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Advances in metabolic research on gastric cancer and its therapeutic implications

YANG Yanping[1], XIAO Wenxuan[1], ZHAO Jiaoya[1], LIU Yi[1, 2]
1. Xi'an Medical University, Xi'an, Shaanxi 710021, China
2. Department of Oncology, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi 710021, China
Corresponding author: LIU Yi, E-mail: liuyi926999@yeah.net

Abstract: Gastric cancer has extensive metastasis and high mortality, and its pathogenesis has not been fully understood. The advent of metabolomics has brought metabolic regulation and cancer research into the spotlight. This article provides an overview of the important metabolic changes caused by gastric cancer, and their therapeutic significance is considered and prospected.
Keywords: Gastric cancer; Glycolysis; Glutaminolysis; Lipid metabolism
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According to the Global Cancer Statistics in 2020, the incidence of gastric cancer ranks fifth, and the mortality ranks fourth worldwide [1]. Gastric cancer is characterized by extensive metastasis and high mortality. Currently, chemotherapy is the primary treatment for metastatic gastric cancer, but the efficacy of chemotherapy is common affected by drug resistance, leading to treatment failure. The mechanism of chemotherapy resistance in gastric cancer is complex and influenced by multiple factors, among which metabolism plays a pivotal role. Alterations in cell metabolism are recognized as a hallmark of malignant tumors [2]. Gastric cancer induces changes in metabolism, providing therapeutic opportunities. Cancer cells exploit metabolic processes for survival, growth, metastasis in a variety of tissue microenvironments and acquire therapeutic resistance. Metabolically targeted chemotherapy has proven effective in cancer treatment, highlighting a therapeutic window that targets malignant metabolism. The study of metabolic changes will provide new strategies for the treatment of gastric cancer, some of which are being evaluated in preclinical models or clinical trials. Relevant research progress is summarized below.

1 Glycolysis and gastric cancer

Tumor cells consume large amounts of glucose for glycolysis even in oxygen abundant environments [3]. Despite its low energy efficiency, glycolysis creates an acidic microenvironment conducive to angiogenesis, tumor progression, and immune evasion [4-5].

Hexokinase (HK), a key enzyme in glycolysis, comprises four HK isotypes (HK1-4), with only HK2 isotype associated with Warburg effect. The expression of HK2 in normal cells is very low or absent [6]. Liu *et al.* [7] analyzed 2 532 cases of solid cancer (including 585 cases of gastric cancer) and showed that increased HK2 expression was associated with poor prognosis. *Shao et al.* [8] reported that SALL4, a zinc finger protein transcription factor, promoted gastric cancer progression through HK2-mediated glycolysis. Li *et al.* [9] observed significant down-regulation of miR-181b in human gastric cancer cells. By targeting its 3'-untranslated region, miR-181b directly inhibited the expression of HK2, a key enzyme in the first step of glycolysis, thereby negatively regulating the glycolysis of gastric cancer cells.

Aldolase (ALDO) catalyzes the cleavage of Fructose 1,6-bisphosphatase (FBP) into dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate [10]. Three aldolase isozymes, ALDOA, ALDOB, and ALDOC, have been identified. ALDOA is the most prevalent subtype reported in almost all kinds of malignant tumors [11]. Jiang *et al.* [12] found high expression of ALDOA in 70.6% of 252 gastric cancer patients, and its expression was an independent prognostic factor for 5-year overall survival (OS) and disease-free survival (DFS) of gastric cancer patients. Silencing the expression of ALDOA by shRNA transfection significantly reduced the growth, proliferation and invasion ability of gastric cancer cell lines.

Enolase catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Three types of enolases have been described in mammals: α-enolase (ENO1), β-enolase, and γ-enolase. Only ENO1 is overexpressed in more than 20 types of malignant tumors, including gastric cancer [13]. Qiao *et al.* [13] found ENO1 overexpression in 56% of 94 gastric cancer tissues and 17% of 53 normal tissues, and the high expression of ENO1 was associated with poor prognosis. In addition, ENO1 was found to be overexpressed in gastric cancer cell lines, and knockdown of ENO1 could inhibit the

proliferation and colony formation and promote apoptosis of gastric cancer cells. Yang *et al.* [14] confirmed the association of high ENO1 expression with poor prognosis in gastric cancer patients, suggesting that ENO1 was involved in the regulation of stem cell-like properties of gastric cancer cells. Qian *et al.* [15] found the increased expression of ENO1 in cisplatin resistant cells of gastric cancer, and knockout of ENO1 by siRNA transfection significantly reduced glycolysis and reversed cisplatin resistance.

Pyruvate kinase (PK) is a rate-limiting enzyme that catalyzes the final steps of glycolysis. There are four PK subtypes in mammals (L, R, M1, and M2), with PKM2 specifically prevalent in tumor cells [16]. Lim *et al.* [17] found observed PKM2 expression in 144 (39.1%) out of 368 human gastric cancer tissues, noting a close association between PKM2 expression and gastric cancer differentiation. PKM2 positive cells accounted for 63.6% in highly differentiated adenocarcinomas, but only 17.7% in signet-ring cell carcinoma (SRCC). Moreover, PKM2 expression was correlated with shorter OS only in SRCC ($P < 0.05$). Shiroki *et al.* [18] reported significantly elevated PKM2 expression in cancer tissues compared to non-cancerous tissues. Knockout of the PKM2 gene led to notable reductions in proliferation, migration, unanchored growth, and spheroidal formation of gastric cancer cells *in vitro*, alongside diminished tumor growth and liver metastasis *in vivo*.

Lactate dehydrogenase (LDH) plays a pivotal regulatory role in glycolysis, comprising five active LDH isoenzymes, mainly composed of A subunit and B subunit. Elevated serum LDH levels are commonly observed in malignant tumor patients and correlate with poor prognosis and treatment resistance. The determination of LDH has become an important auxiliary tool for cancer diagnosis and treatment efficacy monitoring [19]. Sun *et al.* [20] reported a high LDHA expression rate of 76% in 264 gastric cancer specimens, revealing a negative correlation between LDHA expression and OS. The expression of LDHA in gastric cancer was an independent prognostic risk factor for OS. In addition, LDHA knockout in gastric cancer cell lines inhibited in vitro and in vivo cell growth, concurrently reducing lactic acid and ATP production in gastric cancer cells.

2 Glutamine catabolism and gastric cancer

The transition of glutamine-derived nitrogen metabolism from glutamine decomposition to *de novo* nucleotide biosynthesis contributes to the malignant evolution of cancer [21]. Through glutamine decomposition, tumors metabolize large amounts of glutamine into glutamate and ammonia. Glutamic acid is converted to alpha-ketoglutaric acid (α-KG), a process facilitated by oxidative phosphorylation (OXPHOS) and fatty acid (FA) metabolism, providing energy for the Krebs cycle. Simultaneously, glutamate serves as a nitrogen donor for the synthesis of nucleic acids, non-essential amino acids, and glutathione, which is crucial for maintaining the REDOX state [22]. The metabolism of glucose and glutamine coordinates the production of energy and the synthesis of macromolecules, especially the synthesis of FA and reduction equivalents [23]. Glutamine is transported into the cell through the plasma membrane by the transporters SLC1A5, SLC38A1 and SLC38A2. Glutamine is hydrolyzed by glutaminase (GLS) to produce glutamate and ammonia. Wang *et al.* [24] observed elevated levels of glutamate in gastric cancer patients, suggesting a correlation between glutamate and tumor progression. There are at least three subtypes of GLS: GLS1, GLS2, and GAC, all of which are found in mitochondria [25]. GLS was expressed in various gastric cancer cell lines, with increased expression observed under hypoxic conditions. *In vitro* experiments, siRNA knockdown of GLS1 can lead to growth inhibition, while BPTES (GLS inhibitors) have anti-tumor effects on GLS1 overexpressed gastric cancer cell line OCUM-2MD3/hypo cell transplanted tumor mice [26]. Quantitative proteomics studies based on isotope labeling further provided evidence for GLS1 overexpression in gastric cancer. These studies reported a 1.68-fold increase in GLS1 expression, with 75.6% of gastric cancer tissues showing GLS1 overexpression compared to 19.1% in para-cancer tissues. This information collectively supports the significance of glutamine metabolism, specifically GLS1, in the context of gastric cancer development and node metastasis [27]. Wu et al. [28] found the glutamate dehydrogenase (GLUD) expression in all 144 untreated gastric cancer patients, and the higher the GLUD expression, the worse the prognosis. In addition, GLUD silencing by shRNA in gastric cancer cells has been confirmed to have antitumor effects *in vitro* and *in vivo* experiments.

3 Lipid metabolism and gastric cancer

3.1 Fatty acid synthesis metabolism

In the lipid/lipid-soluble phenotype, malignant tumor cells require a large amount of *de novo* synthesis of fatty acids. Because fatty acids are components of cell membranes and are the basis for the synthesis of lipid derivatives for cell signal transduction, so tumors exhibit overexpression of enzymes required for their synthesis [29].

ATP-citrate lyase (ACLY) is a recognized important enzyme for *de novo* synthesis of fatty acids. Acetyl-CoA, an important component of endogenous fatty acid and cholesterol biosynthesis, is produced by ACLY catalyzing the conversion of citric acid to oxaloacetic acid in cytoplasm, providing energy for tumor cell growth and metabolism. Qian *et al.* [30] analyzed ACLY expression of 83 gastric cancer patients, and found a higher ACLY expression in 61% gastric cancer patients. Moreover, patients with elevated ACLY expression levels experienced significantly shorter survival times compared to those with lower expression levels (23 months *vs* 78

months, *P*=0.031). Cheng *et al.* [31] confirmed that miR-133b targeted ACLY and inhibited the proliferation of gastric cancer cells by regulating the expression of peroxissome proliferator-activated receptor-γ (PPARγ), indicating miR-133b could potentially serve as a tumor inhibition target in the treatment of gastric cancer.

Acetyl-CoA carboxylase (ACC) converts acetyl-CoA to malonyl-CoA, which provides the two-carbon building blocks to produce more FA. In mammals, ACC1 and ACC2 are two members of the acetyl-CoA carboxylase family. ACC1, located in the cytoplasm, acts as the initial rate-limiting enzyme in the *de novo* FA synthesis pathway, while ACC2, situated in the outer mitochondrial membrane, generates malonyl-CoA and regulates the activity of carnitine palmitoyltransferase 1 (CPT1) involved in FA β-oxidation [32]. ACC is mainly regulated by AMP-activated protein kinase (AMPK), which inactivates the enzyme through phosphorylation, and protein phosphatase 2A (PP2A), which dephosphorylates and activates the enzyme [33]. Fang *et al.* [34] revealed a significant association between high expression of phosphorylation ACC (pACC) and improved survival rates among gastric cancer patients (*P*=0.006). Additionally, the expression of pACC decreased with the progression of disease stage and lymph node metastasis. Studies *in vitro* have confirmed the overexpression of ACC in gastric cancer cell lines, and the inactivation of ACC by metformin treatment led to increased pACC levels, resulting in significant inhibition of cell proliferation and growth. He *et al.* [35] reported a significant negative correlation between ACC expression and the infiltration level of $CD8^+$ T cells, as well as the activity of immune cell lysis in gastric cancer, suggesting that inhibiting ACC could potentially enhance anti-tumor immunity in gastric cancer.

Fatty acid synthase (FASN) is a key enzyme involved in converting dietary carbohydrates into fatty acids. FASN is an oncogene in gastric cancer and can be used as a potential biomarker. Previous studies have showed an overexpressed FASN in gastric cancer tissues, and its high expression was associated with poor survival outcomes in patients. In addition, FASN expression correlates with immune infiltration, playing an important role in gastric cancer-related immunity [36]. Gastric cancer cells have strong resistance to lost-cell apoptosis. Lost-cell apoptosis resistance promotes the proliferation, migration and invasion, and inhibits the apoptosis of gastric cancer cells. Down-regulation of FASN can inhibit the apoptosis resistance of gastric cancer cells, and is related to the inhibition of p-ERK1/2/Bcl-xL signaling pathway. The above findings suggest that FASN may be a new target for anticancer therapy [37].

Stearoyl CoA desaturase 1 (SCD1) is a rate-limiting enzyme in the endoplasmic reticulum, catalyzing the conversion of saturated fatty acids (SFAs) to monounsaturated fatty acids (MUFAs) [38]. Both SFAs and MUFAs are important components of human cell lipids, basic components of biofilms, and sources of energy and signaling molecules such as cholesterol esters [39]. Notably, the proliferation of tumor cells heavily relies on MUFAs, and in the absence of exogenous sources of MUFAs, their sustenance is entirely contingent upon the activity of SCD1. Gao *et al.* [40] found that SCD1 could increase the number of gastric cancer stem cells (GCSCs) by siRNA knockout and drug inhibition, while inhibition of SCD1 inhibitors or siRNA could weaken the stem-cell property of GCSCs. In addition, inhibition of SCD1 reversed epithelial to stromal cell transformation and reduced metastasis of gastric cancer *in vitro* and *in vivo*. Experimental evidence underscores the role of SCD1 in promoting the growth and migration of gastric cancer cells and conferring resistance against apoptosis induced by iron overload, with heightened SCD1 expression correlating with unfavorable prognoses in gastric cancer patients [41]. In summary, the potential utility of SCD1 as a biomarker and therapeutic target for the early diagnosis of gastric cancer has been demonstrated.

3.2 Cholesterol biosynthesis pathway

The cholesterol biosynthesis pathway is also known as the mevalonate (MEVA) pathway. The rate-limiting step of MEVA pathway is mediated by HMG-CoA reductase (HMGCR), making it the most controlled part of the pathway. Li *et al.* [42] confirmed that overexpression of HMGCR could promote the growth and migration of gastric cancer cells, while downregulation of HMGCR expression could inhibit the growth and migration of gastric cancer cells and the occurrence of tumors, confirming HMGCR as a promising therapeutic target. In recent years, MEVA pathway has become an important regulatory factor and a potential therapeutic target in tumor biology. This pathway controls cholesterol production and post-translational modification of the Rho-GTP enzyme and is involved in several key steps of tumor progression [43]. Studies have reported that simvastatin decreased the growth, migration and invasion ability of gastric cancer cells NCI-N87 and Hs746T. Interestingly, both isoprene and cholesterol reversed these effects, suggesting that inhibitors of the MEVA pathway merit further investigation in the treatment of gastric cancer [44].

3.3 Fatty acid oxidation (FAO)

Carnitine palmitoyl transferase (CPT), including CPT1 and CPT2, plays a key role in FAO. CPT1, located outside the mitochondrial membrane, is considered an indispensable enzyme in the FAO process, which can convert carnitine to fatty acylcarnitine [45]. CPT1 is composed of three isoenzymes, namely CPT1a, CPT1b and CPT1c. CPT2, located in the mitochondrial membrane [46], converting acetyl-CoA into fatty acyl-CoA and promoting FAO [47]. Wang *et al.* [48] found that CPT1a protein expression was correlated with the grade, pathological stage, lymph node metastasis and poor prognosis of gastric cancer patients. Chen *et al.* [49] found that hypoxia-induced high expression of CPT1c

was closely related to poor prognosis and could promote the proliferation of gastric cancer cells.

4 Basis and future direction of blocking metabolic pathways

The activity of these metabolic pathways such as glycolysis, glutamine breakdown, fatty acid synthesis, cholesterol synthesis, and FAO is not unique to malignant cells. However, malignant tumors will utilize the metabolic characteristics of these pathways to a greater extent than normal cells, thus providing a level of specificity for metabolic treatment of cancer. As shown in Figure 1, these are the main metabolic pathways involved in tumor growth and development. It can be seen from the Figure 1 that that blocking key enzymes within these five pathways can influence the corresponding metabolic processes, presenting a potential avenue for effective tumor treatment. If these major pathways are explicitly obstructed, the energy requirements and biosynthesis of macromolecules might not be fully compensated by secondary metabolic pathways. Metabolic cancer involves multiple metabolic pathways. If pathways can be blocked as many as possible at the same time, metabolic cancer treatment may be more effective. Chemical inhibitors targeting metabolically key enzymes in gastric cancer are currently in preclinical and clinical studies. Although clinical drugs simultaneously inhibiting multiple metabolic pathways have not been studied to date, combinations of individual metabolic pathway inhibitors have demonstrated superior antitumor effects compared to single agents. For instance, the combined use of the glycolysis inhibitor Lonidamine and the GLS inhibitor compound 968 exhibited an increased antitumor effect in lung cancer cells compared to their individual application [50]. Similar results were observed in the combination of Lonidamine and 6-diazo-5-oxo-L-norleucine (DON) in leukemia cells [51]. Wang *et al.* [52] found that inhibition of CPT-mediated FA catabolism combined with conventional chemotherapy is a promising treatment strategy for patients with gastrointestinal cancer. FASN inhibitor--orlistat and FAO inhibitor--etomoxir can synergically reduce the viability of prostate cancer cell lines (VCaP, LNCaP) [53].

Interestingly, individualized treatment of these metabolic drugs induces compensatory metabolic changes. Inhibition of lipid oxidation with etomoxir can increase glycolysis and enhance glucose uptake in xenograft tumors of prostate cancer mice [54]. PKM2 depletion or inhibition of glycolysis by 2-deoxyglucose (2-DG) induces compensatory elevation of glutamine breakdown in colon cancer cells [55]. When prostate cancer cells were treated with glycolysis inhibitor, a compensatory effect on glucose and lipid metabolism was observed [56]. When lung cancer cells are treated with FASN inhibitor, compensatory glutamine breakdown and ketone metabolism are induced [57]. Based on the understanding of tumor metabolic heterogeneity and reprogramming, on the one hand, tumors may have single or multiple concurrent super-activated cell subsets. On the other hand, attacking multiple pathways simultaneously might prevent the reprogramming or compensatory metabolic changes caused by a single attack. Consequently, simultaneous targeting of multiple pathways may lead to more effective anti-tumor outcomes. At present, there is no global health regulatory body has approved metabolic inhibitors of any of these five metabolic pathways for the clinical treatment of cancer. However, some glycolysis inhibitor, glutamine breakdown inhibitor, FASN inhibitor, MEVA inhibitor, and FAO inhibitor have been tested in preclinical or clinical studies [58].

Table 1 shows the inhibitors of these metabolic pathways, their targets and stages of development. Current clinical studies have reported that these drugs have certain anti-tumor efficacy and are well tolerated. However, these drugs act only as a single agent. Therefore, there is an urgent need to conduct preclinical studies on large numbers of human cancer cells using any of these five classes of inhibitors. Cervants-Madrid *et al.* [59] found that the systematic combination of clonitramine, DON and orlistat was well tolerated, and these three drugs had anti-tumor effects when injected into nude mice with colon cancer mouse transplanted tumor models. Therefore, triple drug metabolism blockade of malignant phenotype seems to be a feasible and promising cancer treatment approach.

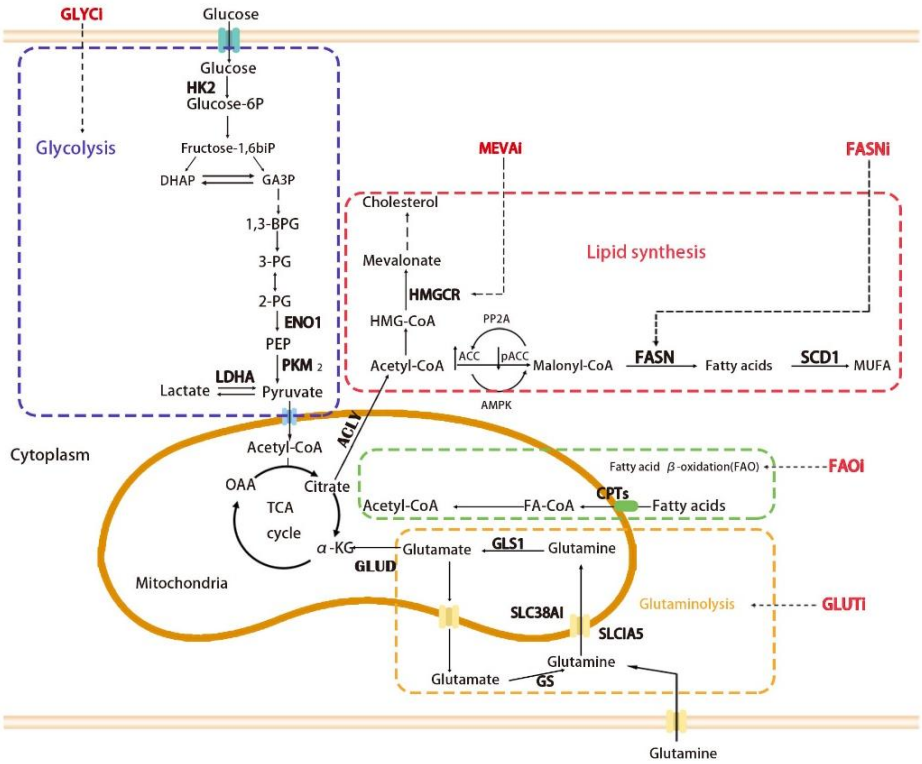

Fig. 1 Major metabolic pathways that support tumour growth and progression

Tab.1 Inhibitor drugs of metabolic pathways in pre-clinical and clinical

Metabolic Pathway	Inhibitor Drugs	Targeting	Phase
Glycolysis [60]	Lonidamine	HK2	Clinical application
	2-DG	HK2	Preclinical
	Sodium oxalate	LDHA	Clinical application
Glutamine Decomposition [61]	DON	GLS1	Clinical application
	BPTES	GLS1	Preclinical
Fatty Acid Synthesis [62]	Orlistat	FASN	Preclinical[a]
	C75	FASN	Preclinical
	TVB-2640(Denifanstat)	FASN	Clinical application
	TVB-3166	FASN	Preclinical
	TVB-3664	FASN	Preclinical
FAO[63]	Etomoxir	CPT1	Preclinical
	Perhexiline	CPT1，CPT2	Preclinical[a]
	ST1326 (Teglicar)	CPT1a	Preclinical
Cholesterol Synthesis [64]	Statin drugs (at least 7 types)	HMGCR	Preclinical and Clinical application[a]

Note: [a], these drugs have been clinically used for indications other than cancer.

5 Conclusion

Numerous preclinical studies have shown that gastric cancer is characterized by high rates of glycolysis and glutamine breakdown, increased rates of fatty acid and cholesterol synthesis, and increased lipid turnover through fatty acid beta-oxidation. Moreover, pharmacological blocking of these metabolic pathways can have antitumor effects. At present, there are some drugs that target various metabolic pathways in gastric cancer. As mentioned earlier, the combination of two or more inhibitors can enhance anti-tumor effects, a strategy that may be more promising than using inhibitors alone. In the study of cancer cell metabolism, the most metabolic changes are glycolysis, glutamine breakdown, and *de novo* synthesis of fatty acids. Therefore, these pathways are natural targets for attacking malignant metabolic phenotypes. The role of known inhibitors and new selective inhibitors of these pathways in the metabolic treatment of gastric cancer warrants further investigation of their preclinical efficacy and feasibility.

Conflict of Interest: None

Reference

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· 研究进展 ·

胃癌的代谢研究进展及其治疗意义

杨艳平[1]，　肖文轩[1]，　赵姣雅[1]，　刘屹[1,2]

1. 西安医学院，陕西 西安 710021；2. 陕西省人民医院肿瘤内科，陕西 西安 710068

摘要：胃癌具有广泛的转移和高死亡率，其病理机制尚不完全清楚。代谢组学的出现，使代谢调节和癌症研究成为研究者关注的焦点。本文概述胃癌引起的重要代谢改变，并对其治疗意义进行思考与展望。

关键词：胃癌；糖酵解；谷氨酰胺分解；脂质代谢

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Advances in metabolic research on gastric cancer and its therapeutic implications

YANG Yanping*, XIAO Wenxuan, ZHAO Jiaoya, LIU Yi

Xi'an Medical University, Xi'an, Shaanxi 710021, China

Corresponding author: LIU Yi, E-mail: liuyi926999@yeah.net

Abstract: Gastric cancer has extensive metastasis and high mortality, and its pathogenesis has not been fully understood. The advent of metabolomics has further brought metabolic regulation and cancer research into the spotlight. This article provides an overview of the important metabolic changes caused by gastric cancer, and their therapeutic significance is considered and prospected.

Keywords: Gastric cancer; Glycolysis; Glutaminolysis; Lipid metabolism

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据 2020 年全球癌症统计，在世界范围内，胃癌的发病率居第五位，死亡率居第四位[1]。胃癌具有广泛的转移和高死亡率。化疗是转移性胃癌的主要治疗方法，但耐药性限制了化疗的有效性，并导致治疗失败。胃癌化疗耐药机制复杂，受多因素影响，其中代谢起着重要作用。细胞代谢改变被认为是癌症的标志之一[2]。胃癌会导致新陈代谢的改变，而这种改变可以在治疗上加以利用。癌细胞利用代谢过程在各种组织微环境中生存、生长和转移，并获得治疗耐药性。靶向代谢的化疗一直是有效的癌症治疗方法，这些疗法的成功证明了靶向恶性代谢的治疗窗口的存在。胃癌代谢改变的相关研究为胃癌的治疗提供新的策略，其中一些正在临床前模型或临床试验中进行评估，本文对相关研究进展进行概述如下。

1　糖酵解与胃癌

肿瘤细胞即使在氧气充足的情况下也要消耗大量葡萄糖进行糖酵解[3]，尽管其能量效率较低，却提供了有利于血管生成、肿瘤进展和免疫逃避的酸性微环境[4-5]。

己糖激酶(HK)是糖酵解的关键酶，有四种 HK 同种型(1~4)，但只有 HK2 同种型与 Warburg 效应相关。HK2 在正常细胞中的表达非常低或不存在[6]。Liu 等[7]对 2 532 例实体癌(包括 585 例胃癌患者)的分析显示，HK2 表达升高与预后不良相关。Shao 等[8]报告了婆罗双树样基因 4(SALL4，一种锌指蛋白转录因子)通过 HK2 介导的糖酵解促进胃癌进展。Li 等[9]研究发现 miR-181b 在人类胃癌中显著下调，miR-181b 通过靶向其 3′-非翻译区，直接抑制糖酵解第一步的关键酶 HK2 的表达，从而负向调节胃癌细胞的糖酵解。

果糖-1,6-二磷酸醛缩酶(ALDO)催化果糖-1,6-二磷酸(FBP)裂解为二羟丙酮-3-磷酸和甘油醛-3-磷酸[10]。有三种醛缩酶同工酶类型，分别为 A、B 和 C。ALDOA 是几乎所有癌症中报告的最丰富的亚型[11]。Jiang 等[12]发现 252 例胃癌患者中 70.6%有 ALDOA 强表达，且 ALDOA 的表达是胃癌患者 5 年总生存和无病生存的独立预后因素，通过 shRNA 转染沉

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通信作者：刘屹，E-mail：liuyi926999@yeah.net

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默 ALDOA 的表达可以显著降低胃癌细胞系的生长、增殖和侵袭能力。

烯醇化酶催化 2-磷酸甘油酸转化为磷酸烯醇丙酮酸。在哺乳动物中描述了这种酶的三种型别:α-烯醇化酶(ENO1)、β-烯醇化酶和 γ-烯醇化酶。仅 ENO1 在包括胃癌在内的 20 多种癌症类型中过表达[13]。Qiao 等[13]分析 94 例胃癌和 53 例正常组织中分别有 56%、17%ENO1 过表达,且高表达与较差预后相关。此外,还发现 ENO1 在胃癌细胞系中过表达,ENO1 表达的敲低抑制胃癌细胞的增殖和集落形成并促进凋亡。Yang 等[14]研究证实 ENO1 的高表达与胃癌患者的预后不良有关, ENO1 参与了胃癌细胞的干细胞样特性的调节。Qian 等[15]发现 ENO1 在胃癌顺铂耐药细胞中表达增加,且用 siRNA 转染敲除 ENO1 可以显著减少糖酵解并逆转顺铂耐药。

丙酮酸激酶(PK)是催化糖酵解终末步骤的限速酶。哺乳动物有 4 种 PK 亚型(L、R、M1 和 M2),但在肿瘤细胞中仅发现 PKM2[16]。Lim 等[17]研究发现在 368 例人胃癌组织中 144 例(39.1%)有 PKM2 蛋白表达,且 PKM2 表达与胃癌分化程度密切相关,PKM2 阳性细胞在高分化腺癌中占 63.6%,但在印戒细胞癌中仅占 17.7%;且只有在印戒细胞癌中 PKM2 表达与较短的总生存期相关($P<0.05$)。Shiroki 等[18]发现 PKM2 在癌组织中的表达明显高于非癌组织,且在敲除 PKM2 基因后,胃癌细胞在体外的增殖、迁移、非锚定生长和球体形成显著减少,在体内肿瘤生长和肝转移也显著减少。

乳酸脱氢酶(LDH)是糖酵解的关键调节酶,有五种活性 LDH 同工酶,主要由 A 亚基和 B 亚基组成。血清 LDH 水平在癌症患者中普遍升高,且与不良预后和治疗抵抗相关,因此 LDH 的测定已成为诊断癌症或监测癌症疗效的重要辅助工具[19]。Sun 等[20]报道了 264 例胃癌标本中 LDHA 的高表达率为 76%;LDHA 在胃癌中的高表达与总生存期的降低有关;胃癌组织中 LDHA 的表达是总生存期的独立预后危险因素。此外,还发现在胃癌细胞系中敲除 LDHA 后,在体外和小鼠模型中抑制了细胞生长,LDHA 基因敲除也减少了胃癌细胞中乳酸和 ATP 的产生。

2　谷氨酰胺分解代谢与胃癌

谷氨酰胺衍生的氮代谢从谷氨酰胺分解向从头核苷酸生物合成的转变促成了癌症的恶性演变[21]。通过谷氨酰胺分解,肿瘤将大量谷氨酰胺代谢为谷氨酸和氨。谷氨酸转化为 α-酮戊二酸(α-KG),后者通过氧化磷酸化(OXPHOS)和脂肪酸合成,为 Krebs 循环提供能量。谷氨酸还作为氮供体以合成核酸、非必需氨基酸和谷胱甘肽,以维持氧化还原状态[22]。葡萄糖和谷氨酰胺的代谢协调了能量的产生和大分子的合成,尤其是脂肪酸和还原当量的合成[23]。谷氨酰胺由转运蛋白 SLC1A5、SLC38A1 和 SLC38A2 通过质膜转运至细胞内。谷氨酰胺经谷氨酰胺酶(GLS)水解产生谷氨酸和氨。Wang 等[24]在一项代谢组学研究中发现 125 例胃癌患者和 54 例对照组患者的谷氨酸水平随肿瘤进展而升高。GLS 至少有三种亚型:GLS1、GLS2 和 GAC,均在线粒体中[25]。GLS 在多种胃癌细胞株中表达,细胞在缺氧条件下表达增多。在体外,siRNA 敲减 GLS1 会导致生长抑制,而 BPTES (GLS 抑制剂)对 GLS1 过表达的胃癌细胞株 OCUM-2MD3/hypo 细胞移植瘤小鼠具有抗肿瘤作用[26]。GLS1 在胃癌中过表达的更有力证据来自一项基于同位素标记的定量蛋白组学的研究,结果发现 GLS1 过表达了 1.68 倍,通过免疫组化验证发现 GLS1 过表达的比例在胃癌组织中为 75.6%,在癌旁组织中为 19.1%,并证实 GLS1 的表达与较大的肿瘤和淋巴结转移有关[27]。Wu 等[28]在 144 例未经治疗的胃癌患者中发现谷氨酸脱氢酶(GLUD)均表达,且 GLUD 表达越高预后越差;此外,在胃癌细胞中用 shRNA 沉默 GLUD,体内外实验均证实沉默 GLUD 具有抗肿瘤作用。

3　脂质代谢与胃癌

3.1　*脂肪酸合成代谢*　在脂质/溶脂表型中,恶性细胞需要大量从头合成脂肪酸,因为脂肪酸是细胞膜的组成部分,也是合成用于细胞信号转导的脂类衍生物的基础,所以肿瘤表现出其合成所需酶的过表达[29]。

ATP-柠檬酸裂解酶,又称 ATP 柠檬酸合成酶(ACLY),是一种公认的脂肪酸从头合成的重要酶。乙酰辅酶 A 是由 ACLY 催化细胞质中柠檬酸转化为草酰乙酸而产生的,是内源性脂肪酸和胆固醇生物合成的重要组成部分,是肿瘤细胞生长和代谢的重要能量来源。Qian 等[30]对 83 例胃癌患者的标本进行了 ACLY 表达分析,发现 51 例(61%)胃癌患者有较高的 ACLY 表达,且过度表达 ACLY 的患者生存时间较短(23 个月 *vs* 78 个月,$P=0.031$)。Cheng 等[31]研究证实 miR-133b 靶向 ACLY 并通过调节过氧化物酶体增殖物激活受体-γ(PPARγ)的表达来抑制胃癌细胞增殖,表明 miR-133b 可以作为胃癌治疗中的肿瘤抑制靶标。

乙酰辅酶 A 羧化酶(ACC)将乙酰辅酶 A 转化为丙二酰辅酶 A,丙二酰辅酶 A 提供了两碳构件以产生更多的脂肪酸。在哺乳动物中,ACC1 和 ACC2 是乙酰辅酶 A 羧化酶系的两个成员。ACC1 定位在细胞质中,是新的脂肪酸合成途径中的第一个限速酶。ACC2 定位于线粒体外膜,产生丙二酰辅酶 A,并调节参与脂肪酸 β-氧化(FAO)的 CPT1 的活性[32]。ACC 主要受 AMPK(AMP 激活的蛋白激酶)和 PP2A(蛋白磷酸酶 2A)的调控,前者通过磷酸化使该酶失活,后者则使该酶去磷酸化并激活[33]。Fang 等[34]研究发现磷酸化 ACC(pACC)的高表达与所有胃癌患者的较好生存率密切相关($P=0.006$),随着疾病分期和淋巴结转移的进展,pACC 的表达下降;体外研究证实胃癌细胞系也过度表达 ACC,二甲双胍治疗使 ACC 失活导致 pACC 增加,从而明显抑制细胞的增殖和生长。He 等[35]报道了 ACC 的表达与胃癌中 $CD8^+$T 细胞的浸润水平和免疫细胞溶解活性呈显著负相关,表明抑制 ACC 可以增强胃癌中的抗肿瘤免疫。

脂肪酸合酶(FASN)是指参与膳食碳水化合物转化为脂肪酸的合成代谢的主要酶。FASN 是胃癌中的一种致癌基

因,可作为一种潜在的生物标志物。已有研究发现,FASN 在胃癌组织中明显过表达,其高表达导致胃癌患者的生存结局较差;此外,FASN 表达与免疫浸润显著相关,可能在胃癌相关免疫中发挥重要作用[36]。胃癌细胞对失巢凋亡有很强的抵抗力,失巢凋亡抵抗促进了胃癌细胞的增殖、迁移和侵袭,同时抑制了胃癌细胞的凋亡;FASN 的下调对胃癌细胞的失巢凋亡抵抗有抑制作用,并与 p-ERK1/2/Bcl-xL 信号通路的抑制有关。以上研究结果提示 FASN 可能是抗癌治疗的一个新靶点[37]。

硬脂酰辅酶 A 去饱和酶 1(SCD1)是内质网中的可将饱和脂肪酸(SFAs)转化为 Δ9-单不饱和脂肪酸(MUFAs) 的限速酶[38]。SFAs 和 MUFAs 都是人类细胞脂质的重要成分,是生物膜的基本成分,也是能量和信号分子(如胆固醇酯)的来源[39]。肿瘤细胞增殖显著依赖于 MUFAs,在缺乏外源 MUFAs 来源的情况下,它们完全依赖于 SCD1 的活性。Gao 等[40]通过 siRNA 敲除和药物抑制等方法发现 SCD1 可增加胃癌干细胞(GCSCs)的数量,而 SCD1 抑制剂或 siRNA 的抑制可减弱 GCSCs 的干细胞性。此外,SCD1 的抑制逆转了上皮细胞向间质细胞的转化,降低了体外和体内胃癌的转移。经实验证实 SCD1 具有促进胃癌肿瘤生长、迁移和对抗铁死亡的功能,SCD1 的高表达与胃癌患者的不良预后有关[41]。综上所述,SCD1 作为胃癌早期诊断的生物标志物和治疗靶点的潜力已经被证实。

3.2　胆固醇生物合成途径　胆固醇生物合成途径,也称为甲羟戊酸(MEVA)途径,其限速步骤由羟甲基戊二酰基辅酶 A 还原酶(HMGCR)介导,使其成为通路中最受控制的部分。Li 等[42]通过实验证实,过表达 HMGCR 可促进胃癌细胞的生长和迁移,而下调 HMGCR 的表达则抑制胃癌细胞的生长、迁移和肿瘤的发生,证实 HMGCR 是一个有前途的治疗靶点。近年来,MEVA 途径成为肿瘤生物学的重要调控因子和潜在的治疗靶点;该途径控制胆固醇的生成和 Rho-GTP 酶的翻译后修饰,与几个关键的肿瘤进展步骤有关[43]。有研究报道,当使用辛伐他汀治疗胃癌细胞系 NCI-N87 和 Hs746T 细胞时,可降低其生长、迁移和侵袭能力。有趣的是,异戊二烯类和胆固醇都逆转了这些作用,这表明 MEVA 途径的抑制剂在胃癌的治疗方面值得进一步研究[44]。

3.3　FAO　肉碱棕榈酰转移酶(CPT)包括 CPT1 和 CPT2,在 FAO 中发挥着关键作用;CPT1 位于线粒体膜外,被认为是 FAO 过程中一种不可或缺的酶,可以将肉碱转化为脂酰肉碱[45]。CPT1 由三种同工酶组成,分别为 CPT1a、CPT1b 和 CPT1c,CPT2 位于线粒体膜内部[46],可使乙酰辅酶 A 转化为脂酰辅酶 A 而促进 FAO[47]。Wang 等[48]研究发现 CPT1a 蛋白表达与胃癌患者的分级、病理分期、淋巴结转移及预后不良相关。Chen 等[49]发现缺氧诱导的 CPT1c 高表达与不良预后密切相关,并可促进胃癌细胞增殖。

4　阻断代谢途径的依据和未来方向

糖酵解、谷氨酰胺分解、脂肪酸合成、胆固醇合成和 FAO 等这些代谢途径的活跃并不是恶性细胞独有的。然而,恶性肿瘤比正常细胞会更大程度地利用这些途径的代谢特征,从而为肿瘤的代谢治疗提供了一定水平的特异性。如笔者自绘的图 1 所示,为肿瘤生长和发展涉及的主要代谢途径,由图可知,可以通过阻断这五条代谢途径的关键酶类,从而阻断相应的代谢途径以达到治疗肿瘤的目的。假设明确阻断这些主要途径,能量需求和大分子的生物合成不太可能被次级代谢途径完全补偿。代谢性癌症涉及多个代谢途径,而不是仅仅一个,假设试图同时阻断尽可能多的代谢途径,那么代谢性癌症治疗可能会更有效。针对胃癌中代谢关键酶的化学抑制剂目前正在临床前和临床研究中。迄今为止,还没有研究出同时抑制多条代谢途径的临床药物,但是已显示与单药相比,联合使用这些代谢途径抑制剂中的任何一种可产生更优的抗肿瘤作用。糖酵解抑制剂氯尼达明和谷氨酰胺酶抑制剂化合物 968 联合使用时,在肺癌细胞中观察到抗肿瘤作用比单用时增加[50]。氯尼达明和谷氨酰胺酶抑制剂 DON 联合使用在白血病细胞中观察到相似的结果[51]。Wang 等[52]研究发现抑制 CPT 介导的 FA 分解代谢联合常规化疗是治疗胃肠癌患者的一种有前途的治疗策略。脂肪酸合成酶抑制剂奥利司他和 FAO 抑制剂 etomoxir 同时抑制 FA 合成可协同降低前列腺癌细胞株(VCaP、LNCaP)的生存活力[53]。

有趣的是,这些代谢药物的个体化治疗可诱导产生代偿性代谢变化。用 etomoxir 抑制脂质氧化可增加糖酵解,并增强前列腺癌小鼠异种移植瘤中葡萄糖的摄取[54]。PKM2 耗竭或 2-脱氧葡萄糖(2-DG)抑制糖酵解可诱导结肠癌细胞谷氨酰胺分解的代偿性升高[55]。当前列腺癌细胞用糖酵解抑制剂处理时,观察到对葡萄糖和脂质代谢的补偿作用[56]。当肺癌细胞用脂肪酸合成酶抑制剂处理时,诱导代偿性谷氨酰胺分解和酮代谢[57]。基于对肿瘤代谢异质性和重编程的认识,一方面,肿瘤可能具有单一或多个并发超激活的细胞亚群。另一方面,同时攻击多条通路可能避免了单一攻击引起的重新编程或代偿性代谢变化。因此,同时攻击多条通路可能产生更好的抗肿瘤效果。目前,全球尚无任何卫生监管机构批准这五条代谢途径中任何一种的代谢抑制剂用于癌症的临床治疗。然而,一些糖酵解抑制剂、谷氨酰胺酶抑制剂、脂肪酸合成抑制剂和 FAO 抑制剂已经在临床前或临床研究中进行了测试[58]。表 1 显示了这些代谢途径的抑制剂,它们的靶标和发展阶段。目前的临床研究报告表明,这些药物具有一定的抗肿瘤疗效和良好的耐受性。然而,这些药物仅作为单一药剂。因此,迫切需要使用这五类抑制剂中的任何一种对大量人类癌细胞进行临床前研究。Cervantes-Madrid 等[59]通过动物实验发现系统性组合使用氯硝胺、DON 和奥利司他耐受性良好,而且这三种药物注射到结肠癌小鼠移植瘤模型的裸鼠身上具有抗肿瘤作用。由此看来,恶性表型的三重药物代谢阻断似乎是可行的和有希望的癌症治疗方法。

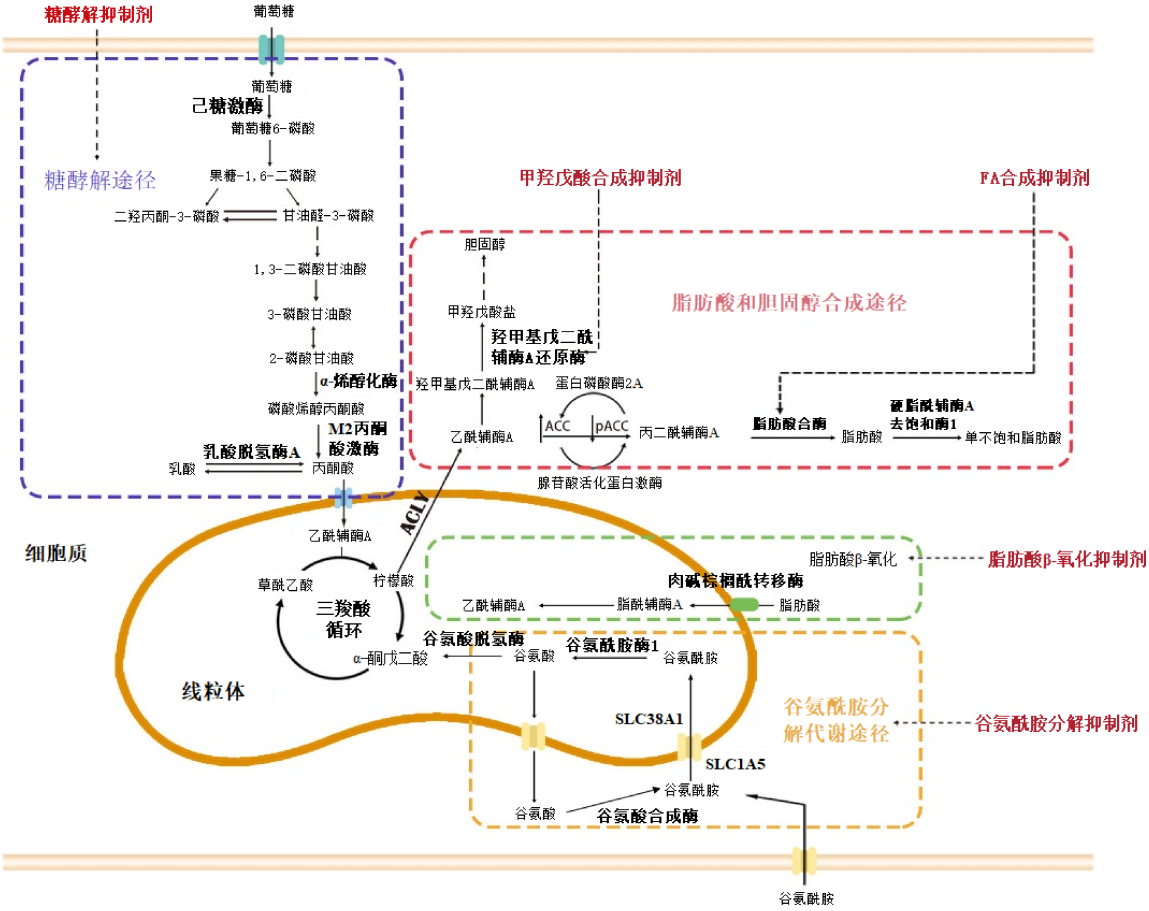

图 1　支持肿瘤生长和发展的主要代谢途径

Fig. 1　Major metabolic pathways that support tumour growth and progression

表 1　代谢途径的临床前和临床抑制剂药物

Tab. 1　Inhibitor drugs of metabolic pathways in pre-clinical and clinical

代谢途径	抑制剂药物	靶标	发展阶段
糖酵解[60]	氯尼达明	HK2	临床应用阶段
	2-DG	HK2	临床前阶段
	草酸钠	LDHA	临床应用阶段
谷氨酰胺分解[61]	DON	GLS1	临床应用阶段
	BPTES	GLS1	临床前阶段
脂肪酸合成[62]	奥利司他	FASN	临床前阶段[a]
	C75	FASN	临床前阶段
	TVB-2640（denifanstat）	FASN	临床应用阶段
	TVB-3166	FASN	临床前阶段
	TVB-3664	FASN	临床前阶段
FAO[63]	依托莫司	CPT1	临床前阶段
	哌克昔林	CPT1，CPT2	临床前阶段[a]
	ST1326（teglicar）	CPT1a	临床前阶段
胆固醇合成[64]	他汀类药物（至少 7 种）	HMGCR	临床前及临床应用阶段[a]

注：[a] 表示这些药物已在临床上用于癌症以外的适应证。

5　结　语

大量临床前研究表明，胃癌表现为糖酵解和谷氨酰胺分解的高比率，脂肪酸和胆固醇合成的速率增加，以及通过 FAO 进行的脂质周转增加。而且，这些代谢途径在药理学上的阻断会产生抗肿瘤作用。目前临床上已经有一些针对胃癌中的各个代谢途径的药物。如前所述，两种或多种抑制剂联用可增强抗肿瘤作用，该策略可能比单独使用抑制剂更有前景。在癌症细胞的代谢研究中，最多的代谢改变是糖酵解、谷氨酰胺分解和脂肪酸的从头合成。因此，这些途径是攻击恶性代谢表型的自然靶标。这些通路的已知抑制剂和新的选择性抑制剂在胃癌的代谢治疗方面的作用有必要进一步探究其临床前疗效和可行性。

利益冲突　无

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