组蛋白去乙酰化酶与酒精相关性肝病

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[摘 要] 酒精相关性肝病(alcohol-related liver disease，ALD)是长期大量饮酒导致的一种常见慢性肝病。早期可无任何症状或表现为轻症酒精性脂肪肝，随后可演变为以肝脏炎症为特征的亚临床脂肪性肝炎，进一步发展为纤维化、肝硬化，晚期严重时可诱发肝功能衰竭和肝细胞癌。目前，戒酒是ALD干预的核心策略，但受制于患者依从性及社会环境等因素，常需联合药物治疗。组蛋白去乙酰化酶(histone deacetylase，HDAC)是蛋白质翻译后修饰的关键功能性催化酶，可通过影响脂质代谢、炎症反应及纤维化等过程，参与ALD的发生和发展，可作为ALD治疗的潜在靶点。多种HDAC相关激动剂和抑制剂在ALD治疗中有一定应用前景，但其亚型特异性作用及临床应用价值仍需进一步明确。对HDAC及其激动剂或抑制剂在ALD中的作用进行系统概括，可为进一步探讨ALD发生、发展机制及推动ALD的精准干预提供思路。

[关键词] 酒精相关性肝病；组蛋白去乙酰化酶；沉默信息调节因子相关酶类；抑制剂；治疗

Histone deacetylases and alcohol-related liver disease

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ABSTRACT Alcohol-related liver disease (ALD) is a common chronic liver disease caused by prolonged excessive alcohol consumption. It may initially be asymptomatic or manifest as mild alcoholic fatty liver, then progress to subclinical steatohepatitis characterized by hepatic inflammation, and eventually develop into fibrosis, cirrhosis, liver failure, or even hepatocellular carcinoma. Although alcohol abstinence remains the primary strategy for ALD management, its effectiveness is often limited by patient adherence and social factors, making combined pharmacological intervention necessary in many cases. Histone deacetylase (HDAC), which is a key enzyme involved in post-translational protein modification, have been implicated in the pathogenesis and progression of ALD through their regulation of lipid metabolism, inflammatory responses, and fibrosis, and are

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therefore considered promising therapeutic targets. Various HDAC-related agonists and inhibitors have shown therapeutic potential in ALD, but their subtype-specific roles and clinical relevance remain to be fully elucidated. This review systematically summarizes the roles of HDAC and their agonists or inhibitors in ALD, in order to provide insight into the mechanisms of ALD progression and to support the development of precise therapeutic strategies and clinical translation.

KEY WORDS　alcohol-related liver disease; histone deacetylases; silent information regulator-related enzymes; inhibitors; therapy

肝脂肪变性被认为是酒精相关性肝病(alcohol-related liver disease，ALD)的最早阶段，近90%的酒精使用障碍患者会出现肝脂肪变性，随着病情发展，炎症和水肿会扩散至健康的肝实质组织，从而引起酒精相关性脂肪性肝炎、肝纤维化、肝硬化，最终导致肝功能衰竭[1-2]。全球疾病负担数据库(Global Burden of Disease，GBD)数据[3]显示，2021年全球ALD患者数约302万，较2000年增长38.68%；酒精相关性肝细胞癌(hepatocellular carcinoma，HCC)患者数约13.2万，较2000年增长94.12%；ALD和酒精相关性原发性肝癌病死数较2000年增长32.6%和76.75%。在北美、欧洲等地区，ALD是肝硬化的首要病因，是引起终末期肝病和肝移植最常见的原因[2, 4]。当前中国尚未构建ALD的流行病学监测体系，但多项区域性研究[5-6]证实，随着饮酒人群比例上升，ALD的患病率和住院率均呈快速增加趋势，所造成的疾病负担日益加重。其中，重症酒精性肝炎(alcoholic hepatitis，AH)预后极差，28 d的病死率高达35%~50%，被公认为临床最危重的肝病类型之一。ALD在中国导致肝硬化的病因中仅次于病毒性肝炎，是亟需应对的重大公共卫生挑战。

ALD的发病机制目前尚未完全阐明，现认为ALD发生可能与细胞因子及炎症介质异常、氧化应激反应、肠道微生态紊乱、脂质过氧化、遗传易感性及营养代谢失调等多种因素密切相关[7]。戒酒联合营养支持是最基础、最核心的治疗措施。然而，对于某些合并相关并发症(如存在认知功能障碍、酒精戒断障碍、肝性脑病)或已进展至ALD终末期的患者，药物治疗是不可或缺的干预手段。糖皮质激素在治疗ALD相关肝损伤时展现出双重效应：一方面，其显著的抗炎特性能够有效提升重症AH患者的生存率；另一方面，该药物可诱发感染和消化道出血等严重并发症，限制了其在临床中的广泛应用[8]。近年来，N-乙酰半胱氨酸、美他多辛、己酮可可碱、S-腺苷蛋氨酸、粒细胞集落刺激因子等新型药物逐步应用于ALD治疗，但受限于药物普遍存在的剂量依赖性不良反应及疗效个体化差异显著等问题，其临床推广仍面临诸多挑战。现阶段仍缺乏一种高效、安全、特异的ALD治疗药物。组蛋白去乙酰化酶(histone deacetylases，HDAC)是蛋白质翻译后修饰的关键功能性催化酶，被认为是ALD治疗的新靶点。本文拟介绍ALD的病理特征、治疗现状，以及HDAC的结构、功能等特点，总结HDAC各亚类在ALD进展中的作用机制，探讨其潜在治疗靶点，旨在为ALD的治疗提供创新性策略。

1 HDAC的概述

在基因表达调控中，HDAC和组蛋白乙酰转移酶(histone acetyltransferases，HATs)对核心组蛋白ε-N-乙酰赖氨酸残基进行去乙酰化和乙酰化修饰，影响核小体结构稳定性和动态解聚程度。生理状况下二者处于动态平衡，其平衡打破可通过多种机制参与疾病病理进程[9]。HDAC催化组蛋白赖氨酸残基的ε-氨基去乙酰化，提高组蛋白分子的净正电荷水平，增强与DNA磷酸骨架之间的静电相互作用力，进而形成致密的异染色质结构。HATs则相反，该酶将乙酰基团共价结合至组蛋白末端残基上，通过中和组蛋白正电荷密度促使核小体结构解聚并形成更为开放的染色质构象，使DNA结合位点充分暴露，从而激活下游靶基因转录并参与生理调控[10]。此外，部分HDAC也能去乙酰化多种非组蛋白，参与细胞生长、分化、凋亡等生物学过程。

哺乳动物HDAC家族包括18种不同亚细胞定位和功能特性的HDAC亚型，基于其与酵母HDAC的序列同源性，可分为Ⅰ、Ⅱ、Ⅲ、Ⅳ 4类[11-12]。Ⅰ类HDAC与酵母蛋白Rpd3具有同源性，包括HDAC1、HDAC2、HDAC3和HDAC8。Ⅰ类HDAC以多蛋白复

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合物的形式起作用并参与各种生理过程，包括转录抑制、染色质组装、细胞周期进程和维持基因组稳定性，主要存在于细胞核中，HDAC3也可存在于细胞质和质膜中[13-15]。II类HDAC与酵母脱乙酰酶Hda1具有同源性，根据催化结构域数量差异分为IIa类和IIb类，其中IIa类包括HDAC4、HDAC5、HDAC7和HDAC9，IIb类包括HDAC6和HDAC10。II类HDAC存在于细胞质溶胶和细胞核中，通过磷酸化控制运动，其HDAC的功能与炎症和迁移等细胞过程有关[16-18]。III类HDAC因与酵母中的沉默信息调节因子2(silent information regulator 2，Sir2)同源，又名Sir2相关酶类(Sir2-related enzyme，Sirt)，Sirt1~Sirt7在细胞核、细胞质和线粒体中均有分布[19-21]。通过调控适应性免疫应答、线粒体能量代谢、氧化应激应答、炎症因子网络等过程，参与代谢综合征、自身免疫性疾病、ALD及肿瘤等疾病的发生、发展，被视为多种疾病治疗的潜在靶点[22-24]。HDAC11是唯一的IV类HDAC，大多分布在细胞核，同源性介于Rpd3和Hda1之间[25]。HDAC11在调节免疫反应、炎症和各种细胞事件中起着至关重要的作用[26-27]。需要强调的是，除Sirt是烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide，NAD^+)依赖性去乙酰化酶外，其余3类HDAC均需要锌离子辅助发挥催化作用[28-30]。

2 HDAC与ALD

体内和体外实验中观察到乙醇暴露以时间和浓度依赖性方式促进大鼠肝细胞中组蛋白3赖氨酸9(histone 3 lysine 9，H3K9)上的乙酰化修饰，最终影响肝脏的基因表达过程[31-33]。在ALD细胞和动物模型中，HDAC各亚型表达水平存在差异，呈上调或下调趋势。通过靶向调控HDAC进而影响表观遗传修饰过程，有望为ALD开辟全新的治疗策略(附图1，https://doi.org/10.57760/sciencedb.31531)。

2.1 I类HDAC与ALD

2.1.1 HDAC1与ALD

研究[34-35]表明，母体乙醇暴露可诱发子代大鼠HATs与HDACs的稳态失衡，导致细胞内蛋白质乙酰化修饰异常，表现为核质内HDAC1表达上调及整体乙酰化水平下降，进而诱发胰岛素抵抗并促进肝细胞脂质蓄积。作为线粒体β氧化的关键限速酶，肉碱棕榈酰转移酶-1A(carnitine palmitoyltransferase-1A，CPT-1A)通过调控脂肪酸向线粒体的转运过程维持肝脏脂质代谢稳态[36]。乙醇可诱导CPT-1A启动子区域组蛋白进行去乙酰化修饰，显著抑制该酶的基因转录活性，这一表观遗传调控机制被认为是酒精性脂肪肝的核心病理环节[37]。HDAC1抑制剂三丁酸甘油酯能有效阻断乙醇诱导的HDAC1募集，通过恢复启动子区域组蛋白乙酰化水平显著提升CPT-1A的转录效率[38]，其代谢产物丁酸钠可对抗乙醇诱导的HDAC1异常升高，发挥抗炎作用[39]。乙醇代谢产生的毒性乙醛可激活核因子-κB(nuclear factor-kappa B，NF-κB)通路，NF-κB的P50亚基通过调节肝细胞中的HDAC1促进肝脂肪变性[40-41]。HDAC1是RE1沉默转录因子(RE1-silencing transcription factor，REST)复合物辅阻遏物的组成部分，角蛋白19(keratin 19，KRT19)通过增强HDAC1和REST辅阻遏蛋白1相互作用来促进CoREST复合物的形成，从而增加脱乙酰酶活性，导致HCC的去分化[42]。在HCC中，除乙酰化外，大多数乳酸化位点也与HDAC1呈正相关[43]。最新研究[44]还发现tRF-31R9J通过HDAC1介导组蛋白乳酸化修饰调控肝细胞铁死亡来改善非酒精性脂肪性肝炎。上述研究证实了HDAC1加剧乙醇诱发的肝组织脂质沉积及病理损伤，为靶向HDAC1治疗ALD提供了重要理论依据。

2.1.2 HDAC2与ALD

在小鼠模型中，HDAC2调节K68位点的乙酰化，发挥对UNC-51样自噬激活激酶1(UNC-51 like autophagy activating kinase 1，ULK1)的拮抗作用，通过ULK1-NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor family pyrin domain containing 3，NLRP3)通路诱导急性肝衰竭小鼠的细胞焦亡[45]。在ALD中，NADPH氧化酶1(NADPH oxidase 1，NOX1)促进活性氧(reactive oxygen species，ROS)的累积，导致结肠上皮细胞的氧化应激损伤，进而通过肠-肝轴促进ALD的发生。HDAC2抑制剂丙酸盐调节基因启动子区域的组蛋白乙酰化水平，抑制NOX1的表达，降低氧化应激引起的肠上皮细胞凋亡水平[46]。HDAC2在HCC中介导程序性死亡配体1(programmed death-ligand 1，PD-L1)核易位，其表达水平随着HCC组织病理学分级的增加而逐渐上调[47]，使用程序性死亡蛋白-1(programmed death-1，PD-1)/PD-L1阻断剂和HDAC抑制剂联合治疗对HCC患者有积极作用[48-49]。在肝纤维化中，HDAC2和DNA甲基转移酶1(DNA methyltransferase 1，DNMT1)相互作用，其过表达与肝纤维化严重程度相关[50-51]。以上研究证实HDAC2可以促进ALD的发生、发展。

2.1.3 HDAC3与ALD

HDAC3在乙醇诱导的小鼠肝脏中的表达增多。与HDAC1类似，HDAC3也可作用于CPT-1A。向

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ALD模型小鼠腹腔注射HDAC抑制剂Trichostatin A (TSA)来抑制HDAC3的暴增，使CPT-1A的表达水平恢复正常，可显著缓解肝损伤和脂肪变性[52]。在ALD中，脂多糖(lipopolysaccharide，LPS)可加重乙醇刺激下的肝细胞炎症反应，LPS在肝细胞炎症中的作用可能由HDAC3-信号转导及转录激活因子(signal transduction and activator of transcription，STAT)3/NF-κB通路介导[53]。正常情况下，HDAC3和GLIS家族锌指蛋白2(GLIS family zinc finger protein 2，GLIS2)形成螯合物以避免过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor，PPAR)-γ的去乙酰化，当GLIS2缺失时，HDAC3会使PPAR-γ去乙酰化，激活肝星状细胞，并导致肝纤维化[54]。此外，HDAC3可调节DNA损伤修复，在肝脏稳态中起着不可或缺的作用。HDAC3的消融会造成受损DNA的积累，最终导致HCC的发生[55-56]。目前多数研究支持抑制HDAC3活性在ALD治疗中的潜在益处，但HDAC3在ALD晚期恶性转化中可能具有保护性。

2.1.4 HDAC8与ALD

AH模型小鼠中HDAC8水平上调，其异常激活会加剧肝脏炎症级联反应，并促进肝实质细胞的损伤；过表达miR-451a可下调HDAC8，抑制肿瘤坏死因子α(tumor necrosis factor α，TNF-α)和白细胞介素(interleukin，IL)-β的分泌，从而改善AH炎症[57]。一种新研究的HDAC8抑制剂被发现能通过上调HDAC8介导的丙酮酸激酶M2亚型(pyruvate kinase M2，PKM2)乙酰化来发挥其抗肿瘤作用，以HDAC8为靶点可能是一种治疗HCC的有前景的方法[58-59]。此外，抑制HDAC8能够下调肝星状细胞活化水平，对治疗肝纤维化有积极作用[60]。因此，HDAC8主要通过促进炎症和纤维化加重ALD。

2.2 II类HDAC与ALD

2.2.1 HDAC6与ALD

HDAC6是负责去除微管蛋白α-tubulin乙酰化的主要去乙酰化酶。乙醇暴露会降低HDAC6蛋白水平，抑制其与微管的结合，从而诱导微管过度乙酰化，直接导致肝细胞内蛋白质运输功能障碍，最终促进ALD发生[31, 61-62]。肝窦内皮细胞(liver sinusoidal endothelial cells，LSECs)作为肝脏重要的代谢细胞，其内源性表达的细胞色素P450 2E1(cytochrome P450 2E1，CYP2E1)和乙醇脱氢酶系统参与乙醇代谢过程。乙醇刺激可显著提高LSECs中热激蛋白90(heat shock protein 90，Hsp90)的乙酰化水平，HDAC6的高表达可以逆转这一状态，从而维持其正常的生物学功能[62]。Toll样受体4(Toll-like receptor 4，TLR4)/NF-κB通路通过介导坏死性凋亡途径来诱导ALD[63]。研究[18, 40]发现，HDAC6抑制剂可显著降低炎症因子TNF-α、IL-1β及IL-6的表达，抑制NF-κB通路，在人类肝组织中具有抗纤维化及抗炎活性。因此，HDAC6在ALD中具有双重作用。

2.2.2 HDAC9与ALD

脂肪酸合酶(fatty acid synthase，FAS)诱导ALD中脂肪变性和肝损伤。研究[64]证实，HDAC9介导的上游刺激因子1(upstream stimulating factor 1，USF-1)去乙酰化可降低*FAS* mRNA的稳定性，同时抑制该基因启动子的转录激活。急性大量乙醇灌胃的小鼠肝脏中HDAC3是唯一呈现表达上调的亚型，而其他检测的HDAC家族成员均出现不同程度的表达抑制，其中*HDAC9*的mRNA水平下降最为明显。值得关注的是，该研究发现FAS的表达水平显著上调。乙醇介导的肝脏HDAC9表达下调可能是促进FAS表达增加和肝脏脂肪变性发生的关键调控机制[65]。因此，HDAC9功能下调诱导ALD的脂代谢紊乱。

2.2.3 其他II类HDAC与ALD

在母鼠妊娠的前21 d内，无论哪个阶段接触乙醇均会导致子代出现持续的代谢功能障碍，表现为细胞应激反应异常和血糖稳态失调，同时HDAC4、HDAC5、HDAC7表达增加。Kang等[66]发现乙醇诱导的巨噬细胞模型中HDAC4表达增加，HDAC4可能会改变线粒体生物发生和糖酵解，导致乙醇刺激的巨噬细胞发生炎症。

2.3 III类HDACs与ALD

2.3.1 Sirt1与ALD

在乙醇诱导的肝细胞或动物肝脏模型中，Sirt1表达受到抑制。此外，在乙醇处理的巨噬细胞中也发现Sirt1和NAD^+表达水平的降低[66]。乙醇增加了人抗原R(human antigen R，HuR)的磷酸化并触发了*HuR-Sirt1* mRNA复合物的解离，进而降低*Sirt1* mRNA水平[67]。在*Sirt1*基因敲除模型小鼠中，乙醇暴露会加剧ALD小鼠的肝脏炎症和脂肪变性[68]。脂联素作为一种脂肪组织分泌的细胞因子，具有保护肝脏免受乙醇损伤的作用，而长期乙醇摄入可通过抑制Sirt1的表达，进而下调肝脏脂联素受体的表达水平[69]。正常肝脏中Sirt1可直接与固醇调节元件结合蛋白1c(sterol regulatory element-binding protein 1c，SREBP-1c)作用使之去乙酰化，负调控该转录因子的生物学活性，从而维持肝脏脂质代谢平衡[70]。在乙醇干预的小鼠中，Sirt1功能受损导致SREBP-1c蛋白稳定性增强，其转录活性显著升高，进而促进脂肪酸合成相关基因的异常表达，导致肝脏脂肪变性，加

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重肝损伤[71]。另有研究[72]发现，青春期大鼠暴露于乙醇后，白色脂肪组织(white adipose tissue，WAT)中Sirt1表达显著上调，抑制SREBP-1c和PPAR-γ，激活叉头框蛋白(forkhead box protein，FOX)O1-脂肪甘油三酯脂酶信号通路，促进WAT的脂肪分解并增加循环游离脂肪酸(free fatty acid，FFA)水平，使过量FFA进入肝脏，促进肝脏脂肪变性。Sirt1-腺苷酸活化蛋白激酶(AMP-activated protein kinase，AMPK)-哺乳动物雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1，mTORC1)信号通路的激活抑制乙醇诱导的脂肪酸合成，促进脂肪酸降解，从而减轻酒精性肝损伤[73]。白藜芦醇则是通过激活AMPK通路来正向调控Sirt1，对乙醇喂养的小鼠发挥保护作用[74]。脂肪酸结合蛋白4(fatty acid-binding protein 4，FABP4)由ALD中的肝细胞分泌，可刺激HCC细胞增殖和迁移。CYP2E1依赖性乙醇代谢抑制Sirt1-FOXO1信号传导，导致FABP4蛋白分泌和中性脂质积累[75]。过氧化物酶体增殖物激活受体γ共激活因子1α(peroxisome proliferator-activated receptor gamma coactivator 1 alpha，PGC-1α)是线粒体呼吸和基因转录的强大刺激剂，过量饮酒会抑制Sirt1/PGC-1α/PPARα通路，导致氧化应激和细胞因子[如C-C motif趋化因子配体2(C-C motif chemokine ligand 2，CCL2)、C-X-C motif趋化因子配体(C-X-C motif chemokine ligand，CXCL)8和CXCL10]水平升高，并伴肝脂肪变性[76]。Sirt1/PGC-1α轴介导的线粒体动力学在乙醇诱导的肝细胞焦亡中起重要作用[77-80]。因此，乙醇对Sirt1/PGC-1α轴的破坏可能是ALD发生的原因之一。高迁移率族蛋白B1(high mobility group box 1，HMGB1)促进肝细胞内质网(endoplasmic reticulum，ER)应激，触发炎症反应和细胞凋亡，加重酒精性脂肪性肝炎，Sirt1通过抑制HMGB1乙酰化和易位来保护肝脏[81-82]。含溴结构域蛋白4(bromodomain-containing protein 4，BRD4)在酒精性肝损伤中起促炎作用，酒精性肝损伤中BRD4过表达抑制Aml-12细胞中Sirt1的表达，负向调节Sirt1/Beclin1轴，加重乙醇诱导的小鼠肝损伤[83]。在另一项乙醇喂养小鼠实验[84]中，嗜中性粒细胞中Sirt1表达显著下调，导致CCAAT/增强子结合蛋白α(CCAAT/enhancer-binding protein alpha，C/EBPα)乙酰化水平升高，进而激活NLRP3和IL-6的表达，促进炎症介质和ROS的产生，亦可加剧肝损伤。miR-34a可直接靶向抑制Sirt1的表达，使巨噬细胞向促炎M1表型极化，增强乙醇诱导肝损伤期间脂肪性肝炎和血管生成[85]。最新研究[86]表明，二氢杨梅素通过调节miR-155-5p/Sirt1/电压依赖性阴离子通道1(voltage dependent anion-selective channel 1，VDAC1)通路，促进肝脏再生，改善酒精性肝损伤。此外，*Sirt1*基因缺陷型小鼠表现出NF-κB蛋白的异常乙酰化修饰，并伴随显著的肝脏炎症反应[87]。相反，在*Sirt1*转基因小鼠模型中，NF-κB信号通路受到显著抑制，IL-6、TNF-α等促炎细胞因子减少，肝脏受到保护[88-90]。Sirt1/核转录因子红系2相关因子2(nuclear factor-erythroid 2-related factor 2，Nrf2)/血红素加氧酶1(heme oxygenase 1，HO-1)通路也被发现可改善乙醇诱导的大鼠肝纤维化[91]。综上，Sirt1抑制ALD进展，靶向Sirt1有望成为ALD治疗的新方向。

2.3.2 Sirt3与ALD

乙醇干预可降低Sirt3在巨噬细胞RAW 264.7中的转录、翻译水平[92]，这一现象在乙醇喂养的动物模型中得到验证[93]。肝特异性*Sirt3*基因敲除小鼠能通过抑制自噬改善乙醇诱导的肝损伤，而上调Sirt3表达水平会加重ALD[94]。但有国外学者[95]发现Sirt3的减少可能通过调控线粒体氧化磷酸化(oxidative phosphorylation，OXPHOS)复合物及铁摄取相关蛋白转铁蛋白受体1(transferrin receptor 1，TfR1)的表达，影响能量代谢并促进铁过载，共同参与ALD的病理进展，且Sirt3在长期饮酒相关的致癌作用中发挥积极作用。另有研究[96]表明，在乙醇摄入的代谢损伤模型中，Sirt3通过AMPK-Sirt3轴促进脂质氧化代谢并抑制脂质积累，其表达上调减弱酒精相关的肝脂肪变性。因此，Sirt3在ALD中主要发挥保护作用。

2.3.3 Sirt6与ALD

Sirt6在乙醇暴露小鼠中表达水平下降。小鼠肝脏Sirt6的缺陷已被证明会导致肝脏脂肪变性、炎症和纤维化，这是酒精性脂肪性肝炎的标志[97]。Kim等[98]报道*Sirt6*转基因小鼠通过抑制炎症级联反应、肝细胞脂质蓄积及ROS水平延缓ALD进程，*Sirt6*基因敲除小鼠则发生了以氧化应激和炎症显著增加为特征的严重肝损伤。同Sirt1表现相同，Sirt6可抑制内质网应激来预防ALD[99]。Sirt6通过负调控肝脏X受体、碳水化合物反应元件结合蛋白和甾醇调节元件结合蛋白1这3种转录因子，促进脂肪酸β氧化，以及抑制甘油三酯合成来维持肝脏脂质稳态。在*Faf2*敲低小鼠的肝脏内，Sirt6和FOXO3协同抑制前蛋白转化酶枯草杆菌蛋白酶/kexin 9型(proprotein convertase subtilisin/kexin type 9，PCSK9)启动子区域的组蛋白H3乙酰化，从而降低肝脏PCSK9水平，增加低密度脂蛋白受体表达，减少血浆低密度脂蛋白胆固醇，最终缓解乙醇诱导的肝脏脂肪变性[100]。因

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此，Sirt6在ALD损伤中发挥保护作用。

2.3.4 Sirt7与ALD

Sirt7在ALD中表达增加。研究[101]发现，乙醇处理后，Sirt7的主要靶点为CCL2。Sirt7通过NF-κB信号通路调控骨髓细胞分泌CCL2，从而促进ALD的发生。髓系细胞特异性*Sirt7*基因敲除显著减轻了乙醇诱导的肝损伤、炎症和细胞浸润，而对脂质代谢途径的影响则较为轻微。乙醇处理在体外和体内通过肝细胞中的CYP2E/ROS轴上调Sirt7并抑制E-钙黏蛋白表达，降低Sirt7活性完全消除了乙醇介导的肝癌转移在体内的促进作用[102]。Ding等[103]证明了Sirt7通过调节SMAD2蛋白和SMAD3蛋白的乙酰化直接调节肝星状细胞活化，诱导肝纤维化的发生。因此，Sirt7促进ALD的发展。

2.3.5 其他Sirts与ALD

ALD患者肝脏病变的严重程度与Sirt2蛋白表达呈负相关，过表达*Sirt2*基因可保护肝细胞免受乙醇诱导的受体相互作用丝氨酸/苏氨酸蛋白激酶3(receptor-interacting serine/threonine-protein kinase 3，RIPK3)依赖性坏死[104]。Sirt4的有效表达显著提高了线粒体质量与功能，并降低了HCC细胞中的线粒体DNA(mitochondrial DNA，mtDNA)和氧化应激水平，诱导HCC细胞分化并抑制其发展[105]。采用Lieber-DeCarli液体饮食饲喂28 d后，小鼠肝脏线粒体中Sirt5表达水平降低，转录调控因子PGC-1α和p53发生异常乙酰化，同时关键信号分子蛋白激酶B(protein kinase B，AKT)和FOXO1的磷酸化水平明显下调，进而破坏线粒体-细胞核间的信号转导通路，导致酒精性肝损伤的发生[106]。

2.4 IV类HDAC与ALD

HDAC11在代谢障碍相关脂肪性肝病的体外和体内模型中均显著过表达，抑制HDAC11可通过促进AMPKα1在Thr172位点的磷酸化，进而调控肝脏的脂肪生成和脂肪酸氧化过程[107]。HDAC11是抗炎细胞因子IL-10的负调控因子[108]。ALD的发生与肠道LPS激活肝内巨噬细胞(Kupffer cells，KCs)并触发炎症级联反应密切相关。KCs作为IL-10的主要分泌细胞，其功能异常直接影响肝脏炎症微环境[109]。乙醇暴露可显著上调KCs中的HDAC11水平，抑制IL-10生成，最终增强KCs对LPS刺激的敏感性，加剧肝脏炎症反应并加速ALD病理进程，同时，HDAC11的表达也受乙醇代谢物及NF-κB通路的调节[110]。在*HDAC11*条件性敲除小鼠中，肝激酶B1(liver kinase B1，LKB1)/AMPK信号通路被激活，糖酵解通路下调，癌症干细胞特性被抑制，HCC的发生率降低，生存期延长[25]。

3 HDAC抑制剂与ALD

多数HDACs抑制剂可通过靶向表观遗传调控机制来延缓ALD进展。HDAC1、HDAC2、HDAC3、HDAC6、HDAC8、HDAC11抑制剂如丁酸钠等[39, 46, 52]，拮抗过度活化的HDAC功能，促进关键调控蛋白的乙酰化修饰[58]，有效抑制乙醇诱导的肝脏脂肪变性及炎症反应过度激活、缓解内质网应激和氧化损伤，并阻断肝星状细胞活化及纤维化进程，发挥肝脏保护作用(附图2，https://doi.org/10.57760/sciencedb.31531)。本文总结的HDACs及相关通路蛋白质见表1。

表1　HDAC及相关通路蛋白

Table 1　HDAC and related pathway proteins

HDAC	ALD	上游通路	下游通路	敲除后ALD模型表型	文献
HDAC1	+	NF-κB	CPT-1A	炎症↓ 肝脂质蓄积↓	[39, 41]
HDAC2	+		NOX1	ROS↓	[46]
HDAC3	+		CPT-1A/STAT3-NF-κB	纤维化↓	[52-53]
HDAC8	+	miR-451a		炎症↓ 纤维化↓	[57]
HDAC6	/		Hsp90	炎症↓ 蛋白质运输↓	[62]
HDAC9	−		FAS	肝脂质蓄积↑	[65]
Sirt1	−	BRD4/miR-34α/miR-155-5p	SREBP-1c/AMPK-mTORC-1/FOXO1/PGC-1α-PPARα/VDAC1/Nrf2/HO-1	炎症↑ 脂质变性↑	[70, 73, 75-76, 83, 86, 91]

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表1(续)

HDAC	ALD	上游通路	下游通路	敲除后ALD模型表型	文献
Sirt3	−	AMPK	OXPHOS/TfR1	脂质变性↑ 能量代谢↓	[95-96]
Sirt6	−		PCSK9/SREBP-1c	炎症↑ 纤维化↑ 脂质变性↑	[100]
Sirt7	+	CYP2E/ROS	CCL2	炎症↓	[101-102]
HDAC11	+		AMPKα1/IL-10	肝脂质蓄积↓	[107, 110]

+：促进作用；−：抑制作用；HDAC：组蛋白去乙酰化酶；ALD：酒精相关性肝病；NF-κB：核因子κB；CPT-1A：肉碱棕榈酰转移酶-1A；NOX1：NADPH氧化酶1；ROS：活性氧；STAT3：信号转导及转录激活蛋白3；Hsp90：热激蛋白90；FAS：脂肪酸合酶；BRD4：含溴结构域的蛋白4；SREBP-1c：固醇调节元件结合蛋白1c；AMPK：腺苷酸活化蛋白激酶；mTORC：哺乳动物雷帕霉素靶蛋白复合物；FOXO1：叉头框蛋白O1；PGC-1α：过氧化物酶体增殖受体γ辅激活因子1α；PPAR：过氧化物酶体增殖物激活受体；VDAC1：电压依赖性阴离子通道1；Nrf2：核转录因子红系2相关因子2；HO-1：血红素加氧酶-1；OXPHOS：氧化磷酸化；TfR1：转铁蛋白受体1；PCSK9：前蛋白转化酶枯草杆菌蛋白酶/kexin 9型；CCL2：趋化因子配体2；CYP2E：细胞色素P450亚型2；IL：白细胞介素。

4 结 语

ALD是长期大量饮酒导致的肝脏疾病，其发病机制尚未完全阐明。组蛋白乙酰化/去乙酰化动态平衡的失调，已被证实参与多种良、恶性疾病的发生及发展过程。越来越多的证据表明，HDAC在ALD进展中扮演重要调控角色。其中，多种HDACs亚型如HDAC1、HDAC3、HDAC6、HDAC8、HDAC11及Sirt1、Sirt3等可作为ALD潜在治疗靶点，其下游信号分子如CPT-1A、FAS、FOXO1、PGC-1α等在ALD病理进程中起重要作用。目前，多种HDACs激动剂和拮抗剂已被开发用于ALD研究，但仅有少数抑制剂进入临床试验阶段，多数仍处于基础研究水平。因此，针对HDAC调控ALD病理过程的靶向干预仍需开展更多系统性研究，以期为临床治疗提供强有力的理论依据。

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