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Advances in Research on the Relationship between Glutamine Metabolism and Breast Cancer

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Abstract: Breast cancer is the highest incidence of cancer in women. In recent years, the incidence of breast cancer has been climbing, and the age is becoming younger and younger. Recent studies have shown that glutamine metabolism can promote the occurrence and progression of breast cancer, and is related to malignant proliferation, metastasis and drug resistance of breast cancer. Targeting glutamine metabolism is an important strategy for the treatment of breast cancer. This article reviews the mechanism of glutamine metabolism in breast cancer cells and its research progress and therapeutic significance in different molecular subtypes of breast cancer.

Keywords: Glutamine; Metabolic Reprogramming; Breast Cancer.

1. Introduction

Breast cancer is a serious threat to women's health. The International Agency for Research on Cancer (IARC) released the latest cancer research data in the world at the end of 2020 [1], among which female breast cancer has replaced lung cancer as the most common cancer, accounting for 11.7% of all new cases, ranking first in the morbidity and mortality of most countries in the world. It is worth noting that, compared with the 2018 Global Cancer Statistics report, the number of new cases of breast cancer in China ranks fourth, next to lung cancer, colorectal cancer and stomach cancer.

Metabolic reprogramming is one of the characteristics of tumor proliferation and growth [2]. Warburg effect and glutamine breakdown are the main characteristic metabolic patterns of cancer in the presence of adequate nutrient supply. Glutamine is a group of essential amino acids under certain conditions. Provide carbon source and nitrogen source for cells to support the biosynthesis, energy metabolism and cell homeostasis of cancer cells, and promote tumor growth [3]. Multiple studies have shown that breast cancer cells with various molecular subtypes have glutamine addiction [4], and if glutamine is deprived, some breast cancer cells will die quickly [5]. Recent studies have shown that glutamine metabolism is widely involved in the proliferation, invasion, metastasis, drug resistance and other links of breast cancer, and is a potential therapeutic target for breast cancer [6]. Therefore, this paper reviews the latest research on the role of glutamine metabolism in breast cancer.

2. Glutamine Metabolism Process

Glutamine is the most abundant amino acid in blood tissues, accounting for 20% of all amino acids [7]. Glutamine enters the cell via solute carrier family 1 neutral amino acid transporter member 5 (SLC1A5, also known as ASCT2) on the cell membrane [8], Glutamine can promote nucleotide biosynthesis and uridine diphosphate n-acetylglucosamine (UDP-GlcNAc) synthesis in cytoplasm to support protein folding and transport [9]. Glutamine enters the mitochondria and is converted to glutamate under the action of glutaminase or transaminase [10], which is converted into alpha-ketoglutaric acid under the action of glutamine dehydrogenase or transaminase and then enters the TCA cycle to power cells.

3. The Role of Glutamine Metabolism in Breast Cancer Progression

Glutamine provides carbon source for breast cancer cells, nitrogen source is used to support the biosynthesis energy metabolism and cell homeostasis of cancer cells, support the proliferation and progression of breast cancer cells, and promote the growth of tumors. Firstly, glutamine is a nitrogen source for nucleotides and non-essential amino acids [11] and a carbon source for the synthesis of fatty acids and citric acid [12]. Secondly, glutamic acid produced by glutamine under the action of glutaminase can promote the production of glutathione. Finally, glutamine regulates the activity of mTOR in various ways, such as activating the mTOR pathway by enhancing the inflow of amino acids including leucine [13].

4. Recent Research Progress of Glutamine Metabolism in Different Molecular Subtypes of Breast Cancer

Breast cancer is a heterogeneous disease with heterogeneous histology, molecular characteristics, clinical course and treatment. The accepted molecular classifications of breast cancer are lumen A, lumen B, HER2-positive and triple-negative breast cancer (basal breast cancer) [14; 15]. Different molecular subtypes of breast cancer have different gene expression patterns, clinical features and therapeutic responses. Studies have shown that there are different metabolic characteristics between ER-positive and ER-negative breast cancers [16].

GLS expression in breast cancer with different molecular subtypes: glutaminase decomposition is mediated by two different subtypes of glutaminase: renal glutaminase and hepatic glutaminase [17]. GLS are generally considered to be oncogenes, regulated by the oncogene c-Myc. GLS2 is generally considered to be a tumor suppressor gene and is

regulated by p53, which is downregulated in liver and brain cancer. Most TNBC cells showed glutamine addiction, while the dependence of luminal breast cancer cells on glutamine was much lower. The expression of GLS in TNBC was significantly higher than that in luminal breast cancer cell lines [18]. The expressions of GLS and glutamine dehydrogenase (GDH) were low in luminalA type and high in HER-2 type [16]. Studies have shown that GLS2 is up-regulated in luminal breast cancer cells, while its expression in TNBC is inhibited by promoter methylation [19]. Compared with ER-positive breast cancer, HER-2 positive breast cancer and TNBC types have higher glutamate levels and lower glutamine levels [20], so it is expected that HER-2 positive breast cancer and TNBC have high glutamine inflow and active glutamine decomposition.

Expression of glutamine transporter in different molecular subtypes of breast cancer:

The expression of glutamine transporter is also different in different molecular subtypes of breast cancer. Studies have shown that the expressions of SLC6A14, SLC7A8 and SLC38A1 are up-regulated in luminal A breast cancer. In luminal type B, SLC6A14, SLC7A8 and SLC38A1 were up-regulated. In TNBC, the expressions of SLC1A5 and SLC7A5 were up-regulated. In HER2 positive breast cancer, SLC7A7, SLC1A5 and SLC7A5 are up-regulated. As the more aggressive molecular subtypes, TNBC and HER2-positive breast cancers require more energy support, and SLC1A5 transporters control the influx of glutamine and are highly expressed in both breast cancer subtypes. Leucine is an important amino acid and mTOR activator that enters the system, SLC7A5 regulates the exchange of glutamine inflow to outflow, and c-myc can regulate SLC1A5 and SLC7A5. Luminal breast cancer cells can generate alanine, proline and glutamic acid by using glutamine [21], while glutamine in TNBC is mainly converted into glutamic acid and lactic acid, which is conducive to the adaptation of tumor cells to anoxic environment. Studies have shown that glutaminase inhibitor CB-839 can quickly kill lumen breast cancer cells, and compared with TNBC cells, CB-839 has a stronger inhibitory effect on lumen breast cancer cells, indicating the key role of proline in glutamine metabolism [22].

Advances in the treatment of glutamine metabolism in breast cancer:

5. Breast Cancer Cells are Characterized by Metabolic Reprogramming, and Metabolic Deprivation Therapy is Safe and Effective Due to the High Demand for Amino Acids in Breast Cancer Cells

Glutaminase is the key and rate-limiting enzyme in the metabolism of glutamine. If the activity of glutaminase is inhibited or the gene is knocked down, the anti-tumor effect can be achieved. Currently, small molecular inhibitors of glutaminase such as 6-diazo-5-oxo-L-methionine, nitrase, and acyclovixin can irreversibly bind to the active site of glutaminase, although most of these are still in the preclinical "tool compound" stage or are limited by toxicity. But allosteric inhibitors of GLS have shown promise in preclinical models of cancer, and one potent compound in this class, CB-839, has progressed to clinical trials. Studies have shown that two allosteric inhibitors of glutaminase, CB-839 and BPTES, can have anti-tumor effects by different mechanisms [23]. CB-839 is an effective and selective glutaminase inhibitor, which has stronger anti-tumor effects on triple negative breast cancer cell lines in particular [24]. CB-839 has shown therapeutic potential in preclinical models of cancer and has entered phase I clinical trials. Metabolic inhibitors (e.g., glutamine inhibitors) are particularly attractive targets for synthetic lethal studies. CB839 has also made progress in clinical trials in combination with other drugs, and CB839 can be used alone or in combination with paclitaxel to treat cancer [25]. The combination of CB-839 and ivermus has been shown in clinical trials to improve outcomes in patients with endocrine drug resistance [26]. As a preclinical tool inhibitor of GLS, BPTES can specifically inhibit GLS1 and enhance the therapeutic effect of cisplatin on TNBC cells.

Glutamine transporter ASCT2 is a key link in glutamine flow into cells. Inhibition or silencing of ASCT2 is a feasible antitumor approach to inhibit tumor glutamine metabolism. Studies have shown that monoclonal antibodies targeting ASCT2 and non-competitive ASCT2 inhibitors can improve the prognosis of breast cancer [27].

6. Summary and Outlook

To sum up, breast cancer is a tumor with a high incidence, and endocrine therapy, monoclonal therapy, chemotherapy and radiotherapy are clinically used in combination with surgery. However, more studies are still needed to minimize the mortality and morbidity. Different molecular subtypes of breast cancer cells have different degrees of glutamine dependence. Inhibiting the metabolism of glutamine in breast cancer cells can effectively inhibit the growth of breast cancer, which is a feasible anti-breast cancer strategy. Previous studies have shown that glutamine metabolism is widely involved in the proliferation, invasion and metastasis of breast cancer, and is closely related to tumor drug resistance, immune escape and programmed cell death. Glutamine metabolism plays an important role in malignant progression and poor prognosis of breast cancer. Targeting genes and pathways associated with glutamyl metabolism could be a potentially successful treatment for breast cancer, particularly triple negative breast cancer. In particular, breast cancer subtypes (HER-2 positive breast cancer and TNBC) have active glutamine metabolism, and targeting glutamine metabolism is a potential therapeutic target.

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