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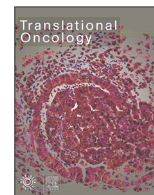

Energy metabolism pathways in breast cancer progression: The reprogramming, crosstalk, and potential therapeutic targets

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ABSTRACT

Breast cancer (BC) is a malignant tumor that seriously endangers health in women. BC, like other cancers, is accompanied by metabolic reprogramming. Among energy metabolism-related pathways, BC exhibits enhanced glycolysis, tricarboxylic acid (TCA) cycle, pentose phosphate pathway (PPP), glutamate metabolism, and fatty acid metabolism activities. These pathways facilitate the proliferation, growth and migration of BC cells. The progression of BC is closely related to the alterations in the activity or expression level of several metabolic enzymes, which are regulated by the intrinsic factors such as the key signaling and transcription factors. The metabolic reprogramming in the progression of BC is attributed to the aberrant expression of the signaling and transcription factors associated with the energy metabolism pathways. Understanding the metabolic mechanisms underlying the development of BC will provide a druggable potential for BC treatment and drug discovery.

Introduction

Breast cancer (BC) is a leading cause of cancer-related deaths in women worldwide. Gene expression profiling brings a considerable impact on our understanding of the biologic heterogeneity of BC and enables us to extensively characterize 4 molecular subtypes of BC (luminal A, luminal B, HER2, and triple-negative BC (TNBC)) [1]. BC incidence varies widely from 27/100,0002 (Central-East Asia and Africa) to 85–94/100,0002 (Australia, North America, and Western Europe) [2]. Both genetic and metabolic features were characterized in BC, and enzyme-associated energy metabolism participated in the tumor cell progression, with the regulation of multiple signaling pathways [3]. Under the combined action of energy metabolism-related genes, signaling pathways, and transcription factors, the tumor exhibits significant metabolic shifting. This results in the unique metabolic profiling of cancer, which is considered to be a hallmark for tumor development [4,5]. Tumor cells overly depend on glucose and glutamate to provide sufficient energy for cell proliferation and invasion. Aberrant expression of energy metabolism-related enzymes regulated by primary signaling pathways, such as the phosphoinositide 3- kinase (PI3K)/protein kinase B (AKT) signaling and AMPK pathway [6], or transcription factors, including c-MYC, p53, and hypoxia-inducible factor (HIF) [7], predominantly results in metabolic reprogramming in BC.

This review addresses the metabolic reprogramming of energy pathways, the crosstalk of major signaling pathways, and the potential therapeutic target related to transcription factors in BC. A better understanding of the metabolic switching in BC may provide a favorable basis for exploring the new anticancer therapeutics.

The reprogramming of multiple energy metabolism pathways

Glycolysis

Glycolysis is the major energy producing process in BC. The cancer cells showed a sufficiently prevalent that elevated uptake of glucose based on ^{8}F-fluorodeoxyglucose, the cancer diagnosis, and monitoring tool of the therapeutic response [8]. Importantly, the enhanced glycolysis and reduced oxidative phosphorylation (OXPHOS) were confirmed in cancer cells by Otto Warburg [9]. Under hypoxic condition in BC, the stabilization of HIF 1 and 2 is increased, which in turn upregulate the expression of several other components of distinct signaling pathways, including several key glycolytic enzymes and glucose transporters (GLUTs) [10]. Glucose uptake is facilitated by GLUTs family by allowing the energy independent transport of glucose across the hydrophobic cell membrane down its concentration gradient, among which 14 members

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were identified in mammalian. The expression of GLUTs showed a diverse level in different BC cell lines, in which GLUT1 levels were higher in basal-like BC cells and T47D cells, whereas the levels of GLUT3/4 were higher in luminal BC cells [11]. GLUT1 is frequently upregulated in the development of BC (Fig. 1) [12,13], which has also confirmed to result in the tumorigenesis of BC [11]. In addition, as a potential biomarker and therapeutic target in BC, GLUT1 overexpression showed a strong association with high histological grade, a negative estrogen receptor (ER) status, and a poor overall survival [14].

Glycolysis refers to the process by which cells break down glucose in the cytoplasm and finally generate pyruvate, which is accompanied by the generation of a small amount of ATP. The anaerobic glycolysis refers to the process of converting glucose to lactate that generates only 2 ATPs per molecule of glucose, much less than 36 ATPs upon complete oxidation of one glucose molecule [15,16], which suggesting that inefficient ATP production is a problem only when resources are scarce. This may be a possible explanation why anaerobic glycolysis is finally selected in proliferating cells.

During the breakdown of glucose in glycolysis, hexokinase 2 (HK2), phosphofructokinase 1 (PFK1), and pyruvate kinase (PK) are key rate-limiting enzymes (Fig. 1). The process in which glucose was converted to glucose-6-phosphate (G6P), which is catalyzed by HK, is the first committed step in glucose metabolism with the production of ATP to meet the energy needs of cancer cells. HK2 is required for initiation and maintenance of BC [17]. Raya showed that 79% of the BC were HK2-positive using immunohistochemistry analysis [18]. High expression of HK2 was also identified in human BC tissues, and its expression was further confirmed to be associated with pathological stage of the tumors, the high mortality of the patients, [17] and poor patient survival [19]. In tumor tissues of BC mouse models, the co-expression of activated Neu and Cre in the mammary gland contributed to increased HK2 expression and the development of mammary gland tumors with complete penetrance [17], suggesting that HK2 is required for ErbB2-driven mammary gland tumorigenesis *in vivo*. Similarly, the elevated expression of HK2 also contributed to the tumor metastasis. In mouse models of BC metastasis, HK2 increased the level and stability of Snail and promoted Snail-mediated epithelial-mesenchymal transition and metastasis [20]. However, HK2 deficiency not only reversed the BC metastasis

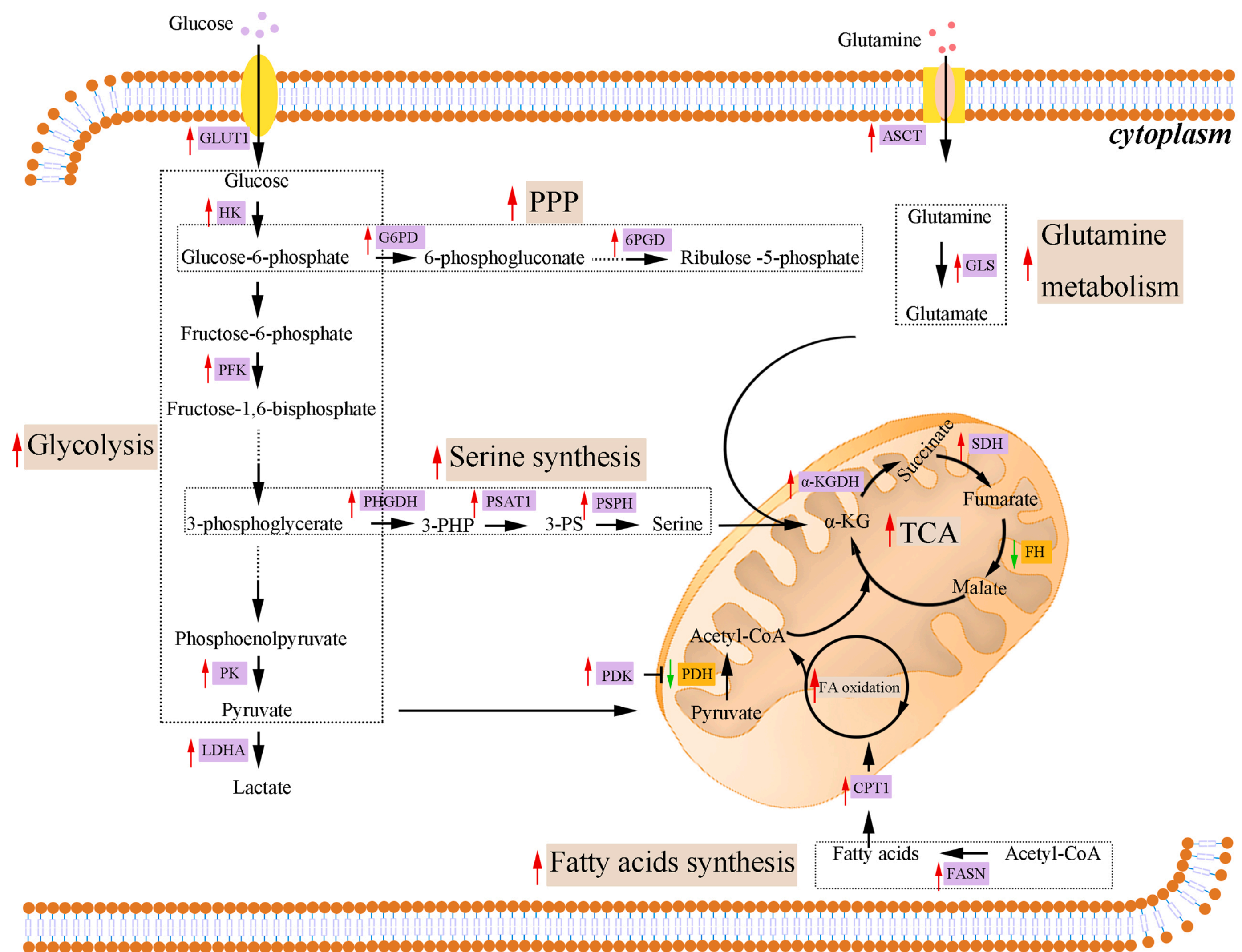

Fig. 1. Overview of the energy metabolic reprogramming in BC. The energy metabolic pathways, including the glycolysis, serine synthesis, glutamine metabolism, PPP, TCA cycle, fatty acids synthesis, and oxidation enhanced in BC, provide the sufficient capacity to maintain cell growth. GLUT1, glucose transporter 1; HK, hexokinase; PFK, phosphofructokinase; PK, pyruvate kinase; TCA, tricarboxylic acid cycle; α-KG, a-ketoglutarate; α-KGDH, α-ketoglutarate dehydrogenase complex; SDH, succinate dehydrogenase; FH, fumarase; LDHA, lactate dehydrogenase A; PPP, pentose phosphate pathway; G6PD, glucose-6-phosphate dehydrogenase; 6PGD, 6-phosphogluconate dehydrogenase; GLS, glutaminase; PHGDH, phosphoglycerate dehydrogenase; PSAT1, phosphoserine aminotransferase1; PSPH, phosphoserine phosphatase; PDK, pyruvate dehydrogenase kinase; PDH, pyruvate dehydrogenase; CPT1, carnitine palmitoyl transferase1; FASN, fatty acid synthase; 3-PHP, 3-phosphate hydroxypyruvate; 3-PS, 3-phosphatidylserine; ASCT, alanine-serine-cysteine-preferring transporter.

described above but also reversed tumorigenesis *in vitro* and *in vivo* of BC [17,20]. In addition, HK2 activity was also confirmed to contribute to therapy resistance, including a role for HK2 in radio-and chemo--resistance in BC. Lentivirus-mediated shRNA knockdown of HK2 expression effectively improved the radio sensitivity of BC by triggering apoptosis [21], which may be achieved by HK2 combined with mitochondria to inhibit the interaction the proapoptotic factors voltage-dependent anion channel (VDAC) and Bax [22]. HK2 physically interacts with mTOR and inhibits its activity, thereby augmenting autophagy that confers resistance to MCF-7 cells toward tamoxifen, suggesting that HK2 poses as therapeutic target for impairing tamoxifen resistance in BC [23].

PFK1 catalyzes the conversion of fructose 6-phosphate to fructose-1,6- bisphosphate. There are three isoforms of human PFK-1, including PFKL (liver), PFKM (muscle), and PFKP (platelet). Study showed that PFKL isoform expression was directly and strongly associated with aggressiveness and glycolytic efficiency in BC cell lines, including MCF10A, MCF-7, and MDA-mb-231 [24] and human BC tissues [25], suggesting that glycolytic efficiency in BC depends primarily on the preferential expression of three PFK isoforms. In BC patients, PFK-1 expression was higher in BC tissues than in paracancer tissues, and PFKP is the principal isoform (~60–70%), followed by PFKM and PFKL. However, PFKL isoform is converted to PFKP with the enrichment of glycolytic activity [25]. PFKP is gaining attention for its significant role in BC progression. Highly expression of PFKP was observed in estrogen receptor-negative and human epidermal growth factor receptor (EGFR) 2-negative BC cell lines [26] and human BC tissues [25]. The knockdown of PFKP significantly attenuated the proliferation and invasiveness in MCF7, SK-BR-3, and MDA-MB-231 BC cells [26], and the role of PFKP in promoting tumor progressive oncology was speculated to be clearly related to transforming growth factor-β1 and MYC proto-oncogene [26]. Not only the foregoing, but the high expression of PFKP associated with the increased PFKP S386 phosphorylation was identified in Wnt signaling-induced BC development in a β-catenin-independent manner [27] or the activation of Krüppel-like factor in BC cells [28]. The prognostic value of PFKP was also further confirmed, which result showed that elevated PFKP levels are associated with basal cells/triple negative subtypes [29] and might serve as a prognostic indicator [29,30]. PFK2 (PFKFB3) is also a key regulator of glycolysis and plays an indispensable regulatory role in BC glycolysis and malignant progression [31]. A highly expressed level of PFKFB3 was observed, and this high level of expression was involved in the poor overall survival of patients with BC [32]. Increased expression of PFKFB3 expedited glucose uptake and glycolysis in cancer cells due to the progesterone and estradiol receptors bind to response elements in the promoter region of *PFKFB3* [33,34]. The inhibition of PFKFB3 impeded the growth of BC cells by suppressing the glycolytic flux [35] and suppressed the protein level of vascular endothelial growth factor α (VEGFα) [32]. Importantly, phosphorylation of PFKFB3 at Ser478 enhanced the stability of PFKFB3 via the ubiquitin-proteasome pathway, which finally heightened the glycolysis and BC cell growth [36]. In conclusion, PFK continues to hold great promise as an important therapeutic target, either as a single agent or in combination with current interventions for BC.

PK catalyzes phosphoenolpyruvate (PEP) to pyruvate with concomitant production of ATP. It contains four isoforms, PKM1, PKM2, PKL, and PKR. Among which, PKM2 is the major isoform expressed in tumor cells [37]. High expression of PKM2 was confirmed in BC tissues [38] and cells (Fig. 1) [39–41], including MCF-7 and MDA-MB-231 lines. Studies showed that the role of PKM2 in promoting tumor is closely related to the increased phosphorylation of signaling pathway. Firstly, PKM2 directly phosphorylated c-MYC at Ser62 to increase the levels of survivin [42] and EGFR [43] and finally activated their downstream signaling in TNBC cells. Secondly, PKM2 overexpression activated the 1 AKT substrate 1 (AKT1S1), an inhibitor of the mammalian target of rapamycin complex 1 (mTORC1). The activation of the mTORC1 signaling contributes to the acceleration of oncogenic growth and autophagy inhibition in cancer cells [44]. In addition, a positive correlation between PKM2 and VEGF-C expression was identified. The levels of VEGF-C mRNA and protein were downregulated, after PKM2 mRNA expression was knocked down, and the cell proliferation was inhibited [41]. Not only that, but knockdown of PKM2 in TNBC cells significantly suppressed the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) through reducing the phosphorylation of p65 at serine 536 and also decreased the expression of NF-κB target genes [40]. A novel downstream target of PKM2 was also identified in BC cells lines, the mammalian sterile 20-like kinase 1, whose nuclear translocation can be promoted via enhancing caspase-3-dependent cleavage by knockdown of PKM2 and finally contributed to apoptosis [45]. Moreover, PKM2 promotes stemness of BC cell through the Wnt/β-catenin pathway [38]. In addition to the role of PKM2 in regulating growth of BC cells, it can regulate glucose metabolism under the mediation of miRNAlet-7a through a feedback loop manner. The let-7a-5p functionally targeted signal transducer and activator of transcription 3 (Stat3), and Stat3 promoted upregulation of heterogeneous nuclear ribonucleoprotein (hnRNP)-A1 expression. The hnRNP-A1 promoted PKM2 expression; however, it also blocked the biogenesis of let-7a-5p to counteract its ability to downregulate the Stat3/hnRNP-A1/PKM2 signaling pathway, which regulates the aerobic glycolysis effect of BC cells [39]. The results showed that the potential role of PKM2 as a target for BC in therapeutic intervention, but high PKM2 expression indicated worse overall survival and progression-free survival in BC patients, which predicted a poorer prognosis of it [38,41,46].

Lactate dehydrogenase (LDH) solves the problem that pyruvate accumulation in the cell [47] through catalyzing the step of aerobic glycolysis converting pyruvate to lactate in the cytoplasm. LDHA and LDHB are two kinds of isoforms of LDH. The expression of LDHA in BC tissues was significantly higher than that in adjacent tissues [48,49], and a 10-fold lactate was generated in 4T1 murine BC cell lines [50]. However, the LDHB was specifically expressed only in normal and endocrine-resistant BC cells [51]. The high expression of LDHA and serum LDH status were closely related to brain metastasis free survival and may be a predictor for TNBC brain metastasis [49]. Patients, whose expression of LDHA and AMPK both showed positive in BC tissues, suggested a shorter overall survival and disease-free survival [52]. In the glucose metabolism, high glucose content induced the expression of microrchidia family CW-type zinc finger 2 (MORC2) by activating c-MYC, which subsequently promoted MORC2 to form a complex with c-MYC to increase LDHA transcription [53], leading to the BC cell migration. Study showed that both LDHA or LDHB knockdown inhibited the cell motility in MCF7 and MDA-MB-231 BC cell lines by reducing the phosphorylation level of ERK1/2 [51], and exogenous lactate supplementation also increased the phosphorylation level of ERK1/2, reduced E-cadherin expression [48], and finally enhanced the cell motility. More interestingly is that stable LDHA silencing alone in human MDA-MB-231 BC cell line with high concentrations of LDHB using lentivirus V-165 cannot change the lactic acid production, glycolytic activity, and the survival [54], indicating that multiple isoforms such as LDHA/B are likely compensatory elements to maintain the production of lactic acid through glycolysis in tumor cells. In addition, LDHA also regulated the tumor microenvironment by modulating immune response via HIF-signaling in 4T1 murine BC cells [55]. The glycolysis can be inhibited by suppressing expression of LDHA using trastuzumab, resulting in tumor growth inhibition [56]. More importantly, combining trastuzumab with glycolysis inhibition resulted in more efficient inhibition of glycolysis, and finally both synergistically inhibited trastuzumab-sensitive and trastuzumab-resistant BC *in vitro* and *in vivo*. The result showed that rewired glucose metabolism can also mediate resistance to trastuzumab.

Amino acid metabolism

Glucose and glutamine are the most important energetic substrate for the cells, in which glutamine is an essential substrate for energy source in highly proliferative cancer cells. High glutamine activity was identified in HER2-type BC [57], suggesting that glutamine dependence increased in proliferative subtypes of BC [57,58]. Study has reported that glutamine metabolism genes were significantly upregulated in both epithelial and stromal cells from BC tissues, which implicates the role of glutamine metabolism in BC growth and metastasis [59]. As a member of amino acid transporters of approximately 430 membrane-bound solute carrier (SLC) transporters [60], alanine-serine-cysteine-preferring transporter 2 (ASCT2; SLC1A5) undertakes the function that mediates the uptake of neutral amino acids including glutamine [61]. Inhibition of ASCT2-mediated transport effectively decreased the glutamine uptake in human BC cell lines by suppressing the mTORC1 signaling pathway, which consequently attenuated the BC cell growth and cell cycle progression [62]. More importantly, the high expression of ASCT2 and glutamine metabolism-related genes, the glutamine–ammonia ligase (GLUL) and glutaminase (GLS) (Fig. 1), was significantly associated with certain oncogenic transcription factors, including c-MYC, RAS, and ATF4 [62,63] in BC cell lines. Studies have shown that AFT4, as a novel regulator, which coordinates with N-MYC to directly activate ASCT2 expression in cancer cell [64,65], further enhancing the role of c-MYC in transcriptionally regulation of glutamine metabolism. It is thus an effective therapeutic strategy that the inhibition of ASCT2-mediated glutamine uptake against human BC [66]. Notably, the cystine/glutamate antiporter (xCT), for example the SLC7A11, which mediates the exchange of the imported cystine with the exported glutamate, plays a vital role in the synthesis of glutathione in order to neutralize reaction oxygen species (ROS) [67]. The reduction of SLC7A11 protein expression may promote the decrease in cystine transport capacity, resulting in decreased reduced glutathione (GSH) synthesis, which finally significantly increased the intracellular ROS in BC cells [67]; however, this process reversed as a consequent of xCT upregulation [68]. The reduction of SLC7A11 protein expression has been confirmed based on ionizing radiation therapy and contributes to the death of BC cells [67]. Glutamine deprivation caused the varying degrees of decrease (61%−89%) in cell growth in MCF-7, MDA-MB-231, and BT-20 BC tumorigenic cell lines [69]. And, glutamine deprivation led to oxidative stress, where superoxide levels were significantly increased in the MCF-7 and MDA-MB-231 cell lines. Miyamoto et al. [70] demonstrated that a reduction of the GSH caused by glutamine deprivation contributed to the accumulation of ROS, and the mechanism was believed to be related to the xCT expression. As the key enzymes in regulating tumor progression, the GLS included two isoenzymes for the regulation of glutamine metabolism, the GLS and GLS2, which catalyzes glutamine to glutamate. In BC, high-grade highly proliferative tumors, for instance the TNBC, showed the higher levels of glutamate and GLS together with low level of glutamine than low-grade tumors and normal breast epithelium [71,72]. The highest stromal expression levels of GLS were observed, revealing the high glutamine activity in HER2- type BC [57]. High expression level of GLS was significantly related to the high expression of MYC [62]. In terms of BC patient outcome, GLS mRNA expression predicts poor patient survival, and high GLS2 mRNA expression predicts better patient survival [73].

Glycine and serine are well-known and classic metabolites of glycolysis that are produced from the intermediate 3-phosphoglycerate. Various serine-/glycine-metabolism–associated proteins expression, including phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1), and 1–3-phosphoserine phosphatase (PSPH) are increased in TNBC (Fig. 1) [74]. Study has confirmed that serine consumption supported the cancer proliferation in TNBC cells [75]. The protein level of PHGDH was increased in 70% of ER-negative BC, and high expression of it significantly increased the serine synthesis flux in BC cells [76]. More interestingly, PHGDH inhibition cannot alter intracellular serine levels but reduce the levels of α-ketoglutarate. Conversely, in high expression of PHGDH BC cells, the serine synthesis pathway promoted nearly 50% of glutamate-derived α-ketoglutarate into the TCA cycle [76], which is important in PHGDH-amplified cell proliferation for BC cells. This result is the cause that why suppression of PHGDH on BC cell proliferation cannot be rescued by supplementation of extracellular serine. Inhibition of PHGDH using RNA interference, CRISPR/Cas9 knockout, or small-molecule PHGDH inhibitors largely abolished the BC cell proliferation and tumorigenesis by attenuating serine synthesis progress [77]. As for the PSAT1, its expression significantly increased along with the clinical grade of TNBC [78], and inhibiting the expression of PSAT1 in TNBC cell lines effectively suppressed the motility and migration. And, low PSAT1 prevented de novo serine biosynthesis and sensitizes luminal BC cells to serine and glycine starvation *in vitro* and *in vivo* [79]. In high isocitrate dehydrogenase (IDH) 2 BC cell lines, PHGDH and PSAT1 catalyzed 20%−30% of glutamate into α-ketoglutarate, which resulted in increased TCA cycle activity and mitochondrial respiration [80]. However, PHGDH or PSAT1 knockout both attenuated the entry of glutamine-derived carbons into α-ketoglutarate. In conclusion, the serine pathway appears to be more important than the glycine pathway for BC cell proliferation and migration, the TNBC in particular, which indirectly suggests that the serine pathway can be a potential target for BC therapy.

Arginine is closely related to the BC progression. BC patients showed a decrease in arginine content compared with healthy people in the serum [81–83]. And, different molecular BC types showed a unique arginine concentration, in which the arginine content in plasma of TNBC was the lowest compared with other molecular subtypes [84], suggesting that it could be a potential discriminant and predictor for BC progression. Arginine is a substrate for NO synthesis, and the ratio of arginine: NO can also be used as an early salivary diagnosis of BC [85]. Supplementation of L-arginine inhibited the BC growth and prolonged the survival times of 4 T1 tumor bearing mice by enhancing innate and adaptive immune responses mediated through suppression of myeloid-derived suppressor cells [86].

The electron transport chain/oxidative phosphorylation

Under hypoxia and nutrient-deprived conditions, the Warburg effect showed that cancer cells experienced a shift from OXPHOS to glycolysis. the enhanced and decreased OXPHOS activity is confirmed in BC cells. Cellular metabolism reprogramming is closely related to reactive oxygen species (ROS) production in cancer cells. Electrons derived from different metabolic processes are channeled into the mitochondrial electron transport chain (ETC) to fuel the OXPHOS process [87]. In this process, the electrons can escape from ETC and be captured by O2, resulting in excessive ROS and ROS-induced DNA damage [88]. Low OXPHOS activity may be attributed to mitochondrial DNA (mtDNA) mutation or less mtDNA content coding for the subunits of OXPHOS protein complexes I to V [89]. In mammals, complexes I and III have been identified as the most relevant sites of ROS production within the ETC [87]. The downregulated activity of complex I in BC cell lines showed a decrease in ROS level, which resulted in increased cell metastatic properties [90]. In addition, mitochondrial OXPHOS-related proteins, the cytochrome *c* oxidase subunit 7a-related polypeptide (COX7RP), were found to be overexpressed in BC and displayed a correlation with poor survival of patients [91]. It regulated the steady-state levels of TCA cycle intermediates, including fumaric acid and succinic acid in hypoxia, which could be induced by upregulated production of succinic acid and malic acid from glutamine metabolism [92]. Hence, most tumors, including TNBC, tend to utilize glycolysis to meet bioenergetic demands and rigidly control the level of ROS by downregulating OXPHOS. Consistently, metabolomics analysis showed that hypoxia upregulated glucose uptake and glycolysis, thus inhibiting the conversion rate of glucose to the TCA cycle for OXPHOS in MDA-MB-231 BC cell lines [93]. However, ROS and OXPHOS are still controversial in

BC, whose regulatory mechanisms still need to be further explored.

In fact, a hybrid metabolic phenotype is characterized by high activity of glycolysis/OXPHOS, which is regulated by high levels of HIF-1/AMPK in TNBC cells [94]. One current proposal is that the metabolic phenotype conferred a strong metabolic reprogramming in TNBC cells to complete the switch between glycolysis and OXPHOS as a compensatory strategy in response to metabolic targeting drugs or an altered tumor environment [95]. Cells with this metabolic phenotype displayed maximum proliferation and clonogenicity relative to cells with either phenotype. Thus, dual targeting of glycolysis and mitochondrial bioenergetics or antioxidant pathways would be more helpful in reducing cellular bioenergetics and promoting BC cell death.

Tricarboxylic acid cycle

Tricarboxylic acid cycle (TCA) cycle possesses a variety of progresses occurring in the mitochondria that starts with the oxidation of acetyl-CoA and generates the carbon dioxide and ATP to maintain the cell survival. However, the hyperactivation of TCA cycle could produce excess ROS, which was believed to be toxic to cells. The metabolic reprogramming of energy pathways in cancer cells was partly because of the defect in the mitochondria TCA cycle and/or mitochondria functions resulting from the mutations of TCA cycle enzymes [96].

Pyruvate dehydrogenase complex (PDH) catalyzes the oxidative decarboxylation of pyruvate into acetyl-CoA and therefore controls the flow of metabolites from glycolysis to the TCA cycle and the subsequent generation of ATP by mitochondrial metabolism (Fig. 1). In oxidized ATM kinase activation (ATM) TNBC stem cells, the upregulated expression of GLUT1, PKM2, and PDHA enhanced the uptake of glucose, increased the pyruvate production, which facilitated glycolytic flux to mitochondrial pyruvate and citrate, thus resulting in accumulation of cytoplasmic acetyl-CoA [97]. Study reported that the deficient PDHX was observed in human breast tumor samples, and it was significantly related to the reduced patient survival [98]. The decreased PDH-E1β subunit of the PDH complex inhibited the activity of PDH due to the prolonged hypoxia. On the one hand, the reduced expression of PDH-E1β was sustained to maintain a highly activity of glycolysis metabolism despite of the oxygen restoration [99]. On the other hand, inhibition of PDH decreased the mitochondrial oxidase and contributed to the BC cell proliferation [98].

The biallelic inactivation of fumarate hydratase (FH) was observed in BC patients [100]. Insufficient FH and succinate dehydrogenase (SDH) in cancer cell impaired glutathione production and increased ROS level [101]. In hypoxia-induced human breast tumorigenic cells, on the one hand, the expression of HIF-1α transcriptionally downregulated the expression of mitochondrial phosphoenolpyruvate carboxykinase (PCK2), which lead to the attenuation of TCA cycle and the accumulation of fumarate [102]. On the other hand, excessive fumarate resulted in glutathione succination, a decrease in $NADPH/NADP^+$ levels, and an increase in ROS levels [102]. Both factors fundamentally contributed to the growth of BC cells. However, FH may not be a major predisposing gene for familial BC [103].

High expression of SDHA in HER-2 BC and low or negative expression in the luminal A subtype was identified, respectively [104]. Stromal SDHB expression rate was highest in HER-2 subtype and lowest in TNBC. Only 3% BC showed the loss expression of SDHA or SDHB [104]. In MDA-MB-231, MCF-7, and 4T1 BC cells, the anti-inflammatory tumor-associated macrophages secreted the cytokine TGF-β, inhibited the protein level of the transcription factor, and consequently down-regulated that of the SDH, which finally promoted the tumorigenesis [105]. The reduced SDH was confirmed to promote the epithelial to mesenchymal transition [106].

The dihydrolipoamide S-succinyltransferase (DLST) is the E2 transferase of α-ketoglutarate dehydrogenase complex (α-KGDH) that catalyzes the irreversible conversion of α-ketoglutarate to succinyl-CoA [107]. High expression of DLST predicted a poor overall and recurrence-free survival in TNBC patients [108]. Suppression of the TCA cycle through DLST depletion decreased the growth and induced death in subsets of human TNBC cell lines [108]. Inhibition of α-KGDH using its inhibitor, (*S*)−2-[(2,6-dichlorobenzoyl) amino] succinic acid, significantly counteracted the BC-associated lung metastasis [109].

Pentose phosphate pathway (PPP)

The PPP is a major pathway of glucose catabolism except for glycolysis, where NADPH is produced as a reducing agent for biosynthesis. The expression of PPP-related enzymes increased in many human cancer cells [110,111]. Among which, glucose-6-phosphate dehydrogenase (G6PD), 6-phosphogluconolactonase (6PGL), 6-phosphogluconate dehydrogenase (6PGD), and nuclear factor erythroid 2-related factor 2 (NRF2) showed a different expression in human BC tissues according to the molecular BC types. G6PD and 6PGL expression increased in human BC tissue compared with the normal adjacent tissue, and G6PD showed the highest expression in HER-2 type [112]. The expression of 6PGD was higher in HER-2 and basal-like subtypes than in the luminal type [112]. However, the expression of NRF2 decreased in all tumor compared with normal tissues. Study showed that inhibition of G6PD attenuated the tumor cell proliferation, cell survival, and increased oxidative stress as the results of augmenting the glycolytic flux, reducing lipid synthesis, and increasing glutamine uptake in MCF7 cells [113]. And, overexpression of NRF2 upregulated expression of G6PD in MCF-7 and MDA-MB-231 cells through the elevated expression of Notch 1, which promoted the BC cell migration [114]. However, depletion of NRF2 significantly increased the basal levels of ROS in metastatic 66cl4 cell lines from the murine 4T1 mammary tumor model and reduced the formation of BC primary tumor and lung metastasis [115]. On the one hand, the antioxidants provided protection against oxidative DNA damage and E2-induced mammary carcinogenesis in part through NRF2 induction in BC [116–118]. On the other hand, the activity of NRF2 is the key to chemotherapy resistance in MCF7 BC cells [119]. The chemotherapeutic agents, such as luteolin, enhanced the chemosensitivity through downregulating the NRF2 expression [120], suggesting that a low NRF2 signature may be key to cellular sensitivity to both chemical carcinogenic stimuli and the cytotoxicity of commonly used chemotherapeutic drugs in established BC [121].

In addition, the transcriptional and translational levels and enzyme activity of 6PGD are aberrantly activated in BC tissues and cell lines. Moreover, inhibition of 6PGD significantly activated AMPK and its downstream substrate acetyl-CoA carboxylase 1 (ACC1), leading to the decrease in activity of ACC1 and lipid biosynthesis, which suppressed the cancer cell growth and survival [122]. Though the inhibition of 6PGD decreased the glucose consumption and increased the glutamine consumption, the ROS level was not changed in BC cell model [123]. These results suggested that G6PD and 6PGD could be the potential therapeutic strategies in BC.

Fatty acids metabolism

Aside from the glucose and amino acids, the fatty acids are another efficient way to gain energy in cancer progression. Fatty acids metabolism plays a vital role in glucose metabolism and is a metabolic phenotype in BC tumors. Fatty acid synthesis and oxidation are generally viewed as counterparts in metabolic reprogramming of tumor cells.

The oncogenic signaling enhanced the fatty acid synthesis in tumor cells. Unlike the normal cells, the tumor cells increased the *de novo* fatty acid synthesis to satisfy their needs for energy and intermediates under conditions of metabolic stress [124]. Fatty acid synthase (FASN) uses acetyl-CoA to generate fatty acids, and its expression was significantly higher in human BC cells compared with normal cells (Fig. 1) [125–127]. In human BC MDA-MB-231 and MCF-7 cells, suppression of FASN using its natural inhibitor induced cancer cell apoptosis [126]. The loss of FASN inhibited the glycolysis activity through

downregulating PI3K/AKT signaling pathway [128], suggesting that FASN is a feasible biomarker and an ideal target for chemosensitization [129] in human BC. The first-in-human dose-escalation study with the oral FASN inhibitor TVB-2640 demonstrated the potential for FASN as a therapeutic target [130]. Genetic or pharmacological inhibition of FASN impeded the HER2+ breast tumor growth in the brain [131], demonstrating that fatty acid synthesis is required for BC brain metastasis. The result suggested that BC growing at this site must rely on the *de novo* fatty acid synthesis to support the requirement for lipids. However, during the acquisition of resistance to HER2 inhibition, metabolic rewiring of BC cells favors reliance on exogenous fatty acids uptake over *de novo* fatty acid synthesis. Among the above mechanisms, the regulation of CD36 is indispensable. As a fatty acid transporter, CD36 was upregulated in BC cells with acquired resistance to the HER2 inhibitor lapatinib, and exogenous FA uptake and metabolic plasticity increased [132]. Inhibition CD36 suppressed the growth of lapatinib-resistant cells, attenuated tumorigenesis, [132] and also impaired metastasis in BC-derived tumors [133], suggesting that CD36 serve as a potential therapeutic target for BC metastases. Leucine deprivation significantly inhibited the expression of FASN *in vitro* and *in vivo*, and this was closely related to the sterol regulatory element-binding protein 1C (SREBP1C) [134]. The SREBP is an independent prognostic marker in BC, whose expression is highly positively correlated with tumor differentiation, tumor-node-metastasis stage, and lymph node metastasis [135]. The O-GlcNAcylation upregulated the expression of SREPB1 in an AMPK-independent manner, which finally increased the FASN expression in MDA-MB-231 and MCF-7 BC cell lines [136].

The first committed step of the fatty acid oxidation begins with long-chain acetyl-CoAs, which is transported to mitochondria by carnitine palmitoyltransferase 1 (CPT1) (Fig. 1). In BC tumor and cell lines, the expression of CPT1A increased in ER-positive compared with ER-negative [137] via upregulating expression of ERRα and peroxisome proliferator activated receptor gamma coactivator 1 (PGC-1) β by activation of AMPK [138], finally countering the effect of AKT inhibition. CPT1A overexpression significantly attenuated the proliferation in MDA-MB231 BC cells when compared with basal expression control. MYC overexpression promoted the upregulation of CPT expression, suggesting the enhanced fatty acid oxidation and increased ATP content in human BC cell lines [139]. The high level of ATP activated the Src oncoprotein by autophosphorylation at Y419. However, the progress was reversed by knocking down of CPT [140]. The transforming growth factor β1 (TGF-β1) also induced an increase in ATP levels with decreased FASN and increased CPT in epithelial-mesenchymal transition MCF-7 cells via the p-AMPK pathway [141]. Moreover, inhibition of CPT2 using RNAi knockdown or a small molecule inhibitor in MYC-high expression TNBC cell lines suppressed the proliferation and growth of cells [139].

Crosstalk of major signaling pathways in BC

AMPK pathway

AMPK is a crucial regulator in cancer metabolism. It is involved in cellular energy metabolism and protects cells from environmental stress, such as cells are hypoxic or nutrient deficient. The activation of AMPK can effectively reduce apoptosis and inhibit the tumor growth [142, 143]. AMPK can conserve ATPs mechanisms by activating the catabolic pathways that produce ATP or inhibiting ATP-consuming processes, such as the lipid biosynthesis and mTORC1-dependent protein biosynthesis [144,145].

AMPK has been suggested to increase GLUT1 expression through various mechanisms [146]. AMPK increased glucose uptake by upregulating the expression of GLUT1 and stimulated aerobic glycolysis, thus increasing lactate production [147]. The downregulated NRF2 expression in MCF-7 and MDA-MB-231 BC cells inhibited the expression of AMPK, which finally attenuated the glycolysis by downregulating the glycolytic enzymes, including HK2, PFKFB3, PKM2, and LDHA [148]. Metformin inhibited BC cell growth by reducing Wnt/β-catenin signaling in an AMPK-activated manner in MCF-7 and MDA-MB-231 cell lines [142]. The combination of metformin with navitoclax or venetoclax efficiently also inhibited tumor growth, conferred survival benefits, and induced tumor infiltration by immune cells through activating AMPK in BC cell lines [143]. Palma et al. demonstrated that AMPK defensed the detrimental effects of mitochondrial complex I inhibition through a manner dependent on pyruvate availability in a human BC cell line [149]. AMPK alleviated the energetic stress associated with BC progression by activating glycolysis, which contributed metformin switch carbohydrate metabolism to ketogenesis, and it exerted the anticancer activity [149]. Moreover, the increased expression and activity of AMPK induced cell death in MDA-MB-231 cells decreased the expression of G6PD and increased the expression of p-ACC and CPT1A (Fig. 2). Thus, the PPP was inhibited and fatty acid oxidation was enhanced, which reprogrammed glycolipid metabolism and destroyed the redox balance [150].

As a tumor suppressor in a broad spectrum of human cancers, liver kinase B1 (LKB1) can dependent phosphorylated AMPK in BC cells (Fig. 2), attenuated the endoplasmic reticulum (ER) stress, and participated in the progress that inhibited BC cell growth with the treatment of adiponectin [151]. And, in turn, LKB1 also promoted the inhibition of cancer cell apoptosis and the activation of autophagy through suppressing the AMPK pathway [152]. In ER-positive BC cells, the chronic tamoxifen treatment activated the expression of AMPK. The AMPK activation promoted activation of AKT, while inhibition of AKT feedback suppressed the expression AMPK. AMPK additionally increased CPT1, which finally lead to the increase in fatty acid oxidation [138]. The molecular mechanism of sorafenib's antitumoral activity in BC is impairment of glucose metabolism by sustained activation of AMPK [147]. Collectively, these results provide further evidence that AMPK is most likely to regulate BC progression and can be utilized as a promising target therapy in the near future.

PI3K/AKT/mTOR signaling pathway

The PI3K/AKT/mTOR complex is a signaling pathway with a major role in essential cellular activities, including the cell metabolism, cell growth, cell proliferation, apoptosis, and angiogenesis [153]. The activation of PI3K/AKT/mTOR signaling induced the energy metabolism reprogramming in cancer cell (Fig. 2). The energy metabolism pathway in BC progression is related to the PI3K/AKT/mTOR signaling pathway, glycolysis in particular [6].

The glycolysis and expression of lipid synthesis genes were upregulated with the activation of AKT/mTORC2 pathway in BC cell lines [154]. The key enzymes of energy metabolism pathways, including G6PD, PFKB, HK2, LDHA, and GLUT1, whose expression increased with the upregulated level of p-AKT. PI3K-dependent AKT activation has a direct relationship with PFK2 phosphorylation [155,156]. The activation of AKT in a PI3K-dependent manner increased the glycolytic activity by phosphorylating PFK2 and producing fructose-2, 6-bisphosphate, which in turn activated the PFK1. The switch that glucose metabolism toward glycolytic flux in BC cells was regulated by PI3K signaling-mediated activity of HK and GLUT1 [157]. The translocation of GLUT1 from the intracellular membrane pool to the plasma membrane was also depended on the PI3K signaling [158]. Jia et al. [159] showed that the inactivation of AKT/mTOR pathway using a bioactive inhibitor in MCF-7 and MDA-MB-231 BC cell lines blocked the cell glycolysis through suppressing glucose uptake, reducing the production of lactic acid, and decreasing the levels of glycolysis-related proteins, including the PKM2, GLUT1, and LDHA. This regulatory mechanism induced by inactivated AKT/mTOR pathway is also largely related to the activation of AMPK (Fig. 2) [160]. Conversely, the anti-tumor efficacy of palbociclib in retinoblastoma protein (Rb)-positive TNBC cells, the PI3K/mTOR signaling significantly inhibited the Rb/E2F/myc axis and reduced the glucose metabolism by

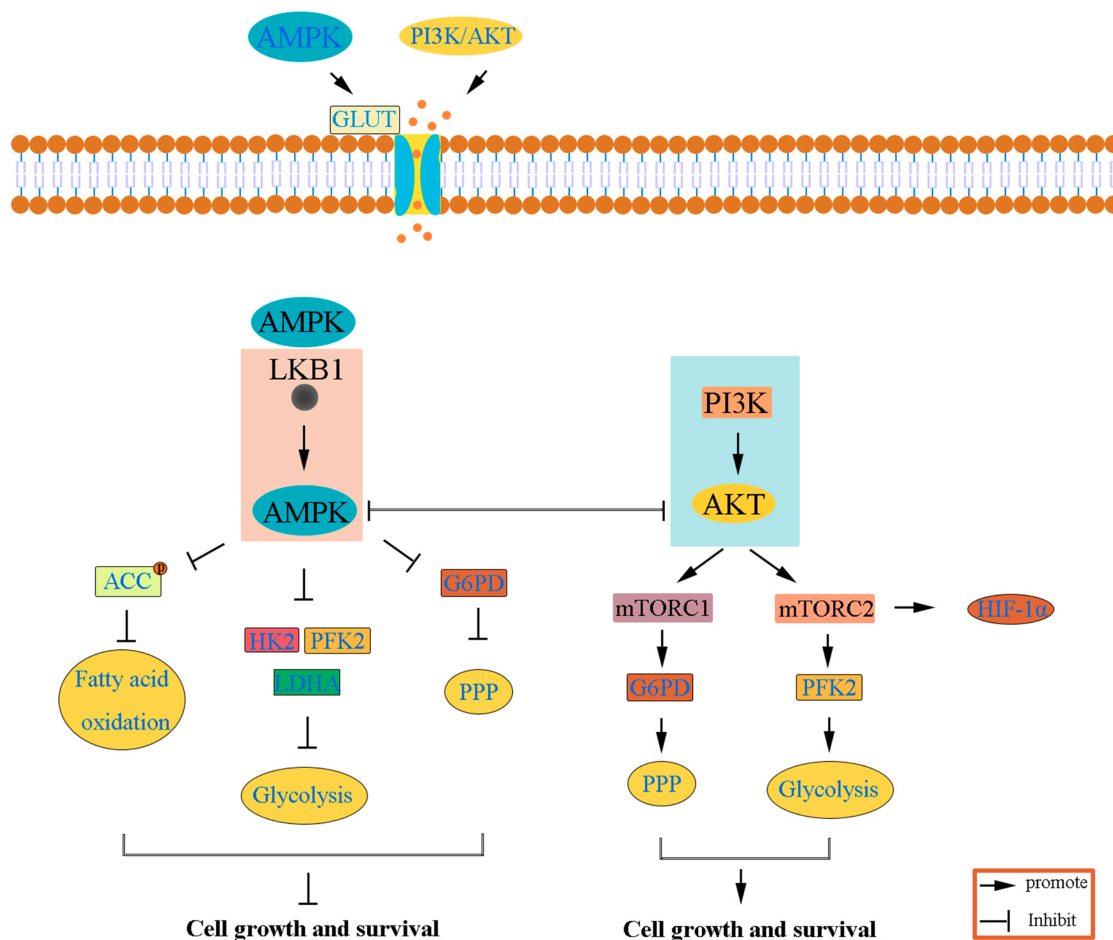

Fig. 2. The crosstalk between AMPK signaling and PI3K/AKT signaling pathway associated with the energy metabolism in BC. The activation of AMPK signaling promotes the AKT activity, and the activation of AKT inhibits AMPK signaling. Both signaling pathways can be involved in BC progression by regulating energy metabolism. PI3K, phosphoinositide 3- kinase; AKT, protein kinase B; G6PD, glucose-6-phosphate dehydrogenase; HK, hexokinase; PFK, phosphofructokinase; LDHA, lactate dehydrogenase A; PPP, pentose phosphate pathway; LKB1, liver kinase B1; ACC, acetyl- CoA carboxylase.

downregulating the expression of GLUT1 [161]. Moreover, the lipid metabolism gene, fat mass, and the obesity-associated gene (FTO) were significantly increased in MCF-7 and MDA-MB-231 cells, lead to the upregulation of HK and PK, and finally enhanced the glycolysis. The potential mechanism behind these effects may be attributed to the activation of PI3K/AKT signaling pathway by increasing the expression of FTO [162]. Wang also demonstrated that beta-naphthoflavone, an agonist of aryl hydrocarbon receptor, contributed to the inactivation of cyclin D1/D3 and CDK4 by suppressing PI3K/AKT signaling and inducing G0/G1 cell cycle arrest and senescence, which could be a potential anticancer drug for ER-positive MCF-7 BC cells [163]. A deuterated analog was equally effective as a standard TNBC therapy (paclitaxel) in downregulating cyclin D1 in TNBC cell lines [164]. In addition, the inhibition of HK2 in tamoxifen-resistant human BC cell lines decreased the cell growth by suppressing Akt/mTOR/HIF-1α axis activity [165]. And study further showed that the inhibition of mTOR activity or increase in AMPK activity reduced the lactate accumulation and cell survival, the results provided evidence that development of tamoxifen resistance may be driven by HIF-1α hyperactivation by modulating Akt/mTOR and/or AMPK signaling pathways in BC cells [165]. In addition, the reactivation of mTOR signaling in lapatinib-resistant BC cells restored the expression of ERRα, and the re-expression of ERRα triggered metabolic adaptations favoring mitochondrial energy metabolism through increased glutamine metabolism [166]. In conclusion, the PI3K/AKT/mTOR signaling pathway is a vital anticancer target for BC, and the downregulation of the pathway may inhibit the BC proliferation and migration.

In fact, BC progression is regulated by multiple signaling pathways and mechanisms. The various key signaling molecules of Wnt signaling are upregulated in BC, and they are involved mainly in the processes of BC proliferation and metastasis [167]. Among which, Wnt/β-catenin, Wnt-planar cell polarity, (PCP) and Wnt-Ca2+ signaling are three well-established pathways participated in regulating immune microenvironment regulation, stemness maintenance, therapeutic resistance, and phenotype shaping in BC [167]. For instance, Wnt3A upregulated PFKP expression in a β-catenin-independent manner, resulting in increased PFK enzyme activity in various cancers, including BC [27]. And the regulatory mechanism of Wnt signaling pathway is inseparable from the crosstalk of AMPK signaling pathways in BC progression [142]. In addition, signal transducer and activator of transcription (STAT) signaling is an early tumor diagnostic marker and is known to promote BC malignancy. The STAT3 gene, a key member of the STAT family, can form a feedback loop to participate in tumor metabolic reprogramming by regulating PKM2 activity and glucose metabolism in BC cells [39]. Moreover, overexpressed and constitutively activated STAT signaling in BC can cooperate with multiple signaling pathways and participate in the regulation of BC proliferation, metastasis, and chemoresistance [168]. In conclusion, BC development is an extremely complex process that involves network crosstalk of multiple signaling pathways. These signaling pathways can serve as powerful clinical targets for BC prevention and therapy.

Potential therapeutic targets for the metabolic pathways associated with transcription factors

In addition to their oncogenic activities, c-MYC, HIF-1α, and p53 act as the key transcriptional regulators of metabolic enzymes and facilitate to be supplied the required energy for cancer cells. Therefore, several targets in the metabolic pathway have been suggested as druggable potential for cancer treatment and drug discovery.

c-MYC

c-MYC was a transcript factor that related to the energy metabolism in cellular processes. Many key enzymes, such as GLUT1, HK2, PFK-1, LDHA, ASCT2, and SLC7A25, are closely associated with c-MYC expression. Under the regulation of c-MYC, the enzymes participated in the BC cell proliferation, differentiation, growth, migration, and other processes [169]. In MYC overexpressing TNBC cell, the metabolic dysregulation is essential for the cell growth. The metabolites associated with fatty acid oxidation significantly increased by MYC overexpression, and the inhibition of fatty acid oxidation dramatically decreased energy metabolism and inhibited tumor growth in a MYC-driven transgenic TNBC model and a MYC-overexpressing TNBC patient-derived xenograft [139]. More importantly, MYC driven tumors in a glutamine dependent manner, study disclosed that the high protein expression of the glutamine metabolism was all associated with high MYC protein in luminal B tumors [170]. Increased MYC heightened cancer cell glutamine metabolic activity by upregulating the expression of ASCT2 and GLS1 [63]. The activation of ASCT2 and GLS1 induced by MYC increased the glutamine uptake and catabolism in cancer cells [171]. The inhibition of MYC significantly decreased the SLC1A5 and GLS expression in BC cells, which finally impeded the BC cell proliferation [172]. As an important anticancer therapy in the treatment of BC, the c-MYC is the potential target for many drugs. The diclofenac [173], decitabine, [174] and primaquine [175] could effectively inhibit the expression of c-MYC in BC cell lines to induce the cell apoptosis, by regulating the key enzymes in the energy pathway. For example, the diclofenac impaired the cell proliferation and glucose metabolism in TNBC through targeting the c-MYC and reducing GLUT1 expression and HK activity [173]. In addition, MYC conferred chemotherapy resistance by regulating mitochondrial OXPHOS in BC stem cells [176]. However, while MYC contributed to the tamoxifen resistance, it resensitized cisplatin in ER positive BC [177], and knockdown of MYC expression in BC cells overcame tamoxifen resistance by the regulation of aspirin [178]. In conclusion, MYC can be feasibly targeted to overcome metabolic plasticity in BC.

HIF-1α

HIF-1α signaling is a key regulator in cancer cell while facing hypoxia. The cancer cell will switch the metabolism to glycolytic pathways by HIF-1α [179]. The increased HIF-1α upregulated the expression of GLUT1 and HK2 [180], and simultaneously inhibited the mitochondrial OXPHOS and TCA cycle via directly transactivating pyruvate dehydrogenase kinase-1 (PDK1), a key enzyme that decreased the activity of PDH by phosphorylation [181]. At the expression level, HIF1α was positively correlated with HK2, LDHA, and PKM2 in BC cell lines [148]. In NRF2-silencing BC cell lines, the accumulation of HIF-1α was hindered and consequently inhibited the hypoxia-inducible expression level of glycolysis-associated genes, including PDK1 and LDHA [182]. The results also demonstrated that after the hypoxic incubation in control cells, the differential metabolites were related to PPP and glycolysis pathway [182], suggesting the role of HIF-1α in regulating cellular metabolism in cancer progress. Therefore, the activity of HIF-1α is a primary target in the potential therapeutic strategies for BC. Some natural compounds, such as sanguinarine [183] and cardamomin [184], significantly inhibited the BC cell growth by downregulating HIF-1α and its downstream signaling pathways. In addition, metformin induced a bidirectional signaling suppression between BC cells and cancer-associated fibroblasts by increasing the phosphorylation of AMPK, which reduced the activity of HIF-1α signaling and subsequently tumor-stromal cross talk [185]. More importantly, enriched HIF expression and transcriptional activity were induced by paclitaxel or gemcitabine in BC cells [186]. It is worth noting that coadministration of HIF inhibitors overcame the resistance of BC stem cells to paclitaxel or gemcitabine *in vitro* and *in vivo*, leading to tumor eradication and improved patient survival. Collectively, inhibition of HIF-1α impeded cancer stem cells expansion and restored the chemotherapy sensitivity in TNBC [176].

p53

The tumor suppressor gene, p53, is involved in almost all pathways related to energy metabolism, including glucose transport, gluconeogenesis, TCA cycle, mitochondrial respiration, and PPP [187]. In BC cell lines, the inhibition of p53 resulted in the energy metabolism reprogramming and upregulated the glucose metabolism-related genes, including PKM2, LDHA, and G6PD [188]. In BC expressing wild-type p53 effectively suppressed the LDHA expression, which downregulated the aerobic glycolysis in human BC cell lines [189]. The result suggested a novel insight that p53 inhibited the development and progression of BC by downregulation of aerobic glycolysis. The bortezomib induced the cell apoptosis in 4T1 BC cell in a p53-independent manner [190]. Similarly, treatment using 5-fluorouracil in MDA-MB-231 BC cell [191] and sodium cantharidate in BC cells increased the expression of p53 and induced apoptosis by regulating energy metabolism [192]. The p53 is important for epirubicin sensitivity; the loss of p53 function was observed in MCF −7 BC cells [193]. Similarly, Qi disclosed that adenovirus-mediated p53 transfection in human BC cell lines enhanced adriamycin cytotoxicity and reversed adriamycin resistance, and that p53 combined with adriamycin dramatically inhibited the growth of subcutaneous xenograft of MCF-7/ADR [194].

Conclusion

Energy metabolism reprogramming is the most characteristic feature of all cancer cells, including BC, which meets the enormous energy demands of tumor cell growth. Undoubtedly, the glycolytic phenotype facilitates the tumor malignancy. BC along with many other cancers displays addiction to glutamine, and high glutamine activity was identified to support biosynthesis, energetics, and homeostasis. Serine metabolism is more important than the glycine pathway for BC cell proliferation and migration. The interplay between amino acids metabolism and the TCA cycle promotes glutamine and serine to α-ketoglutarate, which increases the activity of TCA cycle. The crosstalk among the energy metabolism pathways depends on the genetic makeup, modulation of multiple signaling pathways, and the activities of different transcription factors. Therefore, the transcriptional regulators of metabolic enzymes and signaling pathways provide a potential target for the treatment of BC.

CRediT authorship contribution statement

Xuewei Zheng: Writing – original draft, Writing – review & editing. **Haodi Ma:** Writing – review & editing. **Jingjing Wang:** Writing – review & editing. **Mengjiao Huang:** Writing – review & editing. **Dongliao Fu:** Writing – review & editing. **Ling Qin:** Writing – review & editing. **Qinan Yin:** Visualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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