DOI:10.3724/cbls.2026012 **CSTR**:32203.14.cbls.2026012
文章编号:1004-0374(2026)01-0070-12

乳酸化修饰在肝细胞癌发展中作用的研究进展

吴茹霞,解 震,杜洋洋,张 宁,张榕明,曹明中,陈光顺*
(甘肃中医药大学,兰州 730000)

摘 要:肝细胞癌(hepatocellular carcinoma,HCC)是一种常见的消化系统肿瘤,起病隐匿,致死率高。由于Warburg效应,在HCC中会产生并积累大量乳酸,使乳酸化修饰出现异常。乳酸化修饰作为一种新发现的蛋白质翻译后修饰,可通过影响相关基因表达及蛋白质功能,调节HCC的恶性进程。本文综述了乳酸的代谢及作用,探讨了乳酸化修饰对肝癌细胞增殖、代谢、转移等方面的影响,旨在探讨乳酸和乳酸化对HCC的影响,为肝癌进展预测、疗效评估以及个体化治疗方案的制定提供新的方法与思路。

关键词:肝细胞癌;乳酸化修饰;乳酸;免疫治疗
中图分类号:{Q514};R735.7 **文献标识码**:A

Research progress on the role of lactylation modification in the development of hepatocellular carcinoma

WU Ru-Xia, XIE Zhen, DU Yang-Yang, ZHANG Ning, ZHANG Rong-Ming, CAO Ming-Zhong, CHEN Guang-Shun*
(Gansu University of Chinese Medicine, Lanzhou 730000, China)

Abstract: This comprehensive review aims to systematically clarify how the newly identified post-translational modification—lysine lactylation—reprograms hepatocellular carcinoma (HCC) biology and to evaluate its potential as both a predictive biomarker and a druggable vulnerability. By integrating the most recent *in-vitro*, *in-vivo* and clinical proteomic data, we delineate three core messages. First, lactate is no longer a mere waste product of the Warburg effect: it is a central signalingmetabolite that accumulates up to ten-fold in HCC tissue, fuels an acidic micro-environment, and supplies the substrate for widespread protein lactylation. Second, lactylation operates through both enzyme-dependent (“writer” p300/GCN5/HBO1, “eraser” HDAC1-3/Sirtuins, “reader” Brg1) and enzyme-independent (methylglyoxal-derived lactoyl-glutathione) mechanisms, thereby modulating chromatin accessibility, transcription-factor stability, metabolic-enzyme activity and sub-cellular protein trafficking. Consequently, hyper-lactylation accelerates every hallmark of HCC aggressiveness—G1/S transition (H3K9/56la, CCNE2-K348la), anabolic rewiring (SCD1, AK2, LDHA feedback loops), epithelial–mesenchymal transition (TPX2, PKM2, Rab7A lactylation) and immune escape (PD-L1, NUPR1, MOESIN lactylation)—while also fostering stemness and resistance to lenvatinib, cisplatin and microwave ablation. Third, because lactylation levels correlate tightly with tumour grade, micro-vascular invasion and overall survival, site-specific lactylation signatures (H3K18la, AK2-K28la, CENPA-K124la, USP14-K336la, ABCF1-K430la) can complement classical AFP and imaging-based surveillance. Therapeutically, we propose a “lactylation clamp” strategy: combine (i) lactate-lowering agents (LDH inhibitors such as FX11, MCT1/4 blockers such as AZD3965, HK2 silencers), (ii) selective p300 catalytic inhibitors (e.g., C646 derivatives) to dampen writing, and (iii) SIRT3 agonists or CRISPR-based HDAC1-3 over-expression to enhance erasing, while monitoring target inhibition with quantitative lactyl-proteomics. Importantly, disruption of the lactylation axis re-sensitizes HCC to PD-1 checkpoint blockade, suggesting that lactylation-directed therapy can be synergistic rather than competitive with immunotherapy. Given the safety record of metabolic modulators in humans, we advocate rapid translation of these combinations into neoadjuvant or adjuvant clinical trials, with H3K18la and AK2-K28la as pharmacodynamic end-points. Aiming to dissect the impact of lactate and lactylation on hepatocellular carcinoma, this review seeks to furnish novel

收稿日期:2025-06-19; **修回日期**:2025-08-04
基金项目:甘肃省教育厅优秀研究生“创新之星”项目(2025CXZX-929)
***通信作者**:E-mail:2512445403@qq. com

methodologies and conceptual frameworks for predictingtumour progression, evaluating therapeutic efficacy, and tailoring individualized treatment strategies for HCC patients.

Key words: hepatocellular carcinoma; lactylation; lactate; immunotherapy

肝癌是一种常见消化系统肿瘤，在常见癌症中位居第六位，HCC（占原发性肝癌的80%）是全球癌症致死的三大主因之一[1]。2022年我国肝癌新发病例数36.77万，位居全国肿瘤发病率第4位；死亡人数31.65万，位居全国肿瘤死亡率第2位[2]。肝癌起病隐蔽，容易错过最佳的手术时机，其病理生理学是一个复杂的多步骤过程。近年来，HCC的化疗、免疫治疗等方式正在不断发展，但HCC预后仍不理想[3,4]。

1985年，Brooks团队提出了乳酸穿梭假说，颠覆了之前关于乳酸仅仅是无氧代谢废物的传统观点，明确了乳酸在能量代谢、糖异生以及细胞信号转导中的关键作用[5]。赵英明教授团队[6]2019年发现了乳酸化修饰这一现象，并证实了组蛋白乳酸化修饰可直接调控染色质的基因转录调控。组蛋白乳酸化修饰作为一种新型的组蛋白翻译后修饰，在肿瘤、纤维化、炎症研究中的热度正在不断攀升。乳酸化修饰与HCC关系密切，但目前基础研究仍不充分，故本文综述了乳酸化修饰影响HCC发生发展的主要作用机制，以及乳酸化修饰在肝癌中的临床意义，为乳酸化修饰治疗肝癌提供新的视角。

1　乳酸的代谢及作用

1.1　乳酸的产生

乳酸是一种有机小分子物质，属于羧酸，化学分子式为$C_3H_6O_3$，其产生途径主要包括糖酵解途径以及苹果酸介导的谷氨酰胺途径（图 1）。葡萄糖通过葡萄糖转运蛋白（glucose transporter，GLUT）进入细胞内，随后在己糖激酶（hexokinase，HK）的作用下生成葡萄糖-6-磷酸（G6P）[7]。G6P在细胞质中经过一系列酶促反应，最终生成丙酮酸（PA）[8]。当氧气充

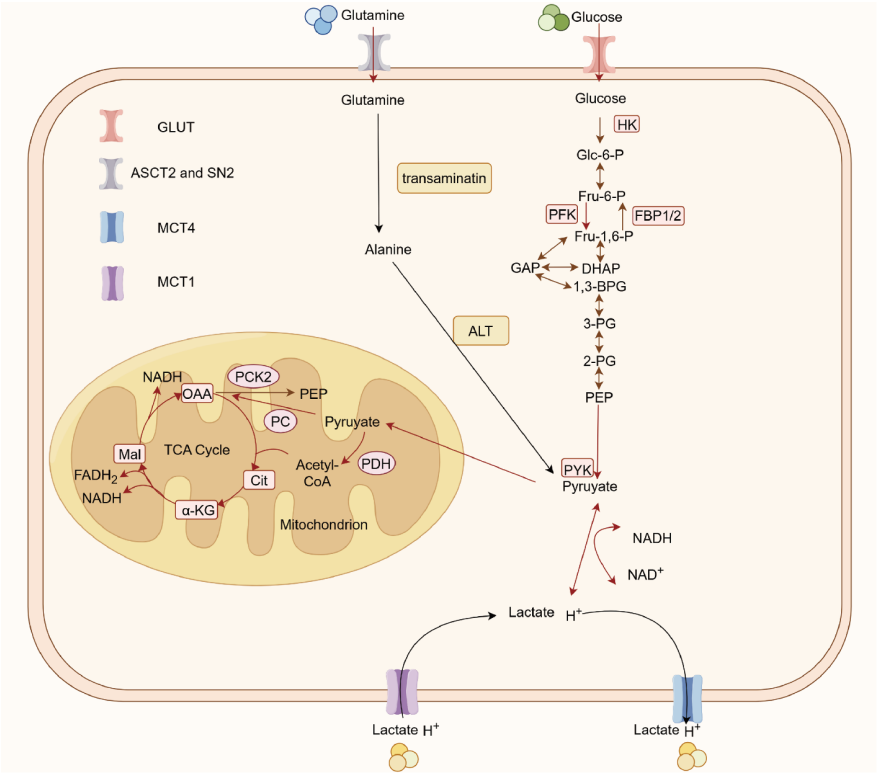

图 1　乳酸产生途径

癌细胞主要通过 Warburg 效应产生乳酸：葡萄糖经丙酮酸和乳酸脱氢酶转化为乳酸。谷氨酰胺也能为乳酸提供碳源，它先转变为丙氨酸，丙氨酸再经转氨作用生成丙酮酸，最后由LDH催化成乳酸。

Figure 1　Lactate production pathway

Cancer cells mainly produce lactate through the Warburg effect, converting glucose to lactate via pyruvate and LDH. Glutamine also fuels lactate by forming alanine, which is transaminated to pyruvate and then converted by LDH.

足时,PA进入线粒体,并在丙酮酸脱氢酶的催化下转化为乙酰辅酶A(acetyl-CoA)。此过程会生成三磷酸腺苷(adenosine triphosphate,ATP)为细胞提供能量支持;但在缺氧条件下,细胞通过糖酵解将葡萄糖分解为PA,PA由乳酸脱氢酶(lactate dehydrogenase,LDH)转化成乳酸。而在癌细胞中,即使氧气充足也倾向于进行糖酵解产生乳酸,这种独特的代谢现象被称作瓦博格效应(Warburg Effect)[9]。这种代谢变化会使肿瘤组织中产生比正常组织高十到数十倍的乳酸[10]。另一种产生乳酸的途径是谷氨酰胺分解产生丙氨酸,经丙氨酸转氨酶作用转化为丙酮酸,再由LDH催化成乳酸。

1.2 乳酸与肿瘤微环境

Warburg效应是在20世纪20年代由德国生理学家奥托·海因里希·瓦尔堡提出的,主要表现为葡萄糖摄取加快,糖酵解活跃,细胞内乳酸水平高,至今仍是癌症的十大特征之一[11]。单羧酸转运体1(monocarboxylate transporter 1,MCT1)对乳酸的亲和力比较高,主要负责将乳酸从细胞内转运到细胞外,维持细胞内乳酸水平的稳定。而在肝细胞癌中,单羧酸转运体4(monocarboxylate transporter 4,MCT4)呈高表达状态,通过促进乳酸排出,增强肿瘤细胞微环境的酸性,从而促进肿瘤进展[12,13]。这种胞外的乳酸堆积从多个方面影响着肿瘤的进展,如图 2所示:(1)直接影响免疫细胞功能。它可以调节免疫抑制细胞及其相关分子,激活细胞内的信号通路,从而改变细胞行为,发挥复杂的免疫抑制作用。同时,这种微环境还会显著影响PD-1的表达以及效应T细胞的功能,从而促使肿瘤细胞逃避免疫监视,最终导致肿瘤的进展[14]。此外,在肿瘤微环境中,巨噬细胞、NK细胞等免疫细胞都可以感知到乳酸的水平,进而激活细胞内的信号通路,调节细胞行为并显著改变其功能[15-17]。(2)形成酸性环境。研究表明,当大量乳酸在细胞外堆积时,形成的pH值在6.0~6.6之间的酸性环境,可促进肿瘤细胞的增殖、侵袭、转移、免疫逃逸[18,19]。(3)为肿瘤细胞代谢提供能源。乳酸在肿瘤细胞中是主要的营养物质,这从根本上改变了乳酸是代谢“废物”的传统看法[20,21]。如非小细

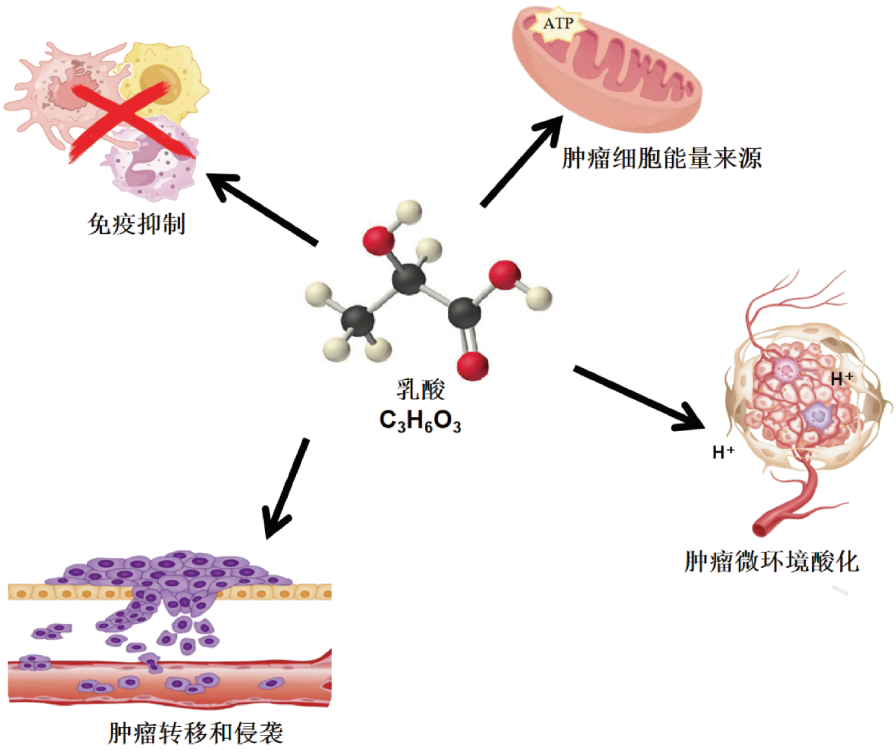

图 2 乳酸在肿瘤微环境中的作用

乳酸过度堆积会直接损害免疫细胞功能,营造酸性的肿瘤微环境,为癌细胞代谢提供能量来源,并促进肿瘤转移与侵袭。

Figure 2 The role of lactate in the tumor microenvironment

Excessive lactate accumulation in the extracellular fluid directly impairs immune-cell function, creates an acidic tumor milieu, fuels cancer-cell metabolism, and promotes tumor invasion and metastasis.

胞肺癌实验显示，进入三羧酸循环中乳酸代谢物是葡萄糖代谢物的两倍，提示乳酸作为肿瘤细胞的能源物质[22]。(4)促进肿瘤转移和侵袭。实验证明，乳酸堆积能够激活相关信号通路，促进肿瘤细胞的上皮-间质转化(EMT)，增强其迁移和侵袭能力[23]。由此可见，乳酸在肿瘤细胞的增殖、转移、免疫逃逸中扮演着核心调控角色，乳酸在肿瘤微环境中具有重要的作用。

2　乳酸化修饰

2019年，赵英明团队[6]首次利用LC/MS技术发现了一种全新的蛋白质翻译后修饰——乳酸化修饰，这是一种由乳酰基与组蛋白赖氨酸残基共价偶联，从而影响染色质基因表达的新型表观遗传修饰。在人类乳腺癌细胞中，他们注意到组蛋白尾部赖氨基酸残基的质量偏移了72.021Da，这和在赖氨酸残基上添加一个乳酰基后出现的质量偏移一致，所以推测赖氨酸残基上添加了乳酸基团；并且利用同位素C13进行追踪，发现内源性与外源性的乳酸都可参加组蛋白赖氨酸的乳酸化修饰[6]。而且近年来研究发现，乳酸化修饰不仅限于组蛋白，还广泛发生于代谢酶、转录因子及结构蛋白等非组蛋白[24,25]。非组蛋白乳酸化修饰可以通过改变蛋白构象、稳定性或互作界面，直接调控细胞代谢重编程、表观遗传及信号转导。赵英明团队[6]发现了酶促依赖的乳酸化修饰，此外，Gaffney等[26]还发现了非酶促乳酸化修饰：糖酵解副产物甲基乙二醛(methylglyoxal，MGO) 在乙二醛酶I的作用下与谷胱甘肽结合，生成乳酰谷胱甘肽(LGSH)，LGSH中的乳酰基可以直接转移到蛋白质赖氨酸残基的ε-氨基上，形成乳酸化修饰，这种修饰过程不依赖特定酶的催化作用。故可将乳酸化修饰分为酶促乳酸化修饰和非酶促乳酸化修饰两种。

2.1　酶促乳酸化修饰

乳酸化修饰的相关酶促反应，主要可以分为三种：写入酶(writer)、擦除酶(eraser)和阅读酶(reader)[27]，如图3所示。赖氨酸乙酰转移酶(lysine acetyltransferase，KAT)家族是催化组蛋白及其他蛋白质乙酰化修饰的重要酶类，其成员包括p300/CBP家族、GNAT家族和MYST家族。近年来，研究发现这

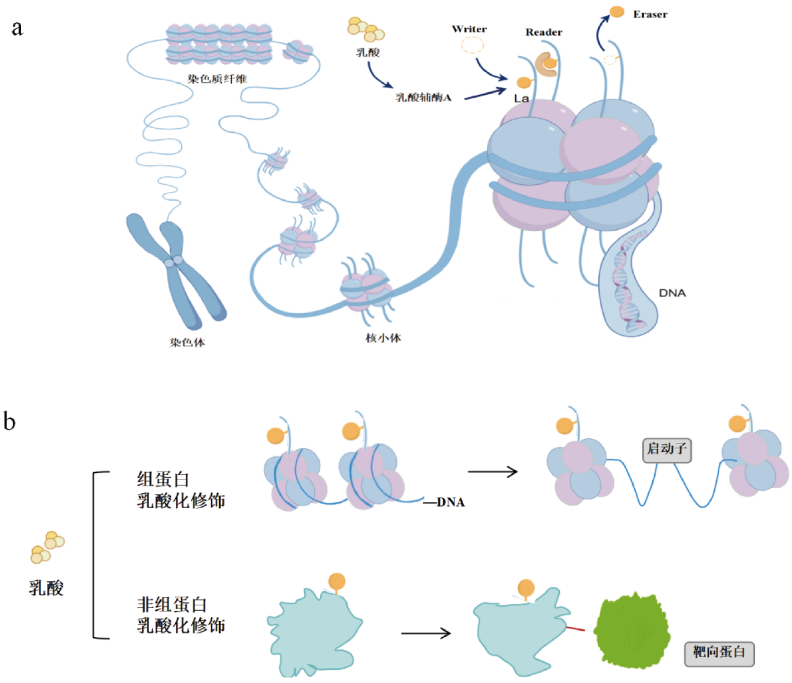

图 3　酶促乳酸化修饰过程

a. 乳酸化水平由写入酶、识别蛋白和擦除酶共同调控。b. 组蛋白乳酸化通过重塑染色质结构来调节启动子活性；非组蛋白乳酸化则通过干扰蛋白相互作用，直接决定靶蛋白的活性。

Figure 3　Enzymatic lactylation modification process

a. Dynamic control of lysine lactylation is achieved by Writers, Readers and Erasers; b. Histone lactylation remodels chromatin to tune promoter activity, whereas non-histone lactylation modulates protein-protein interactions to regulate target-protein function.

些家族中的部分成员也能够促进乳酸化修饰。其中组蛋白乙酰转移酶(histone acetyltransferase,HAT)p300是最早被发现的对乳酸化具有写入功能的蛋白。研究发现,在HEK293T细胞中,p300过表达可引起组蛋白乳酸化水平略有升高;而沉默HCT116和HEK293T细胞中的p300,乳酸化水平明显降低[6]。同样,在不同细胞中通过敲低p300的siRNA 或使用其抑制剂,能够消除p300过表达所导致的乳酸化修饰上调[28-30]。这些研究证实了p300是一个潜在的乳酸化的writer。GCN5是一种重要的赖氨酸乙酰转移酶,参与多种细胞过程,包括基因转录、细胞周期调控和DNA修复[31]。有研究揭示了HBO1靶向的95个内源赖氨酸乳酰化位点,其中大多数位于组蛋白上,其中主要催化组蛋白H3K9位点发生乳酸化[32]。在心肌梗死的相关研究中,Wang等[33]提出白细胞介素-1β(Il–1β)依赖性GCN5募集对组蛋白H3K18乳酸化的催化作用,组蛋白乳酸化促进单核细胞中修复性转录反应的早期远程激活,从而激活心脏的修复过程。在最新的卵巢癌研究中,GCN5不仅可以作为组蛋白乳酸化的writer,还可以催化RAD51在K73位点的乳酸化修饰[34]。研究表明,AARS1可以感知细胞内乳酸水平的变化,还能作为乳酸转移酶催化蛋白质赖氨酸残基的乳酸化修饰,从而影响多种细胞内蛋白的功能,包括p53[35,36]。此外,组蛋白乙酰转移酶、YiaC蛋白、KAT8蛋白也可作为writers在乳酸化修饰中发挥作用[37,38]。

“erasers”是负责去除乳酸化修饰的关键酶,目前发现主要包含两大家族:组蛋白去乙酰化酶(histone deacetylase,HDAC)家族和Sirtuin家族。I类HDAC1~3显著降低了组蛋白中赖氨酸乳酸化水平,以及H3K18和H4K5的乳酸化水平[39]。这表明HDAC1~3在体外作为有效的赖氨酸脱乳酶发挥作用,其中HDAC1和HDAC3显示出组蛋白脱乳酸过程的位点特异性活性[39]。而SIRT1~3 家族成员则主要作为非组蛋白乳酸化的“eraser”。其中SIRT1在多种细胞中广泛表达, SIRT1可以直接去除M2型丙酮酸激酶(pyruvate kinase M2,PKM2)的乳酸化修饰,从而调节糖酵解和细胞增殖[40]。SIRT2在非组蛋白乳酸化中也发挥重要的作用,SIRT2可以降低非组蛋白METTL16的乳酸化修饰,从而调节铜死亡过程[36]。SIRT3是线粒体中的主要去乙酰化酶,也被发现具有去乳酸化的能力。Jin等[41]研究发现,SIRT3可以去除细胞周期蛋白E2(cyclin E2,CCNE2)的乳酸化水平,抑制HCC的生长。此外,SIRT3还可去除Fis1的乳酸化修饰,进而改善线粒体分裂和细胞凋亡[42]。

目前, 对于乳酸化修饰的reader的研究相对有限。Hu等[43]发现, Brg1能够特异性识别并结合H3K18la,并在诱导多能干细胞重编程过程中发挥关键作用。Brg1通过结合H3K18la, 富集在多能性和上皮连接相关基因的启动子区域, 这表明Brg1是H3K18la的“reader”。乳酸化修饰的writer、eraser、reader详见表 1。

表 1 乳酸化修饰的写入酶、擦除酶和阅读酶

Table 1 Writers, erasers, and readers of lactylation modifications

修饰类型	类别	名称	作用位点	参考文献
组蛋白乳酸化修饰	Writer	p300	H3K18、H4K5	[6, 28-30]
	Writer	GCN5	H3K18	[33, 34]
	Writer	HBO1	H3K9	[32]
	Eraser	HDAC1-3	H3K18、H4K5等	[39]
	Reader	Brg1	H3K18la	[43]
非组蛋白乳酸化修饰	Writer	GCN5	RAD51 K73	[33, 34]
	Writer	AARS1	p53等	[35]
	Writer	YiaC	未明确	[37]
	Writer	KAT8	未明确	[38]
	Eraser	SIRT1	PKM2	[40]
	Eraser	SIRT2	METTL16	[36]
	Eraser	SIRT3	CCNE2、Fis1	[41, 42]

2.2 非酶促乳酸化修饰

与酶促乳酸化修饰不同,非酶促乳酸化修饰不需要酶对其进行调控,它通过MGO代谢途径生成的乳酰谷胱甘肽,直接与蛋白质的赖氨酸残基反应,实现修饰[26]。MGO是糖酵解中研究最多的代谢副产物之一,其对许多疾病都有影响[44-46]。MGO是一种活性代谢产物,由糖酵解中间产物二羟基丙酮磷酸和3-磷酸甘油醛等通过一系列化学反应生成。MGO在细胞内通过乙二醛酶途径被清除,首先乙二醛酶1(glyoxalase 1,GLO1)将其捕获为LGSH,然后乙二醛酶2(glyoxalase 2,GLO2)通过释放D-乳酸来再生谷胱甘肽。LGSH对亲核试剂具有反应性,它可以将D-乳酰基转移到赖氨酸残基上,从而完成乳酸化修饰[26]。Zhao等[47]在炎症反应和先天免疫中发现,NF-κB信号通路通过Tristetraprolin介导的mRNA降解,特异性地下调了糖酵解途径中GLO2的表达,LGSH在细胞质中逐渐积累,并诱导蛋白质发

生赖氨酸乳酸化修饰。Trujillo团队[48]通过实验证实,在缺乏初级 LGSH 水解酶和GLO2的RAW264.7巨噬细胞中,LGSH不断积累,组蛋白乳酸化水平增加,炎症反应加剧。这充分证实LGSH是赖氨酸乳酸化修饰的关键因子,对炎症信号转导也发挥了重要的作用。

2.3 乳酸化修饰对蛋白质的影响

组蛋白乳酸化修饰主要通过改变染色质结构进而调节基因表达,非组蛋白乳酸化修饰则是通过改变蛋白质的构象、活性、相互作用和细胞内定位进而调节蛋白质的功能。虽然二者在作用机制和影响范围上存在差异,但它们都可以对蛋白质的功能产生影响。

组蛋白乳酸化修饰可以改变组蛋白的电荷分布及空间构象,使染色质结构变得松散,增加基因启动子区域的可及性,促进基因转录[49]。H3K18la、H3K23la和H4K12la等位点的乳酸化修饰已被证实可以改变染色质的开放状态,进而调节基因TTK和BUB1B的启动子区域,激活其转录,促进肿瘤生长[29]。另外,组蛋白乳酸化修饰在代谢与表观遗传学之间建立了一座桥梁。Li等[29]发现,乳酸化修饰可以激活TTK和BUB1B,从而上调糖酵解酶LDHA的表达,使乳酸产量增加,促进乳酸化修饰,形成正反馈环。同样,在骨生成过程中,内皮细胞通过糖酵解产生乳酸,促进间充质干细胞的组蛋白乳酸化,进而调控成骨基因的表达[50]。

非组蛋白乳酸化修饰则通过改变蛋白质的构象、活性、相互作用及细胞内定位来调节蛋白质的功能。(1)改变蛋白质构象。非组蛋白乳酸化修饰通过将乳酸基团共价直接连接到蛋白质的赖氨酸残基上,改变蛋白质的三维结构,影响蛋白质的活性位点或功能域[51]。Jiang等[52]研究显示,乳酸化修饰通过改变LDHA自身的活性位点构象,进而影响其催化乳酸生成的效率。另有研究发现,在高海拔条件下,HSPB1的K158位点发生了显著的乳酸化修饰,乳酸化改变了HSPB1的构象,从而影响了其与底物蛋白的结合能力[53]。(2)调节酶的活性。非组蛋白乳酸化修饰可以直接影响酶的活性,如在钙化性主动脉瓣疾病模型中发现,醛缩酶A(fructose-bisphosphate aldolase A,ALDOA)的K42位点发生了显著的乳酸化修饰,从而改变ALDOA的构象,直接影响其活性[54]。(3)改变蛋白质间的相互作用。在阿尔茨海默病的研究中[55],淀粉样前体蛋白乳酸化修饰可以抑制其与β-分泌酶的结合,使β淀粉样肽的生成减少。同时,乳酸化修饰促进了淀粉样前体蛋白与CD2相关蛋白的相互作用,加速了淀粉样前体蛋白的内体-溶酶体降解途径。(4)改变蛋白质细胞内定位。乳酸化修饰可以通过改变蛋白质的空间构象和分子相互作用,影响其在细胞内的定位。在HCC中,ABCF1的K430位点乳酸化后,ABCF1进入细胞核,与KDM3A启动子结合,上调KDM3A的表达,使KDM3A-H3K9me2-HIF1A信号轴被激活[56]。

3 乳酸化修饰促进HCC恶性进展

乳酸化修饰的发现极大地推动了疾病研究的进展,其在多种模型和病理学中的作用正在被广泛探索。乳酸化修饰与HCC之间的关联是当前新兴的研究热点。乳酸化修饰因其能够调节蛋白质的功能和稳定性而备受关注。这种调节作用影响了能量代谢、炎症反应和细胞增殖等关键细胞过程,而这些过程与HCC的发生和发展密切相关。随着我们对乳酸化修饰多面性作用的深入了解,开发创新策略以应对全球HCC负担的潜力也在不断增加。

3.1 乳酸化修饰影响肝癌细胞周期和增殖

乳酸化修饰通过影响有丝分裂进程、基因表达等多种机制,影响肝癌细胞周期与增殖,促进肝癌的恶性进展。Liu等[57]发现,乳酸化修饰阻断TPX2与蛋白磷酸酶PP1的结合,增强AURKA的T288磷酸化,从而驱动纺锤体组装和有丝分裂进程。而抑制乳酸生成可降低TPX2乳酸化水平,延缓细胞周期并抑制肿瘤生长。另有研究显示,CCNE2乳酸化可以促进肝细胞癌的生长,而去乙酰化酶可以下调CCNE2的乳酸化水平,以抑制癌细胞的增殖[41]。Pan等[58]发现,组蛋白H3K9和H3K56的乳酸化修饰能够显著上调细胞周期蛋白的表达,推动细胞从G_1期进入S期。研究表明,CENPA在K124位点的乳酸化增强其转录活性,与转录因子YY1协同激活下游基因(如CCND1和NRP2),促进肝癌细胞增殖[59]。Xu等[60]对蜂王浆酸的研究显示,蜂王浆酸通过干扰乳酸产生并抑制H3K9la和H3K14la位点的H3组蛋白乳酰化,抑制肝癌细胞增殖。在低氧环境下,通过敲低GPC3降低了HCC细胞的活力和干性,降低了整体乳酰化和c-Myc乳酰化,进一步降低了c-Myc

的蛋白稳定性和表达,减缓肝癌细胞增殖[61]。

3.2 乳酸化修饰影响肝癌细胞代谢

乳酸化修饰在肝癌细胞中广泛存在,研究表明,乳酸化修饰与乳酸堆积相互促进,乳酸的大量堆积为乳酸化修饰提供“原料”,反之乳酸化修饰通过对细胞代谢的调控促进乳酸的生产,形成正反馈机制[62-64]。如Zeng等[65]发现,HCC细胞内乳酸化水平升高,以组蛋白乳酸化的形式发挥调节作用。H3K14la调节NEDD4的表达,促进了PTEN的降解,而PTEN的降解增加了糖酵解活性,形成了正反馈回路。袁寅团队[56]发现,乳酸作为底物,乳酸化修饰ABCF1-K430la,进而激活HIF1A信号通路,增加乳酸的产生,形成正反馈循环。

乳酸化修饰通过对关键代谢酶的调节,影响肝癌细胞中的代谢过程。研究表明,肝癌细胞中的组蛋白乳酸化通过YTHDC1-m6A-NEAT1轴招募组蛋白乙酰转移酶p300,通过增加硬脂酰辅酶A去饱和酶(stearoyl-CoA desaturase,SCD)启动子区域的组蛋白乙酰化水平,激活SCD的表达,从而通过肝细胞脂质代谢重塑促进肝癌进展[66]。另有研究发现,腺苷酸激酶2(adenylate kinase 2,AK2)的K28位点被乳酸化修饰,这种修饰抑制了AK2的激酶活性,通过影响能量供应和氧化应激参与肝癌细胞的脂质重组[67-69]。

3.3 乳酸化修饰促进肝癌细胞转移

乳酸化修饰可以通过调节转移前微环境形成,调控转移相关基因表达,进而影响肝癌细胞的转移。实验表明,乳酸可促进p300介导的Rab7A蛋白乳酸化,Rab7A的乳酸化抑制其GTPase活性,促使多泡体向质膜而非溶酶体运输,从而增加肿瘤源性外泌体的释放[70]。这些外泌体中富含整合素β4和细胞外基质重塑相关蛋白,能够促进转移前微环境的形成。Qian等[71]验证发现乳酸化修饰的PKM2进入细胞核后,与硫氧还蛋白1结合,降低还原型NF-κB的水平,进而下调chemerin的表达。这一过程最终增强了免疫抑制环境,促进了HCC的转移。在微波消融后的亚致死热应激条件下,H3K18乳酸化水平升高,增强半胱氨酸脱硫酶的转录活性,导致铁硫簇生物合成增加,使肝癌细胞获得抗铁死亡能力,促进转移[72]。Li等[73]发现,LDHA介导的H2BK58乳酸化作用于NDRG1基因,形成代谢重编程与衰老逃逸的表观遗传连接,产生具有转移潜能的细胞亚群。

4 肝癌中乳酸化修饰的临床意义

靶向乳酸化修饰是抑制HCC进程,减轻耐药性,增强抗HCC疗效的新选择[74-76]。乳酸化修饰不仅可以作为预测HCC恶性程度的新型标志物,还可以干扰肿瘤干细胞特性,影响治疗抵抗,并且有望成为HCC治疗的新靶点。

4.1 肝癌的新型标志物

对肝癌样本进行乳酸化修饰分析后发现,肝癌组织中的乳酸化水平显著高于癌旁组织,这表明乳酸化修饰水平的差异可作为肝癌诊断的潜在标志物[67,77]。全球首个HCC乳酸化蛋白质组学分析发现,2 045个乳酸化位点分布在960种蛋白质上。研究发现,H3组蛋白的乳酸化水平在HCC组织中显著升高,目前已证实H3K9la、H3K14la、H3K18la、H3K56la位点的乳酸化水平与肝癌的恶性进程相关,可以被认定为是HCC的潜在诊断标志物[58,60,72,78]。H3K9la和H3K56la修饰通过激活ESM1的转录,从而促进HCC细胞的增殖、迁移和侵袭[79]。Yang等[67]研究发现,AK2的K28位点乳酸化水平在HCC患者中显著上调,通过细胞实验证实,AK2的K28乳酸化会抑制其激酶的活性,导致HCC细胞的能量代谢紊乱,促进HCC细胞增殖。这表明AK2可以作为HCC的潜在诊断标志物。CCNE2的乳酸化水平在HCC中具有显著的诊断价值,有研究证实,HCC组织中的CCNE2 的乳酸化水平显著高于癌旁组织[41]。另外,CENPA、USP14和ABCF1的乳酸化水平也已经被认定为HCC及其转移的潜在诊断标志物[59,80,81]。HCC诊断标志物详见表 2。

表 2 HCC诊断标志物

Table2 Diagnostic biomarkers for HCC

蛋白名称	乳酸化位点	参考文献
H3	H3K9la、H3K14la、H3K18la、H3K56la	[59,61,73,79]
AK2	K28	[81]
USP14	K336	[82]
ABCF1	K430	[57, 83]
CCNE2	K348	[41]
CENPA	K124	[60]

乳酸化修饰不仅可以作为诊断标志物, 更可以作为治疗效果及预后的关键性标志物。Cheng等[77]基于乳酸化相关基因构建了一个预后模型,通过分析乳酸化相关基因的表达水平, 可以预测患

者的治疗及预后效果。Zhang等[82]根据25个乳酸代谢相关标志物的表达，将肝癌患者分为Cluster A和Cluster B两个不同的分子簇，其中Cluster B的患者具有更晚的临床分期、更差的分级和更差的总体生存率。另有研究表明，通过ACACA、MRPL3、MRPS23等乳酸化相关基因建立的预后模型，将肝癌患者分为高评分组和低评分组，其中高分组治疗效果及预后均优于低分组[83]。

4.2 肝癌治疗抵抗

乳酸化修饰通过表观遗传、调控信号通路、干扰肿瘤干细胞特性维持进而影响治疗抵抗。研究表明,组蛋白H3K18la、H3K14la等修饰可直接激活耐药相关基因HECTD2、MCM7、USP34的转录,影响化疗药物的治疗效果[84-86]。乳酸化修饰通过调控KEAP1/NRF2抗氧化通路、PTEN降解反馈环等途径,增强细胞存活能力[86]。与普通肝癌细胞相比,LCSCs表现出更强的糖酵解代谢活性、乳酸积累及更高的乳酸化水平[60]。乳酸化修饰削弱了ALDOA与RNA解旋酶DDX17的结合,从而增强DDX17对LCSCs干性的调控功能[60]。

4.3 基于乳酸化修饰的肝癌治疗新途径

乳酸化修饰与HCC进展关系密切,通过抑制乳酸化相关酶或使用乳酸化抑制剂,可以有效干预HCC的进展。乳酸化过程依赖于LDH、p300、MCT1、MCT、PKM2、HK2、SIRT3、CA3等酶的活性,抑制这些酶的活性可以有效阻断乳酸化的发生,抑制肿瘤进展。LDH是乳酸生成的关键酶,LDH高表达与HCC的Warburg效应和免疫逃逸密切相关。LDH的缺失可以抑制c-Myc/h-Ras驱动的肝癌生长,同时增强了$CD4^+$淋巴细胞的浸润[87]。且有研究证实,可以通过LDH抑制剂降低乳酸化水平,进而抑制HCC的增殖和转移[57]。p300是乳酸化修饰的写入酶,p300的活性与HCC相关蛋白的乳酸化密切相关。研究表明,p300介导的Rab7A乳酸化促进了肝癌细胞外泌体的生成和肺转移[70]。抑制p300可以有效阻断这一过程,从而抑制肿瘤的远处转移。在HCC细胞中,MCT1和MCT4负责乳酸的跨膜运输,二者通过调节乳酸的运输,使细胞内乳酸水平发生改变,进而影响乳酸化修饰[88]。抑制MCT1和MCT4能减少乳酸的运输,降低乳酸化水平,最终达到抑制HCC的恶性进展。PKM2是糖酵解过程中的关键限速酶,负责催化磷酸烯醇式丙酮酸转化为丙酮酸,同时生成ATP。研究发现,在HCC细胞中,PKM2的表达水平与乳酸生成量呈正相关,使肿瘤微环境呈现酸性,进而抑制T细胞活性,发生免疫逃逸[89]。HK2负责催化葡萄糖转化为葡萄糖-6-磷酸,其表达水平在HCC中显著升高[90]。抑制HK2表达可以阻断糖酵解,降低乳酸化修饰水平,从而抑制癌症进展[91]。SIRT3是一种去乳酸化酶,SIRT3通过降低Cyclin E2在K348位点的乳酸化修饰,使其在细胞周期调控中的作用减弱,从而抑制HCC[41]。CA3是一种与细胞代谢和酸碱平衡相关的酶,可以调节细胞内外的碳酸氢盐水平,影响肿瘤的酸性微环境。通过脱乳酸化恢复DUOX2的表达能抑制CA3的过度表达,进而调控肝癌进程[92]。

免疫疗法在治疗肿瘤方面的有效性和安全性已经得到了验证,在肝癌的治疗中也被广泛应用,抗程序性死亡蛋白-1(programmed death-1,PD-1)是主要的免疫治疗方式[93-95]。Ding等[96]发现,PRMT3通过乳酸化修饰激活PDHK1,可以促进乳酸生成,从而使H3K18la上调PD-L1表达,抑制$CD8^+$ T细胞浸润。Cai等[97]发现,乳酸可诱导巨噬细胞组蛋白H3K18乳酸化,从而上调NUPR1转录,NUPR1表达增强TAMs的M2极化,并通过PD-L1/SIRPA通路抑制T细胞功能,从而削弱PD-1抑制剂疗效。该团队还发现,SRSF10通过稳定MYB mRNA上调糖酵解酶,使乳酸含量增加,形成SRSF10-糖酵解-H3K18la正反馈循环,促进M2巨噬细胞极化[98]。乳酸还可以通过MOESIN蛋白的K72位点乳酸化,增强TGF-β/SMAD3信号通路,稳定Treg细胞功能,抑制抗肿瘤免疫[78]。研究表明,阻断PRMT3-PDHK1-乳酸轴,减少PD-L1表达,从而恢复$CD8^+$ T细胞活性[96]。而Gu等[78]研究证实,联合PD-1抗体可显著增强抗肿瘤效果,尤其在MOESIN乳酸化水平低的患者中更敏感。

5 总结与展望

作为一种新兴的蛋白质翻译后修饰,乳酸化修饰在HCC的发生、发展及耐药机制中扮演着关键角色。乳酸化修饰通过影响基因表达、蛋白质功能及细胞代谢,调控肝癌细胞的增殖、代谢、转移和免疫逃逸,从而促进肝癌的恶性进展。乳酸化修饰水平在肝癌组织中显著高于癌旁组织,可作为潜在的诊断标志物。此外,基于乳酸化修饰的靶向治疗策略在增强抗HCC疗效、减轻耐药性方面展现出巨大潜

力,为肝癌治疗提供了新的视角。

虽然乳酸化修饰在HCC中的作用机制取得一定进展,但仍存在诸多不足。未来研究中,需要进一步深入探索乳酸化修饰对HCC的调控机制,明确其在微环境中的功能差异,以期发现更多潜在的治疗靶点。总之,乳酸化修饰在HCC的发生和发展中具有不可忽视的作用。当前的研究成果为这一领域带来了新的研究思路与策略,有助于挖掘针对乳酸化修饰的创新治疗靶点,从而推动HCC治疗策略的创新与发展。

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