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**Targeting metabolism in breast cancer, how far we can go?**

Long JP *et al*.Targeting metabolism in breast cancer

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**Abstract**

Adjuvant therapies of breast cancer have achieved great success in recent years and early breast cancer has been taken as a curable disease or chronic disease. The targeted therapies including endocrine therapy and human epidermal growth factor receptor-2 targeted therapy marked a new era of breast cancer treatment. But, for triple negative breast cancer, there still lack an efficient drug treatment except chemotherapy to improve the overall survival of breast cancer patients. Furthermore, a certain proportion of breast cancer patient could present resistance to drug therapy and it becomes much more difficult to control the deterioration of disease when resistance happens. Recently, altered energy metabolism has been taken one of hallmarks of cancer including breast cancer and it may be linked to drug resistance. Targeting cellular metabolism has becoming a promising strategy to overcome drug resistance in cancer therapy. This review discussed the metabolic reprogramming in breast cancer and the possible complex modulation mechanism of it. We also summarized the recent advances on the metabolic therapy targeted glucolysis, glutaminolysis and fatty acids synthesis in breast cancer.

**Key words:** Breast cancer; Targeted therapy; Metabolism; Drug resistance; Chemotherapy

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**Core tip:** Breast cancer cells could display distinct metabolic [characteristic](http://www.baidu.com/link?url=JljWKqFKpHW2cb-DW7E7HvC9QzZIZwjnJwSMnqLGsMKvONHk9HE8WXdAMILUJxV8uoTy2oIdBDPmpDEIGYINCrwU_fPH4AFkg0-fcw6OpzG" \t "_blank) according to different molecular phenotype. Metabolic regulation in breast cancer cells may have crosstalk with estrogen receptor and human epidermal growth factor receptor-2 signal pathways that makes it more complex to evaluate the efficiency of anti-metabolic drug. On the other hand, the research on target metabolism in breast cancer also will largely help us to understand the complicated mechanism by which anti-metabolic drug improves the efficacy of cancer therapy or overcomes drug resistance.

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**INTRODUCTION**

Breast cancer now has the leading incidence in women cancers. Attributed to the molecular classification of breast cancer based on the hormonal receptor and human epidermal growth factor receptor-2 (HER-2), targeted therapy and other adjuvant therapies prolong the overall survival and greatly decrease the mortality of this disease. However, for locally advanced and metastatic cancer the mortality remains high. We still lack effective methods for treatment when drug resistance occurs and recurrence and metastasis develop secondary, especially for the triple-negative breast cancer (TNBC).

Female have the specific energy metabolic pattern compared to male[1]. Estrogens, progesterone-to-estrogen ratio and androgens levels affect the energy materials transporter and metabolic enzymes expressions in cells[2]. Estrogens may increase the expression of peroxisome proliferation activator receptor, Akt and activate AMP-activated proteinkinase (AMPK), which consequently influence the metabolic process including glucose utility, lipid uptake, storage, lipogenesis and lipid oxidation[3,4]. Endocrine therapy plays a pivotal role in the estrogen receptor (ER) positive breast cancer treatment. Rapamycin, which inhibits mammalian target of rapamycin (mTOR), is a downstream target of Akt, and enhances the susceptibility of breast cancer cells to endocrine therapy[5]. However, there is still a certain proportion of breast cancer patient that present primary resistance to endocrine therapy, and some patients could develop secondary resistance which makes it much more difficult to control the disease progress[6]. The similar condition occurs for chemotherapy and HER-2 targeted therapy in breast cancer. Therefore, researchers are looking for new strategies or compounds to reduce the drug resistance and enhance the therapy efficacy.

Metabolic reprogramming is the primarily and basic factor during cell transformation[7,8]. Foreign stress forces tumor cell to accommodate new circumstance through metabolic reprogramming caused by epigenetic changing and gene mutation. Altered energy metabolism has been taken one of hallmarks of cancer[7]. Mounting evidences also attribute the drug resistance to dysregulated cellular metabolism[9,10]. Recently, much more interests have been focused on targeting metabolic enzymes for cancer therapy or expecting to reverse the drug resistance[11-13]. Cancer cells have distinct metabolic properties including enhanced aerobic glycolysis, fatty acid synthesis and glutaminolysis to sustain immortal proliferation[7,14]. This review will discuss the metabolic reprogramming and the advances in metabolic targeted therapy in breast cancer.

**METABOLIC REPROGRAMMING IN BREAST CANCER**

To meet the abundant requirement of energy and materials for proliferation, most malignant cells present increased aerobic glycolysis, fatty acid synthesis and glutaminolysis, which are distinctive from normal cells[15] (Figure 1). In the year of 1956, Warburg[16] first postulated that cancer cells had a significant high rate of glycolysis than normal cells to produce ATP for proliferation. He also hypothesized that due to the defective function of mitochondria (this was proved wrong afterwards), pyruvate produced from glycolysis was more converted to lactate than acetyl CoA through the tricarboxylic acid (TCA) cycle. This phenomenon is named Warburg effect now and it exists regardless of oxygen availability. For the adaption of the Warburg effect, cancer cells exhibit altered expression of different glucose transporters and glycolysis enzymes. Glucose crosses the plasma membrane *via* glucose transporter proteins (GLUTs) and fourteen types have been identified. Although little is known about the role of glucose transporter in cancer biology, GLUT1, GLUT2, GLUT3, GLUT4, GLUT5 and GLUT12 have been detected in breast cancer cells[17-20]. Different expression patterns of GLUT isoforms in breast cancer may have association with pathological grade, cancer cell differentiation and prognosis. According to molecular subtype of invasive breast cancer, HER-2 positive and TNBC mostly exhibit higher level of glycolysis which need higher level of expression of GLUT[21]. As the most invasive type in breast cancer, TNBC had highest expression of GLUT-1 when compared to other types[21]. Increased activity of enzymes involved in glycolysis like hexokinase (HK) and lactate dehydrogenase-A (LDHA) have also been studied and their expression may affect cancer cell growth property[22,23].

Increased glutamine metabolism is another alternative energy origin for cancer cells including breast cancer and which thought to be a central metabolic pathway cooperated with glycolysis[24,25]. Most cancer cells cannot proliferate without glutamine supply and glutamine addiction provides intermediates for amino acid and lipid synthesis[26]. Under hypoxia condition, proliferating cells including breast cancer cells mostly employ reductive metabolism of glutamine-derived alpha-ketoglutarate to synthesize acetyl CoA for lipid synthesis, that normally should enter into the canonical TCA cycle. That pathway is isocitrate dehydrogenase 1 dependent[27,28]. Intermediate metabolites derived from glutamine metabolism such as antioxidants NADH, glutathione and ammonia could change the reduction-oxidation status in cancer cells, promote stromal cell autophagy, increase tumor growth and drug resistance[25,29]. Cell study showed high glutamine supply protected MCF7 cells from tamoxifen-induced apoptosis[30]. Amino acid transporter-2 (ASCT2), glutaminase 1 (GLS) and glutamate dehydrogenase are three key enzymes involved in glutamine metabolism[31]. Immunohistochemical staining of breast cancer tissues indicated that HER-2 positive and TNBC exhibited the most frequent expression of glutamine metabolism related proteins than other types[32]. Glutamine produces glutamate under the catalytic effect of glutaminase, thus the ratio of glutamate to glutamine may indicate the glutamine metabolic activity[33]. Asiago *et al*[34] reported that an elevated level of glutamate was associated with disease outcome in breast cancer patients. Metabolomics analysis of 270 clinical breast cancer samples and 97 normal breast samples showed that breast cancer cells had higher glutamate-to-glutamine ratio than normal cells, particularly ER-tumor cells[35]. A cell study showed that highly invasive and drug-resistant breast cancer cells were characterized by increased glutamine metabolism with increased glutamate-to-glutamine ratio and greater expression of glutaminase as compared with noninvasive breast cancer cells[36].

Under normal conditions, breast cells utilize circulating lipids for the synthesis of new structural lipids, while breast cancer cells mostly synthesize fatty acids by themselves. The biosynthetic enzyme fatty acid synthase (FASN) is the key enzyme required for the synthesis. FASN expression in breast cancer was first explored during the 1980s when its expression was increased after progestin treatment[37]. Recently, the FASN expression has been taken as an oncogene for its role in carcinogenesis. Up-regulation of FASN has been reported in many different tumors, including breast cancer, and it could be associated with tumor development, recurrence, and prognosis[38]. Immunohistochemistry staining revealed a highest FASN expression in HER-2 breast tumors and lowest in TNBC tumors and the studies in breast cancer cells also obtained the same results[39,40]. Vazquez-Martin *et al*[41] postulated a ‘‘HER2-FASN axis’’ that indicated the bidirectional regulation mechanism between FASN and HER2 and which could enhance cancer cell proliferation, survival, chemo-resistance and metastasis in breast carcinomas.

**MODULATION OF METABOLIC REPROGRAMMING IN BREAST CANCER**

Breast cancer is classified into four molecular subtypes: luminal A, luminal B, HER-2 over expression, and basal types, in which type luminal A accounts for about 70%[42]. The estrogen and HER-2 signal pathway play critical roles in breast cancer carcinogenesis, progression and prognosis. They could interact with each other and other signal pathways as well. Since most cancer cells display high requirement of nutrition intake to accommodate cells proliferation and altered metabolism could be hallmark of cancer development, different molecular subtypes of breast cancer should exhibit distinct metabolic phenotypes. But till now, we still know much less about the modulation mechanism of tumor-specific metabolic changes especially in breast cancer[43]. We also know less about how these changes may change molecular phenotypes of breast cancer and affect response to drug treatment.

Although scientists try hard to find out how signal pathways control the energy metabolism of cancer cell, little is known about the complex network. Hypoxia-inducible factors (HIF) and the proto-oncogene c-Myc are two major regulators in the energy metabolism including glucose, protein and fatty acid metabolisms[44]. Other genes, including *Akt*, *Ras*, *Raf*, *Src* and *EGFR* may also involve in the glycolysis and activating of these genes could cause increase glucose uptake. mTOR inhibitor rapamycin could inhibits cancer cell glucose metabolism by down regulating pyruvate kinase M2, and that may be one mechanism of rapamycin to effectively restore the susceptibility of breast cancer cells to tamoxifen treatment[45]. On the other hand, estrogen-induced HIF-1 accumulation in breast cancer cell stimulate glucose uptake *via* PI3K/Akt signaling pathway[19,46], which also leads to increased mTOR phosphorylation[47]. Another clinical study found out that HIF-1 had highest expression in HER-2 positive breast cancer[21]. It indicated that HIF-1 should have crosstalk with estrogen receptor and HER-2 signal pathways.

*c-MYC* gene controls cancer cell glutaminolysis through several targeted genes. MYC is over-expressed in 30%-50% of high-grade breast tumors[48,49]. Increased MYC expression often indicated increased dependency on glutamine and glucose for survival and might had correlation with drug resistance in breast cancer cells, and inhibition of MYC could reverse the drug resistance[50-52]. In antiestrogen resistant breast cancer cells, MYC could activate unfolded protein response through glucose-regulated protein-78 (GRP78/HSP5A/BiP) and inositol-requiring enzyme-1α (IRE1α/ΕRΝ1) and increase c-Jun N-terminal kinase activation and spliced X-box protein-1 to support cell survival[45]. The inhibition of MYC was shown to decrease glutaminase activity, although there still was different results in drug resistant breast cancer cells and other cells[50,53,54]. Inhibition of glutaminase reversely could decrease MYC expression[51]. Activation of Akt/mTOR signal pathway also stimulate uptake of glutamine through increased glutaminase activity[55]. And the underline mechanism may be through eIF4B dependent control of c-Myc translation[56]. In ER and HER-2 both positive breast cancer cells, up-regulation of HER-2 is one possible mechanism for endocrine treatment resistance. The cross-talk between ER and HER2 could regulate MYC-mediated glutamine metabolism[52]. ER down-regulator fulvestrant could decrease glutamine consumption through inhibition of MYC and glutaminase, and consistent expression of MYC may abrogate the effect of rapamycin on glutaminase[52,56]. Though, the highest glutamine metabolic activity was seen in HER2-type breast cancer, meant a possible correlation between glutamine activity and HER-2 signal pathway[32].

Although the mechanism of over-expression of FASN in breast cancer cells is still uncertain, the potent lipogenic transcription factor sterol-regulatory-element-binding protein 1 (SREBP-1) has been proved that it could regulate FASN expression through the binding with site of FASN promoter with co-activating transcription factors such as NF-Y, Sp1 and Spot14[57,58]. Dietary polyunsaturated fatty acids could suppress FASN expression through the modulation of NF-Y binding to the FASN promoter by SREBP-1c[59]. PI3k-Akt and MAPK signal transduction pathway are also thought to be involved in FASN modulation[60,61]. Under hypoxia condition, *FASN* gene is up-regulated *via* the activation of the Akt followed by the induction of the *SREBP-1* gene[62]. Inhibition of MAP kinase also decreases transcription from the FASN promoter and reduces FASN expression in MCF7 cells[63]. The mTOR inhibitor Rapamycin also could inhibit FASN in breast cancer cells[64]. Recently, there thought to be a “HER2-FASN axis” exists which indicates the bidirectional regulation mechanism between FASN and HER2. The highest level of FASN expression in HER-2 positive breast cancer type also confirms this hypothesis. FASN also could be regulated by estrogen in ER-positive breast cancer cells. Estrogen stimulates FASN expression and inhibiting FASN augments E2-stimulated transcriptional activity and enhances the E2-mediated ER expression synergistically[65].

**TARGETING GLYCOLYTIC ENZYMES**

As a basic energy resource for cancer cells, many enzymes are involved in glucose metabolism. Target metabolism therapy has been proved its efficiency to enhancing anticancer treatments or overcome drug resistance in breast cancer cells, including chemotherapy resistance, endocrine therapy resistance and HER-2 targeted therapy resistance. Besides searching the new agent to block glucose metabolism or induce a switch from glycolysis to mitochondrial respiration, researchers also take much efforts to find out the underlying effect of existing agent on metabolic changes. Sorafenib, is a multi-kinase inhibitor, could down-regulate GLUT-1 expression in breast cancer cells through AMPK-dependent inhibition of the mTORC1 pathway and inhibit cell proliferation and induce apoptosis[66].

The glucose transporter family consists of 14 sodium-independent facilitative glucose transporters (SLC2A1-14 or GLUT1-14). GLUT1 appears to be the predominant glucose transporter in many types of cancer cells including breast cancer[67]. A small compound, WZB117, has showed its inhibitory activity on GLUT1 in MCF-7 breast cancer cells[68]. Synergistic anticancer effects of combined WZB117 with other anticancer drug cisplatin or paclitaxel were also observed. Added with mitochondrial inhibitor, WZB117 had more efficiency in inhibiting cell proliferation, which indicated WZB117 may be more effective in aggressive cancer cells that invariably had mitochondrial dysfunction[68].

Hexokinase-2, the first regulatory enzyme in glycolysis, has important role in glycolysis. 2-DG is a glucose analog and could bind with HK competitively and inhibit glycolysis. Although as a single agent the antitumor effect was not significant, study showed that 2-DG combined with trastuzumab inhibited trastuzumab-sensitive and -resistant breast cancers *in vitro* and *in vivo* models of HER-2 positive breast cancers with more efficient inhibition of glycolysis *via* downregulation of heat shock factor 1 and LDHA[69].

LDHA is the enzyme that catalyzes the conversion of pyruvate to lactate. LDHA knockdown stimulates HER-2-initiated breast cancer cells switch to mitochondrial oxidative phosphorylation, decreases cell proliferation to hypoxic conditions, and interferes with tumorigenicity[70]. While dichloroacetate (DCA), an inhibitor of pyruvate dehydrogenase kinase (PDK), may activate pyruvate dehydrogenase which is governed by PDK and facilitate the conversion of pyruvate to acetyl Co-A, which demonstrate the anti-proliferative properties in highly metastatic disease of DCA[71]. Inhibitor of LDH-A selectively inhibits the growth of HER-2-overexpressing cells and enhances the sensitivity of trastuzumab-resistant breast cancers to trastuzumab treatment[69,23]. Furthermore, downregulation LDH-1 by oxamate shows a synergistical inhibitory effect on taxol-resistant breast cancer cells by promoting apoptosis when combined with taxol[9].

**TARGETING GLUTAMINE METABOLISM**

In many cancer cells, glutamine is used to replenish the TCA cycle and oxidative phosphorylation instead of glucose to produce enough ATP to support cell proliferation[72]. Glutamine-addiction is a common strategy for some cancer cells like breast cancer cells to escape from drug treatment. And glutamine transporter or glutaminolysis are becoming a potential pharmacological target to revert resistant cancer cells to respond to the initial therapy. An amino acid transporter SLC6A14, also known as ATB0,+, is up-regulated specifically in ER-positive breast cancer. Blockade of SLC6A14 in ER-positive breast cancer cells could inhibit mTOR activity, cause cell apoptosis and activate autophagy[73].

Glutaminase, the enzyme that catalyze glutamine to glutamate has drawn much interest for targeted cancer therapy recently. There are two novel glutaminase inhibitors has been discovered: CB-839[74] and 968[51]. CB-839 showed most potent antiproliferative activity in a TNBC cell line while no antiproliferative activity was observed in an estrogen receptor–positive cell line. In xenograft models, CB-839 displayed significant antitumor activity both as a single agent and in combination with paclitaxel. Compound 968 showed the greatest cytotoxic effect in MDA-MB-231 breast cancer cells. Genome analysis proved that compound 968 could induce changes of many anti-apoptotic and/or promote metastasis related genes expression and histone modifications as well, which subsequently activated the apoptosis and decrease invasiveness of MDA-MB-231 cells. It also enhanced chemotherapy sensitivity of breast cancer cells when combined with chemotherapeutic drug doxorubicin.

**TARGETING FATTY ACID METABOLISM**

FASN is the key biosynthetic enzyme in the fatty acid synthesis pathway that synthesize long-chain fatty acids palmitate from malonyl-CoA. And acetyl-CoA carboxylase (ACC) carboxylates acetyl-CoA to malonyl-CoA. Up-regulation of FASN has been reported both in premalignant lesions and most human cancers. In normal cells, fats are absorbed freely and the FASN is down-regulated except lactating breast and cycling endometrium. The unique distribution of FASN in different tissues makes FASN an attractive target for cancer therapy. The inhibition of FASN causes depletion of the end product long chain fatty acids and the accumulation of the substrate malonyl-CoA. There was evidence showed that inhibition of ACC didn’t induce cancer cell apoptosis which meant the accumulation of malonyl-CoA may be the reason for the antitumor effect of FASN inhibition[75,76].

It was illustrated that there could be a bidirectional regulation mechanism between FASN and HER2[41,77]. FASN blockade suppresses HER2 over-expression at the transcriptional level with the up-regulation of the expression of PEA3, a transcriptional repressor of HER-2. HER-2 over-expression stimulates the FASN expression and fatty synthesis, and this HER-2 mediated induction could be inhibited by trastuzumab. Combination FASN inhibitor and trastuzumab stimulate MDA-MB-231/HER-2 cells apoptosis and re-sensitize trastuzumab-resistant breast cancer through down-regulation of HER-2 expression[78,79]. Menendez *et al*[77] hypothesized that FASN inhibition would result in major changes in the synthesis of phospholipids which should increase degradation of HER-2 and enhance the action of the anti-HER-2 antibody trastuzumab.

Furthermore, FASN inhibitor cerulenin demonstrated strong synergism with docetaxel in HER-2 overexpressing and docetaxel-resistant SK-Br3 cells which indicated the role of FASN in HER-2-induced breast cancer chemotherapy resistance[80]. FASN blockade also could induce a synergistic chemosensitization of breast cancer cells to other chemotherapy agents such as paclitaxel, adriamycin, 5-FU and vinorelbine[81-84].

**CONCLUSION**

Breast cancer is a heterogeneous group of neoplasms originating from the epithelial cells that could be divided into various molecular phenotypes. Targeted therapy such as endocrine therapy and HER-2 targeted therapy have achieved great success in breast cancer treatment. But, like chemotherapy resistance, resistance to endocrine therapy and HER-2 targeted therapy give us discouraged results for those patients encountered unfortunately. Recently, cancer research has focused much interest on dysregulated metabolism in cancer cells and metabolic reprogramming is now considered a hallmark of cancer. More and more evidence supports the idea that dysregulated cellular metabolism may be associated with drug resistance in cancer therapy. In breast cancer, many agents targeted specific enzymes in the metabolic pathways including glycolysis, glutaminolysis and fatty acid synthesis have been developed or proposed. Some of them have shown the ability to enhance the efficacy of current therapies and resensitize resistant cancer cells and have been progressed to clinical trials. But to date, for a couple of reasons, none has been put into routine clinical practice. The main reason may be the extremely complexity of the modulation of metabolism and their crosstalk with other signal pathways. Hence, there are three key problems need to be elucidated: (1) Energy pathways may be employed by not only cancer cells but also normal cells. The influence or toxicity of metabolic drugs on normal cells should be evaluated carefully besides its antitumor effect. This question is prominent when combining metabolic drugs targeting different pathways to avoid insufficient effect or drug resistance; (2) For breast cancer, different molecular type may possess specific metabolic phenotype. Even “good” molecular type of breast cancer like Luminal A type may have metastasis of recurrence caused by drug resistance in a relatively short period. So it is critical to find out which specific enzymes for specific molecular phenotype could be the promising targets. And this understanding will help us better distinguish which altered metabolic phenotype may have poorer prognosis and higher invasiveness than other types; (3) It has been postulated that metabolic regulation may have crosstalk with ER and HER-2 signal pathways. The genetic regulators such as c-myc, PI3k/Akt /mTOR and MAPK not only regulate metabolism but also ER and HER-2 signal pathways. They form a complex framework like “FAS-HER-2 axis” and “c-myc-mTOR axis” which determines the growth, apoptosis and drug resistance of cancer cells and completely understanding the framework for breast cancer is still a challenge for developing a successful metabolic therapy. Nevertheless, much efforts and progress have been made in this field and we hope in the near future targeting tumor metabolic pathways may become an important component of the comprehensive treatment of breast cancer.

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**Figure 1 Metabolic reprogramming in malignant cells.** Most malignant cells present increased aerobic glycolysis, fatty acid synthesis and glutaminolysis. The pink circles in the figure show the possible metabolic targets of enzymes or receptors. GLUT: Glucose transporter proteins; HK: Hexokinase; PKM: Pyruvate kinase M; LDH: Lactate dehydrogenase; FASN: Fatty acid synthase; ACS: Acetyl-CoA synthase; IDH: Isocitrate dehydrogenase; GLS: Glutaminase.