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乳酸化修饰在恶性肿瘤中的革新之路

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摘　要

20世纪20年代，Warburg效应揭示肿瘤细胞即使在有氧条件下仍依赖糖酵解生成ATP，颠覆了乳酸作为缺氧代谢废物的认知。此外，乳酸化修饰的发现进一步拓展了乳酸的生物学功能——其不仅是能量代谢产物，更是通过表观遗传重编程驱动肿瘤恶性进展的关键信号分子。本综述系统解析肿瘤微环境中乳酸代谢与转运的动态网络，阐明组蛋白及非组蛋白乳酸化修饰通过调控代谢－表观－免疫交互轴促进肿瘤增殖、转移及耐药的核心机制，并探讨靶向乳酸化修饰的联合治疗策略，为癌症精准治疗提供新方向。

关键词

乳酸，乳酸化，组蛋白乳酸化，非组蛋白乳酸化，恶性肿瘤

Lactyltion in Cancers on the Road to Innovation

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Abstract

In the 1920s, the Warburg effect revealed that tumor cells rely on glycolysis to generate ATP even under aerobic conditions, challenging the traditional view of lactate as a hypoxic metabolic waste product. Furthermore, the discovery of lactylation modification has expanded the biological functions of lactate—it is not only an energy metabolite but also a critical signaling molecule that drives

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malignant tumor progression through epigenetic reprogramming. This review systematically dissects the dynamic network of lactate metabolism and transport within the tumor microenvironment, elucidates the core mechanisms by which histone and non-histone lactylation modifications promote tumor proliferation, metastasis, and drug resistance via regulating the metabolism-epigenetics-immune axis, and explores combination therapeutic strategies targeting lactylation modification, thereby providing novel directions for precision cancer therapy.

Keywords

Lactate, Lactylation, Histone Lactylation, Non-Histone Lactylation, Cancers

1. 概述

乳酸作为糖酵解的代谢副产物，其生成受乳酸脱氢酶(LDH)催化[1]。传统观点认为乳酸是缺氧条件下的代谢废物，而 Warburg 效应的提出揭示了肿瘤细胞的异常糖酵解特征，即使在富氧环境中，仍通过糖酵解产生过量乳酸，导致肿瘤组织乳酸水平显著高于正常组织[2]。体内外研究证实，乳酸不仅是能量代谢产物，更作为自分泌/旁分泌信号，在肿瘤发生、转移及耐药中发挥关键作用，其诱导的肿瘤微环境酸化可促进癌细胞代谢适应、侵袭及免疫逃逸[3]-[5]。因此，肿瘤细胞中乳酸的合成及乳酸信号传导的针对治疗已成为新的治疗方向。

乳酸化修饰是乳酸诱导的新型蛋白质翻译后修饰，作为一种新型的表观遗传调控方式，乳酸诱导的蛋白质乳酸化不仅存在于正常的生理过程[1]，而且在各种疾病，特别是癌症的病因和进展中起着重要作用[6] [7]。因此，对于肿瘤细胞中的乳酸化修饰可能是一种新型治疗靶点，为我们在癌症治疗的进展中提供新的治疗方向。综上所述，乳酸化作为一种新兴的表观遗传修饰类型，为癌症的诊断和治疗提供了新的视角。因此，我们详细总结了乳酸及乳酸化修饰在癌症发生、发展的通路，为癌症的治疗提供新的治疗策略。

2. 癌症中的乳酸代谢

2.1. 乳酸产生的双重途径

葡萄糖经糖酵解生成丙酮酸后进入线粒体，通过三羧酸循环(TCA)氧化为二氧化碳和水；而在低氧环境中，细胞质内乳酸脱氢酶(LDH)将丙酮酸还原为乳酸，维持糖酵解进程[8]。糖酵解是乳酸的主要来源，而肿瘤细胞中乳酸生成还涉及谷氨酰胺代谢：谷氨酰胺经酶促反应转化为 α-酮戊二酸进入 TCA 循环，其碳源通过中间产物最终生成丙酮酸，成为乳酸的次要来源[9]。因此，肿瘤细胞因糖酵解速率异常升高，导致乳酸大量堆积，为其增殖与生存提供关键能量支持。

2.2. 乳酸转运的时空调控

乳酸穿梭机制通过细胞内外乳酸转运维持代谢稳态，其核心由单羧酸转运蛋白(MCT)家族[10]介导，其中 MCT1 和 MCT4 是关键成员：MCT1 在富氧组织中高表达，负责摄取乳酸参与氧化代谢；MCT4 则特异性分布于糖酵解活跃细胞，通过外排乳酸维持胞内酸碱平衡[11] [12]。在肿瘤中，糖酵解型细胞异常

高表达 MCT4，驱动肿瘤微环境酸化，进而促进肿瘤增殖、免疫逃逸及转移[13]。总的来说，乳酸转运不仅实现细胞间代谢协作，更通过塑造酸性微环境，支持肿瘤细胞适应与快速生长(图 1)。

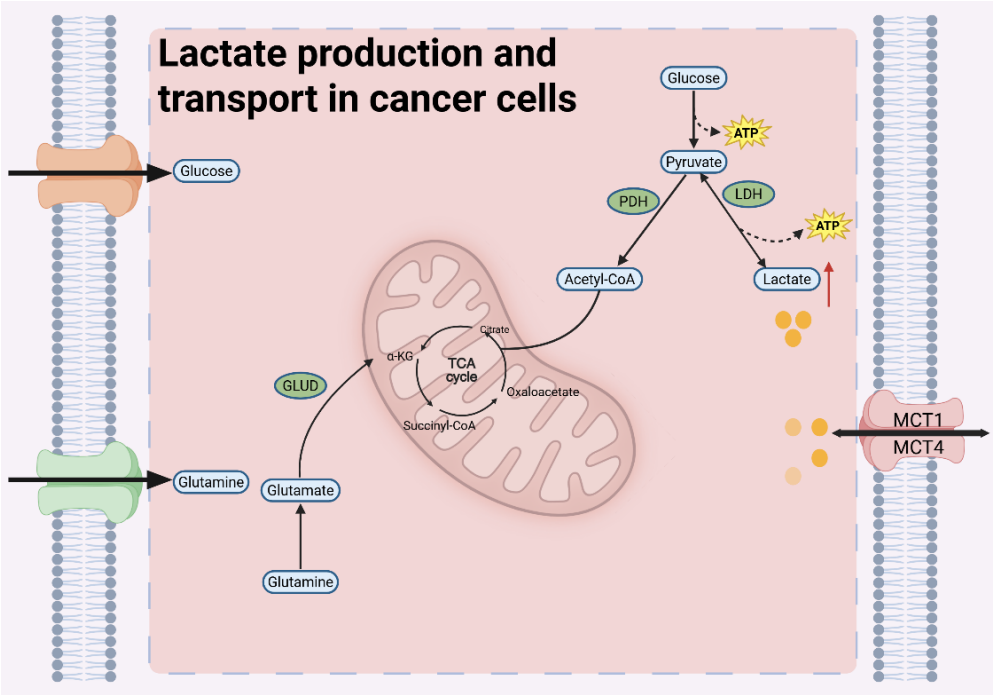

Figure 1. Pathways of lactate production, transport in tumor cells
图 1. 肿瘤细胞中乳酸的产生、转运途径

3. 乳酸与乳酸化修饰

乳酸化修饰最早由 Zhang 等人于 2019 年揭示，其通过在组蛋白尾部的赖氨酸残基上添加乳酸基团实现。研究证实，内源性乳酸升高(如缺氧、细菌感染时)显著增强组蛋白乳酸化水平，而抑制糖酵解或 LDH 活性则降低该修饰，表明其与细胞乳酸代谢密切关联[14]。

组蛋白乳酸化由特定的乳酰基转移酶“writer”和去乳酰化酶“eraser”共同调控，分别在赖氨酸残基上添加或去除乳酰基。随后，被称为“reader”的效应蛋白特异性识别并结合这些修饰，进而影响下游信号通路，调控多种生物过程[15]。最近的研究表明，催化赖氨酸残基乙酰化的酶还具有催化赖氨酸乳酸化(Kla)的能力。迄今为止，几种赖氨酸乙酰转移酶(KATs)，包括 p300 (KAT3B) [14]、CBP (KAT3A) [16]、GCN5 (KAT2A) [17]、HBO1 (KAT7) [18]以及 NAA10 [19]，已被确定为乳酸化的写入酶。此外，AARS1/2 已被确定为一种非经典的乳酸转移酶，能够直接利用乳酸作为乳酸基供体，催化赖氨酸乳酸化(Kla) [20]。然而，鉴定和表征新的乳酸化识别蛋白仍是当前研究的重点领域。

乳酸化修饰不仅存在于组蛋白中，也广泛存在于非组蛋白中(图 1)。在肝细胞癌研究中，通过组学分析鉴定出 9275 个赖氨酸乳酸化位点，其中 99.8% (9256 个)位于非组蛋白，如 PKM2 的乳酸化可促进肝癌细胞增殖与迁移[21]。目前已发现超 2000 个非组蛋白乳酸化位点，涉及 DNA 修复酶(TTK 磷酸化 LDHA1、MRE11)、代谢酶(AK2、FASN)、免疫调控蛋白(cGAS、PD-L1)等[21] [22]。例如，胶质瘤中 ALDH1A3 激活 PKM2，通过“糖酵解–乳酸化–DNA 修复”轴维持肿瘤干性[23]；在前列腺癌中 HIF-1α 乳酸化促进血管生成相关基因转录[24]。因此，非组蛋白乳酸化与疾病关联密切，亟待深入解析其分子机制以挖掘诊疗靶点(图 2)。

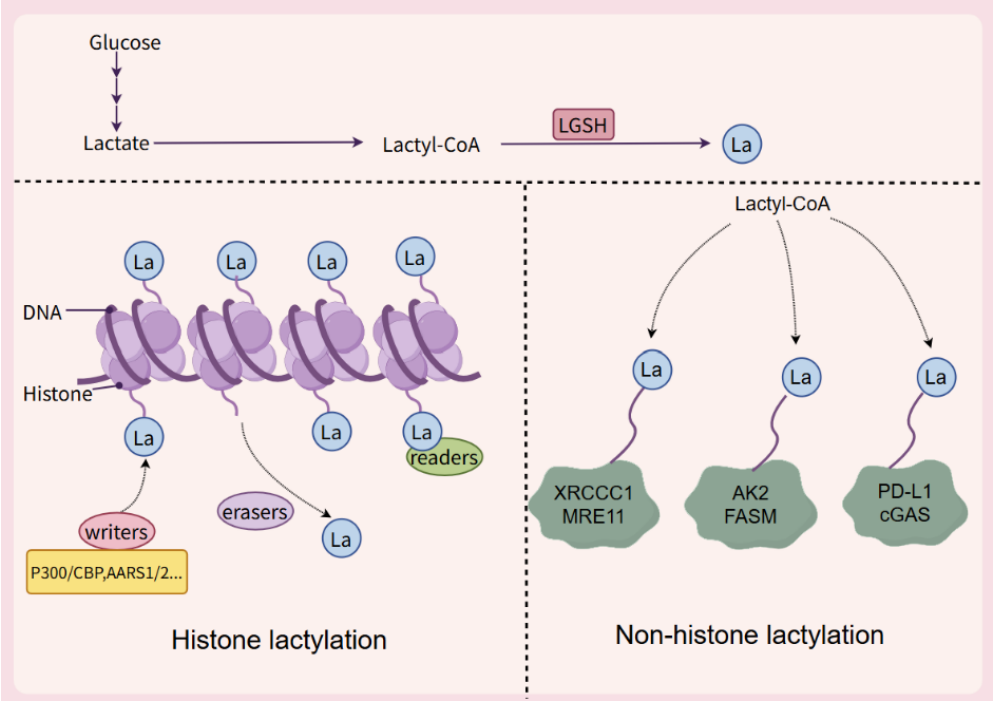

Figure 2. Lactation modification process in tumor cells
图 2. 肿瘤细胞中乳酸化修饰过程

4. 肿瘤与乳酸化修饰

如上所述，肿瘤细胞通过 Warburg 效应产生大量乳酸，导致 TME 中乳酸浓度显著升高。乳酸经单羧酸转运体(MCT1/4)在肿瘤细胞、免疫细胞及基质细胞间穿梭，形成具有信号传导功能的“乳酸池”。组蛋白乳酸化作为核心调控节点，既响应乳酸浓度调节基因表达，又重塑免疫细胞构建免疫抑制微环境。

4.1. 免疫抑制微环境的构建

在肿瘤微环境(TME)中，免疫细胞功能受乳酸代谢显著调控。研究发现，TME 中的乳酸通过抑制 $CD8^+$ T 细胞、自然杀伤(NK)细胞以及树突状细胞等的增殖和功能，进而介导免疫逃逸[25]。对于巨噬细胞，乳酸通过 p300 介导的 H3K18la 修饰激活 *Arg*1、*TGF-β* 等修复基因，驱动其从促炎的 M1 表型向免疫抑制性 M2 表型极化；同时，乳酸激活 HIF-1*α* 通路诱导 PD-L1、IL-10 等分子上调，进一步强化 M2 型巨噬细胞的免疫抑制功能[26] [27]。肿瘤浸润性髓系细胞(TIMs)作为天然免疫调控网络的核心组分，在肿瘤免疫逃逸机制中发挥关键作用。在直肠癌中研究发现，TME 中的乳酸能够通过引发 TIMs 中组蛋白的乳酸化修饰，增强 RNAN6-甲基腺苷(m6A)甲基转移酶 METTL3 的表达，进而通过促进 RNAm6A 修饰并激活 JAK1-STAT3 信号通路，发挥其促癌作用[28]。还可通过上调 CD39/CD73 的表达，增加腺苷生成，激活 A2AR 信号通路，导致髓系抑制细胞(MDSCs)扩增并抑制 NK 细胞活性[29]；直肠癌中该修饰增强 METTL3 介导的 m6A 修饰，激活 JAK1-STAT3 促癌轴[28]。此外，癌症相关成纤维细胞(CAFs)通过糖酵解积累乳酸，除为肿瘤细胞供能外，还诱导胰腺癌细胞神经浸润，协同强化肿瘤微环境酸化[30]。

4.2. 组蛋白乳酸化与表观遗传调控

组蛋白乳酸化通过赖氨酸残基连接乳酸基团调控染色质结构及基因表达，成为代谢向表观信号转化的桥梁。例如，p300 在高乳酸环境中催化 H4K12la，激活癌基因 GCLC 转录，形成“代谢–表观”偶联

[31]。此外，该修饰与乙酰化等表观修饰共享催化机制，如胃癌中 p300 介导的 H3K18la 通过 VCAM1-AKT-mTOR 通路促进转移，而 HDAC 抑制剂可间接抑制乳酸化[32]。

在肿瘤发生中，组蛋白乳酸化可通过表观调控重塑细胞代谢与免疫应答。最新研究发现，乳酸通过诱导组蛋白乳酸化，增强 TGF-β1 的转录活性，激活巨噬细胞中的 Smad3 信号通路，驱动肾脏中巨噬细胞向肌成纤维细胞的转化(MMT)及纤维化进程[33]。另有研究发现，H3K18la 在启动子处富集并激活 TTK 和 BUB1B 的转录，而 TTK 和 BUB1B 又能提高 P300 表达，增加糖酵解。TTK 在 Y239 位点磷酸化 LDHA，激活 LDHA，上调乳酸和 H3K18la 水平，形成糖酵解-H3K18la-正循环/BUB1B 正反馈回路，加剧 PDAC 功能障碍。该发现揭示乳酸代谢与表观遗传调控的密切关联，为 PDAC 乳酸化治疗新策略提供重要依据[34]。

4.3. 驱动肿瘤侵袭与转移

侵袭与转移作为恶性肿瘤的关键特征，受组蛋白乳酸化修饰调控——该表观机制既是肿瘤恶性转化的分子标志，也是驱动癌症死亡的核心因素。例如，乳酸化修饰介导的 FBXO33 基因转录激活通过调控 p53 蛋白多泛素化过程，驱动胆囊癌恶性转移[35]。在神经胶质瘤中，缺氧微环境诱导的 HIF-1α 高表达通过催化 H3K18 乳酸化修饰上调 YTHDF2 基因，增强 YTHDF2 与 BNIP3 的蛋白相互作用，进而通过调控 BNIP3 介导的线粒体自噬重塑细胞代谢，最终影响肿瘤细胞的增殖与侵袭能力[36]。此外，肺癌干细胞来源的外泌体 lncRNA Mir100hg 通过激活组蛋白 H3K14 乳酸化修饰，增强非干细胞肺癌细胞的转移能力[37]。在肝细胞癌(HCC)中，抑制组蛋白乳酸化修饰可显著减弱癌细胞体外恶性表型(包括增殖、迁移及侵袭能力)，并有效抑制体内肿瘤生长及转移[38]。同时，体内外功能研究显示，靶向抑制 PYCR1 可显著抑制 HCC 细胞的增殖、迁移及侵袭能力。机制上，该抑制作用主要通过减少 IRS1 基因 H3K18 位点的组蛋白乳酸化修饰实现：一方面直接抑制 IRS1 蛋白表达，另一方面协同下调糖酵解代谢通路，最终阻断肿瘤恶性表型[39]。

组蛋白乳酸化通过调控上皮–间质转化(EMT)相关基因，驱动肿瘤细胞获得间质表型。例如，在胃癌研究中发现，葡萄糖转运蛋白 3 (GLUT3)可通过增强乳酸脱氢酶 A (LDHA)活性，促进糖酵解衍生的乳酸积累，为组蛋白乳酸化提供充足底物。这一过程伴随关键 EMT 调控基因启动子区的组蛋白乳酸化修饰水平升高，直接诱导上皮标志物 E-cadherin 下调及间质标志物 N-cadherin 上调。功能验证显示，LDHA 过表达可逆转 GLUT3 敲低导致的 EMT 表型缺陷(如细胞侵袭能力下降)，证实 GLUT3-LDHA 轴通过“代谢–表观”偶联直接调控 EMT 进程[40]。此外，在肝细胞癌中，组蛋白乳酸化修饰通过上调内皮细胞特异性分子 1(ESM1)驱动肿瘤血管生成及恶性增殖；而糖酵解抑制剂 2-脱氧-D-葡萄糖(2-DG)可靶向抑制组蛋白乳酸化(Kla)，通过显著上调上皮标志物 E-cadherin 并下调间质标志物 N-cadherin，有效阻断上皮–间充质转化(EMT)进程[38]。然而，目前乳酸化修饰与 EMT 调控的交叉研究仍存在显著空白，其分子互作机制及功能关联亟待系统性探索。

4.4. 调控免疫逃逸

肿瘤微环境中异常糖酵解产生的乳酸除供能外，还作为底物驱动组蛋白乳酸化异常激活，成为免疫逃逸的核心调控机制。乳酸转运至巨噬细胞后诱导 M2 型极化并抑制 $CD8^+$ T 细胞浸润[41]，同时上调 PD-L1、TNFR2 增强 Treg 细胞抑制功能[42]。在非小细胞肺癌中，H3K18la 通过上调 POM121 增强 MYC 核转运，诱导 PD-L1 表达并阻断 $CD8^+$ T 细胞浸润[43]。针对 T 细胞功能的调控，H3K9 乳酸化修饰通过 IL-11/JAK2/STAT3 信号轴，诱导免疫检查点基因表达并介导 $CD8^+$ T 细胞功能耗竭。而靶向 H3K18la 与 H3K9la 的代谢–表观干预策略，可恢复 $CD8^+$ T 细胞效应功能并增强其抗肿瘤应答[44]。

此外，经典免疫检查点 PD-L1 的异常表达也是组蛋白乳酸化修饰的直接调控靶点。PRMT3 可介导 H3K18la 与 PD-L1 启动子特异性结合，驱动乳酸诱导的 PD-L1 表达上调，通过 PD-L1/PD-1 信号轴抑制 T 细胞活化。抗 PD-L1 抗体可逆转这一过程，重塑 $CD8^+$ T 细胞肿瘤浸润能力，提示乳酸化修饰与传统免疫检查点之间存在表观调控协同效应[45]。其他研究还证实，组蛋白乳酸化通过调控 B7-H3 等新兴免疫分子，进一步拓展其在免疫逃逸网络中的分子靶点谱系[46]。

4.5. 介导肿瘤耐药的多维度机制

肿瘤细胞耐药性显著降低化疗有效性，是癌症长期治疗的关键瓶颈，针对组蛋白乳酸化的研究为耐药治疗提供创新靶向策略。组蛋白乳酸化通过 DNA 修复[47]、代谢重编程及铁死亡抑制介导耐药。例如，胶质母细胞瘤中，H3K9la 通过 LUC7L2 介导 MLH1 内含子保留，驱动替莫唑胺耐药，抑制 LDH 可恢复敏感性[48]。非小细胞肺癌中，NNMT-ALDH3A1 与 H3K18la 形成正反馈，介导奥希替尼耐药[49]；卵巢癌中，H4K12la 激活 RAD23A 及同源重组修复[50]，促进铂类耐药[51]。

综上所述，组蛋白乳酸化通过代谢–表观–免疫调控轴在 TME 中构建免疫抑制微环境，驱动肿瘤侵袭、转移、耐药等。尽管其与其他修饰的协同机制及细胞特异性功能有待阐明，仍为癌症精准治疗提供新路径。

5. 组蛋白乳酸化修饰的治疗前景

鉴于乳酸化在癌症代谢中的广泛作用及其对肿瘤和免疫细胞的影响，靶向乳酸化已成为一种很有前景的癌症治疗策略。以下将分述具体干预手段及其机制。

5.1. 抑制乳酸生成与转运

乳酸化修饰的源头是肿瘤细胞糖酵解产生的过量乳酸，因此抑制乳酸生成或转运是核心策略之一，人工合成的葡萄糖类似物 2-脱氧-D-葡萄糖(2-DG)通过竞争性抑制糖酵解关键酶，阻断葡萄糖代谢，在子宫内膜癌及肝细胞癌模型中显著降低组蛋白乳酸化水平并抑制肿瘤生长[52]。然而，其体内代谢快、半衰期短的特性限制了临床转化[53]。相比之下，天然产物 fargesin 作为木兰科植物来源的新型木脂素，靶向糖酵解限速酶丙酮酸激酶 2(PKM2)抑制肿瘤生长并下调组蛋白 H3 乳酸化，有望成为癌症治疗的潜在候选药物[54]。尽管糖酵解抑制剂在耐药治疗、免疫治疗及新兴疗法中的联合应用研究广泛[55] [56]，但单一疗法临床效果尚不明确，凸显非靶向干预在肿瘤治疗中的内在局限。

5.2. 靶向乳酸脱氢酶(LDH)与修饰酶系统

抑制作为乳酸化修饰核心调控酶的乳酸脱氢酶(LDH)，是靶向干预的关键策略。LDH 抑制剂(如 FX11)通过降低细胞内乳酸浓度，减少组蛋白乳酸化并阻断 c-Myc、VEGF 等致癌通路。在肾透明细胞癌中，靶向 LDHA 可阻断 H3K18la 介导的 PDGFRβ 信号轴，抑制血管生成[57]。针对乳酸化修饰酶的干预策略中，P300 溴结构域抑制剂 IACS-70654 通过减少肿瘤相关中性粒细胞浸润、增强 $CD8^+$ T 细胞活性，在三阴性乳腺癌模型中使肿瘤体积缩小 82% [58]。尽管 P300 催化效率较低，但其在高乳酸微环境中的活性增强，提示特定代谢条件对乳酸化修饰的调控作用[59]。

5.3. 阻断乳酸穿梭与免疫联合治疗

MCT1 和 MCT4 是肿瘤细胞中表达的两种主要的单羧酸转运蛋白，分别介导乳酸摄取与排泄，调控能量代谢及微环境酸化[13]。高糖酵解肿瘤中，Treg 细胞通过 MCT1 摄取 TME 中的乳酸，激活 NFAT1 入核上调 PD-1 表达，同时抑制效应 T 细胞 PD-1 表达，削弱免疫治疗效果[60]。因此，MCT 成为肿瘤治

疗的潜在靶点。例如，MCT1 抑制剂 AZD3955 在乳腺癌模型中可降低 MCT 介导的对乳酸的转运[61]，其与抗 PD-1 疗法联用能减少 TME 乳酸释放并增强抗肿瘤免疫[62]。此外，多项临床试验正在评估 MCT 抑制剂与免疫检查点阻断(ICB)的协同效应，提示联合乳酸化修饰抑制剂与免疫疗法或为肿瘤治疗新策略。

5.4. 联合抗血管生成治疗

抗血管生成抑制剂是实体瘤靶向治疗的核心策略之一[63]，其引发的肿瘤微环境缺氧可激活 HIF-1α，驱动糖酵解及乳酸分泌[64]。细胞外乳酸积累可通过 MCT1 介导的摄取进入细胞，促进组蛋白乳酸化修饰[24]。因此，乳酸抑制剂与抗血管生成药物的联合应用可通过阻断异常代谢反馈环，协同增强抗肿瘤疗效。

6. 结论

乳酸化修饰的发现颠覆了人们对乳酸的传统认知，它不仅是肿瘤细胞代谢的“废物”，更是驱动癌症发展的关键信号分子。过去十年，科学家们揭示了乳酸通过表观遗传调控重塑肿瘤微环境、促进免疫逃逸和耐药的机制。例如，中山大学团队发现，乳酸可修饰 DNA 修复蛋白 NBS1，增强肿瘤细胞对化疗损伤 DNA 的修复能力，直接导致耐药表型的产生；而靶向抑制乳酸转运蛋白 MCT 或乳酸转移酶 p300 的策略，已在动物模型中证实能有效抑制肿瘤生长，展现出明确的治疗潜力。然而，当前研究仍面临许多挑战，乳酸化修饰对组蛋白及非组蛋白(如 PD-L1、PKM2)的差异化调控机制尚未完全解析，且肿瘤细胞可通过代谢可塑性规避单一靶点药物攻击。未来研究可借助单细胞多组学与空间代谢组学解析肿瘤微环境中乳酸代谢与修饰的时空特征，开发高特异性乳酸转移酶抑制剂或优化药物递送系统。此外，MCTL 细胞疗法联合 PD-1 抗体在肺癌中实现 71.4%的疾病控制率，司替戊醇等老药新用策略也为逆转耐药提供新思路。这些进展表明，乳酸化修饰研究正从机制解析迈向临床转化，为癌症精准治疗开辟新路径。

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