World Journal of Clinical Oncology

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DOI: 10.5306/wjco.v7.i1.122

World J Clin Oncol 2016 February 10; 7(1): 122-130
ISSN 2218-4333 (online)

MINIREVIEWS

Targeting metabolism in breast cancer: How far we can go?

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Author contributions: Long JP and Li XN drafted the manuscript; Zhang F was responsible for the conception of the manuscript and collected the literature.

Conflict-of-interest statement: The authors have no conflicts of interest for this manuscript.

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Received: May 28, 2015
Peer-review started: May 30, 2015
First decision: August 16, 2015
Revised: October 16, 2015
Accepted: December 8, 2015
Article in press: December 11, 2015
Published online: February 10, 2016

Abstract

Adjuvant therapies for breast cancer have achieved great success in recent years and early breast cancer is now a curable or chronic disease. Targeted therapies, including endocrine therapy and human epidermal growth factor receptor-2 targeted therapy, marked a new era of breast cancer treatment. However, except for chemotherapy, an efficient drug treatment to improve the overall survival of breast cancer patients is still lacking for triple negative breast cancer. Furthermore, a certain proportion of breast cancer patients present with resistance to drug therapy, making it much more difficult to control the deterioration of the disease. Recently, altered energy metabolism has become one of the hallmarks of cancer, including breast cancer, and it may be linked to drug resistance. Targeting cellular metabolism is becoming a promising strategy to overcome drug resistance in cancer therapy. This review discusses metabolic reprogramming in breast cancer and the possible complex mechanism of modulation. We also summarize the recent advances in metabolic therapy targeted glycolysis, glutaminolysis and fatty acids synthesis in breast cancer.

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

Core tip: Breast cancer cells display distinct metabolic characteristics according to different molecular phenotypes. There may be crosstalk with the estrogen receptor and human epidermal growth factor receptor-2 signal pathways in the metabolic regulation in breast cancer cells that make it more complex to evaluate the efficiency of an anti-metabolic drug. On the other hand, the research on target metabolism in breast cancer will also largely help us to understand the complicated mechanism by which an anti-metabolic drug improves the efficacy of cancer therapy or overcomes drug resistance.

Long JP, Li XN, Zhang F. Targeting metabolism in breast cancer: How far we can go? *World J Clin Oncol* 2016; 7(1): 122-130 Available from: URL: http://www.wjgnet.com/2218-4333/full/v7/i1/122.htm DOI: http://dx.doi.org/10.5306/wjco.v7.i1.122

INTRODUCTION

Breast cancer now has the highest incidence of cancer in women. This is 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 that prolong the overall survival and greatly decrease the mortality of this disease. However, mortality remains high for locally advanced and metastatic cancer. We still lack effective methods for treatment when drug resistance occurs and recurrence and metastasis develop, especially in triple negative breast cancer (TNBC).

Females have a specific energy metabolic pattern compared to males[1]. Estrogens, progesterone-to-estrogen ratio and androgen levels affect the energy material transporter and metabolic enzyme expressions in cells[2]. Estrogens may increase the expression of peroxisome proliferator activated receptor, Akt and activate AMP-activated protein kinase (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 estrogen receptor (ER) positive breast cancer treatment. Rapamycin, which inhibits the 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 patients that present with primary resistance to endocrine therapy and some patients could develop secondary resistance which makes it much more difficult to control the disease progress[6]. A similar condition occurs in chemotherapy and HER-2 targeted therapy in breast cancer. Therefore, researchers are looking for new strategies or compounds to reduce drug resistance and enhance the efficacy of therapy.

Metabolic reprogramming is the primary and basic factor during cell transformation[7,8]. Foreign stress forces tumor cells to accommodate new circumstances through metabolic reprogramming caused by epigenetic change and gene mutation. Altered energy metabolism has become one of the hallmarks of cancer[7]. Mounting evidence also attributes the drug resistance to dysregulated cellular metabolism[9,10]. Recently, much more interest has focused on targeting metabolic enzymes for cancer therapy or reversing 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 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 with increased aerobic glycolysis, fatty acid synthesis and glutaminolysis, which are distinctive from normal cells[15] (Figure 1). In 1956, Warburg[16] first postulated that cancer cells had a significantly higher 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 converted to lactate more than acetyl CoA through the tricarboxylic acid (TCA) cycle. This phenomenon is now called the Warburg effect 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 transporters 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 an association with pathological grade, cancer cell differentiation and prognosis. According to the molecular subtype of invasive breast cancer, HER-2 positive and TNBC mostly exhibit higher levels of glycolysis which need higher levels of expression of GLUT[21]. As the most invasive type in breast cancer, TNBC had the 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[22,23].

Increased glutamine metabolism is another alternative energy origin for cancer cells, including breast cancer, and is thought to be a central metabolic pathway cooperating with glycolysis[24,25]. Most cancer cells cannot proliferate without a glutamine supply and glutamine addiction provides intermediates for amino acid and lipid synthesis[26]. Under hypoxic conditions, proliferating cells, including breast cancer cells, mostly employ reductive metabolism of glutamine-derived alpha-ketoglutarate to synthesize acetyl CoA for lipid synthesis that normally enters 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 and increase tumor growth and drug resistance[25,29]. Cell studies showed that a high glutamine supply protected MCF7 cells from tamoxifen-induced apoptosis[30]. Amino acid transporter-2, 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

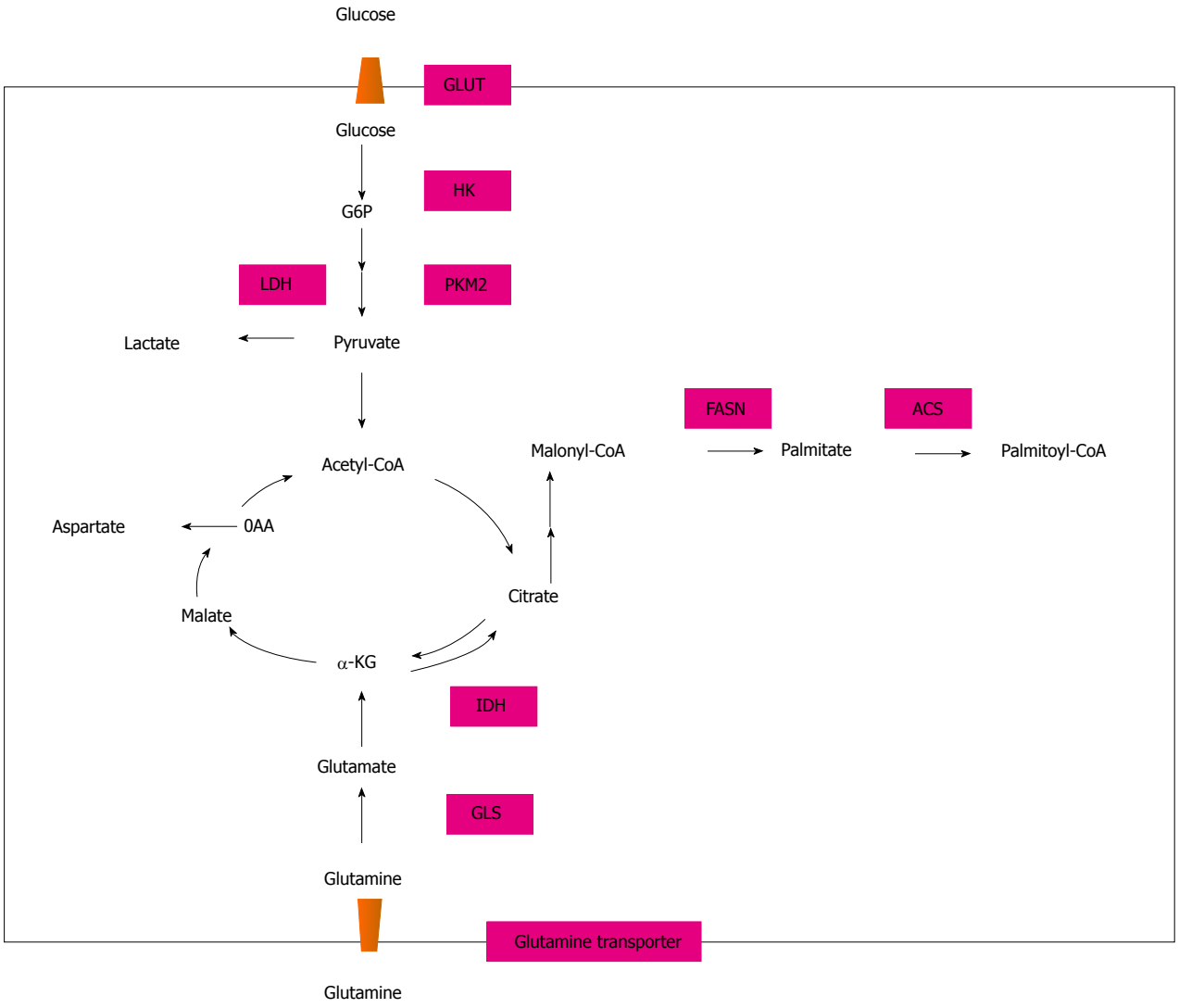

Figure 1 Metabolic reprogramming in malignant cells. Most malignant cells present with increased aerobic glycolysis, fatty acid synthesis and glutaminolysis. The pink circles in the figure show the possible metabolic targets of enzymes or receptors. GLUT: Glucose transporter proteins; HK: Hexokinase;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

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. Metabolomic analysis of 270 clinical breast cancer samples and 97 normal breast samples showed that breast cancer cells had a 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 an increased glutamate-to-glutamine ratio and greater expression of glutaminase 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, FASN expression has been recognized as an oncogene for its role in carcinogenesis. Upregulation of FASN has been reported in many different tumors, including breast cancer, and it may be associated with tumor development, recurrence and prognosis[38]. Immunohistochemistry staining revealed the highest FASN expression in HER-2 breast tumors and lowest in TNBC tumors, with the studies in breast cancer cells obtaining 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 which could enhance cancer cell proliferation, survival, chemoresistance 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 overexpression and basal

types, with type luminal A accounting for about 70%[42]. The estrogen and HER-2 signal pathways play critical roles in breast cancer carcinogenesis, progression and prognosis. They may interact with each other as well as other signal pathways. Since most cancer cells have a high nutrition intake requirement to accommodate cell proliferation and altered metabolism may be a hallmark of cancer development, different molecular subtypes of breast cancer should exhibit distinct metabolic phenotypes. However, to date, 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 are trying hard to find how signal pathways control the energy metabolism of cancer cells, little is known about the complex network. Hypoxia-inducible factors (HIF) and the proto-oncogene c-Myc are two major regulators in energy metabolism, including glucose, protein and fatty acid metabolisms[44]. Other genes, including *Akt*, *Ras*, *Raf*, *Src* and *EGFR,* may also be involved in glycolysis and activating these genes could cause increased glucose uptake. mTOR inhibitor rapamycin may inhibit cancer cell glucose metabolism by downregulating pyruvate kinase M2 and restoring the susceptibility of breast cancer cells to tamoxifen treatment effectively may be one mechanism of rapamycin[45]. On the other hand, estrogen-induced HIF-1 accumulation in breast cancer cells stimulates glucose uptake *via* the PI3K/Akt signaling pathway[19,46] which also leads to increased mTOR phosphorylation[47]. Another clinical study found that HIF-1 had the highest expression in HER-2 positive breast cancer[21]. It indicated that HIF-1 has crosstalk with the ER and HER-2 signal pathways.

The *c-MYC* gene controls cancer cell glutaminolysis through several targeted genes. MYC is overexpressed in 30%-50% of high-grade breast tumors[48,49]. Increased MYC expression often indicates increased dependency on glutamine and glucose for survival, may have a 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 an unfolded protein response through glucose-regulated protein-78 (GRP78/HSP5A/BiP) and inositol-requiring enzyme-1α (IRE1α/ERN1) 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 were 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 the Akt/mTOR signal pathway also stimulates uptake of glutamine through increased glutaminase activity[55] and the underlying mechanism may be through eIF4B dependent control of c-Myc translation[56]. In both ER and HER-2 positive breast cancer cells, upregulation of HER-2 is one possible mechanism for endocrine treatment resistance. The crosstalk between ER and HER2 may regulate MYC-mediated glutamine metabolism[52]. ER downregulator fulvestrant may decrease glutamine consumption through inhibition of MYC and glutaminase and consistent expression of MYC may abrogate the effect of rapamycin on glutaminase[52,56], although the highest glutamine metabolic activity was seen in HER2-type breast cancer, which meant a possible correlation between glutamine activity and the HER-2 signal pathway[32].

Although the mechanism of overexpression of FASN in breast cancer cells is still uncertain, it has been proved that the potent lipogenic transcription factor sterol regulatory element-binding protein 1 (SREBP-1), can regulate FASN expression through binding with the site of the FASN promoter with co-activating transcription factors such as NF-γ Sp1 and Spot14[57,58]. Dietary polyunsaturated fatty acids suppress FASN expression through the modulation of NF-γ binding to the FASN promoter by SREBP-1c[59]. PI3k-Akt and the MAPK signal transduction pathway are also thought to be involved in FASN modulation[60,61]. Under hypoxic conditions, *FASN* gene is upregulated *via* the activation of 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 may also inhibit FASN in breast cancer cells[64]. Recently, a "HER2-FASN axis" is thought to exist which indicates the bidirectional regulation mechanism between FASN and HER2. The highest level of FASN expression in the HER-2 positive breast cancer type also confirms this hypothesis. FASN could also 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. The efficiency of target metabolism therapy has been proved in enhancing anticancer treatments or overcoming drug resistance in breast cancer cells, including chemotherapy resistance, endocrine therapy resistance and HER-2 targeted therapy resistance. Besides searching for a new agent to block glucose metabolism or induce a switch from glycolysis to mitochondrial respiration, researchers are also making much effort to find the underlying effect of existing agents on metabolic changes. Sorafenib is a multikinase inhibitor and may downregulate GLUT-1 expression in breast cancer cells through AMPK-dependent inhibition of the mTORC1 pathway, 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, inclu-

ding breast cancer[67]. A small compound, WZB117, has shown its inhibitory activity on GLUT1 in MCF-7 breast cancer cells[68]. Synergistic anticancer effects of combined WZB117 with other anticancer drugs, cisplatin or paclitaxel, were also observed. Added to the mitochondrial inhibitor, WZB117 was more efficient in inhibiting cell proliferation, which indicated WZB117 may be more effective in aggressive cancer cells that invariably had mitochondrial dysfunction[68].

HK-2, the first regulatory enzyme in glycolysis, has an important role in glycolysis. 2-DG, a glucose analog, binds with HK competitively and inhibits glycolysis. Although as a single agent the antitumor effect was not significant, a study showed that 2-DG combined with trastuzumab inhibited trastuzumab-sensitive and resistant breast cancers in *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 the switch of HER-2-initiated breast cancer cells to mitochondrial oxidative phosphorylation, decreases cell proliferation to hypoxic conditions and interferes with tumorigenicity[70]. 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 demonstrates the antiproliferative properties in highly metastatic diseases of DCA[71]. The 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 of 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 drug treatment. Glutamine transporters 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 $ATB^{0,+}$, is upregulated 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 catalyzes glutamine to glutamate has attracted much interest for targeted cancer therapy recently. Two novel glutaminase inhibitors have been discovered: CB-839[74] and 968[51]. CB-839 showed the most potent antiproliferative activity in a TNBC cell line, while no antiproliferative activity was observed in an ER–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 in many anti-apoptotic and/or promote metastasis-related gene expression and histone modifications as well, which subsequently activate apoptosis and decrease the invasiveness of MDA-MB-231 cells. It also enhanced chemotherapy sensitivity of breast cancer cells when combined with the chemotherapeutic drug doxorubicin.

TARGETING FATTY ACID METABOLISM

FASN is the key biosynthetic enzyme in the fatty acid synthesis pathway that synthesizes long-chain fatty acids palmitate from malonyl-CoA. Acetyl-CoA carboxylase (ACC) carboxylates acetyl-CoA to malonyl-CoA. Upregulation of FASN has been reported both in premalignant lesions and most human cancers. In normal cells, fats are absorbed freely and FASN is downregulated, except in the 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. Evidence showed that inhibition of ACC did not induce cancer cell apoptosis, which meant the accumulation of malonyl-CoA may be the reason for the antitumor effect of FASN inhibition[75,76].

A bidirectional regulation mechanism between FASN and HER2 was illustrated[41,77]. FASN blockade suppresses HER2 overexpression at the transcriptional level with the upregulation of the expression of PEA3, a transcriptional repressor of HER-2. HER-2 overexpression stimulates FASN expression and fatty synthesis and this HER-2 mediated induction can be inhibited by trastuzumab. The combination of FASN inhibitor and trastuzumab stimulates MDA-MB-231/HER-2 cell apoptosis and re-sensitizes trastuzumab-resistant breast cancer through the downregulation 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 the degradation of HER-2 and enhance the action of the anti-HER-2 antibody trastuzumab.

Furthermore, FASN inhibitor cerulenin demonstrated a 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 epithelial cells that can be divided into various molecular phenotypes. Targeted therapy, such as endocrine therapy and HER-2 targeted therapy, has achieved great success in breast cancer treatment. However, like chemotherapy resistance, resistance to endocrine therapy and HER-2 targeted therapy can produce discouraging results. Recently, cancer research has focused 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 that target 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 now been progressed to clinical trials. However, to date, none have been put into routine clinical practice for a couple of reasons. The main reason may be the extremely complex modulation of metabolism and their crosstalk with other signal pathways. Hence, there are three key problems that need to be elucidated: (1) energy pathways may be employed by cancer cells as well as 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 effects or drug resistance; (2) for breast cancer, different molecular types may possess a specific metabolic phenotype. Even a "good" molecular type of breast cancer, like luminal A, may have recurrent metastasis caused by drug resistance in a relatively short period and so it is critical to find which specific enzymes for specific molecular phenotypes could be promising targets. This understanding will help us better distinguish which altered metabolic phenotypes may have a 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 regulate metabolism as well as ER and HER-2 signal pathways. They form a complex framework, like the "FAS-HER-2 axis" and "c-myc-mTOR axis", which determines the growth, apoptosis and drug resistance of cancer cells. Completely understanding the framework for breast cancer is still a challenge for developing a successful metabolic therapy. Nevertheless, much effort and progress has been made in this field and we hope that, in the near future, targeting tumor metabolic pathways may become an important component of the comprehensive treatment of breast cancer.

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P- Reviewer: Matés JM, Song CJ, Tang SY
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