· 综述 ·

组蛋白去乙酰化酶在神经退行性疾病发病机制中的研究进展

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【摘要】 组蛋白乙酰化是表观遗传调控的主要机制之一，由组蛋白乙酰转移酶（histone acetyltransferases，HATs）和组蛋白去乙酰化酶（histone deacetylases，HDACs）共同调控。近年研究发现，HDACs 通过调节错误折叠蛋白的异常积聚、线粒体功能、氧化应激等，与帕金森病（Parkinson's disease，PD）、阿尔茨海默病（Alzheimer's disease，AD）、亨廷顿病（Huntington's disease，HD）等多种神经退行性疾病（neurodegenerative diseases，NDs）的发病机制密切相关。在 NDs 中，组蛋白乙酰化稳态被破坏，向低乙酰化方向转移。越来越多的研究提出了组蛋白去乙酰化酶抑制剂（histone deacetylase inhibitor，HDACi）可用于治疗某些神经退行性疾病的可能性。本文对 HADCs 在 NDs 发病机制中的研究进展进行综述。

【关键词】 组蛋白去乙酰化酶；HDACs；神经退行性疾病；帕金森病；阿尔茨海默病
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Histone deacetylases in pathogenesis of neurodegenerative diseases

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【Abstract】 Histone acetylation is one of the main mechanisms of epigenetic regulation, co-regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs can deacetylate lysine residues of histones and non-histone proteins, regulating almost all biological processes in cells. Many experimental models have confirmed that HDACs are closely related with the pathogenesis of neurodegenerative diseases (NDs) through regulation for deposition of aggregate-prone proteins, mitochondrial function, oxidative stress, etc. In NDs, histone acetylation homeostasis is disrupted, shifting towards hypoacetylation. Recently, a growing number of studies have raised the possibility that histone deacetylase inhibitor (HDACi) could be used to treat some DAs. In this review, we discuss the latest research progress on the comprehensive role of HDACs in pathogenesis of NDs and the possible therapeutic target for treating some NDs.

【Key words】 HDACs; Histone deacetylase; Neurodegenerative diseases; Parkinson's disease; Alzheimer's disease

乙酰化和去乙酰化作为一种重要的蛋白质翻译后修饰，对蛋白质的结构和功能具有重要的调控作用。该过程受 HATs 和 HDACs 的调控。HDACs 通过使组蛋白去乙酰化，使之与 DNA 紧密结合，使染色质结构更加致密，从而抑制转录过程。早期研究表明，HDACi 可通过调节细胞凋亡和分化而作为抗癌药物[1]。

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乙酰化调控的底物几乎参与细胞的所有生物学过程，如细胞周期、能量代谢、细胞骨架动力学等。在神经退行性疾病中，乙酰化平衡严重受损，向低乙酰化转移[2]。人们越来越认识到HDACi具有神经保护作用，并有潜力治疗神经系统疾病[3]，如帕金森病、阿尔茨海默病、肌萎缩性侧索硬化症（amyotrophic lateral sclerosis，ALS）及亨廷顿病等。

在哺乳动物细胞中共发现18种HDACs，可分为四类：Ⅰ类HDACs（HDAC 1，2，3，8）、Ⅱa类HDACs（HDAC 4，5，7，9）、Ⅱa类HADCs（6，10）、Ⅲ类HADCs（SIRT 1 ~7）、Ⅳ类HADCs（HDAC11）[4]。Ⅰ类HDACs主要存在于细胞核中，具有最高的去乙酰化酶活性[5]；Ⅱa类HDACs活性远低于第Ⅰ类，但其含有进、出细胞核的特定序列，其在核膜两侧的分布与活性受其结合蛋白的调控[6]；HDAC11是Ⅳ类HDACs的唯一代表，现对其研究甚少。Ⅲ类HDACs也称sirtuins，包括SIRT（sirtuins）1~7，其中SIRT1~3具有较高去乙酰化活性，SIRT1与SIRT2在细胞核和细胞质中均有表达，但SIRT1主要存在于细胞核中，后者主要存在于细胞质中；SIRT3作为主要的线粒体蛋白，也可存在于细胞核中。

1 HDACs影响神经元存活及突触可塑性

多种HDACs具有神经保护或毒性作用。Ⅰ类HADCs抑制剂丙戊酸（valproic acid，VPA）可能通过减少炎症反应与凋亡，以及激活脑源性神经营养因子（brain-derived neurotrophic factor，BDNF）/蛋白酪氨酸激酶受体B（tyrosine kinase receptor B，TrkB）信号通路[7]，在脓毒症相关性脑病（sepsis associated encephalopathy，SAE）小鼠模型中发挥神经保护作用。大脑中过表达HDAC2和HDAC3会干扰记忆和突触的形成[8-9]。以HDAC2和BDNF为中心的正反馈回路，可介导组蛋白乙酰化和基因的程序性表达，是突触可塑性和记忆的基础[10]。大脑中HDAC4的选择性缺失会导致海马依赖的学习和记忆障碍，以及长期的突触可塑性[11]。在共济失调毛细血管扩张症突变基因（ataxia-telangiectasia mutant gene，ATM）缺失的情况下，蛋白磷酸酶2A（protein phosphatase 2A，PP2A）活性增强导致HDAC4去磷酸化和核积聚，进而调节神经元基因表达，促进神经退行性病变[12]。HDAC6在神经元氧化应激损伤[13]的下游信号通路中发挥作用，其选择性抑制剂可以促进轴突再生，保护神经元。HDAC9抑制乙酰胆碱（acetylcholine，ACh）的生物合成，抑制HDAC9可促进ACh的合成和神经元树突的生长[14-15]。组蛋白去乙酰化被认为是记忆形成过程中染色质可塑性调节的关键过程[16]。Sirtuins通路可调节与衰老相关的神经退行性疾病的基础代谢。

2 HDACs与错误折叠蛋白的异常积聚和自噬

大多数NDs主要的病理改变是错误折叠蛋白在神经元的异常积累，后者对神经元产生毒性作用。路易小体的形成是PD的特征性病理特征，其含有α-突触核蛋白、泛素连接酶（parkin）、泛素等成分，并且血清中α-突触核蛋白可能与PD患者发生认知障碍相关[17]。而错误折叠的α-突触核蛋白在神经元之间的复制和传递，进一步导致神经元功能障碍和凋亡[18]。Tau蛋白过度磷酸化可导致微管损伤，并与β-淀粉样蛋白（amyloid β-protein，Aβ）相互作用，促进Aβ聚集，在AD的发生发展中发挥重要作用[19]。在HD患者中，突变亨廷顿蛋白（mutated Huntington's protein，mHTT）的形成与聚集会损害中枢神经系统，导致舞蹈动作、认知障碍和痴呆。过度表达人类突变型铜-锌超氧化物歧化酶1（superoxide dismutase 1，SOD1）G93A的转基因ALS小鼠在脊髓中表现出特异性的自噬受体聚集和逆行溶酶体转运障碍，导致自噬障碍[20-21]。多种细胞质中的组蛋白去乙酰化酶参与调控异常积累蛋白的降解。

SIRT2和HDAC6作用于α-微管蛋白的不同亚基，诱导微管不稳定性和解聚[22]，对受应激和损伤后细胞的生存和再生不利，可能是细胞清除易聚集蛋白的重要调节因子。同时，有报道称抑制SIRT2可以增加肿瘤抑制因子p53的乙酰化，从而阻断细胞质中p53对自噬[23]的抑制作用。AD患者大脑中HDAC6蛋白水平显著升高[24]。在PD患者的细胞模型中，选择性抑制SIRT2增加微管蛋白乙酰化水平，改善微管介导的转运[25]。此外，SIRT2抑制剂AK-7可减轻纹状体和黑质多巴胺能神经元的损伤，改善运动功能。GUEDES-DIAS等[26]研究发现，HDAC6抑制剂Tubastatin A，可增加HD患者的自噬流，保护神经元，是治疗HD的潜在靶点。

虽然大多数研究表明HDACi具有神经保护作用，但仍有一些相反的结论。最近的研究表明，ATP13A2基因突变通过增加皮质肌动蛋白的乙酰化，促进HDAC6向溶酶体募集，导致自噬小体与溶酶体融合受损[27]，进而导致异常蛋白聚集。HDAC6可介导泛素化蛋白沿微管中心逆行转运，或通过促进热休克蛋白90（heat shock protein 90，HSP90）[28]的

去乙酰化，在错误折叠蛋白的折叠和降解中发挥重要作用。SIRTl 可使热休克因子 1（heat shock transcriptional factor 1，HSF1）去乙酰化，从而提高分子伴侣——热休克蛋白 70（heat shock protein 70，HSP70）的转录水平，进一步增加α-突触核蛋白聚集体的降解[29]。在 PD 模型中，白藜芦醇可直接激活 SIRT1，或可能通过一磷酸腺苷（adenosine monophosphate，AMP）依赖的蛋白激酶（AMP-activated protein kinase，AMPK）/SIRT1 通路[30]和直接乙酰化微管相关蛋白 1 轻链 3（microtubule-associated protein 1 light chain 3，LC3）[31]，有效诱导和促进自噬流的发生，清除易形成聚集物的病理性蛋白。HDAC4 属于Ⅱa 类 HDACs，可以在细胞质和细胞核之间移动，其定位于细胞核时，可使组蛋白去乙酰化，抑制基因转录和翻译[32]。在葡萄糖脑苷脂酶（glucocerebrosidase，GBA）过表达的多巴胺神经元模型中，自噬小体和溶酶体之间的融合障碍导致α-突触核蛋白聚集增加，这与多巴胺能神经元中 HDAC4 核定位增加和基因表达抑制有关，对自噬的干扰可以被 HDAC4 抑制剂[33]纠正。

3 HDACs 与线粒体功能及氧化应激

NDs 的发病机制涉及多种因素引起的线粒体功能障碍，后者最终导致神经元变性、凋亡或坏死[34-35]。PD 大鼠中脑黑质中线粒体复合体 I 和泛素酮的活性显著降低[36]。氧化磷酸化（oxidative phosphorylation，OXPHOS）蛋白干扰线粒体能量代谢，与 AD 模型小鼠淀粉样蛋白相关的认知障碍有关[37-38]。Tau 和 Aβ可通过淀粉样蛋白结合醇脱氢酶（amyloid binds to alcohol dehydrogenase，ABAD）[39]等导致线粒体功能障碍。维持线粒体蛋白质平衡可以延缓 AD 等淀粉样蛋白毒性疾病的发生[40]。ALS 患者线粒体形态存在明显缺陷，骨骼肌线粒体呼吸链复合体活性也降低[41]。

Sirtuins 在大鼠 PD 模型中具有神经保护或毒性作用，可能是通过调节线粒体生物发生和氧化应激来实现的。SIRT1 可上调 PD 细胞模型在氧化应激下过氧化物酶体增殖物激活受体γ辅激活因子 1α（peroxlsome proliferator-activated receptor-γ coactlvator-1α，PGC-1α）的转录水平，减轻线粒体功能损伤[42]。SIRT2 在应激条件下激活核因子κB（nuclear factor kappa-B，NF-κB）的转录，促进炎症和神经元细胞凋亡[43]。AK-7 选择性抑制 SIRT2 可显著减少衰老大鼠纹状体中多巴胺能神经元的缺失，改善鱼藤酮诱导的行为异常[44]。然而，有研究显示了相反的结果，在人神经母细胞瘤细胞中，SIRT2 可增加 FOXO3a（forkhead box O3a）的靶点（如锰超氧化物歧化酶）的表达，抵消活性氧（reactive oxygen species，ROS）的有害影响，保护细胞免受氧化应激损伤[45]。SIRT3 可通过 SIRT3-FOXO3 通路作用于 PINK1（PTEN induced putative kinase 1）蛋白[46]，或通过促进 Parkin 蛋白与电压依赖性阴离子通道 1（voltage-dependent anion channel 1，VDAC1）的相互作用激活缺氧诱导的线粒体自噬。抑制人类胶质瘤细胞中 SIRT3 的表达干扰了缺氧诱导的 LC3 在线粒体上的定位[47]。抑制 SIRT3 还能通过增加 p53-Parkin 结合，阻断 Parkin 的线粒体转位[48]。

AD 的发生也与氧化应激有关，抗氧化治疗可抑制神经元退行性病变，防止 AD 进展至晚期[49-50]。氧化铈纳米颗粒（CeNPs）在体外氧化应激模型中显示了过氧化氢酶和氧化酶的活性，提高了超氧化物歧化酶 1（superoxide dismutase 1，SOD1）转基因小鼠的存活率[51]。SIRT1 可通过调节 PGC-1α去乙酰化，延缓 AD 的进展[52-53]。SIRT3 可激活 FOXO3、锰超氧化物歧化酶（manganese superoxide dismutase，MnSOD）、过氧化氢酶（catalase，CAT）等多种抗氧化因子，预防或延缓氧化应激引起的损伤[54-55]。SIRT3 还可能通过清除线粒体中的自由基，对神经元起保护作用[56]。SIRT3 的过表达促进了 mHTT 细胞的抗氧化作用，增强线粒体功能，并在 HD 中发挥神经保护作用[57]。

4 结论与展望

近年来，神经退行性疾病的发病率逐渐升高，引起人们的广泛关注。然而，这些疾病的发病机制尚不清楚，也缺乏治疗相关疾病的有效药物。越来越多的实验证实，表观遗传学参与调控神经退行性疾病的发病机制，其中组蛋白修饰备受关注[58]。HDACs 已被证明具有神经毒性或神经保护作用[59]。虽然 HDACs 活性的降低可以增强突触功能和记忆能力，但体内其抑制剂辛二酰苯胺异羟肟酸（suberoylanilide hydroxamic acid，SAHA）治疗并不能挽救 AD 小鼠模型的记忆缺陷[60]。从治疗的角度来看，研究特异性/选择性 HDACi 将是有益的。因此，有必要进一步了解每种 HDAC 在神经退行性疾病发展中的作用。未来需要进行更多有针对性的研究，积累更全面的研究数据，从而对神经退行性疾病的发病机制有新的认识，为特异性药物的开发和应用提供新的思路。

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