表观遗传修饰在酒精性肝病长期进展中的作用研究进展

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摘要: 我国酒精性肝病 (alcoholic liver disease, ALD) 患者超过6 000万, 已成为不可忽视的公众健康问题, 加之“酒文化”这一社会问题尚难以解决, 临床上迫切需要安全有效的ALD防治药物。过去针对ALD的研究主要集中在酒精及其有毒代谢产物的直接损伤作用。但近年来研究显示, ALD的致病原因还包括酒精引起的代谢重编程和内源性代谢物紊乱, 这些内源性代谢物虽无直接毒性, 但其长期效应不容忽视, 特别是可通过表观遗传修饰引起广泛和持久的基因表达谱、信号通路激活异常, 把代谢重编程固化为“代谢记忆”, 并最终引起病理性改变, 进而对ALD的长期进展, 特别是肝纤维化/硬化、肝癌的发生产生重要影响。基于此, 本文就酒精性肝病发病过程中相关代谢物引起的重要的表观遗传修饰变化及其对酒精性肝病的影响进行综述。并对中药及活性成分在调节表观遗传方面作用进行分析。结果提示, 调控表观遗传、改变“代谢记忆”或是中药防治ALD的一种新颖的作用机制。

关键词: 中药; 酒精性肝病; 表观遗传修饰; 代谢重编程; 新药研发

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Research advances on the role of epigenetic modifications in the long-term progression of alcoholic liver disease

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Abstract: There are more than 60 million alcoholic liver disease (ALD) patients in China, which has become a public health problem that cannot be ignored. Moreover, the social problem of "alcohol culture" is still hardly to solve, so that safe and effective prevention and treatment for ALD are in urgent need clinically. Previous studies on ALD have focused on the direct damaging effects of alcohol and its toxic metabolites, while recent studies have shown that the pathogenesis of ALD also include alcohol metabolic reprogramming and endogenous metabolites disorder. Although the endogenous metabolites have no direct toxicity, its long-term effect should not be ignored. These endogenous metabolites could change epigenetic modifications, cause widespread and persistent abnormal gene expression and signal pathway activation abnormally to promote metabolic reprogramming and stamp it as "metabolic memory", which manifest pathological changes and promote ALD, especially liver fibrosis/cirrhosis and liver cancer. Based on this, the article reviews the important epigenetic modifications caused by related metabolites in ALD and their associated effects. The role of traditional Chinese medicine (TCM) and its active ingredients in regulating epigenetics was also analyzed. The results suggest that regulation of epigenetics and alteration of "metabolic memory" may be a novel mechanism of TCM in the prevention and treatment of ALD.

Key words: traditional Chinese medicine; alcoholic liver disease; epigenetic modification; metabolic reprogramming; new drug research and development

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随着社会经济的快速发展，我国酒精性肝病 (alcoholic liver disease, ALD) 逐年快速增加，根据 WHO 统计数据我国 ALD 患者已超 6 000 万，占全球 1.5 亿 ALD 患者的 40%[1,2]。ALD 给我国社会经济和公众健康带来的疾病负担不容忽视。肝脏作为酒精的首要代谢器官，也是最易被损伤的器官之一。ALD 在临床上有多种表现，首先是肝脏脂肪变性，进而逐渐进展到脂肪性肝炎、肝纤维化/硬化、肝癌、肝衰竭等[3]。ALD 临床治疗主要是戒酒，除此之外主要是对症治疗，以及营养支持、防治并发症等[4]，尚缺少特效药物。糖皮质激素可降低重症酒精性肝炎的短期死亡率，但对长期生存率并没有改善[5]。其他治疗药物如己酮可可碱、*N*-乙酰半胱氨酸、肿瘤坏死因子 (tumor necrosis factor, TNF) 抑制剂、IL-22 等[6-8]，对于抗氧化、抑制炎症等方面有针对性的干预作用，但对 ALD 防治的总体疗效均不够理想。ALD 的发生发展是患者长期过量饮酒而对肝脏等造成的持续性损伤过程，这一过程是长期的、渐进的，当 ALD 持续长期进展多年后，戒酒并不能有效地使肝脏病理逆转修复 (完全戒酒在临床上有时也是困难的)，单纯地抑制氧化应激或某一特定炎症反应通路也不足以阻断 ALD 的进展。由于 ALD 患者肝脏病理性损伤的持续进展，酒精性肝硬化和肝癌的发生风险持续积累。因此，系统探讨 ALD 发病机制，寻找新的 ALD 治疗策略和药物具有重要意义。

1 过量饮酒对机体的直接损伤作用

根据美国 NIH 国家酒精滥用与酒精中毒研究所 (NIAAA) 的研究，ALD 的发病机制不仅包括乙醇代谢产物的直接损伤作用，还包括过量乙醇在体内代谢过程中引起的广泛的内源性代谢物紊乱及其下游分子事件。在乙醇直接损伤方面的研究认识已经非常充分，如乙醇代谢产物乙醛及活性氧 (reactive oxygen species, ROS) 本身有直接细胞毒性[9]，可导致肝细胞线粒体损伤并诱发肝脏炎症反应；过量乙醇还可引起肠道细胞损伤、肠源性毒素入血，形成肠−肝损伤的恶性循环机制 (图 1)[10]。

2 过量饮酒对机体的代谢重编程及表观遗传调控

除了直接损伤作用，过量酒精代谢过程中还会引起代谢重编程及相关内源性代谢物异常[11,12]。虽然这些内源性代谢物无直接毒性，但可以引起广泛的表观遗传调控作用[13-15]。而已有研究表明，表观遗传修饰与“代谢记忆”密切相关，促进疾病进程[16-18]。这提示饮酒引起的表观遗传修饰能够把酒精引起的代谢重编程固化为“代谢记忆”，促进 ALD 发展和恶化。现阶段多数团队多从神经生物学角度阐明单次饮酒的长期性、潜在性影响，如德国海涅大学 Cambridge 教授团队[19]研究发现青少年时期单次饮酒过量对海马体产生持续性影响。这种单次酒精引起的分子改变形成急性酒精中毒后持久的细胞变化的基础，并且这种可塑的细胞变化持续到原始乙醇刺激之后，对日后发展成酗酒产生持续性影响。然而，系统性梳理饮酒引起的表观遗传修饰，及促进酒精引起的代谢重编程固化为“代谢记忆”，推动 ALD 发展及恶化的相关内容仍非常有限。

酒精代谢过程非常短暂。饮酒后乙醇的血液浓度只能维持 4～12 h[20]，而其代谢产物乙醛、乙酸的血液浓度也分别只能维持 6～7[21]、7～9 h[21-25]。这提示酒精及其直接代谢产物带来的毒性短暂且相对有限。然而酒精导致的机体内源性代谢紊乱长期、一直伴随 ALD 发病及其进程。本研究团队采用临床 ALD 不同疾病进程阶段的患者血清进行代谢组学数据分析发现，不同病程的 ALD 患者均伴随有以脂质代谢紊乱等为特征的内源性代谢产物紊乱，这种持续性的内源性代谢物紊乱伴随 ALD 疾病的发生及疾病进程[26]。值得关注的是，这些内源性代谢物一方面能够直接影响肝细

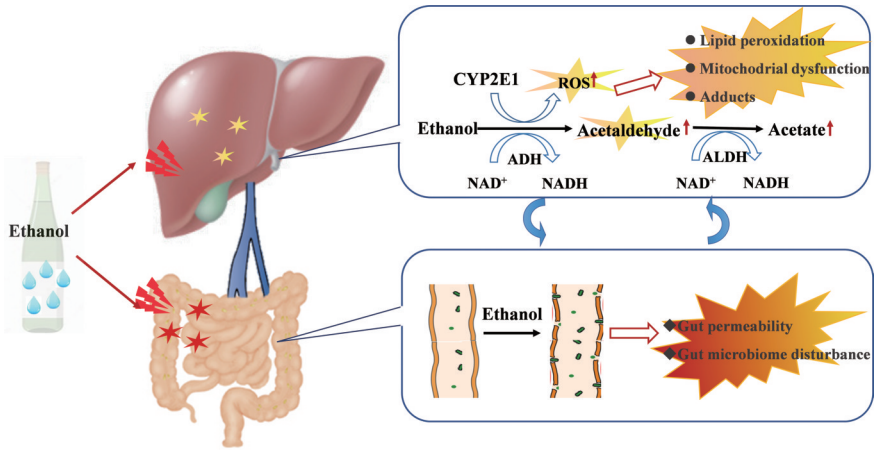

Figure 1 The direct toxicity effect of alcohol administration in liver and intestinal

胞结构和功能, 另一方面能够通过调节表观遗传修饰延长并扩大酒精对肝脏机能的影响力。具体而言, 内源性代谢产物通过调节甲基化、乙酰化修饰调节肝细胞染色体结构, 干预基因表达谱、调节蛋白表达; 通过翻译后修饰影响激酶活性, 调节肝细胞内重要的信号通路的激活状态。通过调节表观遗传, 酒精引起的持续性内源性代谢物异常从肝细胞组成性蛋白谱和饮酒引起的应激性反应等方面, 延长并加剧酒精对肝细胞功能性影响, 促进肝细胞代谢异常固化, 形成 ALD 恶性发展的局面 (图 2)。酒精代谢引起的表观遗传修饰变化不仅能够影响肝实质细胞功能, 还能够调节免疫细胞, 促进炎症反应。长期饮酒通过促进 H3K27 位点甲基化, 富集于 Kupffer 细胞 TGF-β 启动子位置, 且减少 TNF-α 启动子位置富集, 促进促炎因子表达[27]。此外, 长期饮酒引起机体乙酸盐浓度增加, 高浓度乙酸盐通过抑制组蛋白脱乙酰酶, 进而诱导 Th1 和 Th17 细胞活化, 促进炎症反应[28]。越来越多的证据显示, 长期过量饮酒介导的表观遗传学 (epigenetics) 调控通过调节肝实质细胞和免疫细胞[29], 对 ALD 的进展特别是肝纤维化/硬化[30]、肝癌[31]产生的影响, 远超过研究者的传统认知, 是深入阐明 ALD 疾病进展机制, 并指导发现新型治疗药物的重要研究方向。

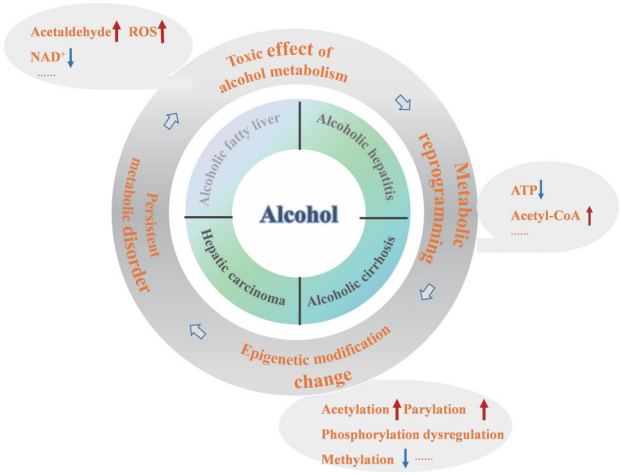

Figure 2　Overview of alcoholic liver disease progression and the associated pathogenic factors

3　ALD 发生发展过程中的表观遗传变化

表观遗传修饰变化与 ALD 疾病进程密切相关。根据 NIAAA 等权威机构的研究, 慢性饮酒可引起氧化型烟酰胺腺嘌呤二核苷酸 (NAD^+)、三磷酸腺苷 (ATP) 和 s-腺嘌呤甲硫氨酸 (SAM) 等内源性代谢物含量异常 (图 3)[32-34]。这些内源性代谢物可通过介导表观遗传修饰对 ALD 发病及疾病进程产生重要作用。具体来说, 这些代谢物是 DNA 和组蛋白甲基化、乙酰化等表观遗传修饰酶的关键性辅酶或底物[35]。

SAM 是体内重要的甲基供体, 生物体内以 SAM 为供体的甲基化修饰 (methylation) 是最重要的生命活动之一, 可以生成甲基化 DNA、磷脂、多胺类等[36]。然而, 长期酒精代谢引起 SAM 合成减少, 促进酒精性肝病发生发展[37]。SAM 不仅是甲基供体, 同时参与谷胱甘肽 (glutathione, GSH) 合成。长期饮酒引起 SAM 合成减少, 减少 GSH 合成, 引起机体抗氧化能力不足, 无法及时消解酒精代谢产生的 ROS 及其他氧化类代谢产物, 加剧酒精引起的肝脏氧应激/脂质过氧化损伤[38]。ROS 积累进一步引起 DNA 链脱氧鸟嘌呤 G 突变为 8-OHdG, 掺入 CpG 岛[39]。CpG 岛中的胞嘧啶残基是常见的 DNA 甲基化位点。8-OHdG 抑制 DNA 甲基转移酶 (DNA methyltransferase, DNMT) 作用, 引起 DNA 低甲基化, 影响染色质的稳定性。长期饮酒引起的 DNA 低甲基化, 增加 c-myc、c-Ha-ras 和 c-Ki-ras 等

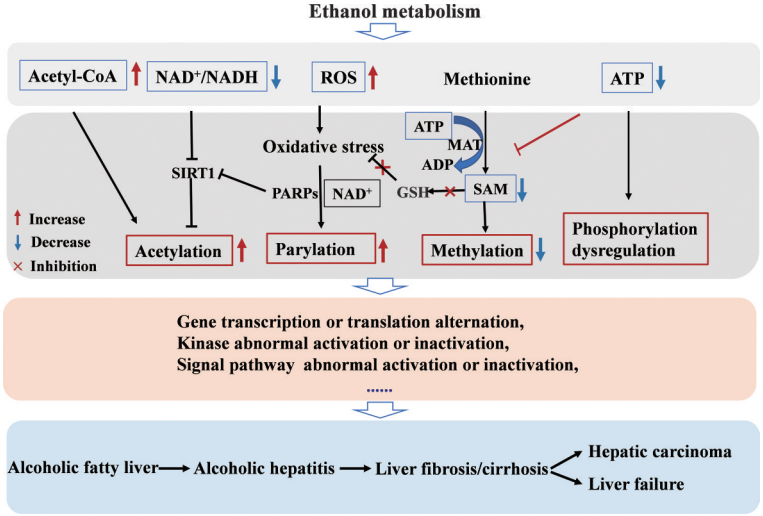

Figure 3　Epigenetic modification changes and their effects caused by alcohol consumption

原癌基因的表达, 诱发肝癌[40]。长期过量饮酒导致DNA低甲基化, 增强ALD小鼠对TNF-α敏感性, 增加肝损伤[41]。此外, 酒精代谢也能够引起组蛋白甲基化。酒精体外研究发现, 酒精引起H3K4甲基化。酒精引起H3K4的甲基化, 还会激活肝脏中肝星状细胞弹性蛋白的表达, 这会导致细胞外基质蛋白的沉积[42]。酒精能够引起模式识别受体Toll样受体4 (Toll-like receptor 4, TLR4) 甲基化, 并且饮酒模式与TLR4甲基化相关[43]。如在轻中度饮酒患者体内, TLR4高甲基化水平与减少的积极与消极的自我唤醒相关 (decreased positive and negative self-reported arousal), 但在重度饮酒人员体内, TLR4甲基化水平与自我唤醒报告和生理性唤醒 (如血压) 增加相关。DNMT活性低下, 减少或耗竭SAM含量, 促进酒精性肝病的发生[44-46], 及其肝硬化、肝癌的进展[47,48]。

酒精代谢调节组蛋白乙酰化作用 (acetylation), 改变基因表达谱。组蛋白乙酰化主要受两大具有相反酶活性的蛋白家族调控: 组蛋白乙酰转移酶 (histone acetyltransferase, HATs) 和去乙酰化酶 (histone deacetylase, HDACs)[49]。一般来说, 组蛋白乙酰化导致转录激活, 而去乙酰化则与基因沉默相关。HATs将乙酰辅酶A的乙酰基连接到组蛋白的赖氨酸残基上, 中和正电荷, 使染色质处于一个开放的构象, 从而导致基因激活。HDACs催化组蛋白去乙酰化, 改变蛋白空间构象, 关闭基因转录状态。HDACs分为I～IV亚蛋白类型。其中, III型HDACs-sirtuins (SIRTs) 是以NAD^+为辅酶的去乙酰化酶, 其活性受到NAD^+含量调控。值得注意的是, NAD^+是酒精代谢相关酶的关键辅酶。长期饮酒使酒精代谢相关酶大量消耗NAD^+, 降低肝细胞NAD^+含量, 抑制SIRTs的去乙酰化作用[50]。同时, 乙醇代谢增加机体乙酸盐浓度, 生成大量乙酰辅酶A, 显著增加乙酰化底物, 促进乙酰化修饰[51-53]。最终, 导致组蛋白过度乙酰化, 改变肝细胞基因表达谱。已有研究表明, 长期饮酒能够持续性抑制SIRT1去乙酰化作用, 调节脂肪生成基因的转录 (如USF1、ChREBP、LXR), 或通过翻译后修饰改变脂质合成相关蛋白激活情况 (如SREBP1 K289乙酰化)[54], 进而持续性抑制脂肪酸β氧化, 促进微管乙酰化积累、降解受损, 引起脂滴积聚, 不断加剧肝脏脂肪堆积[55]。除了调节组蛋白乙酰化修饰以外, 酒精代谢能够抑制SIRT3去乙酰化作用, 引起线粒体蛋白高度乙酰化修饰 (如cyclophilin D乙酰化), 影响线粒体结构, 调节线粒体能量代谢功能[56]。此外, 酒精代谢产物乙醛能够与组蛋白进行加和反应, 引起组蛋白H3和H4的N末端尾部的乙酰化水平显著下调, 扰乱染色质结构促进癌症发生[57]。

甲基化与乙酰化两种表观遗传修饰之间存在相互作用。如DNA甲基化和组蛋白去乙酰化都会抑制基因转录。此外, 组蛋白乙酰化可以诱导DNA去甲基化[58]。然而, 酒精性肝病过程中甲基化与乙酰化修饰之间的相互作用还鲜有报道。

酒精代谢引起二磷酸核糖基化修饰 (parylation), 影响肝细胞命运。长期饮酒, 酒精在乙醇脱氢酶、CYP2E1作用下, 引起乙醛、ROS等氧化型代谢产物积累, 导致DNA损伤[59], 激活多腺苷二磷酸核糖聚合酶家族蛋白PARPs[60]。PARP1参与DNA损伤修复过程, 通过消耗NAD^+底物, 对靶蛋白进行parylation修饰, 募集DNA损伤修复相关蛋白[61]。一方面, PARP1介导的parylation修饰消耗NAD^+底物, 加剧酒精代谢引起的胞内NAD^+耗竭; 另一方面, PARPs介导的parylation是一个消耗ATP的过程。长期乙醇代谢引起的持续性parylation引起ATP持续性、大量消耗, 抑制细胞正常生理活动, 引起持续性肝细胞死亡、肝损伤发生[62]。敲除或抑制PARP1等介导的parylation, 能够抑制或者改善酒精性肝损伤[63]。此外, 由于NAD^+能够作为底物、辅酶因子分别参与PARP1介导的parylation及SIRT1介导的去乙酰化作用, 并且PARPs激活能够抑制SIRT1表达及其去乙酰化, 饮酒引起的持续性parylation合成促进乙酰化修饰积累及其下游分子事件。综上提示, 酒精介导的parylation及乙酰化作用互相联系, 共同促进酒精性肝损伤的发生发展。

持续性饮酒引起不间断的酒精代谢, 这一过程将改变肝细胞能量代谢途径, 引起ATP合成受阻, 并影响多种表观遗传修饰。酒精代谢引起NAD^+含量下降, NAD^+/NADH比例降低, 抑制三羧酸循环, 降低肝细胞ATP产能效率。同时, 酒精代谢引起的多种表观遗传修饰是消耗ATP的过程, 加剧酒精引起的ATP含量下降。值得注意的是, ATP是磷酸化重要的磷酸基团供体, 磷酸化是蛋白翻译后修饰中最为广泛的蛋白活性调节方式和最重要的生命活动调控形式[64]。酒精代谢减少ATP合成, 引起多种激酶磷酸化状态异常, 影响肝细胞状态。如酒精引起AKAP12磷酸化, 促进肝脏星状细胞激活, 促进肝纤维化[65]。酒精抑制Akt磷酸化激活, 进而增加细胞核内FOXO3, 调节基因表达, 改变细胞代谢[66]。酒精代谢引起磷酸化H2AX增加, 提示酒精代谢引起DNA双链断裂, 基因突变诱发癌变的风险增加[67]。此外, ATP作为能量供体、参与多种表观遗传修饰。如ATP参与甲基化供体SAM、parylation修饰的形成过程, 影响甲基化、parylation修饰。同时, 在酒精代谢过程中, 甲基化、parylation修饰加剧酒精代谢

引起的ATP含量降低。

综上提示, ALD疾病进展的机制中乙醇引起的代谢重编程及相关内源性代谢物紊乱 (如NAD^+、SAM、acetyl-CoA、ATP等) 引起的表观遗传修饰的改变, 导致基因表达、激酶活性异常, 不断延长和加剧酒精相关内源性代谢物对肝脏结构和功能影响, 促进肝细胞代谢异常固化, 最终推动ALD从单纯的酒精性脂肪肝向酒精性肝炎、肝纤维化/硬化、肝癌的发展。表观遗传修饰的改变是参与ALD疾病进展的新的重要分子机制之一。以往ALD治疗药物开发集中于调节酒精代谢及其酒精代谢引起的代谢紊乱, 如脂质代谢紊乱[68], 而代谢紊乱引起的表观遗传修饰变化鲜受关注。表观遗传修饰可望成为ALD药物开发的新靶点。

4　酒精性肝病的中医认识与表观遗传的潜在联系

在具体探讨中药调节ALD表观遗传修饰之前, 本研究首先就中医对ALD的认识进行了梳理。中医并不强调酒有直接毒性, 而是认为酒为湿热之品, 久服引起体内"湿"聚, 湿阻运化, 痰浊内生, 肝脾血瘀, 脏腑虚损。故中医治疗ALD往往以健脾化湿为先。这里有一个重要概念值得探讨。中医讲的ALD的"湿证"是什么。首先, 湿证不是ALD的一个疾病阶段, 它贯穿于整个ALD病程, 包括酒精性脂肪肝、酒精性肝炎、肝纤维化/硬化、肝癌。其次, ALD的"湿证"应当不是指某一个基因或者信号通路的紊乱, 而是一群基因或信号通路的改变, 具有广泛性。第三, ALD的湿证大抵是可逆的、可调控的。最近, 有学者提出, 表观遗传修饰可能是中医证候的一种重要的分子机制解释。这反映了中医证候与体质的不同: 体质主要是先天的、遗传的, 故通常认为与基因本身有关; 而证候是后天的、可逆的、可调控的, 可能就与表观遗传调控有一定关联。这一观点给研究ALD湿证有很大的启发, 或许过度饮酒引起的表观遗传改变是ALD湿证的潜在重要机制之一, 中医健脾化湿治疗ALD可能在部分程度上体现了对表观遗传的调控。

5　中药调控ALD表观遗传修饰的研究进展

中药调节表观遗传修饰已有很多报道。临床有效中药可以通过干预表观遗传修饰来逆转疾病进程、改善疾病状态[69-80]。不同药性中药、中药单体及中药复方能够通过调控DNA甲基化、乙酰化修饰等过程发挥重要作用。

基于此, 本研究进一步检索文献库并发现, 已有部分中药调节表观遗传进而改善酒精性肝病的报道 (表1)[71,76,81-84]。如中药成分甜菜碱能够通过调控甲基化调节酒精性肝病发生发展[85]。本课题组基于临床有效的健脾化湿类方剂, 对中药调节表观遗传学进行了较系统的前期探索。研究发现, 健脾化湿类方剂治疗ALD的机制与调控表观遗传密切相关, 其能够调控SAM、NAD^+、ATP含量, 调节SIRT1表达、NAD^+合成限速酶NAMPT表达、抑制parylation缓解酒精性肝损伤。综上, 表观遗传调控是中药治疗酒精性肝病的潜在作用机制, 是包括中药在内新型治疗药物开发的潜在靶点 (图4)。然而, 现阶段中药调节表观遗传的相关研究仍处于起步阶段。

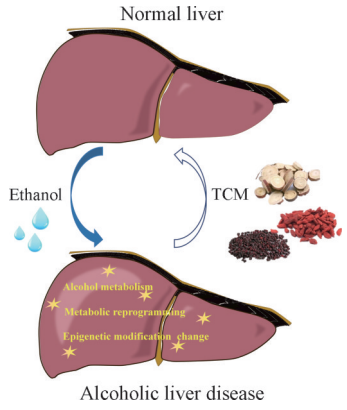

Figure 4　Except for directly regulating ethanol metabolism and metabolic reprogramming, epigenetic regulation has become the potential new targets for the prevention and treatment of ALD. TCM: Traditional Chinese medicine

6　从表观遗传修饰调控角度筛选酒精性肝病治疗药物的策略

补充NAD^+, 促进SAM合成, 或抑制PARPs酶活性, 逆转酒精引起的表观遗传改变 (如乙酰化、甲基化和parylation修饰), 均能够改善ALD, 这说明调控表观遗传有可能成为治疗ALD的新型治疗靶点。NAD^+是

Table 1　The epigenetic modification effect of traditional Chinese medicine and active ingredients on ALD

Potential traditional Chinese medicine	Related disease	Target	Epigenetic modification	Reference
Curcumin	Liver cancer	p16, MGMT	Demethylation	[76]
Yu-Gan granule	Liver cancer	p16, DNMT1, DNMT3A, DNMT3B	Demethylation	[71]
Salvianolic acid A	Alcoholic liver disease	SIRT1	Deacetylation	[81]
Jianpi Huashi formula	Alcoholic liver disease	PARPs, SIRT1	Parylation	
Hovenia dulcis	Alcoholic liver disease	NF-κB	Dephosphorylation	[82]
Glycyrrhizic acid	Alcoholic liver disease	CK-II	Phosphorylation	[83]
Qingganhuoxue Recipe	Alcoholic liver disease	Erk, NF-κB	Dephosphorylation	[84]

调节乙酰化、parylation的重要因子。已有研究报道，酒精性肝炎小鼠模型补充NAD^+前体物质烟酰胺核糖(nicotinamide riboside, NR)，能够激活SIRT1，防治酒精性肝病[32,86]。这一结果提示补充NAD^+，通过调节去乙酰化酶SIRT1，潜在调节肝细胞乙酰化状态，改善酒精性肝病。同时，补充NR能够抑制酒精代谢引起的ROS合成[86]，抑制ROS引起的DNA损伤、PARP1激活与parylation形成。同样地，采用PARP1抑制剂或者敲除PARP1，能够抑制酒精引起的parylation合成，防止酒精性肝病的发生发展。补充SAM，能够改善酒精代谢引起的S-腺苷同型半胱氨酸(S-adenosylhomocysteine, SAH)/SAM比例失调，逆转饮酒引起的GSH含量下降，改善酒精性肝病[87,88]。综上提示，表观遗传修饰调控是包括中药在内的，潜在的新的酒精性肝病治疗药物开发靶点和开发策略。

7 展望

饮酒是人类进化中形成的一种独特生物学和社会学现象，似乎在其他哺乳动物中并不常见。古遗传学对“醉猴假说(drunken monkey theory)”的研究表明，源于1 000万年前的乙醇脱氢酶4的突变可能使灵长类祖先进化出了适应酒精代谢的能力[89]，从而使原始人能够食用富含酒精的发酵水果，获得更高的存活几率，这一时间远早于人类掌握酿酒的时间。时至今日，饮酒已经成为人类社会的重要内容，酒精是世界上最常用的消遣性物质之一，每年针对酒精的消费超过10 000亿美元。尽管人们已经知道过量饮酒是导致200多种疾病和损伤病症的风险因素，由酒精导致的疾病负担在全球疾病和损伤负担的占比高达5.1%[2]，而只要戒除饮酒就会减少损害，但饮酒文化的形成是一个复杂的社会学问题，难以在短时间内被改变。在呼吁社会减少酒精消耗和禁止酒精滥用的漫长过程中，研究者仍迫切需要寻找有效预防和治疗酒精相关疾病特别是酒精性肝病的药物。

本文综述分析了ALD发展过程中过量乙醇引起的内源性代谢物紊乱特点，以及这些内源性代谢物进一步间接地引起表观遗传修饰的可能变化[90,91]，表观遗传修饰又进一步引起了独特的基因转录改变及下游分子生物学事件，参与到ALD疾病进展的多个阶段和不同层面。表观遗传学为认识ALD发病机制和研发防治药物提供了一个新的视角。ALD从本质上讲是一种代谢性疾病，与其他代谢性疾病类似，ALD在中医证候学角度也表现出“湿”的特点，过量乙醇引起的内源性代谢物紊乱，或反映了对ALD“湿证”物质基础的某种认识；内源性代谢物紊乱驱动的表观遗传学改变，或从一个侧面体现了“酒毒湿热之邪”驱动ALD疾病进展的中医病机原理；而“健脾化湿”治法改善代谢紊乱和调控表观遗传或是其阻断ALD疾病进展的一种独特机制。综上，从调控表观遗传的角度筛选和评价健脾化湿中药，可能是发现防治ALD创新药物的一个重要途径和潜在来源。

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利益冲突：所有作者均声明不存在利益冲突。

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