



# The Research Status of Class II Histone Deacetylases Physiological Function

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**Abstract:** Histone deacetylases (HDACs) are proteases, The main function of HDACs are to modify the structure of chromosomes and regulate gene expression in organisms. HDACs can catalyze the deacetylation of histones, regulate histone acetylation process and deacetylation process in the nucleus, and maintain its dynamic balance state, which is closely related to the occurrence of cell apoptosis, oxidative stress and with it inflammatory response, metabolic disorders, senescence, tumor and other processes in living things. There are many members of the HDACs family, as many as 18 of which have been discovered so far, was divided into classesI, classesIIa, classesIIb, classesIII and classesIV, The structure, function, subcellular localization and expression patterns of each enzyme are not the same. In recent years, the physiological function of classII HDACs is more widespread attention by researchers, In this paper, we will review the physiological function of classII HDACs in the regulation of bone formation, skeletal muscle regulation, cardiovascular growth and formation, endothelial cells, cytoskeletal dynamics and so on, It also gives a brief description of possible research directions of HDACs, so that it can be widely used in clinical treatment and play a positive therapeutic role.

**Keywords:** Histone Deacetylases, HDAC, HAT, Dach2, RUNX2

## II类组蛋白乙酰化转移酶的生理功能研究现状

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**摘要:** 组蛋白去乙酰化酶 (histone deacetylases, HDACs) 是一类蛋白酶, 主要作用是修饰染色体的结构和调控基因表达。HDACs催化组蛋白的去乙酰化, 调控细胞核内的组蛋白乙酰化与去乙酰化, 维系其动态平衡状态, 与细胞凋亡、氧化应激等的发生以及炎症、代谢紊乱、衰老和肿瘤等诸多过程密切相关。HDACs家族成员众多, 迄今为止已被发现的家族成员共有18个, 被分为I、IIa、IIb、III类和IV类, 每一类酶的结构、功能、亚细胞定位及表达模式均不相同。近年来, II类HDACs的生理功能受到较为广泛的关注, 本文将对II类HDACs在骨形成调节、骨骼肌调控、

心血管形成与生长、内皮细胞及细胞骨架动力学等方面的生理功能做以综述,并对HDACs可能的研究方向进行简述,为其在临床治疗中能够广泛应用,并发挥积极治疗作用提供依据。

**关键词:** 组蛋白去乙酰化酶, HDAC, HAT, Dach2, RUNX2

## 1. 引言

组蛋白去乙酰化酶 (histone deacetylases, HDACs) 是一类蛋白酶,主要作用是修饰染色体的结构和调控基因表达。一般生理条件下,细胞核内的组蛋白乙酰化与去乙酰化过程由组蛋白乙酰化转移酶 (histone acetyltransferase, HAT) 和HDACs共同调控,且处于动态平衡状态[1]。一旦这个平衡被打破,将会导致细胞凋亡、氧化应激等的发生,并与炎症、代谢紊乱、衰老和肿瘤等多种疾病的发生发展有关[2, 3]。

HDACs家族成员众多,迄今为止已被发现的家族成员共有18个,被分为I、IIa、IIb和IV类,每一类酶的结构、功能、亚细胞定位及表达模式均不相同[4]。除这些熟知的HDACs外,哺乳动物基因组还编码另一组脱乙酰酶,有时也称为III类HDAC。但本文仅对HDAC家族主要成员II类HDACs的生理功能进行阐述。

## 2. IIa类HDAC的生理功能

IIa类HDAC家族成员主要包括HDAC4、5、7和9,它们具有肌细胞增强因子2 (MEF2) 和伴侣蛋白14-3-3的结合位点,是其信号响应的基础[4]。IIa类HDAC与MEF2结合后,在激酶磷酸化的作用下,MEF2被CaMK1或CaMK4激活,启动转录过程;IIa类HDAC与伴侣蛋白14-3-3结合并被运出细胞核[5-8],MEF2发生解离,与HAT p300结合,从而将MEF2从转录阻遏物转化为转录激活因子[9-13]。目前,有研究显示IIa类HDAC可能通过以下两个途径抑制转录活性,一是可能通过它的C-末端结构域募集I类HDAC来实现转录抑制作用[14];二是可能通过它的调节结构域与其他转录抑制因子相互作用,如异染色质蛋白1 (HP1) 和C-末端结合蛋白 (CTBP) 等,充当衔接子来实现转录抑制作用[15-17]。但IIa类HDAC抑制转录的确切机制还有待研究。近年来,IIa类HDACs的生理功能受到较为广泛的关注,并证明IIa类HDACs在骨骼肌调控、骨形成调节、心血管形成与生长、内皮细胞及细胞骨架动力学的调控等方面发挥重要生理调控作用。

### 2.1. HDAC9对骨骼肌的调控作用

骨骼肌纤维的收缩和代谢特性不同,反映了不同的基因表达模式[18]。慢肌纤维或I型肌纤维表现出氧化代谢,具有富含线粒体、血管发达、抗疲劳能力强等特性。相比之下,快肌纤维或II型肌纤维表现出糖酵解代谢,迅速引起收缩和易疲劳等特性。HDAC9与MEF2结合后,MEF2被激活从而促进骨骼肌中钙信号的传导,并且是慢

肌纤维表型的关键调节因子[19]。促进HDAC9的表达,建立负反馈环,从而驱动MEF2自身阻遏物的表达[20]。

同时,HDAC9也被证明可以调节运动神经对骨骼肌的支配作用。Dach2-Hdac9 (Dachshund 2-histone deacetylase 9) 信号系统所介导的肌肉活动对肌肉神经再支配具有抑制作用。Dach2和Hdac9在神经支配的肌肉中高度表达,并且由于肌肉去神经支配而表达量减少。值得注意的是,即使在失神经支配的肌肉中,残留的Dach2和Hdac9也足以抑制肌肉的神经支配[21]。缺乏HDAC9的小鼠对去神经诱导的基因表达变化极为敏感,而在骨骼肌中过表达HDAC9的小鼠对去神经支配的作用不敏感[22]。

### 2.2. HDAC4对骨形成的调控作用

HDAC4在骨的形成中起着重要作用[16]。脊椎动物骨骼中的大多数骨骼由软骨板形成,在软骨内成骨过程中,间质干细胞聚集分化为软骨细胞,而后软骨细胞增殖且软骨基质在某种信号刺激下,这些增殖的软骨细胞停止增殖并出现肥大化,分泌富含X型胶原的基质,随着它的分泌,成骨细胞、血管和其他细胞类型逐渐侵入并产生成熟骨基质[23-25]。Runt相关转录因子2 (RUNX2) 与MEF2转录因子在控制软骨细胞肥大和骨形成中具有重要作用[26]。在HDAC4缺失的情况下,这些因子的转录激活无限制性,并且导致过度的骨形成[16]。

因此,通过抑制MEF2和RUNX2在发育软骨细胞中的活性,能够延迟软骨细胞肥大,从而控制软骨内骨的骨化时间和程度。MEF2直接调节细胞外基质蛋白基因(如X型胶原蛋白1)和血管内皮生长因子 (VEGF) 的表达,这对软骨细胞发育晚期血管生成有着积极作用[27]。RUNX2基因敲除的小鼠的胫骨、股骨、桡骨与尺骨出现无法骨化的现象,软骨细胞成熟受到抑制,肥大软骨细胞分泌的X型胶原大幅减少,终末肥大软骨细胞分泌的骨桥蛋白、骨涎蛋白和基质金属蛋白酶-13未能检测出,同时成骨细胞缺乏;反之,过表达RUNX2则加速软骨细胞成熟[28]。RUNX2上的作用位点定位于Runt结构域,此区域可以结合DNA。HDAC4与RUNX2直接作用,而HDAC4上的作用位点包含了MEF2结合区,故二者结合后可以抑制RUNX2与DNA结合的能力,从而抑制RUNX2靶基因的转录[29],进而控制软骨内骨的骨化程度[30]。

### 2.3. HDAC5和9对心血管生长和功能的调控作用

单独敲除HDAC5或HDAC9的小鼠是可以存活的,而同时敲除HDAC5和9的小鼠则显示出致死性室间隔缺损和心肌壁变薄的倾向,这种情况的发生通常是由心肌细胞的生长和成熟异常所引起[15]。鉴于IIa类HDAC和

MEF2之间的相互作用以及MEF2在控制心肌细胞分化中的重要作用, 这些双重突变小鼠的发育性心脏缺陷也可能是由MEF2的超活化所引起。此外, IIa类HDAC也对参与心肌生长的许多其他转录因子的活性具有调节作用, 例如血清反应因子、心肌素和钙调蛋白结合转录激活因子2 (CAMTA2) [31]。因此, HDAC5和9的缺失可能通过降低心肌细胞基因表达的精确调控, 从而影响心肌细胞的增殖、分化和形态发育。

#### 2.4. HDAC7对内皮细胞的调控作用

在胚胎发育期间, HDAC7在形成心血管系统内层的内皮细胞中特异性表达。小鼠HDAC7缺失, 可引起内皮细胞相互作用的完整性丧失以及血管破裂和出血, 最终导致胚胎死亡, 这一过程往往伴随着基质金属蛋白酶10 (MMP10) 的上调, 扰乱了内皮细胞和平滑肌细胞相互作用。MMP10是内皮细胞分泌的内切蛋白酶, 具有降解细胞外基质的作用。在HDAC7缺失的情况下, MEF2活性升高, 导致MMP10的表达出现明显下降。同时, 金属蛋白酶抑制因子1 (TIMP1) 在内皮细胞中下调, 可能是血管内皮细胞凋亡的次要后果。然后, 当MMP10的表达增强, TIMP1表达下调时, 会进一步加剧血管破坏[17]。

HDAC7参与MMP10表达和血管完整性的控制对于各种人类疾病具有潜在的重要意义。血管渗漏导致循环衰竭是许多危及生命疾病 (例如动脉粥样硬化和动脉瘤) 的发病机理。此外, MMP和TIMP活性之间的不平衡已经显示出深刻地影响心肌梗塞后和肿瘤血管生成期间的血管完整性[32, 33]。因此, HDAC7对MEF2的抑制作用有助于维持血管的完整性。

### 3. IIb类HDAC的生理功能

IIb类HDAC家族主要包括HDAC6和HDAC10。人HDAC6主要定位在细胞质中的去乙酰化酶, 而对HDAC10的功能知之甚少[34-36]。

#### 3.1. HDAC6对细胞骨架的调控作用

HDAC6与其他HDACs不同的是含有两个N端的脱乙酰酶结构域和一个C端锌指结构域。HDAC6可以通过对组蛋白、皮层肌动蛋白、 $\alpha$ -微管蛋白和热休克蛋白90等底物的乙酰化调控而发挥作用[37, 38]。大量研究显示, HDAC6在细胞骨架动力学中具有重要生理作用[4]。

#### 3.2. HDAC10对神经母细胞瘤的调控作用

HDAC10作为神经母细胞瘤不良结果的预测因子, HDAC10抑制剂通过干扰溶酶体内稳态增加化学药物在细胞内的积累, 最终导致神经母细胞瘤细胞死亡, 以达到治疗效果。

### 4. 总结与展望

随着HDAC抑制剂在临床治疗中的应用, 越来越多的学者加入了对HDAC的生物学研究。已被鉴定的去乙

酰化组蛋白的数量正在快速增加, 但我们对蛋白质乙酰化的研究远没有那么深入。鉴于HDAC抑制剂已经在各种临床前研究中表现出积极的治疗作用。那么我们面临的另一个主要挑战是破译个体HDAC在特定疾病过程中的作用并开发特异性HDAC抑制剂。由于HDAC可影响多个靶点, 因此开发选择性阻断HDAC病理作用的抑制剂非常重要。解决这些挑战很可能会扩大治疗窗口并可能增加HDAC抑制剂在各种非肿瘤疾病状态中的临床应用。

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### 参考文献

- [1] 曾考娟, 关日辉, 赖天文, 等. HDAC6在呼吸系统疾病中的作用研究进展[J]. 海南医学, 2019, 30(07):99-913.
- [2] LEE SC, MIN HY, JUNG HJ, et al. Essential role of insulin-like growth factor 2 in resistance to resistance to histone deacetylase inhibitors [J]. *Oncogene*, 2016, 35 (42): 5515-5526.
- [3] Young PE, Youngwoo W, Jin KS, et al. Anticancer effects of a new SIRTinhibitor, MHY2256, against human breast cancer mcf-7 cells via regulation of MDM2-p53 binding[J]. *International Journal of Biological Sciences*, 2016, 12 (12): 1555-1567.
- [4] Haberland M, Montgomery RL, Olson EN. The many roles of histone deacetylases in development and physiology: implications for disease and therapy [J]. *Nature Reviews. Genetics*, 2009, 10 (1): 32-42.
- [5] Vega RB, Harrison BC, Meadows Eric, et al. Protein kinases C and D mediate agonist-dependent cardiac hypertrophy through nuclear export of histone deacetylase 5 [J]. *Mol Cell Biol*, 2004, 24 (19): 8374-8385.
- [6] McKinsey TA, Zhang CL, Lu J, et al. Signal-dependent nuclear export of a histone deacetylase regulates muscle differentiation [J]. *Nature*, 2000, 408 (6808): 106-111.
- [7] Lu J, McKinsey TA, Nicol RL, et al. Signal-dependent activation of the MEF2 transcription factor by dissociation from histone deacetylases [J]. *Proceedings of the National Academy of Sciences*, 2000, 97 (8): 4070-4075.
- [8] Passier R, Zeng H, Frey N, et al. CaM kinase signaling induces cardiac hypertrophy and activates the MEF2 transcription factor in vivo [J]. *Journal of Clinical Investigation*, 2000, 105 (10): 1395-1406.
- [9] Lu J, McKinsey TA, Zhang CL, et al. Regulation of skeletal myogenesis by association of the MEF2 transcription factor with class II histone deacetylases [J]. *Molecular Cell*, 2000, 6 (2): 233-244.

- [10] Youn HD, Grozinger CM, Liu JO. Calcium Regulates Transcriptional Repression of Myocyte Enhancer Factor 2 by Histone Deacetylase 4 [J]. *Journal of Biological Chemistry*, 2000, 275 (29): 22563-22567.
- [11] Wang AH, Bertos NR, Vezmar M, et al. HDAC4, a Human Histone Deacetylase Related to Yeast HDA1, Is a Transcriptional Corepressor [J]. *Molecular and Cellular Biology*, 1999, 19 (11): 7816-7827.
- [12] Miska EA, Karlsson C, Langley E, et al. HDAC4 deacetylase associates with and represses the MEF2 transcription factor [J]. *The EMBO Journal*, 1999, 18 (18): 5099-5107.
- [13] Sparrow DB, Miska EA, Langley E, et al. MEF-2 function is modified by a novel co-repressor, MITR [J]. *The EMBO Journal*, 1999, 18 (18): 5085-5098.
- [14] Fischle W, Dequiedt F, Hendzel MJ, et al. Enzymatic activity associated with class II HDACs is dependent on a multiprotein complex containing HDAC3 and SMRT/N-CoR [J]. *Molecular Cell*, 2002, 9 (1): 45-57.
- [15] Zhang CL, McKinsey TA, Lu JR, et al. Association of COOH-terminal-binding protein (CtBP) and MEF2-interacting transcription repressor (MITR) contributes to transcriptional repression of the MEF2 transcription factor [J]. *J Biol Chem*, 2001, 276 (1): 35-39.
- [16] Zhang CL, McKinsey TA, Olson EN. Association of class II histone deacetylases with heterochromatin protein 1: potential role for histone methylation in control of muscle differentiation [J]. *Mol Cell Biol*, 2002, 22 (20): 7302-7312.
- [17] Dressel U, Bailey PJ, Wang SC, et al. A dynamic role for HDAC7 in MEF2-mediated muscle differentiation [J]. *J Biol Chem*, 2001, 276 (20): 17007-17013.
- [18] Bassel-Duby R, Olson EN. Signaling pathways in skeletal muscle remodeling [J]. *Annu Rev Biochem*, 2006, 75 (1): 19-37.
- [19] Potthoff MJ, Wu H, Arnold MA, et al. Histone deacetylase degradation and MEF2 activation promote the formation of slow-twitch myofibers [J]. *J Clin Invest*, 2007, 117 (9): 2459-2467.
- [20] Haberland M, Arnold MA, McAnally J, et al. Regulation of HDAC9 gene expression by MEF2 establishes a negative-feedback loop in the transcriptional circuitry of muscle differentiation [J]. *Mol Cell Biol*, 2007, 27 (2): 518-525.
- [21] Macpherson Peter C D, Farshi Pershang, Goldman Daniel. Dach2-Hdac9 signaling regulates reinnervation of muscle endplates [J]. *Development (Cambridge, England)*, 2015, 142 (23): 4038-48.
- [22] Méjat, Alexandre, Ramond F, Bassel-Duby R, et al. Histone deacetylase 9 couples neuronal activity to muscle chromatin acetylation and gene expression [J]. *Nature Neuroscience*, 2005, 8 (3): 313-321.
- [23] Vega RB, Matsuda K, Oh J, et al. Histone deacetylase 4 controls chondrocyte hypertrophy during skeletogenesis [J]. *Cell*, 2004, 119 (4): 555-566.
- [24] 梁大伟, 卫小春, 魏垒. 组蛋白去乙酰化酶4在软骨与骨发育中的调控机制[J]. *中华关节外科杂志(电子版)*, 2015, 9(3):394-399.
- [25] Chang S, McKinsey TA, Zhang CL, et al. Histone deacetylases 5 and 9 govern responsiveness of the heart to a subset of stress signals and play redundant roles in heart development [J]. *Mol Cell Biol*, 2004, 24 (19): 8467-8476.
- [26] Song K, Backs J, McAnally J, et al. The transcriptional coactivator CAMTA2 stimulates cardiac growth by opposing class II histone deacetylases [J]. *Cell*, 2006, 125 (3): 453-466.
- [27] Chang S, Young BD, Li S, et al. Histone deacetylase 7 maintains vascular integrity by repressing matrix metalloproteinase 10 [J]. *Cell*, 2006, 126 (2): 321-334.
- [28] Lindsey ML, Mann DL, Entman ML, et al. Extracellular matrix remodeling following myocardial injury [J]. *Ann Med*, 2003, 35 (5): 316-326.
- [29] Jiang Y, Goldberg ID, Shi YE. Complex roles of tissue inhibitors of metalloproteinases in cancer[J]. *Oncogene*, 2002, 21(14):2245-2252.
- [30] Zhang Y, Kwon S, Yamaguchi T, et al. Mice lacking histone deacetylase 6 have hyperacetylated tubulin but are viable and develop normally [J]. *Mol Cell Biol*, 2008, 28 (5): 1688-1701.
- [31] Fiona R. Kolbinger, Emily Koeneke, Johannes Ridinger, et al. The HDAC6/8/10 inhibitor TH34 induces DNA damage-mediated cell death in human high-grade neuroblastoma cell lines[J]. *Archives of Toxicology*, 2018, 92(8): 2649-2664.
- [32] Ridinger Johannes, Koeneke Emily, Kolbinger Fiona R, et al. Dual role of HDAC10 in lysosomal exocytosis and DNA repair promotes neuroblastoma chemoresistance [J]. *Scientific reports*, 2018, 8 (1): 10039.
- [33] Tang X, Gao JS, Guan YJ, et al. Acetylation-dependent signal transduction for type I interferon receptor [J]. *Cell*, 2007, 131 (1): 93-105.
- [34] Zhang X, Yuan Z, Zhang Y, et al. HDAC6 modulates cell motility by altering the acetylation level of cortactin [J]. *Mol Cell*, 2007, 27 (2): 197-213.
- [35] Kovacs JJ, Murphy PJ, Gaillard S, et al. HDAC6 regulates Hsp90 acetylation and chaperone-dependent activation of glucocorticoid receptor [J]. *Mol Cell*, 2005, 18 (5): 601-607.
- [36] Matsuyama A, Shimazu T, Sumida Y, et al. In vivo destabilization of dynamic microtubules by HDAC6-mediated deacetylation [J]. *EMBO J*, 2002, 21 (24): 6820-6831.
- [37] Hubbert C, Guardiola A, Shao R, et al. HDAC6 is a microtubule-associated deacetylase [J]. *Nature*, 2002, 417 (6887): 455-458.
- [38] Yudibeth Sixto-López, Martiniano Bello, José Correa-Basurto. Structural and energetic basis for the inhibitory selectivity of both catalytic domains of dimeric HDAC6 [J]. *Journal of Biomolecular Structure and Dynamics*, 2019, 37 (18): 4701-4720.