**Name of Journal: *World Journal of Clinical Oncology***

**ESPS Manuscript NO: 20142**

**Manuscript Type: Minireviews**

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

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

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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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**Telephone:** +86-571-89992095

**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:**

**Published online:**

**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.

Long JP, Li XN, Zhang F. Targeting metabolism in breast cancer, how far we can go? *World J Clin Oncol* 2015; In press

**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.

**REFERENCES**

1 **Varlamov O**, Bethea CL, Roberts CT. Sex-specific differences in lipid and glucose metabolism. *Front Endocrinol* (Lausanne) 2014; **5**: 241 [PMID: 25646091 DOI: 10.3389/fendo.2014.00241]

2 **Rune A**, Salehzadeh F, Szekeres F, Kühn I, Osler ME, Al-Khalili L. Evidence against a sexual dimorphism in glucose and fatty acid metabolism in skeletal muscle cultures from age-matched men and post-menopausal women. *Acta Physiol* (Oxf) 2009; **197**: 207-215 [PMID: 19508405 DOI: 10.1111/j.1748-1716.2009.02010.x]

3 **Macotela Y**, Boucher J, Tran TT, Kahn CR. Sex and depot differences in adipocyte insulin sensitivity and glucose metabolism. *Diabetes* 2009; **58**: 803-812 [PMID: 19136652 DOI: 10.2337/db08-1054]

4 **D'Eon TM**, Souza SC, Aronovitz M, Obin MS, Fried SK, Greenberg AS. Estrogen regulation of adiposity and fuel partitioning. Evidence of genomic and non-genomic regulation of lipogenic and oxidative pathways. *J Biol Chem* 2005; **280**: 35983-35991 [PMID: 16109719 DOI: 10.1074/jbc.M507339200]

5 **deGraffenried LA**, Friedrichs WE, Russell DH, Donzis EJ, Middleton AK, Silva JM, Roth RA, Hidalgo M. Inhibition of mTOR activity restores tamoxifen response in breast cancer cells with aberrant Akt Activity. *Clin Cancer Res* 2004; **10**: 8059-8067 [PMID: 15585641 DOI: 10.1158/1078-0432.CCR-04-0035]

6 **Milani A**, Geuna E, Mittica G, Valabrega G. Overcoming endocrine resistance in metastatic breast cancer: Current evidence and future directions. *World J Clin Oncol* 2014; **5**: 990-1001 [PMID: 25493235 DOI: 10.5306/wjco.v5.i5.990]

7 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

8 **Hensley CT**, Wasti AT, DeBerardinis RJ. Glutamine and cancer: cell biology, physiology, and clinical opportunities. *J Clin Invest* 2013; **123**: 3678-3684 [PMID: 23999442 DOI: 10.1172/JCI69600]

9 **Zhou M**, Zhao Y, Ding Y, Liu H, Liu Z, Fodstad O, Riker AI, Kamarajugadda S, Lu J, Owen LB, Ledoux SP, Tan M. Warburg effect in chemosensitivity: targeting lactate dehydrogenase-A re-sensitizes taxol-resistant cancer cells to taxol. *Mol Cancer* 2010; **9**: 33 [PMID: 20144215 DOI: 10.1186/1476-4598-9-33]

10 **Wang JB**, Erickson JW, Fuji R, Ramachandran S, Gao P, Dinavahi R, Wilson KF, Ambrosio AL, Dias SM, Dang CV, Cerione RA. Targeting mitochondrial glutaminase activity inhibits oncogenic transformation. *Cancer Cell* 2010; **18**: 207-219 [PMID: 20832749 DOI: 10.1016/j.ccr.2010.08.009]

11 **Schulze A**, Harris AL. How cancer metabolism is tuned for proliferation and vulnerable to disruption. *Nature* 2012; **491**: 364-373 [PMID: 23151579 DOI: 10.1038/nature11706]

12 **Tennant DA**, Durán RV, Boulahbel H, Gottlieb E. Metabolic transformation in cancer. *Carcinogenesis* 2009; **30**: 1269-1280 [PMID: 19321800 DOI: 10.1093/carcin/bgp070]

13 **Tennant DA**, Durán RV, Gottlieb E. Targeting metabolic transformation for cancer therapy. *Nat Rev Cancer* 2010; **10**: 267-277 [PMID: 20300106 DOI: 10.1038/nrc2817]

14 **Cheng T**, Sudderth J, Yang C, Mullen AR, Jin ES, Matés JM, DeBerardinis RJ. Pyruvate carboxylase is required for glutamine-independent growth of tumor cells. *Proc Natl Acad Sci USA* 2011; **108**: 8674-8679 [PMID: 21555572 DOI: 10.1073/pnas.1016627108]

15 **Vander Heiden MG**, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009; **324**: 1029-1033 [PMID: 19460998 DOI: 10.1126/science.1160809]

16 **Warburg O**. On the origin of cancer cells. *Science* 1956; **123**: 309-314 [PMID: 13298683 DOI: 10.1126/science.123.3191.309]

17 **Godoy A**, Ulloa V, Rodríguez F, Reinicke K, Yañez AJ, García Mde L, Medina RA, Carrasco M, Barberis S, Castro T, Martínez F, Koch X, Vera JC, Poblete MT, Figueroa CD, Peruzzo B, Pérez F, Nualart F. Differential subcellular distribution of glucose transporters GLUT1-6 and GLUT9 in human cancer: ultrastructural localization of GLUT1 and GLUT5 in breast tumor tissues. *J Cell Physiol* 2006; **207**: 614-627 [PMID: 16523487 DOI: 10.1002/jcp.20606]

18 **Rogers S**, Docherty SE, Slavin JL, Henderson MA, Best JD. Differential expression of GLUT12 in breast cancer and normal breast tissue. *Cancer Lett* 2003; **193**: 225-233 [PMID: 12706881 DOI: 10.1016/S0304-3835(03)00010-7]

19 **Garrido P**, Morán J, Alonso A, González S, González C. 17β-estradiol activates glucose uptake via GLUT4 translocation and PI3K/Akt signaling pathway in MCF-7 cells. *Endocrinology* 2013; **154**: 1979-1989 [PMID: 23546602 DOI: 10.1210/en.2012-1558]

20 **Krzeslak A**, Wojcik-Krowiranda K, Forma E, Jozwiak P, Romanowicz H, Bienkiewicz A, Brys M. Expression of GLUT1 and GLUT3 glucose transporters in endometrial and breast cancers. *Pathol Oncol Res* 2012; **18**: 721-728 [PMID: 22270867 DOI: 10.1007/s12253-012-9500-5]

21 **Choi J**, Jung WH, Koo JS. Metabolism-related proteins are differentially expressed according to the molecular subtype of invasive breast cancer defined by surrogate immunohistochemistry. *Pathobiology* 2013; **80**: 41-52 [PMID: 22832328 DOI: 10.1159/000339513]

22 **Hennipman A**, van Oirschot BA, Smits J, Rijksen G, Staal GE. Glycolytic enzyme activities in breast cancer metastases. *Tumour Biol* 1988; **9**: 241-248 [PMID: 2973647 DOI: 10.1159/000217568]

23 **Zhao YH**, Zhou M, Liu H, Ding Y, Khong HT, Yu D, Fodstad O, Tan M. Upregulation of lactate dehydrogenase A by ErbB2 through heat shock factor 1 promotes breast cancer cell glycolysis and growth. *Oncogene* 2009; **28**: 3689-3701 [PMID: 19668225 DOI: 10.1038/onc.2009.229]

24 **Cao MD**, Lamichhane S, Lundgren S, Bofin A, Fjøsne H, Giskeødegård GF, Bathen TF. Metabolic characterization of triple negative breast cancer. *BMC Cancer* 2014; **14**: 941 [PMID: 25495193 DOI: 10.1186/1471-2407-14-941]

25 **DeBerardinis RJ**, Cheng T. Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. *Oncogene* 2010; **29**: 313-324 [PMID: 19881548 DOI: 10.1038/onc.2009.358]

26 **Wise DR**, Thompson CB. Glutamine addiction: a new therapeutic target in cancer. *Trends Biochem Sci* 2010; **35**: 427-433 [PMID: 20570523 DOI: 10.1016/j.tibs.2010.05.003]

27 **Leonardi R**, Subramanian C, Jackowski S, Rock CO. Cancer-associated isocitrate dehydrogenase mutations inactivate NADPH-dependent reductive carboxylation. *J Biol Chem* 2012; **287**: 14615-14620 [PMID: 22442146 DOI: 10.1074/jbc.C112.353946]

28 **Metallo CM**, Gameiro PA, Bell EL, Mattaini KR, Yang J, Hiller K, Jewell CM, Johnson ZR, Irvine DJ, Guarente L, Kelleher JK, Vander Heiden MG, Iliopoulos O, Stephanopoulos G. Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. *Nature* 2012; **481**: 380-384 [PMID: 22101433 DOI: 10.1038/nature10602]

29 **Eng CH**, Yu K, Lucas J, White E, Abraham RT. Ammonia derived from glutaminolysis is a diffusible regulator of autophagy. *Sci Signal* 2010; **3**: ra31 [PMID: 20424262 DOI: 10.1126/scisignal.2000911]

30 **Ko YH**, Lin Z, Flomenberg N, Pestell RG, Howell A, Sotgia F, Lisanti MP, Martinez-Outschoorn UE. Glutamine fuels a vicious cycle of autophagy in the tumor stroma and oxidative mitochondrial metabolism in epithelial cancer cells: implications for preventing chemotherapy resistance. *Cancer Biol Ther* 2011; **12**: 1085-1097 [PMID: 22236876 DOI: 10.4161/cbt.12.12.18671]

31 **Martín-Rufián M**, Nascimento-Gomes R, Higuero A, Crisma AR, Campos-Sandoval JA, Gómez-García MC, Cardona C, Cheng T, Lobo C, Segura JA, Alonso FJ, Szeliga M, Albrecht J, Curi R, Márquez J, Colquhoun A, Deberardinis RJ, Matés JM. Both GLS silencing and GLS2 overexpression synergize with oxidative stress against proliferation of glioma cells. *J Mol Med* (Berl) 2014; **92**: 277-290 [PMID: 24276018 DOI: 10.1007/s00109-013-1105-2]

32 **Kim S**, Kim do H, Jung WH, Koo JS. Expression of glutamine metabolism-related proteins according to molecular subtype of breast cancer. *Endocr Relat Cancer* 2013; **20**: 339-348 [PMID: 23507704 DOI: 10.1530/ERC-12-0398]

33 **de la Rosa V**, Campos-Sandoval JA, Martín-Rufián M, Cardona C, Matés JM, Segura JA, Alonso FJ, Márquez J. A novel glutaminase isoform in mammalian tissues. *Neurochem Int* 2009; **55**: 76-84 [PMID: 19428810 DOI: 10.1016/j.neuint.2009.02.021]

34 **Asiago VM**, Alvarado LZ, Shanaiah N, Gowda GA, Owusu-Sarfo K, Ballas RA, Raftery D. Early detection of recurrent breast cancer using metabolite profiling. *Cancer Res* 2010; **70**: 8309-8318 [PMID: 20959483 DOI: 10.1158/0008-5472.CAN-10-1319]

35 **Budczies J**, Pfitzner BM, Györffy B, Winzer KJ, Radke C, Dietel M, Fiehn O, Denkert C. Glutamate enrichment as new diagnostic opportunity in breast cancer. *Int J Cancer* 2015; **136**: 1619-1628 [PMID: 25155347 DOI: 10.1002/ijc.29152]

36 **Simpson NE**, Tryndyak VP, Beland FA, Pogribny IP. An in vitro investigation of metabolically sensitive biomarkers in breast cancer progression. *Breast Cancer Res Treat* 2012; **133**: 959-968 [PMID: 22101407 DOI: 10.1007/s10549-011-1871-x]

37 **Chalbos D**, Chambon M, Ailhaud G, Rochefort H. Fatty acid synthetase and its mRNA are induced by progestins in breast cancer cells. *J Biol Chem* 1987; **262**: 9923-9926 [PMID: 3611068]

38 **Mashima T**, Seimiya H, Tsuruo T. De novo fatty-acid synthesis and related pathways as molecular targets for cancer therapy. *Br J Cancer* 2009; **100**: 1369-1372 [PMID: 19352381 DOI: 10.1038/sj.bjc.6605007]

39 **Kim S**, Lee Y, Koo JS. Differential expression of lipid metabolism-related proteins in different breast cancer subtypes. *PLoS One* 2015; **10**: e0119473 [PMID: 25751270 DOI: 10.1371/journal.pone.0119473]

40 **Wang YY**, Kuhajda FP, Li J, Finch TT, Cheng P, Koh C, Li T, Sokoll LJ, Chan DW. Fatty acid synthase as a tumor marker: its extracellular expression in human breast cancer. *J Exp Ther Oncol* 2004; **4**: 101-110 [PMID: 15500005]

41 **Vazquez-Martin A**, Ortega-Delgado FJ, Fernandez-Real JM, Menendez JA. The tyrosine kinase receptor HER2 (erbB-2): from oncogenesis to adipogenesis. *J Cell Biochem* 2008; **105**: 1147-1152 [PMID: 18814184 DOI: 10.1002/jcb.21917]

42 **Goldhirsch A**, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; [Panel members](http://www.ncbi.nlm.nih.gov/pubmed/?term=Panel%20members%5BCorporate%20Author%5D). Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol* 2011; **22**: 1736-1747 [PMID: 21709140 DOI: 10.1093/annonc/mdr304]

43 **Gordan JD**, Thompson CB, Simon MC. HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation. *Cancer Cell* 2007; **12**: 108-113 [PMID: 17692803 DOI: 10.1016/j.ccr.2007.07.006]

44 **Iqbal MA**, Bamezai RN. Resveratrol inhibits cancer cell metabolism by down regulating pyruvate kinase M2 via inhibition of mammalian target of rapamycin. *PLoS One* 2012; **7**: e36764 [PMID: 22574221 DOI: 10.1371/journal.pone.0036764]

45 **Ko BH**, Paik JY, Jung KH, Lee KH. 17beta-estradiol augments 18F-FDG uptake and glycolysis of T47D breast cancer cells via membrane-initiated rapid PI3K-Akt activation. *J Nucl Med* 2010; **51**: 1740-1747 [PMID: 20956467 DOI: 10.2967/jnumed.110.074708]

46 **Sudhagar S**, Sathya S, Lakshmi BS. Rapid non-genomic signalling by 17β-oestradiol through c-Src involves mTOR-dependent expression of HIF-1α in breast cancer cells. *Br J Cancer* 2011; **105**: 953-960 [PMID: 21897387 DOI: 10.1038/bjc.2011.349]

47 **Yuneva MO**, Fan TW, Allen TD, Higashi RM, Ferraris DV, Tsukamoto T, Matés JM, Alonso FJ, Wang C, Seo Y, Chen X, Bishop JM. The metabolic profile of tumors depends on both the responsible genetic lesion and tissue type. *Cell Metab* 2012; **15**: 157-170 [PMID: 22326218 DOI: 10.1016/j.cmet.2011.12.015]

48 **Blancato J**, Singh B, Liu A, Liao DJ, Dickson RB. Correlation of amplification and overexpression of the c-myc oncogene in high-grade breast cancer: FISH, in situ hybridisation and immunohistochemical analyses. *Br J Cancer* 2004; **90**: 1612-1619 [PMID: 15083194 DOI: 10.1038/sj.bjc.6601703]

49 **Deming SL**, Nass SJ, Dickson RB, Trock BJ. C-myc amplification in breast cancer: a meta-analysis of its occurrence and prognostic relevance. *Br J Cancer* 2000; **83**: 1688-1695 [PMID: 11104567 DOI: 10.1054/bjoc.2000.1522]

50 **Shajahan-Haq AN**, Cook KL, Schwartz-Roberts JL, Eltayeb AE, Demas DM, Warri AM, Facey CO, Hilakivi-Clarke LA, Clarke R. MYC regulates the unfolded protein response and glucose and glutamine uptake in endocrine resistant breast cancer. *Mol Cancer* 2014; **13**: 239 [PMID: 25339305 DOI: 10.1186/1476-4598-13-239]

51 **Simpson NE**, Tryndyak VP, Pogribna M, Beland FA, Pogribny IP. Modifying metabolically sensitive histone marks by inhibiting glutamine metabolism affects gene expression and alters cancer cell phenotype. *Epigenetics* 2012; **7**: 1413-1420 [PMID: 23117580 DOI: 10.4161/epi.22713]

52 **Chen Z**, Wang Y, Warden C, Chen S. Cross-talk between ER and HER2 regulates c-MYC-mediated glutamine metabolism in aromatase inhibitor resistant breast cancer cells. *J Steroid Biochem Mol Biol* 2015; **149**: 118-127 [PMID: 25683269 DOI: 10.1016/j.jsbmb.2015.02.004]

53 **Gao P**, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, Zeller KI, De Marzo AM, Van Eyk JE, Mendell JT, Dang CV. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. *Nature* 2009; **458**: 762-765 [PMID: 19219026 DOI: 10.1038/nature07823]

54 **Liu W**, Le A, Hancock C, Lane AN, Dang CV, Fan TW, Phang JM. Reprogramming of proline and glutamine metabolism contributes to the proliferative and metabolic responses regulated by oncogenic transcription factor c-MYC. *Proc Natl Acad Sci USA* 2012; **109**: 8983-8988 [PMID: 22615405 DOI: 10.1073/pnas.1203244109]

55 **Csibi A**, Fendt SM, Li C, Poulogiannis G, Choo AY, Chapski DJ, Jeong SM, Dempsey JM, Parkhitko A, Morrison T, Henske EP, Haigis MC, Cantley LC, Stephanopoulos G, Yu J, Blenis J. The mTORC1 pathway stimulates glutamine metabolism and cell proliferation by repressing SIRT4. *Cell* 2013; **153**: 840-854 [PMID: 23663782 DOI: 10.1016/j.cell.2013.04.023]

56 **Csibi A**, Lee G, Yoon SO, Tong H, Ilter D, Elia I, Fendt SM, Roberts TM, Blenis J. The mTORC1/S6K1 pathway regulates glutamine metabolism through the eIF4B-dependent control of c-Myc translation. *Curr Biol* 2014; **24**: 2274-2280 [PMID: 25220053 DOI: 10.1016/j.cub.2014.08.007]

57 **Xiong S**, Chirala SS, Wakil SJ. Sterol regulation of human fatty acid synthase promoter I requires nuclear factor-Y- and Sp-1-binding sites. *Proc Natl Acad Sci USA* 2000; **97**: 3948-3953 [PMID: 10759542 DOI: 10.1073/pnas.040574197]

58 **Donnelly C**, Olsen AM, Lewis LD, Eisenberg BL, Eastman A, Kinlaw WB. Conjugated linoleic acid (CLA) inhibits expression of the Spot 14 (THRSP) and fatty acid synthase genes and impairs the growth of human breast cancer and liposarcoma cells. *Nutr Cancer* 2009; **61**: 114-122 [PMID: 19116881 DOI: 10.1080/01635580802348666]

59 **Teran-Garcia M**, Adamson AW, Yu G, Rufo C, Suchankova G, Dreesen TD, Tekle M, Clarke SD, Gettys TW. Polyunsaturated fatty acid suppression of fatty acid synthase (FASN): evidence for dietary modulation of NF-Y binding to the Fasn promoter by SREBP-1c. *Biochem J* 2007; **402**: 591-600 [PMID: 17313375 DOI: 10.1042/BJ20061722]

60 **Kuhajda FP**. AMP-activated protein kinase and human cancer: cancer metabolism revisited. *Int J Obes* (Lond) 2008; **32** Suppl 4: S36-S41 [PMID: 18719597 DOI: 10.1038/ijo.2008.121]

61 **Menendez JA**, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nat Rev Cancer* 2007; **7**: 763-777 [PMID: 17882277 DOI: 10.1038/nrc2222]

62 **Furuta E**, Pai SK, Zhan R, Bandyopadhyay S, Watabe M, Mo YY, Hirota S, Hosobe S, Tsukada T, Miura K, Kamada S, Saito K, Iiizumi M, Liu W, Ericsson J, Watabe K. Fatty acid synthase gene is up-regulated by hypoxia via activation of Akt and sterol regulatory element binding protein-1. *Cancer Res* 2008; **68**: 1003-1011 [PMID: 18281474 DOI: 10.1158/0008-5472.CAN-07-2489]

63 **Yang YA**, Han WF, Morin PJ, Chrest FJ, Pizer ES. Activation of fatty acid synthesis during neoplastic transformation: role of mitogen-activated protein kinase and phosphatidylinositol 3-kinase. *Exp Cell Res* 2002; **279**: 80-90 [PMID: 12213216 DOI: 10.1006/excr.2002.5600]

64 **Yan C**, Wei H, Minjuan Z, Yan X, Jingyue Y, Wenchao L, Sheng H. The mTOR inhibitor rapamycin synergizes with a fatty acid synthase inhibitor to induce cytotoxicity in ER/HER2-positive breast cancer cells. *PLoS One* 2014; **9**: e97697 [PMID: 24866893 DOI: 10.1371/journal.pone.0097697]

65 **Menendez JA**, Oza BP, Atlas E, Verma VA, Mehmi I, Lupu R. Inhibition of tumor-associated fatty acid synthase activity antagonizes estradiol- and tamoxifen-induced agonist transactivation of estrogen receptor (ER) in human endometrial adenocarcinoma cells. *Oncogene* 2004; **23**: 4945-4958 [PMID: 15094777 DOI: 10.1038/sj.onc.1207476]

66 **Fumarola C**, Caffarra C, La Monica S, Galetti M, Alfieri RR, Cavazzoni A, Galvani E, Generali D, Petronini PG, Bonelli MA. Effects of sorafenib on energy metabolism in breast cancer cells: role of AMPK-mTORC1 signaling. *Breast Cancer Res Treat* 2013; **141**: 67-78 [PMID: 23963659 DOI: 10.1007/s10549-013-2668-x]

67 **Young CD**, Lewis AS, Rudolph MC, Ruehle MD, Jackman MR, Yun UJ, Ilkun O, Pereira R, Abel ED, Anderson SM. Modulation of glucose transporter 1 (GLUT1) expression levels alters mouse mammary tumor cell growth in vitro and in vivo. *PLoS One* 2011; **6**: e23205 [PMID: 21826239 DOI: 10.1371/journal.pone.0023205]

68 **Liu Y**, Cao Y, Zhang W, Bergmeier S, Qian Y, Akbar H, Colvin R, Ding J, Tong L, Wu S, Hines J, Chen X. A small-molecule inhibitor of glucose transporter 1 downregulates glycolysis, induces cell-cycle arrest, and inhibits cancer cell growth in vitro and in vivo. *Mol Cancer Ther* 2012; **11**: 1672-1682 [PMID: 22689530 DOI: 10.1158/1535-7163.MCT-12-0131]

69 **Zhao Y**, Liu H, Liu Z, Ding Y, Ledoux SP, Wilson GL, Voellmy R, Lin Y, Lin W, Nahta R, Liu B, Fodstad O, Chen J, Wu Y, Price JE, Tan M. Overcoming trastuzumab resistance in breast cancer by targeting dysregulated glucose metabolism. *Cancer Res* 2011; **71**: 4585-4597 [PMID: 21498634 DOI: 10.1158/0008-5472.CAN-11-0127]

70 **Fantin VR**, St-Pierre J, Leder P. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. *Cancer Cell* 2006; **9**: 425-434 [PMID: 16766262 DOI: 10.1016/j.ccr.2006.04.023]

71 **Gudi R**, Bowker-Kinley MM, Kedishvili NY, Zhao Y, Popov KM. Diversity of the pyruvate dehydrogenase kinase gene family in humans. *J Biol Chem* 1995; **270**: 28989-28994 [PMID: 7499431 DOI: 10.1074/jbc.270.48.28989]

72 **Fan J**, Kamphorst JJ, Mathew R, Chung MK, White E, Shlomi T, Rabinowitz JD. Glutamine-driven oxidative phosphorylation is a major ATP source in transformed mammalian cells in both normoxia and hypoxia. *Mol Syst Biol* 2013; **9**: 712 [PMID: 24301801 DOI: 10.1038/msb.2013.65]

73 **Karunakaran S**, Ramachandran S, Coothankandaswamy V, Elangovan S, Babu E, Periyasamy-Thandavan S, Gurav A, Gnanaprakasam JP, Singh N, Schoenlein PV, Prasad PD, Thangaraju M, Ganapathy V. SLC6A14 (ATB0,+) protein, a highly concentrative and broad specific amino acid transporter, is a novel and effective drug target for treatment of estrogen receptor-positive breast cancer. *J Biol Chem* 2011; **286**: 31830-31838 [PMID: 21771784 DOI: 10.1074/jbc.M111.229518]

74 **Gross MI**, Demo SD, Dennison JB, Chen L, Chernov-Rogan T, Goyal B, Janes JR, Laidig GJ, Lewis ER, Li J, Mackinnon AL, Parlati F, Rodriguez ML, Shwonek PJ, Sjogren EB, Stanton TF, Wang T, Yang J, Zhao F, Bennett MK. Antitumor activity of the glutaminase inhibitor CB-839 in triple-negative breast cancer. *Mol Cancer Ther* 2014; **13**: 890-901 [PMID: 24523301 DOI: 10.1158/1535-7163.MCT-13-0870]

75 **Pizer ES**, Thupari J, Han WF, Pinn ML, Chrest FJ, Frehywot GL, Townsend CA, Kuhajda FP. Malonyl-coenzyme-A is a potential mediator of cytotoxicity induced by fatty-acid synthase inhibition in human breast cancer cells and xenografts. *Cancer Res* 2000; **60**: 213-218 [PMID: 10667561]

76 **Zhou W**, Simpson PJ, McFadden JM, Townsend CA, Medghalchi SM, Vadlamudi A, Pinn ML, Ronnett GV, Kuhajda FP. Fatty acid synthase inhibition triggers apoptosis during S phase in human cancer cells. *Cancer Res* 2003; **63**: 7330-7337 [PMID: 14612531]

77 **Menendez JA**, Vellon L, Lupu R. Targeting fatty acid synthase-driven lipid rafts: a novel strategy to overcome trastuzumab resistance in breast cancer cells. *Med Hypotheses* 2005; **64**: 997-1001 [PMID: 15780499 DOI: 10.1016/j.mehy.2004.09.027]

78 **Menendez JA**, Vellon L, Mehmi I, Oza BP, Ropero S, Colomer R, Lupu R. Inhibition of fatty acid synthase (FAS) suppresses HER2/neu (erbB-2) oncogene overexpression in cancer cells. *Proc Natl Acad Sci USA* 2004; **101**: 10715-10720 [PMID: 15235125 DOI: 10.1073/pnas.0403390101]

79 **Vazquez-Martin A**, Colomer R, Brunet J, Menendez JA. Pharmacological blockade of fatty acid synthase (FASN) reverses acquired autoresistance to trastuzumab (Herceptin by transcriptionally inhibiting 'HER2 super-expression' occurring in high-dose trastuzumab-conditioned SKBR3/Tzb100 breast cancer cells. *Int J Oncol* 2007; **31**: 769-776 [PMID: 17786307 DOI: 10.3892/ijo.31.4.769]

80 **Menendez JA**, Lupu R, Colomer R. Inhibition of tumor-associated fatty acid synthase hyperactivity induces synergistic chemosensitization of HER -2/ neu -overexpressing human breast cancer cells to docetaxel (taxotere). *Breast Cancer Res Treat* 2004; **84**: 183-195 [PMID: 14999148]

81 **Menendez JA**, Vellon L, Colomer R, Lupu R. Pharmacological and small interference RNA-mediated inhibition of breast cancer-associated fatty acid synthase (oncogenic antigen-519) synergistically enhances Taxol (paclitaxel)-induced cytotoxicity. *Int J Cancer* 2005; **115**: 19-35 [PMID: 15657900 DOI: 10.1002/ijc.20754]

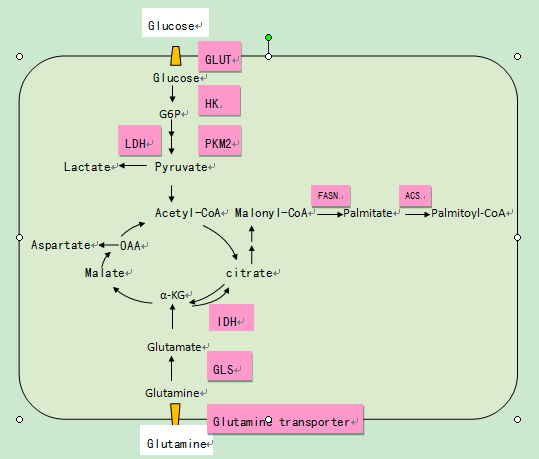
82 **Liu H**, Liu Y, Zhang JT. A new mechanism of drug resistance in breast cancer cells: fatty acid synthase overexpression-mediated palmitate overproduction. *Mol Cancer Ther* 2008; **7**: 263-270 [PMID: 18281512 DOI: 10.1158/1535-7163.MCT-07-0445]

83 **Vazquez-Martin A**, Ropero S, Brunet J, Colomer R, Menendez JA. Inhibition of Fatty Acid Synthase (FASN) synergistically enhances the efficacy of 5-fluorouracil in breast carcinoma cells. *Oncol Rep* 2007; **18**: 973-980 [PMID: 17786362 DOI: 10.3892/or.18.4.973]

84 **Menendez JA**, Colomer R, Lupu R. Inhibition of tumor-associated fatty acid synthase activity enhances vinorelbine (Navelbine)-induced cytotoxicity and apoptotic cell death in human breast cancer cells. *Oncol Rep* 2004; **12**: 411-422 [PMID: 15254710]

**P- Reviewer:** Matés JM, Song CJ, Tang SY **S- Editor:** Gong XM

**L- Editor:** **E- Editor:**



**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.