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MINIREVIEWS

Glutamine addiction and therapeutic strategies in pancreatic cancer

Lin-Lin Ren, Tao Mao, Pin Meng, Li Zhang, Hong-Yun Wei, Zi-Bin Tian

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Abstract

Pancreatic cancer remains one of the most lethal diseases worldwide owing to its late diagnosis, early metastasis, and poor prognosis. Because current therapeutic options are limited, there is an urgent need to investigate novel targeted treatment strategies. Pancreatic cancer faces significant metabolic challenges, principally hypoxia and nutrient deprivation, due to specific microenvironmental constraints, including an extensive desmoplastic stromal reaction. Pancreatic cancer cells have been shown to rewire their metabolism and energy production networks to support rapid survival and proliferation. Increased glucose uptake and glycolytic pathway activity during this process have been extensively described. However, growing evidence suggests that pancreatic cancer cells are glutamine addicted. As a nitrogen source, glutamine directly (or indirectly *via* glutamate conversion) contributes to many anabolic processes in pancreatic cancer, including amino acids, nucleobases, and hexosamine biosynthesis. It also plays an important role in redox homeostasis, and when converted to α-ketoglutarate, glutamine serves as an energy and anaplerotic carbon source, replenishing the tricarboxylic acid cycle intermediates. The present study aims to provide a comprehensive overview of glutamine metabolic reprogramming in pancreatic cancer, focusing on potential therapeutic approaches targeting glutamine metabolism in pancreatic cancer.

Key Words: Pancreatic cancer; Glutamine metabolism; Cancer treatment; Therapeutic strategies

Core Tip: Most pancreatic ductal adenocarcinomas (PDAC) are diagnosed at an advanced stage, missing the opportunity for surgical treatment and responding poorly to radiotherapy and targeted therapies. Glutamine is a non-essential amino acid that is found in high levels in normal humans. Glutamine metabolism could provide raw material for the synthesis of important molecules and meet the needs of rapid growth and proliferation of tumor cells. The study of glutamine metabolic pathways targeting PDAC may provide new strategies for pancreatic cancer treatment.

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INTRODUCTION

Pancreatic cancer is a lethal malignancy with a five-year survival rate of 3%-5%[1,2]. This high mortality rate can be mainly attributed to late disease presentation when patients are no longer candidates for surgical resection[3]. Moreover, because pancreatic cancer responds poorly to radiotherapy, chemotherapy and targeted therapy, new treatment methods are urgently needed to improve the current treatment dilemma. The proliferation of pancreatic connective tissue and severe blood supply deficiency results in local tumor cells being exposed to a microenvironment of nutrient deprivation, hypoxia, and high oxidative stress.

Cancer cells must undergo metabolic reprogramming and reshape their energy metabolic pathways to meet the energy requirements for metabolism, proliferation, and growth, which are primarily manifested as increased aerobic glycolysis of glucose, active catabolism of glutamine, and enhanced autophagy[4,5]. Glutamine is believed to have a significant role in pancreatic cancer cells as it undergoes deamination to α-ketoglutarate (aKG) to support the tricarboxylic acid (TCA) cycle *via* glutaminolysis, using glutamine as a fuel source[6].

Glutamine is a non-essential amino acid with a high content in the normal human body that can provide a nitrogen source for the synthesis of purine and pyrimidine nucleotides, participate in the TCA cycle, and contribute to its carbon backbone, particularly when carbon is diverted to glycolytic pathways. Glutamine also promotes essential amino acid uptake, activates the mammalian target of rapamycin (mTOR), aids in the recycling of excess ammonia and glutamate, and regulates redox homeostasis[7-9]. Relevant studies have confirmed that glutamine demand is significantly increased in pancreatic cancer, and "Glutamine Addiction" exists in tumor cells[10-12]. Glutamine metabolism produces energy and is an important synthetic raw material for rapid tumor cell growth and proliferation.

In addition, the NADPH and glutathione produced during metabolism can help tumor cells maintain redox homeostasis[13]. Targeting specific metabolic pathways in cancer cells, particularly the glutamine pathway, may be a novel approach to cancer, according to a number of recent studies[14-16]. In this review, we systematically summarize the metabolic status of glutamine in pancreatic cancer, as well as the research progress in targeting the glutamine metabolic pathway in pancreatic cancer treatment.

METABOLISM OF GLUTAMINE IN THE HUMAN BODY

Glutamine accounts for nearly 4.7% of the amino acids that make up human proteins. In some special functional proteins, such as the protein involved in forming the epidermal barrier structure, the proportion can reach 25%. Because glutamine is in high demand in the body, it is also known as the conditionally essential amino acid[17]. The initial production of glutamine takes place in in the skeletal muscle, in the pulmonary, and in the adipose tissue. This process is coordinated by glutamate ammonia ligase (GLUL), a cytosolic enzyme that catalyzes glutamine synthesis from glutamate and ammonium ions (NH_4^+). Glutaminase (GLS) located in mitochondria is responsible for catalyzing the conversion of glutamine into glutamate in intestinal mucosa, immune cells, renal tubule cells, and liver[18].

Glutamine is not able to cross the plasma membrane and has to be transported into the cells by transporters. There are 14 transporters in total, which are divided into four families: SLC1, SLC6, SLC7 and SLC38[19]. When glutamine enters the cell, it is incorporated into various metabolic pathways as a nitrogen or carbon source. As a nitrogen source, glutamine mainly synthesizes nucleotides (pyrimidine and purine), non-essential amino acids (NEAAs), and glucosamine. For DNA and RNA, however, de novo nucleotide synthesis is essential. It is supported by glutamine, which together with nitrogen, is involved in the production of purines and pyrimidines[20,21]. The carbon in glutamine is used as a carbon source in gluconeogenesis, TCA cycle, and glutathione metabolism.

Gluconeogenesis is an important process for maintaining glucose homeostasis under various conditions, and glutamine is a major gluconeogenic precursor[22]. To maintain redox homeostasis, NADPH and reduced glutathione molecules are primarily responsible for neutralizing reactive oxygen species (ROS). The reaction catalyzed by cysteine ligase produces γ-glutamylcysteine from glutamate and cysteine in the first step of glutathione synthesis. And Gln is a vital substrate in this first step[23]. Other NEAAs can be synthesized from Gln-derived glutamate, including alanine, aspartate, proline, serine, and acetyl-serine[24].

DYSREGULATION OF GLUTAMINE METABOLISM IN PANCREATIC CANCER

Glutamine is more abundant in rapidly proliferating tumor cells and some common cells, such as intestinal epithelial and immune cells. This cell-intrinsic regulation of nutrient partitioning is accomplished through the mTORC1 signaling pathway and the expression of genes involved in glucose and glutamine metabolism[24]. Numerous studies have described the dysregulation of glutamine metabolism in various cancer contexts[25-34] after Roberts *et al*[25] described the first observation of enhanced glutamine metabolism.

The molecules involved in glutamine metabolism dysregulation differ between cancer types. Alanine, serine, cysteine-preferring transporter 2 (ASCT2), GLUL, and GLS genes related to glutamine metabolism are highly expressed in triple-negative breast cancer patients[35]. The expression of the GLS II pathway in prostate cancer cells increased with tumor cell aggressiveness[36]. Similarly, glutamine metabolism changes are observed in pancreatic cancer patients[5,37-41]. The amino acid transporter SLC6A14 was significantly overexpressed in pancreatic cancer cells, tissues, and patient-derived xenografts in comparison to normal pancreatic tissue or normal pancreatic epithelial cells.

α-Methyltryptophan, a SLC6A14 pharmacological blocker, decreased pancreatic cancer cell growth *in vitro* and *in vivo* by inducing amino acid starvation[37]. The decreased blood vessel density in pancreatic cancer favors its resistance to chemotherapy and contributes to its aggressiveness due to the high degree of hypoxia[42,43]. Glutamine is metabolized by hypoxic pancreatic tumor cells in order to survive. The hexosamine biosynthetic pathway links glucose and glutamine metabolism, allowing the protein modification of O-linked N-acetylglucosamine. Hypoxia increases hexosamine biosynthetic pathway gene transcription and O-glycosylated protein levels, and the O-linked N-acetylglucosaminylation of proteins is necessary for the survival of hypoxic pancreatic cancer cells[38].

Cancer cell progression is inhibited by cellular senescence, which causes cell cycle arrest in damaged or dysfunctional cells[44]. The generation of NADPH and maintenance of the cellular redox state in pancreatic cancer depend on glutamine carbon flowing through mitochondrial aspartate transaminase (GOT2). Elevated ROS following GOT2 downregulation can produce p27-mediated senescence, a cyclin-dependent kinase inhibitor[40].

NON-CANONICAL GLUTAMINE METABOLIC PATHWAY IN PANCREATIC CANCER

Pancreatic cancer growth requires glucose. Furthermore, pancreatic cancer cells are highly sensitive to glutamine deprivation, indicating that Gln is important for pancreatic cancer growth. Pancreatic cancer can be significantly inhibited by impaired GLS activity[39]. To replenish TCA cycle metabolites, glutamine can be converted into αKG *via* two mechanisms: glutamate dehydrogenase (GLUD1) or transaminases[45]. In contrast, most cells use GLUD1 in the mitochondria to convert Gln-derived glutamate to αKG to fuel the TCA cycle[46,47]. Pancreatic cancer is dependent on a specific pathway for the fuel of the TCA cycle, in which aspartate derived from glutamine is transported to the cytoplasm where it is processed to oxaloacetate (OAA) by aspartate transaminase (GOT1). This OAA is then converted to malate and pyruvate, which is thought to increase the ratio of NADPH to $NADP^+$ and possibly maintain the redox state of the cell. The viability of pancreatic cancer cells is significantly reliant on this sequence of reactions, as the knockdown of any component enzyme in this series significantly suppresses pancreatic cancer growth *in vitro* and *in vivo*[39] (Figure 1).

GLUTAMINE METABOLIC REPROGRAMMING IN PANCREATIC CANCER

Several studies have found that oncogenic alterations in cancer cells reprogram glutamine metabolism[39]. The transcriptional regulatory capabilities of the oncogene Myc facilitate the coordination of gene expression necessary for cells to participate in glutamine catabolism, which exceeds the demands of cancer cells for protein and nucleotide biosynthesis. The reliance of mitochondrial metabolic reprogramming on glutamine catabolism for the maintenance of cellular viability and replenishment of the TCA cycle results from Myc-dependent glutaminolysis. And PI3K or AKT activation is not required for the ability of Myc-expressing cells to engage in glutaminolysis.

Transcriptional binding of the proto-oncogene c-MYC to the promoter regions of high-affinity glutamine importers, including the sodium-dependent neutral amino acid transporter type 2 and its isoform, results in enhanced glutamine uptake and reduced contribution of glucose to mitochondrial-dependent phospholipid synthesis[48].

Kras mutations are a common type of mutation in pancreatic cancer, with $Kras^{G12D}$ being the most common oncogenic form[49]. Loss of $Kras^{G12D}$ heterozygosity ($Kras^{G12D}$-LOH) leads to the increasement of proliferation and invasion capacity in pancreatic cancer cells[50].

As a stress-response gene, regulated in DNA damage and development 1 (REDD1) is expressed in response to hypoxic condition, nutrient deficiency, and other stress factors. Moreover, REDD1 is a vital upstream regulator of the mTOR[51], which is a serine/threonine protein kinase involved in non-canonical anaplerotic glutamine metabolism[52]. $Kras^{G12D}$-LOH increased non-canonical glutamine metabolism and REDD1 expression. Moreover, REDD1 knockdown inhibited $Kras^{G12D}$-LOH-induced upregulation of Gln metabolism, effectively impairing $Kras^{G12D}$-LOH pancreatic cancer cell growth, motility, and invasion[53]. The oncogenic Kras mutation reactivates glutamine metabolism, increases the production of reduced NADPH, and restores cellular redox homeostasis through macromolecule synthesis.

To produce metabolic precursors for NADPH production, mitochondrial glutamine-derived aspartic acid must be transported into the cytoplasm. Mitochondrial uncoupling protein 2 (UCP2) catalyzes the transportation process and significantly promotes tumor growth. Compared to the wild-type cell lines, UCP2-silenced Kras mutant cell lines have lower glutaminolysis, NADPH/$NADP^+$, and glutathione/glutathione disulfide ratios and higher ROS levels. Fur-

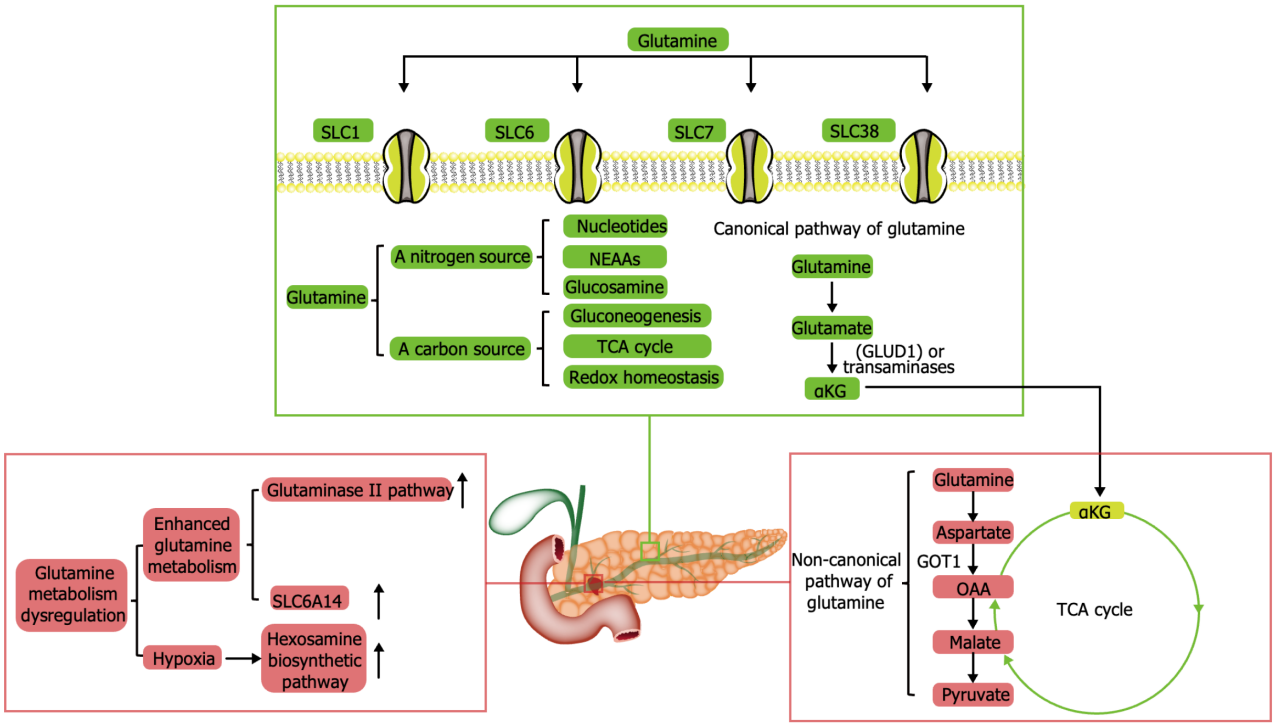

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Figure 1 Metabolism of glutamine in pancreatic cancer. Glutamine enters the cells through four receptors (SLC1, SLC6, SLC7, and SLC38) and can be incorporated into various metabolic pathways either as a nitrogen source or as a carbon source, which is important for the synthesis of nucleotides, non-essential amino acids, glucosamine and gluconeogenesis, the tricarboxylic acid (TCA) cycle, and glutathione metabolism. Under normal physiological conditions, glutamine can be converted to α-ketoglutarate by canonical pathway to replenish the TCA cycle metabolites, which is differ from the non-canonical pathway of glutamine using in pancreatic cancer. TCA: Tricarboxylic acid; αKG: α-ketoglutarate; GOT1: Aspartate transaminase; OAA: Oxaloacetate; GLUD1: Glutamate dehydrogenase; NEAAs: Non-essential amino acids.

thermore, the growth of Kras mutant pancreatic cancer cells was strongly inhibited by UCP2 silencing *in vitro* and *in vivo* [54].

p53 is an important tumor suppressor that orchestrates specific cellular responses to various stress signals associated with tumor suppression, including transient cell cycle arrest, cellular senescence, and cell apoptosis. Other important cellular processes, including metabolism, maintenance of the stem cell, tumor invasion and metastasis, and communication within the tumor microenvironment, have also been reported to be under p53 regulation[55]. The metabolic functions of p53 help cells adapt to and survive limited periods of metabolic stress by resisting the switch to glycolysis in cancers[56].

GLS2, a p53 target gene, encodes mitochondrial GLS that catalyzes glutamine hydrolysis. The expression of GLS2 is upregulated by p53 in unstressed and stressed states. GLS2 regulates energy metabolism *via* increasing the production of glutamate and αKG, leading to increased mitochondrial respiration and ATP generation. Moreover, GLS2 can modulate the antioxidant defense function *via* upregulation of the glutathione (GSH) and downregulation of the ROS levels in cells, protecting cells from apoptosis caused by oxidative stress. Consistent with these functions of GLS2, p53 activation elevates glutamate and αKG levels, mitochondrial respiration rate, and GSH levels while decreasing ROS levels in cells [57]. Due to poor vascularization in the pancreatic cancer microenvironment and increased glutamine catabolism during rapid tumors growth, cancer cells are often exposed to a glutamine depleted microenvironment.

A conserved role for the protein phosphatase 2A (PP2A)-associated protein α4 in the sensing of glutamine has been reported. Upon depletion of glutamine, the assembly of an adaptive PP2A complex which contains the B55α regulatory subunit (Ppp2r2a) is promoted by α4 *via* providing the catalytic subunit. And B55α is specifically induced by glutamine deprivation in a ROS-dependent manner to activate p53 *via* direct interaction and dephosphorylation of EDD (a B55α-interacting protein) and to promote cell survival[58].

Arginine methylation of proteins is a common post-translational modification that is involved in a variety of cellular processes such as signal transduction, gene transcription, and metabolism. Malate dehydrogenase 1 (MDH1), a necessary enzyme for glutamine metabolism, is regulated by R248 site methylation and protein arginine methyltransferase 4 mediated MDH1 methylation. Methylation at R248 inhibits MDH1 post-translational mechanisms by disrupting MDH1 dimerization, which modulates mitochondrial respiration and glutamine-dependent production of NADPH in pancreatic cancer cells. MDH1 downregulation inhibits mitochondrial respiration, glutamine metabolism, and the sensitization of pancreatic cancer cells to oxidative stress and cell proliferation. Wild-type MDH1 re-expression protects pancreatic cancer cells from oxidative damage and restores cell growth and cloning activity. When the clinical sample was examined, it was found that the pancreatic cancer sample was in a hypomethylated state of MDH1 at R248[59].

Metabolomic comparisons revealed that pancreatic cancer tissue had low glucose levels, higher glycolytic intermediates, creatine phosphate, and the amino acids glutamine and serine, which are two main metabolic substrates. However, pancreatic cancer cells accumulate essential amino acids. Further research revealed that the accumulation of essential amino acids may occur from extracellular proteins which are degraded through macropinocytosis, resulting in an excess of most other amino acids[41]. These extracellular proteins are in sufficient quantities to meet the cellular requirement of glutamine. Ras-transformed pancreatic cancer cells transport extracellular proteins into the cell *via* macropinocytosis. The transported protein in the cell is degraded proteolytically, releasing amino acids, such as glutamine[60].

Glutamine is a key nutrient in tumorigenesis and a significant carbon and nitrogen source for biosynthetic reactions. A recent study indicated that tumor microenvironment-hosting cells do not utilize the nutrient like cancer cells do[61]. Liu *et al*[62] demonstrated that pancreatic stellate cells, the resident mesenchymal cells of the pancreas, express more glutamine synthetase than pancreatic cancer cells. Moreover, depletion of glutamine synthetase in pancreatic stellate cells impairs pancreatic cancer cell proliferation *in vivo* and *in vitro*. Mechanistically, researchers found that the β-catenin/TCF 7 complex directly binds to the glutamine synthetase promoter and upregulates glutamine synthetase to promote glutamine synthesis capacity and pancreatic stellate cell pro-tumor effect[62] (Figure 2).

GLUTAMINE METABOLISM AND CHEMO-RESISTANCE

With limited and ineffective medical and surgical treatment, pancreatic cancer is a most aggressive disease. Pancreatic cancer patients with inoperable lesions are treated with systemic chemotherapy, a therapeutic intervention to which most develop resistance. In tumor cells, the necessary raw materials can be provided from glutamine metabolism for over-activated glycolysis and oxidative phosphorylation reaction. Glutamine metabolism can also directly induce chemo-resistance in tumor cells by affecting the homeostasis of glucose, lipid, and protein metabolism.

In humans, the SLC1A5 gene, which consists of eight exons, has two transcribed variants (NM_005628.2 and NM_001145145.1) that differ from each other in the transcription initiation site. The long transcript of SLC1A5, which is also known as ASCT2, lacks exon 2 encodes 541 amino acids, whereas the short variant that lacks exon 1 encodes 339 amino acids. The SLC1A5 variant plays an important role in metabolic reprogramming. SLC1A5 can transport glutamine into the mitochondria *via* a mitochondrial-targeting signal at its N-terminal. HIF-2α mediates hypoxia-induced gene expression of the SLC1A5 variant. SLC1A5 variant overexpression in pancreatic cancer cells is involved in glutamine-induced ATP production and the synthesis of glutathione and confers resistance to gemcitabine (GEM)[63].

In addition, SLC7A8 gene-encoded L-type amino acid transporter 2 (LAT2) may promote glycolysis and decrease GEM sensitivity in pancreatic cancer by regulating two glutamine-dependent positive feedback loops (the LAT2/p-mTORSer2448 loop and the glutamine/p-mTORSer2448/glutamine synthetase loop). The study also showed that the reduced chemotherapy sensitivity caused by LAT2 upregulation in pancreatic cancer cells could be reversed by GEM in combination with an mTOR inhibitor (RAD001)[64].

Pancreatic cancer is characterized by severe hypoxia, which can reduce chemotherapy sensitivity[65]. Recent studies have demonstrated that an increase in glutamine catabolism in pancreatic cancer is the primary mechanism inducing hypoxia, and an *in vitro* 3D cell printing model of hypoxia based on extracellular matrix components has confirmed that glutamine catabolism is significantly increased in chemically resistant pancreatic cancer cells compared to that in chemically reactive pancreatic cancer cells[66]. Further studies have revealed that the rate of oxygen consumption rate is increased by elevated glutamine metabolic flux through oxidative phosphorylation (OXPHOS) in the mitochondrial, promoting hypoxia and chemical resistance. A glutamine antidote can alleviate hypoxia and improve chemotherapy efficacy *in vitro* and *in vivo*[66].

TCGA database revealed that wild-type isocitrate dehydrogenase (wtIDH1) was highly expressed in pancreatic cancer samples. Additionally, higher isocitrate dehydrogenase (IDH1) expression in pancreatic cancer patients is related to a poorer survival rate[67]. Cancer cells rely on wtIDH1 to produce NADPH and αKG for adaptive survival under nutritional constraints. These products support cancer cells under metabolic stress *via* antioxidant defense mechanisms (NADPH) and mitochondrial function (αKG). The experimental results suggest that wtIDH1 is actived by cellular NADPH and αKG, which is of great importance for the chemotherapy efficacy against pancreatic cancer.

5-Fluorouracil (5-FU), a common component of multi-drug treatment strategies in pancreatic cancer, works by converting intracellularly to its active metabolites *via* disrupting the synthesis of RNA and thymidylate synthase, resulting in cytotoxicity[68]. 5-FU treatment of pancreatic cancer cells increases ROS and apoptosis while inducing wtIDH1. An increase in ROS usually accompanied by accumulation of HuR and NRF-2. These compensations can protect cells from ROS damage *via* activation antioxidant defense mechanisms, leading to chemical resistance[69,70].

Kras mutations are most common in pancreatic cancer, and transcriptional reprogramming associated with Kras and abnormal signaling are thought to have a vital role in the development of chemotherapy resistance[71]. To meet the high anabolic needs of pancreatic cancer, carcinogenic Kras up-regulates glycolytic pathways and reprograms glutamine metabolism (manifested as glutamine dependence). GEM and other nucleotide analogs bind to replicated DNA, impairing the synthesis and repair of DNA and conferring cytotoxicity. In order to overcome the competitive inhibition of DNA synthesis, *de novo* synthesis is employed in tumor cells and thus resistance to nucleotide analogs is developed.

Therefore, limitation of the intracellular glutamine availability and inhibition of the glutamine synthetic nucleotides utilization by tumor cells can inhibit the natural nucleotide pool of tumor cells and effectively enhance the chemical sensitivity of tumor cells[72]. Capsid-optimized adenovirus-associated virus 8 vectors was used to deliver the CRISPR-CasRx system to pancreatic cancer *in situ* tumors and patient-derived tumor xenografts, demonstrating that CasRx

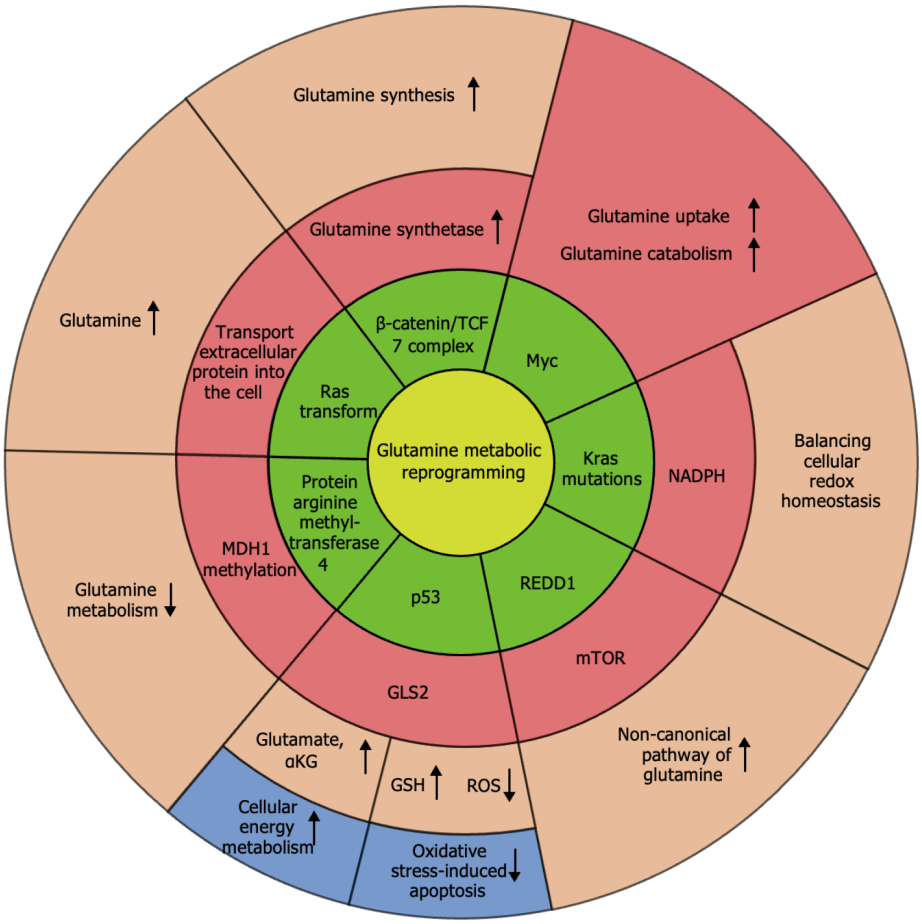

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Figure 2 Glutamine metabolic reprogramming. Glutamine is a key nutrient in tumourgenesis and Glutamine metabolic reprogramming in pancreatic cancer help enhance metabolic use of glutamine in cancer cells. Pancreatic cancer cells affect glutamate metabolism through Myc, Kras mutations, regulated in DNA damage and development 1, p53, Protein arginine methyltransferase 4, Ras transform, β-catenin/TCF 7 complex. REDD1: Regulated in DNA damage and development 1; ROS: Reactive oxygen species; GLS: Glutaminase; mTOR: the mammalian target of rapamycin; MDH1: Malate dehydrogenase 1; GSH: Glutathione.

accurately and efficiently silenced the expression of $Kras^{G12D}$ mutants in pancreatic ductal adenocarcinoma cells guided by $Kras^{G12D}$-specific gRNA. CasRx knockdown of $Kras^{G12D}$ mutants can prevent abnormal activation of downstream signaling induced by $Kras^{G12D}$ mutants, thereby inhibiting tumor growth and improving GEM sensitivity in pancreatic cancer[73].

Glutamine metabolism may also contribute to tumor resistance by influencing protein post-translational modifications. The glutamine analog 6-diazo-5-oxo-L-norleucine treatment can make pancreatic cancer more sensitive to GEM. It has been identified that 6-diazo-5-oxo-L-norleucine can inhibit the hexosamine pathway, causing changes in the level of glycosylation of the entire cell proteome and thus affecting tumor sensitivity to chemotherapy[74]. Based on TCGA dataset analysis, Ganguly *et al*[75] observed mucin 5AC (MUC5AC) depletion in native mouse organoids and human pancreatic cancer cells which increased GEM sensitivity *in vitro* and *in vivo*.

Further analysis revealed that MUC5AC mediated β-catenin nuclear accumulation, which caused c-Myc transcription upregulation, increasing the uptake and utilization of glutamine, deoxycytidine triphosphate biosynthesis, and GEM resistance. Drug inhibitors and gene silencing of the MUC5AC/beta-catenin/c-Myc axis inhibited glutamine metabolism and sensitized MUC5AC-expressing pancreatic cancer cells and tumor organoids to GEM therapy[75].

When nab-paclitaxel was added to GEM, the median overall survival increased to 8.5-9.4 mo, however the median overall survival is 6.7 mo in GEM alone group[76]. Continuous induction of c-Myc plays an important role in nab-paclitaxel-resistant cells, and loss of c-Myc restores the sensitivity to nab-paclitaxel. However, the exact regulatory pathway involved remains unknown[77]. Drug resistance to chemotherapy is an important cause of poor prognosis in pancreatic cancer patients, and glutamine dependence caused by local metabolic reprogramming plays an important regulatory role in the occurrence of chemical drug resistance. Therefore, targeting the glutamine metabolic pathway may improve the chemotherapy effect on pancreatic cancer patients, which merits further investigation.

TARGETING GLUTAMINE METABOLISM IN PANCREATIC CANCER

Because glutamine metabolism is dependent on tumor cells and plays a role in tumor chemotherapy resistance, making it a potential anti-cancer target, many compounds have become the focus of research targeting glutamine metabolism from

initial transport to a subsequent conversion to alpha-ketoglutaric acid[78,79].

GLS converts glutamine to glutamate during glutamine catabolism. Inhibiting GLS activity can reduce the antioxidant capacity of pancreatic cancer cells and inhibit cell proliferation. There are two GLS subtypes in mammalian cells: renal GLS1 and hepatic GLS2. GLS1 shows a widely expression in normal tissues, whereas GLS2 is primarily expressed in the liver, brain, pituitary gland and pancreas[80]. Inhibiting GLS, which inhibits the catalytic hydrolysis of glutamine to glutamate, is the most direct way to target glutamine breakdown. Bis-2-(5-phenylacetamido-1, 2, 4-thiadiazol-2-yl) ethyl sulfide (BPTES) is a specific GLS1 inhibitor with an allosteric, time-dependent property[81]. BPTES uniquely binds to the GLS tetramer oligomerisation interface[82]. Monotherapy with BPTES nanoparticles, a GLS inhibitor, produced significant tumor inhibition in a orthotopic transplantation mouse model[83].

The main glutamine transporter that determines intracellular glutamine levels is ASCT2, which is a key member of the amino acid transport system ASC family[84]. The mRNA level of ASCT2 was dramatically increased in both pancreatic cancer tissue samples and cancer cells. Kaplan-Meier mapping analysis revealed that high ASCT2 expression in pancreatic cancer was significantly associated with TNM stage and poor prognosis in these individuals[85]. Pancreatic cancer cell growth was significantly inhibited by ASCT2 activity blocking, either with L-γ-glutamyl-p-nitroaniline, a ASCT2 inhibitor, or with a specific shRNA silencing ASCT2 expression. Furthermore, ASCT2 knockdown may induce apoptosis through the Akt/mTOR signaling pathway[12]. Rajeshkumar *et al*[86] conducted an unbiased study to determine the anti-tumor efficacy of drugs targeting the metabolic pathways of multiple pancreatic cancer patient-derived xenografts and to determine whether genomic alterations are associated with specific metabolic patterns and thus sensitivity to specific metabolic inhibitors. The results indicated that the GLS inhibitor BPTES and aminotransferase inhibitor aminoacetate inhibited tumor growth, but no clear pattern was associated with tumor genomic status[86].

Ivosidenib (AG-120), a recently developed IDH1 inhibitor, disrupts the redox balance in local tissues, resulting in elevated ROS levels and enhanced chemotherapy-induced apoptosis in pancreatic cancer cells[67]. The United States Food and Drug Administration has approved Ivosidenib (AG-120) for treating mutant IDH1 cholangiocarcinoma and certain hematological malignancies[87]. Recent studies have confirmed that AG-120 is an effective wtIDH1 inhibitor in the tumor microenvironment (such as low nutrient levels), and inhibition of wtIDH1 can disrupt the redox balance, increase ROS levels, and enhance chemotherapy-induced apoptosis of pancreatic cancer cells, all of which play a role in pancreatic cancer inhibition[67,88].

GOT1 contributes to the antioxidant capacity of pancreatic cancer[39], and the antioxidative capacity of cancer cells supports their fitness and survival[89]. The present study identified that Aspulvinone O (AO), a novel inhibitor of GOT1 and glutamine metabolism, can sensitize pancreatic cancer cells to oxidative stress and inhibit cell proliferation. Moreover, selective AO inhibition of GOT1 dramatically reduced the proliferation of pancreatic cancer *in vivo* and *in vitro* [90]. Similarly, studies have demonstrated that a covalent small-molecule inhibitor (PF-04859989), a known kynurenine aminotransferase 2 inhibitor, has pyridoxal-5'-phosphate-dependent inhibitory activity against GOT1 and selective growth inhibition in pancreatic cancer cell lines[91].

In addition, various strategies have been tried in pancreatic cancer patients to treat the Kras mutation and its downstream signaling pathway. Attempts have been made to block the localization of Ras protein on the plasma membrane, to inhibit downstream oncogenic signaling *via* Kras effectors (including MEK1/2, Erk1/2 or Akt) targeting alone or in combination, and to inhibit Kras proteins directly. Due to compensatory mechanisms and toxicity associated with small therapeutic windows, the majority of clinical trials have been directed at targeting downstream pathways, with limited clinical benefit[92].

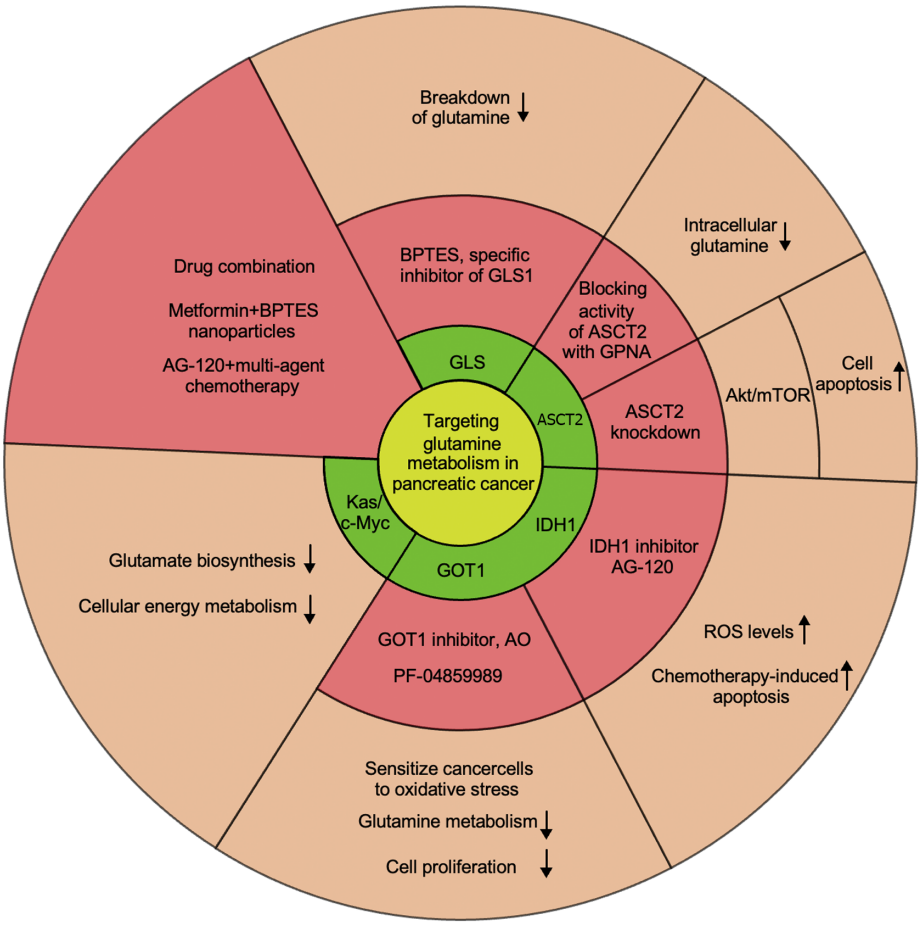
C-Myc is located downstream of Kras and is associated with a number of oncogenic and proliferative pathways in various cancers, including pancreatic cancer. C-Myc provides adequate energy for cancer metabolism and substrate for the synthesis of organic molecules by increasing aerobic glycolysis and modulating the biosynthesis of glutamate biosynthesis in glutamine. Overexpression of C-Myc is correlated with resistance to chemotherapy in pancreatic cancer, and small molecules accelerating the ubiquitination and degradation of C-Myc have shown efficacy in the treatment of pancreatic cancer in preclinical studies[93,94].

However, cancer cells demonstrate strong metabolic compensation ability when a single drug to inhibit key enzymes in the glutamine metabolic pathway is used, making long-term tumor suppression difficult[95,96]. Metabolomic analysis revealed that tumor cells could survive by relying on glycolysis and the synthesis of glycogen following GLS inhibition. Metformin was chosen for application with BPTES nanoparticles based on this finding, and the reduction in pancreatic tumors was significantly more significant than treatment alone[83].

It is suggested that combining glutamine-metabolizing enzyme inhibitors with other anti-metabolic drugs is a promising avenue for further exploration. In addition, pharmacological inhibition of IDH1 by AG-120 is an attractive option for combination therapy with cytotoxic chemotherapy in pancreatic cancer patients, and a phase Ib trial of AG-120 in combination with multi-agent chemotherapy in pancreatic cancer patients has been initiated[67] (Figure 3).

CONCLUSION

Owing to the high incidence of metastatic disease and limited treatment responses, pancreatic cancer is expected to be the second most lethal cancer by 2040[97]. Currently, there are few effective treatment options for pancreatic cancer. Although new combination chemotherapy has improved, the prognosis is often poor due to the rapid development of resistance to chemotherapy. Therefore, there is an urgent need for new treatment strategies to improve the prognosis of the patients[98]. Metabolic reprogramming has attracted renewed interest in recent years. Cancer cells undergo metabolic reprogramming to promote cell growth and proliferation.



DOI: 10.4251/wjgo.v15.i11.1852

Figure 3 Targeting glutamine metabolism in pancreatic cancer. A few compounds that target glutamine metabolism by inhibiting glutaminase 1, Ivosidenib (AG-120) or aspartate transaminase (GOT1), blocking activity of alanine-serine-cysteine transporter 2 (ASCT2), ASCT2 knockdown, affecting Kas/c-Myc are studied for the treatment of pancreatic cancer. ROS: Reactive oxygen species; GLS: Glutaminase; BPTES: Bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl) ethyl sulfide; AO: Aspulvinone O; mTOR: Mammalian target of rapamycin; IDH1: Isocitrate dehydrogenase.

The vital role of glutamine in cell metabolism determines its importance in cancer research. Recently, we have gained a new understanding of the changes in pancreatic cancer metabolism, targeting key enzymes of glutamine metabolism and glutamine transporters and supplementing glutamine metabolism inhibitors during chemoradiotherapy have shown certain anti-tumor effects, but there are still many challenges to developing targeted metabolism into an effective anticancer therapy for clinical application. Owing to the complex feedback loops and parallel and interacting energy supply networks in pancreatic cancer cells, it may be difficult to obtain satisfactory results by inhibiting a single pathway in the energy metabolic pathway of cancer cells. The combined application of multiple anti-metabolic drugs and multi-target intervention has a broad development potential, and individualized treatment based on tumor cell metabolic patterns may further improve the therapeutic effect in pancreatic cancer.

FOOTNOTES

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