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乳酸化在消化系统肿瘤中的研究进展

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摘要 乳酸化作为一种新兴的表观遗传修饰, 近年来被发现对消化系统肿瘤的代谢重编程、肿瘤微环境调控等具有重要影响。乳酸通过其代谢中间体乳酰辅酶A(lactyl-CoA)介导乳酸化修饰, 该过程作为新型翻译后修饰机制, 通过乳酸基团与赖氨酸残基特异性结合, 调控组蛋白与非组蛋白的构象与功能, 进而与基因表达调控、肿瘤生长侵袭转移、免疫逃逸及化疗耐药形成密切相关。该文系统综述了乳酸代谢和乳酸化的分子机制及其在胃癌、结直肠癌、肝癌等消化系统肿瘤中的生物学功能和临床意义, 同时探讨了靶向乳酸及乳酸化的治疗策略, 包括抑制乳酸代谢通路、干预乳酸化修饰以及联合治疗的新方向。尽管乳酸化的分子机制研究及靶向药物开发面临挑战, 但其作为潜在治疗靶点的研究已展现出了广阔的前景, 为消化系统肿瘤的精准诊疗和抗耐药治疗提供了全新思路。

关键词 乳酸代谢; 乳酸化修饰; 消化系统肿瘤; 代谢重编程; 表观遗传重塑; 肿瘤微环境; 靶向治疗

The Research Progress of Lactylation in Gastrointestinal Tumors

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Abstract Lactylation, an emerging epigenetic modification, has recently been found to have significant effects on the metabolic reprogramming of gastrointestinal tumors and the regulation of the tumor microenvironment. Lactate mediates lactylation modification via its metabolic intermediate lactyl-CoA. This novel post-translational modification mechanism regulates the conformation and functionality of both histones and non-histone proteins through the specific conjugation of lactate moieties to lysine residues, thereby demonstrating critical associations with gene expression regulation, tumor progression (including growth, invasion, metastasis), immune evasion, and chemoresistance.This review systematically summarizes the molecular mechanisms of lactate metabolism and lactylation, as well as their biological functions and clinical significance in gastrointestinal cancers such as gastric cancer, colorectal cancer, and liver cancer. The article also discusses therapeutic strategies targeting lactate and lactylation, including inhibition of lactate metabolism pathways, intervention in lactylation modifications, and novel directions for combination therapy. Despite the challenges in studying the molecular mechanisms of lactylation and developing targeted drugs, research on lactylation as a potential therapeutic target shows great promise and provides new insights into the precise diagnosis, treatment, and overcoming chemotherapy resistance in gastrointestinal tumors.

Keywords lactate metabolism; lactylation modification; gastrointestinal tumors; metabolic reprogramming; epigenetic remodeling; tumor microenvironment; targeted therapy

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1 消化系统恶性肿瘤的介绍

1.1 消化系统恶性肿瘤流行病学特征

消化系统恶性肿瘤是一组发生在消化道及其相关器官中的癌症类型, 包括食管癌、胃癌、结直肠癌、肝细胞癌、胰腺癌、胆囊癌等。消化系统恶性肿瘤占全球所有癌症发病率的25%以上, 占癌症相关死亡率的35%[1]。在中国, 消化道恶性肿瘤占恶性肿瘤相关死亡人数的45%, 主要的肿瘤死因中, 除肺癌外, 其余四个分别为肝癌、胃癌、结直肠癌和食管癌。值得注意的是, 中国肝癌的病例数占全球总数的一半以上, 而胰腺癌的五年生存率仅为7.2%[2-4]。

1.2 代谢重编程和表观遗传重塑

众所周知, 代谢重编程和表观遗传重塑是癌症发生的标志之一, 二者密切相关, 相互调控。

肿瘤代谢重编程是癌症发生发展的关键特征, 其中最典型的变化之一是糖酵解功能增强。肿瘤细胞的代谢重编程以Warburg效应为显著标志, 即便在有氧条件下, 仍优先选择糖酵解途径产生能量, 并大量生成乳酸[5]。增强肿瘤细胞糖酵解的主要目的是获得更多的中间代谢物, 这些代谢物作为信号分子或者能量来源。同时, 糖酵解产生的乳酸可驱动细胞外基质酸化, 改变微环境, 这不仅为肿瘤细胞侵袭创造有利条件, 降解细胞外基质便于肿瘤细胞迁移, 还通过诱导上皮–间质转化(epithelial-mesenchymal transition, EMT)增强细胞迁移和侵袭能力[6-7]; 同时, 酸性环境严重抑制免疫细胞功能, 干扰免疫细胞代谢及信号转导通路, 削弱其抗肿瘤活性, 为肿瘤细胞免疫逃逸提供契机[8-10]。

表观遗传重塑在肿瘤的发生发展中亦扮演着至关重要的角色。正常的表观遗传调控机制中蛋白质修饰尤为重要, 如乙酰化、甲基化、泛素化, 可以影响染色质结构, 从而调节基因转录, 而不改变基因序列, 这些过程对于维持正常的细胞功能至关重要[11]。而这些表观遗传过程的畸形有助于肿瘤的发生和发展, 致肿瘤抑制基因失活或癌基因激活, 从而促进细胞的恶性转化和治疗适应[12–14]。在人类肿瘤中, 已经发现许多蛋白质修饰的异常活动参与了肿瘤的发生。例如蛋白质去乙酰化和甲基化过表达以及泛素化的异常活动可促进肿瘤的发生、增殖和转移[11,15]。此外, 蛋白质修饰的异常活动也成为了癌症获得性耐药的关键因素[16]。近年来, 蛋白质乳酸化修饰作为一种新兴的表观遗传修饰方式, 为理解肿瘤生物学提供了全新视角。蛋白质乳酸化修饰分为组蛋白乳酸化修饰和非组蛋白乳酸化修饰。组蛋白乳酸化修饰主要发生在组蛋白的赖氨酸残基上, 其修饰水平的动态变化能够精准调控基因表达。在某些消化系统肿瘤里, 组蛋白H3赖氨酸残基的乳酸化修饰增强, 促使染色质结构松弛, 使得原本紧密缠绕的DNA得以暴露, 为转录因子的结合创造有利条件, 进而激活一系列原癌基因的表达, 如促进细胞增殖的*MYC*基因以及抑制细胞凋亡的*BCL-2*基因等的表达[17-18], 同时, 这种修饰也可能抑制部分抑癌基因的表达, 削弱细胞的自我修复与凋亡调控能力, 共同推动肿瘤细胞的恶性增殖与发展。除组蛋白外, 众多非组蛋白也受乳酸化修饰的深刻影响, 广泛参与肿瘤相关信号通路的调控, 从而影响肿瘤细胞的物质合成、能量代谢, 增强肿瘤细胞的迁移、侵袭能力以及对微环境变化的适应性, 促进肿瘤的转移与复发, 像*P53*基因通过乳酸化修饰, 从而抑制其相分离、DNA结合而导致*P53*活性降低, 最终促进肿瘤的发生[19]。

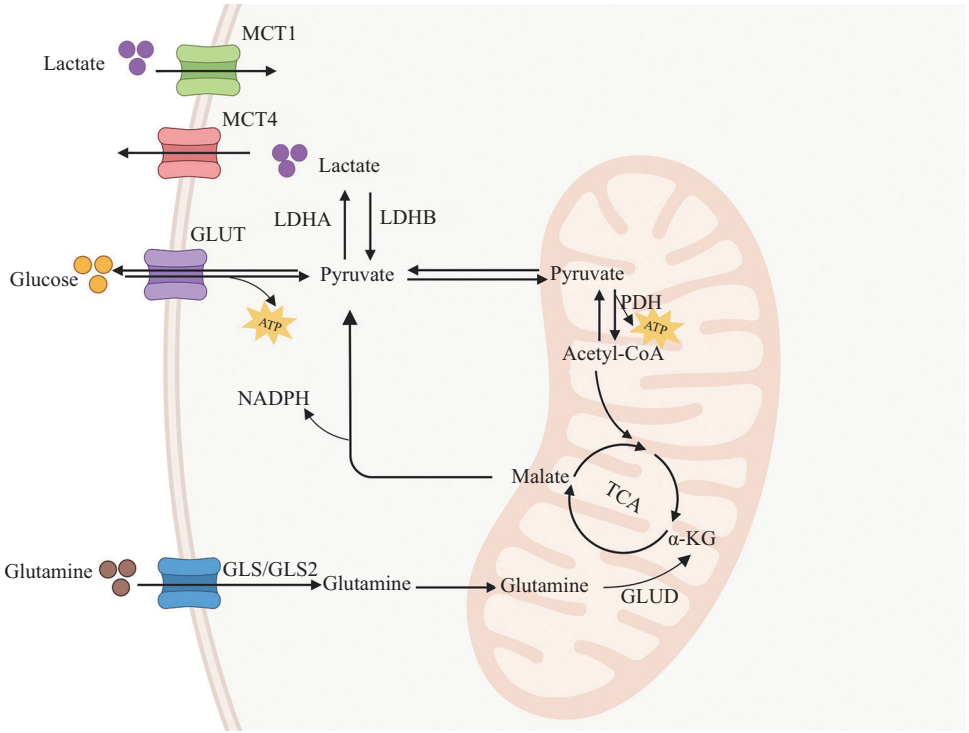
乳酸代谢及乳酸化修饰在肿瘤代谢重编程和表观遗传重塑中发挥着核心作用, 对肿瘤细胞的生物学行为及肿瘤微环境产生深远影响。本文旨在全面概述目前在胃肠道恶性肿瘤中乳酸和乳酸化的机制和作用以及靶向乳酸和乳酸化作为治疗手段的临床意义。

2 乳酸代谢

2.1 乳酸的产生和清除

乳酸以D-乳酸、L-乳酸的形式存在于体内。其中, L-乳酸是人体的主要形式, 参与各种生物过程。乳酸产生主要有糖酵解和谷氨酰胺降解两条途径, 在不同生理和病理条件下发挥关键作用, 为细胞供能、维持内环境稳定及参与肿瘤发生发展等过程。在正常生理状态下, 当细胞内氧气供应充足时, 葡萄糖会进入糖酵解途径。这一过程中, 葡萄糖首先在细胞质中逐步转化为丙酮酸, 随后丙酮酸会进入线粒体, 在丙酮酸脱氢酶的催化下形成乙酰辅酶A, 乙酰辅酶A通过三羧酸循环被进一步氧化分解, 最终生成二氧化碳和水, 并释放出大量能量。然而, 当细胞面临缺氧或低氧状况, 如人体进行剧烈运动时, 肌肉细胞对氧气的需求急剧增加, 氧气供应相对不足; 或者在感染等病理状态下, 局部组织的氧气供应受

到影响。此时，为了确保糖酵解过程能够持续进行，从而为细胞提供必要的能量，丙酮酸会在乳酸脱氢酶A(lactate dehydrogenase A, LDHA)的催化作用下，于细胞质中接受氢原子被还原为乳酸[23-24]。这一反应使得细胞在缺氧环境下仍能通过糖酵解获取一定的能量，以维持细胞的基本代谢和功能(图1)。



乳酸产生、清除、运输。当细胞内氧气供应充足时，葡萄糖会经历糖酵解，葡萄糖首先通过葡萄糖转运体(GLUT)进入细胞质中，逐步转化为丙酮酸，随后丙酮酸会进入线粒体，在丙酮酸脱氢酶的催化下形成乙酰辅酶A，乙酰辅酶A通过三羧酸循环(TCA)被进一步氧化分解，最终生成二氧化碳和水。然而，当细胞面临缺氧或低氧状况时，为了维持糖酵解，从而为细胞提供必要的能量，丙酮酸被乳酸脱氢酶A(LDHA)催化在细胞质中生成乳酸。另外，进入细胞质的谷氨酰胺通过谷氨酰胺酶转化为谷氨酸。然后，谷氨酸在谷氨酸脱氢酶等酶的作用下转化为α-酮戊二酸，并进入TCA循环。在这个周期中，源自谷氨酰胺的碳被转化为草酰乙酸，然后转化为苹果酸并退出线粒体。随后，苹果酸在细胞质中被转化为NADPH和丙酮酸，丙酮酸再在LDHA的作用下被还原为乳酸。乳酸清除主要通过乳酸脱氢酶B(LDHB)将乳酸氧化生成丙酮酸，随后在丙酮酸脱氢酶的催化下形成乙酰辅酶A，然后在TCA中形成二氧化碳、水并提供能量。另一种清除途径涉及激活肝脏和骨骼肌细胞中的糖异生，乳酸转化为葡萄糖，然后释放到血液中并进一步代谢，为身体提供能量。乳酸主要通过MCT1输入细胞，通过MCT4从细胞中输出乳酸。缺氧癌细胞通过LDHA产生乳酸，然后通过MCT4被释放到细胞外间隙。随后，含氧正常细胞通过MCT1吸收乳酸，并通过LDHB将其转化为丙酮酸，从而产生ATP。LDH: 乳酸脱氢酶; PDH: 丙酮酸脱氢酶; GLS: 谷氨酰胺酶; GLUD: 谷氨酸脱氢酶; α-KG: α-酮戊二酸; GLUT: 葡萄糖转运体; MCT: 单羧酸转运蛋白。

Lactate production, clearance, and transport. When there is an adequate supply of oxygen in the cell, glucose undergoes glycolysis, where glucose first enters the cytoplasm through the GLUT (glucose transporter) and is gradually converted into pyruvate, which then enters the mitochondria and is catalysed by pyruvate dehydrogenase to form acetyl coenzyme A. Acetyl coenzyme A is further oxidised and broken down through the TCA (tricarboxylic acid cycle), ultimately producing carbon dioxide and water. However, when cells are faced with hypoxic or low oxygen conditions, in order to maintain glycolysis and thus provide the cells with the necessary energy, pyruvate is catalysed by LDHA (lactate dehydrogenase A) to produce lactate in the cytoplasm. In addition, glutamine that enters the cytoplasm is converted to glutamate by glutaminase. Glutamate is then converted to alpha-ketoglutarate by enzymes such as glutamate dehydrogenase and enters the TCA cycle. During this cycle, carbon derived from glutamine is converted to oxaloacetate, which is then converted to malate and exits the mitochondria. Subsequently, malate is converted in the cytoplasm to NADPH and pyruvate, which is then reduced to lactate in the presence of LDHA. Lactate is cleared primarily through the oxidation of lactate to pyruvate by LDHB (lactate dehydrogenase B), followed by the formation of acetyl coenzyme A catalysed by pyruvate dehydrogenase, which is then used to form carbon dioxide, water, and provide energy in the TCA. Another clearance pathway involves the activation of gluconeogenesis in the liver and skeletal muscle cells, where lactate is converted to glucose, which is then released into the bloodstream and further metabolised to provide energy for the body. Lactate is mainly imported into cells via MCT1 and exported from cells via MCT4. Hypoxic cancer cells produce lactate via LDHA, which is then released into the extracellular space via MCT4. Subsequently, oxygenated normal cells take up lactate via MCT1 and convert it to pyruvate via LDHB to produce ATP. LDH: lactate dehydrogenase; PDH: pyruvate dehydrogenase; GLS: glutaminase; GLUD: glutamate dehydrogenase; α-KG: alpha-ketoglutarate; GLUT: glucose transporter; MCT: monocarboxylic acid transporter protein.

图1　乳酸的产生、清除和运输(此图通过bioRender制作)

Fig.1　Lactate production, clearance, and transport (this image was created via bioRender)

除了糖酵解途径产生乳酸外, 谷氨酰胺降解途径也是乳酸的另一重要来源[20]。谷氨酰胺进入癌细胞的细胞质后, 会在谷氨酰胺酶的催化下转化为谷氨酸。接着, 谷氨酸在谷氨酸脱氢酶等酶的作用下进一步发生转化, 生成α-酮戊二酸, 并进入三羧酸循环(tricarboxylic acid cycle, TCA cycle)。在三羧酸循环中, 来自谷氨酰胺的碳元素会经过一系列复杂的代谢反应, 转化为草酰乙酸, 随后草酰乙酸又会转变为苹果酸并从线粒体中排出。最后, 苹果酸在细胞质中转化为NADPH和丙酮酸, 丙酮酸再在LDHA的作用下被还原为乳酸。这一系列反应构成了谷氨酰胺降解产生乳酸的完整代谢途径(图1)。

乳酸在体内的积累会导致乳酸性酸中毒[21]。人体可通过新陈代谢有效、快速地从组织和循环中去除乳酸。乳酸清除的主要方法是通过乳酸脱氢酶B(LDHB)将乳酸氧化生成丙酮酸, 随后在丙酮酸脱氢酶的催化下形成乙酰辅酶A, 然后在三羧酸循环中形成二氧化碳、水并提供能量[22-23]。另一种清除途径涉及激活肝脏和骨骼肌细胞中的糖异生, 乳酸转化为葡萄糖, 然后释放到血液中并进一步代谢, 为身体提供能量[10,24](图1)。

2.2 乳酸的运输

乳酸可以通过单羧酸转运蛋白(monocarboxylic acid transporter protein, MCT)蛋白家族在细胞内和细胞外环境之间运输[25], 其中MCT1、MCT2和MCT4主要与乳酸转运有关, 并在各种组织中表达, 包括肌肉、心脏、神经和肝脏[26]。MCT1和MCT2的主要功能是将乳酸输入细胞, MCT4的主要功能是从细胞中输出乳酸[27-28]。 在肿瘤微环境中, 缺氧癌细胞通过LDHA产生乳酸, 然后通过MCT4释放到细胞外间隙。随后, 含氧正常细胞通过MCT1吸收乳酸, 并通过LDHB将其转化为丙酮酸, 从而产生ATP[29](图1)。

2.3 乳酸的功能

第一, 乳酸作为一种代谢底物, 其主要功能是产生丙酮酸, 由LDHB催化, 然后通过糖异生生成葡萄糖, 用作能量来源[30-32]。第二, 乳酸调节脂肪酸代谢, 脂肪酸的合成对于细胞膜的结构和功能、能量的储存以及信号转导等都是必不可少的, 乳酸作为信号转导分子调节细胞功能, 包括调节炎症反应和细胞增殖[10,33]。第三, 乳酸盐作为细胞间或组织间氧化还原信号分子, 是氧化还原平衡的重要贡献者, 当氧化辅酶与还原辅酶的比例不平衡时, 乳酸通过调节其他形式的能量代谢来稳定细胞的氧化还原状态, 防止氧化还原反应不平衡对机体造成危害[34]。除了这些功能外, 乳酸可以通过上述讲到的新兴的表观遗传修饰乳酸化来调节基因转录[35]。

3 蛋白质乳酸化

3.1 乳酸化的特征

3.1.1 *乳酸浓度是乳酸化的主要驱动因素* 乳酸化的关键底物主要来源是细胞内代谢产物乳酸[36-37]。

3.1.2 *乳酸化位点* 乳酸化修饰主要特异性发生于赖氨酸残基, 通过调控组蛋白及非组蛋白的翻译后修饰状态, 进而影响相关蛋白的生物学功能。多种癌细胞中已鉴定出超千种乳酸化蛋白[19,38]。

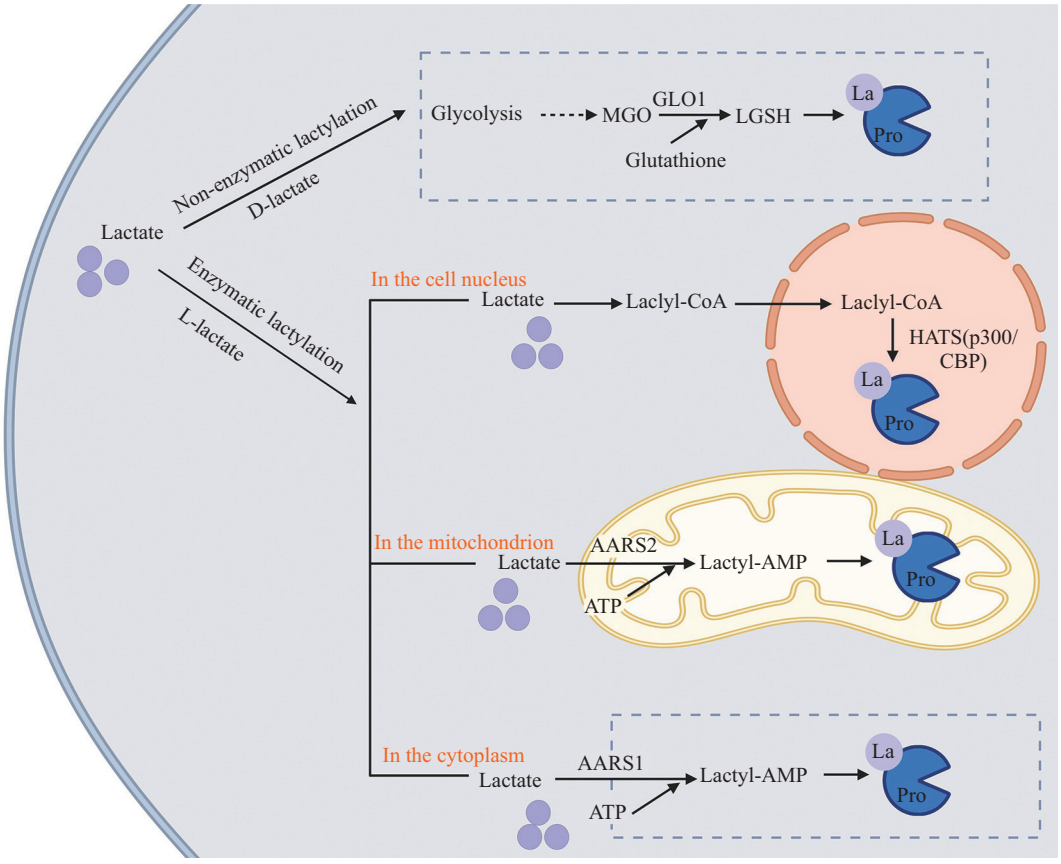
3.1.3 *与基因表达调控相关* 乳酸化通过影响染色质结构及基因启动子区域调节基因表达, 特别是在肿瘤细胞的代谢重编程、免疫逃逸及耐药中发挥作用。在肿瘤发生发展进程中, 肿瘤微环境中乳酸产生和蛋白质乳酸化修饰参与肿瘤细胞代谢途径调节[39-40]、免疫逃逸及耐药形成等核心环节。以肝癌为例, 众多差异表达的乳酸化修饰蛋白深度参与细胞代谢通路重塑[41], 包括糖酵解、三羧酸循环及线粒体功能调节等, 成为肿瘤细胞代谢重编程的关键驱动因素; 在免疫调节方面, 肿瘤微环境中乳酸积累及蛋白乳酸化修饰显著增强免疫抑制特性[42-43], 通过修饰肿瘤相关巨噬细胞、调节性T细胞等免疫细胞活性及功能, 营造利于肿瘤细胞生长、免疫逃逸的微环境[44-45]; 耐药机制层面, 肿瘤细胞借助乳酸化修饰改变自身代谢状态及关键蛋白功能, 增强对化疗药物及靶向药物的耐受性, 如结直肠癌中肿瘤细胞经乳酸化修饰上调相关蛋白表达, 激活自噬途径抵御药物杀伤[46]。

3.2 乳酸化的机制

乳酸化可分为酶促和非酶促两种机制。

3.2.1 *酶促乳酸化* L-乳酸参与酶促乳酸化, 酶促乳酸化包括两种不同的途径。第一种途径, 核内组蛋白乙酰转移酶(histone acetyltransferases, HATs)其关键酶类如p300/CBP通过其溴结构域(bromodomain)识别乳酰辅酶A(lactyl-CoA), 催化乳酰基转移至组蛋白(如H3K18、H4K12)的赖氨酸残基, 驱动染色质重塑和促癌基因转录, 这一过程依赖LDH生成

的lactyl-CoA作为供体, 而非直接利用游离乳酸[35,47]; 第二种途径是利用氨基酰基TRNA合成酶1/2(aminoacyl-tRNA synthetases 1/2, AARS1/2), 这些酶具有乳酸传递酶活性, 直接催化乳酸与ATP生成lactyl-AMP, 然后将乳酸基转移到底物蛋白上的赖氨酸残基上, 导致乳酸化修饰[48-49]。AARS1主要定位于细胞质[19,48], 而AARS2在线粒体中发挥功能[49]。值得注意的是, 尽管在肿瘤细胞内几乎无法检测到lactyl-CoA且其浓度仅为细胞中乙酰辅酶A(acetyl-CoA)的1/1 000, 传统乙酰转移酶(如p300)的乳酸化催化效率受到显著限制。因此, AARS1/2可能通过以下机制成为肿瘤细胞乳酸化修饰的关键催化酶: (1) 特异性识别乳酸代谢中间体, 绕过lactyl-CoA依赖的限速步骤; (2) 利用其独特的结构域(如AARS1的编辑结构域)实现高亲和力底物结合[50]。然而, 目前关于这两类酶的反应动力学参数(如*k*cat/*K*m)、位点选择特异性及其在肿瘤不同亚细胞区室中的功能分化仍缺乏系统性研究[37,51](图2)。



乳酸化可分为酶促和非酶促两种机制, 酶促乳酸化包括两种不同的途径。第一种途径, 核内组蛋白乙酰转移酶(histone acetyltransferases, HATs)其关键酶类如p300/CBP识别乳酰辅酶A(lactyl-CoA), 催化乳酰基转移至组蛋白(如H3K18、H4K12)的赖氨酸残基, 这一过程依赖LDH生成的lactyl-CoA作为供体, 而非直接利用游离乳酸; 第二种途径是利用氨基酰基TRNA合成酶1/2(aminoacyl-tRNA synthetases 1/2, AARS1/2), 这些酶具有乳酸传递酶活性, 直接催化乳酸与ATP生成lactyl-AMP, 然后将乳酸基转移到底物蛋白上的赖氨酸残基上, 导致乳酸化修饰。AARS1主要定位于细胞质, 而AARS2在线粒体中发挥功能。非酶促乳酸化主要在糖酵解副产物甲基乙二醛(methylglyoxal, MGO)与谷胱甘肽在甲基乙二醛解毒酶1(GLO1)的作用下形成乳酰化谷胱甘肽(LGSH), LGSH作为底物进行乳酸化修饰。

Enzymatic lactonisation consists of two distinct pathways. In the first pathway, intranuclear HATs (histone acetyltransferases) whose key enzymes such as p300/CBP recognise lactyl-CoA (lactyl-coenzyme A) catalyse the transfer of lactoyl groups to lysine residues of histones (e.g., H3K18, H4K12), a process that relies on LDH-generated lactyl-CoA as a donor rather than directly using free lactate; the second pathway uses AARS1/2 (aminoacyl-tRNA synthetases 1/2), which have lactate-transferring enzyme activity, to directly catalyse the generation of lactyl-AMP from lactate and ATP, and then transfer the lactate group to lysine residues on substrate proteins, resulting in lactation modifications. Non-enzymatic lactylation is mainly carried out through the formation of LGSH (lactylated glutathione) as a substrate for lactylation modification by the glycolytic by-product MGO (methylglyoxal) and glutathione in the presence of methylglyoxal detoxifying enzyme GLO1.

图2　乳酸化的机制(此图通过bioRender制作)

Fig.2　Mechanisms of lactation (this image was created via bioRender)

3.2.2 非酶促乳酸化 D-乳酸参与非酶促过程。非酶促乳酸化主要在糖酵解副产物甲基乙二醛(methylglyoxal, MGO)与谷胱甘肽在甲基乙二醛解毒酶1(glyoxalase 1,GLO1)的作用下形成乳酰化谷胱甘肽(lactoylglutathione, LGSH), 而LGSH可作为底物进行乳酸化修饰[52](图2)。

3.3 乳酸化与乙酰化之间的串扰

乙酰化是最早发现的蛋白质酰化修饰之一, 与乳酰化有相似之处, 因为两者都属于酰化修饰类别并利用类似的书写蛋白和擦除蛋白。 然而, 它们在细胞内执行不同的功能[53]。

这两种修饰都与酰基辅酶A作为底物相连接(lactyl-CoA和acetyl-CoA)。乙酰化和乳酸化都倾向于发生在赖氨酸残基上。当这些修饰发生在组蛋白上时, 它们通常共享位点, 如H3K18、H3K27、H3K23、H3K26[35], 表明这两种修饰之间可能存在串扰。例如, 巨噬细胞在遇到细菌刺激时或在肝星状细胞中, 均表现出乙酰化水平逐渐降低而乳酸化水平增加[30,35]。然而, 乳酰辅酶A是乳酸化底物, 但癌细胞中其内源浓度极低(约0.011 pmol/10^6细胞), 比哺乳动物细胞中的乙酰-CoA浓度低约1 000倍[50], U-13C6-葡萄糖掺入动力学也表明, 乳酸化达到稳定状态的时间(24小时)明显长于乙酰化(6小时)[35]。综上所述, 目前的证据似乎表明, 在大多数情况下, 乳酸化的竞争性不如乙酰化。

乳酸化与乙酰化共用“写入酶”(如p300/CBP)。例如: 巨噬细胞摄取细胞外乳酸, 通过p300/CBP依赖机制促进高迁移率族蛋白B1(high mobility group box-1 protein, HMGB1)的乳酸化。同时, 它通过Hippo/YAP途径抑制去乙酰化酶SIRT1, 通过β-arrestin2激活乙酰转移酶p300/CBP, 从而刺激HMGB1乙酰化。这些发现表明, HMGB1的乳酸化修饰和乙酰化修饰存在共同的靶点[54]。

常见的去乙酰化酶如HDAC1~3和SIRT1~3也具有去乳酸化能力, 其中HDAC3是一种有效的“擦除剂”[55]。然而, HDACs显示出对修饰类型和位置的明确偏好, 一类HDAC抑制剂已被发现可促进肝星状细胞中H3K18的乙酰化, 同时抑制同一位点的乳酸化[30]。HDAC1通过RNA干扰显著增加H4K5位点的乳酸化水平, 而HDAC2干扰不影响该位点的乳酸化, 这提示HDAC1具有位点特异性调控作用[55]。

乳酸化通常与乙酰化形成平衡, 协同调控染色质开放状态和基因表达。

4 乳酸及乳酸化在消化系统肿瘤中的机制和作用

4.1 乳酸在消化系统肿瘤中的积聚

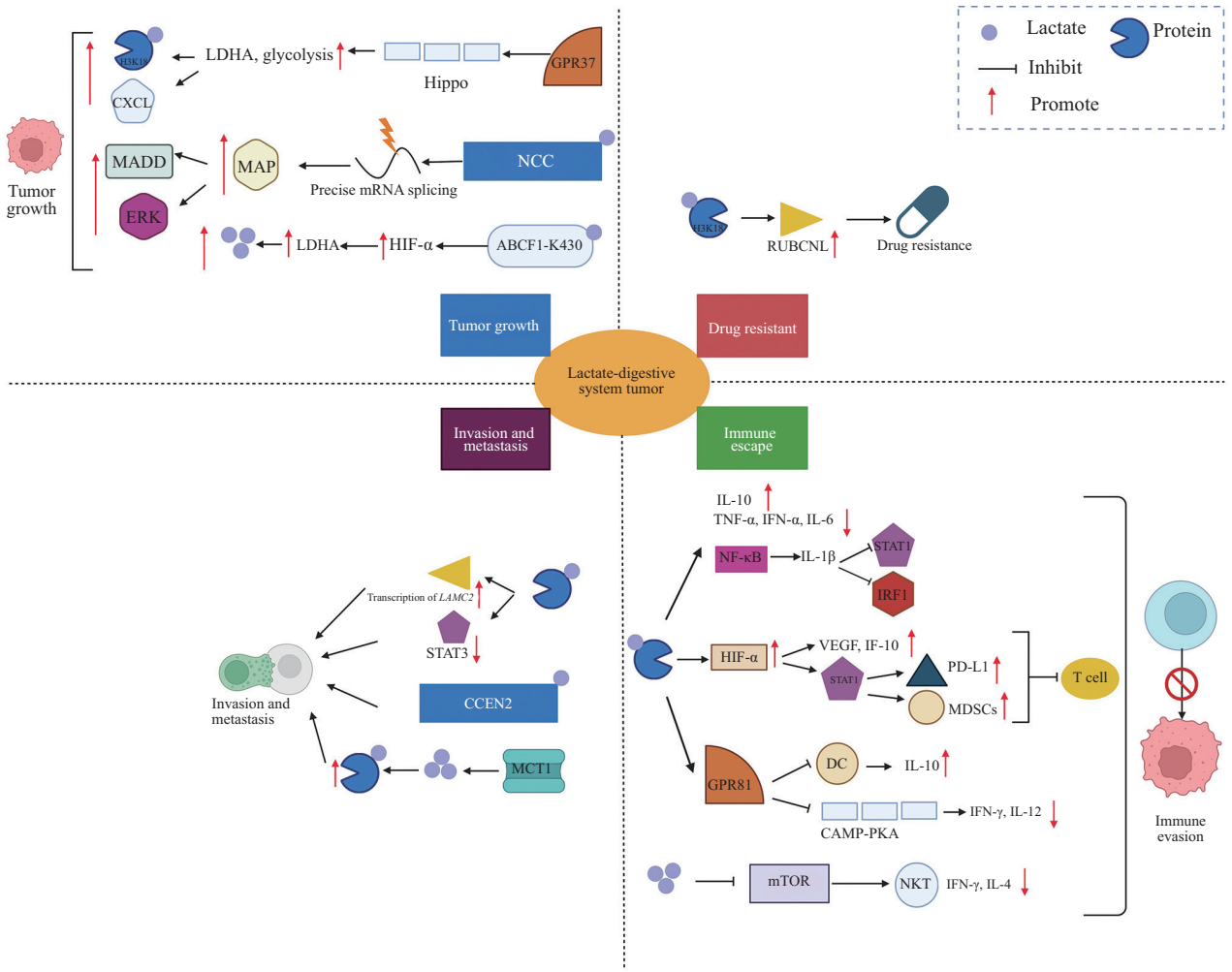
在不同类型的消化系统肿瘤中, 乳酸水平升高, 这一上升主要是由于Warburg效应, 乳酸的积聚是肿瘤细胞的代谢改变的一个标志[5]。目前一些先进技术可以测定消化系统肿瘤中乳酸的浓度, 如质子磁共振波谱是一种非侵入性的成像技术, 广泛用于测量体内的乳酸浓度, 允许实时监测肿瘤的代谢变化[56-57]。液相色谱–质谱联用技术(liquid chromatography-tandem mass spectrometry, LC-MS)以高灵敏度和高特异度精确地定量肿瘤组织和血液样本中的乳酸水平[58]。

研究表明, 与正常组织相比, 消化系统肿瘤的乳酸水平显著升高。 在食管癌组织中, LDHA的过表达导致乳酸的过量产生与积累。重编程的糖酵解为肿瘤细胞快速增殖提供能量和碳源, 同时产生的乳酸通过酸化肿瘤微环境促进血管生成, 并抑制免疫细胞活性[59]。胰腺癌中存在乳酸正反馈机制, 例如通过NUSAP1-LDHA-乳酸回路不断驱动糖酵解和乳酸产生[29]。同样在结直肠癌、胃癌和肝癌中也有类似发现, 表明高乳酸水平与癌症发展和不良预后存在关联[60-61], 因此, 系统解析乳酸稳态失衡的分子机制(包括糖酵解通量调控、单羧酸转运体功能异常及表观代谢重编程), 并通过靶向干预乳酸代谢轴关键节点(如抑制LDHA酶活性或调控NUSAP1介导的信号转导网络), 将为开发针对肿瘤微环境重塑和免疫逃逸的精准治疗策略提供新范式。

4.2 乳酸化在消化系统肿瘤中的进展

乳酸化修饰通过重构组蛋白与非组蛋白表观遗传景观, 建立了细胞代谢重编程与基因表达调控的分子桥梁, 对肿瘤的发生、侵袭转移和免疫逃避有重要影响(图3)。

4.2.1 促进肿瘤生长 乳酸化通过激活与细胞增殖和存活相关的基因, 促进肿瘤的快速生长。例如: 结直肠癌中G蛋白偶联受体37(G protein-coupled receptor 37, GPR37)激活Hippo通路, 促进LDHA的表达和糖酵解, 最终促进H3K18乳酸化和趋化因子1(chemokine 1, CXCL1)和CXCL5的上调, 从而满足快速分裂的肿瘤细胞的代谢需求, 支持肿瘤的持续



乳酸化修饰通过重构组蛋白与非组蛋白表观遗传景观, 建立了细胞代谢重编程与基因表达调控的分子桥梁, 对肿瘤的发生、侵袭转移和免疫逃避有重要影响。

Lactation modification establishes a molecular bridge between cellular metabolic reprogramming and gene expression regulation by reconfiguring the epigenetic landscape of histones and non-histone proteins, with important implications for tumorigenesis, invasion and metastasis, and immune evasion.

图3 乳酸化在消化系统肿瘤中的进展(此图通过bioRender制作)

Fig.3 Advances in lactation in tumours of the digestive system (this image was created via bioRender)

生长和扩展[62]; 肝内胆管癌中核仁(nucleolin, NCL)蛋白的乳酸化, 通过精确的mRNA剪接上调丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK), 激活死亡结构域蛋白(MAPK death domain, MADD), 并激活细胞外调节蛋白激酶(extracellular regulated protein kinase, ERK)信号转导来促进肝内胆管癌的进展[63]; 在肝细胞癌中, 非组蛋白ABCF1的430位点乳酸化(ABCF1-K430la)激活缺氧诱导因子-1α(hypoxia inducible factor-1α, HIF-1α), HIF-1α诱导癌细胞中LDHA的表达, 进一步促进乳酸的产生, 形成乳酸-ABCF1 K430Kla-HIF-1α-乳酸的闭环回路, 促进HCC进展[64]。

4.2.2 *增强侵袭和转移能力* 蛋白质乳酸化通过激活某些基因促进细胞外基质的降解, 或者蛋白质乳酸化通过诱导的基因表达改变可以促进EMT, 赋予肿瘤细胞迁移和侵袭能力[65-67]。例如: 食道癌中组蛋白H3K9乳酸化促进*LAMC2*转录, 从而促进细胞增殖和侵袭[68]; 肝细胞癌中低信号转导因子和转录激活因子3(transducer and activator of transcription 3, STAT3)表达与高乳酸化水平和不良预后相关。周期蛋白E2(CCNE2)在赖氨酸348位点的乳酸化作用增强了癌细胞的侵袭性和增殖能力[69]; 胰腺癌中乳酸化相关基因*LRGs*的表达与胰腺癌的增殖和迁移能力密切相关。LRGs中*MCT1*基因在乳酸化过程中起着关键作用, 研究表明, MCT1通过乳酸运输调节癌细胞的乳酸化水平, 间接影响癌细胞的增殖迁移能力[70]。

4.2.3 调节免疫逃逸 乳酸化通过调控参与免疫调节的基因表达, 帮助癌细胞逃避免疫监视[71]。乳酸化作用通过以下多种关键的信号通路和分子机制抑制促炎细胞因子, 增强抗炎因子, 产生免疫抑制的肿瘤微环境, 包括以下三方面:

(1) 组蛋白乳酸化促进巨噬细胞向M2型抗炎表型极化[72], 即抗炎因子白介素-10(interleukin-10, IL-10)表达水平增加、促炎因子肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)表达水平降低, 同时抑制促炎因子, 如白介素-6(interleukin-6, IL-6)、干扰素-γ(interferon-γ, IFN-γ)的产生[73]。此外, 乳酸化修饰可能直接抑制核因子κB(nuclear factor kappa-B, NF-κB)通路, 减少白介素IL-1β(interleukin-1β, IL-1β)等炎症信号释放, 并干扰STAT1通路和干扰素调节因子1(interferon regulatory factor 1, IRF1)介导的干扰素应答, 进一步削弱先天免疫反应[74-75]。

(2) 蛋白质乳酸化激活HIF-1α, 诱导血管内皮生长因子(vascular endothelial growth factor, VEGF)和IL-10分泌, 促进血管生成并抑制T细胞浸润[76]。HIF-1α与STAT3通路协同上调PD-L1表达, 通过PD-1/PD-L1轴抑制$CD8^+$ T细胞功能。STAT3的持续激活还可促进髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)的扩增, 通过精氨酸酶-1(arginase-1, Arg1)和活性氧(reactive oxygen species, ROS)耗竭微环境中的必需氨基酸, 直接抑制T细胞增殖与杀伤活性[77-78]。

(3) 蛋白质乳酸化通过G蛋白偶联受体GPR81抑制树突状细胞(dendritic cell, DC)的抗原呈递功能, 增加IL-10表达水平, 并降低cAMP-PKA通路活性, 从而减少促炎因子白介素-12(interleukin-12, IL-12)和IFN-γ的释放[79-80]。同时, 乳酸还通过抑制mTOR信号转导阻断肿瘤微环境中NKT细胞的IFN-γ和促炎因子白细胞介素-4(IL-4)产生, 从而阻止这些免疫细胞的激活[81]。

在肝细胞癌中, 这种免疫抑制的肿瘤微环境通过改变调节性T细胞(Treg)中的Moesin蛋白, 进而增强其与转化生长因子-β(transforming growth factor-β, TGF-β)信号通路的相互作用, 最终使Treg获得免疫抑制功能, 导致肿瘤细胞的免疫逃逸, 促进肿瘤细胞免疫耐受性生长[66-67,82]。在胃癌组织中乳酸化水平明显高于正常组织, 且表现出丰富的免疫细胞渗透, 尤其是巨噬细胞的高度渗透和基因组不稳定性的增加, 且免疫检查点抑制剂(immune checkpoint inhibitor, ICI)在高乳酸化水平的胃癌中表现出较低的反应率, 上述特征表明高乳酸化水平机体有着更高程度的肿瘤免疫功能障碍和免疫逃逸[83]。

4.2.4 产生耐药 乳酸化还与肿瘤细胞的化疗耐药性相关。在结直肠癌中, 肿瘤来源的乳酸促进H3K18乳酸化, 从而增强自噬蛋白RUBCNL的表达, 促进自噬过程, 使结直肠癌细胞对贝伐珠单抗产生耐药性。另外对贝伐单抗耐药的结直肠癌患者表现出组蛋白乳酸化水平升高[46]。

5 靶向乳酸化及乳酸化相关代谢通路的治疗潜力

5.1 靶向乳酸化相关代谢通路

5.1.1 干扰糖酵解和乳酸代谢 癌细胞通过糖酵解提供快速生长所需的能量, 并产生大量乳酸, 这为乳酸化提供了基础。因此, 靶向糖酵解乳酸代谢提供了一种间接的策略来调节乳酸化。

抑制糖酵解酶。研究发现, 用抗精神药物Penfluridol靶向磷酸果糖激酶(phosphofructokinase, Liver, PFKL)抑制糖酵解并以AMPK/FOXO3a/BIM依赖性方式抑制食管癌肿瘤发生, 且在裸鼠肿瘤异种移植模型中发现Penfluridol治疗对小鼠的肝脏、肾脏和肺等重要器官没有毒性作用, 这一定程度表明抗精神病药物Penfluridol是一种潜在的抗癌剂[84]。人参皂甙Rh4通过靶向食管癌中的磷脂酰肌醇3-激酶(phosphoinositide 3-kinase, PI3K)/蛋白激酶B(protein kinase B, AKT), 抑制有氧糖酵解和PD-L1的表达从而抑制肿瘤发生发展, 另外顺铂是治疗食管癌使用最广泛的化疗药物[85], 研究结果表明Rh4在治疗食管癌中诱导的毒副作用较顺铂少[86]。2-脱氧葡萄糖(2-deoxy-D-glucose, 2-DG)抑制己糖激酶, 阻止葡萄糖代谢, 导致胃癌细胞中乳酸水平减少从而间接降低乳酸化水平[87]。

靶向肿瘤细胞的乳酸代谢和信号通路可能是治疗癌症的有效策略, 例如靶向NUSAP1。NUSAP1是一种微管相关蛋白, 可以与c-Myc和HIF-1α结合, 作用于*LDHA*基因启动子区域, 上调LDHA的表达。LDHA作为限速酶, 促进糖酵解, 产生乳酸。反过来, 乳酸可以通过诱导乳酸化来稳定NUSAP1, 抑制其降解。靶向NUSAP1可以抑制LDHA表达, 间接抑制肿瘤进展[29]。

靶向ALDOB/PDK1/乳酸/CEACAM6轴的治疗策略可能为结直肠癌患者提供新的治疗选择。缩醛酶B(ALDOB)被认为是结直肠癌Warburg效应的潜在调节者, 它能激活丙酮酸脱氢酶激酶1(pyruvate dehydrogenase kinase 1, PDK1)从而促进乳酸的产生和分泌, 促进结直肠癌细胞中细胞增殖、化疗耐药并影响癌胚抗原(carcinoembryonic antigen, CEA)的表达。研究发现分泌的乳酸可增强相邻细胞中的LDHB表达, 并且是ALDOB介导的表型的关键调节剂。ALDOB对CEA表达的影响是ALDOB介导的乳酸分泌引起的生物能量变化的下游效应。此外, 癌胚抗原相关细胞黏附分子-6(carcinoembryonic antigen-related cell adhesion molecule 6, CEACAM6)控制结直肠癌细胞的增殖和化疗耐药性。因此, 乳酸化相关基因在结直肠癌的发展过程中起着重要作用, 并可能成为新的治疗靶点[88]。

5.1.2 *抑制乳酸转运体* 抑制乳酸转运体MCT1和MCT4也显示出抗肿瘤作用, 阻断MCT会增加食管癌细胞的凋亡水平, 并降低其增殖能力, 研究表明MCT1抑制剂AZD3965, 具有作为食管癌的新型抗肿瘤药物的潜力[89-92]。胰腺癌的研究中MCT1通过乳酸转运调节胰腺癌细胞中的乳酸化。实验表明, 降低MCT1水平及其乳酸化可显著抑制肿瘤进展, 表明靶向MCT1/乳酸化相关信号通路具有作为胰腺癌治疗策略的潜力[70]。

5.2 靶向乳酸化

5.2.1 *去乙酰化酶*(histone deacetylase, HDAC)*抑制剂和SIRT3去乳酸化酶* HDAC抑制剂[如伏立诺他(Vorinostat)和帕比司他(Panobinostat)]可降低乳酸化水平, 从而调节与肿瘤生长和免疫逃逸相关的基因表达, 同时临床研究显示其常见不良反应包括血小板减少、中性粒细胞减少、腹泻症状减轻及食欲减退[30,93-94]。

SIRT3去乳酸化酶可以通过去除CCNE2蛋白上的乳酸化基团来抑制肝癌细胞的增殖功能。晶体学研究阐明了SIRT3介导的CCNE2 K348位点去乳酸化的分子机制。此外, 和厚朴酚通过激活SIRT3促进CCNE2去乳酸化来促进其抗肝细胞癌作用[69]。

5.2.2 *抑制乳酸化修饰* 某些天然药物成分可以通过抑制组蛋白乳酸化修饰发挥抗肝癌作用。例如, DML(demethylzeylasteral)通过抑制H3组蛋白乳酸化来抑制肝癌肝细胞(LCSCs)诱导的致瘤性, 在裸鼠肝癌模型中, DML通过调节H3组蛋白乳酸化对癌症生长的抑制作用已得到证实, 同时, 在裸鼠肿瘤异种移植模型中未观察到DML的生物毒性作用。这在一定程度上表明DML有可能发展成为一种安全有效的补充抗癌药物[95]。此外, 蜂王浆酸可以特异性抑制H3K9和H3K14位点的乳酸化, 证明其具有抑制肝癌细胞增殖、转移和凋亡的作用[41], 并且相关研究证明蜂王浆酸是一种天然化合物, 可有效降低肝癌患者因使用顺铂引起的肾毒性, 可用于预防这种不良反应[96]。另外, GPC3(glypican-3)的敲低通过降低乳酸化修饰水平来抑制缺氧微环境中肝细胞癌细胞的生长、干性和葡萄糖摄取, 表明GPC3介导的乳酸化可能代表肝细胞癌的新治疗方向[97]。

前蛋白转化酶枯草杆菌蛋白酶/kexin9型(proprotein convertase subtilisin/kexin 9, PCSK9)通过调节肿瘤细胞EMT和PI3K/AKT信号转导在结肠癌的进展和转移中发挥重要作用, 并通过介导巨噬细胞迁移抑制因子(migration inhibitory factor, MIF)和乳酸水平在巨噬细胞的表型极化中发挥重要作用。敲低PCSK9表达抑制M2巨噬细胞极化, 也可通过降低乳酸、蛋白质乳酸化和MIF水平促进M1巨噬细胞极化[98]。

5.2.3 *靶向乳酸转移酶* 针对乳酸转移酶的抑制剂可以通过改变涉及癌细胞存活和增殖的关键信号通路来抑制肿瘤进展和转移。尽管乳酸化相关的具体酶尚未完全明确, 但研究正在探索针对乳酸化转移酶的特定抑制剂, 以抑制肿瘤进展和转移[19,48]。

5.3 联合治疗

将乳酸代谢抑制剂与免疫治疗或化疗结合, 可增强抗肿瘤效果。例如, 乳酸脱氢酶抑制剂联合免疫检查点抑制剂可逆转乳酸引起的免疫抑制[99-102]。

将乳酸化抑制剂与免疫治疗或靶向治疗结合, 可增强抗肿瘤疗效, 克服单一治疗的耐药性[103-104]。例如, 联合使用抑制乳糖化和自噬的药物可以提高贝伐单抗在结直肠癌中的疗效[46]。

因此, 针对乳酸代谢和乳酸化的新的治疗策略值得进一步探索。

6 前景和挑战

乳酸化作为一种新兴的表观遗传修饰, 已广泛认定其在肿瘤代谢重编程、免疫微环境调控和基因表达中的重要作用。通过乳酸代谢产物驱动的修饰

过程, 乳酸化与肿瘤的发生、侵袭、免疫逃逸和耐药性密切相关。然而, 乳酸化的具体底物来源、关键酶的特异性及其在不同肿瘤类型中的具体作用机制尚未完全明了。未来的研究将侧重于整合多组学技术和大数据分析, 全面解析乳酸及乳酸化在肿瘤中的分子网络, 揭示其在肿瘤分子分型中的特定关系, 为个性化治疗方案的制定提供理论支持。同时, 研究还需聚焦乳酸化酶的精准开发, 探索新型高效乳酸化调控分子, 并通过临床试验验证乳酸化靶点在肿瘤治疗中的疗效。治疗策略方面, 通过靶向LDH和MCT通路来减少肿瘤微环境中的乳酸积累, 从而缓解酸性环境对免疫系统的抑制; 同时, 靶向乳酸化关键酶, 干预组蛋白和非组蛋白的乳酸化, 阻断肿瘤细胞的代谢重编程和增殖; 联合免疫治疗以及放化疗与乳酸代谢干预的多模式协同治疗也将提升治疗效果。尽管乳酸在肿瘤中的双重作用和耐药性机制仍需进一步探索, 靶向乳酸化的技术难点和副作用问题仍需克服, 但通过加速临床转化、跨学科协作以及新型靶点的挖掘, 乳酸化靶向治疗有望推动抗肿瘤疗法的突破与升级。

参考文献 (References)

[1] HUANG J, LUCERO-PRISNO D E, ZHANG L, et al. Updated epidemiology of gastrointestinal cancers in East Asia [J]. Nat Rev, 2023, 20(5): 271-87.

[2] 王鹏, 樊建春, 贾举名, 等. SHP2在消化系统肿瘤中的研究进展[J]. 中国比较医学杂志(WANG P, FAN J C, JIA J M, et al. Research progress of SHP2 in digestive system tumors [J]. Chin J Comp Med), 2024, 34(5): 159-68.

[3] 李未鹏, 林风池, 封龙飞, 等. 中医药诱导铁死亡治疗消化系统肿瘤的研究现状[J]. 中国临床药理学杂志(LI W P, LIN F C, FENG L F, et al. Current research status of traditional Chinese medicine inducing ferroptosis in the treatment of digestive system tumors [J]. Chin J Clin Pharmacol), 2024, 40(22): 3338-42.

[4] 曹毛毛, 陈万青. 中国恶性肿瘤流行情况及防控现状[J]. 中国肿瘤临床 (CAO M M, CHEN W Q. Current status of malignant tumor prevalence and prevention in China [J]. Chin J Clin Oncol), 2019, 46(3): 145-9.

[5] WANG Y, PATTI G J. The Warburg effect: a signature of mitochondrial overload [J]. Trends Cell Biol, 2023, 33(12): 1014-20.

[6] JIANG J, ZHENG Q, ZHU W, et al. Alterations in glycolytic/cholesterogenic gene expression in hepatocellular carcinoma [J]. Aging, 2020, 12(11): 10300-16.

[7] ORRE C, DIEU X, GUILLON J, et al. The long non-coding RNA SAMMSON is a regulator of chemosensitivity and metabolic orientation in MCF-7 doxorubicin-resistant breast cancer cells [J]. Biology, 2021, 10(11): 1156.

[8] BROOKS G A. The science and translation of lactate shuttle theory [J]. Cell Metab, 2018, 27(4): 757-85.

[9] RABINOWITZ J D, ENERBÄCK S. Lactate: the ugly duckling of energy metabolism [J]. Nat Metab, 2020, 2(7): 566-71.

[10] LI X, YANG Y, ZHANG B, et al. Lactate metabolism in human health and disease [J]. Signal Transduct Target Ther, 2022, 7(1): 1-22.

[11] LI H, LI S, LIN Y, et al. Artificial exosomes mediated spatiotemporal-resolved and targeted delivery of epigenetic inhibitors [J]. J Nanobiotechnol, 2021, 19(1): 364.

[12] GOPI L K, KIDDER B L. Integrative pan cancer analysis reveals epigenomic variation in cancer type and cell specific chromatin domains [J]. Nat Commun, 2021, 12(1): 1419.

[13] XING X L, LIU Y, LIU J, et al. Comprehensive analysis of ferroptosis- and immune-related signatures to improve the prognosis and diagnosis of kidney renal clear cell carcinoma [J]. Front Immunol, 2022, 13: 851312.

[14] ZHANG J, ZHENG Z, ZHENG J, et al. Epigenetic-mediated downregulation of zinc finger protein 671 (ZNF671) predicts poor prognosis in multiple solid tumors [J]. Front Oncol, 2019, 9: 342.

[15] LYU Y, YANG Y, TALWAR V, et al. Hypoxia-inducible factor 1 recruits FACT and RNF20/40 to mediate histone ubiquitination and transcriptional activation of target genes [J]. Cell Rep, 2024, 43(4): 113972.

[16] NATU A, VERMA T, KHADE B, et al. Histone acetylation: a key determinant of acquired cisplatin resistance in cancer [J]. Clin Epigenetics, 2024, 16(1): 8.

[17] PANDKAR M R, SINHA S, SAMAIYA A, et al. Oncometabolite lactate enhances breast cancer progression by orchestrating histone lactylation-dependent c-Myc expression [J]. Transl Oncol, 2023, 37: 101758.

[18] CHEN M, CEN K, SONG Y, et al. NUSAP1-LDHA-glycolysis-lactate feedforward loop promotes Warburg effect and metastasis in pancreatic ductal adenocarcinoma [J]. Cancer Lett, 2023, 567: 216285.

[19] ZONG Z, XIE F, WANG S, et al. Alanyl-tRNA synthetase, AARS1, is a lactate sensor and lactyltransferase that lactylates p53 and contributes to tumorigenesis [J]. Cell, 2024, 187(10): 2375-92.

[20] FERON O. Pyruvate into lactate and back: from the Warburg effect to symbiotic energy fuel exchange in cancer cells [J]. Radiother Oncol, 2009, 92(3): 329-33.

[21] BENNIS Y, BODEAU S, BATTEUX B, et al. A study of associations between plasma metformin concentration, lactic acidosis, and mortality in an emergency hospitalization context [J]. Crit Care Med, 2020, 48(12): e1194-202.

[22] SOREZE Y, BOUTRON A, HABAROU F, et al. Mutations in human lipoyltransferase gene LIPT1 cause a Leigh disease with secondary deficiency for pyruvate and alpha-ketoglutarate dehydrogenase [J]. Orphanet J Rare Dis, 2013, 8: 192.

[23] JHA M K, LEE I K, SUK K. Metabolic reprogramming by the pyruvate dehydrogenase kinase-lactic acid axis: linking metabolism and diverse neuropathophysiologies [J]. Neurosci Biobehav Rev, 2016, 68: 1-19.

[24] EMHOFF C A W, MESSONNIER L A, HORNING M A, et al. Gluconeogenesis and hepatic glycogenolysis during exercise at the lactate threshold [J]. J Appl Physiol, 2013, 114(3): 297-306.

[25] ENERSON B E, DREWES L R. Molecular features, regulation,

and function of monocarboxylate transporters: implications for drug delivery [J]. J Pharm Sci, 2003, 92(8): 1531-44.

[26] HALESTRAP A P. The SLC16 gene family-structure, role and regulation in health and disease [J]. Mol Aspects Med, 2013, 34(2/3): 337-49.

[27] SUN S, LI H, CHEN J, et al. Lactic acid: no longer an inert and end-product of glycolysis [J]. Physiology, 2017, 32(6): 453-63.

[28] CONTRERAS-BAEZA Y, SANDOVAL P Y, ALARCÓN R, et al. Monocarboxylate transporter 4 (MCT4) is a high affinity transporter capable of exporting lactate in high-lactate microenvironments [J]. J Biol Chem, 2019, 294(52): 20135-47.

[29] WANG T, YE Z, LI Z, et al. Lactate-induced protein lactylation: a bridge between epigenetics and metabolic reprogramming in cancer [J]. Cell Prolif, 2023, 56(10): e13478.

[30] RHO H, TERRY A R, CHRONIS C, et al. Hexokinase 2-mediated gene expression via histone lactylation is required for hepatic stellate cell activation and liver fibrosis [J]. Cell Metab, 2023, 35(8): 1406-23.

[31] YANG Z, YAN C, MA J, et al. Lactylome analysis suggests lactylation-dependent mechanisms of metabolic adaptation in hepatocellular carcinoma [J]. Nat Metab, 2023, 5(1): 61-79.

[32] LI Y, MO H, WU S, et al. A novel lactate metabolism-related gene signature for predicting clinical outcome and tumor microenvironment in hepatocellular carcinoma [J]. Front Cell Dev Biol, 2022, 9: 801959.

[33] FENG T, ZHAO X, GU P, et al. Adipocyte-derived lactate is a signalling metabolite that potentiates adipose macrophage inflammation via targeting PHD2 [J]. Nat Commun, 2022, 13(1): 5208.

[34] LIU X, ZHANG Y, ZHUANG L, et al. NADPH debt drives redox bankruptcy: SLC7A11/xCT-mediated cystine uptake as a double-edged sword in cellular redox regulation [J]. Genes Dis, 2021, 8(6): 731-45.

[35] ZHANG D, TANG Z, HUANG H, et al. Metabolic regulation of gene expression by histone lactylation [J]. Nature, 2019, 574(7779): 575-80.

[36] HE Y, HUANG Y, PENG P, et al. Lactate and lactylation in gastrointestinal cancer: current progress and perspectives [J]. Oncol Rep, 2025, 53(1): 6.

[37] LI H, SUN L, GAO P, et al. Lactylation in cancer: current understanding and challenges [J]. Cancer Cell, 2024, 42(11): 1803-7.

[38] ZHOU J, MA X, LIU X, et al. The impact of histone lactylation on the tumor microenvironment and metabolic pathways and its potential in cancer therapy [J]. Genes Genomics, 2024, 46(9): 991-1011.

[39] NEWSHOLME P, ROWLANDS J, ROSE'MEYER R, et al. Metabolic adaptions/reprogramming in islet beta-cells in response to physiological stimulators-what are the consequences [J]. Antioxidants, 2022, 11(1): 108.

[40] XU X, PENG Q, JIANG X, et al. Metabolic reprogramming and epigenetic modifications in in cancer: from the impacts and mechanisms to the treatment potential [J]. Exp Mol Med, 2023, 55(7): 1357-70.

[41] XU H, LI L, WANG S, et al. Royal jelly acid suppresses hepatocellular carcinoma tumorigenicity by inhibiting H3 histone lactylation at H3K9la and H3K14la sites [J]. Phytomedicine, 2023, 118: 154940.

[42] NGWA V M, EDWARDS D N, PHILIP M, et al. Microenvironmental metabolism regulates antitumor immunity [J]. Cancer Res, 2019, 79(16): 4003-8.

[43] IVASHKIV L B. The hypoxia-lactate axis tempers inflammation [J]. Nat Rev Immunol, 2020, 20(2): 85-6.

[44] VITALE M, CANTONI C, PIETRA G, et al. Effect of tumor cells and tumor microenvironment on NK-cell function [J]. Eur J Immunol, 2014, 44(6): 1582-92.

[45] GABRILOVICH D I, NAGARAJ S. Myeloid-derived suppressor cells as regulators of the immune system [J]. Nat Rev Immunol, 2009, 9(3): 162-74.

[46] LI W, ZHOU C, YU L, et al. Tumor-derived lactate promotes resistance to bevacizumab treatment by facilitating autophagy enhancer protein RUBCNL expression through histone H3 lysine 18 lactylation (H3K18la) in colorectal cancer [J]. Autophagy, 2024, 20(1): 114-30.

[47] CHEN Y, WU J, ZHAI L, et al. Metabolic regulation of homologous recombination repair by MRE11 lactylation [J]. Cell, 2024, 187(2): 294-311.

[48] JU J, ZHANG H, LIN M, et al. The alanyl-tRNA synthetase AARS1 moonlights as a lactyltransferase to promote YAP signaling in gastric cancer [J]. J Clin Invest, 2024, 134(10): 174587.

[49] MAO Y, ZHANG J, ZHOU Q, et al. Hypoxia induces mitochondrial protein lactylation to limit oxidative phosphorylation [J]. Cell Res, 2024, 34(1): 13-30.

[50] VARNER E L, TREFELY S, BARTEE D, et al. Quantification of lactoyl-CoA (lactyl-CoA) by liquid chromatography mass spectrometry in mammalian cells and tissues [J]. Open Biol, 2020, 10(9): 200187.

[51] HE Y, SONG T, NING J, et al. Lactylation in cancer: mechanisms in tumour biology and therapeutic potentials [J]. Clin Transl Med, 2024, 14(11): e70070.

[52] GAFFNEY D O, JENNINGS E Q, ANDERSON C C, et al. Non-enzymatic lysine lactoylation of glycolytic enzymes [J]. Cell Chem Biol, 2020, 27(2): 206-13.

[53] GUERTIN D A, WELLEN K E. Acetyl-CoA metabolism in cancer [J]. Nat Rev Cancer, 2023, 23(3): 156-72.

[54] YANG K, FAN M, WANG X, et al. Lactate promotes macrophage HMGB1 lactylation, acetylation, and exosomal release in polymicrobial sepsis [J]. Cell Death Differ, 2022, 29(1): 133-46.

[55] MORENO-YRUELA C, ZHANG D, WEI W, et al. Class I histone deacetylases (HDAC1-3) are histone lysine delactylases [J]. Sci Adv, 2022, 8(3): eabi6696.

[56] CHEUNG S M, HUSAIN E, MASANNAT Y, et al. Lactate concentration in breast cancer using advanced magnetic resonance spectroscopy [J]. Br J Cancer, 2020, 123(2): 261-7.

[57] SHIRBANDI K, RIKHTEGAR R, KHALAFI M, et al. Functional magnetic resonance spectroscopy of lactate in Alzheimer disease: a comprehensive review of Alzheimer disease pathology and the role of lactate [J]. Top Magn Reson Imaging, 2023, 32(2): 15-26.

[58] AFSHAR M, VAN HALL G. LC-MS/MS method for quantitative profiling of ketone bodies, α-keto acids, lactate, pyruvate and their stable isotopically labelled tracers in human plasma: an analytical panel for clinical metabolic kinetics and interactions [J]. J Chromatogr B Analyt Technol Biomed Life Sci, 2023, 1230: 123906.

[59] LUO H S, XU H Y, DU Z S, et al. Prognostic significance of

baseline neutrophil count and lactate dehydrogenase level in patients with esophageal squamous cell cancer treated with radiotherapy [J]. Front Oncol, 2020, 10: 430.

[60] YANG J, REN B, YANG G, et al. The enhancement of glycolysis regulates pancreatic cancer metastasis [J]. Cell Mol Life Sci, 2020, 77(2): 305-21.

[61] SUN L, ZHANG Y, YANG B, et al. Lactylation of METTL16 promotes cuproptosis via m6A-modification on FDX1 mRNA in gastric cancer [J]. Nat Commun, 2023, 14(1): 6523.

[62] ZHOU J, XU W, WU Y, et al. GPR37 promotes colorectal cancer liver metastases by enhancing the glycolysis and histone lactylation via Hippo pathway [J]. Oncogene, 2023, 42(45): 3319-30.

[63] YANG L, NIU K, WANG J, et al. Nucleolin lactylation contributes to intrahepatic cholangiocarcinoma pathogenesis via RNA splicing regulation of MADD [J]. J Hepatol, 2024, 81(4): 651-66.

[64] HONG H, HAN H, WANG L, et al. ABCF1-K430-lactylation promotes HCC malignant progression via transcriptional activation of HIF1 signaling pathway [J]. Cell Death Differ, 2025: 1-19.

[65] YANG H, YANG S, HE J, et al. Glucose transporter 3 (GLUT3) promotes lactylation modifications by regulating lactate dehydrogenase A (LDHA) in gastric cancer [J]. Cancer Cell Int, 2023, 23(1): 303.

[66] HUANG Y F, WANG G, DING L, et al. Lactate-upregulated NADPH-dependent NOX4 expression via HCAR1/PI3K pathway contributes to ROS-induced osteoarthritis chondrocyte damage [J]. Redox Biol, 2023, 67: 102867.

[67] LONG L, XIONG W, LIN F, et al. Regulating lactate-related immunometabolism and EMT reversal for colorectal cancer liver metastases using shikonin targeted delivery [J]. J Exp Clin Cancer Res, 2023, 42(1): 117.

[68] ZANG Y, WANG A, ZHANG J, et al. Hypoxia promotes histone H3K9 lactylation to enhance LAMC2 transcription in esophageal squamous cell carcinoma [J]. iScience, 2024, 27(7): 110188.

[69] JIN J, BAI L, WANG D, et al. SIRT3-dependent delactylation of cyclin E2 prevents hepatocellular carcinoma growth [J]. EMBO Rep, 2023, 24(5): e56052.

[70] PENG T, SUN F, YANG J C, et al. Novel lactylation-related signature to predict prognosis for pancreatic adenocarcinoma [J]. World J Gastroenterol, 2024, 30(19): 2575-602.

[71] CHEN L, HUANG L, GU Y, et al. Lactate-lactylation hands between metabolic reprogramming and immunosuppression [J]. Int J Mol Sci, 2022, 23(19): 11943.

[72] ZHANG L, LI S. Lactic acid promotes macrophage polarization through MCT-HIF1α signaling in gastric cancer [J]. Exp Cell Res, 2020, 388(2): 111846.

[73] COLEGIO O R, CHU N Q, SZABO A L, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid [J]. Nature, 2014, 513(7519): 559-63.

[74] LI H, LIU C, LI R, et al. AARS1 and AARS2 sense L-lactate to regulate cGAS as global lysine lactyltransferases [J]. Nature, 2024, 634(8036): 1229-37.

[75] DUAN Y, ZHAN H, WANG Q, et al. Integrated lactylome characterization reveals the molecular dynamics of protein regulation in gastrointestinal cancers [J]. Adv Sci, 2024, 11(35): 2400227.

[76] GARDNER D K. Lactate production by the mammalian blastocyst: manipulating the microenvironment for uterine implantation and invasion [J]? Bioessays, 2015, 37(4): 364-71.

[77] 曹馨, 张进萍, 涂丽英, 等. PD-1/PD-L1轴的作用及其在胃肠道肿瘤免疫治疗中的意义[J]. 生物化学与生物物理进展(CAO X, ZHANG J P, TU L Y, et al. The effects of the PD-1/PD-L1 Axis and its implications for immunotherapy in gastrointestinal tract cancers [J]. Prog Biochem Biophys), 2024, 51(8): 1834-47.

[78] 黄丽葶. MDSCs在消化系统肿瘤中的作用及其靶向治疗的研究进展[J]. 临床医学进展(HUANG L T. The role of MDSCs in digestive system tumors and research progress in targeted therapy [J]. Adv Clin Med), 2024, 14(9): 925-33.

[79] ZHANG Y, PENG Q, ZHENG J, et al. The function and mechanism of lactate and lactylation in tumor metabolism and microenvironment [J]. Genes Dis, 2022, 10(5): 2029-37.

[80] LIU X, LI S, CUI Q, et al. Activation of GPR81 by lactate drives tumour-induced cachexia [J]. Nat Metab, 2024, 6(4): 708-23.

[81] HARMON C, ROBINSON M W, HAND F, et al. Lactate-mediated acidification of tumor microenvironment induces apoptosis of liver-resident NK cells in colorectal liver metastasis [J]. Cancer Immunol Res, 2019, 7(2): 335-46.

[82] GU J, ZHOU J, CHEN Q, et al. Tumor metabolite lactate promotes tumorigenesis by modulating MOESIN lactylation and enhancing TGF-β signaling in regulatory T cells [J]. Cell Rep, 2022, 39(12): 110986.

[83] YANG H, ZOU X, YANG S, et al. Identification of lactylation related model to predict prognostic, tumor infiltrating immunocytes and response of immunotherapy in gastric cancer [J]. Front Immunol, 2023, 14: 1149989.

[84] ZHENG C, YU X, LIANG Y, et al. Targeting PFKL with penfluridol inhibits glycolysis and suppresses esophageal cancer tumorigenesis in an AMPK/FOXO3a/BIM-dependent manner [J]. Acta Pharm Sin B, 2022, 12(3): 1271-87.

[85] TOSHIMITSU H, HASHIMOTO K, TANGOKU A, et al. Molecular signature linked to acquired resistance to cisplatin in esophageal cancer cells [J]. Cancer Lett, 2004, 211(1): 69-78.

[86] DENG X, ZHAO J, QU L, et al. Ginsenoside Rh4 suppresses aerobic glycolysis and the expression of PD-L1 via targeting AKT in esophageal cancer [J]. Biochem Pharmacol, 2020, 178: 114038.

[87] MARUYAMA T, MIYAZAKI H, LIM Y J, et al. Pyrolyzed deketene curcumin controls regulatory T cell generation and gastric cancer metabolism cooperate with 2-deoxy-d-glucose [J]. Front Immunol, 2023, 14: 1049713.

[88] CHU Y D, CHENG L C, LIM S N, et al. Aldolase B-driven lactagenesis and CEACAM6 activation promote cell renewal and chemoresistance in colorectal cancer through the Warburg effect [J]. Cell Death Dis, 2023, 14(10): 660.

[89] POLAŃSKI R, HODGKINSON C L, FUSI A, et al. Activity of the monocarboxylate transporter 1 inhibitor AZD3965 in small cell lung cancer [J]. Clin Cancer Res, 2014, 20(4): 926-37.

[90] GRASA L, CHUECA E, ARECHAVALETA S, et al. Antitumor effects of lactate transport inhibition on esophageal adenocarcinoma cells [J]. J Physiol Biochem, 2023, 79(1): 147-61.

[91] COLEN C B, SHEN Y, GHODDOUSSI F, et al. Metabolic targeting of lactate efflux by malignant glioma inhibits invasiveness and induces necrosis: an *in vivo* study [J]. Neoplasia, 2011, 13(7): 620-32.

[92] CURTIS N J, MOONEY L, HOPCROFT L, et al. Pre-clinical pharmacology of AZD3965, a selective inhibitor of MCT1:

DLBCL, NHL and Burkitt's lymphoma anti-tumor activity [J]. Oncotarget, 2017, 8(41): 69219-36.

[93] OGURA M, ANDO K, SUZUKI T, et al. A multicentre phase II study of vorinostat in patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma [J]. Br J Haematol, 2014, 165(6): 768-76.

[94] KAUFMAN J L, MINA R, JAKUBOWIAK A J, et al. Combining carfilzomib and panobinostat to treat relapsed/refractory multiple myeloma: results of a multiple myeloma research consortium phase I study [J]. Blood Cancer J, 2019, 9(1): 3.

[95] PAN L, FENG F, WU J, et al. Demethylzeylasteral targets lactate by inhibiting histone lactylation to suppress the tumorigenicity of liver cancer stem cells [J]. Pharmacol Res, 2022, 181: 106270.

[96] HAMAD R, JAYAKUMAR C, RANGANATHAN P, et al. Honey feeding protects kidney against cisplatin nephrotoxicity through suppression of inflammation [J]. Clin Exp Pharmacol Physiol, 2015, 42(8): 843-8.

[97] YAO G, YANG Z. Glypican-3 knockdown inhibits the cell growth, stemness, and glycolysis development of hepatocellular carcinoma cells under hypoxic microenvironment through lactylation [J]. Arch Physiol Biochem, 2024, 130(5): 546-54.

[98] WANG L, LI S, LUO H, et al. PCSK9 promotes the progression and metastasis of colon cancer cells through regulation of EMT and PI3K/AKT signaling in tumor cells and phenotypic polarization of macrophages [J]. J Exp Clin Cancer Res, 2022, 41(1): 303.

[99] ZHAI X, YANG Y, WAN J, et al. Inhibition of LDH-A by oxamate induces G_2/M arrest, apoptosis and increases radiosensitivity in nasopharyngeal carcinoma cells [J]. Oncol Rep, 2013, 30(6): 2983-91.

[100] GARCÍA-CASTILLO V, LÓPEZ-URRUTIA E, VILLANUEVA-SÁNCHEZ O, et al. Targeting metabolic remodeling in triple negative breast cancer in a murine model [J]. J Cancer, 2017, 8(2): 178-89.

[101] MURAMATSU H, SUMITOMO M, MORINAGA S, et al. Targeting lactate dehydrogenase-A promotes docetaxel-induced cytotoxicity predominantly in castration-resistant prostate cancer cells [J]. Oncol Rep, 2019, 42(1): 224-30.

[102] MANERBA M, DI IANNI L, FIUME L, et al. Lactate dehydrogenase inhibitors sensitize lymphoma cells to cisplatin without enhancing the drug effects on immortalized normal lymphocytes [J]. Eur J Pharm Sci, 2015, 74: 95-102.

[103] ZHANG Y, SONG H, LI M, et al. Histone lactylation bridges metabolic reprogramming and epigenetic rewiring in driving carcinogenesis: oncometabolite fuels oncogenic transcription [J]. Clin Transl Med, 2024, 14(3): e1614.

[104] QU J, LI P, SUN Z. Histone lactylation regulates cancer progression by reshaping the tumor microenvironment [J]. Front Immunol, 2023, 14: 1284344.