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Expanding the view of breast cancer metabolism: Promising molecular targets and therapeutic opportunities

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ABSTRACT

The changes in breast cancer cells that contribute to tumor evolution, heterogeneity, metastasis and ultimately drug resistance are shaped by numerous genetic changes including alterations in cellular metabolism. These include intermediary metabolic pathways such as glycolysis, the citric acid cycle oxidative phosphorylation, amino acid synthesis and lipid metabolism. However, cancer cells also exhibit key alterations in other metabolic pathways involved in drug metabolism such as cytochrome P450 enzymes, sulfotransferase and steroid sulfatases that are involved in the synthesis of estrogens and themselves serve as drug targets. In this review we bring together these two sides of metabolism, discuss the evidence underpinning their role in breast cancer development and bring to light promising therapeutic targets and up and coming pharmacologic agents.

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1. Introduction

There is extensive evidence showing that the metabolism of both exogenous and endogenous substances influences breast cancer growth. Moreover, it is clear that metabolism can influence each unique breast cancer subclass in diverse ways and to varying degrees. These metabolic changes have been categorized in an assortment of ways, for example, many involve changes in energy metabolism such as in the way that glucose, amino acids, and lipids are processed. Others can involve the modulation of hormone synthesis and metabolism, for example, estrogen and downstream metabolites. Finally, others involve the modulation of xenobiotic metabolism, which can contribute to the effectiveness and/or resistance to therapeutic agents. The intent of this review is to describe the current understanding of the role of metabolism, in all its various forms (e.g., energy, hormone, and drug metabolism) and how changes in metabolism influence breast cancer growth. Alterations in metabolism, broadly defined, offer several opportunities to discover new treatment approaches and to improve the effectiveness of currently available treatments. Therefore, a second goal of this review is to describe some of the therapeutic targets within these metabolic pathways and the progress that has been made to develop agents that effectively modulate these targets.

Exhaustive efforts have been undertaken to stratify breast tumors into sub-classes beyond estrogen, progesterone, and HER-2 receptor status by using gene expression profiling and histologic appearance (Perou et al., 2000; Sorlie et al., 2001; Sotiriou et al., 2003; Schnitt, 2010). For example, breast cancers are classified in broad bins as either basal or luminal based whether they are enriched with basal epithelial cells or luminal epithelial cells, respectively (Perou et al., 2000). Basal-like breast tumors, which include triple negative breast cancer (estrogen receptor-minus, progesterone receptor-minus and HER-2-minus), more commonly harbor TP53 and MYC mutations leading to a loss of function for TP53 and overexpression of MYC (Cancer Genome Atlas, 2012; Tang et al., 2014). In addition, approximately 80% of BRCA1 dysfunctional tumors are grouped with basal-like tumors (Schnitt, 2010). Luminal breast tumors on the other hand can be subdivided into Luminal A and Luminal B on the basis of high expression of hormone receptors (ER, PR, HER-2) with some variability in the expression of HER-2

Abbreviations: BL-1, Basal like 1; BL-2, Basal like 2; BRCA-1, Breast cancer 1; BCRP, Breast cancer resistant protein; BCSC, Breast cancer stem cell; CYP, Cytochrome P450; D-2HG, D-2-hydroxyglutarate; DCA, Dichloroacetic acid; DHEA, Dehydroepiandrosterone; ER, Estrogen receptor; FASN, Fatty acid synthase; GLUT1, Glucose transporter 1; HER-2, Human epidermal growth factor receptor 2; HIF-1, Hypoxia-inducible factor 1; HK-1, Hexokinase-1; HK-2, Hexokinase-2; IDH-1, Isocitrate dehydrogenase 1; IDO, Indoleamine 2,3-dioxygenase; IM, Immunomodulatory; LC-MS/MS, Liquid chromatography tandem mass spectrometry; LDHA, Lactate dehydrogenase A; LAR, Luminal androgen receptor; M, Mesenchymal; MSL, Mesenchymal stem-like; MRP, Multidrug-resistant protein; NADPH, Nicotinamide adenine dinucleotide phosphate; OATP, Organic anion transporter polypeptides; OXPHOS, Oxidative phosphorylation; PAPS, 3′-Phospho-adenosine-5′-phosphosulfate; PARP, Poly-ADP-ribose polymerase; PC, Phosphatidylcholine; PDH, Pyruvate dehydrogenase; PDK1, Pyruvate dehydrogenase kinase 1; PFK1, Phosphofructokinase 1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase; PHGDH, Phosphoglycerate dehydrogenase; PPP, Pentose-phosphate-pathway; PR, Progesterone receptor; PTEN, Phosphatase and tensin homolog; ROS, Reactive oxygen species; SDHC, Succinate dehydrogenase complex; SLCO, Solute carrier organic anion transporter; STS, Steroid sulfatase; SULT, Sulfotransferase; TCA, Tricarboxylic acid cycle; TDO, Tryptophan 2,3-dioxygenase; TIL, Tumor infiltrating lymphocyte; TNBC, Triple negative breast cancer.

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(Schnitt, 2010). Luminal A and B breast cancers more commonly have PI3KCA mutations compared to basal-like tumors (Tang et al., 2014; Mishra & Ambs, 2015). Both basal-like and luminal-like breast tumors generally overexpress MYC (Cancer Genome Atlas, 2012). A third broad bin or category of breast tumors is the HER-2 type which are ER-negative, PR-negative and HER-2 positive (Schnitt, 2010). The HER-2 type commonly have TP53 mutations and PI3KCA mutations (Cancer Genome Atlas, 2012). These classifications provide some guidance on treatment selection: luminal subtypes can be treated with tamoxifen, aromatase inhibitors and fulvestrant; basal-like subtypes can be treated with conventional cytotoxic chemotherapeutic agents and PARP inhibitors; and HER-2 sub-types can be treated with trastuzumab, pertuzumab, and lapatinib (Higgins & Baselga, 2011). However these groupings are still very broad. Lehmann et al. analyzed gene expression profiles of triple negative breast cancers and identified gene expression clusters which they segregated into subtypes that display selective sensitivity to targeted therapy (Lehmann et al., 2011). They identified 6 different TNBC subtypes: Basal-like 1 and Basal-like 2 (BL-1 and BL-2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and a luminal androgen (LAR) subtype (Lehmann et al., 2011). They then went a step further and, based on the gene expression profile, measured the sensitivity of each subtype to “matched” chemotherapeutic agents. For example, the BL-1 subtype expresses high levels of cell cycle and DNA damage response genes. The BL-2 subtype expresses high levels of growth factor genes and genes involved in glycolysis and gluconeogenesis and were more sensitive to cisplatin whereas the M and MSL subtypes responded to PI3K/mTOR inhibitor NVP-BEZ235 and src inhibitor dasatinib. The LAR subtype on the other hand was more sensitive to the androgen receptor antagonist bicalutamide. These studies underscore the significant heterogeneity seen with breast cancer that have led to refinements in our ability to diagnosis and categorize breast tumors. The evolutionary process that leads to heterogeneity within and between breast tumors is poorly understood but what is becoming clear is that this heterogeneity may explain variability in underlying cell physiology that leads to alterations in treatment response (Zardavas et al., 2015). Development of chemoresistance following treatment with conventional chemotherapeutic agents yields breast cancer cells with a more glycolytic metabolism which can be exploited therapeutically using inhibitors of metabolism in tandem with conventional agents (Silva et al., 2012). Likewise metastatic breast cancers also exhibit a heavy reliance on glycolysis and development of a glycolytic phenotype correlates with enhanced aggressiveness and multi-drug resistance (Harris, 2002; Milane et al., 2011; Dupuy et al., 2015). This may provide a therapeutic avenue to more specifically target aggressive, metastatic breast cancers that are driven, in part by changes in metabolic phenotype (Dupuy et al., 2015). Indeed, targeting aberrant metabolism in breast cancer cells using inhibitors of glycolysis, oxidative phosphorylation, lipid metabolism, amino acid synthesis, and drug metabolizing enzymes may offer a viable avenue to counter drug resistance, improve tumoral immune responses, and target metastatic cells.

2. General overview of intermediary metabolism in breast cancer

The most significant alterations in intermediary metabolism seen in breast tumors arise from mutations in genes regulating glycolysis, mitochondrial oxidative phosphorylation and amino acid metabolism. Defining the metabolic defects in breast cancer cells is of profound clinical significance because it can provide us with a picture of the path breast cancer takes during its oncogenic evolution and this may ultimately lead to identification of tangible therapeutic targets.

2.1. Glycolysis

Most cancers, including breast cancer, are heavily reliant on aerobic glycolysis to produce energy for sustained growth and proliferation (Gambhir et al., 2001; Gambhir, 2002). This phenomena which is known as the Warburg effect, has some important advantages for cancer cells because it enables rapid generation of ATP and reduced production of reactive oxygen species (ROS) in tumor microenvironments with intermittent or sustained hypoxia (Cairns et al., 2011). Aerobic glycolysis has the added benefit of yielding metabolic intermediates that can be used by the pentose-phosphate-pathway (PPP) to produce NADPH and precursors of nucleotides, amino acids, lipids and sugars (Cairns et al., 2011; Dang, 2012). Aberrant glycolysis in cancer appears to be driven by mutations in well know genes that are drivers of oncogenesis such as MYC, Ras, PI3K, Akt, PTEN and TP53 (Barthel et al., 1999; Shaw, 2006). Although there are some exceptions, given the central and pivotal role these genes play in normal cellular growth and proliferation it has been difficult to develop clinically useful therapeutic agents to modulate their function in cancer cells. Targeting the downstream products of these genes, especially those upon which cancer cells have become dependent, appears to be a potentially more fruitful approach. A recent analysis of metabolite levels in ER-positive and ER-negative tumors showed that ER-negative tumors have higher levels of glycolytic and glycogenolytic metabolites and there were measurable differences in these metabolites between ER-positive and ER-negative tumors (Tang et al., 2014). Compared with ER-positive tumors, ER-negative tumors exhibited higher levels of glycolytic metabolites corresponding to the first three steps in glycolysis including glucose-6-phosphate (produced from glucose by the actions of hexokinase), fructose-6-phosphate (produced from glucose-6-phosphate by the enzyme phosphoglucoisomerase) and fructose-1,6-bisphosphate (produced from fructose-6-phosphate by phosphofructokinase 1) (Tang et al., 2014). The increased levels of these metabolites can be explained in part by the expression patterns of the aforementioned oncogenes and tumor suppressors and their downstream signaling mediators in breast cancer. For example MYC in cooperation with hypoxia-inducible factor 1 (HIF-1) governs the expression of hexokinase (Kim et al., 2007). Based on gene expression profiling, MYC amplification and overexpression correlates with the more aggressive and metastatic BRCA-1 deficient ER-negative tumors that appear to have a heavier reliance on glycolysis (Aulmann et al., 2002; Grushko et al., 2004; Wei et al., 2005; Lehmann et al., 2011; Tang et al., 2014). Recently, Privat et al. performed metabolomic analysis of the triple-negative SUM1315 breast cancer cell line (which is ER-negative, PR-negative and deficient for BRCA-1) and compared their metabolic profile to SUM1315 cells forced to overexpress BRCA-1 (Neve et al., 2006; Privat et al., 2014). This study revealed that overexpression of BRCA-1 led to downregulation of genes involved in glycolysis including the glucose transporter SLC2A1 (GLUT1), HK-1 and HK-2 (Hexokinase-1 and -2) which catalyzes the initial step in glycolysis, PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase) which regulates an allosteric activator of PFK1, and LDHA (Lactate dehydrogenase A) which catalyzes the conversion of pyruvate to lactate. Several promising studies have identified small molecule inhibitors of several of these enzymes including PFKB3 and GLUT, although their efficacy in BRCA-1 deficient breast cancers remains to be demonstrated (Clem et al., 2008; Chan et al., 2011; Liu et al., 2012; Boyd et al., 2015). Nevertheless, these authors conclude that overexpression of BRCA-1 down regulates glycolysis. They also show that BRCA-1 overexpression increases the TCA cycle and oxidative phosphorylation (discussed more below) as well as altering levels of free fatty acids and glutathione metabolism. The latter event presumably provides buffering capacity against ROS generation. The precise mechanism explaining how BRCA-1 influences these changes in cellular metabolism remain to be fully elucidated although it likely relates to mutation and over-activation of Akt and HIF-1 (Barthel et al., 1999; Shaw, 2006). On the other hand, how HIF-1 becomes dysregulated in cancer is not entirely clear, however increasing tumor hypoxia appears to be a major contributor. HIF-1 transcriptionally regulates nearly all of the genes involved in glycolysis. A recent study by Dupuy et al. shows that aggressively metastatic breast cancer cells have elevated levels of glycolysis that is principally driven by HIF-1 and that silencing HIF-1

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