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乳酸代谢及乳酰化在乳腺癌细胞中的作用机制研究

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摘要 乳腺癌是全世界女性最常见的恶性肿瘤, 也是导致女性肿瘤患者死亡的最重要因素。近期研究表明乳腺癌与乳酸浓度升高相关, 因此研究乳酸对乳腺癌生理学的影响是必不可少的。乳酸是一种糖酵解产物, 是线粒体呼吸的重要能量来源, 乳酸在细胞之间移动并在细胞通讯中起重要作用, 发挥着能量代谢的作用。乳酸可以通过组蛋白和非组蛋白的乳酰化调节基因转录, 乳酰化作为乳酸功能的重要组成部分参与肿瘤增殖和其他生物过程。乳酸可以通过塑造酸性肿瘤微环境、募集免疫细胞, 从而促进乳腺癌进展。靶向乳酸生成、调节乳酸转运和调节乳酰化可能是乳腺癌的潜在治疗方法。该文对乳酸代谢及乳酰化在乳腺癌中的作用, 进行了全面的综述和总结, 以期为未来的研究提供参考和方向。

关键词 乳腺癌; 乳酸; 乳酰化; 乳酸代谢

Study on the Mechanism of Lactic Acid Metabolism and Lactylation in Breast Cancer Cells

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Abstract Breast cancer is the most common malignant tumor in women worldwide and the leading cause of death among female cancer patients. Recent studies have shown that breast cancer is associated with elevated lactate levels, so it is essential to study the physiological effects of lactate on breast cancer. Lactate is a product of glycolysis and an important energy source for mitochondrial respiration. Lactate moves between cells and plays an important role in cell communication, and functions in energy metabolism. Lactate can regulate gene transcription through histone and non-histone lactylation and participate in tumor proliferation, and other biological processes. Lactate can promote breast cancer progression by shaping the acidic tumor microenvironment and recruiting immune cells. Targeting lactate production, regulating lactate transport, and lactylation may be potential therapeutic methods for breast cancer. This article provides a comprehensive review and summary of the role of lactic acid metabolism-lactylation in breast cancer, aiming to provide references and directions for future research.

Keywords breast cancer; lactic acid; lactylation; lactic acid metabolism

乳腺癌(breast cancer, BC)是全球女性最普遍的癌症, 占全球所有新发癌症病例的12.5%, 其发病率随着年龄的增长而增加, 显著降低患者的生活质量, 并构成沉重的经济负担[1]。复发、肿瘤转移引起的并发症导致90%的乳腺癌患者死亡, 因此早期诊断和治疗对患者预后十分重要[2]。影响乳腺癌的

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因素多种多样, 可能与生活方式、遗传因素和环境影响有关。家族史是公认的乳腺癌风险因素, 大约5%~10%的病例归因于遗传因素[3]。BC的主要疗法包括手术、放疗、化疗、内分泌治疗和靶向治疗等[4]。虽然这些治疗方法已经取得了一定的成果, 但全球乳腺癌死亡率仍居前位, 仍然存在着一些问题[5]。因此, 寻找乳腺癌治疗方法的重要性不言而喻。近年来, 乳酸对肿瘤微环境的显著影响已得到广泛关注。

乳酸(lactic acid, LA)是一种代谢产物, 通常在肌肉运动或缺氧条件下产生, 研究表明, 乳酸在肿瘤生长和转移中也起着重要的作用[6]。糖酵解作为乳酸的一种代谢物, 被认为是肿瘤代谢最重要的特征之一, 研究发现, 肿瘤细胞的生长依赖于糖酵解, 乳酸可以在糖酵解肿瘤细胞和氧化性肿瘤细胞之间穿梭, 是它们之间的代谢纽带[7]。在糖酵解过程中, 丙酮酸分子通过细胞质乳酸脱氢酶(lactate dehydrogenase, LDH)的作用转化为乳酸, 而不是直接进入三羧酸(tricarboxylic acid, TCA)循环, 乳酸通过单羧酸转运蛋白4(monocarboxylate transporter 4, MCT4)从细胞质输出到细胞外液, MCT1将乳酸输入到细胞质, 然后, 不同种类的免疫细胞受到高水平乳酸肿瘤微环境的影响, 抑制抗肿瘤免疫反应[8]。此外, 乳酸还可作为肿瘤细胞与其他肿瘤微环境细胞之间的代谢纽带, 帮助肿瘤更好地适应环境并逃避免疫攻击[9]。最近研究表明, 乳酸还可用于产生乳酰辅酶A(lactoyl coenzyme A, lactyl-CoA), 并通过组蛋白乳酰化影响基因转录[10]。

乳酰化, 也被称为赖氨酸乳酰化(lysine lactylation, Kla), 是一种新兴的翻译后修饰, 涉及乳酸与蛋白质中赖氨酸残基的共价键, 由乳酸积累诱导, 从而对基因表达调节产生影响[11]。乳酸在细胞内积累可以直接调节基因表达, 组蛋白乳酰化水平受乳酸剂量依赖性调节[12]。乳酰化可以影响蛋白质的功能、稳定性和相互作用, 从而参与各种生理和病理过程肿瘤发生[13]。本文综述了乳酸代谢及乳酰化在乳腺癌中的作用, 通过更全面地揭示乳酸的作用机制, 我们能够更有效地探索乳腺癌临床治疗的新方案, 并确定未来的研究重点。

1 乳酸的产生、代谢过程

乳酸的产生途径主要取决于糖酵解, 癌细胞通过糖酵解产生乳酸和腺嘌呤核苷三磷酸(adenine nucleotide triphosphate, ATP), 这种现象被称为Warburg效应[14]。线粒体功能受损会加速乳酸生成, 酸化肿瘤微环境并促进细胞存活[15]。乳酸脱氢酶催化丙酮酸转化为乳酸。在正常的氧化代谢条件下, 丙酮酸可以被线粒体内的丙酮酸脱氢酶氧化成为乙酰辅酶A, 进而参与ATP循环产生能量。然而, 在缺氧下, 线粒体中的丙酮酸脱氢酶失去活性, 无法将丙酮酸氧化成为乙酰辅酶A, 导致丙酮酸积累。此时, 乳酸脱氢酶催化丙酮酸氧化还原反应, 生成乳酸[16]。此外, 丙氨酸氨基转移酶将丙氨酸转化为谷氨酸, 也可产生乳酸[17]。乳酸代谢主要由乳酸–丙酮酸循环和糖异生途径完成。丙酮酸脱氢酶催化酮酸氧化为乙酰辅酶A, 生成NADH, 同时丙酮酸通过酮酸脱氢酶氧化为乙酰辅酶A, 进入三羧酸循环, 产生ATP[18]。此外, 癌细胞可通过谷氨酰胺分解代谢生成乳酸, 谷氨酰胺经酶解产生谷氨酸进而转化为α-酮戊二酸进入三羧酸循环, 最终生成苹果酸并转化为丙酮酸, 为乳酸合成提供原料[19](图1)。

2 乳酸的跨膜转运

乳酸的跨膜转运主要依赖MCT或G蛋白偶联受体81(specific receptor G protein-coupled receptor 81, GPR81)。MCT负责乳酸跨膜转运, MCT4将细胞内的乳酸转运到细胞外, MCT1将细胞外的乳酸转运到细胞内[20]。在正常组织中, 高亲和力的MCT1根据跨膜乳酸梯度转移乳酸维持乳酸稳态。而细胞内乳酸浓度高的肿瘤细胞依靠低亲和力MCT4进行乳酸转运[21]。MCT的转运机制主要包括单羧酸类物质的结合和跨膜转运两个步骤: 当MCT的羧基末端朝向细胞外时, MCT内侧结合单羧酸形成复合物; 随后MCT的构象改变驱动复合物跨膜, 释放单羧酸类物质至胞外, 同时MCT的羧基末端向细胞内翻转, 准备接受下一轮单羧酸类物质的结合和跨膜转运。这种双向构象转换使MCT可持续转运单羧酸类物质[22-23]。乳酸作为GPR81配体, 刺激GPR81信号通路, 影响代谢相关基因的表达并促进肿瘤生长[24]。

3 乳酸在乳腺癌疾病中的作用

3.1 乳酸促进乳腺癌细胞血管生成

乳酸积累可通过激活血管内皮生长因子(vascular endothelial growth factor, VEGF)、转化生长因子、缺氧诱导因子-1α(hypoxia-inducible factor-1α, HIF-1α)来刺激乳腺癌细胞血管生成[25]。乳酸可影

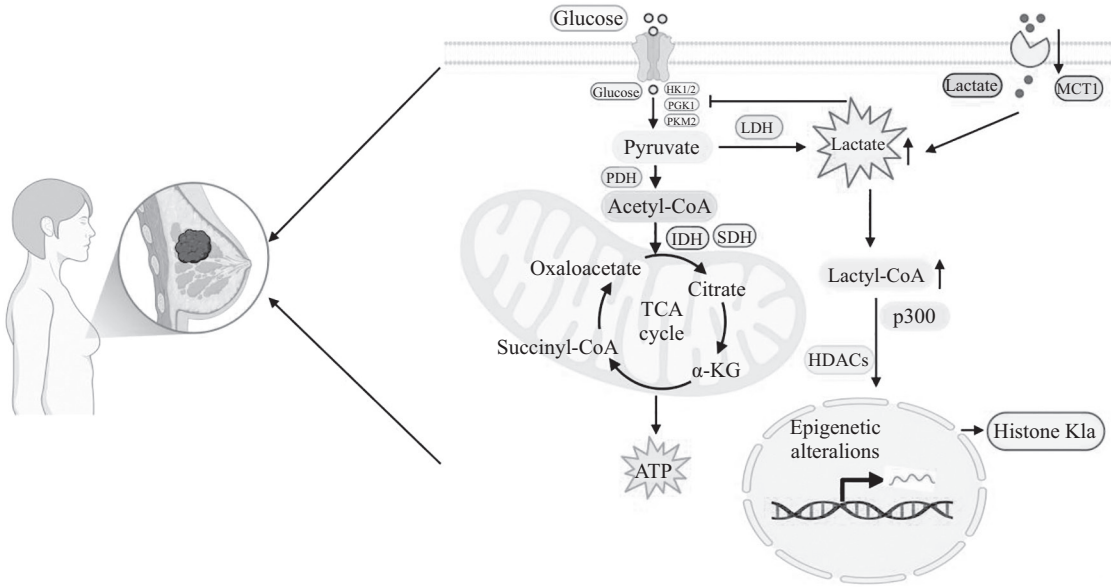

图1 乳酸在乳腺癌疾病中的代谢过程

Fig.1 The metabolic process of lactic acid in breast cancer

响缺氧诱导基因的表达，从而增加HIF-1α蛋白的积累量。HIF-1α作为肿瘤细胞需氧糖酵解的关键调控分子，不仅能支持肿瘤细胞的能量代谢，还能通过调节血管生成蛋白VEGF的表达来推动肿瘤血管生成过程[26]。代谢重编程使乳腺癌细胞糖酵解活性增强，产生大量乳酸，并通过MCT4将其外排至肿瘤微环境。邻近内皮细胞摄取乳酸后，将其代谢为丙酮酸，进而激活HIF-1α/NF-κB/IL-8信号通路，刺激内皮细胞迁移和血管生成[27]。与此同时，肿瘤细胞的高糖酵解活性消耗大量葡萄糖，形成局部低血糖状态，诱导肿瘤组织中VEGF表达上调。此外，缺氧微环境通过诱导肿瘤细胞释放VEGF等因子，进而上调内皮细胞糖酵解相关酶的表达，构成了一个驱动血管生成的正反馈循环[28]。乳酸通过激活GPR81信号通路，在肿瘤进展中诱导肿瘤血管生成。GPR81在乳腺癌细胞中的沉默抑制了内皮细胞管的形成，GPR81可能刺激乳腺癌细胞中内皮细胞的产生，从而影响血管生成[29]。研究表明，乳酸可驱动巨噬细胞M2极化以促进乳腺癌增殖、迁移和血管生成，此外，抑制细胞外信号调节激酶(extracellular signal-regulated Kinase, ERK)/信号转导与转录激活因子3(signal transducer and activator of transcription 3, STAT3)信号转导可以阻断乳酸诱导的M2巨噬细胞极化，从而抑制肿瘤生长和血管生成，乳酸-ERK/STAT3信号通路刺激巨噬细胞M2样极化是乳腺癌进展的驱动因素[41]。因此，乳酸通过激活HIF-1α、VEGF信号轴促进肿瘤血管生成，靶向乳酸代谢通路可双重阻断这些促癌进程。

3.2 乳酸促进乳腺癌细胞转移

肿瘤转移是造成癌症患者死亡的最主要因素，乳酸可以促进乳腺癌细胞转移。研究发现，G蛋白偶联受体132(G protein-coupled receptor 132, Gpr132)的膜受体可以感知并响应来自乳腺癌细胞的乳酸信号，巨噬细胞改变其功能，进而刺激乳腺癌向远处器官转移，乳酸-Gpr132轴通过刺激肿瘤−巨噬细胞相互作用成为乳腺癌转移的驱动因素[30]。此外，也有研究发现，乳酸能够通过诱导上皮−间充质转化(epithelial-mesenchymal transition, EMT)过程，增强细胞迁移能力，促进血管生成并协助免疫逃逸，从而为癌症转移创造有利条件[31]。JIN等[32]研究发现，HCAR1在乳腺癌细胞中高表达，其敲除可以显著抑制乳腺癌细胞的增殖、迁移和糖酵解。总的来说，乳酸激活了羟基羧酸受体1受体，从而通过糖酵解调节细胞能量代谢来促进乳腺癌细胞生长和转移。乳酸通过调控EMT、激活促转移信号通路及诱导免疫逃逸，显著促进乳腺癌细胞的侵袭、迁移和远处转移，靶向乳酸代谢及其下游效应分子或为抑制乳腺癌转移的新策略。

3.3 乳酸可以影响乳腺癌细胞耐药

耐药性是影响癌症患者预后的关键临床因素，

严重影响患者总生存率, 最新研究发现, 乳酸微环境积累与肿瘤耐药性形成存在显著关联[33]。具体而言, 乳酸能够增强乳腺癌细胞对化疗药物的抵抗能力。研究发现, 磷脂酰肌醇3-激酶(phosphoinositide 3-kinase, PI3K)/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)通路抑制剂抑制了乳腺癌细胞的增殖, 但当乳酸作为主要代谢底物时, 这些抑制剂没有效果。乳腺癌细胞可以利用乳酸作为主要能量来源, 使它们能够在葡萄糖剥夺中存活较长时间, 这种活性赋予了乳腺癌细胞对PI3K/mTOR抑制剂的耐药性[34]。也有研究发现, 雌激素相关受体α(estrogen-related receptor α, ERRα)的激活可以促进线粒体活性和乳酸代谢, 进而诱导乳腺癌细胞产生靶向治疗耐药。这一发现也揭示了联合使用PI3K/mTOR抑制剂与ERRα拮抗剂的临床潜力[35]。此外, 乳酸可以影响免疫细胞与肿瘤细胞之间的相互作用, 介导耐药性的发展。肿瘤相关巨噬细胞通过其细胞外囊泡(extracellular vesicles, EV), 传递一种可稳定HIF-1α的长链非编码RNA(HIF-1α-stabilizing long noncoding RNA, HISLA), 以此介导了乳腺癌细胞有氧糖酵解的增强。相应地, 阻断HISLA的EV传递可以抑制乳腺癌的糖酵解和化疗耐药[36]。因此, 乳酸通过酸化肿瘤微环境、激活PI3K/mTOR信号通路显著增强乳腺癌细胞对化疗药物的耐药性, PI3K/mTOR抑制剂联合ERRα拮抗剂可能有效逆转乳腺癌细胞耐药, 为未来进一步研究提供依据。

3.4 乳酸促进乳腺癌细胞免疫逃逸

肿瘤微环境中乳酸的异常积累, 会直接抑制T细胞、巨噬细胞等免疫细胞的增殖及其功能活性[37]。LDHA通过调控乳腺肿瘤糖酵解过程从三个关键途径重塑免疫微环境。首先, 通过乳酸生成激活HIF-1α介导的缺氧信号通路: LDHA抑制可降低HIF-1活性和减少VEGF-A分泌, 同时下调MCT1表达减少乳酸外排, 从而增强$CD3^+$/$CD4^+$ T细胞浸润, 抑制促瘤免疫细胞功能, 最终抑制肿瘤血管生成、肿瘤增殖和转移[38]; 其次, 乳酸积累形成酸性微环境, 促进乳腺癌细胞免疫逃逸: LDHA介导的乳酸−丙酮酸代谢循环可中和TME酸性, 增强$CD8^+$ T细胞浸润, 并增强程序性死亡受体1(programmed death-1, PD-1)抗体免疫治疗效果[39]; 最后, LDHA驱动趋化因子配体2(C-C motif chemokine ligand 2, CCL2)分泌增加, 促进肿瘤相关巨噬细胞浸润: LDHA通过增加乳酸水平和CCL2分泌促进TAM浸润, 特别是诱导M2型极化, 进而加速乳腺癌进展[40]。在三阴性乳腺癌中, LDHB介导的有氧糖酵解增强导致乳酸生成增加, 进而促进肿瘤进展, 乳酸积累通过上调血管内皮生长因子和精氨酸酶1的表达, 诱导M2型巨噬细胞极化, 最终促进肿瘤细胞增殖[41]; 研究表明, 当LDHC被抑制时, 肿瘤微环境中TCA的乳酸供应减少, 导致肿瘤浸润性T细胞的能量代谢障碍, 显著降低$CD8^+$ T细胞的抗肿瘤活性。这种代谢重编程最终削弱了免疫监视功能, 促进了乳腺癌的免疫逃逸[42]。此外, 乳酸也通过激活肿瘤微环境中的GPR81受体来促进乳腺癌细胞免疫逃逸, 从而诱导程序性死亡配体1(programmed cell death ligand 1, PD-L1)的产生并抑制抗原呈递过程, 最终帮助乳腺癌细胞逃避免疫系统的识别与攻击[43]。

4 乳酸通过乳酰化调节基因表达

乳酸被证实是组蛋白赖氨酸乳酰化的供体, 并表明Kla是一种新型的表观遗传修饰, 发生在乳酸衍生蛋白翻译后[44]。令人惊讶的是, 组蛋白Kla在缺氧或细菌攻击刺激的细胞中的基因启动子上积累以产生乳酸, 从而直接调控基因表达[45]。乳酰化有两种修饰途径。L-乳酸可形成乳酰辅酶A, 在组蛋白乙酰转移酶的催化下介导乳酰化。此外, 甲基乙二醛可在谷氨酸蛋白酶1的催化下形成乳酰谷胱甘肽, 乳酰谷胱甘肽还可以介导蛋白质的乳酰化, 不需要酶催化, 乳酰谷胱甘肽可在谷氨酸蛋白酶2的作用下分解成谷胱甘肽和D-乳酸, L和D-乳酸介导的乳酰化均可被组蛋白去乙酰化酶1/2/3消除[46]。目前关于乳酰化的研究主要集中在组蛋白和非组蛋白上, 这两者都已被揭示对肿瘤发展具有重要影响。

4.1 组蛋白乳酰化

组蛋白乳酰化影响关键基因转录。在乳腺癌细胞中, 乳酸水平升高会促进组蛋白H3第18位赖氨酸乳酰化(histone 3 lysine 18 lactylation, H3 K18la)修饰在启动子区域(−70至+3)的富集, p300可能是H3K18la修饰的关键催化酶, 但其对H3K18la的动态调控主要依赖乳酸催化功能, 而非自身表达水平。有氧糖酵解速率的提升通过启动子水平组蛋白乳酰化促进细胞原癌基因(cell proto-oncogenes, c-Myc)表达, 进一步转录上调丝氨酸/精氨酸剪接因子10(serine/arginine-rich splicing factor 10,

SRSF10), 以驱动乳腺癌细胞中小鼠双微体同源蛋白4和B细胞淋巴瘤-X大亚型蛋白的选择性剪接。限制关键糖酵解酶的活性会影响c-Myc-SRSF10轴以抑制乳腺癌细胞的增殖[47]。此外, 钾通道亚家族K成员1可通过激活LDHA促进H3 K18乳酰化, 从而驱动乳腺癌细胞的生长和转移[48]。除H3 K18la外, 近期研究发现H4 K12乳酰化还能通过抑制Schlafen家族蛋白5表达促进三阴性乳腺癌的进展[49]。这些发现表明, 组蛋白乳酰化为表观遗传调控提供了新的分子机制。

4.2 非组蛋白乳酰化

非组蛋白乳酰化, 促进肿瘤细胞的增殖。乳酸优先影响代谢相关蛋白, 并且可以建立正反馈途径。乳酸通过增强糖酵解可以促进HIF-1α产生, 并且乳酸可以从基因调控层面增强肿瘤的环境抵抗力[50]。此外, 非组蛋白KLA调节Treg细胞和巨噬细胞来重塑肿瘤免疫微环境, 有利于肿瘤免疫逃逸[51-52]。这些研究表明非组蛋白KLA在肿瘤细胞代谢重编程、肿瘤细胞耐药性和免疫中起重要桥接作用。非组蛋白乳酰化已被证实是多种生理病理过程的重要调控机制, 然而乳腺癌中的非组蛋白乳酰化尚未得到充分研究, 这一领域亟待更深入的探索。

综上, 乳酰化调节癌症相关基因表达, 是驱动乳腺癌发展的关键机制, 其在肿瘤发展中起到关键作用。

5 抗乳酸产生和乳酰化抑制策略

5.1 靶向LDH抑制乳酸产生

由于葡萄糖浓度和糖酵解速率直接调控乳酰化水平, 提示乳酰化修饰依赖于细胞内乳酸代谢动态, 为肿瘤治疗提供了新思路, 通过靶向降低乳酸浓度或抑制乳酸活性可有效阻断肿瘤进展。在糖酵解过程中, LDH是丙酮酸转化为乳酸的关键酶, 使用LDH抑制剂抑制乳酸生成减少乳酰化修饰, 最终阻断依赖乳酰化信号途径。研究发现, 没食子黄素是没食子酸的衍生物, 是乳酸脱氢酶抑制剂, 在三阴性乳腺癌和雌激素受体阳性、孕激素受体阳性(ER^+/PR^+)的乳腺癌模型中没食子黄素可靶向抑制LDHA和LDHB的表达与活性, 从而抑制乳腺癌细胞的增殖[53]。在乳腺癌治疗研究中, 多种LDHA抑制剂展现出潜在疗效。草酸钠是一种LDHA抑制剂, 已在ER^+/PR^+乳腺癌中证实其具有抗肿瘤作用。N-羟基吲哚作为高效LDHA抑制剂, 在两种亚型中均表现出显著活性。此外, 棉酚衍生物FX-11作为特异性LDHA靶向药物, 在ER^+/PR^+乳腺癌中已获得系统研究验证[54-55]。然而, 现有LDH抑制剂在体内抗肿瘤效果有限, 这可能与其代谢稳定性差、抑制效力不足或递送效率低下等因素有关, 因此, 需要开展更多针对LDH抑制剂的研究。

5.2 靶向MCT调控乳酸转运

单羧酸转运蛋白家族包含四个亚型(MCT1~4), 它们介导乳酸等单羧酸化合物的跨膜质子偶联转运。其中, MCT1和MCT4虽具有不同的底物特异性和抑制敏感性, 但在乳腺癌中表达显著上调[56]。研究表明, AZD3965是一种MCT1和MCT2双重抑制剂, 干扰了肿瘤细胞间乳酸介导的代谢耦合, 阻断了糖酵解细胞与氧化磷酸化细胞之间的能量协作。AZD3965展现出理想的联合治疗潜力, 通过靶向乳酸代谢抑制乳腺癌增殖,为阻断肿瘤代谢重编程提供了新策略[57]。研究发现, AR-C155858和AZD3965对MCT1介导的乳腺癌细胞中L-乳酸摄取产生缓慢可逆的抑制作用, 其中AR-C155858代表了MCT1的潜在底物[58]。靶向MCT介导的乳酸转运通过破坏肿瘤微环境代谢共生、阻断乳酸信号转导, 为乳腺癌治疗提供了多靶点干预的新策略。

5.3 靶向乳酰化酶和特异性赖氨酸乳酰化

细胞通过葡萄糖转运体(glucose transporter, GLUT)摄取葡萄糖后, 经糖酵解酶催化生成丙酮酸。靶向抑制糖酵解限速酶可有效阻断糖酵解, 从而减少乳酸生成。p300作为首个被发现的乳酰化酶, 在介导组蛋白和非组蛋白乳酰化过程中发挥关键作用[59]。乳酰化过程可被p300抑制剂直接抑制, 值得注意的是, p300抑制剂CCS1477与EP3160的临床试验已启动, 目前正在招募受试者[60]。最新证据表明, p300还通过介导干扰素γ(interferon gamma, IFN-γ)诱导的PD-L1表达参与免疫逃逸[61], 这为克服PD-1/PD-L1通路耐药提供了新思路。此外, 据报道, 去甲基化锌醛是一种三萜类抗肿瘤化合物, 通过抑制H3组蛋白乳酰化和干扰代谢应激来抑制癌症, 可有效增强抗肿瘤药物的疗效[62]。蜂王浆酸是一种天然物质, 能够通过降低H3K9la和H3K14la的乳酰化水平, 从而抑制肿瘤发展[63]。尽管靶向乳酰化酶及特异性赖氨酸修饰已展现巨大潜力, 但如何提高抑制剂的选择性、解析位点特异性功能, 以及优化联合治疗策略, 仍是

未来研究的重要方向。

5.4 中药及其化合物抗乳酸产生的作用机制

近年来, 中药及其活性成分因其多靶点、低毒性的特点, 在调控乳酸代谢方面展现出潜在优势。部分中药复方及天然化合物可通过调节糖酵解途径、乳酸转运体表达等方式抑制乳酸生成, 从而延缓乳腺癌疾病进展。研究表明, 阳和汤可下调HIF-1α、丙酮酸激酶M2(pyruvate kinase M2, PKM2)、LDHA和GLUT1的mRNA及蛋白表达水平, 提示其能下调糖酵解关键分子表达。此外, 阳和汤对早期乳腺癌肺转移的皮下肿瘤生长具有抑制作用, 进一步证实其可能通过HIF-1α介导的糖酵解调控途径抑制乳腺癌肺转移[64]。研究发现, 从凤仙花中提取的活性成分2-甲氧基-1,4-萘醌能够显著抑制三阴性乳腺癌细胞的糖酵解活性, 并下调糖酵解相关分子的表达。其作用机制表现为GLUT1依赖性, 且可能通过调控蛋白激酶B(protein kinase B, Akt)信号通路介导[65]。JIN等[66]研究发现, 小豆蔻素通过抑制mTOR/p70核糖体蛋白S6激酶(p70 ribosomal protein S6 kinase, p70S6K)通路进而抑制HIF-1α的表达, 其还可抑制核因子E2相关因子(nuclear factor E2-related factors, Nrf2)表达, 增加细胞内活性氧(reactive oxygen species, ROS)表达水平, 最终诱导乳腺癌细胞凋亡。此外, 桦木酸是一种天然五环萜烯, 其通过抑制乳酸产生、葡萄糖摄取和降低细胞外酸化率, 调控陷窝蛋白-1(caveolin-1, Cav-1)/NF-κB/c-Myc信号通路抑制乳腺癌细胞中的有氧糖酵解[67]。此外, 也有研究发现, 桦脂酸通过靶向GRP78介导的糖酵解和ER应激凋亡途径抑制乳腺癌转移[68]。7-氨基羧基香豆素2通过线粒体丙酮酸载体1抑制乳酸诱导乳腺癌细胞上皮−间充质转化[69]。柴胡皂苷A通过抑制Akt/STAT3通路, 进而减少乳腺癌细胞的葡萄糖摄取、乳酸及ATP生成, 最终抑制糖酵解[70]。黄芩素通过逆转由HIF-1α驱动的关键糖酵解环节(包括抑制葡萄糖摄取、乳酸产生), 抑制有氧糖酵解, 进而与他莫昔芬在抑制乳腺癌细胞增殖上产生协同增效作用[71]。综上所述, 中药复方及其活性成分可通过干预糖酵解关键酶、调控HIF-1α信号通路等途径, 有效抑制乳酸过度生成。这些发现不仅揭示了中药多靶点调控乳酸代谢的独特优势, 也为开发抗乳酸相关疾病的新型药物提供了理论依据(表1)。

6 乳腺癌中乳酰化相关的生物标志物

探索乳酰化修饰在乳腺癌中的潜在生物标志物, 不仅为理解其分子机制提供新视角, 还可能为临床诊断、预后预测及靶向治疗开辟新途径。研究发现, 基于乳酰化相关基因的表达差异, 鉴定了乳腺癌的两个亚型, 并构建了一个由7个基因(*RAD51*、*NEK10*、*PCP2*、*IDO1*、*CASP14*、*CLSTN2*和*IGHG1*)组成的预后特征。该特征被用于进一步探究乳酰化在乳腺癌进展中的作用。此外, 乳腺癌组织中乳酰化相关基因(*ARID3A*、*CCNA2*、*DDX39A*、*EHMT2*、*G6PD*、*H2AX*、*HMGA1*、*KIF2C*、*MKI67*、*RACGAP1*、*RFC4*、*STMN1*、*EFNA3*、*VCAN*和*NUP50*)的差异表达提示这些乳酰化相关基因可作为乳腺癌诊断或治疗靶点[72]。LIN等[73]研究发现, 8个Kla-lncRNAs中有7个(MIR4435-2HG、EGOT、ST7-AS1、ERICH6-AS1、LINC00310、OTUD6B-AS1、LINC01871)与乳腺癌预后相关, 因此有必要进一步探索PDCD6IP-DT的潜在作用。也有研究证实了组蛋白H4K12lac在三阴性乳腺癌中的表达和预后重要性, 强调了其作为生物标志物的潜力[74]。乳酰化修饰在乳腺癌中的研究揭示了其作为诊断和预后生物标志物的巨大潜力。然而, 乳酰化修饰的动态调控机制及其临床应用仍需进一步探索, 以期为乳腺癌患者提供更精准的治疗策略和生存收益。

7 结论

乳酸是糖酵解的最终产物, 是通过多种生理和病理过程(例如缺氧、肿瘤进展)产生的。然而, 乳酸不只是一种代谢废物, 还调节着多种生物过程。乳酸及乳酰化在乳腺癌疾病的发展中起着至关重要的作用。在这篇综述中, 我们总结了乳酸在肿瘤组织中如何产生、代谢、转输和积累, 以及它如何影响乳腺癌的进展。靶向乳酸的产生和转运、调节循环乳酸水平和抑制乳酰化可能是未来治疗乳腺癌的潜在策略。需要深入研究来证实乳酸在乳腺癌疾病中的作用。总而言之, 增强乳酸−乳酰化的认识将有助于更好地理解乳腺癌发生和发展生物过程, 将为探索改善乳腺癌患者预后的新型治疗靶点铺平道路。

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表1 乳腺癌中乳酸–乳酰化相关的可能治疗靶点

Table 1 Potential therapeutic targets related to lactic acid and lactylation in breast cancer

靶点 Target	机制 Mechanism	功能 Function	参考文献 References
Gallocatechin	Inhibit the expression of LDHA and LDHB	Inhibit the proliferation of breast cancer cells	[53]
Sodium oxalate	Inhibit the expression of LDHA	Hinder the progression of breast cancer	[54]
N-hydroxyindole	Inhibit the expression of LDHA	Inhibit breast cancer	[54]
Gossypol derivative FX-11	Target LDHA	Inhibit breast cancer	[55]
AZD3965	Inhibit the expression of MCT1 and MCT2	Block tumor metabolic reprogramming	[57]
AR-C155858 AZD3965	Targeting MCT	Block the progression of breast cancer	[58]
Zinc aldehyde for demethylation	Inhibit the lactylation of H3 histone	Inhibit cancer	[62]
10-hydroxy-2-decenoic acid	Reduce the lactylation of H3K9la and H3K14la	Inhibit tumors	[63]
Yanghe decoction	Down-regulate key molecules of glycolysis	Inhibit lung metastasis of breast cancer	[64]
2-methoxy-1,4-naphthoquinone	Regulate the Akt signaling pathway and inhibit glycolytic activity	Inhibit triple-negative breast cancer cells	[65]
Cardamonin	Inhibit mTOR/p70S6K/HIF-1α	Induce apoptosis of breast cancer cells	[66]
Betulinic acid	Hinder lactic acid production, glucose uptake and reduce the extracellular acidification rate	Inhibit the proliferation of breast cancer cells	[67]
Betulinic acid	Target GRP78 to mediate glycolysis	Inhibit breast cancer metastasis	[68]
7-aminocoumarin	Lactic acid is inhibited through mitochondrial pyruvate vector 1	Induce epithelial-mesenchymal transition in breast cancer cells	[69]
Saikosaponin A	Reduce the content of lactic acid and ATP, as well as glucose uptake	Inhibit breast cancer	[70]
Baicalein	Restrict glucose uptake, lactic acid production and ATP generation	Enhance the anti-proliferative effect of tamoxifen on breast cancer cells	[71]

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