives for therapy

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Abstract

Hearing loss is one of the most frequent health issues in industrialized countries. The pathogenesis and molecular mechanisms of hearing loss are still unclear. Histone deacetylases (HDACs) are emerging as key enzymes in many physiological processes, including chromatin remodeling, regulation of transcription, DNA repair, metabolism, genome stability and protein secretion. Recent studies indicated that HDACs are associated with the development and progression of hearing loss. Dysfunction of HDACs could promote the oxidative stress and aging in the inner ear. In light of considering the current stagnation in the development of therapeutic options, the need for new strategies in the treatment of hearing loss has never been so pressing. In this review, we will summarize the reported literatures for HDACs in hearing loss and discuss how HDAC family members show different performances for the possibility of process of diseases development. The possibility of pharmacological intervention on hearing loss opens a novel path in the treatment of hearing loss.

Keywords: Histone deacetylase; HDAC inhibitor; Cochlea; Inner ear; Hearing loss

Contents

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1. Introduction

Hair cells of organ of Corti are susceptible to acoustic trauma, ototoxic drugs, infections or aging, thus resulting in permanent hearing loss (Brigande and Heller, 2009; Kurabi et al., 2016; Layman et al., 2015). Unlike non-mammalian vertebrates such as birds and fish, damaged hair cells of mammals are unable to regenerate thereby resulting in permanent hearing loss (Forge et al., 1993; Warchol et al., 1993). As a consequence, it is of great importance to develop strategies to prevent hair cell impairment or promote hair cell regeneration. A possible role of histone deacetylases (HDACs) has emerged. HDACs are emerging as key enzymes in many physiological processes, including chromatin remodeling, regulation of transcription, DNA repair, metabolism, protein secretion and stem cell regulation (Haigis and Sinclair, 2010; Mohseni et al., 2013).

Most studies of HDACs have been focused on aging-relative diseases and cancer (Haigis and Sinclair, 2010; Hubbard and Sinclair, 2014; Longo and Kennedy, 2006; Park et al., 2016; Lee et al., 2016). Many HDAC inhibitors have been reported to have neuro-protection or anti-aging activities. Improved understanding of the role of HDACs and molecular mechanisms underlying their function will be beneficial to further establish the utility of HDACs as hearing impairment targets. Thus, the development of small molecules targeting HADCs as anti-hearing loss therapeutics has been a focus of recent studies. This review will focus on the functions of HADCs in hearing loss and the potential of HADC inhibitors in the treatment of hearing loss.

2. Brief overview of histone deacetylases and histone deacetylases inhibitors

2.1. Histone deacetylase family members

HDACs play essential parts in many important functions for humans, leading to condensation of the chromatin structure and repression of gene expression (Shakespear et al., 2011; Mohseni et al., 2013; Yang and Seto, 2008). Eighteen distinct histone deacetylases are grouped into classes I–IV based on sequence homology to the original yeast enzymes and domain organization (Nakagawa and Guarente, 2011; Witt et al., 2009). Classes I, II and IV (HDAC1–11) are viewed as "classical" HDACs and they bear homology to each other as well as orthology to the same *Saccharomyces cerevisiae* proteins (Rpd3 and Hda1) which catalyze deacetylation in a Zn^{2+}-dependent manner (de Ruijter et al., 2003; Yang and Seto, 2008) (Fig. 1). Class I contains HDAC1, HDAC2, HDAC3 and HDAC8, while classes IIa and IIb contain HDAC4, HDAC5, HDAC7 and HDAC9, and HDAC6 and HDAC10, respectively. Class IV only comprises HDAC11 whose phylogenetics differ from classes I and II (Joshi et al., 2013; Voelter-Mahlknecht et al., 2005). While Class III, Sirtuins (Silencing information regulator 2, Sir2), contains seven members (SIRT1–SIRT7) that bears homology to the *Saccharomyces cerevisiae* protein (Nakagawa and Guarente, 2011). In contrast to the classical HDACs, Sirtuins are nicotinamide–adenine–dinucleotide (NAD^+) dependent deacetylases and ADP-ribosyltransferases (Feige and Auwerx, 2008; Frye, 1999).

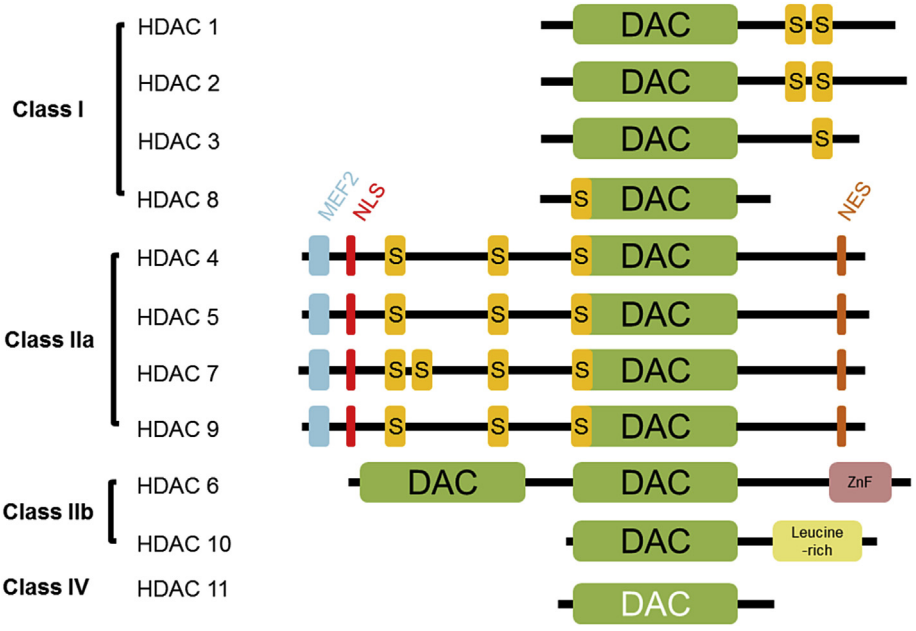

Fig. 1. Simplified depiction of the 11 human HDACs. DAC marks the conserved deacetylation domains, S are serine residues that can be phosphorylated. MEF2 denotes a binding domain for the transcription factor myocyte enhancer factor 2 and ZnF depicts a zinc finger motif. NLS and NES are nuclear localization and nuclear export sequences, respectively.
Adapted from Haberland et al. (2009) and Joshi et al. (2013).