•综述•

组蛋白去乙酰化酶3在糖尿病及其并发症中的作用及其抑制剂的研究进展

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摘要: 组蛋白去乙酰化酶3 (histone deacetylase 3, HDAC3) 是一种表观遗传修饰酶, 在糖尿病及其并发症的发生与发展中发挥重要作用。研究报道, 在1型糖尿病中, HDAC3活性增加与胰岛β细胞功能障碍有关; 而在2型糖尿病中, HDAC3通过调控肝脏、脂肪和肌肉组织的代谢, 影响胰岛素抵抗和信号转导。此外, HDAC3在糖尿病心肌病、视网膜病变和肾病等并发症中扮演了关键角色。通过选择性抑制HDAC3, 可以改善胰岛素敏感性并减轻慢性炎性, 改善胰岛细胞功能, 有望成为糖尿病及其并发症治疗的新策略。

关键词: 组蛋白去乙酰化酶3; 糖尿病; 糖尿病并发症; 胰岛素抵抗; 胰岛β细胞

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The role of histone deacetylase 3 in diabetes and its complications, and the research progress on histone deacetylase 3 inhibitors

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Abstract: Histone deacetylase 3 (HDAC3) is an epigenetic modification enzyme that plays a crucial role in the development and progression of diabetes and its complications. Studies have reported that increased HDAC3 activity is associated with pancreatic β-cell dysfunction in type 1 diabetes, while in type 2 diabetes, HDAC3 affects insulin resistance and signaling by regulating the metabolism of the liver, adipose tissue, and muscle. Additionally, HDAC3 plays a key role in diabetic complications such as cardiomyopathy, retinopathy, and nephropathy. Selective inhibition of HDAC3 has the potential to improve insulin sensitivity, reduce chronic inflammation, and enhance pancreatic cell function, offering a promising new therapeutic strategy for diabetes and its complications.

Key words: histone deacetylase 3; diabetes; complications of diabetes; insulin resistance; islet β cell

组蛋白的乙酰化和去乙酰化是广泛存在于生物体内的重要表观遗传修饰方式, 在调控蛋白质功能、染色质结构以及基因表达中发挥关键作用。组蛋白去乙酰化酶 (histone deacetylase, HDACs) 是负责组蛋白去乙酰化的主要调控蛋白, 可诱导组蛋白去乙酰化, 使其与带负电荷的DNA紧密结合, 引起染色质密化, 从而抑制基因转录[1]。此外, HDACs还参与调控多种非组蛋白的去乙酰化修饰, 在细胞功能上具有多效作用, 如调节组蛋白与DNA结合的亲和力、基因转录的活化水平、蛋白质的相互作用及稳定性等[2]。研究表明, HDACs和多种疾病的发生发展密切相关[3], 其中, HDAC3被认为是多个疾病的潜在靶点, 如癌症[4]、神经系统疾病[5-7]、糖尿病[8]、心血管疾病[9]、炎症和免疫相

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关疾病等[10,11]。

目前, 已上市的HDACs抑制剂多为非选择性抑制剂, 临床上主要用于肿瘤治疗。近年来, HDAC3的选择性抑制剂, 如BRD3308和RGFP966等, 相继被发现[12]。研究表明, HDAC3选择性抑制剂能够通过保护胰岛β细胞、调节炎症和免疫反应, 以及影响氧化代谢等途径改善糖尿病[8], 有望成为非肿瘤疾病的新药选择。基于这些研究进展, 本文将综述HDAC3生理功能、其与糖尿病及其并发症的关系, HDAC3抑制剂在改善糖尿病及其并发症中的研究进展, 以及HDAC3选择性抑制剂在新药开发中的最新进展, 旨在为开发HDAC3选择性抑制剂作为抗糖尿病及其并发症新型治疗药物提供思路。

1 HDAC3生理功能概述

目前, 人体内共鉴定出18种HDACs亚型, 分为4类。I类HDACs包括HDAC1、2、3和8, 主要位于细胞核内; 其中HDAC3也存在于细胞质中。II类HDACs在细胞质和细胞核之间穿梭, 根据其催化区域又细分为IIa类 (HDAC4、5、7和9) 和IIb类 (HDAC6和10)。III类HDACs被称为sirtuins, 与酵母Sir2蛋白具有同源性, 包含7种烟酰胺腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide, NAD^+) 依赖性酶。IV类HDACs主要指HDAC11, 位于细胞核中, 与其他HDACs同源性低[1]。

与其他I类HDACs相比, HDAC3具有独特性, 其依赖核受体辅阻遏物1 (nuclear receptor corepressor 1, NCoR1) 或视黄酸和甲状腺激素受体 (thyroid hormone receptor, 也称NCoR2或SMRT) 与去乙酰化酶激活结构域 (deacetylase activating domain, DAD) 相互作用, 形成复合物完成相应的酶促反应[13], 参与调节发育、免疫与代谢等过程。HDAC3在机体整个发育过程中能够整合来自环境的复杂信号并将其传递至基因组, 影响并调控多个生长发育阶段, 如维持脑和神经系统发育[14-16]、协调肺部[17,18]及骨骼发育[19,20]等。此外, HDAC3还调控与免疫相关的过程, 包括肠道免疫[21]、免疫细胞稳态及自身免疫反应等[22-25]。在代谢调控方面, HDAC3同样发挥重要作用, 如通过调节组蛋白去乙酰化的昼夜节律以控制肝脏脂质代谢和稳态[26,27]、调控棕色脂肪组织介导的产热和能量平衡[28]、维持心脏功能及心肌能量代谢[29], 以及维持肠道内稳态和代谢[30,31]等。

除了去乙酰化酶活性 (deacetylase activating, DA) 外, HDAC3还具有DA非依赖 (DA-independent) 的作用。研究表明, HDAC3缺失会引起组织器官病变和功能障碍。如在肝脏特异性敲除HDAC3的小鼠中, 脂肪生成相关基因上调, 导致严重的肝脂肪变性, 破坏代谢稳态[26,32]; 甚至引发DNA复制紊乱和基因组稳定性丧失, 进而导致肝细胞癌[33]。心脏特异性缺失HDAC3会引起脂肪酸摄取、氧化和磷酸化相关基因上调, 导致心脏代谢异常[29]。全身性HDAC3敲除则会导致胚胎致死[34]。然而, 当与HDAC3形成复合物的NCOR1蛋白中的478位点由酪氨酸突变为丙氨酸, 或HDAC3催化位点298由酪氨酸突变为苯丙氨酸 (Y298F) 时, HDAC3的酶活性消失[35,36], 但失去酶活性的HDAC3突变体 (HDAC3-Y298F) 仍可以发挥HDAC3的部分生理功能。如HDAC3-Y298F能够抑制小鼠肝脏中脂肪生成相关基因的表达, 从而部分缓解肝脂肪变性[37]。以上结果证实了HDAC3的非酶作用在维持正常组织器官功能中的重要性。因此, 区分HDAC3酶活性与非酶依赖作用对深入理解HDAC3在不同组织中的功能, 以及开发调节HDAC3的药物具有重要意义。

2 HDAC3与糖尿病

近年来研究显示, HDAC3与糖尿病的发病机制密切相关, 选择性抑制HDAC3具有治疗糖尿病的优良潜力。

2.1 HDAC3与1型糖尿病

1型糖尿病 (type 1 diabetes mellitus, T1DM) 是一种慢性自身免疫性疾病, 主要由于免疫介导的胰腺β细胞破坏[38]。研究表明, HDAC3表达及活性增加, 通过免疫途径介导β细胞破坏、凋亡, 胰岛素分泌严重障碍[39]。目前T1DM的治疗主要是胰岛素替代疗法, 能够减少β细胞破坏或恢复功能性β细胞数量的药物是研究的热点。因此, HDAC3选择性抑制剂可能具有治疗T1DM的应用前景。

2.2 HDAC3与2型糖尿病

2型糖尿病 (type 2 diabetes mellitus, T2DM) 约占所有糖尿病病例的90%, 其主要原因是胰岛β细胞功能受损和/或外周组织对胰岛素的敏感性降低, 导致机体代谢紊乱和血糖异常升高[40]。作为一种典型的代谢性炎性疾病, T2DM的发病机制涉及遗传和环境因素的复杂相互作用, 抑制HDAC3可通过抗炎和抗凋亡等途径改善胰岛β细胞功能, 增强外周组织对胰岛素的敏感性, 从而发挥抗T2DM作用。

2.2.1 HDAC3与外周胰岛素抵抗 胰岛素抵抗是指外周组织对胰岛素的敏感性降低, 导致葡萄糖摄取和代谢障碍。在T2DM的病程中, 肝脏、脂肪和骨骼肌等组织常表现出胰岛素抵抗[41,42], 而HDAC3与这些过程密切相关。

肝脏特异性敲除HDAC3的小鼠胰岛素敏感性显著增加。这是由于HDAC3调节脂滴内脂质合成和储

存路径, 从而影响肝脏葡萄糖的产生和输出[32]。这与HDAC3调节氧化物酶体增殖物激活受体γ (peroxisome proliferators-activated receptors γ, PPARγ) 的表达和活性有关[26,43]。此外, 回补失去酶活性的HDAC3突变体 (HDAC3-Y298F) 可以改善HDAC3敲除小鼠肝脏的脂质代谢紊乱, 一定程度缓解了脂肪肝病变[37], 提示HDAC3的非酶依赖作用在肝脏脂质代谢中发挥重要作用。丁酸钠 (一种I类HDAC抑制剂, 主要靶向HDAC1、2和3) 通过抑制HDAC3活性, 增强肝细胞中成纤维细胞生长因子21 (fibroblast growth factor 21, FGF21) 的表达, 促进肝脏脂肪酸氧化并改善肥胖症的代谢失调[44,45]。以上研究表明, HDAC3参与调控肝脏脂质代谢, 从而影响肝脏的胰岛素敏感性, 且其去乙酰化酶活性和非酶依赖作用可能发挥不同的调控作用。

脂肪组织中的HDAC3同样与胰岛素抵抗密切相关。特异性敲除脂肪组织中HDAC3能够诱导白色脂肪组织 (white adipose, WAT) 棕色化, 增加脂肪酸氧化[46], 从而改善脂肪组织的葡萄糖处理能力。同时, HDAC3通过抑制PPARγ以及cAMP反应元件结合蛋白 (cAMP-response element binding protein, CREB)[47], 从而抑制脂肪细胞中胞质磷酸烯醇丙酮酸羧激酶 (phosphoenolpyruvate carboxykinase, PEPCK) 的表达, 进而抑制甘油三酯生成并导致脂肪生成不足。此外, 脂肪细胞中HDAC3可与SMRT协同抑制PPARγ[48], 特异性抑制HDAC3能够诱导PPARγ乙酰化, 激活其功能[49], 增加脂肪细胞的葡萄糖摄取和脂质积累[50]。值得注意的是, 与噻唑烷二酮类PPARγ激动剂不同, HDAC3特异性抑制剂HD-75能够在没有PPARγ配体的条件下促进PPARγ转录, 改善胰岛素抵抗, 同时避免了噻唑烷二酮类药物的不良反应[49]。

骨骼肌是胰岛素诱导葡萄糖摄取的主要部位, 其胰岛素抵抗被认为是T2DM发病的关键因素之一[51]。研究显示, 小鼠骨骼肌特异性缺失HDAC3会引起严重的系统性胰岛素抵抗, 这是由于HDAC3缺失会增加氨基酸分解, 进而引起三羧酸循环的回补反应 (anaplerotic reactions), 促进线粒体脂质氧化, 降低肌肉葡萄糖利用率和胰岛素敏感性[52], 表明HDAC3在调控骨骼肌代谢中扮演重要角色[53], 但其对肌肉组织胰岛素抵抗的调节作用不同于其他组织。

总而言之, HDAC3与胰岛素抵抗密切相关, 其调节作用涉及众多通路或关键分子并具有组织特异性。选择性抑制HDAC3活性能够通过改善肝脏和脂肪组织的胰岛素敏感性, 有效治疗T2DM, 但HDAC3缺失可能会加重肝脏和肌肉组织的胰岛素抵抗, 提示HDAC3在不同组织中可能具有不同功能, 其去乙酰化酶活性和非酶依赖作用可能介导不同的生物学效应。因此, 在开发HDAC3抑制剂作为抗T2DM药物时应格外注意其组织靶向性以及去乙酰化酶活性和非酶依赖作用的不同影响。

2.2.2 HDAC3与β细胞功能 除了外周胰岛素抵抗外, 胰岛素分泌障碍是T2DM发病的另一主要病因。早期, 胰岛β细胞可能通过代偿性增加胰岛素分泌来弥补其效应不足, 但随着循环中游离脂肪酸和葡萄糖水平的持续升高, β细胞功能会逐渐失代偿, 最终导致衰竭和高血糖[54]。在T2DM发生与发展过程中, HDAC3对胰岛β细胞形态和功能的调控作用十分重要。

研究表明, HDAC3选择性抑制剂BRD3308可通过降低胱天蛋白酶3 (cysteinyl aspartate specific proteinase 3, caspase-3) 活性, 减少胰岛β细胞凋亡[55]; BRD3308还能够促进非肥胖T2DM小鼠胰岛β细胞增殖, 抑制其胰岛中单核细胞浸润和细胞凋亡[56], 通过减轻β细胞内质网应激和炎症保护β细胞功能, 促进胰岛素分泌和合成[57]。此外, 小分子抑制剂RGFP966也表现出类似的β细胞功能保护作用[58]。

然而, 对于HDAC3对β细胞形态和功能的影响仍存在争议, 不同的实验条件导致完全相反的实验结果。研究表明, 通过RIP-Cre系统对小鼠β细胞HDAC3进行特异性敲除, 其表现出胰腺胰岛素含量降低。此外, 采用siRNA特异性沉默MIN6细胞中的HDAC3同样表现出胰岛素基因转录减少[59]。然而, 采用MIP-CreERT系统对小鼠胰岛β细胞中的HDAC3进行特异性敲除, 其表现出胰岛β细胞功能紊乱在一定程度上改善, 且胰岛素分泌能力增强[60]。

以上结果表明, 采用不同基因编辑工具获得的研究结果有差异, HDAC3对胰岛β细胞的功能仍需要进一步确认。虽然选择性抑制HDAC3活性可改善T2DM胰岛β细胞功能, 但HDAC3对胰岛β细胞功能的多重调控作用仍需深入研究, 推测HDAC3非酶依赖作用是调控胰岛β细胞功能的重要途径。

2.2.3 HDAC3与慢性炎症 T2DM是一种慢性炎性疾病已成共识, 持续的慢性炎症不仅参与T2DM的发生与发展, 还与多种T2DM并发症密切相关。免疫失衡作为T2DM的潜在治疗靶点引起了研究者的极大兴趣[61,62]。研究表明, T2DM患者体内的HDAC3活性和表达水平不仅与其糖化血红蛋白、胰岛素水平相关, 还与循环中炎症标志物 (如TNF-α和IL-6) 水平呈显著正相关[63], 这表明HDAC3在T2DM发生的炎症免疫机制中具有重要作用。

PPARs是调控脂肪酸氧化和炎症的重要靶点, 其

功能依赖于不同刺激环境下多种辅助调节因子的相互作用, 从而选择性激活或抑制特定基因的转录, HDAC3通过与PPARα相互作用, 调控炎症相关基因的表达[64]。此外, 在炎症条件下, 细胞质中的核因子κB抑制蛋白α (inhibitor of NF-κB α, IκBα) 能够通过调节HDAC3的核转位, 抑制HDAC3进入细胞核, 从而通过炎症免疫通路调节葡萄糖和脂质代谢[65]。

HDAC3在巨噬细胞炎症反应中起关键作用。研究表明[66], 精氨酸酶1 (arginase 1, ARG1) 和鸟氨酸脱羧酶 (ornithine decarboxylase, ODC) 通过抑制HDAC3发挥抗炎作用, 抑制ODC或去除ARG1会增加经脂多糖 (lipopolysaccharides, LPS) 处理的巨噬细胞中HDAC3的表达, 进而加剧炎症反应。此外, HDAC3还与动脉粥样硬化等脂质驱动的炎性疾病的进展直接相关, 是唯一在人类动脉粥样硬化病变中上调的HDACs, 且与炎性巨噬细胞密切相关[4,67,68]。因此, HDAC3的抑制在调控动脉粥样硬化进展的固有免疫反应中至关重要。

此外, 已知IL-4可通过替代激活途径诱导巨噬细胞分泌抗炎细胞因子[69]。研究表明, HDAC3在巨噬细胞中作为替代激活基因表达的负调节因子, 其特异性缺失小鼠体内炎症显著减轻[25]。另一项研究指出, HDAC3活性增加会促进巨噬细胞向M1型转化, 从而加重炎性反应[63]。

然而, HDAC3独特的酶活性与非酶依赖作用赋予其双重调控作用, 既可抑制也可激活转录[70]。通过突变NCor1/2的去乙酰化酶活化区域或HDAC3的催化位点298 (Y298F), 尽管HDAC3的酶活性丧失, LPS仍能通过非经典途径激活巨噬细胞炎性基因表达[70]。而在HDAC3特异性缺失的小鼠骨髓源巨噬细胞中, LPS诱导的炎性反应明显减弱[22,70]。对比DAD突变小鼠与HDAC3缺失小鼠对LPS刺激的反应, 前者的致死率显著升高且体内促炎细胞因子IL-6和TNF表达水平明显增加[70]。这表明, HDAC3的酶活性和非酶依赖作用在不同炎性刺激介导的炎性反应中具有独特的调控作用, 需要分别地深入研究。

综上所述, HDAC3是炎性免疫反应的关键调控因子, 通过炎性免疫通路与T2DM密切相关。然而, HDAC3在不同的炎性反应中的具体调控机制尚未明确。在开发HDAC3抑制剂药物时, 应慎重考虑其酶活性/非酶依赖作用在炎性反应中的作用。

3 HDAC3与糖尿病并发症

3.1 HDAC3与糖尿病心肌病

糖尿病心肌病 (diabetic cardiomyopathy, DCM) 是一种发生于糖尿病患者的心肌疾病, 特征是在没有冠状动脉疾病、高血压和心脏瓣膜疾病的情况下发生心力衰竭[71], 是导致糖尿病患者死亡的主要原因之一。

HDAC3抑制可以保护心脏免受糖尿病引起的损伤, 这一作用机制与血糖调控无显著关联。如在使用HDAC3特异性抑制剂RGFP966治疗糖尿病小鼠时, 其血糖水平未受影响, 但心脏肥大和纤维化等病理表现得到明显改善。其主要机制是通过阻断糖尿病状态下细胞外信号调节激酶1/2 (extracellular signal regulated kinases 1/2, ERK1/2) 的激活, 增加双特异性磷酸酶5 (dual specificity phosphatase 5, DUSP5) 基因启动子区组蛋白H3乙酰化, 进而诱导DUSP5表达, 发挥心脏保护作用[72]。

3.2 HDAC3与糖尿病视网膜病变

糖尿病视网膜病变 (diabetic retinopathy, DR) 是糖尿病的严重并发症之一, 长期高血糖会引发视网膜氧化应激, 并激活炎症级联反应[73]。

研究表明, HDAC3的活性与视网膜神经节细胞的凋亡密切相关[74], 在DR模型小鼠中, HDAC3的表达随病程的进展显著增加, 且与caspase3和微管相关蛋白1轻链3 beta (microtubule-associated protein 1 light chain 3 beta, LC3B) 等细胞凋亡和自噬标志物的表达量呈正相关[75]。HDAC3抑制剂RGFP966通过降低还原型烟酰胺腺嘌呤二核苷酸磷酸氧化酶2 (NADPH oxidase 2, Nox2) 的表达, 增加超氧化物歧化酶2 (superoxide dismutase 2, SOD 2) 的表达, 从而减轻视网膜中的氧化应激、炎症和细胞凋亡, 改善DR症状[76]。此外, 血管内皮生长因子 (vascular endothelial growth factor, VEGF) 是糖尿病视网膜新生血管形成的关键因子, VEGF表达升高会破坏血液−视网膜屏障并引发炎性反应[77]。研究发现, 在DR小鼠玻璃体内特异性沉默HDAC3 (shRNA) 可抑制VEGF和丙二醛 (malondialdehyde, MDA) 产生, 同时通过下调G蛋白亚基αi2 (G protein subunit alpha i2, GNAI2) 的表达, 增加SOD活性, 减少视网膜神经节细胞的凋亡[78]。因此, HDAC3抑制剂对DR具有潜在的治疗效果。

3.3 HDAC3与糖尿病肾病

糖尿病肾病 (diabetic nephropathy, DN) 是糖尿病患者常见的微血管并发症之一[79]。

研究表明, HDAC3是糖尿病肾小球系膜细胞中重要的HDACs[80], 其异常表达会通过多种信号通路加剧DN的发生与进展[81], 并与肾脏衰老、肾细胞癌和肾纤维化等的发生密切相关[82,83]。炎性反应是DN发病的关键因素之一[84], 而NF-κB信号通路的激活则是该机制中的重要环节[85]。通过小分子化合物抑制HDAC3/NF-κB的信号转导, 可有效减少相关炎性反应和脂质

堆积, 从而缓解高脂饮食导致的肾损伤[86]。此外, 足细胞在维持肾小球结构和功能中发挥关键作用[87]。无论是通过HDAC3特异性沉默 (shRNA) 或是使用选择性抑制剂RGFP966, 均可阻断转化生长因子-β (transforming growth factor-β, TGF-β) 对microRNA-30家族成员miR-30d的抑制作用, 减少足细胞损伤, 进而发挥抗DN的作用[88]。

3.4 HDAC3与其他糖尿病并发症

HDAC3与糖尿病脑卒中发病密切相关[89], 其抑制可通过增强氧化代谢、抑制细胞凋亡和促进自噬等途径对糖尿病脑缺血再灌注损伤起到保护作用[90]。

此外, HDAC3抑制剂还能够改善糖尿病引起的其他心血管相关并发症。如HDAC3抑制可激活核因子E2相关因子2 (nuclearfactor erythroidderived 2-like 2, Nrf2) 信号通路, 减少炎性反应和氧化应激, 从而改善T2DM导致的内皮功能障碍[91]; 同时, HDAC3抑制还可促进FGF21合成和分泌, 产生主动脉保护作用[92]。

糖尿病神经病变也是常见的糖尿病并发症之一[93]。研究表明, 通过抑制HDAC3并募集共济失调蛋白2 (ataxin 2 like, Atxn2l) 基因, 能够促进雪旺细胞髓鞘形成, 改善糖尿病神经病变[94]。

4 HDAC3抑制剂研究进展

HDACs于20世纪90年代首次被发现, 其在氨基酸侧链的翻译后修饰中发挥重要作用, 三十多年来, 人们对HDACs的认识不断加深, 基于这些认识, 研发出了一系列HDACs抑制剂用于多种疾病的治疗[1,12,95]。其中, I类HDACs因其相似的结构, 特别是底物结合位点附近的区域, 成为研究最多的HDACs类型, 这可能是其选择性较差的主要原因[96]。目前已批准上市的HDACs抑制剂, 如帕比司他 (panobinostat)[97]、贝利司他 (belinostat)[98]等, 均为非选择性抑制剂, 主要用于肿瘤治疗。然而, 这些非选择性抑制剂由于选择性低, 可能引发胃肠道恶心以及血液系统、心脏和肾功能不全等[99-101]等不良反应。

作为HDACs家族的重要且独特的成员, HDAC3在胚胎和器官发育、生理学、代谢和氧化应激等中发挥关键作用。目前, 研究中报道的HDAC3抑制剂主要包括苯甲酰胺类、邻氨基苯基类、异羟肟酸盐、苯甲酰肼类和硫醇类等[12]。

苯甲酰胺类HDAC3抑制剂基于其苯甲酰胺骨架, 通过靶向活性位点中的锌离子, 形成锌离子结合基团 (zinc binding groups, ZBGs) 而发挥作用。因此, 苯甲酰胺类化合物具有很大潜力, 相关研究仍在进行[102]。MS-275 (恩替诺特, entinostat) 是一种典型的苯甲酰胺骨架HDACs抑制剂, 其在较低浓度下 (IC_{50} = 0.95 mmol·L^{-1}) 有效抑制HDAC3, 近期研究表明, MS-275能够增强胰岛素分泌[103], 并预防由IL-1β和TNF-α诱导的β细胞凋亡[104], 展现出糖尿病治疗的潜力。然而, 由于MS-275选择性较差, 对HDAC1和HDAC2也有一定抑制作用 (IC_{50}值分别为0.19和0.41 mmol·L^{-1})[4], 并且导致人肝癌细胞Hep3B中p21$^{WAF/Cip1}$的表达增加[105]。因此, 对其结构进行优化以改善选择性的研究仍在进行中。此外, BRD3308是一种优化设计的苯甲酰胺骨架HDAC3抑制剂 (IC_{50} ≤ 0.064 mmol·L^{-1}), 研究表明其能够保护胰岛β细胞免受炎症和代谢损伤[55,57], 具有抗糖尿病的潜力。

RGFP966是一种*N*-(邻氨基苯基) 甲酰胺结构的HDAC3选择性抑制剂 (IC_{50} = 0.08 μmol·L^{-1})[106], 在15 μmol·L^{-1}浓度下对其他HDACs亚型无抑制作用, 并且能够透过血脑屏障, 是目前广泛用于研究的高选择性HDAC3抑制剂, 处于临床前研究阶段。RGFP966相关的研究主要聚焦于改善炎症[10,107]、神经性[108-110]以及脑部疾病[111,112]。现有研究表明, RGFP966对糖尿病及其并发症同样具有一定的治疗潜力, 能够通过保护β细胞免受凋亡, 进而改善链脲佐菌素 (streptozotocin, STZ) 诱导的糖尿病小鼠糖耐量受损[58], 减少视网膜中的氧化应激、炎症和细胞凋亡[76], 并在治疗DCM[72]、DR[76]、DN[81]等并发症中发挥不同程度的改善作用。

异羟肟酸盐类化合物通过与I类HDACs活性位点的锌离子结合形成ZBG, 作为泛HDACs抑制剂具有很强的抑制活性, 但其在体内不稳定[113], 并且由于强烈的Zn^{2+}螯合基团, 增加了脱靶效应和不可预测的临床毒性风险[114]。目前FDA批准的基于异羟肟酸的HDAC抑制剂包括伏立诺他 (vorinostat)[115]、贝利司他[116]和帕比司他[117]等, 主要用于恶性肿瘤的治疗[4]。

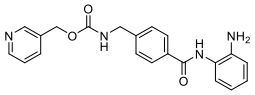
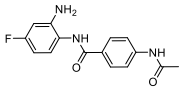
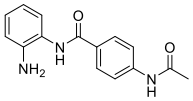
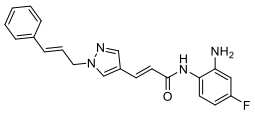
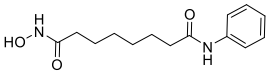
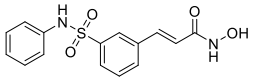
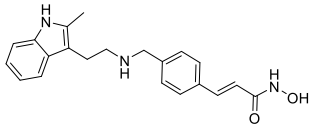
此外, 苯甲酰肼类化合物也表现出强大的HDACs抑制活性。与上述几类化合物不同, 部分具有较高的HDAC3抑制活性, 并引入了靶向I类HDACs的非金属螯合基团的新型药效团, 在抑制组蛋白去乙酰化方面优于氨基苯甲酰胺类抑制剂, 并通过激活关键的肿瘤抑制通路发挥强大的抗肿瘤作用[114,118]。

以上研究为进一步探索相关分子机制提供了重要依据, 为了更清晰地展示研究内容及其关联性, 表1[55,58,98,102,119-124]汇总了目前已报道的关键分子及其功能。尽管研究者们不断研发和优化新型HDAC3抑制剂, 但由于这些化合物的选择性仍不够理想, 目前尚未投入临床使用[4]。开发具有高选择性的HDAC3抑制剂用于疾病治疗仍然任重道远。

5 总结与展望

HDAC3在HDACs家族中具有独特的地位, 它不

Table 1 Advances in histone deacetylase 3 (HDAC3) inhibitors research

Category	Inhibitor	Chemical structure	Reported pharmacological action	Indication	Global highest development status
Benzamides[102]	Entinostat (MS-275)[119,120]		Modulates tumor immune microenvironment, reduces immunosuppressive cells such as myeloid-derived suppressor cells and FOXP3 Tregs	Breast cancer; metastatic breast cancer	Approved for market
	BRD3308[55]		Protects pancreatic *β*-cells, antidiabetic effects		Preclinical research
	Tacedinaline[121]		Inhibits clonal growth and induces caspase activation; arrests G2/M and subG1 cell cycles in VM-CUB1 and UM-UC-3 cells	Multiple myeloma; lung cancer; small cell lung cancer	Phase III clinical trials
Anilinobenzamide derivatives	RGFP966[58]		Improves inflammation, neurogenic and brain-related diseases, protects *β*-cells		Preclinical research
Hydroxamate derivatives	Vorinostat[122]		Inhibits deacetylation of key autophagy markers, interfering with autophagy and autophagic cell death	Cutaneous T-cell lymphoma	Approved for market
	Belinostat[98]		Restores normal gene expression in cancer cells by inducing histone acetylation and stimulates other pathways like immune response and p27 signaling cascade	Peripheral T-cell lymphoma	Approved for market
	Panobinostat[123,124]		Inhibits cell proliferation and induces caspase activation in multiple myeloma cell lines; suppresses proliferation of diffuse intrinsic pontine glioma cells	Glioma; diffuse intrinsic pontine glioma; diffuse midline glioma	Approved for market

仅能作为核受体共阻遏物复合物的一部分发挥强大的酶活性功能; 还能够通过其本身特殊的生理作用展现独特的非酶依赖的作用[1]。HDAC3 与线粒体功能、代谢和氧化应激等密切相关, 因此其抑制剂在多种慢性疾病中展现出潜在的疗效[96], 包括癌症、糖尿病和肥胖等[12] (图 1)。尽管近年来的实验研究初步证实了 HDAC3 抑制剂在糖尿病治疗中的应用潜力, 但目前尚无候选化合物进入临床试验阶段[12]。

随着对 HDAC3 研究的深入, 其与糖尿病及其并发症的关系逐渐受到重视。现有研究表明, HDAC3 选择性抑制剂的开发和应用有助于糖尿病及其并发症的精确化和个体化治疗。此外, 由于去乙酰化酶活性和

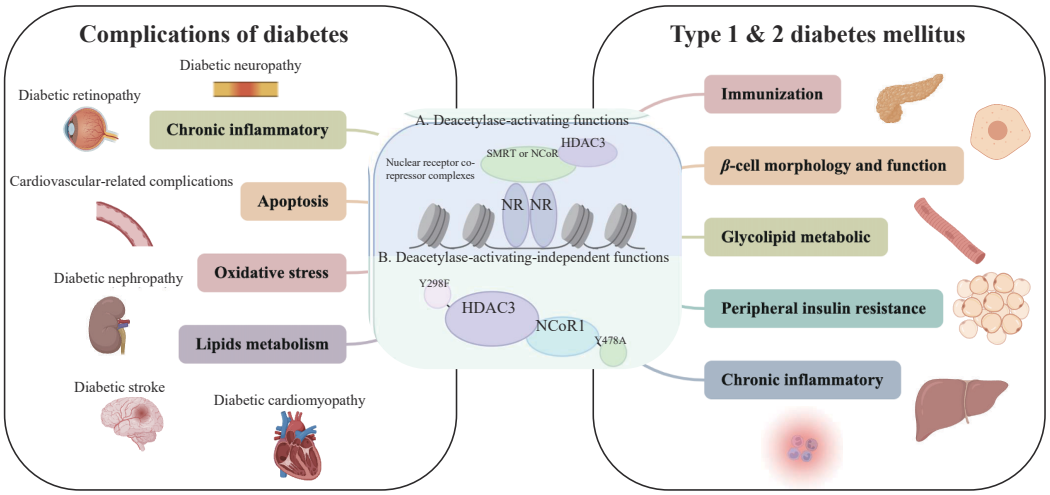


Figure 1 Physiological function and mechanism of action of HDAC3

非酶依赖作用同时存在, 开发靶向HDAC3的药物时需要区别这两种功能的调控。HDAC3及其选择性抑制剂的开发仍需进一步探索。因此, 研发具有新颖作用的HDAC3特异性抑制剂作为抗糖尿病新药具有优良潜力。

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