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组蛋白去乙酰化酶抑制剂的研究进展*

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摘要:核小体是真核生物染色质的基本单位,通过对组蛋白核心的 N-端的乙酰化、甲基化、磷酸化、遍在蛋白化的修饰作用而影响细胞的功能。组蛋白乙酰化酶(histone acetylase HAT)及组蛋白去乙酰化酶(Histone Deacetylases HDAC)之间的动态平衡控制着染色质的结构和基因表达。当组蛋白去乙酰化水平增加,乙酰化水平相对降低,即会导致正常的细胞周期与代谢行为的改变而诱发肿瘤,及神经退行性变。组蛋白去乙酰化酶抑制剂(Histone Deacetylases-inhibitor HDACi)目前是国内外研究的热点。其中,曲古霉素 A(Trichostatin A TSA),是最早发现的天然组蛋白去乙酰化酶抑制剂;伏立诺他(Suberoylanilide Hydroxamic Acid SAHA)已经美国 FDA 批准用于治疗皮肤 T 细胞淋巴瘤。本文就 HDACi 分类及其功能出发综述 HDACi 的作用机制及研究进展。

关键词:组蛋白乙酰化酶;组蛋白去乙酰化酶;组蛋白去乙酰化酶抑制剂

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Progress on Histone Deacetylase Inhibitors*

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ABSTRACT: Nucleosome is the basic unit of eukaryotic chromatin. The acetylation, methylation, phosphorylation modification of histone N-terminal, will affect the cell function. The balance of histone acetylase and deacetylase in epigenetic modifications is critical to the regulation of chromatin structure and gene expression. When increased the levels of histone deacetylation, acetylation levels relatively reduction that would affect the normal cell cycle and metabolic changes in behavior induced tumors and neurodegeneration. Histone deacetylase inhibitors have become the hot field of researches. Trichostatin A (TSA), is one of the earliest discovered natural histone deacetylase inhibitor; Vorinostat (Suberoylanilide Hydroxamic Acid SAHA) has been approved by the FDA for the treatment of cutaneous T-cell lymphoma. This review describes the HDACi classification, and function. Summary HDACi mechanism of action and research progress.

Key words: Histone acetylase; Histone deacetylase; Histone deacetylase inhibitor

Chinese Library Classification(CLC): Q55, Q75, Q78 **Document code:** A

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前言

核小体是真核生物染色质的基本单位,由八聚体的组蛋白核心:包括各一对的 H2A,H2B,H3,H4;以及 DNA 链和连接 DNA 链的组蛋白 H1 组成。(图 1)

通过对其 N-端的乙酰化、甲基化、磷酸化、遍在蛋白化的修饰作用而影响细胞的功能。组蛋白乙酰化酶(histone acetylase HAT)对其 N-端进行乙酰化修饰,从而使核小体结构松散,促进基因转录。组蛋白去乙酰化酶(Histone Deacetylases HDAC)对其 N-端进行去乙酰化修饰,抑制转录,引起细胞的凋亡、死亡。(图 2)

组蛋白乙酰化酶(HAT)和组蛋白去乙酰化酶(HDAC)之间的动态平衡控制着染色质的结构和基因表达。当组蛋白去乙酰化水平增加,乙酰化水平相对降低,即会导致正常的细胞周期

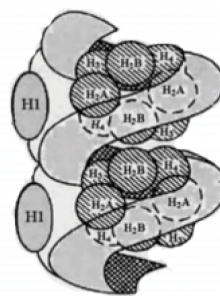


图 1 组蛋白结构示意图

Fig.1 The structure of histone

与代谢行为的改变而诱发肿瘤,及神经退行性变。组蛋白去乙酰化酶抑制剂(Histone Deacetylases-inhibitor HDACi)目前在临

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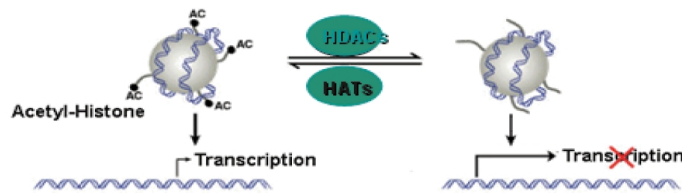
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组蛋白乙酰化修饰调控基因表达



HDAC: 组蛋白去乙酰化酶 Histone deacetylase

HAT: 组蛋白乙酰基转移酶 Histone acetyltransferase

图2 组蛋白的乙酰化和去乙酰化调控基因表达

Fig.2 The balance of histone acetylase and deacetylase regulate the gene expression

床应用广泛。其中,伏立诺他(Suberoylanilide Hydroxamic Acid SAHA)已经美国FDA批准用于治疗皮肤T细胞淋巴瘤。本文就HDACi分类及其功能出发综述HDACi的作用机制及研究进展。

1 HDAC 分类及其功能

1.1 分类

组蛋白去乙酰化酶(HDAC)根据其对于酵母蛋白的同源性而分为4类^[1]。

Class I:包括HDAC1、HDAC2、HDAC3、HDAC8。其与酵母RPD3有相似的催化位点。局限于细胞核内,主要调控组蛋白乙酰化修饰,调控细胞的存活、增殖。

Class II a:包括HDAC4、HDAC5、HDAC7、HDAC9。穿梭于核和胞浆之间。

Class II b:包括HDAC6、HDAC10。具有两个催化基团,主要存在于胞浆中。

Class II:类似酵母HDA1,调控组蛋白及非组蛋白的乙酰化修饰。具有组织特异性作用^[2,3]。

Class III:与酵母Sir2家族蛋白具有同源性。催化不依赖Zn²⁺,依赖辅酶I(NAD⁺)。不能被I、II类HDACi抑制。与细胞衰老和能量代谢的调节相关。

Class IV:包括HDAC11。是目前新发现的组蛋白去乙酰化酶,包含I型和II型HDAC的两种催化位点,且亦穿梭于核和胞浆中。

其活性趋势为:HDAC8>HDAC1>HDAC3>HDAC6^[1]

1.2 功能

HDAC在基因转录抑制过程中具有重要作用,HDAC能够增强带正电荷的组蛋白与带负电荷的DNA之间的相互作用,局部组蛋白的去乙酰化可以稳定核小体的结构,使染色体的结构更加紧密,构型不易发生变化,阻碍DNA与转录因子结合,达到抑制基因转录的功能^[4];在启动子附近局部的去乙酰化常伴随基因沉默。HDAC可与某些转录因子(例如E2F、Stat3、p53、NF- κ B、Klf3、TFII及Rb蛋白)发生相互作用,从而调节基因转录^[5]。此外,HDAC不仅能与调节基因转录的组蛋白发生相互作用,而且它还与某些细胞稳定性相关的非组蛋白有关联^[6]。I

型HDAC中的HDAC1、2对癌细胞增生的调控较重要,他们在活体中与其他因子形成蛋白复合物从而发挥效应,而I型HDAC中的HDAC3可调节TFII-1等转录因子并可抑制多种核受体;II型HDAC与肌细胞增强因子(MEF)2^[7]有关,MEF2与DNA结合可调节肌肉细胞的分化,II型HDAC中的HDAC6可调节微管细胞的活动性,HDAC10有一定的募集功能。

许多人类的癌症中,组蛋白的乙酰化和去乙酰化水平都有改变^[8-14]。如Rubinstein-Taybi综合征,会在CREB蛋白发生突变,从而影响组蛋白的乙酰化活性。然而,因为组蛋白去乙酰化酶结构的异常而引起的癌症较少。但在许多癌症中,组蛋白去乙酰化酶(HDAC)的表达都是增加的。例如:HDAC2和HDAC3在结肠癌中的表达增加^[8-12];HDAC1在胃癌中表达增加^[13,14]。

2 HDACi 的分类及功能

2.1 HDACi 的分类及临床应用

组蛋白去乙酰化酶抑制剂(HDACi)可以划分为四类^[1]:

1)羟肟酸类:包括SAHA、TSA、CBHA、LAQ-824、PDX-101、LBH-589、ITF2357;其中:曲古霉素A(TSA),是最早发现的天然组蛋白去乙酰化酶抑制剂;伏立诺他(SAHA)已经美国FDA批准用于治疗皮肤T细胞淋巴瘤。

2)环肽类:以Depsipeptide为代表,其在T-细胞淋巴瘤、血液肿瘤及实体肿瘤的治疗方面有肯定的作用;

3)脂肪酸类:包括NaB、Phenyl butyrate、Valproic Acid、AN-9;其抑制作用弱于羟肟酸类,Valproic Acid在骨髓发育不良综合征的单一疗法中有治疗作用。

4)苯甲酰胺类:包括MS-275、MGCD0103。

2.2 HDACi 的功能

组蛋白去乙酰化酶抑制剂(HDACi)协同的或者单独的用于许多疾病的治疗中,包括:放射线损伤治疗、化学疗法、表观遗传治疗、定向靶治疗^[8,10,15-18]。目前关于抗癌症方面的研究非常广泛^[19]。组蛋白去乙酰化酶抑制剂可以导致DNA损伤,正常细胞可以修复这种损伤,而异常细胞不能,从而杀死癌细胞^[20,21]。伏立诺他(SAHA)可以引起急性髓样白血病细胞的DNA损

伤^[22]。丁酸钠(NaB)也有抗抑郁及抗焦虑作用^[23],故在心理学方面亦有研究;还可用于治疗阿尔茨海默氏病^[24]。

体内试验中丁酸钠(NaB)对顺铂引起的耳毒性具有保护作用^[25]。体外实验中证实:组蛋白去乙酰化酶抑制剂(HDACi)在不减少耳蜗毛细胞对庆大霉素摄取的情况下,可通过抑制组蛋白去乙酰化酶的去乙酰化作用,调节组蛋白的乙酰化水平,从而保护耳蜗毛细胞,减轻庆大霉素引起的耳蜗毛细胞损伤^[26]。体内实验亦证实:丁酸钠(NaB)对庆大霉素的耳毒性具有保护作用,且此作用是通过降低组蛋白的去乙酰化水平实现的^[27]。

3 小结及展望

下一步阐明组蛋白去乙酰化酶抑制剂(HDACi)的下游通路才能发展更多有效的治疗策略^[28,29]。

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