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组蛋白去乙酰化酶抑制剂在心脏重构中的机制和应用

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摘要　组蛋白的乙酰化/去乙酰化参与调控多种信号通路，在影响基因表达和应激导致的心脏病理性重构中起着关键作用。应用组蛋白去乙酰化酶抑制剂能显著改善心脏重构，逆转病态纤维化及心肌细胞肥大。该文将就组蛋白去乙酰化酶抑制剂对心脏的保护作用进行综述，并简要介绍几种在改善心脏重构上具有应用前景的组蛋白去乙酰化酶抑制剂。

关键词　组蛋白乙酰化/去乙酰化；组蛋白去乙酰化酶抑制剂；心脏重构
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Mechanism and application of histone deacetylase inhibitors in cardiac remodeling

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Abstract

Acetylation/deacetylation of histones is involved in the regulation of various signaling pathways and plays a key role in modulating gene expression and stress-induced pathological remodeling of the heart. Histone deacetylase inhibitors significantly ameliorate cardiac remodeling, reverse pathological fibrosis, and attenuate cardiomyocyte hypertrophy. This review summarizes the cardioprotective effects of HDAC inhibitors and briefly introduces several compounds with therapeutic prospects for improving cardiac remodeling.

Key Words　Histone Acetylation/Deacetylation; Histone Deacetylase Inhibitors; Cardiac Remodeling

心脏重构是当今中老年群体生命健康的主要威胁之一，揭示其发病机制不仅能够加速相关心血管疾病的研究进展，同时对临床诊疗具有重要的指导意义，有助于对患者进行早期诊断、干预和优化管理，显著改善预后，避免不良结局的发生。组蛋白去乙酰化酶抑制剂(histone deacetylase inhibitors，HDACI)具有多种生物学作用，如抗炎、抗氧化、抗凋亡、抗纤维化等，过去的诸多实验[1-2]均可证实HDACI能在一定程度上逆转心脏重构，改善心功能障碍。

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1　心脏重构与组蛋白乙酰化/去乙酰化

在心肌梗死和慢性高血压等病理性应激作用下，心脏会经历一个以心肌细胞肥大和间质纤维化为典型特征的重构过程，称为心脏重构[3]。心脏重构是慢性心力衰竭（chronic heart failure，CHF）的必经阶段，是指在内源性和/或外源性因素作用下心脏结构和功能发生改变[4-5]。组蛋白修饰作为表观遗传学的重要组成部分，已被证实在心脏重构过程中发挥关键作用。组蛋白在相关酶作用下发生甲基化、乙酰化、磷酸化、腺苷酸化、泛素化、糖基化等修饰的过程被称为组蛋白修饰。而组蛋白去乙酰化酶（histone deacetylases，HDACs）是调控组蛋白修饰的重要途径。组蛋白的乙酰化与去乙酰化分别由组蛋白乙酰转移酶（histone acetyltransferases，HATs）和组蛋白去乙酰化酶介导进行。HATs 和 HDACs 能够通过将乙酰基转移或去除到赖氨酸残基上来拮抗调控组蛋白尾部的乙酰化水平[6-7]。心脏重构的发生涉及基因的重编程，乙酰化调控在此过程中能够传递信号，诱导下游基因重编码，进而影响心脏的结构和功能[8]。目前尚缺乏针对心脏重构的特异性治疗手段，组蛋白乙酰化修饰的这一可逆调控作用为改善病理性心脏重构提供了理论基础。

2　组蛋白去乙酰化酶的分类与功能

迄今为止，已鉴定出 18 种哺乳动物的组蛋白去乙酰化酶，并将其分为 4 大类：Ⅰ类 HDACs（HDAC1、2、3 和 8），Ⅱ类 HDACs（HDAC4、5、6、7、9 和 10），Ⅲ类 HDACs 又称 SIRT（Sirtuin，SIRT）家族和Ⅳ类 HDACs（HDAC11）[9-10]。这 4 类 HDACs 都在转录调控和蛋白质修饰中发挥重要作用（见表 1）。HDACs 活性越高，组蛋白与 DNA 的结合越紧密，转录蛋白难以与高度螺旋化的 DNA 结合，基因转录受到抑制[11]。HDACs 还能催化多种非组蛋白中乙酰基的去除，包括转录因子，如 E2F、p53、c-Myc 和 NF-κB，以及调节细胞稳态的信号介质，如 Stat3、Smad7 等，从而在调节转录和蛋白质翻译后修饰（post-translational modification，PTM）中发挥作用[12]。然而，在对心脏的调控方面，不同类别的 HDAC 表现出了不同的相关性，Ⅰ类和Ⅱa 类 HDACs 与心脏重构的发生最为紧密，二者分别通过不同的分子途径来促进或抑制心肌肥厚。Ⅱb 类参与心脏疾病中的微管蛋白乙酰化、细胞运动的调控等。Ⅲ类 HDACs 可能对心脏及血管损伤具有保护作用。Ⅳ类 HDACs 目前研究较少，在细胞的增殖、分化过程中发挥作用[20-22]。以上 4 类 HDACs 在功能上具有差异，可能与它们的结构、分布及作用方式的复杂性有关。Ⅰ、Ⅱ和Ⅳ类 HDACs 是锌依赖性酶，Ⅲ类 HDACs 则需要烟酰胺腺嘌呤二核苷酸（NAD^+）来维持其酶活性[13]。Ⅰ类 HDACs，特别是 HDAC1、2、3 是典型的表观遗传调控蛋白，这些 HDACs 通常以 Sin3、NuRD（nucleosome remodelling and deacetylation）、CoREST（co-repressor for element-1-silencing transcription factor）等多蛋白复合物的形式存在于细胞核，由转录因子募集到基因调控元件中，从而影响表达[14]。Ⅱa 类 HDACs 的氨基端存在调控决定域，能与多种转录因子和辅助因子结合[15]，Ⅱb 类则具有两个去乙酰化酶结构域[13]。

表 1　哺乳动物 HDACs 的分类及其对心脏重构的影响

分类	成员	对心脏的作用
Ⅰ类	HDAC1、2、3 和 8	主要参与心脏细胞生长增殖和病理性重构过程。HDAC1 和 2 能够抑制心脏保护和抗肥厚基因的表达[16-17]，HDAC8 促进心肌肥大和纤维化[18]
Ⅱ类	Ⅱa 类：HDAC4、5、7 和 9；Ⅱb 类：HDAC6 和 10	Ⅱa 类参与心脏发育和病理性重构，通过抑制 MEF2 对抗心肌肥厚[19]；Ⅱb 类中的 HDAC6 参与心脏疾病中的微管蛋白乙酰化、肌原纤维僵硬和骨骼肌萎缩[20-22]
Ⅲ类/SIRT 家族	SIRT1～7	在心脏稳态中起作用，能通过降低氧化应激减轻血管紧张素Ⅱ诱导的心脏肥厚[23-25]
Ⅳ类	HDAC11	能够通过与转录因子相互作用调控包含细胞周期在内的多种生物过程

3　组蛋白去乙酰化酶抑制剂（HDACI）改善心脏重构的机制

近年来，较低且耐受剂量良好的 HDACI 在对抗心脏重构方面产生了良好的效果，已具备重要的临床价值[26-28]。HDACI 可改善糖尿病性心肌病小鼠模型的心脏功能，减少心脏间质胶原及超氧化物的产生，减轻心室肥厚并抑制心脏重构[29]。HDACI 在大鼠和小鼠的心脏舒张功能障碍模型中能够通过增强心肌肌原纤维的舒张特性来改善心脏的舒张功能[30]。同样，在心脏舒张功能障碍的猫模型中的研究[31]显示，泛组蛋白去乙酰化酶抑制剂 Vorino-

stat可逆转压力过载引起的左心室肥厚(left ventricular hypertrophy,LVH),减轻左室扩张,改善左室收缩和舒张功能。然而,由于HDAC种类的多样性和功能的复杂性,使用泛抑制剂显然会削弱某些HDACs的心脏保护作用,例如Ⅱa类HDACs可以通过抑制肌细胞增强因子2(myocyte enhancer factor 2,MEF2)的活性抑制心肌肥厚[19],对抗心力衰竭及心脏重构的发展。由此可见,与"全面覆盖式"的泛组蛋白去乙酰化酶抑制剂相比,"定点突破式"的选择性抑制剂具有更高的临床价值及应用前景。在4类HDACs中,Ⅰ类HDACs对心脏病理性重构的贡献最为突出,随着疾病的进程其在心脏细胞内的含量也会出现相应的变化。Ⅰ类HDACs亚型HDAC1/2在动物心脏成纤维细胞中的表达会随着慢性心力衰竭的进展而上调,使用Ⅰ类HDACI则可以逆转肌成纤维细胞的活化[32]。HDAC2/3抑制剂曲古菌素A(trichostatin A,TSA)在小鼠压力负荷诱导的心脏重构模型中能够减轻先前存在的心肌肥厚和左心室功能障碍[33],这些现象均表明使用Ⅰ类HDACI能够改善心脏重构,维持心脏正常结构及功能。

HDACI抑制心脏肥厚和纤维化的作用与基因表达的变化有关[34-36]。HDACI能够控制心脏激酶信号网络。例如:Ⅰ类HDACs抑制剂能通过上调DUSP5抑制细胞外信号调节激酶(extracellular signal regulated kinase,ERK),从而抑制心肌细胞肥大[37]。Ⅱ类HDACs抑制剂能减少心肌细胞中NADPH氧化酶-2(NADPH-oxidase 2)的表达,减轻损失及炎症反应。Ⅲ类HDACI可通过上调SOD2表达抑制血管紧张素Ⅱ诱导的心肌肥厚及线粒体中活性氧(reactive oxygen species,ROS)的产生[23-25]。HDACI还能有效对抗心脏纤维化。在$CD90^+$成纤维细胞中,HDACI降低了Akt的磷酸化,Akt是一个重要的内皮-间质转化参与者。因此,逆转内皮-间质转化诱导的心脏成纤维细胞纤维化通路是HDACI一种可能的抗纤维化机制[38-39]。除了逆转成纤维细胞的诱导形成之外,调节成纤维细胞的增殖和凋亡可能是HDACI影响纤维化的另一可能机制。在HDACI的作用下,细胞数量减少,p21和p53基因表达升高,活化形式的Caspase-3蛋白上调[32]。p21参与细胞生长阻滞,p53则诱导细胞凋亡。在心脏中,p53可以调节心脏转录组的变化,影响心脏的兴奋-收缩耦联、线粒体生物发生和氧化磷酸化[40-41]。HDACI介导的心源性转录程序激活,在很大程度上需要细胞内乙酰化p53蛋白的积累[42]。同样,p53的稳定性及其转录活性已被证明可通过HDACs直接去乙酰化赖氨酸残基372/382(K373/382)而受到调控[43]。另一方面,应用抑制剂治疗后,慢性心力衰竭的心脏心肌凋亡水平并未增加,这表明HDACI的使用不会诱导心肌细胞过度死亡[32]。HDACI除了通过上述途径作用于心脏之外,染色质和非染色质对蛋白质活性的直接影响也被认为是其对抗病理性左室肥大的重要机制之一[34]。

值得注意的是,虽然包括心脏重构在内的多种心血管疾病都有望成为HDAC抑制剂的新适应证,但使用HDACI可能会加重血管钙化[26]。这是否会影响HDACI类药物的安全性还有待进一步研究。

4 总结

由于组蛋白去乙酰化酶对心脏重构的发生发展起着重要作用,HDACI成为心脏疾病领域一种研究前景广阔的药物。但通过上述总结可以看出HDACI通常不具备组织、器官特异性,其作用范围较广,且组蛋白乙酰化/去乙酰化作为正常的生物学过程,不应该被单一地抑制,因此选择性HDACI的研发越来越受到关注与重视(4种常见选择性HDACI总结如下,见表2)。同时,心脏重构的发展受遗传、环境等多种因素影响,处于动态变化当中,是一个长期、复杂的过程,组蛋白的乙酰化/去乙酰化修饰对它的解释作用有限。这就要求我们熟悉心脏重构的病理生理基础,对HDACs的作用机制进行更深入的探索,为临床治疗心脏重构提供更为有效的新方案,使广大患者获益。

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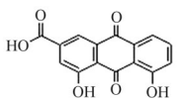
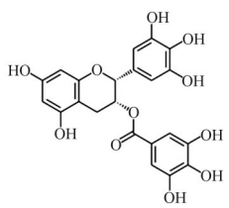
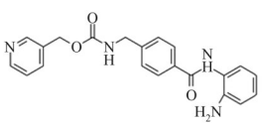
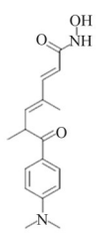
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表 2　四种选择性 HDACI 的结构、靶点及其改善心脏重构的功能

名称	结构	作用位点	对心脏的作用
大黄酸（Rhein）		Ⅰ/Ⅱ类 HDACs	抑制胶原收缩，在心脏重构中具有抗纤维化特性[44]
表没食子茶素没食子酸酯（epigallocatechin gallate，EGCG）		HDAC1，HDAC5	减轻小鼠压力过负荷引起的心脏重构，逆转心脏扩张，减少间质纤维化程度和胶原沉积；调节心肌肌钙蛋白 I 的表达[45-47]
恩替诺特（Entinostat）		HDAC1，HDAC2	提高心脏间质细胞的修复功能，在慢性心力衰竭模型中有效减弱心肌重构，改善左室收缩能力[48]
曲古菌素 A（trichostatin A，TSA）		HDAC1，HDAC2，HDAC3	减轻小鼠压力过负荷引起的心脏重构，逆转心肌肥厚，改善左室功能[33]

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