·综　述·

谷氨酰胺代谢和肿瘤耐药机制研究进展

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［摘　要］ 恶性肿瘤细胞表现出显著的代谢重塑特征，具体表现在对谷氨酰胺（glutamine，Gln）等代谢底物的摄取能力显著增强。这种代谢改变不仅为肿瘤细胞内异常活跃的糖酵解途径和线粒体氧化磷酸化过程提供必要的代谢前体物质，同时通过干扰糖类、脂类以及氨基酸代谢的动态平衡，直接导致肿瘤组织对化学治疗药物产生耐药性。然而，对于肿瘤细胞如何调控Gln代谢可塑性以逃避肿瘤药物的杀伤，目前尚没有系统性阐述，同时也缺乏针对Gln代谢在不同癌症类型、不同微环境中作用差异性的梳理以及临床转化失败原因的深入分析。文章总结了Gln代谢在肿瘤耐药形成过程中的关键调控作用及其耐药机制，首次提出“Gln代谢-微环境-免疫逃逸”三维耐药模型，并指出当前靶向治疗的三大瓶颈，以期为改善恶性肿瘤耐药性的临床治疗策略提供理论依据和方法学参考。

［关键词］ 谷氨酰胺；代谢重编程；肿瘤微环境；耐药；谷氨酰胺转运体；蛋白质翻译后修饰；表观遗传调控；DNA损伤修复
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Research progress on glutamine metabolism and tumor drug resistance mechanisms

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［**Abstract**］ Malignant tumor cells undergo profound metabolic reprogramming，manifested by a markedly enhanced capacity for the uptake of specific metabolic substrates，most notably glutamine（Gln）. This metabolic adaptation not only provides essential precursors to support aberrantly active glycolysis and mitochondrial oxidative phosphorylation but also disrupts the homeostatic balance of carbohydrate，lipid，and amino acid metabolism，thereby directly contributing to the adaptive resistance of tumor tissues to chemotherapeutic agents. Despite its significance，a systematic understanding of how tumor cells modulate Gln metabolic plasticity to evade drug-induced cytotoxicity remains elusive. Furthermore，there is a notable lack of in-depth analyses addressing the context-dependent variability of Gln metabolism across different cancer types and microenvironments，as well as the underlying causes of the failures in clinical translation. This review systematically delineates the key regulatory roles and mechanistic pathways through which Gln metabolism drives the acquisition of drug resistance in malignant tumors. For the first time，we propose a three-dimensional resistance framework-termed the“Gln metabolism-microenvironment-immune evasion”model and identify three major bottlenecks inherent in current targeted therapeutic strategies. Collectively，this review aims to establish a theoretical foundation and provide methodological insights to inform and improve clinical treatment strategies for drug-resistant malignant tumors.

［**Key words**］ glutamine；metabolic reprogramming；tumor microenvironment；drug resistance；glutamine transporters；protein post-translational modifications；epigenetic regulation；DNA damage repair

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恶性肿瘤治疗过程中，药物耐受是临床面临的重要挑战。在持续性抗癌治疗的压力下，恶性细胞可产生耐药性，其特征包括基因组稳定性维持能力提升、药物靶点表达下调以及代谢相关信号异常活化等。这种适应性改变显著降低了肿瘤组织对细胞毒性药物的敏感性，严重影响化疗效果。更为严峻的是，治疗后的残留肿瘤细胞仍保持增殖潜能，往往成为疾病复发的重要根源，最终影响患者的长期预后。代谢重编程作为恶性肿瘤的关键生物学特征，通过重构能量代谢网络支持细胞异常增殖，并在肿瘤微环境中获得生存优势，最终形成药物抵抗，其中，谷氨酰胺（glutamine，Gln）代谢途径在此过程中扮演核心角色。作为维持细胞生长的关键营养物质，Gln不仅为肿瘤组织提供必需的碳骨架和氨基供体，还通过调控糖类、脂类及氨基酸代谢网络的动态平衡，直接诱发肿瘤细胞对化疗药物的抵抗。文章系统总结了Gln代谢在肿瘤细胞耐药中的调控功能及其作用机制，对跨膜转运系统、代谢关键酶以及肿瘤微环境等进行重点探讨。通过系统阐明Gln代谢与药物耐受的内在关联，为开发新型抗肿瘤药物提供理论支撑和潜在的干预目标。

1 Gln代谢

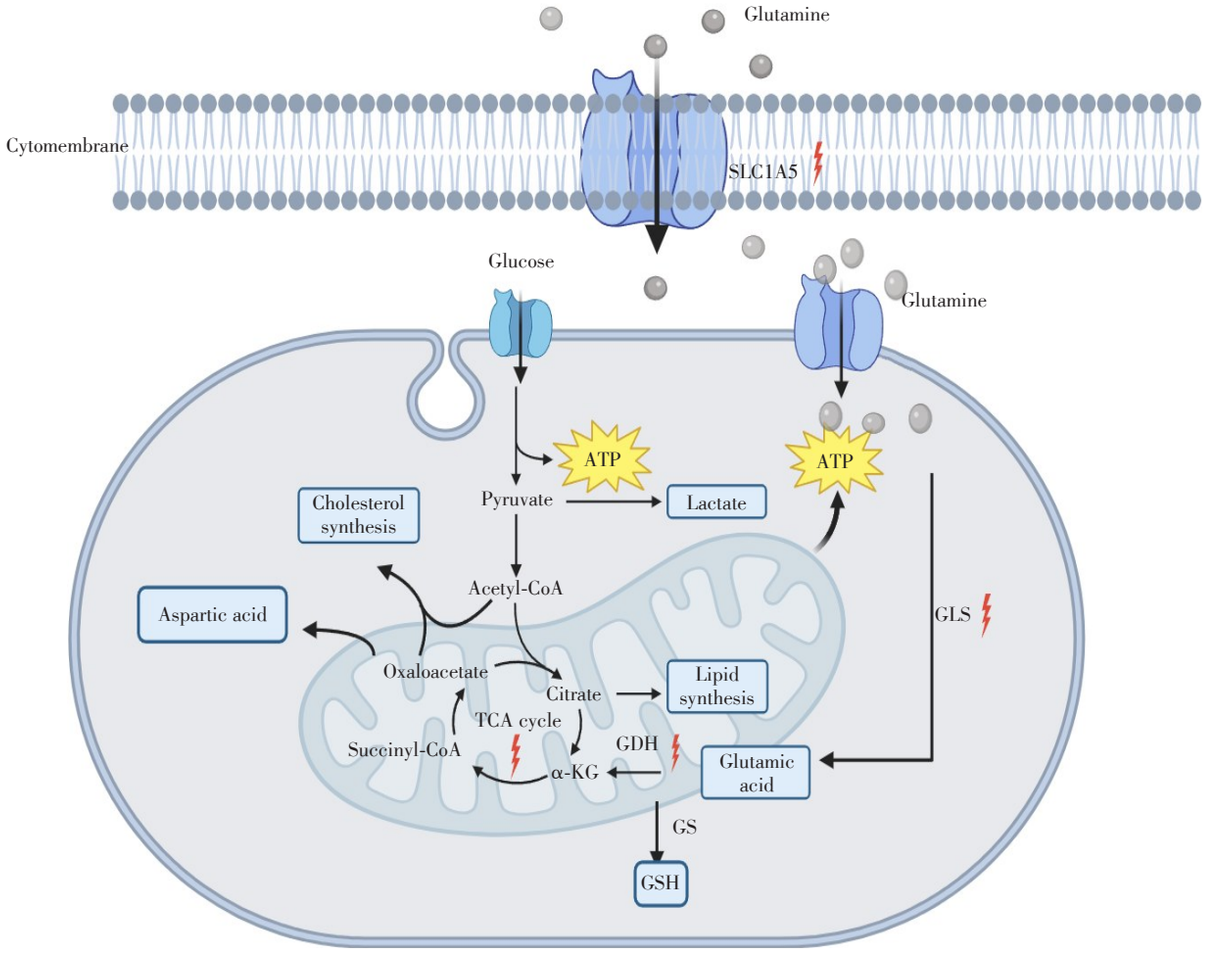
Gln作为机体重要的代谢底物，在血液循环系统和骨骼肌组织中具有较高浓度，约占血液中游离氨基酸总量的20%，是血浆氨基酸组成中占比最高的氨基酸。在正常生理代谢状态下，Gln既可作为生物合成的碳骨架供体，又能为细胞提供必需的氮元素。在三羧酸（tricarboxylic acid，TCA）循环中，细胞外的Gln通过细胞膜上的Gln转运体SLC1A5进入细胞内，在谷氨酰胺酶（glutaminase，GLS）的作用下转化为谷氨酸（glutamate，Glu），进而在谷氨酸脱氢酶（glutamate dehydrogenase，GDH）或转氨酶（amino-transferase，TG）的作用下生成α-酮戊二酸（alpha-ketoglutarate，α-KG），α-KG通过TCA循环中的氧化磷酸化生成ATP为细胞供能[1]。值得注意的是，上述4步反应为耐药机制提供可直接干预的节点（图1），恰好对应4个已进入临床试验的抑制剂靶点。

此外，Gln可作为核苷酸合成和非必须氨基酸合成的氮源。核苷酸是细胞增殖所必需的含氮化合物，Gln作为核苷酸从头合成中不可替代的氮源供体，直接参与嘌呤环和嘧啶环的构建，其γ-氮在嘌呤合成的5个反应中被利用[2]，依赖Gln作为氮源的氨基甲酰磷酸合成酶Ⅱ（carbamoyl phosphate synthetase Ⅱ，CPSⅡ）是嘧啶合成的限速酶[3-4]。此外，Gln还能够通过生成天冬氨酸（aspartic acid，Asp）间接提供碳骨架。Gln脱去酰胺基团，生成Glu，Glu-草酰乙酸转氨酶1（glutamate-oxaloacetate transaminase 1，GOT1）能够介导Glu与草酰乙酸（oxaloacetate，OAA）之间的氨基转移，促进Asp的生成[5]。在Glu-丙酮酸转氨酶（glutamate-pyruvate transaminase，GPT）和磷酸丝氨酸转氨酶（phosphoserine aminotransferase，PSAT）的催化下，Gln衍生的Glu还可为丙氨酸及磷酸丝氨酸的合成提供氮源供体[5]。值得注意的是，Glu可作为谷胱甘肽（glutathione，GSH）合成的前体物质，协同NADPH发挥还原剂的作用，维持胞内氧化还原平衡，保障细胞正常增殖[6]。

2 肿瘤细胞中的Gln代谢重编程

肿瘤的恶化进程与其独有的异常能量代谢有密切关系。为适应肿瘤细胞增殖对生物合成前体、能量供应及氧化还原能力的迫切需求，肿瘤细胞会对其代谢途径进行重新编程，对肿瘤发展的多个阶段乃至耐药性的形成均有显著影响。肿瘤细胞更依赖Gln代谢维持其生长所需的能量需求，表现为肿瘤细胞的“Gln成瘾”现象[6]。Quek等[7]发现Gln成瘾在三阴性乳腺癌（triple-negative breast cancer，TNBC）中通过促进葡萄糖氧化支持肿瘤细胞的能量需求和快速增殖。在肿瘤细胞重编程中，由Gln代谢产生的α-KG一方面在TCA循环中通过氧化脱羧生成NADH，为氧化磷酸化提供能量，从而维持肿瘤细胞的高ATP需求，另一方面，在缺氧条件下，通过还原羧化途径转化为OAA和乙酰辅酶A参与柠檬酸的合成，促进脂肪酸合成[8]，这一过程对于维持肿瘤细胞的高能量需求和生物合成需求至关重要。此外，相比正常细胞，肿瘤细胞通过增强Gln代谢，产生更多的代谢中间物用于合成核酸、蛋白质和脂质，支持细胞的快速增殖和生长[9]。同时，肿瘤细胞在快速增殖过程中会产生大量的活性氧（reactive oxygen species，ROS），需要更强的抗氧化防御机制，其通过增强Gln代谢，生成更多的Glu，进一步促进GSH的合成，清除ROS，保护细胞免受氧化损伤。

Gln代谢重编程在肿瘤细胞中起着关键作用，通过增强Gln的摄取、代谢和利用，支持细胞的能量代谢、生物合成和抗氧化防御。这种重编程不仅满足ATP需求，更重要的是提供核苷酸、脂类合成前体，并维持GSH/NADPH氧化还原缓冲系统，从而直



Extracellular Gln enters the cell *via* the membrane transporter SLC1A5 and is catalyzed by GLS to produce glutamate. Glu is then deaminated by glutamate dehydrogenase to generate α-ketoglutarate, which enters the tricarboxylic acid cycle and subsequently undergoes oxidative phosphorylation to produce ATP, thereby supplying energy for cellular processes. Intermediate products of the TCA cycle can be further converted into oxaloacetate, which is catalyzed by GOT1 to produce aspartate, or together with acetyl-CoA, participate in cholesterol synthesis. Glu also serves as a precursor for glutathione synthesis, working in concert with NADPH to maintain intracellular redox homeostasis. In addition, glucose is metabolized *via* glycolysis to generate pyruvate, which can be either converted into lactate or enter mitochondria to produce acetyl-CoA for the TCA cycle. The red lightning bolt symbols in the figure indicate steps corresponding to inhibitors that have entered clinical trials.

图1　谷氨酰胺代谢示意图

Figure 1　Schematic diagram of glutamine metabolism

接对抗化疗诱导的ROS爆发，为开发新的治疗策略提供了潜在靶点。然而，不同恶性肿瘤对Gln代谢的依赖环节和代偿策略存在显著差异（表1），例如，^{13}C示踪实验显示，TNBC细胞内>50%的α-KG来源于Gln，且下游TCA循环代谢物^{13}C富集度显著高于非TNBC亚型，首次从亚型水平证实TNBC对Gln-α-KG轴的高度依赖，同时提示不同癌症类型对Gln代谢依赖程度存在显著异质性[8]。这种异质性主要源于三重分子基础：①致癌驱动基因决定代谢成瘾模式，骨髓细胞瘤病毒癌基因同源物（myelocytomatosis concogene，MYC）扩增通过抑制miR-23a/b间接上调GLS1[10]，而kirsten大鼠肉瘤病毒癌基因同源物（kirsten rat sarcoma viral oncogene homolog，KRAS）突变则通过Hippo-YAP1通路上调多种氨基酸转运体[11]；②微环境特征进一步调控代谢可塑性，缺氧诱导因子（hypoxia-inducible factor，HIF）激活糖酵解，高基质肿瘤中肿瘤相关成纤维细胞（cancer-associated fibroblast，CAF）通过谷氨酰胺合成酶（glutamine synthetase，GS）分泌Gln形成代谢耦合，且免疫细胞浸润激活信号转导与转录激活因子3（signal transducer and activator of transcription 3，STAT3）-GLS1正反馈环[12]；③代谢基线同时影响靶向敏感性，如异柠檬酸脱氢酶（isocitrate dehydrogenase，IDH）野生型胶质母细胞瘤（glioblastoma，

GBM）依赖外源性Gln[13]，肝激酶B1（liver kinase B1，LKB1）缺失通过AMPK失活解除对乙酰辅酶A羧化酶（acetyl-CoA carboxylase，ACC）的抑制，促进脂肪酸合成，同时增强Gln依赖性，从而提高GLS1抑制敏感性。这三重因素相互交织，精准识别Gln代谢异质性是实现恶性肿瘤分层治疗的关键[14]。

表1　主要癌症类型谷氨酰胺代谢特征与核心干预靶点差异

Table 1　Glutamine metabolism characteristics and core intervention target differences in major cancer types

Cancer type	Core dependency	Key molecular marker	Main compensatory pathway	Core intervention target	Reference
Triple-negative breast cancer	GLS1-α-KG-TCA cycle	MYC↑，LKB1 wild-type	fatty acid oxidation（FAO）↑，SSP↑	GLS1	[15]
Pancreatic ductal adenocarcinoma	SLC1A5/SLC38A5-uptake	KRAS mutation，stroma-rich	Autophagy↑，CAF coupling	SLC1A5_var	[16]
Clear cell renal cell carcinoma	Reductive carboxylation - lipid synthesis	VHL-，HIF-2α↑	Glycolysis↑，pentose phosphate pathway（PPP）	HIF-2α+GLS1	[17]
Non-small cell lung cancer	GLS1-Glu-GSH	EGFR-T790M，GLS1↑	Glycolysis↑，nucleotide synthesis↑	GLS1+SLC7A11	[18]

3　Gln代谢与肿瘤耐药机制

3.1　Gln相关代谢酶影响肿瘤耐药

GLS作为一种线粒体内的关键酶，参与Gln代谢过程，能够催化Gln转化为Glu，而Glu进一步代谢生成α-KG，进而参与调控其他代谢通路。GLS分为GLS1和GLS2，虽然都能催化Gln生成Glu和游离氨，但两者在肿瘤细胞中的表达活性有显著差别，GLS2在大多数情况下被认为是一种肿瘤抑制因子[19]，且在多种实体瘤中普遍低表达。在多种肿瘤细胞中，GLS1通过抗氧化作用、提供能量以及激活信号通路，促进肿瘤耐药性。在表皮生长因子受体（epidermal growth factor receptor，EGFR）突变的非小细胞肺癌（non-small cell lung cancer，NSCLC）患者中，尤其是携带T790M耐药突变的个体，GLS1的活性显著上调，通过生成更多的α-KG维持TCA循环，支持细胞的能量需求，从而帮助肿瘤细胞逃避奥希替尼等靶向药物的抑制[20]。部分经靶向药处理后的肿瘤细胞获取碳源的方式会出现从葡萄糖依赖到Gln依赖的转变，Gln代谢增强，GLS1水平升高使得α-KG生成增多，从而促进肿瘤细胞存活导致耐药。例如，mTOR激酶抑制剂治疗后的GBM中，糖酵解水平被抑制，Gln代谢依赖性增强，GLS1和Glu水平升高，α-KG随之升高并作为主要补充物，导致GBM对mTOR抑制剂耐药[21]。此外，研究表明，CB-839和mTOR抑制剂依维莫司的联合使用显著抑制了TNBC细胞的增殖，并克服了对化疗药物的耐药性[22]，然而，CB-839单药在NSCLC Ⅱ期未达主要终点，需联合mTOR或SLC7A11抑制剂以阻断代偿[23]，由此可间接推断，GLS1通过生成Glu维持GSH合成，减少氧化应激的同时，激活mTORC1信号通路，促进细胞增殖并影响肿瘤耐药。因此，针对GLS的特异性抑制剂，如BPTES和CB-839等，通过抑制GLS的活性，显著降低肿瘤细胞内Gln的生物利用度，进而有效抑制恶性肿瘤的增殖，这在一些肿瘤模型中取得了一定的抗肿瘤效果。最新研究发现，一种源自COL1A1基因的环状RNA circCOL1A1在结直肠癌组织中显著高表达，通过竞争性吸附miR-214-3p，解除miR-214-3p对GLS1的抑制作用，进而促进Gln分解代谢，为肿瘤细胞提供能量和生物合成原料，驱动肿瘤细胞耐药[24]。

GDH在Gln代谢中发挥关键作用，特别是在葡萄糖不足或缺氧条件下[25]。GDH催化Glu脱氨生成α-KG，该代谢产物随后整合入TCA循环，为细胞提供能量代谢支持并参与高能化合物的生物合成过程，这在整合Gln碳源和氮源的代谢中至关重要。GDH1是GDH的一种亚型，GDH1在肿瘤细胞中异常高表达，与肿瘤细胞的增殖、迁移和耐药密切相关，GLUD1是编码GDH1的基因，过表达GLUD1的肺癌细胞表现出更强的多西他赛耐受能力以及更强的转移和迁移能力，但这些变化在沉默GLUD1后被抑制，而在回补α-KG后又抵消了沉默GLUD1带来的抑制作用[26]，因此可以推测化疗药处理后的

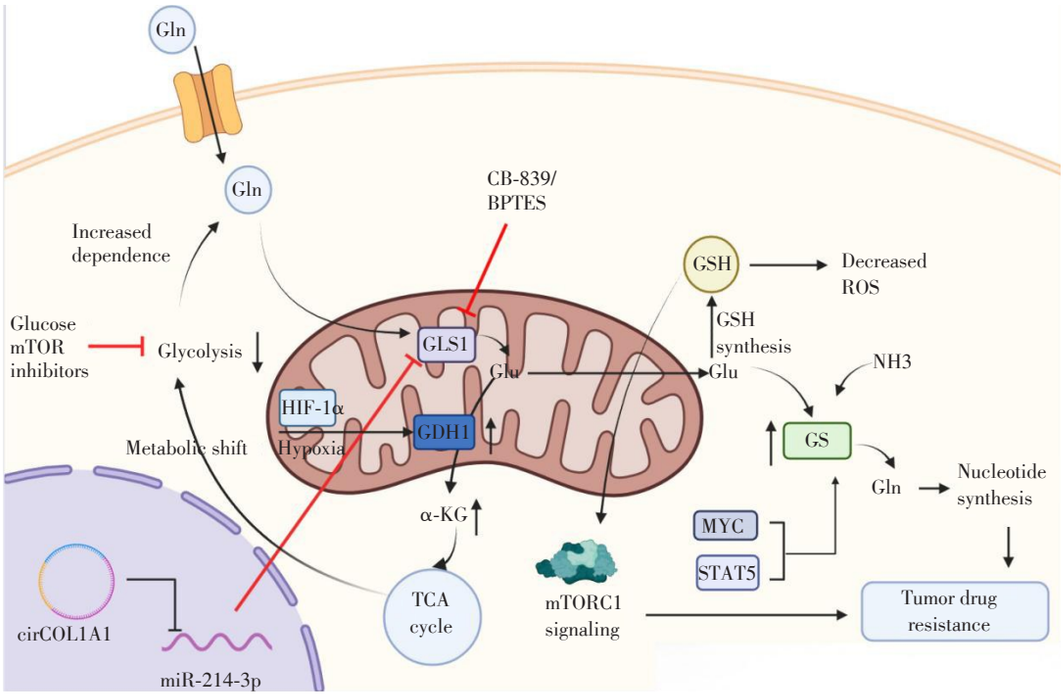
肿瘤细胞中GLUD1表达增强，进一步生成更多的α-KG从而导致耐药。在低氧条件下，肺癌细胞中的HIF-1α蛋白水平上调，促进了GDH的表达，GDH的高表达增强了Gln代谢，增加了细胞内的α-KG水平，从而维持了细胞的能量代谢和氧化还原平衡，有助于肺癌细胞抵抗顺铂等化疗药物的毒性，导致耐药性的产生[27]。

GS作为唯一从头合成Gln的酶，可催化细胞内Glu和游离氨生成Gln，有助于维持细胞内的Gln水平，在多种肿瘤中表达上调，与肿瘤生长、增殖、转移密切相关。研究发现，MYC和STAT5上调GS的表达，催化Glu转化为Gln，导致核苷酸的产生增加，从而导致肿瘤耐药[28]。

综上所述，Gln相关代谢酶通过多种机制影响肿瘤细胞的耐药性，包括促进α-KG的回补，促进核苷酸生成等，这些代谢酶的调控为肿瘤治疗提供了新的靶点和策略（图2）。

3.2 Gln转运体影响肿瘤代谢

溶质载体（solute carrier，SLC）蛋白家族是位于细胞膜表面的一类小分子转运蛋白。在肿瘤细胞中，SLC1A5作为Gln的主要转运通道，其功能是将胞外Gln转运至胞内，为Gln依赖性代谢通路提供底物。多项研究证实，相比正常组织，SLC1A5在肺腺癌、乳腺导管癌、肝细胞癌等多种恶性肿瘤中的表达水平明显升高[29]。这种过表达状态显著增强了肿瘤组织对Gln的摄取能力，支持肿瘤细胞的代谢重编程，提升细胞的抗氧化能力和能量供应效率。研究发现，SLC1A5的2型剪切体过表达使得Gln摄入量增多，增加了Gln代谢产生的Glu，进而促进GSH的合成，减少吉西他滨引起的DNA损伤，从而增强肿瘤细胞对吉西他滨的耐药性[29]。此外，SLC1A5的高表达促进了Gln介导的ATP生成，维持肿瘤细胞的能量稳态，增强其在化疗药物作用下的生存能力。例如，在胰腺癌中，HIF-2α诱导的



Extracellular Gln is transported into the cell *via* specific transporters and is subsequently catalyzed by GLS1 in the mitochondria to produce Glu. This step can be blocked by GLS1 inhibitors, such as CB-839 or BPTES. Glu is then catalyzed by GDH1 to generate α-KG, which enters the tricarboxylic acid cycle to provide energy. Under hypoxic conditions, HIF-1α upregulates the expression of GDH1. Following treatment with mTOR kinase inhibitors, tumor cells undergo a metabolic shift, characterized by suppressed glycolysis and increased dependence on Gln, ultimately leading to tumor drug resistance. Glu can also be recycled to Gln *via* catalysis by GS. MYC and STAT5 upregulate GS expression, promoting the conversion of Glu to Gln, which results in increased nucleotide production and subsequently contributes to tumor drug resistance. Furthermore, Glu serves as a precursor for glutathione synthesis. GSH not only exerts antioxidant effects by reducing reactive oxygen species levels but also activates the mTORC1 signaling pathway, thereby promoting tumor drug resistance. CircCOL1A1 enhances Gln metabolism by competitively sponging miR-214-3p, thereby relieving the inhibitory effect of miR-214-3p on GLS1.

图2　谷氨酰胺代谢酶介导的肿瘤耐药机制

Figure 2　Mechanisms of glutamine metabolic enzyme-mediated tumor drug resistance

SLC1A5变体过表达导致Gln摄取增加，进而增加ATP和GSH的合成，促使胰腺癌细胞对吉西他滨产生耐药性[30]。与定位于质膜的经典SLC1A5不同，SLC1A5_var是SLC1A5的线粒体剪切变体，特异性分布于线粒体内膜，以同源三聚体形式介导细胞质Gln向线粒体基质的转运。其变构抑制剂iMQT-020通过变构解离SLC1A5_var三聚体阻断线粒体Gln摄取，引发TCA循环受阻、GSH耗竭与ROS积累，诱导肿瘤细胞死亡。同时α-KG匮乏抑制DNA去甲基化酶TET活性，导致PD-L1基因启动子去甲基化，PD-L1表达上调，iMQT-020与PD-1/PD-L1抗体协同激活抗肿瘤免疫应答[31]。

除此之外，SLC7A8也是氨基酸转运蛋白，主要参与氨基酸的跨膜运输。在胆管癌（cholangiocarcinoma，CCA）的研究中发现，SLC7A8在吉西他滨耐药的CCA细胞中显著高表达。通过siRNA技术敲低SLC7A8的表达，可以显著增强CCA细胞对吉西他滨的敏感性，抑制细胞生长[32]。SLC7A8可激活mTORC1，激活的mTORC1抑制蛋白酶体活性从而增强SLC7A8的稳定性，形成正反馈循环，促使肿瘤细胞摄取更多的Gln并合成GSH，进一步诱导其对吉西他滨耐药[33]。

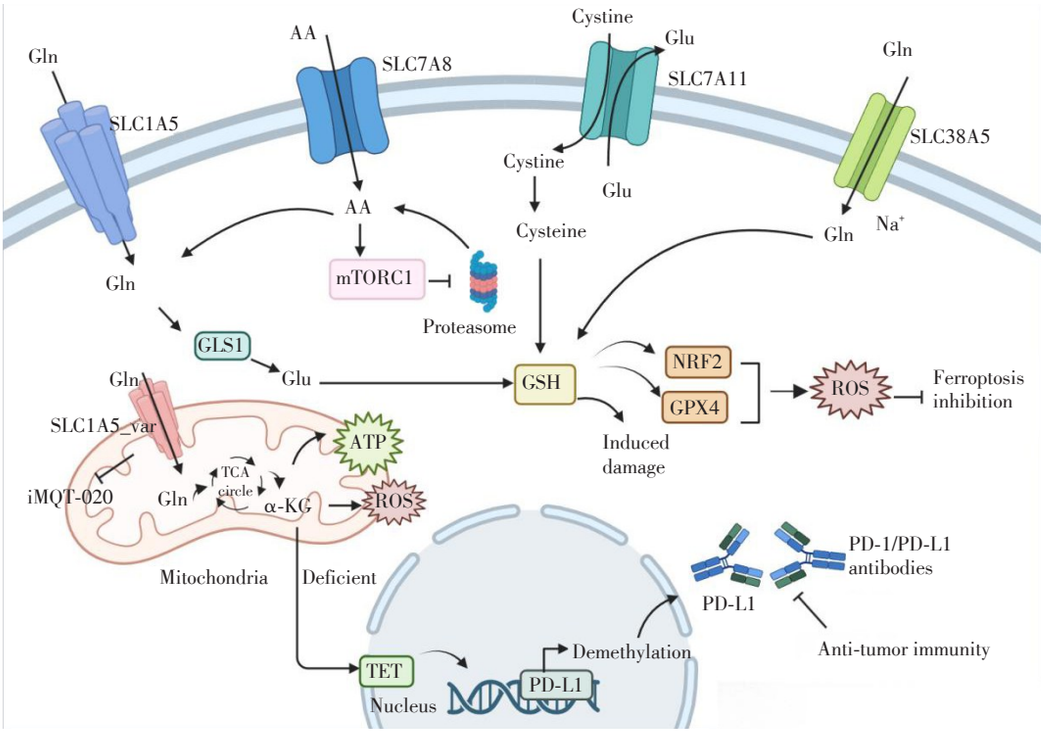
SLC7A11是Glu-胱氨酸逆向转运蛋白，与Gln代谢途径存在协同作用，“Gln-Glu-胱氨酸-GSH”代谢协同环路在多种实体瘤中高表达并介导耐药。在胰腺导管腺癌（pancreatic ductal adenocarcinoma，PDAC）的研究中，SLC7A11敲低联合吉西他滨使肿瘤体积缩小74%，单药仅缩小31%[34]。细胞外的胱氨酸通过SLC7A11转运体被摄取到细胞内，Gln代谢产生的Glu为胱氨酸还原后的半胱氨酸提供了合成GSH的必要底物[3]。在临床研究中，SLC1A5抑制后，胞内Glu/α-KG比率下降使激活转录因子4（activating transcription factor 4，ATF）4激活，诱导SLC7A11转录上调，胱氨酸摄取增多，从而导致GSH合成量上升，形成“Glu外排-胱氨酸摄取-GSH合成”代偿环路，导致单一转运体靶向治疗失效[1]。因此SLC7A11的高表达可以增强GSH的合成，从而提高细胞的抗氧化能力，帮助肿瘤细胞抵抗化疗药物引起的氧化应激，而SLC7A11抑制剂（如磺胺嘧啶）可以通过抑制GSH合成，削弱细胞的抗氧化能力，增强肿瘤细胞对化疗药物的敏感性[35]。研究发现，SLC7A11高表达的顺铂耐药细胞对铁死亡诱导化合物表现出交叉耐药性，SLC7A11通过维持GSH的水平，抑制铁死亡，促进肿瘤细胞的生长，进而导致耐药[36]。同时，在GBM中，SLC7A11的高表达增加了细胞对氧化应激的抵抗力，降低了化疗药物的效果[37]。此外，SLC7A11通过促进Glu的外排，间接影响Gln的代谢。Glu作为Gln代谢的产物，其外排会导致细胞内Glu/α-KG池的耗竭，从而激活Gln的分解，增加对Gln的摄取，这种代谢重编程也可能会增强肿瘤细胞的耐药性。综上所述，当细胞外胱氨酸充足时，环路主要合成GSH，通过抗氧化、抗铁死亡导致耐药。当细胞外胱氨酸不足或ROS被大量清除后，Glu的持续外排则导致胞内Glu/α-KG浓度下降，细胞通过上调GLS以回补α-KG并维持TCA循环，使细胞对Gln的“摄取-分解”速率进一步提高，形成代谢重编程并导致Gln依赖型耐药。

近年来，新发现的Gln转运体为肿瘤代谢研究提供了新靶点。2023年，Kim等[38]首次报道SLC38A5作为新型钠离子依赖性中性氨基酸转运体，在胰腺癌吉西他滨耐药中发挥关键作用。SLC38A5转运的Gln有助于胰腺癌细胞的GSH合成，随后合成的GSH通过调控NRF2和GPX4相关基因调节细胞内ROS水平，使得ROS不断积累从而显著减少铁死亡，最终导致胰腺癌吉西他滨耐药。同时在原位小鼠模型中，沉默SLC38A5可通过抑制肿瘤生长和转移恢复吉西他滨敏感性，这也从侧面验证了SLC38A5可作为针对胰腺癌吉西他滨耐药的新型治疗靶点。

Gln是肿瘤细胞消耗量最大的氨基酸，绝大多数Gln转运体直接或间接影响Gln代谢，它们通过增强抗氧化能力，支持能量代谢等方式满足肿瘤细胞的需求并影响耐药（图3）。目前，V-9302（SLC1A5抑制剂）因靶点不专一（同时作用于SLC38A2）且SLC1A5缺失后癌细胞可依赖SLC38A2代偿摄取Gln，已停止单药Ⅱ期开发[9]；磺胺嘧啶则因大剂量骨髓抑制与叶酸代谢干扰而止步于Ⅰ期体外研究[39]。2024—2025年多项研究一致指出，联合阻断SLC1A5+SLC38A2或联合免疫检查点抑制剂，可克服代偿通路并降低不良反应，是未来临床转化的主要方向[31]。

3.3 Gln代谢引起的肿瘤微环境改变影响肿瘤耐药

肿瘤组织所处的特殊微环境主要由肿瘤细胞、基质成分、免疫细胞及其分泌产物（包括各类信号分子和趋化因子）以及细胞外基质（extracellular matrix，ECM）蛋白共同构成[34]。在肿瘤微环境中，Gln代谢的动态变化可能显著影响邻近正常细胞，特别是免疫细胞的生理状态[40]。恶性肿瘤表现出



Multiple solute carrier transporters on the cell membrane are involved in the transmembrane transport of Gln and related amino acids. SLC1A5 serves as the primary Gln transporter, facilitating the uptake of extracellular Gln into the cytoplasm, where it is subsequently catalyzed by GLS1 to generate Gln. SLC7A8 mediates amino acid uptake and activates mTORC1 signaling, forming a positive feedback loop that enhances SLC7A8 stability, thereby promoting Gln uptake and glutathione synthesis. SLC7A11 functions as a Gln-cystine antiporter, mediating cystine uptake and Glu efflux, thereby providing the cysteine substrate required for GSH synthesis. GSH suppresses reactive oxygen species accumulation by activating the NRF2-GPX4 pathway, consequently inhibiting ferroptosis and inducing chemotherapy resistance. SLC38A5, a novel sodium-dependent Gln transporter, similarly facilitates GSH synthesis and antioxidant defense. The mitochondrial splice variant SLC1A5_var, localized to the inner mitochondrial membrane, mediates the transport of cytoplasmic Gln into the mitochondrial matrix. Its allosteric inhibitor, iMQT-020, blocks this process, leading to TCA cycle disruption, GSH depletion, and ROS accumulation, which collectively induce tumor cell death. Concurrently, α-ketoglutarate deficiency inhibits the activity of the DNA demethylase TET, resulting in hypomethylation of the PD-L1 gene promoter and subsequent upregulation of PD-L1 expression. The iMQT-020 synergizes with PD-1/PD-L1 antibodies to activate anti-tumor immunity.

图3　谷氨酰胺转运体介导的肿瘤耐药机制

Figure 3　Mechanisms of glutamine transporter-mediated tumor drug resistance

的对Gln的竞争性摄取特性，导致局部微环境内Gln浓度显著下降，迫使免疫细胞发生代谢重塑以应对营养匮乏。这种适应性改变往往伴随着免疫功能抑制，为肿瘤细胞创造免疫逃逸条件，进而导致肿瘤细胞耐药（图4）[15]。例如，在多种实体瘤模型中，肿瘤细胞高表达SLC1A5/GLS导致微环境Gln耗尽，T细胞与NK细胞被迫转向糖酵解，其干扰素（interferon，IFN）-γ分泌量下降60%~80%，显著削弱抗肿瘤免疫，导致肿瘤细胞对吉西他滨、顺铂耐药[9]。肿瘤微环境中的免疫抑制细胞包括肿瘤相关巨噬细胞（tumor-associated macrophage，TAM）和髓源抑制细胞（myeloid-derived suppressor cell，MDSC）等。在肿瘤微环境中，M2型肿瘤相关巨噬细胞（M2-type tumor-associated macrophage，M2-TAM）的高比例通常与肿瘤耐药性相关。TAM通过释放Gln，为肿瘤细胞补充额外的营养来源，使其维持充足的Gln供给，从而提升肿瘤细胞的生物合成活性并促进治疗抵抗[1]。此外，Gln代谢通过促进TCA循环，在调控TAM表型转化中具有重要作用。抑制GLS活性可诱导免疫抑制型M2-TAM向促炎型M1-TAM转化，进而增强机体的抗肿瘤免疫应答，并可能克服肿瘤细胞的耐药性[41]。研究表明，在HER2阳性胃癌中，肿瘤细胞通过细胞分裂周期蛋白42（cell division cycle 42，CDC42）激活NF-κB p65，调节GLS1的表达，并与IQ基序GTP酶激活蛋白1（IQ motif containing GTPase activating protein 1，IQGAP1）相互作用，驱动GLS1微囊泡的分泌。这一过程不仅增强了肿瘤细胞自身的Gln代谢，还借助微囊泡将代

谢产物传递给巨噬细胞，进而诱导M2-TAM极化和促血管生成功能，导致曲妥珠单抗耐药[41]。此外，TAM分泌的IL-6可以激活肿瘤细胞中的STAT3信号通路，同时上调了GSH含量，促进Gln代谢，维持ROS水平，增强肿瘤细胞耐药性[28]。在乳腺癌中，TAM经历代谢重塑，显著提升Gln代谢水平，促进ATP大量合成，这些ATP被主动分泌至胞外，经CD39与CD73作用生成腺苷。腺苷分子与T细胞表面A2A受体特异性结合后，可显著抑制T淋巴细胞活化及增殖，进而强化肿瘤组织的免疫逃避能力，最终导致耐药[42]。

CAF是肿瘤微环境中最常见的一类细胞，其通过多种机制影响肿瘤细胞的Gln代谢，增强其代谢能力和耐药性。在前列腺癌中，CAF分泌的Gln和乳酸被肿瘤耐药细胞摄取，形成代谢耦合，即肿瘤耐药细胞与CAF之间通过代谢产物的交换和共享，形成的一种协同代谢状态，因此肿瘤耐药细胞能够表现出更高效的Gln和乳酸摄取能力，并诱导线粒体氧化磷酸化，支持肿瘤细胞的代谢需求，减少ROS的产生，从而增强耐药性[43]。研究表明，GS在CAF中上调4~7倍，CAF通过GS催化氨和Glu生成Gln并分泌到胞外供肿瘤细胞摄取，该回路不仅为肿瘤细胞提供了能量支持，还使肿瘤细胞在面对药物压力时获得代谢弹性与耐药性[44]。另外，CAF中Ras信号通路的上调导致Gln合成增加，并通过巨胞饮作用使CAF能够更有效地摄取细胞外的营养物质，进一步支持其代谢需求。CAF分泌的Gln被肿瘤细胞摄取后，促进其线粒体代谢，增强能量代谢和生物合成能力[43]，肿瘤细胞通过这种代谢重编程不仅能够增强Gln代谢和线粒体代谢，还能够部分绕过雄激素剥夺治疗（androgen deprivation therapy，ADT）的抑制，在维持其能量代谢和生物合成需求的同时，使得肿瘤细胞对ADT产生耐药性。除此之外，CAF通过上调PYCR1，将Gln的γ-氮转化为Ⅰ型胶原脯氨酸羟化的必需底物脯氨酸，使得CAF中胶原分泌增多，从而导致ECM硬化，ECM的重塑阻碍了药物渗透并诱导肿瘤细胞氧化磷酸化增强，最终介导多药耐药[45]。由此可见，CAF通过分泌Gln，支持肿瘤细胞的代谢需求，形成代谢耦合，同时还可通过激活信号通路等方式，帮助肿瘤细胞在化疗药物的压力下维持生长和存活。因此，靶向CAF及其分泌的Gln等代谢产物可能成为逆转肿瘤耐药性的潜在治疗策略。

此外，肿瘤微环境内存在的各类代谢物可显著调控肿瘤细胞的Gln代谢途径，从而影响其对治疗药物的敏感性。研究表明，在NSCLL细胞系中，分别采用基础培养基与添加胎牛血清的培养基进行培养时，肿瘤细胞的Gln利用水平呈现显著区别。深入分析揭示，培养体系中的胱氨酸浓度是导致该现象的关键因素。胱氨酸经还原反应生成半胱氨酸后，可促进GSH的生物合成，从而提升细胞清除ROS的能力，并降低其对Gln代谢途径的依赖程度。由于胎牛血清富含胱氨酸成分，这些胱氨酸分子通过特定转运蛋白进入胞内，引起细胞质内Glu浓度上升，这一系列代谢重编程过程最终削弱了肿瘤细胞对Gln的代谢需求，致使CB-839等Gln酶抑制剂的抗肿瘤效果受到限制[46]。因此，肿瘤微环境中代谢底物的变化可通过调控Gln代谢通路及细胞内氧化还原稳态，改变肿瘤细胞对代谢靶向药物的敏感性，最终诱导耐药性的形成。

Gln在肿瘤微环境中通过调节代谢途径、影响免疫细胞功能以及促进肿瘤细胞代偿的机制，最终导致肿瘤产生耐药性。因此，靶向Gln代谢可能是克服肿瘤耐药性的重要策略，但需要结合肿瘤微环境的异质性进行综合治疗。

3.4 Gln代谢与蛋白质翻译后修饰

Gln代谢能够通过影响蛋白质的翻译后修饰来促进肿瘤的耐药性。Gln类似物6-重氮-5-氧代-L-正亮氨酸-3-8（6-diazo-5-oxo-L-norleucine，DON）处理胰腺癌细胞，能够提高肿瘤细胞对化疗药物吉西他滨的敏感度。研究发现，DON能够抑制细胞内的己糖胺生物合成途径，进而改变细胞中蛋白质的糖基化修饰水平，这种修饰的变化最终影响了肿瘤细胞对化疗的敏感度[47]。此外，最新研究表明，Gln剥夺引起的DNA高甲基化是可逆的，补充Gln或α-KG即可恢复去甲基化能力，提示周期性Gln代谢干预可避免持续耐药[34]。

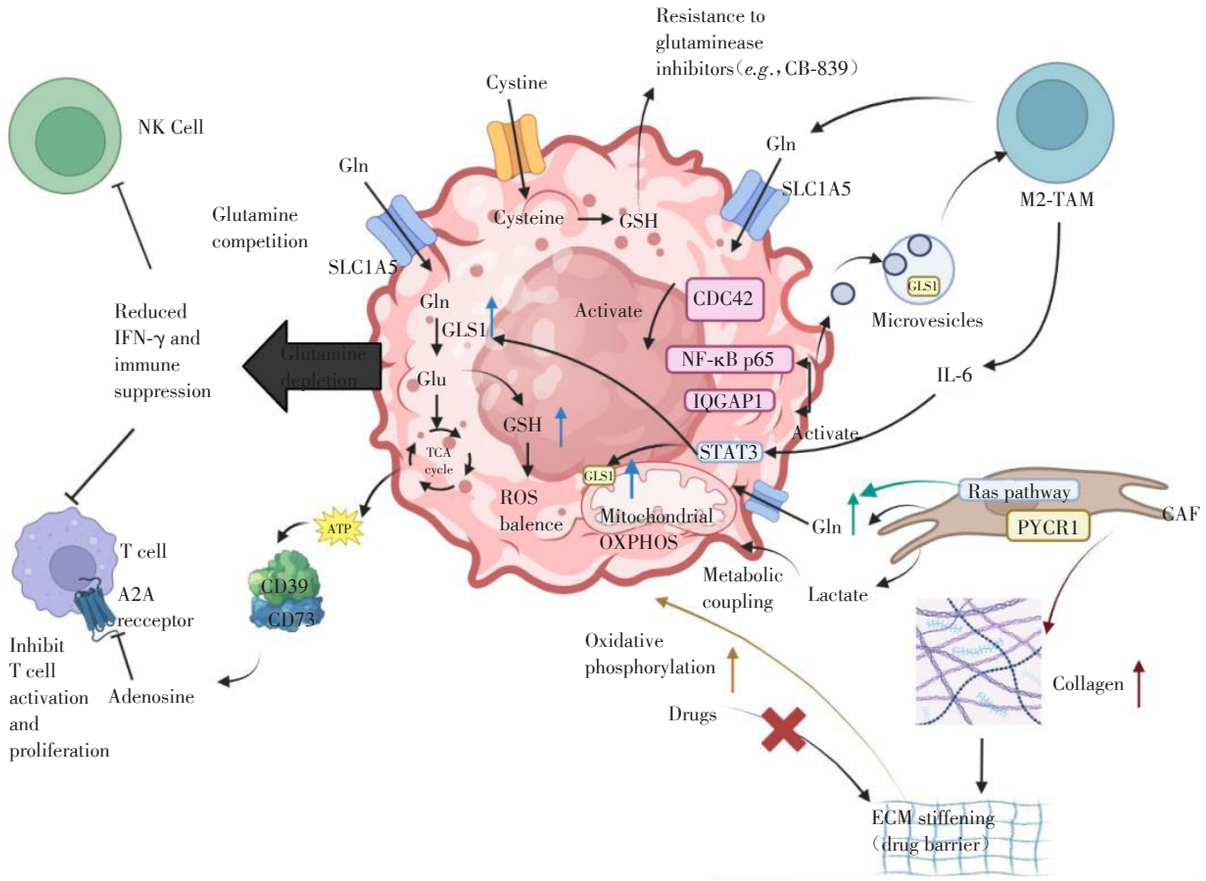
3.5 Gln代谢与表观遗传调控

肿瘤细胞能够通过调控表观遗传诱导耐药性的产生。以KRAS突变的结肠癌细胞为例，SLC25A22（一种线粒体Glu/H^+转运蛋白）可促进Gln代谢产物琥珀酸的积累，进而引起DNA局部甲基化水平上升，激活Wnt信号通路，从而增强结肠癌细胞对化疗药物的耐受性[48]。相反，在Gln匮乏或应用Gln代谢抑制剂的情况下，肿瘤细胞中的DNA损伤修复酶ALKBH因缺乏其底物α-KG而受到抑制，导致DNA烷基化损伤的积累，使肿瘤细胞对DNA烷化剂的敏感性增加[49]。这些研究揭示了Gln代谢通过影响表

观遗传机制，能够导致肿瘤细胞对化疗药物耐药。

3.6 Gln代谢与DNA损伤修复

肿瘤细胞能够通过提升核苷酸代谢水平以及DNA损伤修复能力，抵御化疗药物或放疗引发的DNA损伤，进而促使耐药性形成。核苷酸代谢是细胞合成DNA和RNA的基础，其代谢过程涉及多种酶和代谢途径。5-氟尿嘧啶（5-fluorouracil，5-FU）是一种经典的抗代谢药物，主要用于治疗结直肠癌等肿瘤，在某些结直肠癌细胞中，Gln代谢增强通过提供更多的代谢中间体，支持核苷酸代谢的进行，并通过增强核苷酸代谢，补充因5-FU抑制而减少的核苷酸池，从而维持DNA合成和修复的正常进行，这种代谢重编程使得肿瘤细胞能够抵抗5-FU的毒性作用，进而发展耐药性[50]。顺铂耐药细胞对营养匮乏的敏感性与其对Gln的显著依赖性密切相关，即在营养匮乏条件下，这些细胞更容易死亡，原因在于它们高度依赖Gln以维持生存和生长。而在某些顺铂耐药肿瘤细胞中，Gln主要通过参与核苷酸的生物合成途径发挥作用，而非参与TCA循环或氧化还原反应。Obrist等[51]研究表明，补充Gln可以挽救



Tumor cells competitively uptake Gln from the microenvironment through high expression of SLC1A5 and GLS1, leading to local Gln depletion and establishing a Gln competition microenvironment. This nutrient scarcity forces metabolic reprogramming in T cells and natural killer cells, resulting in reduced IFN-γ secretion and subsequent immune suppression. Concurrently, tumor cells activate NF-κB p65 *via* CDC42 and interact with IQGAP1 to drive the secretion of GLS1-containing microvesicles, which induce M2-type tumor-associated macrophage (TAM) polarization. M2-TAM secretes IL-6 to activate STAT3 signaling in tumor cells, further upregulating GLS1 expression and glutathione synthesis, thereby forming a positive feedback loop. In addition, TAM converts ATP into adenosine *via* CD39 and CD73; adenosine then binds to the A2A receptor on the surface of T cells, inhibiting T cell activation and proliferation. Cancer-associated fibroblasts form a metabolic coupling with tumor cells, secreting Gln and lactate that are taken up by tumor cells. This enhances mitochondrial oxidative phosphorylation, maintains reactive oxygen species homeostasis, and confers resistance to glutaminase inhibitors (*e.g.*, CB-839). Activation of the Ras signaling pathway in CAF increases Gln synthesis. Furthermore, CAF promotes collagen secretion and extracellular matrix stiffening through upregulation of PYCR1, thereby forming a drug barrier that impedes drug penetration and ultimately leads to multidrug resistance.

图4 肿瘤微环境中谷氨酰胺代谢介导的耐药机制

Figure 4 Mechanisms of glutamine metabolism-mediated drug resistance in the tumor microenvironment

顺铂耐药细胞免受饥饿诱导的死亡。Tardito等[52]研究指出，促进TCA循环并不能有效抑制Gln缺乏的铂耐药GBM细胞的死亡。进一步的质谱代谢组学研究和对Gln代谢的特定干预揭示，在这些顺铂耐药细胞中，补充的Gln主要用于核苷酸的生物合成，从而促进肿瘤细胞的增殖并导致耐药。在曲妥珠单抗耐药的乳腺癌模型中，肿瘤细胞通过上调NADH脱氢酶（泛醌）1α亚复合物亚基4类似蛋白2（NADH dehydrogenase[ubiquinone]1 alpha subcomplex subunit 4-like 2，NDUFA4L2）显著增强核苷酸合成与线粒体呼吸，快速补充dNTP池并提高Gln驱动的NADPH产出，从而有效清除ROS、减轻DNA损伤，与此同时，Gln代谢为DNA损伤修复通路提供稳定的核苷酸供应和能量，使细胞得以逃避曲妥珠单抗诱导的凋亡，最终导致获得性耐药与患者的不良预后[50]。

4 Gln代谢的代偿网络与耐药形成

肿瘤细胞在面临Gln代谢靶向干预时，可激活多层次代偿机制以维持代谢稳态和存活能力，这是导致单药治疗失败的核心原因。基于现有研究，文章系统梳理了Gln代谢的四大代偿网络（图5）。

转运体层面的代偿构成了肿瘤细胞抵御Gln摄取抑制的首要防线。当SLC1A5被抑制后，肿瘤细胞可通过上调SLC38A2维持Gln摄取能力。研究表明，V-9302虽能有效抑制SLC1A5，但同时阻断SLC38A2，导致其抗肿瘤效应难以区分靶点特异性，而SLC1A5基因敲除的癌细胞可完全依赖SLC38A2代偿，恢复Gln内流和细胞增殖[53]。

在代谢酶层面，GLS1抑制触发了更为广泛的代谢重编程。肿瘤细胞通过多种途径回补α-KG以维持TCA循环：一方面增强脂肪酸氧化（fatty acid oxidation，FAO）直接提供乙酰辅酶A进入TCA循环，另一方面上调磷酸戊糖途径（pentose phosphate pathway，PPP）产生NADPH以维持氧化还原稳态，同时激活糖酵解增强乳酸生成，通过乳酸-丙酮酸循环间接补充TCA循环中间产物[54]。尤为关键的是，在CB-839耐药的TNBC细胞中，FAO相关基因肉碱棕榈酰转移酶1A（carnitine palmitoyltransferase，CPT1A）表达显著上调，形成“Gln-脂肪酸”代谢转换[55]。

与此同时，抗氧化系统也启动相应的补偿机制。GLS1抑制导致Glu生成减少、GSH合成受限时，肿瘤细胞可通过增强SLC7A11介导的胱氨酸摄取，直接利用外源性半胱氨酸绕过Glu依赖的GSH合成途径[3]。

更为复杂的是，微环境层面的代谢耦联为肿瘤细胞提供了外部支持。当肿瘤细胞自身Gln合成受阻时，可诱导CAF高表达GS，将Glu和氨转化为Gln并分泌至胞外，形成“CAF-肿瘤细胞”代谢耦联[43]。这种代谢偶联不仅限于CAF，TAM等基质细胞同样可通过Gln分泌支持肿瘤细胞存活。

5 Gln代谢-微环境-免疫逃逸三维耐药模型

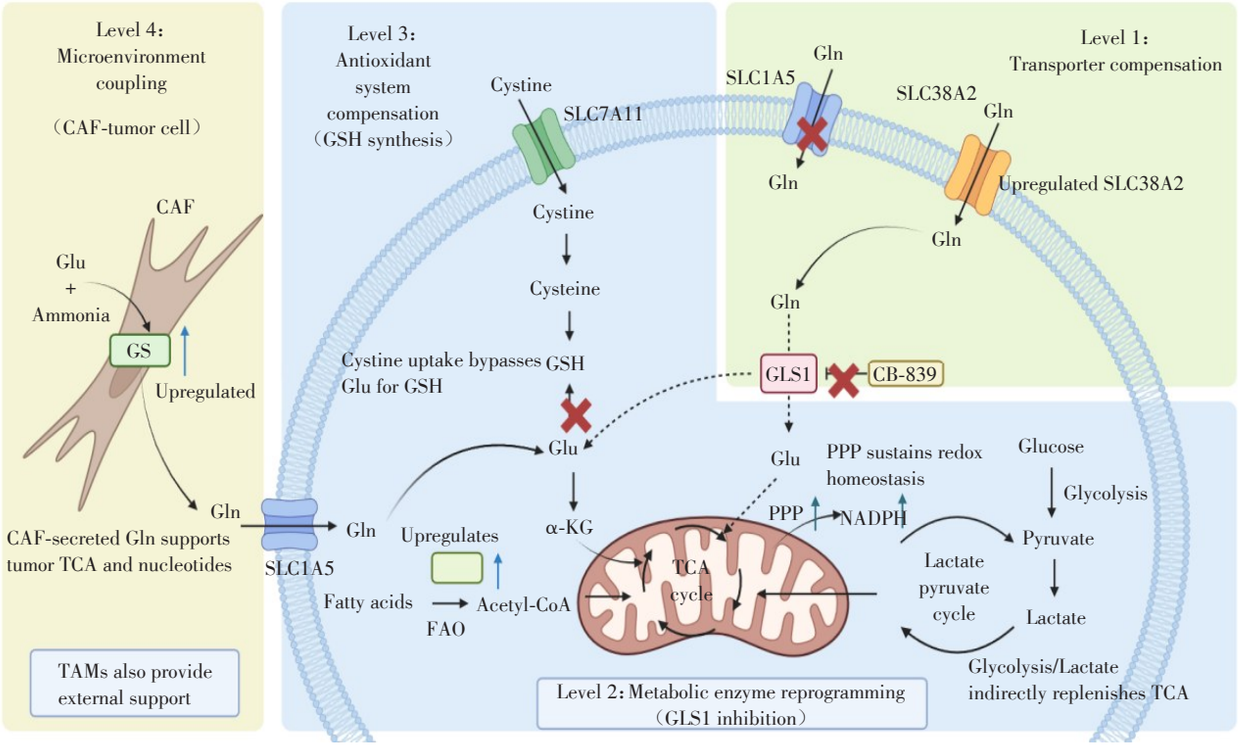
传统肿瘤耐药研究多聚焦于单一维度（代谢酶、转运体或微环境）解析Gln代谢与耐药的关系，然而，临床实践中单纯靶向Gln代谢（如CB-839）虽能抑制肿瘤细胞增殖，却常因微环境代谢重塑和免疫抑制而失效；单纯免疫检查点抑制剂（如PD-1抗体）在“冷肿瘤”中响应率低下，这些均提示代谢、微环境、免疫三者形成动态互作网络，共同驱动耐药。于是，笔者首次提出“Gln代谢-微环境-免疫逃逸”三维耐药模型，旨在整合多维度机制，为克服耐药提供系统性干预框架。

5.1 三维模型的交互机制

三维模型由3个相互作用的维度构成：代谢重编程、微环境重塑以及免疫逃逸。3个维度通过正反馈环路相互强化，最终形成药物抵抗、肿瘤进展和转移复发的耐药表型（图6）。

肿瘤细胞的代谢掠夺通过多重机制重塑微环境。肿瘤细胞高表达SLC1A5和GLS1，将微环境Gln浓度从正常水平迅速降至T细胞活化所需阈值以下，导致T细胞线粒体功能障碍和免疫抑制[56]。在胰腺癌模型中，肿瘤细胞SLC1A5过表达并通过竞争性摄取Gln形成代谢剥夺微环境，导致$CD8^+$T细胞毒性降低、耗竭评分增加，PD-1治疗效果受限[16]，这一证据直接支持代谢-微环境-免疫的因果链。同时，GLS1分解Gln产生的大量氨加速了Treg募集，形成“代偿性免疫抑制”[57]。有研究进一步证实，氨代谢重编程激活CAF的促肿瘤表型，形成代谢-基质恶性循环[44]。

微环境营养缺乏与代谢废物堆积激活免疫细胞应激通路，驱动促肿瘤表型极化，TAM的M2极化是核心环节。微环境Gln缺乏使TAM线粒体氧化磷酸化受阻，AMPK激活后STAT6磷酸化，上调IL-10等M2标志物[58]，最终分泌IL-6、转化生长因子-β和血管内皮生长因子促进肿瘤细胞上皮间质转化和耐药[59]。前文所提及的HER2阳性胃癌中肿瘤细胞通过外泌体传递GLS1至TAM，增强其Gln代谢能力，诱导M2极化和曲妥珠单抗耐药，也是代谢-微环



Level 1（transporter compensation）: following SLC1A5 inhibition, tumor cells maintain Gln uptake by upregulating SLC38A2. Level 2（metabolic enzyme reprogramming）: when the conversion of Gln to Glu is blocked by GLS1 inhibitors（*e.g.* CB-839）, tumor cells compensate by enhancing fatty acid oxidation to directly supply acetyl-CoA to the tricarboxylic acid cycle. Concurrently, they upregulate the pentose phosphate pathway to generate NADPH for maintaining redox homeostasis and activate glycolysis to indirectly replenish TCA cycle intermediates *via* the lactate-pyruvate shuttle. Level 3（antioxidant system compensation）: when reduced Glu availability limits glutathione synthesis, tumor cells enhance cystine uptake *via* SLC7A11, directly utilizing exogenous cysteine to bypass the glutamate-dependent GSH synthesis pathway. Level 4（microenvironmental metabolic coupling）: tumor cells induce cancer-associated fibroblasts to highly express GS, which converts Glu and ammonia into Gln for secretion into the extracellular space, establishing a“CAF-tumor cell”metabolic coupling. Additionally, tumor-associated macrophages can also provide exogenous Gln to support tumor cells.

图5　谷氨酰胺代谢四大代偿网络

Figure 5　Four compensatory networks of glutamine metabolism

境-免疫三维互作的直接证据。

免疫抑制细胞分泌细胞因子激活肿瘤细胞信号通路，进一步强化代谢重编程，形成闭环，IL-6-STAT3-GLS1正反馈环是核心机制[60]。M2-TAM分泌的IL-6结合肿瘤细胞IL-6R，激活肿瘤细胞STAT3，上调GLS1转录，增强Gln分解，产生大量氨，进一步促进M2-TAM极化，形成“代谢-免疫”正反馈闭环。

5.2　三维模型的临床验证与转化价值

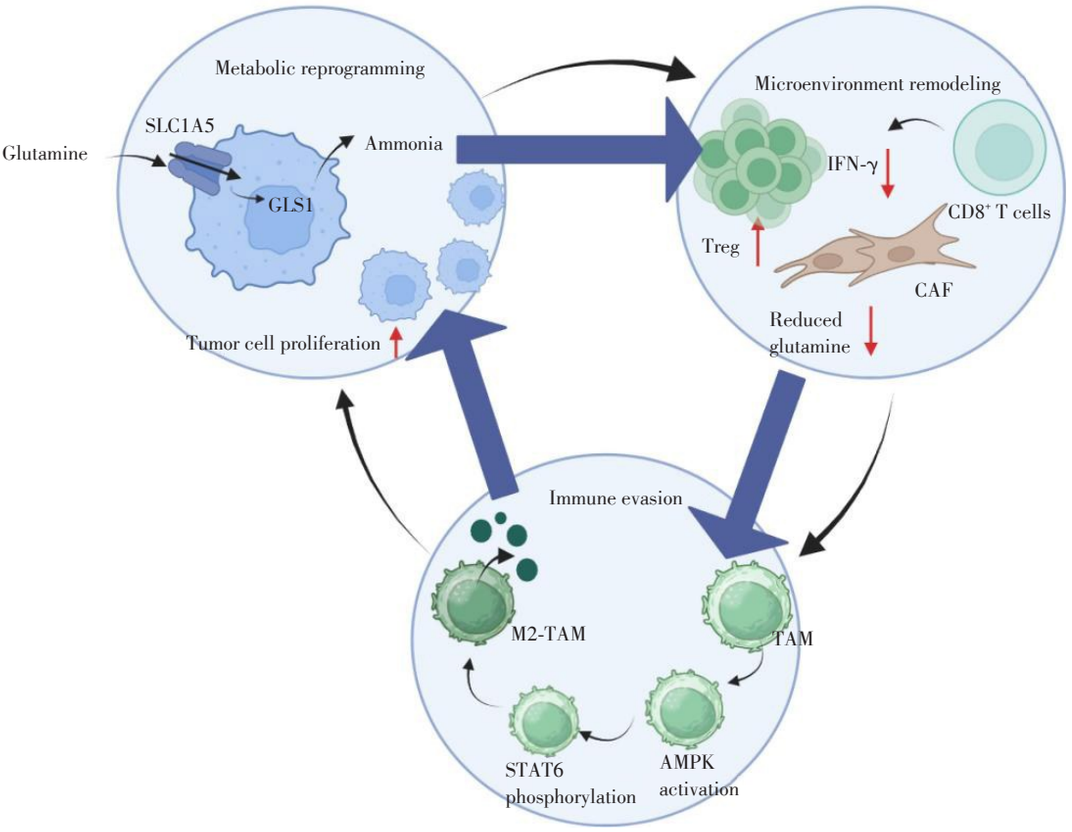
三维模型在多种癌种中获得临床相关性验证。胰腺癌中，SLC1A5高表达、微环境Gln缺乏及Treg比例升高构成的高三维评分患者，对吉西他滨联合PD-1治疗反应较差，而低评分患者疗效显著改善[41]。GBM中，IL-6-STAT3-GLS1环路和T细胞耗竭构成三维网络，联合靶向该环路可显著延长生存期[60]。

基于三维模型，笔者提出“代谢抑制-微环境调控-免疫激活”三维联合治疗原则，通过同时阻断肿瘤细胞代谢代偿、重塑免疫抑制性微环境并恢复抗肿瘤免疫功能，以克服肿瘤细胞对单一代谢靶向药物的耐药局限。

5.3　模型的创新性与局限性

三维模型通过多维度整合突破单一代谢或单一免疫视角，直接解释为何代谢靶向必须与免疫治疗联合。同时，具有明确的转化导向，每个维度都对应可干预的靶点，能够直接指导临床试验的设计。

然而，该模型目前也存在一定局限性。其临床验证尚不充分，现有证据多为临床前模型，前瞻性临床试验仍在进行中；其次，定量工具有待完善，缺乏经过临床验证的三维评分标准；此外还存在癌症类型特异性问题，在血液肿瘤和部分免疫热肿瘤中的适用性有待进一步验证。



The three-dimensional resistance model of Gln metabolism-microenvironment-immune evasion consists of three interacting dimensions. Metabolic reprogramming dimension (upper left): tumor cells highly express SLC1A5 and GLS1 to extensively uptake and catabolize Gln, producing ammonia and promoting tumor cell proliferation. Microenvironment remodeling dimension (upper right): metabolic scavenging leads to Gln depletion in the microenvironment, resulting in reduced IFN-γ secretion and functional impairment of $CD8^+$ T cells. The substantial ammonia generated from GLS1-mediated Gln catabolism accelerates regulatory T cell recruitment. Concurrently, ammonia metabolic reprogramming activates the pro-tumorigenic phenotype of cancer-associated fibroblasts, establishing a metabolic-stromal vicious cycle. Immune evasion dimension (lower): nutrient scarcity in the microenvironment impairs mitochondrial oxidative phosphorylation in tumor-associated macrophages. Following AMPK activation, STAT6 phosphorylation drives M2-type polarization, leading to the secretion of cytokines such as IL-6. The three dimensions mutually reinforce one another through positive feedback loops: IL-6 secreted by M2-TAM activates STAT3 signaling in tumor cells, which further upregulates GLS1 expression, thereby forming a "metabolic-immune" closed loop. Collectively, these interactions drive drug resistance, tumor progression, metastasis, and recurrence.

图6　谷氨酰胺代谢-微环境-免疫逃逸三维耐药模型的交互机制

Figure 6　The interaction mechanisms of the "glutamine metabolism-microenvironment-immune evasion" three-dimensional drug resistance model

6　总结与展望

Gln代谢在肿瘤耐药中的作用机制已逐渐被揭示，其通过多种途径影响肿瘤细胞的生物学行为和对治疗的反应（表2）。一方面，Gln代谢通过影响相关代谢酶和转运体的活性，调控肿瘤细胞的代谢重编程，进而影响肿瘤耐药性。另一方面，Gln代谢还通过重塑肿瘤微环境，促进免疫抑制细胞（如M2型巨噬细胞和调节性T细胞）的极化，削弱抗肿瘤免疫反应，从而进一步加剧肿瘤耐药性。此外，Gln代谢还通过调节DNA损伤修复、蛋白质翻译后修饰以及代谢产物的积累，增强肿瘤细胞的生存能力，使其能够抵抗化疗和靶向治疗的攻击。

尽管如此，当前研究仍面临诸多挑战。首先，Gln代谢在肿瘤中的具体作用机制尚未完全明晰，不同肿瘤类型以及同一肿瘤不同发展阶段中Gln代谢的差异还需深入研究，以便更精准地针对不同情况制定治疗策略。其次，虽然已经发现了一些Gln代谢相关的潜在治疗靶点，但开发出高效、不良反应小且具有良好药代动力学特性的药物并将其运用于临床仍面临巨大困难，药物在体内的稳定性、靶向性以及如何避免产生耐药性等问题亟待解决

表2 谷氨酰胺代谢与肿瘤耐药相关重大研究进展（2020-2025）

Table 2 Major research advances in glutamine metabolism and tumor drug resistance（2020-2025）

Year	Core discovery	Key target	Tumor type	Resistance mechanism	Clinical translational significance	Reference
2020	SLC25A22 - mediated glutamine metabolism promotes 5 - FU resistance in KRAS - mutant colorectal cancer	SLC25A22, succinate, Wnt pathway	Colorectal cancer	Succinate accumulation induces DNA hypermethylation, activates Wnt signaling, and enhances stemness properties	Suggests that combined metabolic intervention with epigenetic drugs can reverse resistance	[48]
2021	SLC7A11 in KRAS-mutant pancreatic cancer resists ferroptosis induction by maintaining GSH synthesis	SLC7A11, GSH -GPX4	Pancreatic cancer	High SLC7A11 expression promotes cystine uptake, maintains GSH synthesis, inhibits lipid peroxidation, resists ferroptosis, leading to resistance to ferroptosis inducers in KRAS - mutant pancreatic cancer	First validation of the SLC7A11 - GSH axis resistance mechanism in KRAS-mutant tumors	[36]
2021	SLC1A5 upregulation by HIF - 2α in pancreatic cancer enhances glutamine uptake and gemcitabine resistance	SLC1A5, HIF - 2α	Pancreatic cancer	Glutamine - dependent ATP and GSH synthesis enhanced, antioxidant capacity and energy supply	Suggests targeting SLC1A5 variants or combining with HIF - 2α inhibitors	[30]
2022	Apatinib induces amino acid imbalance and activates ATF4 to reprogram glutamine metabolism, leading to resistance	ATF4, SLC1A5, ASNS, GCN2/eIF2α	Non - small cell lung cancer	Apatinib induces amino acid metabolic imbalance, activates the GCN2/eIF2α/ATF4 amino acid stress response pathway, upregulates SLC1A5 and ASNS expression, promotes glutamine uptake and metabolism, forming adaptive resistance	Combined inhibition of ATF4 reverses resistance, providing a new strategy to overcome targeted therapy resistance	[1]
2023	First discovery of the important role of SLC38A5 as a novel glutamine transporter in tumor resistance	SLC38A5, GSH, PI3K/AKT/mTOR - SREBP1-SCD1	Pancreatic cancer, breast cancer, and multiple tumors	SLC38A5 mediates glutamine uptake, inhibits ferroptosis through GSH synthesis antioxidant or PI3K/AKT/mTOR - SREBP1 - SCD1 axis, promoting chemotherapy resistance	SLC38A5 as a novel metabolic target and resistance marker, providing precision intervention strategies for chemotherapy resistance in pancreatic cancer, breast cancer, etc.	[38]
2023	CAF - tumor cell glutamine metabolic coupling: CAF - secreted glutamine supports tumor cell survival and promotes resistance	CAF, GS, SLC1A5	Breast cancer, pancreatic cancer	CAFs highly express GS to catalyze glutamine synthesis and transport it to tumor cells, promoting their glutamine-addictedmetabolism and enhancing chemotherapy resistance	First systematic elucidation of the microenvironment metabolic coupling resistance mechanism, providing a basis for targeting CAF	[43]

（续表2）

Year	Core discovery	Key target	Tumor type	Resistance mechanism	Clinical translational significance	Reference
2024	circCOL1A1 promotes glutaminolysis through the miR-214-3p/GLS1 axis	circCOL1A1 miR-214-3p, GLS1	Colorectal cancer	Enhances glutamine catabolism, provides energy and biosynthetic precursors, promotes tumor proliferation and metastasis	circCOL1A1 as a prognostic marker, targeting this axis can inhibit tumor metabolism and progression	[24]
2025	The mitochondrial glutamine transporter SLC1A5_var and its allosteric inhibitor iMQT-020 achieve spatially specific targeting of tumor glutamine metabolism for the first time	SLC1A5_var, iMQT-020 (allosteric inhibitory site)	Pancreatic cancer, lung cancer, breast cancer, and multiple solid tumors	iMQT-020 blocks mitochondrial glutamine uptake, leading to TCA cycle impairment, reduced GSH synthesis, and ROS accumulation, triggering energy crisis and oxidative stress, and inducing tumor cell death	Highly selective and low-toxicity metabolic inhibitor, synergistic with PD-1/PD-L1 antibodies, providing a new strategy to overcome GLS inhibitor resistance	[31]

（表3）。再者，肿瘤细胞具有高度的异质性和适应性，在针对Gln代谢进行治疗时，肿瘤细胞可能会通过其他代谢途径的代偿来维持生存和增殖，如何全面阻断肿瘤的代谢逃逸途径也是未来研究需要攻克的重点。

此外，Gln代谢的复杂性也提示单一靶点的干预可能难以取得理想的治疗效果，联合治疗策略的开发显得尤为重要。总之，Gln代谢在肿瘤耐药中

表3　Gln代谢靶向药物临床转化现状（按靶点类型分类）

Table 3　Clinical translation status of glutamine metabolism-targeted drugs (classified by target type)

Target type	Representative drug	Development stage	Clinical trial result	Core failure reason	Reference
Transporter inhibitor	V-9302 (SLC1A5 inhibitor)	Preclinical (discontinued)	Showed antitumor activity in preclinical studies, but efficacy was not related to SLC1A5 inhibition	Lack of target specificity: simultaneously inhibits multiple amino acid transporters; significant off-target effects	[61]
	iMQT-020 (SLC1A5_var, mitochondria-specific)	Preclinical optimization stage	Pancreatic cancer model: 75% tumor suppression, 40% CR rate when combined with PD-1, high selectivity, low toxicity	Not yet entered clinical validation	[31]
Metabolic enzyme inhibitor	CB-839 (GLS1 inhibitor)	Phase Ⅱ (discontinued)	RCC combined with everolimus: PFS HR=0.83 (P=0.29); TNBC and CRC did not meet endpoints; monotherapy in NSCLC failed	① Metabolic compensation: FAO ↑, glycolysis ↑, SLC7A11-GSH loop activation; ② Lack of biomarkers: did not screen for MYC/LKB1-high expression population; ③ Normal tissue toxicity: high GLS1 expression in intestine/kidney	[62]
	BPTES (GLS1 inhibitor)	Preclinical (discontinued)	Poor water solubility, poor pharmacokinetics, did not enter clinic	Physicochemical property limitations: poor druggability, low bioavailability	[63]
Combination regimen	CB-839 + Everolimus	Phase Ⅱ (partially positive)	TNBC: significantly inhibited tumor proliferation, overcame monotherapy resistance	Combination strategy relatively successful	[64]

的作用机制复杂且多样，其研究不仅为理解肿瘤耐药提供了新的视角，也为开发新型治疗策略带来了希望。未来研究应聚焦于开发双靶点抑制剂，阻断代偿环路，同时探索“代谢-免疫”联合方案，解析不同恶性肿瘤特异性代偿网络，避免“一刀切”式临床试验。只有系统阐明Gln代谢的时空异质性，才能真正把代谢靶向药物推向耐药肿瘤治疗的临床一线。

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Conflict of Interests：

All authors declare no competing interests.

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Chen Yiwen was responsible for literature collection and manuscript writing. Zhang Jingjing was responsible for manuscript revision. Zhang Xiongfei was responsible for supervising topic selection, confirming the research direction, and revising the manuscript.

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