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Research progress of amino acid metabolism affecting gastric cancer by regulating PI3K/AKT/mTOR signaling pathway

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Abstract: In the tumor microenvironment, amino acids are important nutrients constituting immune cells and tumor cells. Some proteins or key enzymes in the metabolism process are expected to become tumor diagnostic markers or therapeutic targets. It was found that the contents of some amino acids were obviously different between normal people and gastric cancer patients. Amino acid metabolism has also been confirmed to be involved in the activation of the PI3K/AKT/mTOR pathway, which is one of the main pathways regulating the growth, proliferation, division and autophagy of tumor cells. Amino acid metabolism can be used as a signal molecule to affect the occurrence, development and prognosis of gastric cancer by activating related targets of this pathway. In addition, amino acid metabolism plays an important biological role in the activation and differentiation of immune cells, which can affect the immune function of tumors by regulating immune cells and immune factors.

Keywords: Amino acid metabolism; PI3K / AKT / mTOR; Gastric cancer; Immunity; Autophagy; Glutamine; Leucine; Arginine; Aspartate

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Gastric cancer (GC) is the fifth most common cancer worldwide and the third most common cause of cancer death. *Helicobacter pylori* (Hp) infection, age, high salt intake, and low contents of fruits and vegetables in diet are risk factors for GC [1]. Although the incidence and mortality of GC have decreased with the improvement of dietary structure and increased awareness of pathogenic factors, the prognosis of GC patients is still poor. Currently, common treatments include surgery and chemotherapy [2], and the 5-year survival rates of patients can be significantly improved through surgical resection for early GC. However, there is no specific clinical indication for early GC, thus most patients are already in the advanced stage at the time of diagnosis and have lost the opportunity for surgery, resulting in a poor prognosis [3]. In recent years, the pathological features and the tendency of GC have still been unclear, and metabolomics research found differences in amino acid metabolism between normal people and GC patients.

1 Amino acid metabolism regulates GC progression

Amino acids are the essential components of proteins and play an important role in the biosynthesis of nucleotides, lipids, glutathione, glucosamine, and polyamines [4]. Diet-induced changes in the concentration of amino acids are closely related to the activation of signaling pathways [5]. At the same time, amino acids are important nutrients that constitute immune cells and tumor cells, and are involved in the composition of the human immune system [6]. Abnormal amino acid metabolism is one of the characteristics of tumors, and amino acid metabolism is involved in the progression of tumors. It can damage the normal function of immune cells in the tumor microenvironment (TME).

In the last century, the “Warburg effect” was discovered by researchers, which indicates the relationship between metabolomics and tumor progression [7]. It reveals the reprogramming of glucose metabolism within tumor cells. However, in addition to abnormal glucose metabolism in tumor cells, abnormal amino acid metabolism has also gradually attracted the attention of researchers. During the occurrence and progression of GC, reprogramming of amino acid metabolism is one of the most significant features, including the uptake rate of amino acids, metabolic pathways of amino acids, metabolites, or abnormalities in key enzymes in tumor cells [8]. Some proteins or key enzymes in the metabolic process are expected to become diagnostic markers of tumors or therapeutic targets. At present, there is no evidence shows that the amino acid metabolism has a direct influence on the occurrence and progression of GC. However, through metabolomics testing, the amino acid content in GC patients' blood, urine, and tissues showed significant differences

compared with those of normal people, and these differences in amino acid metabolism may provide a direction for how amino acid metabolism influences GC [9].

In addition to the rapid proliferation, the progression of GC is closely related to its surrounding environment. Therefore, improving the TME of GC is also an essential factor to be considered in treating GC. Alteration of TME is a hallmark change in tumors. In the TME, tumor cells activate immune cells under the condition of amino acid withdrawal by regulating the balance of amino acid metabolism. Thus, more amino acids will be used for tumor cells' proliferation and invasion, and inhibition of immune cells' normal function [6]. In the TME, there are a variety of immune cells, such as regulatory T cells (Treg), tumor-associated macrophages (TAM), myeloid-derived suppressor cells (MDSC), etc. [10], especially effector T cells, whose infiltration capacity can be decreased under multiple factors. They can also inhibit infiltrating effector cells to affect antigen presentation and recognition, which will lead to immune surveillance malfunction and tumor immune escape, thus impairing the body's anti-tumor immune response [11].

2 Different amino acids regulate occurrence and progression of GC via PI3K/AKT/mTOR signaling pathway

2.1 Several ways of PI3K/AKT/mTOR signaling pathway regulating GC

PI3K-AKT is an agonist of cell survival and metabolism, which is involved in apoptosis, autophagy, and other functional states of GC cells. Its regulation of GC progression generally includes several forms: participating in the angiogenesis of GC tumor cells, inducing apoptosis and autophagy in GC cells, promoting cell invasion, metastasis, and other processes in GC [12].

2.1.1 Involvement in angiogenesis of GC tumor cells

Angiogenesis is the foundation of the formation, proliferation, and metastasis of GC cells [13], and it has been found that vascular endothelial growth factor (VEGF) plays a driving role in the occurrence and progression of GC. The literature reveals that VEGF is closely relevant to micro-vessel density, tumor invasiveness, and tumor metastasis, verifying the importance of angiogenesis in occurrence and progression of GC. Therefore, VEGF has become a target in the present anti-angiogenic treatment of GC [14]. Chen *et al.* [15] found that inhibition of the AKT signaling pathway helps to induce the expression of CRMP4, which can reduce cell proliferation and metastasis in GC cells in a VEGF-mediated pathway.

2.1.2 Induction of apoptosis and autophagy in GC cells

Abnormal apoptosis is one of the crucial factors in occurrence and progression of tumors. B-cell lymphoma-2 (Bcl-2) and p53 are the primary factors affecting apoptosis [16]. Wang *et al.* [17] found that Hp-infected GC cells showed reduced manifestations of increased cell proliferation and decreased apoptosis after the PI3K/AKT signaling pathway was inhibited.

2.1.3 Promotion of invasion and metastasis in GC cells

Metastasis and invasion are essential processes in the growth of most tumor cells, and the metastasis of GC is promoted by activating the signaling targets in the PI3K/AKT signaling pathway. Thy-1 antigen (CD90) is located at chromosome 11q23.3, and CD90 plays a key role in occurrence and progression of tumors of GC by regulating cell proliferation, invasion, and metastasis. Gao [18] *et al.* found that CD90 up-regulated the levels of PI3K, AKT, p-AKT-Ser473, and down-regulated the expression of PTEN and p53, which indicated that CD90 may affect the invasion and metastasis of GC by regulating the PI3K/AKT signaling pathway.

2.2 Glutamine

Glutamine is the most abundant amino acid in human plasma and is involved in glutamate biosynthesis. It is a product of the glutaminase (GLS) activity and a source of amino acids for non-essential amino acids such as alanine, aspartic acid, serine, and glycine. These non-essential amino acids are important for macromolecular synthesis [19]. Glutamate is hydrolyzed by glutamate dehydrogenase and then converted to α-ketoglutarate to formulate the tricarboxylic acid (TCA) cycle. α-ketoglutarate is a substrate for the dioxygenases that modify proteins and DNA. Glutaminolysis is the conversion of glutamine to glutamate, which produces energy via lactate [20]. This phenomenon is more prominent in tumor cells, where glutamine synthesized by the normal pathway is not sufficient for the rapid proliferation and progression of the tumor cells themselves. Accordingly, there is glutamine addiction in tumor cells.

Glutamine metabolism regulates the proliferation, growth, invasion, and metastasis of GC cells by activating the PI3K/AKT/mTOR signaling pathway. Studies have illustrated that genes related to the PI3K/AKT/mTOR signaling pathway are commonly activated in GC patients, and glutamine modulation of this pathway is beneficial to inhibit GC [21]. It has been reported that ASCT2, a Na^+-dependent neutral amino acid transporter, encoded by the solute carrier family 1, member 5 (SLC1A5) gene, is the primary transporter protein responsible for the uptake of glutamine into cancer cells. Ye *et al.* [22] found that glutamine could inhibit the growth of GC cells by regulating the expression of ASCT2. Additionally, mTOR, a key signaling node that regulates protein translation, cell growth, and autophagy, plays the most important role in the relevant targets activated by glutamine metabolism [23]. Among the complexes composed of mTOR, the dysregulation of mTORC1 is a key factor in occurrence and progression of tumors, and glutamine participates in the activation process of mTORC1. It has been reported

that glutamine can be a signaling regulator of mTORC1 to promote leucine uptake [24], promoting the composition of mTORC1 and localization of lysosome fusion.

2.3 Leucine

Leucine is a proteinogenic amino acid that typically regulates growth by activating the mechanistic target of rapamycin complex 1 (mTORC1) to control the synthesis of protein and lipids and processes such as autophagy. Studies have shown that amino acids are signaled to mTORC1 through Rag guanosine triphosphatases (GTPases) [25], and Rag proteins are a family of four related small GTPases that interact with mTORC1 in an amino-acid-sensitive manner [26]. Rags are obligate hetero-dimers, with RagA or RagB pairing with RagC or RagD [27]. Leucine stimulates Rags to switch to their active nucleotide-binding state, allowing them to bind to Raptor and recruit mTORC1 to the lysosomal surface.

Leucine and arginine in the cytoplasm signal to mTORC1 via a unique pathway consisting of the GATOR1 and GATOR2. It has been reported that SAR1B is a leucine sensor that regulates mTORC1 signaling based on intracellular levels of leucine. Under leucine-sufficient conditions, SAR1B binds to leucine, undergoes a conformational change, and dissociates from the GATOR2 dissociation, thereby causing mTORC1 activation [28]. In addition, it has been shown that Sestrin 2, a direct leucine sensor upstream of the mTORC1 pathway, binds to GATOR2 and inhibits its function under leucine starvation, and that leucine disrupts the Sestrin2-GATOR2 interaction by binding to Sestrin 2. The leucine-binding capacity of Sestrin2 is vital to activate intracellular mTORC1 [25]. In addition, it has been reported that transporter proteins containing two subunits, SLC7A5 (LAT1) and SLC3A2, mediate leucine transport. The expression of these two subunits is up-regulated when the T cell receptor (TCR) is involved in T cell activation. That inhibition of SLC7A5 causes a closed state and suppresses the anti-tumor function of human T cells [29]. Sinclair *et al.* [30] found that leucine is involved in the activation of the mTORC1 signaling pathway in T cells through the L-type amino acid transporter 1 (LAT1, also known as SLC7A5). At the same time, the protein expression of SLC7A5 regulates T-cell metabolism. This suggests that leucine can regulate the immune function of tumors by activating the mTORC1 signaling pathway in T cells via the SLC7A5, thus affecting tumor progression.

2.4 Arginine

Arginine is a semi-essential amino acid with various metabolic and regulatory roles. It serves as a proteinogenic amino acid and a precursor of critical molecules such as nitric oxide, creatine, and glutamate [31]. Arginine is one of only three amino acids that can directly activate the mTOR pathway, and its main pathway is to directly activate the mTOR signaling pathway through cellular sensors [32]. The specific ways are as follows:

1. Arginine activation of mTORC1 requires SLC38A9, a member of solute carrier family 38 (SLC38), a lysosomal arginine transporter that regulates amino acid-dependent mTORC1 activity via the Rag-Ragulator complex [35-36].

2. Arginine disrupts the interaction between tuberous sclerosis complex (TSC) and mTORC1, thereby activating the mTOR signaling pathway [35].

3. Arginine disrupts the CASTOR-GATOR2 complex by binding to CASTOR1, which suggests that arginine can activate the mTORC1 pathway by binding to CASTOR1 [36]. GATOR1, composed of DEPDC5, Nprl2, and Nprl3, inhibits mTORC1 signaling by acting as a GTPase-activating protein (GAP) for RagA/B, allowing Rag A to bind the component of mTORC1 complex, and redistribute mTORC1 to the lysosome [37]. In contrast, GATOR2 (composed of Mios, WDR24, WDR59, Seh1L, and Sec13) is a positive regulator of mTORC1 signaling and interacts with GATOR1 on the lysosomal membrane [5]. This could explain why arginine is a potent activator of mTOR, and arginine deprivation leads to immediate inactivation of mTOR [37]. The mTOR signaling pathway plays an important role in occurrence and progression of tumors of GC. Therefore, arginine can influence the process of GC progression by participating in the modulation of the mTOR signaling pathway, which is one of the treatments of GC in clinical practice.

Arginine metabolism is mainly regulated by two enzymes: arginase 1 (ARG1) and nitric oxide synthase (NOS). Citrulline is catalyzed by argininosuccinate synthetase 1 (ASS1) and argininosuccinate lyase (ASL) to produce arginine, which is broken down into ornithine and urea by ARG1. Ornithine generates citrulline via ARG and ornithine carbamoyl transferase (OCT), thus realizing the role of this metabolic cycle. NOS promotes the oxidative hydrolysis of arginine to produce NO, which is involved in the anti-inflammatory and immune processes, and is essential in maintaining regular cellular immune activity. It has been reported that NO inhibits T-cell proliferation and promotes T-cell apoptosis, thereby modulating tumor immunity [38]. In addition, cysteoaspartase-8 (caspase 8) has long been known to promote apoptosis and is part of the mechanism of cytotoxic chemotherapy. Nanthakumaran *et al.* [39] found that arginine activates cellular immunity via caspase 8 thereby inhibiting the proliferation of GC cells. Therefore, arginine can also inhibit the progression of GC by modulating the immune function of tumors.

2.5 Other amino acids

Aspartic acid is an α-amino acid, which belongs to non-essential amino acids in the human body. In GC cells, aspartic acid and asparagine can be involved in the proliferation of GC cells and regulate intracellular signaling. Studies have shown that extracellular supplementation of asparagine can maintain protein translation and promote tumor growth when glutamine is

deficient in tumor cells [40].

Tryptophan is an essential amino acid that participates in a variety of human activities and maintains regular cellular functions. It has an important role in tumor metabolism. In addition to protein synthesis, tryptophan regulates a series of processes in the TME and tumor metabolism through the kynurenine pathway, including inflammatory response, immune response, and so on. According to the literature, kynurenine pathway metabolites can rapidly activate the PI3K/AKT signaling pathway, promote tumor cell proliferation, and inhibit apoptosis [41].

Serine and glycine are important in the proliferation of GC cells. Their related metabolic enzymes and metabolites will regulate the growth of tumors. When the intake of exogenous serine is insufficient, the tumor cells can produce endogenous serine through the serine synthesis pathway, and both endogenous and exogenous serine contribute to the proliferation of tumor cells. Glycine in tumor cells can be synthesized in various ways, and many metabolic enzymes in its synthesis pathway regulate tumor growth by interacting with transcription factors [8]. Therefore, targeting serine and glycine may provide a new idea for tumor therapy.

3 Outlook

Reprogramming of amino acid metabolism is one of the crucial features of GC. The proliferation of GC cells is rapid, and a series of metabolic disorders often occur during this process, resulting in the formation of the TME. The comparison of amino acid metabolism between patients with GC and normal people can provide a new treatment for GC. In tumor cells, on the one hand, amino acids can change the TME and activate signaling pathways through the regulation of metabolic pathways. Amino acid metabolism has been proved to be involved in the activation of the PI3K/AKT/mTOR signaling pathway. However, the roles of some amino acids in the PI3K/AKT/mTOR signaling pathway still need to be clarified. On the other hand, amino acid metabolism plays an important biological role in the activation and differentiation of immune cells, which can affect the immune function of tumors through the regulation of immune cells and immune factors. Therefore, if the mechanism of interaction between amino acid metabolism and immunity can be investigated, it will provide a theoretical basis for researching relevant antitumor drugs and other drugs in the future.

Conflict of interest None

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· 研究进展 ·

氨基酸代谢调控胃癌 PI3K/AKT/mTOR 信号通路的研究进展

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摘要：在肿瘤微环境中，氨基酸是构成免疫细胞和肿瘤细胞的重要营养物质，其代谢过程中的部分蛋白质或关键酶有望成为肿瘤诊断标志物或治疗靶点。研究发现部分氨基酸含量在正常人和胃癌患者中存在明显差异。氨基酸代谢也被证实参与激活 PI3K/AKT/mTOR 通路，该通路是调节肿瘤细胞生长、增殖、分裂、自噬等活动的主要通路之一，氨基酸代谢可作为信号分子，通过激活该通路相关靶点来影响胃癌的发生发展及转归预后；此外，氨基酸代谢对于免疫细胞的激活和分化有着重要生物学作用，可以通过调控免疫细胞和免疫因子对肿瘤的免疫功能产生影响。

关键词：氨基酸代谢；PI3K/AKT/mTOR 通路；胃癌；免疫；自噬；谷氨酰胺；亮氨酸；精氨酸；天冬氨酸

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Research progress of amino acid metabolism regulating PI3K/AKT/mTOR signaling pathway in gastric cancer

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Abstract: In the tumor microenvironment, amino acids are important nutrients constituting immune cells and tumor cells. Some proteins or key enzymes in the metabolism process are expected to become tumor diagnostic markers or therapeutic targets. It was found that the contents of some amino acids were obviously different between normal people and gastric cancer patients. Amino acid metabolism has also been confirmed to be involved in the activation of the PI3K/AKT/mTOR pathway, which is one of the main pathways regulating the growth, proliferation, division and autophagy of tumor cells. Amino acid metabolism can be used as a signal molecule to affect the occurrence, development and prognosis of gastric cancer by activating related targets of this pathway. In addition, amino acid metabolism plays an important biological role in the activation and differentiation of immune cells, which can affect the immune function of tumors by regulating immune cells and immune factors.

Keywords: Amino acid metabolism; PI3K/AKT/mTOR pathway; Gastric cancer; Immunity; Autophagy; Glutamine; Leucine; Arginine; Aspartate

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胃癌是全球第五大常见癌症，也是第三大常见癌症死亡原因。其危险因素包括幽门螺杆菌(*Helicobacter pylori*, Hp)感

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染、年龄、高盐摄入量以及饮食中水果和蔬菜含量低[1]。尽管随着饮食结构的改善,人们对幽门螺杆菌感染等胃癌致病因素的认识增强,胃癌的发病率和死亡率所有下降,但胃癌患者的预后仍然较差。目前常用的治疗手段包括手术治疗、化疗等[2],早期胃癌经手术切除后可以明显提高患者的 5 年生存率,但由于早期胃癌没有特异性临床指征,多数患者就诊时已处于进展期而失去手术机会,导致预后较差[3]。近年来,胃癌发生发展的机制尚不明确,运用代谢组学研究发现正常人与胃癌患者之间存在氨基酸代谢差异。

1　氨基酸代谢调控胃癌发生发展

氨基酸是组成蛋白质的基本成分,对核苷酸、脂质、谷胱甘肽、氨基葡萄糖和多胺的生物合成具有重要作用[4];由饮食引起的氨基酸浓度变化与信号通路的激活密切相关[5]。同时,氨基酸是构成免疫细胞和肿瘤细胞的重要营养物质,参与构成人体免疫系统[6];氨基酸代谢异常是肿瘤的特征之一,氨基酸代谢参与肿瘤的发生发展并能影响肿瘤微环境(tumor microenvironment, TME)中免疫细胞的正常功能。

20 世纪,研究人员发现的瓦博格效应(Warburg effect)不仅指明了代谢组学与肿瘤发生发展的关系[7],还揭示了肿瘤细胞内部葡萄糖代谢重编程的现象。然而,在肿瘤细胞中除了糖代谢异常外,氨基酸代谢异常也逐渐引起研究人员的注意。在胃癌的发生发展过程中,氨基酸代谢重编程是其重要特征之一,包括肿瘤细胞内氨基酸的摄取速率、氨基酸的代谢途径、代谢产物或代谢关键酶异常等[8],其代谢过程中的部分蛋白质或关键酶有望成为肿瘤诊断标志物或治疗靶点,目前尚没有研究表明氨基酸代谢对胃癌发生发展有直接影响,然而通过代谢组学检测,胃癌病人的血液、尿液、组织中氨基酸含量与正常人相比均出现较大差异[9],这些氨基酸代谢差异有可能为氨基酸代谢影响胃癌提供方向。

胃癌的发生发展,除了胃癌细胞自身的快速增殖特性之外,还与其周围环境密切相关,因此,改善胃癌 TME 也是胃癌治疗过程中需要考虑的重要因素。TME 改变是肿瘤的一个标志性变化。在 TME 中,肿瘤细胞通过调控氨基酸代谢平衡,使免疫细胞处于氨基酸饥饿状态,从而将更多的氨基酸用于肿瘤细胞自身增殖与侵袭,并抑制免疫细胞的正常功能[6]。在 TME 中,存在多种免疫细胞,如调节性 T 细胞(regulatory T cell, Treg)、肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)、髓源性抑制细胞(myeloid-derived suppressor cell, MDSC)等[10],特别是效应 T 细胞,在多种因素的作用下,其浸润能力降低,同时能抑制浸润的效应细胞,影响抗原的提呈和识别,导致免疫监视失能和肿瘤免疫逃逸,从而损害机体的抗肿瘤免疫反应[11]。

2　不同氨基酸通过 PI3K/AKT/mTOR 信号通路调控胃癌发生发展

2.1　PI3K/AKT/mTOR 信号通路调控胃癌　PI3K-AKT 是细胞生存和代谢的激动器,参与胃癌细胞的凋亡、自噬及其它功能状态等。其调控胃癌的发生发展一般包含几种不同形式:参与胃癌肿瘤细胞血管生成、诱导胃癌细胞凋亡和自噬、促进胃癌细胞侵袭、转移等过程[12]。

2.1.1　参与胃癌肿瘤细胞血管生成　血管生成在胃癌细胞形成、增殖和转移过程中处于根基地位[13],研究发现,血管内皮生长因子(vascular endothelial growth factor, VEGF)对胃癌的发生发展起到驱动作用。据文献报道,VEGF 与微血管密度、肿瘤侵袭性及肿瘤转移密切相关,证实了血管生成在胃癌发生发展中的重要性。因此,VEGF 是目前抗血管生成治疗胃癌的重要靶点[14]。Chen 等[15]研究发现抑制 AKT 信号通路有助于诱导 CRMP4 表达,从而可以通过 VEGF 介导的方式减少胃癌细胞中的细胞增殖和转移。

2.1.2　诱导胃癌细胞凋亡和自噬　细胞凋亡异常是肿瘤发生发展的重要因素之一,B 淋巴细胞瘤-2、抑癌基因 p53 等是影响细胞凋亡的主要因子[16]。王丽萍等[17]研究发现,PI3K/AKT 通路被抑制后,Hp 感染的胃癌细胞增殖增加、凋亡降低等表现均降低。

2.1.3　促进胃癌细胞侵袭和转移　迁移与侵袭是大部分肿瘤细胞生长的重要环节,通过激活 PI3K/AKT 通路中的信号靶点,可促进胃癌的转移。Thy-1 细胞表面抗原(CD90)位于人染色体 11q23.3 上,CD90 通过调节细胞增殖、侵袭转移等,在胃癌的发生发展中起关键作用,Gao 等[18]选取人胃癌细胞研究发现,CD90 上调了 PI3K、AKT、p-AKT-Ser473 的水平,并下调了 PTEN 和 p53 的表达,提示 CD90 通过调控 PI3K/AKT 通路影响胃癌的侵袭和转移。

2.2　谷氨酰胺　谷氨酰胺是人体血浆中含量最多的氨基酸,参与谷氨酸的生物合成,谷氨酸是谷氨酰胺酶反应的产物,同时也是丙氨酸、天冬氨酸、丝氨酸和甘氨酸等非必需氨基酸的氨基来源,这些氨基酸都是大分子合成所需的基本物质[19]。谷氨酸在谷氨酸脱氢酶的水解下,进而转化为 α-酮戊二酸,供给三羧酸(TCA)循环,α-酮戊二酸是修饰蛋白质和 DNA 的双加氧酶的底物。谷氨酰胺的分解是在线粒体中脱氨转化为谷氨酸通过乳酸产生能量[20],这一现象在肿瘤细胞中更加突出,通过正常途径合成的谷氨酰胺不能满足肿瘤细胞自身快速的增殖发育,因此在肿瘤细胞中存在着“谷氨酰胺依赖”现象。

谷氨酰胺代谢通过激活 PI3K/AKT/mTOR 通路参与调节胃癌细胞增殖、生长、侵袭和转移。研究表明,胃癌患者与 PI3K/AKT/mTOR 信号通路相关基因被普遍激活,谷氨酰胺调控该通路对抑制胃癌的发生具有良好作用[21]。有文献报道,溶质连接载体家族 A1 成员 5(SLC1A5)基因编码的 Na^+依赖的中性氨基酸转运蛋白 ASCT2 是负责摄取谷氨酰胺进入癌细胞的主要转运蛋白,Ye 等[22]研究发现,谷氨酰胺能通过调节 ASCT2 的表达来抑制胃癌细胞生长。此外,能够调节蛋白质翻译、细胞生长和自噬的关键信号节点 mTOR 是谷胱氨酸代谢激活的相关靶点中最重要的部分[23],在组成 mTOR 的复合物中,mTORC1 的失调在肿瘤的发生发展中是关键因素,谷氨酰胺参与 mTORC1 的激活过程,有研究报道,谷氨酰胺作为信号调节 mTORC1,促进其对亮氨酸的摄取[24],进而促进 mTORC1 组成和溶酶体定位。

2.3　亮氨酸　亮氨酸是一种蛋白源氨基酸,通常情况下,亮氨

酸通过激活 mTORC1 蛋白激酶来控制蛋白质和脂质合成以及自噬等过程来调节生长等活动，研究表明，氨基酸通过 Rag 鸟苷三磷酸酶（GTPases）向 mTORC1 传递信号[25]，Rag 蛋白是 4 个相关的小 GTP 酶家族，以氨基酸敏感的方式与 mTORC1 相互作用[26]，Rags 是 RagA 或 RagB 与 RagC 或 RagD 组成的专一性异二聚体[27]。亮氨酸刺激使 Rags 转变为其活跃的核苷酸结合状态，允许它们与 Raptor 结合并招募 mTORC1 到溶酶体表面。

胞质中的亮氨酸和精氨酸通过由 GATOR1 和 GATOR2 复合物组成的独特途径向 mTORC1 传递信号，有文献报道，SAR1B 是一种亮氨酸传感器，能根据细胞内亮氨酸水平来调控 mTORC1 的信号传导，在亮氨酸充足的条件下，SAR1B 与亮氨酸结合，经历构象变化并与 GATOR2 解离，从而引起 mTORC1 活化[28]。另外，有研究表明，Sestrin2 是 mTORC1 通路上游的直接亮氨酸传感器，在亮氨酸缺乏时与 GATOR2 结合并抑制其功能，亮氨酸通过与 Sestrin2 结合来破坏 Sestrin2-GATOR2 相互作用。亮氨酸与 Sestrin2 结合是其激活细胞内 mTORC1 的重要部分[25]。另外，有文献报道，含有 SLC7A5（LAT1）和 SLC3A2 两大亚基的转运蛋白参与介导转运亮氨酸，T 细胞受体（T cell receptor，TCR）在 T 细胞激活过程中参与表达时，这两个亚基表达增高，抑制 SLC7A5 会使人 T 细胞处于失活状态并减弱其抗肿瘤功能[29]。Sinclair 等[30]研究发现，亮氨酸通过 SLC7A5 转运蛋白参与激活 T 细胞中 mTORC1 信号通路，同时，SLC7A5 的蛋白表达调控着 T 细胞代谢。这提示，亮氨酸可以通过 SLC7A5 转运蛋白激活 T 细胞中 mTORC1 信号通路来参与调控肿瘤的免疫功能，从而影响肿瘤的发生发展。

2.4　*精氨酸*　精氨酸是一种具有多种代谢和调节作用的条件性必需氨基酸，既是一种蛋白源氨基酸，也是一氧化氮、肌酸和谷氨酸等关键分子的前体[31]，精氨酸是三种可以直接激活 mTOR 途径的氨基酸之一，其主要途径是通过细胞传感器来直接激活 mTOR 信号通路[32]。具体方式如下：（1）精氨酸激活 mTORC1 是通过 SLC38A9 实现的，SLC38A9 是溶质载体家族 38（SLC38）的成员，是一种溶酶体精氨酸传感器，有研究表明，SLC38A9 是一种氨基酸转运蛋白，通过 Rag-Ragulator 复合物调节氨基酸依赖的 mTORC1 活性[33-34]；（2）精氨酸破坏结节性硬化症和 mTORC1 之间的相互作用，从而激活 mTOR[35]；（3）精氨酸通过与 CASTOR1 结合破坏 CASTOR-GATOR2 复合物，这表明，精氨酸可以通过与 CASTOR1 结合来激活 mTORC1 通路[36]，GATOR1 由 DEPDC5、Nprl2 和 Nprl3 组成，通过作为 Rag A/B 的 GAP 抑制 mTORC1 信号，允许 Rag A 结合 mTORC1 组分 RAPTOR（mTOR 的调节相关蛋白）并将 mTORC1 重新分布到溶酶体[37]；相反，GATOR2 是由 Mios、WDR24、WDR59、Seh1L 和 Sec13 组成的五聚体复合物，是 mTORC1 信号的正调节因子，与溶酶体膜上的 GATOR1 相互作用[5]。这可以解释为什么精氨酸是 mTOR 的有效激活剂，而精氨酸剥夺导致 mTOR 立即失活[37]。mTOR 信号通路对于胃癌的发生发展起着重要作用，因此，精氨酸能通过参与调控 mTOR 信号通路影响胃癌发生发展的过程，这也是临床上治疗胃癌的手段之一。

精氨酸的代谢主要受两种酶的调节：精氨酸酶（arginase，ARG）1 和一氧化氮合成酶（nitric oxide synthase，NOS）。瓜氨酸在 ASS1 和 ASL 的催化下生成精氨酸，精氨酸在 ARG1 的作用下分解为鸟氨酸和尿素，鸟氨酸通过 ARG 和鸟氨酸氨甲酰基转移酶生成瓜氨酸，从而实现这一代谢循环。NOS 能促进精氨酸氧化水解生成 NO，NO 能参与消炎和免疫过程，对维持细胞的正常免疫活动具有重要作用，有文献报道，NO 能抑制 T 细胞增殖，并能促进 T 细胞凋亡，从而调控肿瘤免疫[38]。此外，半胱天冬酶-8（caspase 8）长期以来被认为促进了肿瘤细胞凋亡，也是细胞毒性药物治疗肿瘤的部分机制，Nanthakumaran 等[39]研究发现，精氨酸通过 caspase 8 激活细胞免疫从而抑制胃癌细胞增殖。因此，精氨酸还能通过调控肿瘤的免疫功能来抑制胃癌的发生发展。

2.5　*其他氨基酸*　天冬氨酸是一种 α-氨基酸，属于人体非必须氨基酸，在胃癌细胞内，天冬氨酸和天冬酰胺不仅参与胃癌细胞自身的增殖，还调控着细胞内的信号传导。研究表明，当肿瘤细胞中谷氨酰胺缺乏时，外源补充天冬酰胺可以维持蛋白质的翻译并促进肿瘤的生长[40]。

色氨酸是人体必需氨基酸，参与人体多种生命活动及维持细胞正常功能，对肿瘤代谢具有重要作用。除了合成蛋白质外，色氨酸还通过犬尿氨酸代谢途径参与调节 TME 和肿瘤代谢中的一系列过程，包括炎症反应、免疫反应等。根据文献报道，犬尿氨酸通路代谢物能够快速激活 PI3K/AKT 信号通路，促进肿瘤细胞增殖并抑制凋亡[41]。

丝氨酸和甘氨酸在胃癌细胞的增殖过程中起着重要作用，其相关代谢酶及代谢产物会调控肿瘤的生长，当外源性丝氨酸摄入不足时，肿瘤细胞可通过丝氨酸合成途径产生内源性丝氨酸，内源性和外源性丝氨酸都有助于肿瘤细胞的增殖。肿瘤细胞内的甘氨酸不仅有多种合成方式，而且其合成途径中的许多代谢酶通过与转录因子相互作用参与肿瘤生长调控[8]，因此，丝氨酸和甘氨酸的靶向治疗或能为肿瘤治疗提供新思路。

3　展　望

氨基酸代谢重编程是胃癌的重要特征之一，胃癌细胞增殖迅速，往往会出现一系列代谢紊乱从而形成 TME，通过检测胃癌患者与正常人相比的细小氨基酸代谢差异，能为临床治疗胃癌提供新手段。在肿瘤细胞中，一方面，氨基酸能通过调控代谢途径改变 TME 并参与信号通路的激活，氨基酸代谢被证实了参与 PI3K/AKT/mTOR 信号通路的激活，然而，部分氨基酸在 PI3K/AKT/mTOR 信号通路中的作用尚未明确；另一方面，氨基酸代谢对于免疫细胞的激活和分化有着重要生物学作用，可以通过调控免疫细胞和免疫因子对肿瘤的免疫功能产生影响；因此，如果能对氨基酸代谢与免疫相互作用机制进行研究，将会为未来相关抗肿瘤药物及其他药物的研究提供理论依据。

利益冲突　无

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