DOI:10.3724/cbls.2026007 **CSTR**:32203.14.cbls.2026007
文章编号:1004-0374(2026)01-0118-15

肝细胞癌中氨基酸代谢重编程的研究进展

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摘 要:氨基酸代谢重编程在肝细胞癌(hepatocellular carcinoma,HCC)发生发展中起关键作用。HCC中谷氨酰胺、支链氨基酸、精氨酸等代谢存在异常,关键代谢酶(如GLS1、ASS1)和调控因子(c-Myc、mTORC1)表达失调,驱动肿瘤细胞增殖、侵袭、转移并重塑肿瘤微环境,促进肿瘤免疫逃逸。同时,代谢物(如α-KG、GSH)及表观遗传调控也参与其中。目前,靶向代谢酶药物开发(如GLS1抑制剂、ARG)、Met限制疗法及氨基酸代谢酶免疫联合治疗(IDO抑制剂、靶向DLAT-AUH轴)展现出治疗潜力。本文阐述了HCC中氨基酸代谢的作用机制及相关靶向治疗策略研究进展。

关键词:肝细胞癌;氨基酸代谢;代谢重编程;靶向治疗
中图分类号:R735.7 **文献标识码**:A

Research progress on amino acid metabolic reprogramming in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) remains a global public crisis, with high morbidity and mortality rates and significant limitations in current therapeutic strategies. Metabolic reprogramming serves as a vital energy source and underlying driver of tumor progression. This review aims to systematically summarize the molecular mechanisms of amino acid metabolic reprogramming in HCC, highlight therapeutic targets and biomarkers, and explore potential clinical translation strategies. We first describe the abnormal characteristics of amino acid metabolism in HCC, including glutamine (Gln), branched-chain amino acids (BCAAs), arginine (Arg), serine (Ser), glycine (Gly), and tryptophan (Trp). Glutamine serves as a critical nurient for HCC cells. Glutaminase (GLS) catalyzes its catabolism, supports cellular biosynthesis, and promotes HCC progression. Glutamate-oxaloacetate transaminase (GOT) is involved in Gln metabolism, enhancing cancer cells' resistance to ferroptosis induced by glutamine deprivation and to damage caused by reactive oxygen species (ROS). BCAAs accumulate in HCC tissues due to impaired catabolic pathways, activating the mTORC1 signaling pathway to promote proliferation. Arg metabolism is regulated by enzymes such as argininosuccinate synthetase 1 (ASS1) and argininosuccinatelyase (ASL), thereby promoting tumorigenesis and metastasis. Additionally, Ser, Gly biosynthesis and Trp catabolism are reprogrammed to support tumor growth and immune escape. In addition, the molecular regulation of these metabolic abnormalities involves amino acid transporters (e.g., SLC7A5, SLC1A5), upstream regulators (e.g., c-Myc, mTORC1, p53), and non-coding RNAs, which synergistically modulate amino acid uptake, metabolism, and signaling transduction. Metabolites such as α-KG, pyruvate (Pyr) and glutathione (GSH) further participate in pathway crosstalk and maintain redox homeostasis. Subsequently, the mechanisms by which amino acid metabolic reprogramming drives HCC progression are clarified. HCC cells modulates the tumor microenvironment by competing for nutrients with immune cells (e.g., depleting Gln to suppress T cell function)

收稿日期:2025-07-19; **修回日期**:2025-08-28
基金项目:辽宁省科学技术计划(2023JH2/20200093)
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and promoting the formation of immunosuppressive phenotypes to facilitate tumor immune escape. It also regulates endothelial cells and cancer-associated fibroblasts to enhance angiogenesis and extracellular matrix remodeling. Moreover, crosstalk between metabolism and epigenetics (e.g., SAM-mediated DNA methylation, succinylation modification) further amplifies tumorigenic signals. We then summarizes promising therapeutic strategies targeting amino acid metabolism. These strategies include developing drugs against metabolic enzymes (e.g., GLS1 inhibitor CB-839, MAT2A inhibitor FIDAS-5), using arginine degrading agents (e.g., Peg-rhArg1, ADI-PEG 20), implementing methionine (Met) restriction therapy, and exploring immune combination therapies (e.g., IDO1 inhibitor combined with anti-PD-1, targeting the DLAT-AUH axis). Besides, the single-target therapies may be limited by metabolic network plasticity and compensatory mechanisms, highlighting the need for combined strategies targeting multiple metabolic nodes. Finally, we point out current challenges and future directions. The existing biomarkers lack sufficient validation, and the spatiotemporal heterogeneity of amino acid metabolism, as well as its crosstalk with lipid and glucose metabolism, remain relatively under-explored. Future research should leverage multi-omics technologies and advanced models (e.g., PDO) to validate metabolic biomarkers. Also, in-depth investigation of the interaction between metabolism and the immune microenvironment should be further explored. Understanding these mechanisms through systematic research could improve treatment precision and efficacy and optimize combined therapeutic strategies.

Key words: hepatocellular carcinoma; amino acid metabolism; metabolic reprogramming; targeted therapy

肝癌是全球重大公共卫生威胁,2022年GLOBOCAN数据显示,全球肝癌发病86.6万例,死亡75.9万例,是第三大癌症死因[1]。肝细胞癌(hepatocellular carcinoma,HCC)是最常见的恶性肝肿瘤,约占原发性肝癌的80%[2]。然而,现有治疗手段均存在局限性:HCC对传统化疗不敏感,且患者常因肝功能受损难以耐受全身化疗;手术切除受基础疾病制约,影响预后[3];靶向治疗药物虽可延长患者生存期,但肿瘤异质性导致疗效预测困难[4,5],因此亟需寻找有效生物标志物以优化治疗方案。

肿瘤代谢是肿瘤研究的核心领域。自“Warburg effect”[6]被提出后,代谢重编程被证实为肿瘤获取能量的重要途径。近年研究发现,癌细胞为适应营养匮乏的微环境,高度依赖氨基酸代谢等非糖酵解途径[7]。氨基酸不仅参与蛋白质的合成,还作为代谢因子调控癌细胞生长,随着多组学和单细胞技术的发展,氨基酸代谢已成为肿瘤精准治疗的潜在靶点。本综述将系统总结HCC中氨基酸代谢重编程的分子机制、新型治疗靶点与生物标志物,并探讨临床转化策略。

1 肝细胞癌中氨基酸代谢的异常特征

1.1 关键氨基酸的代谢改变

1.1.1 谷氨酰胺

谷氨酰胺(glutamine,Gln)是HCC细胞高度依赖的关键氨基酸,其代谢异常与肿瘤恶性表型密切相关[8]。作为三羧酸循环(tricarboxylic acid cycle,TCA)和核苷酸合成的原料,Gln在肿瘤能量代谢中发挥核心作用[9]。谷氨酰胺酶(glutaminase,GLS)有两种同工酶GLS1和GLS2,催化Gln分解为谷氨酸(glutamic acid,Glu),深度参与肿瘤细胞生物合成[10]。研究显示,GLS1在HCC组织中高表达,且随疾病进展升高[11]。GLS1表达水平与肿瘤分级[12]、血清甲胎蛋白(alpha-fetoprotein,AFP)水平[13]及TNM(tumor node metastasis staging system)分期[14]密切相关,在HCC诊断中具有较高敏感性和特异性,并与患者预后呈负相关。GLS1在HCC组织中高表达,其激活受癌基因MYC[15]、Rho GTPase[16]及Notch[17]等多重信号通路调控。GLS1高表达通过激活TGF-β/Wnt信号通路诱导上皮-间质转化(epithelial-mesenchymal transition,EMT),增强癌细胞的迁移和侵袭能力[18],靶向抑制GLS1可通过调控活性氧(reactive oxygen species,ROS)水平及Wnt/β-连环蛋白通路降低HCC细胞干性[11],提示其作为治疗靶点的潜在价值。GLS2在HCC中的功能具有细胞特异性和环境依赖性,敲低GLS2可抑制癌细胞生长[19],并使HCC细胞对电离辐射更敏感[17]。

谷氨酸草酰乙酸转氨酶(glutamate-oxaloacetate transaminase,GOT)以细胞质GOT1和线粒体GOT2两种形式存在,参与Gln代谢,介导Glu和草酰乙酸转化为α-酮戊二酸(α-ketoglutarate,α-KG)和天冬氨酸(aspartic acid,Asp)。GOT1可促进HCC细胞抵抗Gln剥夺引发的铁死亡,Gln剥夺联合GOT1抑制可更有效地抑制HCC细胞增殖[20]。GOT2在正常肝脏组织中特异性高表达,但是随着HCC的恶性进展,GOT2的表达下降,并且与患者不良预后相关[21]。

HCC中GOT2的降低介导了Gln代谢重编程,转向合成还原性谷胱甘肽(glutathione,GSH),通过抵抗ROS损伤维持肿瘤细胞氧化还原稳态,激活PI3K/AKT/mTOR信号通路从而促进HCC的恶性进展[21]。

1.1.2 支链氨基酸(亮氨酸、异亮氨酸、缬氨酸)

支链氨基酸(branched-chain amino acids,BCAAs)包括缬氨酸(valine,Val)、亮氨酸(leucine,Leu)和异亮氨酸(isoleucine,Ile),可激活雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1,mTORC1)信号通路[22-24]。HCC肿瘤组织中BCAAs水平显著高于癌旁组织,但其氧化代谢中间产物却明显减少,提示BCAAs分解代谢通路在HCC中严重受损[25]。与之相符的是,HCC中除支链氨基酸转氨酶(branched-chain amino acid transaminases,BCATs)基因呈异常高表达,其他包括支链α-酮酸脱氢酶(branched-chain α-keto acid dehydrogenase,BCKDH)在内的多种参与BCAAs分解代谢的酶表达均下降,导致BCAAs无法正常氧化供能,转而通过mTORC信号驱动肿瘤细胞增殖[26]。BCKD激酶(BCKD kinase,BCKDK)在HCC肿瘤组织中表达升高,其可磷酸化BCKDH并抑制其活性。体外研究证实降低BCAAs含量、应用mTOR抑制剂雷帕霉素或抑制BCKDK活性,均可显著抑制HCC细胞增殖[25]。BCAAs代谢异常与mTOR通路激活的协同效应,使其成为HCC治疗的潜在干预靶点[27]。

1.1.3 精氨酸和鸟氨酸

精氨酸(arginine,Arg)可与脯氨酸(proline,Pro)等相互转化,并能通过激活mTORC1促进细胞生长;同时,Arg对细胞代谢的调控作用部分独立于mTOR通路,展现出更复杂的调控机制[28,29]。HCC中Arg含量升高,作为第二种信使样分子通过与转录因子RBM39(RNA-binding motif protein 39)结合,激活代谢基因表达促进肿瘤发生[28]。其中的靶基因天冬酰胺合成酶(asparagine synthetase,ASNS)促进天冬酰胺(asparagine,Asn)合成,进一步促进Arg的摄取[28]。

Arg在精氨酸酶(arginase,ARG)催化下生成鸟氨酸(ornithine,Orn)和尿素(urea)。鸟氨酸循环又称尿素循环,将体内多余的氮转化为无毒的尿素,是肝脏氨解毒的核心途径,主要包含五种关键酶:氨基甲酰磷酸合成酶1(carbamoyl phosphate synthetase 1,CPS1)、鸟氨酸氨基甲酰转移酶(ornithine transcarbamylase,OTC)、精氨基琥珀酸合成酶1(argininosuccinate synthetase 1,ASS1)、精氨酸代琥珀酰裂解酶(argininosuccinatelyase,ASL)以及ARG。CPS1在HCC中呈现高甲基化且表达广泛下调[30],黄曲霉毒素B1可抑制其表达,诱导癌细胞凋亡[31]。ASS1同样在HCC中因DNA甲基化表达降低,不仅可以作为预后生物标志物,还能预测Arg剥夺疗法的疗效[32]。ASS1沉默可促进HCC细胞的迁移和侵袭,其敲低会增加信号转导和转录激活因子3(signal transducer and activator of transcription 3,STAT3)在Ser727位点的磷酸化,并通过DNA结合抑制因子1(inhibitor of DNA binding 1,ID1)促进HCC侵袭和转移,加速肿瘤转移[32]。ASL在HCC组织和细胞系中表达升高,敲低ASL可抑制HCC细胞增殖并诱导细胞凋亡[33]。OTC定位在线粒体基质,催化Orn和氨甲酰磷酸(carbamoylphosphate,CP)生成Arg,OTC缺乏或沉默会扰乱尿素代谢并促进HCC细胞增殖,且OTC低表达患者预后较差[34]。此外,精氨酸酶1(ARG1)在HCC中表达显著下降,但ARG1过表达却增强HCC细胞Huh7转移和侵袭能力,导致EMT过程中波形蛋白、N-钙黏蛋白和β-连环蛋白等关键因子的蛋白及mRNA表达显著增加[34]。这些研究结果提示Orn代谢相关酶在HCC代谢重编程中发挥关键作用。

1.1.4 其他氨基酸

细胞增殖依赖丝氨酸(serine,Ser)和甘氨酸(glycine,Gly)的生物合成,为癌细胞提供大分子合成前体与一碳单位。磷酸甘油酸脱氢酶(phosphoglycerate dehydrogenase,PHGDH)是Ser从头合成的限速酶。在HCC中,精氨酸甲基转移酶(protein arginine methyltransferases,PRMTs)介导的PHGDH R236位点甲基化可显著激活PHGDH活性,促进Ser合成并维持氧化还原稳态,推动HCC的恶性进展[35]。IGF2BP3蛋白乳酸化修饰增加,促进丝氨酸合成和S-腺苷甲硫氨酸(S-adenosylmethionine,SAM)生成,参与HCC对酪氨酸激酶抑制剂仑伐替尼的耐药[36]。

丝氨酸羟甲基转移酶2(serine hydroxymethyltransferase 2,SHMT2)能够催化Ser和四氢叶酸(tetrahydrofolic acid,THF)转化为Gly和5,10-甲烯四氢叶酸(5,10-CH2-THF),是细胞内一碳代谢的关键步骤,对肝细胞的生长至关重要[37]。敲低SHMT2的表达会加剧肝缺血再灌注损伤,延缓肝再生;而异

常活化的SHMT2通过重塑代谢途径,显著增强肿瘤细胞在缺血微环境中的生存能力[38,39]。在Hep3B、HepG2和Huh7三种人源HCC细胞系中,SHMT2的mRNA和蛋白表达水平均显著高于永生化正常肝细胞系THLE2(transformed human liver epithelial-2)[37];抑制SHMT2表达可有效抑制HCC细胞的增殖与致瘤性,其中,在人肿瘤异种移植小鼠模型中,SHMT2表达下调后Huh7细胞完全丧失成瘤能力;反之,SHMT2过表达则进一步促进HCC细胞的增殖[40]。此外,SHMT2在HCC[41]和肝内胆管癌[42]患者的组织中呈过表达,且其表达水平与患者预后呈负相关,提示SHMT2可作为HCC潜在的预后生物标志物与治疗靶点。

色氨酸(Tryptophan,Trp)代谢与肿瘤免疫密切相关。Trp经吲哚胺2,3-双加氧酶(indoleamine 2,3-dioxygenase,IDO)或色氨酸双加氧酶(Trp-2,3-dioxygenase,TDO)分解生成犬尿氨酸(kynurenine,Kyn)。IDO在HCC组织中呈高表达[43,44],促Trp分解产生Kyn,重塑肿瘤微环境的免疫状态[45]。同时,Trp代谢活跃的HCC细胞可通过促进微环境中的Trp代谢,抑制三级淋巴结构(tertiary lymphoid structures,TLS)的成熟,而靶向抑制TDO2可增加TLS中$CD8^+$ T细胞浸润[46]。此外,MYC驱动的肝癌依赖于增强的Trp摄取,通过无Trp饮食剥夺可以阻止MYC驱动肝癌的生长[47]。

1.2 氨基酸代谢的分子调控机制

1.2.1 氨基酸转运体的细胞特异性表达对氨基酸代谢的调控

氨基酸转运体由溶质载体(solute carrier family,SLC)家族基因编码,介导氨基酸跨膜转运,其表达是调控微环境中氨基酸分配与代谢竞争的关键因素。肿瘤细胞常通过高表达特定转运体获取代谢优势,HCC细胞中由*SLC7A5*基因编码的L型氨基酸转运体1(L-type amino acid transporter 1,LAT1)呈高表达,可高效摄取Leu、组氨酸(histidine,His)等氨基酸,为细胞增殖提供原料,同时通过消耗微环境中的氨基酸,限制周围免疫细胞的营养供应[48,49]。此外,HCC细胞中由*SLC1A5*基因编码的丙氨酸-丝氨酸-半胱氨酸转运载体2(alanine-serine-cysteine transporter 2,ASCT2)上调,增强Gln摄取以支持TCA循环及生物合成,进一步强化代谢竞争优势[50]。

T细胞的功能受转运体表达的动态调控。T细胞激活依赖转运体上调,初始T细胞向效应T细胞分化时,需通过SLC7A5增强Leu摄取以激活mTOR信号通路[51];而在肿瘤微环境中,肿瘤细胞SLC7A5的高表达会竞争性导致T细胞Leu缺乏,使其增殖受阻并向耗竭表型转化[52]。

1.2.2 参与氨基酸代谢调控的转录因子与信号通路

c-Myc和mTORC1等在氨基酸转运体的转录调控中发挥关键作用。c-Myc作为原癌基因,可结合氨基酸转运体基因的启动子,上调其表达,增强肿瘤细胞对氨基酸的摄取能力,并通过调控下游基因网络,提升细胞内氨基酸代谢通量,为肿瘤细胞的生物合成提供原料[53]。mTORC1作为细胞生长的核心调控因子,激活后通过磷酸化STK39等下游分子,调控氨基酸转运体的转录,影响氨基酸摄取[54]。在HCC中,mTOR异常激活驱动转运体转录上调,促进氨基酸摄取以满足肿瘤增殖需求。小GTP酶RHEB是经典mTORC1激活剂,泛素结合酶UBE2F-泛素连接酶SAG通路介导RHEB的K169位点拟素化修饰后,增强其活性及溶酶体定位以激活mTORC1,进而调控氨基酸转运体的转录[55]。

值得注意的是,c-Myc与mTORC1信号通路存在显著的协同关联。在c-Myc过表达驱动的HCC发展进程中,mTORC1通路持续激活[56];研究显示,mTORC1是c-Myc诱导的小鼠HCC发展的关键效应器[57]。机制上,c-Myc可通过上调SLC1A5、SLC7A6等氨基酸转运蛋白的表达,激活mTORC1通路,形成协同促癌效应[58]。此外,mTORC1能与转录因子协同增强氨基酸转运体的表达,形成正反馈环路,加速HCC的恶性进展。

p53是经典抑癌基因,野生型p53在HCC中可通过转录抑制胱氨酸(cystine,Cys)-Glu转运体SLC7A11的表达,减少细胞对Cys的摄取,进而抑制GSH合成,增强肿瘤细胞对氧化应激的敏感性并促进细胞铁死亡[59];而突变型p53则常失去这一调控功能,促进HCC的进展[59]。

NF-κB作为炎症相关的关键转录因子,在HCC中被慢性炎症信号激活后,可上调代谢酶GLS1的表达,增强Gln分解代谢,为肿瘤细胞提供能量和生物合成原料[60];同时,代谢产物的积累可进一步激活NF-κB通路,形成“炎症-代谢”正反馈循环,促进HCC的恶性进展[61]。

此外,HCC的发生具有显著的性别差异,男性患

者比例明显高于女性，雌激素-雌激素受体信号通路在阻止HCC发生中发挥关键作用[62]。作为核受体转录因子，雌激素受体α(estrogen receptor α，ERα)通过影响下游靶基因的表达，抑制炎症和乙肝病毒并维持脂代谢稳态等，抑制HCC的发生[63]。本实验室研究结果证实，赖氨酸乙酰转移酶8(lysine acetyltransferase 8，KAT8；又称males absent on the first，MOF)和去泛素化调节蛋白ATXN7L3能够通过表观遗传学机制影响ERα介导的基因转录及其功能[64,65]。最新研究发现，限时进食以性别依赖方式影响肝脏代谢，且肝脏ERα-介导的氨基酸代谢在这一过程中发挥关键作用[66]。在限时进食条件下，肝细胞内雌激素通路下游靶基因富集在氨基酸代谢和脂质代谢相关通路，说明雌性动物中雌激素可能通过促进肝脏消耗氨基酸来维持肝脏脂质的合成，来响应限时进食的特异性代谢需求[66]。这提示雌激素-ERα也是影响氨基酸代谢的关键通路，但其在HCC细胞内对氨基酸代谢的影响仍有待阐明。有研究发现雄激素受体(androgen receptor，AR)也参与氨基酸代谢的调控。在前列腺癌中，AR可通过调控Gln转运体[67]及代谢酶GLS1[68]的表达，影响肿瘤细胞对Gln的摄取与分解利用，进而参与肿瘤代谢重编程过程。目前，在HCC中AR与氨基酸代谢的具体关联及分子机制尚未明确。

1.2.3 非编码RNA对氨基酸代谢的调控

非编码RNA常通过影响基因表达参与HCC中的氨基酸代谢调控。c-Myc能通过转录抑制miR-23b，解除其对靶基因GLS的抑制作用，进而上调Gln分解代谢水平[69]。长链非编码RNA LINC01234在HCC组织中呈高表达且其表达水平与患者不良预后显著相关，LINC01234可通过直接结合ASS1的启动子区域，抑制p53等转录因子对ASS1的转录激活作用，从而下调ASS1的表达[70,71]。

1.3 代谢产物的功能影响

1.3.1 中间代谢物

在氨基酸代谢网络中，α-KG是连接TCA与多种氨基酸代谢的关键节点，可由谷氨酸脱氢酶 (glutamate dehydrogenase，GDH)催化Glu脱氨生成[72]，同时α-KG可通过转氨基作用生成Glu，进而参与Pro、Arg等非必需氨基酸的合成调控。此外，α-KG作为α-酮酸家族成员，还参与BCAAs的转氨基过程，通过调节BCAT的活性，影响BCAAs的分解代谢与肿瘤细胞的增殖信号激活[73]。

在HCC中，α-KG是异柠檬酸脱氢酶1(isocitrate dehydrogenase 1，IDH1)的关键催化产物，通过调控缺氧诱导因子1α(hypoxia-inducible factor 1α，HIF1α)信号通路抑制肿瘤生长。作为脯氨酰羟化酶(prolyl hydroxylases，PHD)的电子供体，α-KG在氧气存在时促使HIF1α羟基化，该步骤是抑癌蛋白VHL介导的HIF1α泛素化及蛋白酶体降解的关键[74]。天然小分子香附素(Scu)作为首个IDH1小分子激动剂，可通过选择性修饰IDH1的Cys297位点，促进活性IDH1二聚体形成，大幅提升α-KG的生成水平[74]。Scu激活IDH1后产生的α-KG，既能促使HIF1α泛素化降解，抑制HCC细胞糖酵解，又能招募免疫细胞至肿瘤微环境、阻断程序性死亡受体-配体1 (programmed cell death-ligand 1，PD-L1)表达，展现出显著的抗HCC效果，表明靶向激活IDH1以调控α-KG水平可成为HCC治疗的潜在有效策略[74]。

另一关键代谢物是丙酮酸(pyruvate，Pyr)，其通过转氨基作用生成丙氨酸(alanine，Ala)，参与丙氨酸-葡萄糖循环。在HCC细胞中，丙酮酸脱氢酶激酶(pyruvate dehydrogenase kinase，PDK)的激活可抑制Pyr进入TCA，促使其更多地参与Ala合成，导致肿瘤微环境中Ala积累，进而抑制T细胞的增殖与细胞毒性功能[75,76]。此外，在HCC中，参与苯丙氨酸(phenylalanine，Phe)和酪氨酸(tyrosine，Tyr)分解代谢的谷胱甘肽S-转移酶Z1(glutathione S-transferase zeta 1，GSTZ1)表达下降，导致琥珀酰丙酮(succinylacetone，SA)累积[77]。一方面，SA水平的升高促进KEAP1(cysteine-rich protein kelch-like ECH-associated protein 1)的烷基化，引起关键的抗氧化转录因子核因子E2相关因子2(nuclear factor erythroid 2-related factor 2，NRF2)的活化，NRF2进而介导胰岛素样生长因子1受体(IGF-1 receptor，IGF1R)的转录激活，从而抵抗细胞凋亡[77]；另一方面，由于与α-KG结构相似，SA竞争性抑制PHD活性，从而增强HIF1α的蛋白稳定性，促进血管内皮生长因子(vascular endothelial growth factor，VEGF)的表达并促进血管生成[78]，形成代谢与信号通路的交叉调控。

1.3.2 氧化还原代谢物

还原型GSH作为细胞内的高效还原剂，在体内抗氧化防御体系中占据核心地位，其合成依赖Glu、半胱氨酸(cysteine，Cys)和Gly的供应，因此GSH水平可反

向调控这三种氨基酸的代谢平衡。GSH及其关联酶类共同构成人体内重要的内源性抗氧化系统,也在HCC发生发展过程中发挥重要作用[79]。在抗氧化反应中,GSH与GPx协同作用,通过提供电子将有机过氧化物还原成无害的醇类和水,自身被氧化为二硫化谷胱甘肽(glutathione disulfide,GSSG)。同时,在谷胱甘肽还原酶(glutathione reductase,GR)的催化下,GSSG还可转化为GSH,实现循环利用[80]。此外,GSH还能通过谷胱甘肽S-转移酶(glutathione S-transferase,GST)与亲电性外源性物质直接结合,发挥解毒功能[81]。

有研究观察到HCC肿瘤组织中GSH、GST、GR和GPx的含量都较肝脏良性病变组织降低[82]。但更多的研究显示,HCC内GSH及相关酶增加,从而抵抗高水平的氧化应激。与正常肝细胞相比,HCC细胞系内存在高水平GSH[83]。在HCC中,GSH合成过程中的限速酶谷氨酰半胱氨酸连接酶(glutamate-cysteine ligase,GCL,又称γ-glutamylcysteine synthetase,γ-GCS)的表达及活性升高,并与预后差相关[84,85]。而由于GCL和参与GSH合成的谷胱甘肽合成酶(glutathione synthetase,GS)的高表达,HCC肿瘤组织内的GSH也明显升高[86]。GSH进而通过维持GPx4的活性抑制铁死亡[87]。同时,HCC组织线粒体内GSH水平升高[88]。此外,GPx2、GPx4和GPx7均在HCC组织中高表达,且其表达水平与恶性程度相关[89,90]。

2 氨基酸代谢重编程驱动肝癌进展的机制

如上所述,氨基酸代谢的改变在HCC细胞的抗凋亡、生长增殖、侵袭转移及血管生成等过程中发挥重要作用。此外,氨基酸代谢重编程还参与调节肿瘤微环境,并且代谢产物与表观遗传学机制存在交叉调控。

2.1 肿瘤微环境调控

2.1.1 免疫细胞

氨基酸代谢深入参与肿瘤微环境中免疫反应的调节。肝癌细胞内SLC1A5转运蛋白表达升高,与髓系细胞竞争Gln,导致微环境中Gln含量匮乏,驱动髓系细胞发生营养应激并激活IRE1α/XBP1轴,进而诱导GPR109A$^+$免疫抑制性髓系细胞的形成,最终介导免疫逃逸和治疗抵抗[91]。Gln代谢对于细胞毒性T细胞的功能也至关重要,当Gln摄入下降时,细胞毒性T细胞发生内质网应激反应,进一步下调其功能[92]。也有研究观察到参与Asn代谢的具有天冬酰胺酶和异天冬氨酸肽酶活性的ASRGL1(asparaginase and isoaspartyl peptidase 1)在HCC内高表达,并伴有单核细胞、中性粒细胞、肿瘤相关巨噬细胞、Th1和T细胞的浸润[93],但其内在机制仍有待于深入分析。

Trp分解生成Kyn,而Kyn是调节性T细胞中芳基烃受体(aromatic hydrocarbon receptor,AHR)的激活剂,可诱导T细胞分化,抑制树突状细胞和T细胞功能,重塑肿瘤微环境的免疫状态,促进肿瘤免疫逃逸[45]。同时,Kyn引起AHR活化还能促进肿瘤局部巨噬细胞中CD39的表达,进而抑制CD8$^+$ T细胞的功能[94]。

Trp代谢还通过影响HCC局部的微环境来调控肿瘤内三级淋巴结构(tertiary lymphoid structures,TLS)成熟和T/B细胞功能[46]。TLS的形成与更好的免疫治疗反应和临床结局相关,HCC中未成熟的发育轨迹异常的“偏离”型TLS与抑制免疫治疗效果相关[46]。在“偏离”型TLS内部B细胞的Trp代谢通路活性显著上调,IDO1/2和TDO2表达升高,而促进TLS发育的关键转录因子表达下降[46]。在空间结构上,“偏离”型TLS附近的HCC肿瘤细胞自身Trp代谢也活跃,TDO2等代谢酶表达增多,而TDO2抑制剂可增加TLS中CD8$^+$ T细胞浸润,说明HCC内由肿瘤细胞所形成的Trp富集的代谢微环境抑制免疫治疗反应[46]。

2.1.2 内皮细胞

内皮细胞是血管生成的核心组分,VEGF是血管生成的主要活化因子,HIF1α是介导VEGF转录的核心转录因子。如前所述,α-KG在氧气存在条件下促使HIF1α羟基化、泛素化及蛋白酶体降解[74];SA与结构相似的α-KG相竞争,从而增强HIF1α的蛋白稳定性,促进VEGF的表达并促进血管生成[78]。而Gln代谢产生的ROS可激活HIF-1α,进而促进VEGF表达,诱导肿瘤血管生成,为肿瘤细胞的生长和转移提供营养物质和氧气供应[95]。

2.1.3 癌症相关成纤维细胞

癌症相关成纤维细胞(cancer-associated fibroblasts,CAFs)是肿瘤微环境中的主要细胞成分,与肿瘤细胞具有代谢共生关系。在鳞状细胞癌中,CAFs衍生的Asp维持癌细胞增殖,而癌细胞衍生的Glu平衡

CAFs的氧化还原状态，促进细胞外基质重塑[96]。在胰腺导管腺癌中CAFs可通过上调BCATs分解Leu、Ile等支链氨基酸，为肿瘤细胞提供能量和合成原料，加速其增殖[97]。此外，在三阴性乳腺癌中，CAFs中Gln合成增多，分泌至细胞外基质，并被肿瘤细胞摄取支持其生物合成需求以应对肿瘤微环境的营养匮乏[98]。目前，在HCC中CAFs氨基酸代谢的状态和调控机制仍有待于系统探究。

2.1.4 神经细胞

近年来研究发现，神经浸润是多种外周实体瘤的普遍特征，神经细胞参与肿瘤微环境的复杂构建[99]。肿瘤内浸润的神经纤维通过释放神经递质，影响表达相应受体的免疫细胞功能与肿瘤细胞行为[100]。HCC组织内存在交感神经和副交感神经成分，释放肾上腺素、去甲肾上腺素、多巴胺、血清素和乙酰胆碱等多种神经递质，通过精确调节AKT/mTOR、ERK和NF-κB等关键通路影响肿瘤细胞及免疫细胞，从而驱动肿瘤进展、免疫逃避和化疗耐药[101]。如HCC中存在胆碱能神经细胞的异常浸润，释放乙酰胆碱激活肿瘤细胞表面的毒蕈碱受体(muscarinic acetylcholine receptors，mAChRs)，通过ERK/STAT3通路驱动肿瘤增殖与转移[102]。同时，HCC细胞内神经生长因子(nerve growth factor，NGF)高度表达，其可能以旁分泌方式促进血管生成和肿瘤周围神经形成[103]。目前，在HCC中神经细胞相关氨基酸代谢改变仍有待于深入研究。

2.2 表观遗传与代谢的交叉调控

SAM作为DNA甲基化的主要甲基供体，其水平受SAM代谢调控[104]。蛋氨酸(methionine，Met)经甲硫氨酸腺苷转移酶2A(methionine adenosyltransferase 2A，MAT2A)分解代谢产生SAM，当该代谢通路发生改变时，SAM水平的波动将影响DNA甲基化模式，进而调控基因表达，推动HCC进展。HCC细胞中异常的SAM可导致DNA甲基化水平降低，激活原癌基因表达，从而促进肿瘤发生[105]。此外，多数HCC细胞在急性Met剥夺后会出现细胞周期停滞，并伴随严重的DNA损伤。同时，小鼠模型显示，饲喂Met和胆碱缺乏(methionine-choline deficiency，MCD)饮食，会通过活化肝星状细胞(hepatic stellate cells，HSC)促进胶原沉积，进而显著加重肝纤维化[105,106]，提示Met代谢与HCC微环境的动态变化密切相关。

琥珀酰化修饰作为新兴调控机制，在HCC代谢中发挥关键作用[107]。细胞内琥珀酰辅酶A(succinyl-coenzyme A，S-CoA)可作为赖氨酸琥珀酰化的供体分子[108]；同时，去琥珀酰酶及组蛋白去乙酰化酶(histone deacetylase，HDAC)家族蛋白SIRT5[109]、SIRT7[110]和HDAC1/2/3[108,111]等参与酶促调控过程。3-酮酸辅酶A转移酶1(3-ketoacid coenzyme A transferase 1，OXCT1)在HCC细胞中呈高表达，不仅催化酮体氧化，还可作为新型琥珀酰转移酶，利用S-CoA促进抑癌蛋白LACTB的K284位点琥珀酰化，抑制其蛋白酶活性并增强线粒体呼吸功能，进而驱动HCC细胞增殖与肿瘤进展[107]。这些发现揭示了代谢产物与蛋白质修饰的双向调控机制，为靶向HCC代谢异常提供了新的研究方向。图1总结了氨基酸代谢重塑在HCC中的作用。

3 基于氨基酸代谢的肝癌治疗策略

3.1 靶向氨基酸代谢的药物开发

3.1.1 谷氨酰胺代谢抑制剂

Gln代谢异常在肿瘤进展中起关键作用，其分解限速酶GLS1已成为重要靶点。在HCC中，代表性药物CB-839(Telaglenastat)是可逆性GLS1抑制剂，临床前研究证实其具有广谱抗肿瘤活性[112]。在HCC1806细胞模型中，CB-839抑制细胞增殖，并通过激活caspase 3/7诱导细胞凋亡[113]。Gln拮抗剂JHU083可降低HIF-1α，抑制肿瘤血管生成能力，进而抑制肿瘤细胞生存和转移[114]。在HCC中，JHU083促进$CD8^+$ T细胞增殖并促进抗PD-1疗效[115]。值得关注的是，GLS1抑制剂联合IFRD1(interferon related developmental regulator 1)缺失可显著增强Gln限制的抗癌疗效，提示代谢酶抑制剂与表观遗传调控因子的协同作用或为HCC治疗的新方向[116]。

3.1.2 其他氨基酸代谢酶抑制剂

Met代谢相关酶也是HCC治疗的新靶点。MAT2A是Met分解代谢的关键限速酶，其抑制剂可诱导HCC细胞衰老。抑制MAT2A能够引发HCC细胞周期停滞，并诱导DNA损伤，而糖原合成激酶3(glycogen synthase kinase 3，GSK3)抑制剂可选择性清除这些衰老细胞[105,117]。二者联合在多种HCC模型中可显著抑制肿瘤生长，同时对正常肝细胞保持低毒性，这种联合治疗策略为临床干预提供了新

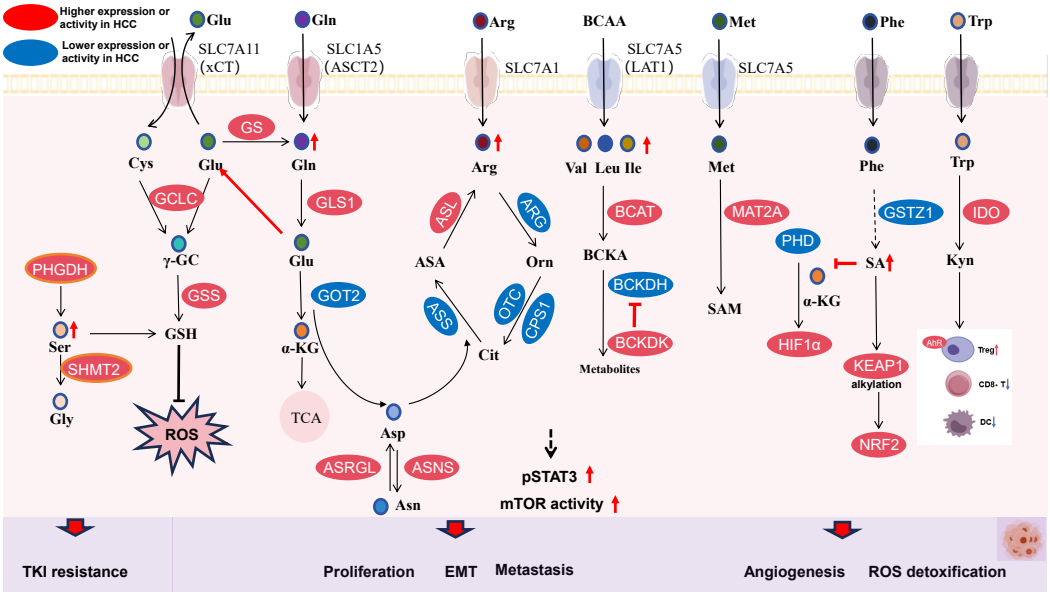


图1 氨基酸代谢重塑在HCC中的作用

Glu,谷氨酸;Cys,半胱氨酸;GCLC,谷氨酸半胱氨酸连接酶;γ-GC,γ-谷氨酸半胱氨酸;GSS,谷胱甘肽合成酶;GSH,谷胱甘肽;Ser,丝氨酸;PHGDH,磷酸甘油酸脱氢酶;SHMT2,丝氨酸羟甲基转移酶2;Gly,甘氨酸;Gln,谷氨酰胺;GS,谷氨酰胺合成酶;Arg,精氨酸;GLS1,谷氨酰胺酶1;GOT2,谷氨酸草酰乙酸转氨酶:a-KG,a-酮戊二酸;ASL,精氨酸代琥珀酰裂解酶;ASA,精氨酸琥珀酸;ASS,精氨酸琥珀酸合成酶;Cit,瓜氨酸;OTC,鸟氨酸氨基甲酰转移酶;CPS1,氨基甲酰磷酸合成酶1;Orn,鸟氨酸;ARG,精氨酸酶;BCAA,支链氨基酸;Val,缬氨酸;Leu,亮氨酸;Ile,异亮氨酸;BCAT,支链氨基酸转氨酶;BCKA,支链氨基酸酮酸;BCKDH,支链α-酮酸脱氢酶;BCKDK,BCKD激酶;Met,蛋氨酸;MAT2A,甲硫氨酸腺苷转移酶2A;SAM,S-腺苷甲硫氨酸;PHD,脯氨酰羟化酶;HIF1α,缺氧诱导因子1;PHE,苯丙氨酸;GSTZ1,谷胱甘肽S-转移酶Z1;SA,琥珀酰丙酮;NRF2,核因子E2相关因子2;Trp,色氨酸;IDO,吲哚胺2,3-双加氧酶;Kyn犬尿氨酸。

Figure 1 The function of amino acid metabolic reprogramming in hepatocellular carcinoma

Glu, glutamic acid; Cys, cystine; GCLC, glutamate-cysteine ligase catalytic subunit; γ-GC, γ-glutamylcysteine; GSS, glutathione synthetase; GSH, glutathione; Ser, serine; PHGDH, phosphoglycerate dehydrogenase; SHMT2, serine hydroxymethyltransferase 2; Gly, glycine; Gln, glutamine; GS, glutamine synthetase; Arg, arginine; GLS1, glutaminase 1; GOT2, glutamate-oxaloacetate transaminase 2; α-KG, α-ketoglutarate; ASL, argininosuccinatelyase; ASA, argininosuccinic acid; ASS, argininosuccinate synthetase; Cit, citrulline; OTC, ornithine transcarbamylase; CPS1, carbamoyl phosphate synthetase 1; Orn, ornithine; ARG, arginase; BCAA, branched-chain amino acid; Val, valine; Leu, leucine; Ile, isoleucine; BCAT, branched-chain amino acid transaminase; BCKA, branched-chain keto acids; BCKDH, branched-chain α-keto acid dehydrogenase; BCKDK, BCKD kinase; Met, methionine; MAT2A, methionine adenosyltransferase 2A; SAM, S-adenosylmethionine; PHD, prolyl hydroxylase; HIF1α, hypoxia-inducible factor 1α; Phe, phenylalanine; GSTZ1, glutathione S-transferase zeta 1; SA, succinylacetone; NRF2, nuclear factor erythroid 2-related factor 2; Trp, tryptophan; IDO, indoleamine 2,3-dioxygenase; Kyn, kynurenine.

方向。纳米表观药物MFMP由纳米颗粒整合MAT2A抑制剂FIDAS-5、巨噬细胞膜和抗PD-L1组成,能够增强HCC细胞抗原性,进而增强肿瘤细胞识别及T细胞杀伤能力,具有一定的转化应用前景[118]。

3.2 精氨酸降解剂

在HCC中,Arg代谢异常表现为ASS1的普遍缺失,导致肿瘤细胞依赖外源性Arg[28],这为限制外源Arg降解疗法的研发提供了理论依据。在进展性HCC中,聚乙二醇化重组人精氨酸酶1(pegylated recombinant human arginase 1,Peg-rhArg1)以剂量依赖的方式诱导Arg耗竭[119,120]。聚乙二醇偶联精氨酸脱亚胺酶(arginine deiminase,ADI-PEG 20)可通过降解循环中的Arg,选择性杀伤ASS1缺失的HCC细胞,然而其单药抗肿瘤效果有限,需通过联合治疗方案进一步提升疗效[121,122]。

3.3 蛋氨酸限制疗法

Met作为人体唯一含硫的必需氨基酸,其饮食限制策略在肿瘤治疗中颇具潜力。肝细胞核因子4α(hepatocyte nuclear factor 4α,HNF4α)作为关键转录因子,可调控胱硫醚β合成酶(cystathionine β-synthase,CBS)、胱硫醚γ裂解酶(cystathionine γ-lyase,CTH)等含硫氨基酸代谢酶的表达。低Met饮食可显著抑

制HNF4α阳性HCC细胞的增殖，而HNF4α缺失的HCC细胞对SAM限制产生抗性，但恢复CBS/CTH通路可逆转该抗性，证实HNF4α通过调控含硫氨基酸代谢影响HCC对Met限制的敏感性[123]。同时，也有研究发现，在不进行药物治疗的情况下，间歇性Met剥夺饮食通过增强HCC细胞对铁死亡的敏感性而发挥抗肿瘤效应，并可与抗程序性死亡受体1(programmed death 1，PD-1)协同以增强T细胞介导的抗肿瘤免疫反应[124]。而在抗肿瘤免疫中起重要作用的T细胞活化尤其需要Met，Met限制的抑癌效果可能取决于恶性肿瘤细胞与免疫细胞对Met的相对依赖性，提示Met限制饮食的应用时机及策略仍需深入研究[125]。

3.4 氨基酸代谢酶作为免疫联合治疗的新靶点

3.4.1 IDO抑制剂与色氨酸代谢干预

免疫疗法在HCC治疗中的疗效和反应率有限，亟待对其联合治疗策略进行探究。Trp分解代谢的关键限速酶IDO1抑制剂在黑色素瘤等肿瘤模型中已展示出治疗潜力[126]。同时，基于靶向蛋白降解PROTAC技术的IDO1降解剂研发已取得进展，为治疗提供新途径[127]。在HCC动物模型中，IDO1抑制剂Abrine能够抑制肿瘤免疫逃逸，Abrine与抗PD-1联合显著抑制肿瘤生长并提高$CD4^+$或$CD8^+$ T细胞的浸润，增强抗PD-1的治疗效果[128]。

3.4.2 靶向DLAT-AUH轴调节亮氨酸代谢

mTOR作为连接氨基酸代谢与免疫应答的关键枢纽，其抑制剂与抗PD-L1抗体在HCC治疗中具有应用潜力[129]。在HCC细胞中，丙酮酸代谢酶二氢硫辛酰胺S-乙酰转移酶(dihydrolipoamide S-acetyltransferase，DLAT)乙酰化修饰Leu分解代谢关键酶AUH(AU RNA-binding methylglutaconyl-coenzyme A hydratase)，抑制其活性导致Leu积累，并持续激活mTORC1信号通路。这一代谢重编程过程不仅驱动癌细胞增殖，还通过营造氨基酸饥饿的肿瘤微环境，抑制$CD8^+$ T细胞功能，同时促进T细胞增殖，形成免疫抑制状态[22]。基于此，装载AUH K109R突变体编码mRNA的脂质纳米颗粒(LNP-mRNA)可恢复Leu正常分解代谢，有效阻断mTORC1激活，重塑肿瘤免疫微环境，在细胞和动物水平有效抑制HCC的增殖[22]。上述研究表明，靶向调控氨基酸代谢酶、干预关键氨基酸代谢通路，有望成为HCC免疫联合治疗的创新策略和重要靶点。

3.5 治疗策略对氨基酸代谢重编程的反向调控及潜在影响

在靶向氨基酸代谢酶的药物开发中，除了直接抑制肿瘤细胞的代谢异常外，另一个值得关注的层面是治疗策略本身可能反向调控肿瘤细胞的氨基酸代谢重编程，进而影响疗效或诱导抵抗。Gln代谢抑制剂在阻断Gln分解的同时，可能通过激活肿瘤细胞的代偿机制，增强对Ser等替代营养物质的摄取与利用，以维持TCA循环和生物合成需求[130]。在ASS表达缺陷的细胞中，应用精氨酸脱亚胺酶(ADI-PEG20)降解Arg后，会诱导肿瘤细胞内ASS的转录激活，通过内源性合成Arg而削弱对外源性Arg的依赖，导致药物敏感性下降[131]。这些结果提示单一靶向代谢酶的策略可能因代谢网络的可塑性而受限，联合靶向多种代谢节点以减少抵抗有可能为联合治疗提供思路。表1总结了氨基酸代谢的肝癌治疗策略。

4 总结与展望

目前，临床常用的HCC标志物如AFP、异常凝血酶原PIVKAII(protein induced by vitamin k absence or antagonist-II)等与氨基酸代谢的关联性较弱，而新发现的代谢标志物，如血清牛磺结合胆汁酸等尚缺乏大样本队列验证，制约了靶向氨基酸代谢精准治疗的应用。针对当前的研究难点和重点，在高精度代谢标志物验证技术方面，尝试构建结合基因组、蛋白质组、特定氨基酸比值、代谢酶活化水平等指标的氨基酸代谢标志物临床预测模型，可望解决单一标志物敏感性不足的问题。同时，在类器官(patient-derived organoids，PDO)模型中，肿瘤细胞的Gln摄取率与临床样本的一致性很高，提示其可能规避传统二维细胞模型与临床疗效脱节的问题[133]。随着新兴技术与研究模型的快速发展应用，如PDO、患者来源肿瘤异种移植(patient-derived tumor xenograft，PDX)模型等，HCC氨基酸代谢标志物研究有望取得新进展。

同时，氨基酸代谢的时空异质性，即不同肿瘤分期、不同肝内微环境中氨基酸代谢特征的差异及其对治疗的影响，也是亟待探索的方向。目前研究多聚焦于单一氨基酸或代谢通路，对氨基酸代谢网络协同调控尚需深入探索。而且，氨基酸代谢并非孤立存在，其与脂质代谢、糖代谢等其他

表1 靶向氨基酸代谢的肝癌治疗策略

Table 1 Therapeutic strategies targeting amino acid metabolism in liver cancer

治疗策略	具体药物/疗法	靶点	作用机制	研究阶段	参考文献
靶向代谢酶药物	CB-839	GLS1	可逆性抑制GLS1,干扰Gln代谢	临床前	[116,132]
	JHU083	GLS	抑制GLS,拮抗Gln代谢通路	临床前	[114]
	FIDAS-5	MAT2A	抑制MAT2A,阻断Met分解代谢,诱导肝癌细胞周期阻滞和DNA损伤,导致细胞衰老	临床前	[105]
	MFMP	MAT2A等	纳米颗粒整合MAT2A抑制剂FIDAS-5、巨噬细胞膜和抗PD-L1组成,增强抗肿瘤免疫	临床前	[118]
	Abrine	IDO1	抑制Trp分解代谢,提高$CD4^+$或$CD8^+$ T细胞的浸润,增强抗PD-1的治疗效果	临床前	[128]
Arg降解剂	rhArg-PEG	Arg	为Peg-rhArg1,将Arg转化为Orn,限制外源Arg利用	临床试验(II期)	[119,120]
	ADI-PEG 20	Arg	为ADI-PEG 20,降解循环中Arg	临床试验(III期)	[122]
氨基酸限制疗法	间歇性Met剥夺	一碳代谢通路	间歇性限制Met摄入,增强HCC细胞对铁死亡的敏感性	临床前	[124]
LNP-mRNA	AUHK109R-mRNA-LNP	AUH	装载AUH K109R突变体编码mRNA的脂质纳米颗粒,恢复Leu分解,重塑肿瘤免疫微环境	临床前	[22]

代谢通路之间存在复杂的动态交叉互作,比如Gln代谢异常可能通过重塑线粒体功能影响脂肪酸合成[134]。针对特殊人群的代谢特征研究也需加强,例如合并非酒精性脂肪肝等基础肝病的HCC患者,其氨基酸代谢可能存在独特表型。未来,越来越成熟的多组学联合和时空组学技术可望揭示代谢通路间的动态互作。

此外,代谢与免疫微环境的深度互作是另一重要研究方向,如肿瘤微环境中的"代谢共生"现象,肿瘤细胞与髓系细胞[91]、巨噬细胞[135]之间的氨基酸竞争及代谢物的相互影响[136],而其中涉及的细胞间传递机制和动态调控仍需深入探索。而有研究报道肝窦内皮细胞的氨基酸转运异常可能阻碍T细胞浸润[137],提示非免疫细胞氨基酸代谢调控对肿瘤免疫的作用也不应被忽视。相关机制的系统研究及阐明有望优化联合免疫治疗策略,提高治疗精确性并获得更好的治疗效果。

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