· 综述 ·

# 组蛋白去乙酰化酶在抑郁障碍中的研究进展

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【摘要】 抑郁障碍由于病因不明及药物治疗的有限性, 导致其在医疗、社会及经济上成为一个棘手问题。表观遗传调控在神经系统发育及精神疾病中起着重要作用, 近年来许多动物应激模型证实在大脑特定区域存在某些组蛋白去乙酰化酶表达异常, 从而产生抑郁样行为。组蛋白去乙酰化酶抑制剂作为表观遗传调控的药物能够调节基因转录, 被证实能产生一定的抗抑郁效应。本文就组蛋白去乙酰化酶及其抑制剂在抑郁障碍中的研究进行综述, 旨在为治疗抑郁障碍提供更广阔的选择。

【关键词】 抑郁障碍; 组蛋白去乙酰化酶; 应激模型; 抗抑郁药

**Research progress of histone deacetylase in depressive disorder** *Ren Shaoyu, Liu Jiaying*

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【Abstract】 Depressive disorder is a serious medical, public and economic problem because of its unknown etiology and limitation of drug treatment. Epigenetic regulation plays an important role both in neural development and psychiatric disorders. In recent years many stress animal models identified abnormal expression of some histone deacetylases in particular brain regions which lead to depression-like behaviors. Histone deacetylase inhibitors, as a kind of epigenetic regulatory drugs, can regulate gene transcription, thus have antidepressant effect. This paper reviews the research progress of histone deacetylase and its inhibitors in depressive disorder and provides a wider range of options for the treatment of depressive disorder.

【Key words】 Depressive disorder; Histone deacetylases (HDAC); Stress model; Antidepressant

抑郁障碍是一种常见的精神疾病, 表现为心境低落、兴趣缺失、精力减少, 是致残的主要原因之一, 同时也是增加全因死亡率的一个主要因素[1]。由于抑郁障碍病因复杂, 抗抑郁治疗目前也面临着许多挑战[2]。虽然目前临床中有许多抗抑郁药物, 如选择性5-羟色胺再摄取抑制剂(SSRIs)、5-羟色胺/去甲肾上腺素再摄取抑制剂(SNRIs)等, 但有相当一部分人群对于这些药物不能表现出很好的治疗效果[3], 甚至对于重度抑郁患者, 仅有1/3在初始治疗后达到缓解[4]。研究发现, 一些精神疾病可能存在大脑某些特殊区域的表观遗传学改变[5-8]。组蛋白修饰是表观遗传调控中的一个主要机制, 组蛋白乙酰化及去乙酰化在神经精神疾病中是当前研究热点之一[9-11]。组蛋白乙酰化促进转录发生, 而组蛋白去乙酰化抑制转录发生, 这一调节过程是由组蛋白乙酰基转移酶(HAT)和组蛋白去乙酰化酶(HDAC)共同决定[12]。本文针对HDAC及HDAC抑制剂(HDACi)在抑郁障碍中的研究进展进行综述。

一、HDAC的结构与分类

根据序列同源性和结构组成, HDAC分为四类。Ⅰ类HDAC包括HDAC1、HDAC2、HDAC3、HDAC8, 位于细胞核, 在许多组织中均有表达并和基因表达有关。Ⅱ类HDAC与细胞分化有关, 其中Ⅱa类HDAC包括HDAC4、HDAC5、HDAC7、HDAC9, 位于细胞质和细胞核; Ⅱb类HDAC包括HDAC6、HDAC10, 位于细胞质。Ⅲ类HDAC包括沉默信息调节因子(SIRT)1~SIRT7, 与其他类HDAC不同的是, 这一类依赖于NAD+。Ⅳ类HDAC包括HDAC11, 其结构与其他类HDAC亦不相同[13]。

二、HDAC的生理作用及HDACi的治疗作用

HDAC能够将组蛋白尾的乙酰基去除, 使得带正电荷的组蛋白和带负电荷的DNA 结合更为紧密,

进一步抑制转录发生，因此在细胞增殖、细胞迁移、细胞凋亡和血管生成中有着重要作用[14]。其中，HDAC1、HDAC2具有高度的序列同源性，并且在中枢神经系统发育中发挥不同的功能[15]，而SIRTs具有抗神经退行性变的潜能[16]。

HDACi是一组具有不同种类、能提高细胞核内和细胞质蛋白转录后赖氨酸残端乙酰化水平的药物，并能改变这些蛋白的活性和功能。目前，许多HDACi被合成或从自然产物中分离出来，共分为四类，即异羟肟酸[如辛二酰苯胺异羟肟酸(SAHA)、曲古菌素A]、环四肽(如trapoxin B、罗米地辛)、苯甲酰胺(如恩替诺特、CI-994)和脂肪族/短链脂肪酸(如丙戊酸)[17]。不同的HDACi具有不同的靶向特异性、药物代谢动力学特性和实验用途、临床用途[18]。自20世纪90年代HDACi的研究便已开展，且在动物模型及患者中可表现为抗肿瘤生长特性[19]。

三、HDAC在抑郁障碍患者及动物模型中的研究

HDAC在大脑的表达具有细胞和区域特异性，HDAC10主要在一些神经元中表达，而HDAC2、3、4、5、11在一些少突胶质细胞中表达，HDAC1、2在星形胶质细胞和神经元中均有表达[20-21]。研究发现，重度抑郁障碍患者中的背外侧前皮质HDAC4、5、6、8均升高，扣带回和外周血白细胞HDAC2也升高[22]。但HDAC的相关研究仍以动物模型为主，许多研究证据发现，重度抑郁障碍和抑郁样行为的动物模型中的HDACs表达存在异常[8, 23-27]。对于这些抑郁动物模型，无论全身应用或是局部应用HDACi，都会表现出抗抑郁效应[3]。

在抑郁障碍中，关于HDAC2的研究最多。Hobara等[28]发现，当重度抑郁障碍患者处于抑郁期(而非缓解期)时，其外周血白细胞中的HDAC2 mRNA水平升高。同样，在一项人体尸检研究中发现，重度抑郁障碍患者背外侧前额叶皮层的HDAC2水平较对照组明显升高[29]。在许多建立抑郁大鼠和小鼠模型的研究中，HDAC2也出现不同水平的升高。在慢性不可预见性压力小鼠模型中，扣带回皮质HDAC2活动水平明显升高[30]。Zheng等[31]建立了妊娠小鼠压力模型，值得注意的是，其子鼠也表现出抑郁样行为，同时伴随着HDAC2水平升高和H3K14乙酰化水平降低。在慢性超温和压力小鼠模型中，其伏隔核中的HDAC2 mRNA水平升高，且这一改变能被丙咪嗪逆转[32]。在酒精依赖大鼠抑郁模型中，海马区HDAC2水平升高，乙酰化H3K9水平降低，应用SAHA处理后这一改变也能恢复正常[33-34]。与以上结论不同的是，也有研究发现在慢性应激小鼠的海马HDAC2水平出现降低[35]。

HDAC5也被发现与抑郁障碍存在一定的相关性。Hobara等[28]也发现，在处于抑郁期而非缓解期的重度抑郁障碍患者中，外周血白细胞中HDAC5 mRNA水平升高。一般而言，HDAC5在抑郁动物模型研究中也会存在异常升高。在慢性可变应激小鼠模型中，其海马CA1区的HDAC5表达上调[36]；而在慢性不可预知压力小鼠模型中，除了HDAC5表达上调外，还伴随H3K14、H3K23、H4K16的乙酰化水平增加[37]。获得性无助小鼠模型也表现出HDAC5表达增加，在其腹腔内注射HDACi后抑郁样症状减轻，同时伴随脑源性神经营养因子(BDNF)的下降，这可能与HDAC5和BDNF的4号外显子启动子结合增加有关。同样，敲除HDAC5亦能够减轻模型小鼠的抑郁样症状[38]。相反，有研究发现，在社会失败应激小鼠模型中，其伏隔核HDAC5表达水平降低，应用丙咪嗪治疗后HDAC5表达水平上调[32]。

HDAC6抑制剂在突触形成过程中能增加一些特定蛋白的赖氨酸残基乙酰化水平，从而证明了HDAC6在心境障碍中的调节作用[39-40]。在双相情感障碍患者中，HDAC4仅在抑郁期表达增加，HDAC6、HDAC8在抑郁期和缓解期表达均减少，且这些患者无论接受哪种抗抑郁药物治疗，如三环类、四环类、SSRIs、SNRIs或心境稳定剂(如锂盐、丙戊酸)，其HDAC表达水平均无明显改变[28]。对创伤性脑外伤小鼠过表达海马区的HDAC4能改善焦虑、抑郁样行为和记忆功能[11]。

在重度抑郁障碍和双相障碍患者中观察到在抑郁期均具有SIRTs(尤其是SIRT1、2、6)的下降，并且在缓解期能恢复正常，这表明SIRT1、2、6可作为心境障碍所处阶段的潜在标志[41]。在小鼠模型中，慢性压力能够减少海马SIRT1的活性，应用药物学方法或基因抑制海马SIRT1功能则导致抑郁样行为增多。相反，增强SIRT1活性能够阻断抑郁的发展[42]。

四、HDACi在抑郁障碍动物模型中的研究

HDACi在精神疾病及神经病学领域作为心境稳定剂和抗癫痫药也有很长的研究历史[43]。近几年，HDACi在抑郁障碍动物模型研究中较为广泛[26, 33]。许多HDACi除了通过抑制HDAC表现抗抑郁作用外，还有许多复杂机制产生抗抑郁效应，其中包括BDNF、磷酸化cAMP反应元件结合蛋白(CREB)的

活化等。

丙戊酸(VPA)是一种短链脂肪酸类HDACi，其作为一种抗惊厥药物，在心境障碍中也被作为心境稳定剂使用[44]，是研究药物常用的HDACi。在强迫游泳实验的SD大鼠中，显微注射VPA到腹外侧额眶部皮质能够调节抑郁模型大鼠的记忆过程并且诱导抗抑郁效应[45]。在慢性不可预知压力模型中，通过VPA灌胃能够导致模型动物焦虑和抑郁样症状减少，同时伴有肾上腺皮质酮降低、酪氨酸羟化酶减低及海马BDNF表达水平升高[8, 46]。VPA之所以能够改善快感缺乏和压力应激，可能与伏隔核HDAC3减少和MC4R基因表达增加有关[47]。VPA除了抑制HDAC外，其抗抑郁作用还与磷脂酰肌醇3-羟激酶(PI3K)和雷帕霉素靶蛋白(mTOR)活化有关[48]。另外，VPA对神经元细胞膜的$K^+$通道也有直接效应，通过阻断$Ca^{2+}$、$Na^+$、电压门控$K^+$通道阻止N-甲基-D-天冬氨酸(NMDA)调节的神经元激活[49]。

丁酸钠属于短链脂肪酸，能够抑制HDAC1、2、7的表达。通过强迫游泳实验和悬尾实验，丁酸钠在小鼠中表现出的抗抑郁效应与TTR基因的组蛋白4乙酰化水平增加有关[50]。在慢性约束压力小鼠模型中，丁酸钠也能影响海马区HDAC2、组蛋白3乙酰化、CREB和BDNF的水平[24]。在慢性不可预知温和压力诱导抑郁小鼠模型中，丁酸钠能够促进海马5-HT浓度增加、BDNF表达增加，并且使得损伤的血-脑脊液屏障得以恢复[51]。在脂多糖诱导抑郁小鼠模型中，丁酸钠能够改变其海马区一些相关基因表达，从而阻止抑郁的产生或进展，神经炎症反应和氧化氮化应激被抑制可能是其中的参与机制[52-53]。

MS-275是一类特殊的Ⅰ类HDACi，通过在慢性社会失败压力模型小鼠的内侧前额叶皮质注射这一药物能表现出稳定的抗抑郁样效应[54]，其抗抑郁样效应与组蛋白3乙酰化水平增加和腹外侧眶皮质的CREB、BDNF水平升高有关[55]。SAHA能够改善酒精撤退小鼠模型的抑郁症状，使得模型小鼠海马HDAC2、H3K9乙酰化水平得以恢复[33]。SAHA还在皮质酮诱导的慢性应激小鼠模型中发挥着与经典抗抑郁药氟西汀类似的作用，其能改善下丘脑-垂体-肾上腺轴改变伴随的焦虑抑郁症状[56]。左旋乙酰肉碱作为一种快速抗抑郁药物也有研究，在慢性不可预测压力小鼠及大鼠模型的腹腔中注射这一药物，2～3 d内能够表现出快而持久的抗抑郁效应，其机制与促进海马和前额叶皮层的BDNF转录有关[57]。

与以上HDACi不同的是，SIRT抑制剂能促进抑郁症状产生。有研究证明，增加大鼠海马的SIRT1活化能够阻止慢性不可预知温和压力下的慢性抑郁样行为发生，而注入SIRT1抑制剂能诱导抑郁前行为的发生[42]。与此相同的报道，应用tenovin-D3抑制SIRT2能够导致大鼠抑郁样行为发生及海马神经发生受损，且通过海马内灌注使得SIRT2过表达则能够逆转慢性不可预知压力诱导的抑郁样行为并促进神经发生[58]。

也有一些非典型HDAC抑制或促进剂能对HDAC产生影响，进一步产生抗抑郁效应。在慢性不可预见性应激(CUS)大鼠模型中，氯胺酮能够下调HDAC5表达，其中的机制可能与$Ca^{2+}$/钙调蛋白依赖的蛋白激酶Ⅱ(CaMK Ⅱ)和蛋白激酶D(PKD)依赖的HDAC5磷酸化有关[23]。氯胺酮还能增加BDNF的表达从而产生抗抑郁样作用[59]。CPP作为NMDA受体拮抗剂，能够刺激大鼠海马神经元HDAC5磷酸化和出核转运，这也伴随着CaMK Ⅱ核PKD的磷酸化，而敲除HDAC5，能够阻断CPP的抗抑郁效应[60]。在慢性不可预测温和压力诱导大鼠模型中，H2S也具有抗抑郁效应，这与其能够上调海马SIRT1的表达有关[61]。

五、HDACi治疗抑郁障碍的前景

目前尚未有临床试验评估HDACi在治疗心境障碍中的应用，因此上述HDACs参与抑郁发病及HDACi治疗抑郁障碍的机制是在临床研究前进行的动物实验验证，同时其不良反应也未进行完整评估。值得注意的是，HDACi的抗抑郁效应除了对HDAC的影响外，还有许多复杂的机制仍需要研究。当前HDACi在治疗抑郁障碍方面的有利效应已得到证实，MS-275联合氟西汀能够增加后者的抗抑郁效应[62]，丁酸钠与氟西汀联合亦有相同效果[63]。也有研究发现，联合应用ACY-738(HDAC6抑制剂)和西酞普兰，其效应与40倍西酞普兰活性相当[64]。因此，HDACi与经典抗抑郁药(如SSRIs)的联合应用是今后研究的一个重要方向，也为重度抑郁障碍包括耐药抑郁障碍患者的治疗提供了一项新的选择。

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·综述·

# 外周血MLR、NLR与急性脑梗死的相关性研究进展

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【摘要】 急性缺血性脑卒中是危害我国人民生命和健康的最主要的疾病之一，炎性反应与急性脑梗死密切相关，炎性标志物水平的高低反映了炎症的严重程度，尤其是外周血单核细胞与淋巴细胞比值(MLR)、中性粒细胞与淋巴细胞比值(NLR)作为近年来新兴的炎性指标，受到了广泛的关注。现就外周血MLR、NLR与急性脑梗死发生、进展、预后等方面的相关性研究进行综述。

【关键词】 急性脑梗死； 单核细胞与淋巴细胞比值； 中性粒细胞与淋巴细胞比值； 综述

**Study on the correlation between MLR and NLR in peripheral blood and acute cerebral infarction**

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【Abstract】 Acute ischemic stroke is one of the major diseases which endanger the lives and health of people in China. Inflammatory reaction is closely associated with acute cerebral infarction, and the level of inflammatory markers reflects the severity of inflammation. Especially MLR (monocyte to lymphocyte ratio) and NLR (Neutrophil to lymphocyte ratio) in peripheral blood, as emerging indicators of inflammation in recent years, have been widely concerned. This article reviews the correlation between MLR and NLR in peripheral blood, and the occurrence, progression and prognosis of acute cerebral infarction.

【Key words】 Acute cerebral infarction； Monocyte to lymphocyte ratio； Neutrophil to lymphocyte ratio； Review

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