DOI: 10.11844/cjcb.2026.11.0015
中国细胞生物学学报 Chinese Journal of Cell Biology 2026, 48(11): 2682–2692 CSTR: 32200.14.cjcb.2026.11.0015

乳酸代谢紊乱与乳酸化在不同肝脏疾病中的作用与干预策略

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摘要 乳酸作为一种重要的能量底物, 其功能已远超代谢终产物的范畴。乳酸化, 作为组蛋白修饰乃至非组蛋白修饰的关键调控机制, 在肝脏生理与病理过程中的作用日益凸显。肝病的发生发展涉及葡萄糖代谢重编程及其引发的乳酸积累。该文旨在系统阐述乳酸代谢及乳酸化在肝病, 包括代谢功能障碍相关脂肪性肝病、肝纤维化、肝细胞癌及急性肝损伤等进展中的作用, 并重点聚焦于乳酸化影响肝病进展的具体机制。该文还探讨了以乳酸代谢和乳酸化过程为靶点的潜在治疗策略, 为肝病的诊断和精准治疗提供了新的视角与理论依据。

关键词 乳酸; 乳酸化; 代谢功能障碍相关脂肪性肝病; 肝纤维化; 肝细胞癌

Roles of Lactate Metabolic Dysregulation and Lactylation in Different Liver Diseases and Their Intervention Strategies

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Abstract Lactate, as an important energy substrate, has functions that extend far beyond the scope of a metabolic end product. Notably, lactylation, serving as a key regulatory mechanism in histone and even non-histone modifications, has increasingly highlighted its significance in hepatic physiology and pathology. The pathogenesis and progression of liver diseases involve glucose metabolic reprogramming and the consequent accumulation of lactate. This review aims to systematically elaborate on the roles of lactate metabolism and lactylation in the progression of various liver diseases, including metabolic dysfunction-associated steatotic liver disease, liver fibrosis, hepatocellular carcinoma, and acute liver injury, with a particular focus on the mechanisms by which lactylation influence disease progression. This review also discusses potential therapeutic strategies targeting lactate metabolism and lactylation modification processes, offering new perspectives and a theoretical foundation for the diagnosis and precise treatment of liver diseases.

Keywords lactate; lactylation; metabolic dysfunction-associated steatotic liver disease; liver fibrosis; hepatocellular carcinoma

收稿日期: 2026-03-28 接受日期: 2026-09-11
甘肃省妇幼保健院科研基金(批准号: GMCCH2024-3-20)和甘肃省卫生健康行业科研项目(批准号: GSWSKY2024-30)资助的课题
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Received: March 28, 2026 Accepted: September 11, 2026
This work was supported by the Scientific Research Fund of Gansu Provincial Maternity and Child-Care Hospital (Grant No.GMCCH2024-3-20) and the Health Industry Scientific Research Project of Gansu Province (Grant No.GSWSKY2024-30)
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肝脏疾病包括代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)、肝纤维化、肝硬化、急性肝损伤和肝细胞癌(hepatocellular carcinoma, HCC)等[1]。据统计, 肝病相关死亡约占全球总死亡人数的4%, 每年约有200万人因此死亡, 提示肝病已成为全球公共卫生负担[2]。乳酸是葡萄糖经糖酵解生成丙酮酸后, 由乳酸脱氢酶(lactate dehydrogenase, LDH)催化还原产生的重要代谢产物[3]。在生理状态下, 乳酸作为糖代谢的终产物, 其水平受到氧化、脂肪酸合成等多种途径调控, 以维持机体的代谢稳态及酸碱平衡, 当乳酸生成量增加或清除受阻时, 血乳酸水平异常升高, 严重者可发生乳酸性酸中毒[4]。肝脏是乳酸代谢的核心场所。正常状态下肝脏能通过糖异生途径清除乳酸[5]。肝细胞乳酸摄取和糖异生能力下降, 导致肝细胞的乳酸清除能力下降; 同时, 受损肝组织糖酵解活性增强, 进一步促进乳酸生成及高乳酸微环境形成[6]。此外, 持续乳酸积累可加重炎症反应、免疫失衡和促进代谢重编程, 推动肝病进展[7]。赖氨酸乳酸化(lysine lactylation, Kla)是将乳酰基共价连接至蛋白质的赖氨酸残基, 通过修饰组蛋白及非组蛋白, 调控基因表达和蛋白质功能[8]。Kla修饰过程由特定酶催化, 在此过程中, 积累的乳酸先转化为直接底物乳酰辅酶A(lactyl coenzyme A, lactyl-CoA), 进而将乳酰基团转移至蛋白质的特定位点, 完成乳酸化过程[4]。本文系统阐述了乳酸代谢及乳酸化修饰在肝损伤、肝纤维化及HCC等中的调控机制, 为深入理解乳酸化修饰在肝病中的作用提供了重要依据。此外, 文章指出乳酸化作为潜在治疗靶点, 有望为肝病干预提供新的方向。

1 乳酸的产生

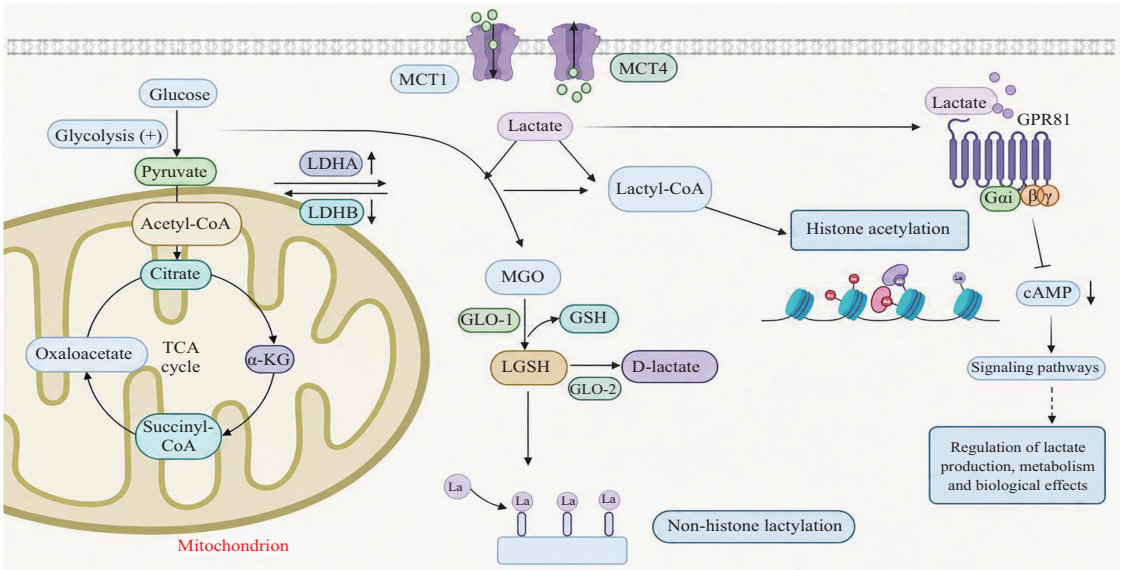
乳酸是糖酵解的重要终产物, 由丙酮酸经乳酸脱氢酶催化还原生成; 乳酸既可在组织缺氧时因糖酵解增强而生成量增加, 也可在氧气充足条件下因有氧糖酵解增强而大量生成, 即Warburg效应。当组织处于缺氧条件下时, 线粒体氧化磷酸化及三羧酸循环(tricarboxylic acid cycle, TCA cycle)受限, 细胞主要通过增强糖酵解, 促使底物水平磷酸化增强来维持三磷酸腺苷(adenosine triphosphate, ATP)供应。在这一过程中, 葡萄糖经己糖激酶2(hexokinase 2, HK2)、丙酮酸激酶M2型(pyruvate kinase M2, PKM2)等关键酶催化生成丙酮酸。由于缺氧限制了丙酮酸在线粒体内的氧化, 其向TCA循环转化的比例降低, 更多丙酮酸在乳酸脱氢酶A(lactate dehydrogenase A, LDHA)催化下以烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)为供氢体被还原为乳酸, 同时再生NAD^+, 以维持糖酵解持续进行[5,9]。此外, 谷氨酰胺是乳酸生成的另一重要来源。谷氨酰胺在线粒体内经分解代谢生成α-酮戊二酸, α-酮戊二酸进入TCA循环后产生苹果酸。苹果酸在胞质中经苹果酸酶催化而转化为丙酮酸, 并最终由LDHA催化生成乳酸[10]。谷氨酰胺通过补充TCA循环中间物, 也间接促进了乳酸生成[11]。

2 乳酸的跨膜转运

乳酸转运分为细胞间和细胞内, 主要通过单羧酸转运蛋白(monocarboxylate transporters, MCTs)家族实现。MCTs属于质子耦联型转运蛋白, 承担着乳酸跨膜转运的任务, 将细胞内的乳酸转运到细胞外, 或将细胞外的乳酸转运到细胞内, 此外, MCT还可以转运其他单羧酸类物质, 如丙酮酸、丁酮酸等[12]。MCT1和MCT4是MCT家族中最为重要的成员, MCT1对乳酸亲和力较高, 主要介导氧化代谢活跃的细胞摄取乳酸, 在特定浓度梯度下亦可参与乳酸外排; MCT4亲和力较低但转运能力较强, 主要负责高糖酵解细胞内乳酸和H^+的外排。MCT1与MCT4协同介导糖酵解细胞与氧化代谢活跃的细胞之间的乳酸穿梭, 从而维持细胞内外乳酸稳态及能量代谢平衡[13]。此外, G蛋白偶联受体81(G protein-coupled receptor 81, GPR81)是乳酸特异性感受器, 可感知细胞外乳酸变化并激活下游信号通路, 调控细胞代谢、炎症反应及其他生物学效应, 但不直接参与乳酸的跨膜转运[14](图1)。

3 乳酸化

赖氨酸乳酸化是一种由乳酸代谢介导的新型蛋白质翻译后修饰, 根据修饰底物可分为组蛋白乳酸化和非组蛋白乳酸化。Kla水平与内源性乳酸浓度密切相关。在M1型巨噬细胞中, 细胞外乳酸摄取和细胞内葡萄糖代谢均可促进组蛋白Kla形成, 而缺氧诱导的乳酸积累可提高组蛋白Kla水平, 进而促进糖酵解基因表达, 增加乳酸生成量[8]。组蛋白乳酸化主要通过调控染色质状态和基因转录发挥作用, 目前已在核心组蛋白H2A、H2B、H3和H4中鉴定出多个赖氨酸位点, 其中H3K18la研究最为深入, 其主要富集于启动子和增强子区域, 可促进靶基因转录激活[15]。除



LDHA: 乳酸脱氢酶A; LDHB: 乳酸脱氢酶B; MCT1: 单羧酸转运蛋白1; MCT4: 单羧酸转运蛋白4; GPR81: G蛋白偶联受体81; TCA cycle: 三羧酸循环; α-KG: α-酮戊二酸; MGO: 甲基乙二醛; GLO-1: 乙二醛酶1; GLO-2: 乙二醛酶2; GSH: 谷胱甘肽; LGSH: *S*-D-乳酰谷胱甘肽; cAMP: 环磷酸腺苷。向上箭头: 上调; 向下箭头: 下调; T型符号: 抑制; +: 激活。

LDHA: lactate dehydrogenase A; LDHB: lactate dehydrogenase B; MCT1: monocarboxylate transporter 1; MCT4: monocarboxylate transporter 4; GPR81: G protein-coupled receptor 81; TCA cycle: tricarboxylic acid cycle; α-KG: α-ketoglutarate; MGO: methylglyoxal; GLO-1: glyoxalase 1; GLO-2: glyoxalase 2; GSH: glutathione; LGSH: *S*-D-lactoylglutathione; cAMP: cyclic adenosine monophosphate. Upward arrow: upregulation; downward arrow: downregulation; T-shaped symbol: inhibition; +: activation.

图1　乳酸代谢及乳酸化在肝病中的作用示意图(此图通过BioRender制作)

Fig.1　Schematic diagram of lactate metabolism and lactylation modification in liver diseases (this image was created using BioRender)

H3K18外, 研究已鉴定出具有调控功能的组蛋白乳酸化位点, 包括H2BK6、H3K9、H3K14、H3K23、H3K56、H4K5、H4K8以及H4K12等[16]。非组蛋白乳酸化则发生于代谢酶、转录因子及信号调控蛋白等底物上, 可通过改变蛋白质活性、稳定性及相互作用参与代谢重编程; HCC乳酸化组学研究鉴定出9 256个非组蛋白Kla位点, 这些位点主要富集于糖、脂质、氨基酸和核苷酸代谢相关蛋白[17]。乳酸化由写入者(Writers)、擦除者(Erasers)和读取者(Readers)共同维持动态平衡。Writers主要负责将乳酰基添加至组蛋白或非组蛋白的赖氨酸残基, 其中p300/CBP相关因子(p300/CBP-associated factor, PCAF)和赖氨酸乙酰转移酶7(lysine acetyltransferase 7, KAT7)可介导乳酸化标记的形成[18]; 此外, 丙氨酰-tRNA合成酶1(alanyl-tRNA synthetase 1, AARS1)和线粒体丙氨酰-tRNA合成酶2(alanyl-tRNA synthetase 2, mitochondrial, AARS2)可直接感知L-乳酸, 并利用ATP生成乳酰腺苷酸中间体(lactyl adenylate intermediate, lactyl-AMP), 进而催化组蛋白及非组蛋白乳酸化[19]。Erasers通过水解并去除赖氨酸上的乳酰基, 使乳酸化具有可逆性, 目前主要包括HDAC1-3(histone deacetylases 1-3)和SIRT1-3(Sirtuin 1-3)[20]。Readers则能够识别特定乳酸化位点, 并募集染色质重塑或转录调控复合物, 将乳酸化标记转化为基因表达变化; 现有研究已鉴定Brahma相关基因1(Brahma-related gene 1, BRG1)以及双PHD指蛋白2(double PHD fingers 2, DPF2)等潜在组蛋白乳酸化Readers[21]。总体而言, Writers负责建立乳酸化标记, Erasers负责清除标记, Readers负责识别并传递其功能信息, 三者共同将乳酸代谢状态与染色质重塑、基因转录及蛋白质功能调控联系起来。综上, Kla作为一种广泛存在且相对保守的新型表观遗传修饰, 与肝脏代谢重编程密切相关, 在多种肝病的发生发展中发挥重要调控作用, 提示其可能成为肝病靶向干预的潜在靶点。

4　不同肝脏疾病中的乳酸代谢和乳酸化

4.1　MASLD中的乳酸代谢与乳酸化调控

MASLD可由单纯脂肪变性逐步进展为脂肪性肝炎、肝纤维化、肝硬化甚至HCC[22]。在疾病进展过程中, 肝细胞能量代谢发生重塑, 糖酵解增强、乳酸清除不足共同导致乳酸在肝组织中积累, 且乳酸水平随病情加重而升高[23]。Lu等[24]发现, MASLD状态下肝细胞

糖酵解和TCA循环过度激活, 伴随乳酸生成量增加及线粒体呼吸功能代偿性减退, PCAF可通过促进LDHB K82位点乙酰化抑制LDHB活性, 使LDHB的乳酸清除能力降低, 并通过增强H3K9乙酰化加重脂质沉积; 抑制PCAF则可减轻肝脂肪变性[25]。乳酸积累还可通过乳酸化调控脂质代谢。研究发现, 线粒体丙酮酸载体1(mitochondrial pyruvate carrier 1, MPC1)缺失可升高肝细胞乳酸水平, 并影响脂肪酸合酶(fatty acid synthase, FASN) K673位点乳酸化, 抑制其酶活性, 从而减少脂质合成和沉积[26]。此外, LDHA诱导的H3K18la可增强甲基转移酶样3(methyltransferase-like 3, *METTL3*)启动子活性, 上调METTL3表达并促进m^6A甲基化修饰; 该过程通过YTH结构域家族蛋白3(YTH domain family protein 3, YTHDF3)促进硬脂酰辅酶A去饱和酶1(stearoyl-CoA desaturase 1, SCD1)表达从而参与MASLD进展[27]。由此可见, 乳酸代谢异常与乳酸化共同参与肝脏脂质代谢调控, 但不同蛋白和位点的乳酸化可产生不同的生物学效应。阐明乳酸代谢与乳酸化在MASLD中的调控机制, 有助于为该病的干预提供新的研究方向。

4.2 肝纤维化中的乳酸代谢与乳酸化调控

肝纤维化是病毒性肝炎、酒精或药物等所致慢性肝损伤的修复反应, 其机制为肝星状细胞(hepatic stellate cells, HSCs)活化并向肌成纤维细胞样表型转化, 导致胶原及细胞外基质过度沉积, 最终肝纤维化可进展为肝硬化甚至HCC[28-29]。近年研究发现, 代谢重编程是HSCs活化的重要特征, 其中糖酵解增强可导致乳酸生成增加与积累, 进而加快肝纤维化进程。糖酵解酶6-磷酸果糖-2-激酶/果糖-2,6-二磷酸酶3(6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, PFKFB3)表达上调可增加HSCs糖酵解通量, 胞质多聚腺苷酸化元件结合蛋白4(cytoplasmic polyadenylation element-binding protein 4, CPEB4)则可通过促进PFKFB3表达加重肝纤维化[30]。此外, 在肝纤维化过程中, 低氧诱导因子-1α(hypoxia-inducible factor-1α, HIF-1α)可转录激活*LDHA*等糖酵解相关基因, 而LDHA主要在胞质中催化丙酮酸向乳酸转化; Wnt/β-连环蛋白通路可上调HIF-1α和LDHA表达, 促进HSCs糖酵解重编程、乳酸积累及纤维化进展[31]。随着乳酸生成量增加, 其转运作用可放大HSCs活化。在肝脏中, 乳酸经MCT1/MCT4转运积累后, 可激活HSCs从而促进肝纤维化。与此同时, 乳酸还可作为信号分子激活GPR81, 增强HSCs的糖酵解活性, 促进肝纤维化; 相反, GPR81缺失可通过激活CREB/Smad7信号通路发挥抗纤维化作用, 提示GPR81可能是乳酸代谢干预肝纤维化的重要靶点[32]。除作为代谢产物和信号分子外, 乳酸还可通过乳酸化参与纤维化相关基因表达调控。研究表明, HK2可通过增加糖酵解通量和促进乳酸生成, 间接影响组蛋白H3第18位赖氨酸乳酸化(histone H3 lysine 18 lactylation, H3K18la)水平及相关基因表达; HK2的缺失会直接导致H3K18la水平下降, 有效抑制乳酸化及肝星状细胞的活化从而减轻肝纤维化[33]。进一步研究发现, H3K18la可通过上调SRY框转录因子9(SRY-box transcription factor 9, SOX9)表达, 促进HSCs分化和细胞外基质沉积, 加快肝纤维化进程[34]。此外, 组蛋白乳酸化还可通过H4K3la调控Th17细胞分化及白细胞介素-17A(interleukin-17A, IL-17A)分泌, 促进干扰素调节因子4(interferon-regulatory factor 4, IRF4)表达并激活HSCs[35]。胰岛素样生长因子2 mRNA结合蛋白2(insulin-like growth factor 2 mRNA-binding protein 2, IGF2BP2)也可通过m^6A依赖性方式增强糖酵解关键酶醛缩酶A(aldolase A, *ALDOA*) mRNA稳定性, ALDOA催化果糖-1,6-二磷酸裂解为磷酸二羟丙酮和甘油醛-3-磷酸, 增强糖酵解活性并促进乳酸大量生成, 且通过组蛋白乳酸化上调α-平滑肌肌动蛋白(alpha-smooth muscle actin, α-SMA)表达, 最终促进肝纤维化发展[36]。

值得注意的是, 肝纤维化中的乳酸代谢异常并非局限于HSCs, 而是涉及肝巨噬细胞、肝细胞、淋巴细胞及肝窦内皮细胞等多种细胞的代谢互作。在纤维化微环境中, 转化生长因子-β(transforming growth factor-β, TGF-β)可激活单核细胞和巨噬细胞, 并通过HIF-1α依赖的方式增强糖酵解, 促进乳酸生成及p300介导的组蛋白H4第12位赖氨酸乳酸化(histone H4 lysine 12 lactylation, H4K12la)。H4K12la在髓系细胞触发受体2(triggering receptor expressed on myeloid cells 2, *TREM2*)启动子富集, 促进单核细胞分化为TREM2高表达巨噬细胞, 进而由TREM2稳定LDHA, 形成TREM2/LDHA/H4K12la环路, 持续增强巨噬细胞的促纤维化表型, 而阻断该环路可减轻肝纤维化[37]。此外, 肝巨噬细胞中HK2上调可增强糖酵解并提高H3K18la水平, 促进糖酵解相关基因表达和M1型极化, 从而加重炎症反应并持续激活HSCs[38]。受损肝细胞同样是纤维化微环境中乳酸

的重要来源。研究表明，肝细胞糖酵解产生的乳酸可经MCT1进入$CD4^+$ T细胞，提高*IRF4*启动子区域H3K18la水平，促进Th17分化及IL-17A分泌，继而激活HSCs并促进细胞外基质沉积[39]。肝窦内皮细胞亦参与代谢相关的促纤维化进程，纤维化相关的细胞外基质硬化能进一步诱导其糖酵解增强，并通过核因子-κB(nuclear factor-κB, NF-κB)介导C-X-C基序趋化因子配体1(C-X-C motif chemokine ligand 1, CXCL1)的表达，促进炎症细胞募集和早期肝纤维化，而内皮细胞特异性抑制糖酵解可减轻肝纤维化[40]。综上，肝纤维化中的乳酸代谢紊乱及乳酸化修饰涉及HSCs、肝巨噬细胞、肝细胞、T细胞和肝窦内皮细胞等多种细胞，靶向乳酸生成、转运及乳酸化调控可能为肝纤维化治疗提供新的策略。

4.3 HCC中的代谢重塑与乳酸化

HCC是全球常见且致死率较高的恶性肿瘤。2022年全球癌症统计数据显示，肝癌新发病例数居恶性肿瘤第六位，死亡病例约80万例，在所有癌症中其死亡率位列第三[41]。代谢重编程是HCC的重要特征，糖酵解增强和乳酸积累不仅可满足肿瘤细胞的能量与物质合成需求，还可持续改变局部代谢和免疫微环境。积累的乳酸能够加重组织缺氧并激活HIF-1α，增强糖酵解，促进乳酸生成[42]，同时，乳酸也可通过调控肝细胞生长因子(hepatocyte growth factor, HGF)、诱导肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)表达并上调程序性死亡配体-1(programmed cell death ligand 1, PD-L1)水平，促进免疫抑制性肿瘤微环境形成和肿瘤进展[43-44]。此外，乳酸的生物学效应还取决于单羧酸转运蛋白介导的跨膜转运。MCT1在HCC组织中高表达，其介导的乳酸摄取可抑制腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)活性，进而上调固醇调节元件结合蛋白1(sterol regulatory element-binding protein 1, SREBP1)和SCD1表达，参与HCC中铁死亡调控[45-46]；在调节性T细胞中，MCT1上调可通过促进乳酸利用，进而提升其免疫抑制功能，且该现象与抗PD-1治疗耐药及不良预后相关[47]。MCT4同样在HCC中高表达，可通过维持肿瘤细胞pH稳态增强其增殖、侵袭和转移能力；抑制或敲低MCT4可诱导细胞死亡，并降低转运蛋白颗粒复合物亚基5(transport protein particle complex subunit 5, TRAPPC5)表达水平，从而抑制HCC细胞增殖和迁移[48-50]。除作为代谢产物和信号分子外，乳酸还可作为底物参与赖氨酸乳酸化，将代谢变化进一步转化为蛋白质功能和基因表达改变。研究显示，HCC中乳酸化总体水平升高并与患者不良预后相关[51]。

组蛋白乳酸化可通过调控染色质状态和癌基因表达促进肿瘤进展。H3K56乳酸化可通过调控癌基因表达促进HCC进展；ATP结合盒转运蛋白亚家族F成员1(ATP-binding cassette sub-family F member 1, ABCF1) K430位点乳酸化则可激活KDM3A/H3K-9me2/HIF-1α信号轴，进一步推动HCC进展[52-53]。非组蛋白乳酸化可直接改变代谢酶和细胞周期调控蛋白的活性，从而参与HCC进展。赖氨酸28的乳酸化可显着抑制ATP代谢酶腺苷酸激酶2(adenylate kinase 2, AK2)的活性，增强HCC细胞增殖和迁移能力[54]；细胞周期蛋白E2(cyclin E2, CCNE2)的乳酸化可促进肿瘤细胞增殖和生长；而SIRT3被激活后，可通过诱导细胞凋亡并抑制体内肿瘤形成，对CCNE2乳酸化介导的促癌作用发挥拮抗效应[55]。此外，Xklp2靶向蛋白(targeting protein for Xklp2, TPX2)乳酸化可破坏其与蛋白磷酸酶1的相互作用，促进极光激酶A(aurora kinase A, AURKA) T288位点磷酸化，加快细胞周期进程并促进HCC进展[56]。因此，在HCC中，乳酸积累既是代谢重编程的结果，也可经乳酸转运和乳酸化重塑肿瘤代谢与免疫微环境，提示针对乳酸生成与转运以及关键蛋白乳酸化的干预，可能为HCC治疗和克服免疫治疗耐药提供新的靶点。

4.4 急性肝损伤中的乳酸代谢与乳酸化调控

急性肝损伤可由药物、缺血缺氧、感染或毒性刺激等多种因素诱发，其病理进程常伴随肝细胞能量代谢重编程。乳酸生成与清除失衡及其介导的蛋白乳酸化，可导致组织损伤，成为推动急性肝损伤进展的重要机制[57]。临床研究显示，乳酸水平升高与肝损伤患者死亡风险增加及预后不良密切相关，提示乳酸代谢紊乱是反映疾病进展的重要特征[58]。在对乙酰氨基酚诱导的肝损伤中，SIRT1/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)/LDHB通路受抑后，线粒体乳酸水平升高并伴随蛋白乳酸化增强，从而加重肝细胞病理损伤；而上调PGC-1α可促进LDHB表达，促进乳酸向丙酮酸转化，减少乳酸积累并减轻肝损伤[59]。乳酸积累还可通过乳酸化将代谢异常转化为炎症和细

胞死亡信号。研究发现, 过量乳酸可诱导巨噬细胞NEDD4(neural precursor cell expressed, developmentally down-regulated 4)乳酸化, 削弱其对Caspase-11的泛素化降解作用, 增加Caspase-11蛋白稳定性, 促进炎症性细胞死亡并加重肝损伤; SIRT1介导的去乳酸化则可恢复NEDD4泛素化活性, 降低Caspase-11水平[60]。热休克蛋白A12A亦可通过抑制肝细胞糖酵解和乳酸生成, 减少高迁移率族蛋白B1(high mobility group box 1, HMGB1)乳酸化并抑制其核质转位和分泌, 进而阻断HMGB1介导的巨噬细胞激活并缓解肝损伤[61]。由此可见, 在急性肝损伤中, 乳酸积累既反映代谢重编程和乳酸清除障碍, 又可通过NEDD4、H3K18和HMGB1等乳酸化驱动炎症、焦亡和细胞损伤, 提示靶向乳酸代谢及乳酸化或可成为急性肝损伤的干预新策略。

4.5 急性肝衰竭中的乳酸代谢与乳酸化调控

急性肝衰竭(acute liver failure, ALF)以短时间内大量肝细胞损伤、坏死和急剧衰退为主要特征, 其病理进程常伴随显著的能量代谢紊乱[62]。肝脏是乳酸清除和糖异生的主要器官, 肝细胞功能受损使乳酸利用和清除能力下降, 导致乳酸在肝组织中积累[57]。这种代谢失衡表现为血清LDH和血乳酸水平升高, 而且与疾病严重程度及不良预后密切相关[63-64], 随着研究深入, 积累的乳酸还可作为赖氨酸乳酸化的代谢底物, 将能量代谢异常转化为表观遗传和蛋白功能改变[65]。急性肝损伤时, 丙酮酸脱氢酶复合物(pyruvate dehydrogenase complex, PDHC)、LDH等代谢酶可向细胞核转位, 引起核内乙酰辅酶A和乳酸增加, 并伴随组蛋白H3高乙酰化; 抑制相关代谢酶活性或组蛋白乙酰化可减轻肝细胞坏死, 提示代谢产物介导的核内修饰参与肝损伤进程[66]。在此基础上, 乳酸依赖的蛋白乳酸化可放大ALF的炎症反应并促进肝细胞死亡[67]。在α-鹅膏毒肽诱导的急性肝衰竭中, 乳酸积累可促进HMGB1乳酸化, 增强其介导的炎症反应并促进细胞凋亡, 从而加重肝细胞损伤[68]。因此, ALF中的乳酸积累可反映肝脏代谢清除障碍, 也可通过乳酸化连接代谢重编程、表观遗传调控, 为急性肝衰竭的干预提供了新的调控思路。

5 靶向乳酸代谢与乳酸化的肝病干预策略

5.1 中药化合物靶向糖酵解酶

在HCC、肝纤维化及急性肝损伤过程中, 糖酵解增强不仅可促进乳酸积累, 还可通过重塑炎症微环境、诱导肝星状细胞活化以及促使肿瘤细胞代谢适应推动疾病进展。因此, 抑制HK2、血小板型磷酸果糖激酶(phosphofructokinase, platelet, PFKP)、PKM2和LDHA等关键糖酵解酶, 是调控乳酸生成的重要策略。天然化合物具有多靶点协同调节的特点, 其中槲皮素可抑制肝窦内皮细胞HK2、PFKP和PKM2表达, 降低糖酵解通量及乳酸生成量, 进而减少中性粒细胞浸润并缓解肝损伤和肝纤维化; 同时, 其还可通过抑制HK2依赖性糖酵解阻碍HCC进展[69-72]。木香烃内酯通过下调HK2表达抑制糖酵解介导的肝星状细胞活化, 从而减轻肝纤维化[73-74]。姜黄醇可阻断Kruppel样因子5(Kruppel-like factor 5, KLF5)/LDHA通路, 减少乳酸生成并延缓肝纤维化进展[75-77]。除天然化合物外, 靶向乳酸生成的抑制剂也可影响肝病的进展。3-溴丙酮酸和2-脱氧-D-葡萄糖可分别抑制HK2活性和葡萄糖代谢, 与索拉非尼联用能够增强对肝癌细胞增殖、迁移及存活的抑制作用[78-79]。LDHA作为丙酮酸向乳酸转化的关键酶, 也是肝病重要的靶点。培黄素、喹啉-3-磺胺类药物和草胺酸盐通过抑制LDHA表达减少乳酸合成, 从而抑制肝癌细胞增殖[78,80-81]。总体来看, 靶向糖酵解关键酶可通过抑制乳酸生成及其相关代谢重编程, 为肝损伤、肝纤维化和HCC的干预提供潜在治疗策略。

5.2 中药化合物靶向乳酸化

随着乳酸化研究的深入, 肝病干预已由调控乳酸生成和转运, 延伸至乳酸化。乳酸化可通过影响组蛋白转录调控和非组蛋白功能参与肝病进展, 因此可能成为连接代谢重编程与表观遗传调控的重要治疗靶点。在HCC中, 部分天然化合物可通过抑制组蛋白乳酸化发挥抗肿瘤作用。蜂王浆酸通过降低H3组蛋白H3K9la和H3K14la位点的乳酸化水平, 抑制HCC细胞增殖、迁移并促进其凋亡[82-83]。去甲泽拉木醛通过抑制H3组蛋白乳酸化, 削弱肝癌干细胞致瘤性, 并抑制其增殖、迁移[84-85]。除组蛋白外, 非组蛋白乳酸化同样参与HCC进展。磷脂酰肌醇蛋白聚糖-3(glypican-3, GPC3)可促进乳酸生成并驱动c-Myc乳酸化, 加快HCC恶性进展[86]。此外, 管花苷A可通过调控非组蛋白ABCF1乳酸化影响HCC进展[53]。丹酚酸B可降低*LDHA*、*NLRP3*和*IL-1β*启动子区域H3K18乳酸化水平, 抑制巨噬细胞M1型极化和NLRP3/Caspase-1/IL-1β炎症通路激活,

进而减轻肝损伤与纤维化进展[87-88]。鸢尾黄素可促进tRNA来源片段31-R9J(tRNA-derived fragment 31-R9J, tRF-31R9J)与HDAC1的相互作用, 抑制铁死亡相关基因位点的组蛋白乳酸化和乙酰化修饰, 从而减少肝细胞铁死亡及MASLD中的脂质积累[89]。综上, 乳酸化是肝病干预的新靶点, 但其作用具有靶蛋白特异性, 未来仍需明确关键位点及调控机制。不同肝脏疾病中乳酸代谢与乳酸化的差异化作用见表1。

6 讨论

乳酸代谢紊乱及乳酸化贯穿MASLD、肝纤维化、HCC、急性肝损伤和急性肝衰竭等过程。糖酵解增强、线粒体氧化障碍和乳酸清除受限均可导致

表1 不同肝脏疾病中乳酸代谢与乳酸化的差异化作用

Table 1 Differential roles of lactate metabolism and lactylation in different liver diseases

调节因子或药物 Regulators or drugs	靶点 Target	机制 Mechanism	疾病 Disease	参考文献 References
MPC1	FASN K673 lactylation	Inhibition of FASN activity, reducing lipid synthesis and deposition	MASLD	[26]
LDHA	H3K18la	Enhancing *METTL3* promoter activity, promoting m^{6}A modification and SCD1 upregulation, thereby promoting MASLD progression	MASLD	[27]
Tectorigenin	Histone lactylation	Inhibition of histone lactylation at ferroptosis-related gene loci, reducing hepatocyte ferroptosis and lipid accumulation	MASLD	[89]
CPEB4	PFKFB3	Enhance glycolytic flux and lactate production in HSCs, thereby promoting HSC activation and fibrosis	Liver fibrosis	[30]
HIF-1α	LDHA	Promoting glycolytic reprogramming, lactate accumulation, and fibrosis progression in HSCs	Liver fibrosis	[31]
HK2	H3K18la	Upregulation of SOX9, promoting HSC differentiation and extracellular matrix deposition	Liver fibrosis	[33-34]
IGF2BP2	ALDOA	IGF2BP2 stabilizes *ALDOA* mRNA in an m^{6}A-dependent manner, thereby enhancing glycolysis and lactate production	Liver fibrosis	[36]
TREM2	H4K12la	H4K12la enrichment at the *TREM2* promoter, promoting TREM2 overexpression and fibrosis	Liver fibrosis	[37]
HK2	H3K18la	HK2 upregulation enhances glycolysis and H3K18la, promoting M1 polarization and inflammation, and sustaining HSC activation	Liver fibrosis	[38]
Costunolide	HK2	HK2 downregulation inhibits glycolysis-mediated HSC activation and alleviates liver fibrosis	Liver fibrosis	[73-74]
Curcumol	LDHA	Blockade of the KLF5/LDHA pathway reduces lactate production and delays liver fibrosis progression	Liver fibrosis	[75-77]
Royal jelly acid	H3K9la and H3K14la	Inhibit HCC cell proliferation and migration, and promote apoptosis	HCC	[82-83]
Demethylzeylasteral	Histone H3 lactylation	Attenuation of liver cancer stem cell tumorigenicity, with inhibition of proliferation and migration	HCC	[84-85]
Galloflavin, quinoline-3-sulfonamide, glufosinate ammonium	LDHA	Inhibition of LDHA and reduced lactate synthesis, leading to suppressed HCC cell proliferation	HCC	[78,80-81]
3-bromopyruvic acid, 2-DG plus sorafenib	HK2	Inhibition of LDHA reduces lactate synthesis, thereby suppressing the proliferation of HCC cells	HCC	[78-79]
SIRT1	LDHB	Increased lactate and protein lactylation, aggravating liver injury	ALI	[59]
SIRT1 delactylation	NEDD4 lactylation	Stabilization of Caspase-11 and promotion of inflammatory cell death	ALI	[60]
HSPA12A	HMGB1 lactylation	Inhibition of hepatocyte glycolysis and lactate production, reducing HMGB1 lactylation, nucleocytoplasmic translocation, and secretion, and attenuating macrophage activation	ALI	[61]
α-amanitin	HMGB1 lactylation	Lactate accumulation promotes HMGB1 lactylation, amplifying inflammation and apoptosis, and aggravating hepatocyte injury	ALF	[67-68]

乳酸积累, 乳酸可通过MCT1/MCT4介导的细胞间穿梭、GPR81信号转导及蛋白质乳酸化修饰, 参与炎症放大、纤维化及肿瘤进展等病理过程。然而, 现有研究仍存在不足。乳酸水平升高究竟是肝损伤的伴随结果还是致病因素, 尚缺乏严格的时序和因果验证。肝细胞、肝星状细胞、巨噬细胞、淋巴细胞和肝窦内皮细胞均参与乳酸的生成、摄取和利用, 但不同细胞间乳酸来源、转运方向及相互作用尚未被阐明。目前, 乳酸化研究主要聚焦于H3K18la等少数修饰位点及有限的非组蛋白底物, 其Writers、Erasers和Readers的底物识别特征、细胞类型依赖性, 以及与乙酰化、甲基化和m^6A修饰之间的相互作用仍有待深入阐明。在治疗策略方面, 靶向HK2、PKM2、LDHA、MCT1/MCT4或关键乳酸化位点, 可能通过减少乳酸生成、阻断乳酸穿梭或纠正异常乳酸化发挥作用; 槲皮素、木香烃内酯、姜黄醇和丹酚酸B等天然化合物也显示出多靶点干预潜力。未来研究应明确不同肝病阶段中乳酸积累的时序变化及因果作用, 治疗策略应由整体抑制乳酸积累转向细胞及位点特异性调控, 并明确天然化合物的作用靶点、药效基础与安全性, 推动其由机制探索向肝病精准干预转化。

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