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The Function of GPT2 in Tumor Progression

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Abstract: Glutamate pyruvate transaminase 2 (GPT2) is one of the GPTs and is widely used as a biomarker of hepatocellular injury, along with GPT1. GPT2, a glutamine-metabolizing transaminase found in mitochondria, catalyzes the reversible process between glutamate, pyruvate, α-ketoglutarate, and alanine. Compared to GPT1, the intracellular abundance of GPT2 is higher, suggesting that its enzymatic activity has a considerable role in glucose metabolism, amino acid metabolism, and lipid metabolism. In recent years, it has been discovered that deletion or mutation of *GPT2* causes malignant transformation of tumors and that its expression level is closely correlated with tumor development. It is for this reason that the level of GPT2 can be used to reflect the metabolism level of the tumor cells in the body and can indicate metastasis based on its changes. The metabolism level of GPT2 in tumor cells is expected to be a marker in the tumor diagnostic process and subsequently contribute to early detection, thus improving tumor diagnosis and patient prognosis. This paper presents an overview of the current state of GPT2 research in the progression of tumors.

Keywords: Glutamate pyruvate transaminase 2; Glutamine; Isoenzymes

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1. Introduction

The biological characteristics of tumors have been one of the research directions in cancer treatment, and targeted cancer treatment is considered one of the most common areas of study. The key reason for tumor proliferation, which requires large amounts of nutrients to sustain itself and promotes its own development due to its abnormally active metabolism, is the metabolic reprogramming that occurs. Since the initial discovery of the Warburg effect in cancer cells, there has been an emphasis on the glucose metabolism of cancer cells[1]. However, as a result of additional research on energy metabolism, scientists have demonstrated the significant role of glutamine in tumor metabolism[2,3], discovering that glutamine is the second biggest source of nutrient, only after glucose, in tumors; therefore, glutamine metabolism is now regarded as a major characteristic in addition to glucose metabolism[4,5]. Targeting the abnormal metabolism of tumor cells is anticipated to be a novel anti-cancer approach. Understanding the role of glutamine metabolism in tumors is therefore essential for the further development of targeted adjustment of metabolism in tumor cells. This can provide some basis for early diagnosis and even treatment of tumors, thus improving patient prognosis through glutamine levels. Glutamate pyruvate transaminase 2 (GPT2) plays a crucial role in glutamine metabolic activity and is present in higher levels in tumor cells than in normal cells. Clarifying the link between glutamine, GPT2, and tumors can therefore guide the search for molecular markers of tumors and the prevention and treatment of tumors.

2. Structure and function of *GPT2* gene

GPT1 and GPT2 catalyze the reversible ammonia interaction between alanine and 2-ketoglutarate to generate pyruvate and glutamate, ultimately playing a crucial role in the intermediate metabolism of glucose and amino acids. GPT1 and GPT2 share 78% and 69% similarities at the genetic and protein levels, respectively. The human *GPT2* gene encodes a 3.9-kb mRNA comprising 12 exons that cover roughly 50 kb of the genome and is located on chromosome 16q12.1[6]. GPT2 has been researched for its three primary effects on cancer cells (**Figure 1**)[7]. Mitochondrial GPT2 can promote cell survival and growth by maintaining tricarboxylic acid (TCA) cycle back-up after glutaminase (GLS) inhibition, and elevated reactive oxygen species following GLS inhibition can induce GPT2 expression by activating transcription factor 4. Moreover, suppression of GPT2 is coupled with decrease of GLS activity to reduce cancer cell growth and enhance cell death[7]. (2) Glutamine carbon is engaged in the aspartate, glutamate (Glu), and TCA cycle metabolism through glutaminolysis[8], and the high rate of glutaminolysis promotes rapid proliferation by supplying precursors to the low flux biosynthetic pathway[9]. (3) Urothelial carcinoma-associated 1 (UCA1) binds to and stimulates the binding of heterogeneous nuclear ribonucleoprotein (hnRAP) I/L to the GPT2 promoter, resulting in the elevation of GPT2 expression and increased glutamine-derived carbon in the TCA cycle[10]. In addition, tumor cells frequently depend on GPT2 and its conversion product glutamate or α-ketoglutarate (α-KG) to maintain the synthesis of mitochondrial metabolites, take up essential amino acids, act as nitrogen donors in nucleotide and amino acid biosynthesis[11], produce antioxidants to remove reactive oxygen species, regulate redox potential in cells, promote signal transduction[4,12], and regulate autophagy through the rapamycin target protein mammalian target of rapamycin (mTOR) pathway[13]. These actions suggest that mutations or deletions of *GPT2* may play a significant role in the nutritional supply of tumor cells and may increase tumor proliferation and invasion[14]. Glutamine has also been demonstrated to inhibit tumorigenesis[15], which is why a thorough understanding of GPT2 metabolism is required for the development of metabolic treatment techniques that target cancer cells.

3. Regulatory mechanism of GPT2

3.1. Synthesis of GPT2 is closely related to glutamine synthetase (GS)

The dynamic balance between glutamine anabolism and catabolism is critical in tumorigenesis (**Figure 2**). GS is required for the *ab initio* synthesis of GPT2 in the liver and surrounding tissues, which is crucial for cancer growth and development[16]. GPT2 has been demonstrated to be abundant in blood. GS utilizes Glu as a precursor and catalyzes the condensation of Glu and ammonia to produce glutamine. It is predominantly expressed in the lung, brain, and muscle[16], and GS is essential for

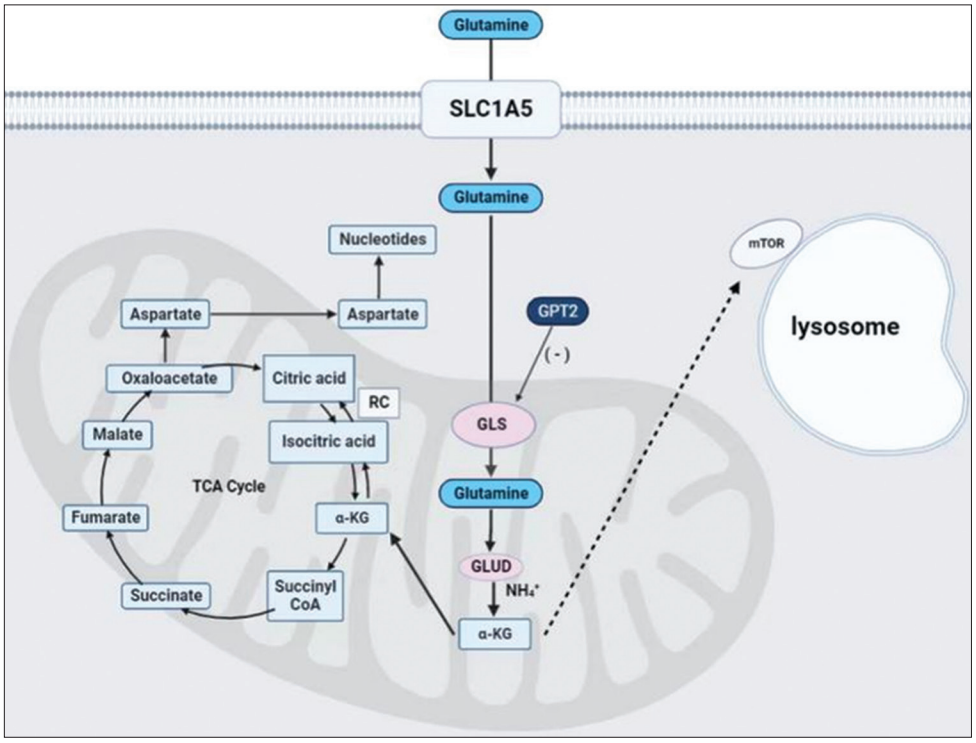

Figure 1. Glutamine metabolic pathway and GPT2.
GLUD: Glutamine dehydrogenase; α-KG: α-ketoglutarate; mTOR: mammalian target of rapamycin; GLS: Glutaminase.

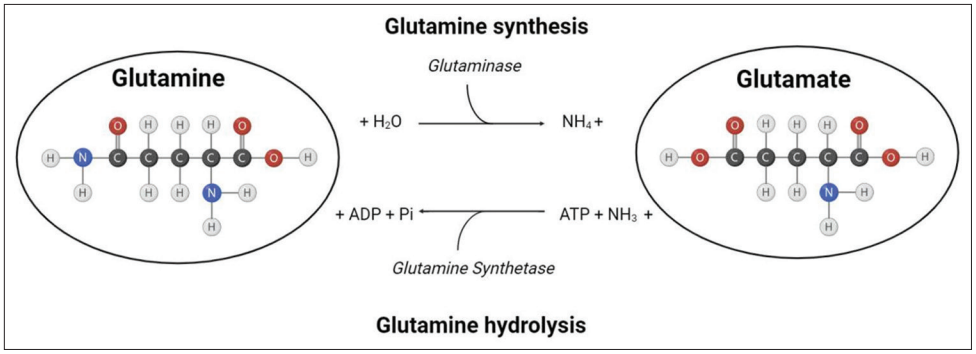

Figure 2. Glutamine synthesis and degradation. Glutamine synthetase uses glutamate (Glu) as a precursor and catalyzes the condensation of Glu with ammonia to form glutamine; glutaminase hydrolyzes glutamine to Glu.

ammonia detoxification[17] and pancreas regeneration[18]. Recent research indicates that GS is highly expressed in a number of cancers, including ovarian cancer[19] and hepatocellular carcinoma[20]. GS is utilized when cells are deficient in GPT2 to maintain cell proliferation and have a compensatory effect. Benzylserine (BenSer), an inhibitor of the GPT2 transporter ASCT2, was used by Ye *et al.* to treat gastric cancer, and their results showed that the proliferation of gastric cancer cells was inhibited, and the number of gastric cancer cells was significantly reduced by simultaneous inhibition of ASCT2 and GS[21]. In addition, Eelen *et al.*[22] discovered that GS influences endothelial cell migration and is involved in regulating RHOJ signaling, suggesting that GS has a clear role in angiogenesis. GS is also implicated in controlling macrophage tropism toward the M2 phenotype and reducing inflammatory and adaptive responses, all of which imply that GS could be a potential molecular marker for tumor detection[23].

3.2. Decomposition of GPT2 is closely related to GLS

GLS is the essential enzyme for the hydrolysis of glutamine into Glu and is the first enzyme engaged in the regulation of glutamine catabolism[24]. It has been shown that when GLS acts on GPT2, it promotes the breakdown of GPT2, and that inhibition of both can effectively inhibit the growth and development of cancer cells and their invasion process[7]. The various mammalian GLS isoform genes encode two isozymes, renal GLS1, and hepatic GLS2[25]. The elevated expression of GLS in many tumors contributes to tumor growth, development, and invasiveness; GLS is a potential target for suppressing cancer cell proliferation, and numerous pervasive small-molecule inhibitors of the glutamine metabolic pathway have emerged[26]. MiR-122 can decrease the proliferation of hepatocellular carcinoma by inhibiting GLS[27], and miR-1-3p can increase cell proliferation and invasion in bladder cancer cells by targeting GLS[28]. All of these tests give ample evidence that GLS promotes tumor formation through glutamine catabolism, and hence, it is able to guide the diagnosis of malignancies.

4. The role of GPT2 in tumor progression

GPT2 is strongly associated with the development of numerous types of tumors, and decreasing GPT2 levels can restrict the growth of tumor cells, suggesting a new methodology to cancer treatment and drug discovery.

4.1. The role of GPT2 in breast cancer progression

Breast cancer is one of the most prevalent malignancies in the world, and its prevalence and fatality rate are both rising. Varied subtypes of breast cancer have different molecular mechanisms and physiological conditions since they are heterogeneous tumors. The search for a new diagnostic biomarker is particularly crucial because the treatment of metastatic breast cancer is still very challenging since only the early-stage breast cancer is treatable. Cao *et al.* found that GPT2 could promote tumorigenesis in breast cancer cells by activating Sonic Hedgehog signaling, as GPT2 overexpression reduced intracellular α-KG and increased the stability of hypoxia-inducible factor 1-alpha (HIF-1α), which, in turn, activated the Sonic Hedgehog (Shh) signaling pathway to increase the stemness of breast cancer cells[29]. Mitra *et al.* showed that GPT2 can serve as a hub between glycolysis and glutamine catabolism and is strongly increased in invasive breast tumors, especially of the triple-negative subtypes. Its absence leads to the impairment of the mTOR complex 1 activity and the induction of autophagy, which, in turn, induces the mTOR signaling pathway to inhibit the growth of breast cancer cells and to promote autophagy[30].

4.2. The association of GPT2 with the progression of hepatocellular carcinoma

Primary hepatocellular carcinoma (HCC) is one of the most lethal and aggressive cancers in the world, with a high fatality rate. There are few therapy options currently available for HCC. In general, surgical resection, liver transplantation, and local ablation therapy have the ability to cure patients with the early- and intermediate-stage

HCC. For patients with advanced, inoperable HCC, and multikinase inhibitors (such as sorafenib or lenvatinib) are the primary choice for systemic treatment. Despite this, pharmacological therapy is still associated with a significant number of negative effects. Therefore, innovative molecular indicators are required to expedite their diagnosis and enhance the prognosis of affected patients. Chronic and acute disruption of liver receptor homolog 1 in stem cells affects glutamine-induced back-up and α-KG availability, which suppresses the mTORC1 pathway in an α-KG-dependent manner, thereby lowering the metastatic invasiveness of HCC[31].

4.3. The function of GPT2 in the development of colorectal cancer

Colorectal cancer (CRC) is one of the most widespread and susceptible malignancies worldwide, as well as one of the main causes of death among humans. The cure percentage and cure rate are significantly higher if the CRC is discovered at an early stage. Although colonoscopy has been recognized as the gold standard for CRC screening, attributed to the high level of sensitivity and specificity, there are alternative screening methods. Nevertheless, it is expensive and labor-intensive and requires skilled endoscopists and patient compliance. Therefore, biomarkers are still required to enable the early detection of tumors and to improve diagnostic efficacy and patient prognosis. GPT2 has also been applied in the diagnosis of CRC in recent years, and Wang *et al.* revealed that the cells of signet ring cell carcinoma (SRCC), a variant of CRC, can boost the proliferation and invasive capabilities of the cells through the synergistic effect of GPT2 and SLC1A5[32]. Chen *et al.* discovered that *PIK3CA* mutations reprogramed GPT2 metabolism to drive CRCs through activation of the PI3K-MEK/PDK1-GPT2 signaling axis, indicating that *PIK3CA* mutations may serve as biomarker to predict patient response to drugs targeting glutamine metabolism[33].

4.4. The role of GPT2 in the progression of non-small-cell lung cancer (NSCLC)

NSCLC accounts for a substantial fraction of lung cancers. Lung cancer is also one of the top causes of death in humans. Tumors are typically locally progressive or metastatic at the time of diagnosis, resulting in a dismal prognosis for the disease. NSCLC comprises adenocarcinoma, squamous cell carcinoma, and large cell lung cancer. The limited efficacy of drug-based treatments, such as cisplatin, and targeted therapies introduced in the previous decade, as well as the inability to detect mutations in around 50% of NSCLC cases demand the search for novel therapeutic targets. Caiola *et al.* found that when GPT2 inhibitors were used, NSCLC severely impaired its access to energy and could only regain energy through the use of extracellular alanine, indirectly reflecting that GPT2 could promote the growth, development, and invasive ability of NSCLC[34].

4.5. The role of GPT2 in the progression of bladder cancer

Bladder cancer is one of the most prevalent genitourinary cancers. Although cystoscopic biopsy is presently the gold standard for identifying bladder cancer, it can be painful and stressful for patients, and thus, this technique is difficult to be popularized for its application. GPT2 also has a role in the development of bladder cancer. According to recent research, this finding may help us improve the diagnostic efficacy of bladder cancer. Zhao *et al.* reported that binding of the long-chain noncoding RNA uroepithelial carcinoma-associated 1 (UCA1) to hnRNP I/L elevated GPT2 expression to promote Glu-driven TCA back-up, subsequently promoting the proliferation and distant metastasis of bladder cancer cells[10].

4.6. The role of GPT2 in the progression of renal cell carcinoma

Renal cell carcinoma is also a common type of cancer in the genitourinary system. The most common type of renal cell carcinoma, based on the histological and molecular subtypes, is renal clear cell carcinoma. Despite the use of various new diagnostic and surgical strategies, many patients still develop local recurrence or distant metastases. Despite being the first-line treatments for metastatic renal cell carcinoma, the efficacy of targeted drugs, such as tyrosine kinase inhibitors and mTOR, is compromised during the diagnosis of renal cell carcinoma, which is usually detected too late at screening, resulting in a lower survival rate. New biomarkers and their molecular mechanisms should be discovered to design better treatment options for renal clear cell carcinoma. Recently, GPT2 has also been found to play a role in the development of renal cell carcinoma, and GPT2 may serve as a molecular marker to help us improve the diagnostic efficacy and thus the prognosis of patients. Wu *et al.* discovered that βII spectrin (SPTBN1) expression was significantly downregulated in renal clear cell carcinoma. The downregulation was attributed to the activation of GPT2-dependent glycolysis, which, in turn, promoted the development of renal clear cell carcinoma. Therefore, SPTBN1 may be a possible target for the treatment of renal clear cell carcinoma[35].

4.7. The role of GPT2 in astrocytoma progression

Glioblastoma is the most common and serious malignancy of the adult central nervous system. Classified by the World Health Organization as a grade IV astrocytoma, it is classified according to molecular type as proneural, classic, and mesenchymal. The prognosis remains poor

despite a combination of treatments, including maximal surgical resection, radiotherapy, and chemotherapy. Metabolic reprogramming is now considered to be one of the hallmarks of cancer, thereby spawning the research on the connection between GPT2 and astrocytoma. As such, GPT2 could also be a diagnostic and prognostic target in astrocytomas, leading to improved diagnosis and prognosis. Moreira *et al.* found that upregulation of GLS isoform 2 (GLSiso2) gene was associated with the development of astrocytomas, particularly in glioblastomas, where GLSiso2 could upregulate GPT2 in relation to glutathione synthesis-related genes, thereby favoring tumor cell survival, and the GPT2 upregulation mainly occurs in the most aggressive mesenchymal subtypes, thereby reducing sensitivity to oxidative stress and making them less sensitive to radiotherapy and alkylation[36].

5. Summary and prospects

To maintain the high demand for cell proliferation, cancer cells must undergo coordinated reprogramming of metabolic pathways that regulate amino acid synthesis, glycolysis, oxidative phosphorylation, TCA cycle, and pentose phosphate pathway. This renders cancer cells highly dependent on intracellular antioxidant mechanisms and increases their demand. It may also generate a tailored vulnerability of tumor cells to GPT2 and inspire the development of novel cancer treatment targets. These findings, from the Warburg effect in tumors to the redefining of the central role of GPT2 in tumor cell metabolism, demonstrate the rapid development in the field of cancer metabolism. In this article, significant cancer-related advances in GPT2 and its related metabolic enzymes are summarized. The development of targeted GPT2 inhibitors based on the role of GPT2 in tumor progression is an important direction for cancer therapy; subsequently, a thorough understanding of the role of GPT2 in tumor metabolism is crucial. The metabolism of tumors has consistently been one of the most widely studied topics in cancer therapy. During the rapid growth of tumors with an abnormally active metabolism, metabolic reprogramming occurs, with glucose and glutamine serving as the primary nutrients for tumors. Understanding the involvement of glutamine metabolism in tumors is therefore crucial for the development of strategies to target cancer cells. In conclusion, GPT2-based regulation of tumor cell proliferation and its applications still possess considerable research potential.

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Conflict of interest

The authors declare no potential conflicts of interest.

Author contributions

Chong Li and Huake Wang initiated and conceived the idea of the work. Jun Xie wrote the manuscript. Haifeng Wang and Hongjin Shi revised the manuscript. All authors contributed to the literature search.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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