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综述

乳酸化修饰在肝癌发生发展中的作用研究进展

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摘要 乳酸化(lactylation)是近几年发现的一种通过乳酸分子与蛋白质氨基酸残基结合而产生的翻译后修饰。肝细胞癌(HCC)是世界范围内癌症死亡的主要原因之一, 目前临床上缺乏对HCC有效的筛查和治疗手段。乳酸化修饰可通过多途径(包括参与细胞外基质重塑、影响信号通路和代谢途径)调节肝癌细胞功能, 并在免疫微环境的调节中发挥重要作用。该文讨论了乳酸化与肝癌发生发展和预后的相关性, 并总结了目前乳酸化对肝癌的影响及治疗方法, 为未来肝癌治疗策略的发展提供了新思路。

关键词 乳酸化; 肝癌细胞; 肿瘤微环境; 翻译后修饰

Research Progress on the Role of Lactylation Modification in the Occurrence and Development of Liver Cancer

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Abstract Lactylation is a recently discovered post-translational modification that occurs through the binding of lactate molecules to amino acid residues in proteins. HCC (hepatocellular carcinoma) is one of the leading causes of cancer-related mortality worldwide, and there is currently a lack of effective screening and treatment methods for HCC in clinical practice. Lactylation modification can regulate the functions of hepatocellular carcinoma cells through multiple pathways, including extracellular matrix remodeling, modulation of signaling pathways, and metabolic pathways, with significant effects particularly in the regulation of the immune microenvironment. This paper discusses the correlation between lactylation and the occurrence, development, and prognosis of liver cancer, and summarizes the current impact of lactylation on liver cancer and its therapeutic approaches, providing new insights for the development of future treatment strategies for liver cancer.

Keywords lactylation; hepatocellular carcinoma; tumor microenvironment; post-translational modification

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肝细胞癌(hepatocellular carcinoma, HCC)是原发性肝癌中最常见的病理类型, 占所有原发性肝癌的75%~85%[1]。根据全国肿瘤登记中心2022年统计, 我国原发性肝癌的新发病例数为36.77万, 其中HCC占比超过80%, 从流行病学分布来看, HCC的新发病例数在所有癌症中位列第四, 发病率排名第五, 而死亡人数和死亡率均居第二位[2]。由于HCC起病隐匿、恶性程度高及早期可能发生远处转移, 许多患者在确诊时已无手术指征。对于中晚期及不可切除的HCC患者, 通常采用经动脉化疗栓塞(transarterial chemoembolization, TACE)和系统性治疗(如靶向药物索拉非尼、仑伐替尼等), 以延长患者生存期并控制疾病进展[3]。鉴于HCC的高度异质性导致其分子机制复杂, 现有靶向药物疗效差异显著且耐药问题突出, 因此寻找新靶点以实现精准治疗成为亟待解决的难题[4]。

乳酸是葡萄糖代谢过程中由乳酸脱氢酶A(lactate dehydrogenase A, LDHA)催化丙酮酸还原而生成的重要中间体。乳酸不是代谢废物, 而是骨骼肌[5]、心脏[6]、脑[7]、恶性细胞[8]等组织和细胞的通用代谢燃料, 同时还参与细胞调控过程(如巨噬细胞极化等), 并作为连接糖酵解与氧化磷酸化的代谢缓冲物[9]。乳酸还可作为信号分子, 调节免疫细胞功能[9]、脂解[10]、伤口愈合[11]、细胞稳态维持等[12-13]。乳酸作为底物提供细胞生长和发育所需的能量, 同时可共价修饰到组蛋白赖氨酸残基上[14-15], 形成可调节蛋白质功能和细胞生理过程的乳酸化修饰。近年来的研究指出, 乳酸化修饰在肝癌细胞代谢、肿瘤微环境调控、增殖分化以及耐药性方面具有重要影响。因此, 乳酸化修饰的研究不仅为理解肝癌的发生与发展提供了新视角, 还为开发新治疗策略提供了潜在靶点。靶向乳酸化相关信号通路或代谢途径, 不仅可以调控肿瘤微环境酸度、抑制肿瘤细胞免疫逃逸, 从而克服HCC耐药性, 还能够干预代谢重编程、细胞增殖及侵袭转移等关键生物学过程。这为多维度提升HCC治疗效果提供了潜在策略。

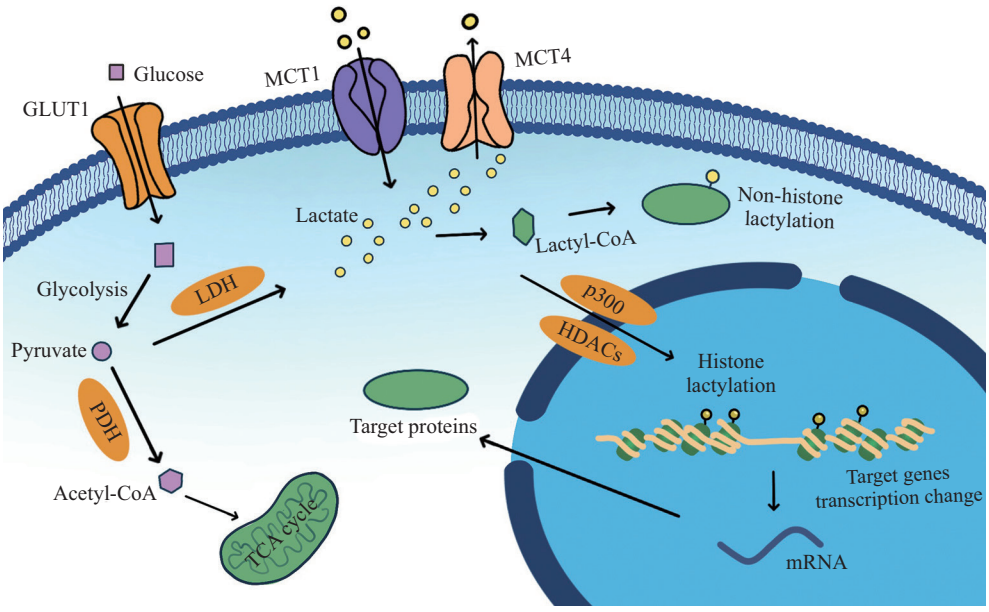
1 乳酸化修饰

1.1 乳酸代谢与乳酸化修饰

在癌细胞中即使有充足的氧气可以支持线粒体氧化磷酸化, 它也倾向于将葡萄糖转化为乳酸, 即“Warburg效应”。其主要特征表现为快速消耗大量葡萄糖、持续活跃的糖酵解反应以及乳酸的过量生成[16]。乳酸不仅是能量来源, 还通过参与代谢途径为生物合成提供前体分子。其转运依赖单羧酸转运蛋白(monocarboxylat transporters, MCTs), 而外排的乳酸会酸化微环境, 抑制免疫细胞功能, 促进肿瘤免疫逃逸。更重要的是, Warburg效应虽与乳酸化修饰无直接关联, 但为其提供了底物来源。乳酸通过赖氨酸乳酸转移酶将乳酸分子转移到特定靶蛋白的赖氨酸残基上, 形成乳酸化修饰, 从而调控相关蛋白的功能(图1)。目前研究表明, 乳酸化修饰广泛靶向组蛋白与非组蛋白, 组蛋白如H3K18la、H3K9la、H4K12la等可通过改变染色质结构增强基因转录活性; 非组蛋白如p53(K120la、K370la、K139la等)、HIF-1α(K32la、K391la等)、STAT3(K685la等)及MYC(K148la等)的乳酸化修饰可调控其蛋白稳定性或信号转导功能。此外, 乳酸化相关基因(如*AARS1*、*LDHA*、*p53*、*β-alanine*、*MRE11*等)的异常表达已被证实与HCC的代谢重编程及耐药性密切相关[17]。肝癌细胞通常表现出显著的代谢重编程, 增强的糖酵解导致大量乳酸的产生。这不仅加剧了肿瘤微环境的酸化, 还通过乳酸化修饰改变了细胞的生物学特性, 显著影响了肝癌的发生和发展。因此, 乳酸代谢与乳酸化修饰之间存在密切关联, 并通过多层次的作用共同影响肿瘤的进程。未来的研究还需要深入探索乳酸化修饰的全局性的靶点, 以及它在各种疾病中的动态调控作用, 从而为精准干预提供理论依据。

1.2 乳酸化修饰对蛋白质功能的影响

2019年, ZHANG等[14]提出了乳酸化这一新型蛋白质翻译后修饰, 其研究发现, 乳酸可通过诱导M1型巨噬细胞中组蛋白的赖氨酸乳酸化修饰, 激活稳态相关基因的转录调控。组蛋白是构成真核生物染色质的基本蛋白质, 乳酸化修饰通过改变其构象和染色质状态, 增强转录因子与DNA的结合, 从而调控基因转录活性。值得注意的是, 癌细胞中组蛋白乳酸化水平的动态变化不仅与胞内乳酸浓度呈正相关[18], 还可能通过影响基因表达, 使肿瘤细胞适应代谢紊乱的病理微环境。在肿瘤相关炎症调控方面, 乳酸化修饰具有双重作用: 在生理性炎症中, 缺氧环境下的高乳酸和低pH有利于清除病原体; 而在肿瘤微环境中, 乳酸化修饰通过抑制$CD8^+$T细胞功能或诱导$CD4^+$T[19]细胞向Th17表型分化, 并驱动



乳酸生成的有两种途径, 其一为糖酵解产生的丙酮酸经乳酸脱氢酶(LDH)催化生成乳酸, 其二为单羧酸转运蛋白(MCTs)从细胞外提取乳酸。胞内乳酸转化为乳酸辅酶A进而作为乳酸化修饰的底物, 促进组蛋白和非组蛋白的乳酸化。

Lactate can be produced through two pathways: the conversion of pyruvate (derived from glycolysis) to lactate catalyzed by LDH (lactate dehydrogenase), and the extraction of lactate from the extracellular environment via MCTs (monocarboxylate transporters). Lactyl-CoA is further derived from intracellular lactate and serves as a substrate for lactylation modifications, promoting the lactylation of both histone and non-histone proteins.

图1 乳酸代谢和乳酸化修饰示意图

Fig.1 The diagram illustrates the metabolism of lactate and the process of lactylation

巨噬细胞从M1表型转变为M2表型[20], 从而促进促癌性炎症反应。与此同时, 乳酸通过诱导抗炎基因表达[21]和抑制树突状细胞的抗原递呈[22], 协同促进肿瘤免疫逃逸。此外, 髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)的扩增及其对先天适应性免疫的抑制作用[23], 主要与乳酸浓度变化导致的微环境酸化相关, 此过程独立于乳酸化修饰机制。

非组蛋白的乳酸化修饰研究同样取得了重要进展。有研究团队利用液相色谱–串联质谱(liquid chromatography-tandem mass spectrometry, LC-MS/MS)对灰葡萄孢(*Botrytis cinerea*)进行了赖氨酸乳酸化分析, 鉴定出273个赖氨酸乳酸化(Kla)位点, 其亚细胞分布呈核–线粒体–细胞质三级梯度(36%:27%:25%)[24]。另一研究显示, 在肝癌临床样本中发现的9 275个Kla位点中, 非组蛋白占比达99.8%(9 256个位点), 证实Kla是广泛存在的修饰类型。此外, 腺苷酸激酶2(adenylate kinase 2, AK2)的乳酸化与HCC不良预后相关[25]。HONG的团队[26]发现, 肝组织和肝癌组织中存在差异乳酸化蛋白质(differentially lactylated proteins, DLPs)富集现象, 这些DLPs主要参与生物合成与代谢调控过程。亚细胞定位结果显示, DLPs主要定位于细胞质, 这与乳酸代谢的核心场所高度契合。在细胞质中, 乳酸可以氧化分解成二氧化碳和水, 通过微生物异生作用合成葡萄糖和糖原, 并通过丙氨酸循环参与氨基酸代谢[27]。

2 乳酸化修饰在HCC进展中的作用

2.1 乳酸化修饰与HCC细胞外基质

肿瘤微环境(tumor microenvironment, TME)在肿瘤的发生、发展和转移中起着重要作用, 主要由细胞外基质(extracellular matrix, ECM)、成纤维细胞和脉管系统构成[28]。ECM由胶原蛋白(如I型、III型胶原)、蛋白聚糖和纤连蛋白等非细胞成分组成, 调节细胞的增殖、侵袭及干性维持。值得注意的是, ECM的重塑与癌症发展密切相关, 大量胶原蛋白、纤连蛋白等ECM成分的沉积促进肿瘤纤维化, 为肿瘤细胞提供保护屏障。ECM的组成成分和含量发生显著改变包括乳酸等代谢产物的积累以及胶原蛋白、纤连蛋白等关键成分的异常增加[29], 这些变化通过调控ECM的重构、降解与再生过程, 影响ECM

与肿瘤细胞间的相互作用, 最终形成具有侵袭性特征的肿瘤微环境[30]。值得注意的是, TME酸化不仅可直接促进ECM重构, 还会通过改变乳酸代谢稳态间接影响乳酸化修饰过程。作为慢性肝病的病理特征, 肝纤维化表现为ECM成分过度沉积, 对肝损伤的愈合和修复至关重要[31-32]。持续的肝纤维化可导致纤维重塑, 损害肝功能, 并可能进展为肝硬化、肝功能衰竭和肝癌。更重要的是, 乳酸化修饰通过改变ECM相关蛋白(如胶原蛋白和纤连蛋白)的结构和功能, 促进ECM的异常沉积和纤维化[29]。此外, 乳酸通过改变肿瘤微环境的pH值或直接修饰ECM降解酶[如基质金属蛋白酶(matrix metalloproteinases, MMPs)], 调控其活性, 从而影响ECM的降解与再生平衡[33]。研究表明组蛋白H3上第18位赖氨酸的修饰位点(HK18)的乳酸化通过增强转录因子SOX9的转录活性, 促进肝纤维化相关基因的表达, 从而加剧ECM的过度沉积[34]。这些发现提示, 乳酸化修饰通过直接修饰ECM相关蛋白或间接调控ECM降解酶的活性, 改变ECM组成、含量和功能, 在肝癌的进展中发挥重要作用。降低组蛋白乳酸化水平已成为改善肝纤维化的潜在干预措施。

2.2 乳酸化修饰与HCC增殖、迁移和侵袭

研究表明, 细胞周期蛋白E2(CyclinE2, CCNE2)的乳酸化修饰可促进HCC生长, 而去乙酰化酶丝氨酸脱乙酰化酶3(Sirtuin3, SIRT3)的激活能够通过调控CCNE2乳酸化水平抑制肝癌增殖和迁移。基于SILAC(stable isotope lbeling by amino acids in cell culture)的定量蛋白质组学证实, SIRT3被厚朴酚激活时可诱导CCNE2的去乳酸化, 从而抑制HCC细胞生长。在表观遗传调控方面, 着丝粒蛋白A(centromer protein A, CENPA)在HCC中显著上调, 与不良预后相关, 其基因敲除可以抑制肝癌细胞的生长[35]。CENPA通过与转录因子YY1协同作用, 激活细胞周期蛋白D1(CyclinD1, CCND1)和神经纤毛蛋白2(neuropilin-2, NRP2)的表达。此外, 在赖氨酸124(K124)处的乳酸化修饰可增强CENPA蛋白活性, 进一步促进靶基因转录[36]。此外, 关键代谢酶的乳酸化修饰同样影响HCC进程。YANG的团队[25]证实, K28的乳酸化可抑制AK2的功能, 促进HCC细胞增殖和转移。与HCC密切相关的还有Wnt/β-catenin信号通路异常活化, *β-catenin*基因敲除通过抑制Wnt信号通路调节细胞干性, 而β-catenin的乳酸化修饰可能通过稳定蛋白结构增强其促增殖作用[37]。此外, 在侵袭转移方面表现为乳酸代谢异常引发的间接效应, 研究发现乳酸直接增强整合素与细胞外基质的结合能力从而促进癌细胞迁移[38]。细胞外pH的降低进一步增强了癌细胞的运动性和侵袭性[39]。在多种人类原发性癌中, 乳酸水平的升高与肿瘤转移潜能的增强呈正相关[40]。

2.3 乳酸化修饰与HCC代谢过程

通常情况下, Kla优先靶向代谢途径相关酶类(如氧化还原酶、脱氢酶等), 调控包括三羧酸循环、碳水化合物、氨基酸、脂肪酸及核苷酸代谢在内的关键代谢网络。乳酸化修饰虽然并不直接导致乳酸代谢异常, 但其对代谢途径的调控可间接改变乳酸的代谢水平。糖酵解代谢不仅作为主要能量来源和生物合成来源, 还被视为信号分子和基因表达的调节因子, 是HCC等恶性肿瘤的核心代谢特征[41]。糖酵解代谢的异常增强是HCC的重要特征之一, 而乳酸化修饰与这一代谢重编程过程密切相关[42]。此外, 一些干预性研究进一步揭示了乳酸化修饰对糖酵解调控的核心作用。蜂王浆酸(royal jelly acid, RJA)通过减少乳酸生成, 抑制H3组蛋白的乳酸化修饰, 进而调节糖酵解代谢[43]。去甲泽拉木醛(demethylzeylasteral, DML)则通过抑制H3组蛋白的乳酸化, 削弱由肝癌干细胞(liver cancer stem cell, LCSC)引发的致瘤性。这些结果表明, 乳酸化修饰可能通过直接调控糖酵解代谢及细胞信号通路从而在HCC中发挥支持性作用[44]。

在非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)中, MPC1蛋白水平与肝脏脂质沉积呈正相关, *MPC1*的敲除可以改善肝脏脂质沉积, 而FAP673位点的乳酸化或是此过程的重要机制。鉴于NAFLD晚期有可能转变为肝癌, 因此乳酸化对NAFLD的影响可能间接影响肝癌的进展[45]。

2.4 乳酸化修饰与HCC免疫微环境

免疫细胞及其相关因子是TME的重要组成部分, 他们参与消除或促进肿瘤的发展过程, 既可以帮助机体清除肿瘤, 同时又可以被肿瘤所用从而影响疾病进展和治疗应答, 是肿瘤防治的重要靶标[46-47]。近年来的研究发现, 乳酸化修饰与HCC的免疫微环境密切相关。

TME中的癌细胞与免疫细胞(包括树突状细胞、NK细胞、T细胞等)能感知胞外乳酸水平, 触

发细胞内信号转导并影响细胞功能[48]。当外部存在过多乳酸时T细胞介导的免疫反应将会被抑制，因此，通过平衡或降低TME的酸度可以提高免疫治疗的抗肿瘤效果。在乳腺癌以及肺癌中发现，乳酸直接激活TME中的G蛋白偶联受体81(G protein-coupled receptor 81, GPR81)诱导程序性死亡配体1(programmed death-ligand 1, PD-L1)表达，该过程依赖于乳酸分子与受体的特异性结合，而非乳酸化修饰作用。其机制涉及抗原呈递细胞功能抑制，导致肿瘤抗原无法被有效呈递至T细胞，最终介导肿瘤免疫逃逸[49-51]。此外，糖酵解中间体磷酸烯醇丙酮酸(phosphoenolpyruvate, PEP)水平的降低会损害T细胞的功能[52]，而乳酸化诱导的环磷酸腺苷(Cyclin adenosine monophosphate, cAMP)依赖性蛋白激酶信号转导也被视为有效的免疫抑制机制[53]。PEP与cAMP这两者均与乳酸代谢异常相关，与蛋白质翻译后修饰无直接关联。在肝细胞癌特异性机制中，乳酸的促癌效应还通过乳酸化修饰实现，乳酸通过增强膜–细胞骨架交联蛋白(membrane-organizing extension spike protein, MOESIN)的乳酸化促进调节性T(Treg)细胞的产生并增强其功能，从而促进肿瘤发展。研究发现，乳酸可通过稳定Treg细胞维持其免疫抑制作用，而降解乳酸可显著减少Treg细胞分化并减弱其功能，进而解除其免疫抑制并增强抗肿瘤免疫应答。MOESIN中赖氨酸残基Ly72的乳酸化增强了其与转化生长因子TGF-β受体I及下游信号转导分子SMA3的相互作用，从而促进了信号转导。联合使用抗PD-1(程序性死亡蛋白1, anti-programmed cell death protein 1)与乳酸脱氢酶抑制剂的治疗效果强于单独使用抗PD-1治疗[54]。这些研究均有力证实了乳酸化修饰在HCC免疫微环境中的独立调控地位。

2.5 乳酸化修饰与HCC耐药性

乳酸在很大程度上导致TME酸化和癌细胞耐药。酸性环境破坏许多弱碱性药物(如蒽环类药物和顺铂)的效力[55]，从而阻碍其细胞摄取。具体来说，乳酸使癌细胞对上皮生长因子受体(epidermal growth factor receptor, EGFR)酪氨酸激酶抑制剂(tyrosine kinase inhibitors, TKIs)产生耐药性[56]，持续和长期使用间充质–上皮转化因子(mesenchymal-epithelia transition factor, MET)或EGFR TKIs治疗癌症会使糖酵解和乳酸生成增加。这种代谢物促使癌相关成纤维细胞(cancer-associated fibroblasts, CAFs)增加肝细胞生长因子(hepatocyte growth factor, HGF)的生成和分泌，而HGF反过来激活癌细胞中的MET，从而克服因TKI的抑制作用而产生耐药。此外，乳酸通过G蛋白偶联受体GPR81参与肝癌细胞的化疗耐药[57]。乳酸盐及其酸性TME还具有免疫抑制作用，导致免疫疗法的效果不足。乳酸通过调节肿瘤微环境和代谢途径，间接导致多种癌症的放射耐药[58]，具体而言，高乳酸浓度通过改变细胞内氧化还原状态，降低癌细胞对氧化应激的敏感性，从而使其对依赖于氧化应激的治疗手段(如过氧化氢、高剂量抗坏血酸和光动力治疗)产生耐药[59-60]。

在HCC中，乳酸通过增强细胞增殖和抑制细胞凋亡来增加HCC耐药性。乳酸通过激活PI3K/Akt和MAPK信号通路，促进多种癌细胞的增殖和存活，同时乳酸通过抑制PHD2稳定HIF-1α[61-62]，从而进一步增强肿瘤细胞的增殖能力。此外，乳酸还可通过抑制细胞凋亡增加耐药性。乳酸可以直接或间接稳定HIF-1α，诱导糖酵解相关基因(如*LDHA*、*MCT1*)的表达，使癌细胞适应缺氧环境并避免凋亡[63]。乳酸还可通过激活PI3K/Akt通路，增加抗凋亡蛋白(如Bcl-2)的表达水平，同时抑制促凋亡因子(如Bad和caspase类蛋白)的活性[64]，从而进一步抑制细胞凋亡。乳酸代谢异常并不仅仅依赖于乳酸化修饰，其作用机制还包括通过激活信号通路(如PI3K/Akt、MAPK)、代谢重编程(如糖酵解增强)以及转录调控(如HIF-1α激活)等。APICELLA等[56]证明，长期使用TKIs治疗会导致依赖EGFR或MET的癌细胞中糖酵解和乳酸生成增加，从而激活MET依赖的信号通路，造成癌细胞对TKIs的持续抵抗。DÜVEL等[65]结合多组学方法表明，乳酸通过激活HIF-1α，调控HIF-1α下游代谢基因的转录程序，增加哺乳动物雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1, mTORC1)的表达水平并激活糖酵解途径，从而促进细胞增殖和耐药。因此，乳酸代谢在肿瘤耐药中发挥着重要作用。

3 乳酸化修饰的治疗策略与预后生物标志物

3.1 靶向乳酸化修饰的治疗策略及药物

乳酸化修饰及其相关酶的研究表明，靶向乳酸化修饰是抑制肿瘤进展和增强抗肿瘤作用的新选

择, 为抗肿瘤药物开发提供了潜在的新靶点[66]。乳酸化修饰通常发生在乳酸代谢和转运相关的重要蛋白上, 因此针对这些过程的干预可能成为治疗肿瘤的关键。例如, 抑制细胞内乳酸代谢关键酶LDHA可以有效减少乳酸化修饰, 并且几种LDH抑制剂如Oxamate(包括氨基甲酸甲酯、乙酰羟酸酰胺)、棉酚等均显示出抑制肿瘤细胞增殖的潜力[67-70]。未来的研究将聚焦于提高这些抑制剂的特异性及减少副作用。此外, 乳酸通过MCTs在细胞间转运, 靶向这些转运蛋白也被认为是改善癌症耐药治疗的重要策略[71]。目前已发现多种MCTs抑制剂, 包括α-氰基-4-羟基肉桂酸盐、根皮素和山莨菪碱, 其中山莨菪碱可以抑制乳酸化修饰并已用于治疗实体瘤[72-73]。部分MCTs抑制剂已进入临床应用[74-75], 与此同时, 新型小分子抑制剂(如AZD3965)对MCT1具有显著抑制效果并展现出免疫调节活性[76]。乳酸化修饰在肿瘤免疫治疗中也起到了关键作用。在对PD-1抗体治疗有效的HCC患者Treg细胞中的乳酸化水平较低, 而乳酸可以通过调节Treg细胞中MOESIN的乳酸化促进肿瘤进展[54]。不仅如此, 乳酸还促进巨噬细胞和中性粒细胞的PD-L1表达, 诱导肿瘤免疫抵抗[77]。临床研究表明, 结合MCT1抑制剂AZD3965与抗PD-1疗法可减少乳酸向TME的释放, 增强抗肿瘤免疫[78]。这些研究为开发基于乳酸代谢和乳酸化修饰的联合治疗策略提供了理论依据。

3.2 预后标志物

CHENG等[79]研究通过生物信息学分析获取了HCC预后相关的乳酸化基因并以此构建了有效的HCC的预后模型, 其中低风险评分的患者对大多数靶向药物和免疫疗法的治疗反应更好, 而高风险评分的患者对大多数化疗药物以及索拉非尼更敏感, 表明乳酸化相关基因标记可作为HCC临床有效治疗的生物标志物。WU团队[80]预测*N61*、*OSB2*和*UN11B*与HCC的预后、免疫治疗和化疗耐药相关, 提示*N61*、*OSB2*和*UN11B*可能是HCC新的候选治疗靶点。

4 讨论与展望

随着对肝癌生物学特性的深入研究, 乳酸化修饰在其发生和发展中的重要性逐渐显现。然而, 关于乳酸化修饰在肝癌中的作用机制研究仍处于起步阶段。尽管基础研究已有一定进展, 但肝癌的临床研究仍非常有限。这些研究往往较为分散, 且乳酸化与其他翻译后修饰(如乙酰化、甲基化等)之间的相互作用尚不明确。因此, 本文系统地总结了相关研究, 探讨了乳酸及乳酸化修饰在肝癌中的潜在机制及其临床应用前景。乳酸代谢异常在肝癌中的机制可分为两类: 乳酸化修饰的直接作用(如组蛋白/非组蛋白功能调控)和独立于乳酸化修饰的其他因素(如缺氧、MCTs转运、肝功能异常)。未来的研究可以专注于开发新型小分子药物或生物制剂, 靶向乳酸代谢通路或相关酶, 以改善患者的预后。同时, 联合现有治疗手段(如逆转微环境酸化等)以增强抗肿瘤效果和克服耐药性将是一个值得深入探索的领域。此外, 乳酸化修饰特征有可能作为肝癌早期诊断和预后的生物标志物。通过分析肝癌患者组织和血清样本中的乳酸化水平, 可以为临床提供新的筛查工具, 从而提高医疗团队早期发现和干预的可能性。

随着精准医学的发展, 针对乳酸化修饰的个体化治疗策略将成为未来肝癌管理的重要组成部分。结合基因组学、代谢组学等技术, 根据患者的具体乳酸代谢特征制定个性化治疗方案, 有助于提高治疗的有效性并减少不必要的副作用。总之, 乳酸化修饰在肝癌研究中逐步展现其深远的临床意义。未来的探索有望为肝癌患者提供更有效的治疗策略, 推动肝癌管理向更高效、精准的方向发展。

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