Front. Med. 2021, 15(2): 178–207
https://doi.org/10.1007/s11684-020-0793-6

REVIEW

# Metabolism and immunity in breast cancer

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**Abstract** **Breast cancer is one of the most common malignancies that seriously threaten women's health. In the process of the malignant transformation of breast cancer, metabolic reprogramming and immune evasion represent the two main fascinating characteristics of cancer and facilitate cancer cell proliferation. Breast cancer cells generate energy through increased glucose metabolism. Lipid metabolism contributes to biological signal pathways and forms cell membranes except energy generation. Amino acids act as basic protein units and metabolic regulators in supporting cell growth. For tumor-associated immunity, poor immunogenicity and heightened immunosuppression cause breast cancer cells to evade the host's immune system. For the past few years, the complex mechanisms of metabolic reprogramming and immune evasion are deeply investigated, and the genes involved in these processes are used as clinical therapeutic targets for breast cancer. Here, we review the recent findings related to abnormal metabolism and immune characteristics, regulatory mechanisms, their links, and relevant therapeutic strategies.**

**Keywords** breast cancer; metabolism; immunity; cancer stem cells

## Introduction

Breast cancer, the second most common malignancy, accounts for 16.1% of all new cases of female cancer in China in 2014 [1]. Current therapies, including surgery, chemotherapy, radiotherapy, and endocrine and target therapy, have achieved remarkable advances. However, disadvantages, such as drug resistance and bone marrow suppression, limit the effectiveness of available therapies. In addition, these treatments have little effect on the triple negative breast cancer (TNBC). Therefore, further understanding of the mechanisms of breast cancer may contribute to the treatment of patients with breast cancer. In recent years, research on the abnormal metabolism of cancer cells, which is regarded as a promising field for cancer therapy, has become the focus. The Nobel Prize in Physiology or Medicine in 2018 is awarded to Tasuku Honjo and James Allison for their contributions to cancer immunotherapy. Immunotherapy exhibits great potentials in cancer treatment. Interestingly, the abnormal metabolism seems to be inextricably linked to a dysfunctional immune system in cancer cells [2,3]. In this review, advances in abnormal metabolism and immunity in breast cancer are provided.

Received September 29, 2019; accepted April 17, 2020
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## Breast cancer and subtypes

Increasing reports on breast cancer focus on the variations in metabolism among breast cancer subtypes. The molecular and metabolism characteristics are also different between estrogen receptor (ER)-positive and ER-negative breast cancers [4]. ER-positive breast cancers are divided into two subtypes, namely, luminal A and luminal B. ER-negative breast cancers are also divided into HER2-enriched and basal-like subtypes (i.e., TNBC). Luminal B tumors mainly depend on lipid metabolism for tumor growth, but HER2 and basal-like breast cancers (BLBCs) prefer to alter glucose/glutamine metabolism [5]. The features of metabolism in various subtypes of breast cancer are discussed below.

### Breast cancer subtypes

ER-positive breast cancers are the most common types of breast cancer. This subtype is further divided into two subtypes, namely, luminal A and luminal B. At the DNA level, luminal A tumors show few mutations across the

genome, low chromosomal copy-number changes, low Ki67 expression, and few p53 mutations. Luminal A tumors tend to decrease the clinical grade, and majority of these tumors shows good prognosis and low recurrence score.

Compared with luminal A tumors, luminal B tumors have higher number of mutations across the genome, higher number of chromosomal copy-number changes, and more p53 mutations at the DNA level [6]. Luminal B tumors have the most methylation frequencies among breast cancer subtypes [7] and tend to show high clinical grade and high recurrence and/or survival rate.

The HER2-enriched subtype represents nearly 15% among breast cancers [8], showing the overexpression of HER2, a member of the erythroblastic leukemia viral oncogene homolog receptor family. HER2 is an important oncodriver that promotes cell proliferation and inhibits cell apoptosis in breast cancer [9]. At the DNA level, the HER2-enriched subtype shows the highest rates of mutations, including PIK3CA and p53 mutations, across the genome. The HER2-enriched subtype tends to have high grade and poor prognosis [10]. Interestingly, the HER2-enriched subtype is found in the tumors uniquely enriched with high frequency of mutations of the apolipoprotein B mRNA editing enzyme catalytic subunit 3B (APOBEC3B). The APOBEC3B, a subclass of APOBEC cytidine deaminases, is mutated in many cancer types [11]. A growing body of literature suggests that amplified HER2 plays an important role in regulating breast cancer stem cells (BCSCs) related to drug resistance and recurrence [12–14]. The regulation of BCSCs by HER2 is likely to be found in other breast cancer subtypes. In other subtypes, the HER2 expression has heterogeneity in BCSC populations, which may be related to the tumor microenvironment. According to this phenomenon, trastuzumab, a drug approved to be used for the treatment of the HER2-enriched subtype, may be effective in some patients with HER2-negative breast cancer [15].

BLBC, which constitutes at least 10% of breast cancers, has a unique genomic signature and the greatest intrinsic diversity [16]. Among breast cancers, BLBC has the lowest methylation frequencies and the second highest mutation frequency after the HER2-enriched subtype at the DNA level. BLBC has a mass of PIK3CA and p53 mutations. Interestingly, BLBCs may be associated with breast cancer susceptibility gene-1 (BRCA-1) mutations, which may cause hereditary breast cancer [17]. BLBCs have the worst prognosis among the breast cancer subtypes.

## Glucose metabolism among breast cancer subtypes

As described above, most mutations of p53 occur in the basal-like and HER2-enriched tumors [6]. The wild-type p53 can promote aerobic respiration and inhibit glycolysis by regulating the expression of cytochrome c oxidase complex (COX), cytochrome c oxidase 2 (SCO2), p53-induced glycolysis, and apoptosis regulator (TIGAR) [18]. In breast cancer cells, the mutation of p53 shifts normal glucose metabolism toward aerobic glycolysis [19,20]. The phosphatidylinositol 3-kinase (PI3K) mutation frequencies are the highest in ER-positive breast cancers and can stimulate glycolysis through the PI3K/Akt/mTOR signaling pathway [21]. The expression level of c-Myc is remarkably elevated in BLBCs, thereby promoting aerobic glycolysis and lactate production [22]. Simultaneously, c-Myc also drives glutamine metabolism by enhancing glutamine transporters and glutaminase (GLS) expression [23,24].

The accumulation of downstream glycolytic intermediates varies among the breast cancer subtypes. The levels of glucose-6-phosphate and fructose-6-phosphate are lowest in the luminal A subtype and highest in BLBC. The levels of fructose-1,6-bisphosphate (F1,6BP) vary between ER-positive and ER-negative breast tumors [5] due to highly expressed epidermal growth factor (EGF) signaling in the BLBC, which activates the initial step but blocks the last step during glycolysis. In turn, F1,6BP enhances the activity of the EGF receptor (EGFR) by direct binding, thereby increasing the excretion of lactate in TNBC [25]. Moreover, several intermediates of the pentose phosphate pathway (PPP), such as ribulose 5-phosphate and xylulose 5-phosphate, are elevated in the HER2-enriched molecular subtype. Overall, the glucose utilization is drastically enhanced in ER-negative breast cancers [5].

## Amino acid and lipid metabolism among breast cancer subtypes

Glutamine metabolism, which varies substantially among breast cancer subtypes, is important and studied well among amino acid metabolism. The deprivation of glutamine can inhibit the malignant progression of breast cancer especially in malignant subtypes. Among breast cancer subtypes, the HER2-enriched subtype has the highest glutamine metabolic level because of the elevated expression of GLS and glutamate dehydrogenase (GLUD) [26–28]. In addition, in the HER2-enriched subtype, increased levels of peroxisome proliferator-activated receptor γ (PPARγ) and coactivator-1α (PGC-1α) lead to the overexpression of GLS and GLUD1. High GLS and GLUD1 expression levels are correlated with poor clinical outcome in patients with breast cancer [29].

In recent years, increasing investigations show considerably different characteristics of lipid metabolism among the breast cancer subtypes [30]. A study suggests that TNBC needs glucose glutamine and requires more exogenous lipid uptake and storage than receptor-positive breast cancers [31]. Camarda *et al*. have performed metabolomics and shown that fatty acid oxidation (FAO)

intermediates, such as acyl-carnitines (AC), are drastically elevated in MYC-driven TNBC [32]. The gene signature associated with lipid metabolism implicates that FAO is the critical metabolism pathway for TNBC.

## Breast cancer and abnormal metabolism

The breast cancer metabolism has also been investigated regardless of the breast cancer subtype. The remodeling of cancer cell metabolism represents an essential hallmark of cancers, including breast cancer (Table 1) [33,34]. Breast cancer cells enhance aerobic glycolysis ("Warburg effect") to produce lactate for the tumor microenvironment. Breast cancer cells utilize folate and acetate to accelerate lipid biosynthesis and need glutamine, which protects cells from reactive oxygen species (ROS) elevation and apoptosis. Thus, the abnormal metabolism may act as potential and effective targets for breast cancer treatment.

### Breast cancer and glucose metabolism

Glucose metabolism, a major energy source, is upregulated and dysfunctional in cancer cells, including breast cancer cells (Fig. 1). In general, glucose metabolism includes aerobic glycolysis, PPP, tricarboxylic acid cycle (TCA), gluconeogenesis, and other approaches. Here, we introduce the first four glucose metabolic pathways in breast cancer.

#### *Warburg effect*

Cancer cells are still metabolized primarily by high glycolysis even under sufficient oxygen. This phenomenon, known as aerobic glycolysis or the Warburg effect, contributes to cancer cell proliferation and metastasis [43]. Glucose is eventually converted into lactate in the cytoplasm by the Warburg effect. More than 10 genes encoding glucose transporters (GLUTs) and glycolytic enzymes play important roles in the Warburg effect. In the first step, the effective transport of glucose contributes to the abundant glucose consumption in cancer cells, the phenomenon of which is caused by the overexpression of GLUTs [44]. In breast cancer, high levels of GLUT1 expression is associated with tumor subtypes, high grade, and poor prognosis [45]. However, the upregulated GLUT family expression cannot fully explain the increased effective glucose transport in breast cancer, suggesting the involvement of another GLUT. Sodium–glucose cotransporter 1 (SGLT1) can utilize sodium gradients to maintain intracellular glucose levels independent of extracellular glucose concentration. The expression of SGLT1 is upregulated in many cancer types and regulates EGFR activity to promote cell growth in TNBC [46–49]. In the second step, intracellular glucose is converted into pyruvate under the catalysis of nine types of glycolytic enzymes. Three key enzymes act as rate-limiting agents, including HK2, PFK, and PKM, and have high expression levels, facilitating the malignant development in breast cancer cells [50–52]. For example, the expression level of HK2 determines the malignant degree and the phenotype of breast cancer *in vitro* and *in vivo* models [53]. In the third step, even in the presence of oxygen, lactate dehydrogenase (LDH) still converts pyruvate into lactate in cancer cells. The LDH family includes LDHA, LDHB, LDHC, and LDHD [54]. LDHA plays an important role in aerobic glycolysis in breast cancer because of the high affinity for pyruvate compared with LDHB [55]. In breast cancer cells, the high levels of LDHA contribute to promote cancer cell proliferation, invasion, and even epithelial mesenchymal transition [54]. Overall, the Warburg effect is essential for the breast cancer cell malignant development and growth.

**Table 1** Abnormal metabolism in breast cancer

| Metabolism | Specific classification of metabolism | Level of metabolism in breast cancer | Reference |
|---|---|---|---|
| Glycometabolism | Glucose uptake | Increase | [35] |
| | Warburg effect | Increase | [1] |
| | TCA cycle | Abnormal | [1] |
| | Pentose phosphate pathway | Increase | [36] |
| | Gluconeogenesis | Decrease | [37] |
| Lipid metabolism | Fatty acid uptake | Uncertain but important | [38] |
| | *De novo* fatty acid synthesis | Increase | [39] |
| | Fatty acid oxidation | Increase | [40] |
| Amino acid metabolism | Glutamine metabolism | Increase | [41] |
| | Serine and glycine metabolism | Increase | [42] |
| | Cysteine metabolism | Increase | [42] |
| | Arginine metabolism | Uncertain | [42] |

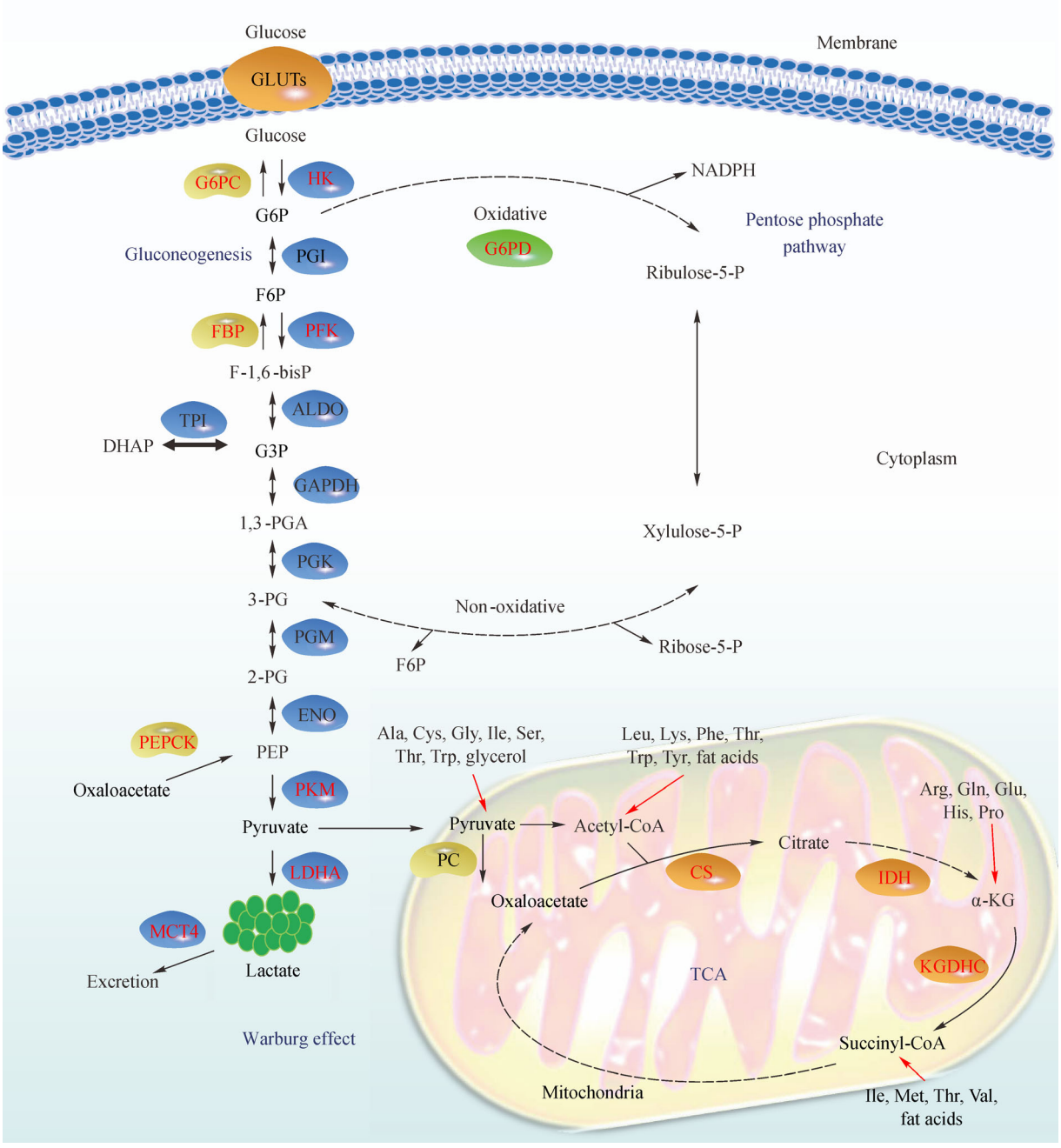


**Fig. 1** Glucose metabolism. HK, PFK, and PK are the three key enzymes in glycolysis. G6PD regulates the rates of the PPP by catalyzing the oxidation. In general, pyruvate is oxidized into carbon dioxide and water in the mitochondria, which is catalyzed by three key enzymes, namely, CS, IDH, and KGDHC. Pyruvate is converted to lactate by LDHA in cancer cells, and lactate is expelled from the cell by MCT4. Gluconeogenesis can influence glycolysis, TCA, PPP, and other processes indirectly via the rates of glucose production. Three key enzymes control the gluconeogenic flux, including PEPCK, FBP, and G6PC. Abbreviations: G6P, glucose 6-phosphate; F6P, fructose 6-phoshate; F-1,6-bisP, fructose-1,6-bisphosphate; G3P, glyceraldehyde 3-phosphate; 1,3-PGA, 1,3-disphosphoglycerate; 3-PG, glyceraldeyde 3-phosphate; 2-PG, glyceraldeyde 2-phosphate; PEP, phosphoenolpyravate; TCA, tricarboxylic acid cycle; α-KG, α-ketoglutarate; GLUTs, glucose transporters; HK2, hexokinase 2; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; PFK, 6-phosphofructo kinase; ALDO, aldolase; TPI, triose phosphate isomerase; PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; ENO1, enolase; PKM, pyruvate kinase; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; CS, citrate synthase; IDH, isocitrate dehydrogenase; KGDHC, α-ketoglutarate dehydrogenase complex; G6PD, glucose 6-phosphate dehydrogenase; PC, pyruvate carboxylase; PEPCK, phosphoenolpyruvate carboxykinase; FBP, fructose-1,6-bisphosphatase; G6PC, glucose-6-phosphatase.

*PPP*

The PPP, a glycolysis branch, produces NADPH and ribose-5-phosphate. The PPP serves a pivotal role in supporting nucleic acid and fatty acid (FA) syntheses and protects cells from stress-induced death [56]. The PPP follows two biochemical processes in the cytoplasm, namely, oxidative and nonoxidative processes.

Cancer cells can improve PPP through various channels and ways, thereby promoting proliferation and survival [36]. The glucose 6-phosphate dehydrogenase (G6PD) regulates the rates of the PPP by catalyzing the irreversible step. The expression levels of G6PD are different in various breast cancer subtypes and positively correlated with poor prognosis in patients [57]. In addition to the function in PPP, the low expression level of G6PD may activate the AMP-activated protein kinase (AMPK) signaling pathway and inhibit the breast cancer cell proliferation and survival [58].

*TCA*

The TCA cycle is a series of chemical reactions that generate energy and/or intermediate products through the oxidation of pyruvate into carbon dioxide and water [59]. The TCA cycle is very important for many biochemical pathways, such as energy metabolism, macromolecule synthesis, and redox balance. However, the TCA cycle is regarded as a process in which enzymes have valueless mutation and pointless regulatory function. However, recent reports show that a number of mutations in genes encoding enzymes, including aconitase, isocitrate dehydrogenase 1 (IDH1), fumarate hydratase, and succinate dehydrogenase in the TCA cycle raise the risk of some cancer types [60–63]. Mutations in the genes of mitochondrial DNA, such as the genes encoding ATPase 6 and NADH dehydrogenase subunit, which cause TCA cycle dysfunction, are the most commonly mutated genes in breast cancer [64].

*Gluconeogenesis*

Gluconeogenesis converts noncarbohydrate carbon substrates to free glucose for energy. Gluconeogenesis, which affects the regulation of the Warburg effect in cancer cells, has been paid less attention than glucose catabolism [37]. Gluconeogenesis can influence glycolysis, TCA, PPP, and other approaches indirectly via the rates of glucose production. Three key enzymes control the gluconeogenic flux, including phosphoenolpyruvate carboxykinase (PEPCK), fructose-1,6-bisphosphatase (FBPase), and glucose-6-phosphatase. For example, in addition to increasing the synthesis of glucose and glutamine, PEPCK can accelerate the rates at which noncarbohydrate substances are converted to ribose [65]. In addition, the high levels of FBPase are positively correlated with breast cancer metastases, suggesting that gluconeogenesis may be another potential target for metabolic treatment in patients with breast cancer [66].

## Breast cancer and lipid metabolism

In recent years, the dysfunctional lipid metabolism is progressively being regarded as a hallmark of cancer (Fig. 2). Clinical data show that postmenopausal obese women have a 20%–40% higher risk of developing breast cancer than lean women [67]. Except generating energy and forming cell and organelle membranes, lipids can transduce biological signals as second messengers.

Lipid metabolism includes three aspects, namely, *de novo* FA synthesis, FA uptake and transport, and FAO. During malignant transformation, unlike normal tissues, cancer cells upregulate *de novo* synthesis instead of lipid uptake to meet the increasing demand for biomass production [68,69]. The lipid uptake and storage increase in various cancer types [70–72]. In breast cancer, several lipid metabolic genes are closely related to the malignancy of tumors, such as proliferation, metastasis, and drug resistance [73,74].

*De novo FA synthesis*

In the *de novo* synthesis, FA is synthesized from two sources, namely, glucose and glutamine. Glucose is the major substrate for the *de novo* FA synthesis [75,76] and catalyzed into acetyl-CoA or/and citrate, which are the precursors for FAs, through glycolysis and TCA. In addition, glutamine, the most abundant amino acid in body, can participate in the FA synthesis through the conversion in TCA in the mitochondria [77,78].

In the first step of the *de novo* FA synthesis, ATP citrate lyase (ACLY) catalyzes citrate to acetyl-CoA, thereby connecting lipid metabolism and two other kinds of metabolism, namely, glucose and amino acid metabolism. The overexpression of ACLY promotes tumor cell growth in various cancer types especially breast cancer [79]. In addition to its catalysis, ACLY suppresses cell senescence by inhibiting the AMPK activity directly and the p53 expression indirectly [80]. AMPK can phosphorylate and inactivate acetyl-CoA carboxylase (ACC) 1, thus strongly inhibiting FA synthesis [81].

In another rate-limiting step, ACC converts acetyl-CoA to malonyl-CoA. Conversely, malonyl-CoA decarboxylase catalyzes the reverse reaction, whereas malonyl-CoA is oxidized and decomposed into carbon dioxide and acetyl-CoA. Mammalian cells control the balance between FA

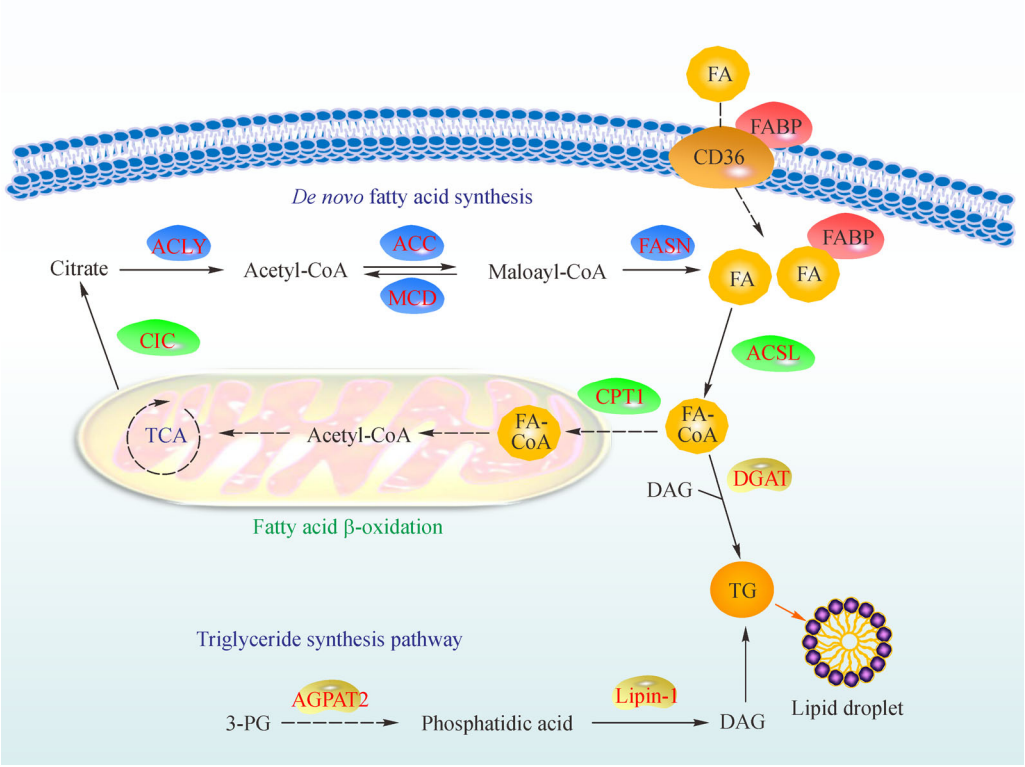


**Fig. 2** Lipid metabolism. In the *de novo* fatty acid synthesis, citrate is catalyzed into FA by ACLY, ACC, and FASN sequentially. CD36 and FABPs are involved in the intake of FA. FA needs to be transformed to FA-CoA before they enter the subsequent metabolism, including anabolism or catabolism. During fatty acid β-oxidation, FA-CoA is transported into the mitochondria and then oxidized, the rate of which is limited by CPT1. FA-CoA and DAG are synthesized into TG catalyzed by DGAT. During triglyceride synthesis, the glycolytic intermediate 3-PG is converted into DAG by AGPT2 and lipin-1, and DAG is ultimately converted into TG. Abbreviations: ACLY, ATP citrate lyase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; FABP, fatty acid binding protein; AGPAT2, acylglycerol-3-phosphate acyltransferase 2; CPT1, carnitine palmitoyltransferase 1; CIC, citrate carrier; FA, fatty acid; TG, triglyceride; DAG, diacylglycerol; 3-PG, glyceraldeyde 3-phosphate; DGAT, diacylglycerol acyltransferase; AGPAT2, acylglycerol-3-phosphate acyltransferase 2.

synthesis and degradation by the malonyl-CoA levels.

In FA anabolism, FA synthase (FASN) utilizes malonyl-CoA and acetyl-CoA to synthesize a saturated FA. Among the many critical enzymes of lipid metabolism, FASN is a key and elevated metabolic oncogene in many cancer types. The activity of FASN is positively correlated with cancer progression and chemoresistance. According to almost 200 cases of metastatic breast cancer, the positivity rates of FASN are correlated with the positivity of HER-2 [82]. Furthermore, the overexpression of FASN is remarkably associated with relapse and metastasis in patients with HER2-enriched breast cancer. In nontumorigenic breast epithelial cell lines (MCF10A), the HER2 overexpression can upregulate the expression level of FASN.

*FAO*

Lipolysis involves two procedures: mobilization of lipid droplets (LDs) and FAO. Previous evidence suggests that mobilization of LDs by lipolysis is attributed by the LD-associated lipases and autophagy-lysosome pathway [83]. FAO occurs in the mitochondria. FAs must be converted to FA-CoA to enter subsequent metabolic reactions, including anabolism or catabolism. This central reaction is catalyzed by long-chain acyl-coenzyme A synthase (ACSL). Five ACSL isoforms, including ACSL1, ACSL3, ACSL4, ACSL5, and ACSL6, are present in the human organism. ACSL4 is remarkably overexpressed in invasive breast cancers. Moreover, ER signaling pathways can regulate the levels of ACSL1, ACSL4, and ACSL5 [84]. ACSL4 can downregulate the antineoplastic drug sensitivity by promoting the expression of drug resistance genes in cancer cells [85].

*FA uptake and transport*

For a long time, the vast bulk of investigative effort on FA and cancers has focused on the *de novo* FA synthesis. However, the exogenous FA uptake is essential for cancer

cell proliferation. The absorption of exogenous palmitate can protect breast cancer cells from the proapoptotic effect of FASN inhibition [86]. Compared with normal diet intake, a high-fat intake independently increases breast cancer incidence in mice or in Sprague Dawley rats [87].

In addition, attention has been paid to the abnormal localization of FAs in cancer cells. The FA-binding protein 4 (FABP4) transports FAs to various cellular compartments to exert various metabolic functions. The FABP4 can regulate the gene expression and the malignant phenotype in breast cancer aside from the uptake and the intracellular storage of FAs [88–90]. For example, exogenous FABP4 elevates the expression levels of the FA transport proteins CD36 and FABP5 and promotes the proliferation of breast cancer cells [91].

## Breast cancer and amino acid metabolism

The increase in amino acid synthesis satisfies the demands of rapid proliferation in breast cancer cells (Fig. 3). Besides the primary units of proteins, amino acids act as regulated metabolite to support cancer cell growth. Fifteen amino acids are identified with remarkably elevated levels compared with normal samples, which can serve as hallmarks for the early diagnosis of breast cancer [92]. Among these research, glutamine, serine, and glycine are given attention.

### *Glutamine metabolism*

The increased metabolism of glutamine, the most abundant free amino acid, is a common metabolic alteration in cancer [93]. GLS converts glutamine to glutamate, which is the initial step in glutamine catabolism. The GLUD1 catalyzes glutamate to α-ketoglutarate (α-KG). These two enzymes dominate the rate of glutamine metabolism. The glutamine metabolism affects the chemotherapy resistance of cancer cells. In endocrine-resistant breast cancer cells, overexpression of cellular-myelocytomatos (c-Myc) can use glutamine to support enough metabolism by enhancing the GLS expression in the short-term glucose deprivation, thus maintaining cell survival [24,94]. Moreover, cancer cells can generate several ATP through oxidative phosphorylation driven by glutamine [95].

In addition, cancer cells require effective amino acid transport proteins to bring amino acids in and out of the cell plasma membrane. Amino acid transport proteins are membrane-bound solute carrier transporters. In breast cancer, glutamine is heavily consumed for proliferation and survival, and its intracellular concentration is regulated by high-efficiency amino acid transport proteins especially SLC1A5 and SLC7A5 [96]. In TNBC, overexpressed SLC1A5, SLC7A5, and SLC6A14 promote glutamine metabolism and tumor growth [97,98].

### *Serine and glycine metabolism*

The increased serine synthesis promotes cell proliferation by providing raw materials for biosynthesis in breast cancer [99,100]. In serine synthesis pathways, the glycolytic intermediate 3-phosphoglycerate is oxidized into serine, catalyzed by phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase, and phosphate ester hydrolysis (PSPH). In addition, serine can be converted into glycine, whose methyl groups can provide one-carbon metabolism required for synthesis of folate and other organic substances. Glycine is also an integral part of glutathione, which sustains the redox balance in mammalian cells. A recent report has suggested that suppressing the uptake and the biosynthesis of glycine may selectively impair rapidly proliferating cells by prolonging the $G_1$ phase of the cell cycle [101]. Therefore, targeting glycine may inhibit cancer cell growth without damaging normal cells.

Several enzymes involved in serine and glycine metabolism are considered hallmarks for the malignancy of tumors. The expression levels of PHGDH, PSPH, and SHMT are elevated in TNBC and decreased in luminal A [102], and these results are inversely proportional to the clinical prognosis [101]. Interestingly, serine deficiency inhibits cell growth in several breast cancer cell lines. Additionally, when serine is depleted, cancer cells unexpectedly replenish serine by exhausting glycine and one-carbon units and even nucleotide pools. The above phenomenon indicates that serine plays an important role in supporting cell proliferation by the mechanisms besides one-carbon metabolism in breast cancer cells [103].

## Master transcription factors for glucose, lipid, and amino acid metabolism

### *Hypoxia-inducible factor (HIF) 1*

Hypoxia is regarded as an essential regulator in the development of breast cancer. HIFs especially HIF1 play a crucial role in cellular hypoxia adaptation [104]. HIF1 are heterodimers composed of an $O_2$-regulated subunit (HIF1α) and a constitutively expressed subunit (HIF1β) [105].

The HIF1 expression is upregulated dramatically in TNBC [6]. The high level of HIF1 is a marker of poor clinical outcomes in human breast cancer [106,107]. Mechanically, HIF1 has important function on multiple malignant aspects of breast cancer, including proliferation, metastasis, pathological damage, and poor prognosis [108–113]. For example, HIF1 promotes primary tumor growth and metastasis to lung by upregulating the expression of

angiopoietin-like 4 and L1 cell adhesion molecule (L1CAM) in breast cancer [114].

In breast cancers, the overexpression of HER-2 increases the HIF1α protein expression via the PI3K/AKT/FRAP pathway under normoxic conditions [115]. Conversely, HIF1α can be degraded by von Hippel–Lindau (VHL), thus inhibiting breast cancer cell invasiveness and metastatic propensity [116,117]. SHARP1, an important regulator of tumor-malignant phenotype, also promotes the independent HIF-1α proteasomal degradation of oxygen levels and VHL [118].

Given that many cancer cells are exposed to hypoxic

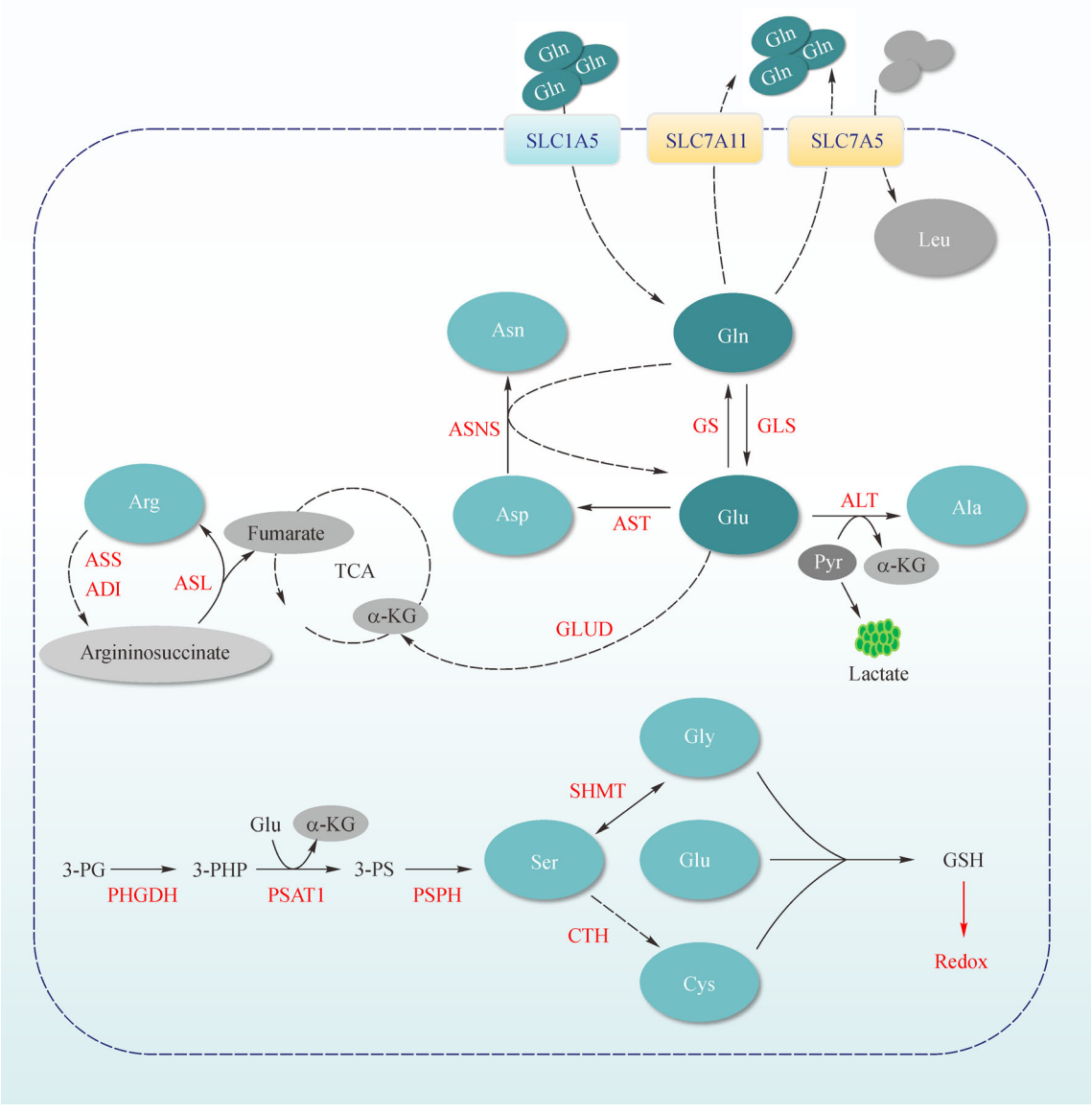


**Fig. 3** Amino acid metabolism. Glutamine uptake is regulated by SLC1A5, SLC7A5, and SLC7A11. Glutamine is converted into glutamate by GLS, and the counter-reaction is catalyzed by GS. GLUD catalyzes glutamate to α-KG. Glutamate is converted into alanine by ALT and converted into aspartic acid by AST. ASNS utilizes glutamine as a nitrogen donor to turn aspartic acid to asparagine. In addition, the glycolytic intermediate 3-PG is oxidized into serine catalyzed by PHGDH, PSAT1, and PSPH. Serine is converted into glycine by SHMT and converted into cysteine catalyzed by CTH. Glutamate, glycine, and cysteine are synthesized into GSH, which sustains the redox balance. Abbreviations: Ala, alanine; Glu, glutamate; Gln, glutamine; Aln, asparagine; Asp, aspartic acid; Gly, glycine; Ser, serine; Leu, leucine; Asn, asparagine; Cys, cysteine; α-KG, α-ketoglutarate; GSH, glutathione; PHGDH, phosphoglycerate dehydrogenase; PSAT1, phosphoserine aminotransferase; PSPH, phosphate ester hydrolysis; SHMT, serine hydroxymethyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GS: glutamine synthetase; GLS, glutaminase; GLUD, glutamate dehydrogenase; ASNS, asparagine synthetase; 3-PG, 3-phosphoglycerate; ASS, argininosuccinate synthetase; ASL, argininosuccinate lyase; ADI, arginine deiminase; ASNS, asparagine synthetase; SLCs, membrane-bound solute carriers; CTH, cystathionine γ-lyase.

environments during malignant tumor growth, the metabolic reprogramming from OXPHOS to aerobic glycolysis is recognized as cancer cell adaption to hypoxia. HIF1 is remarkably associated with abnormal glucose metabolism in various cancer types [119–121]. GLUT1 is responsible for basal glucose uptake to maintain the Warburg effect with increased glucose consumption in cancer cells. The expression level of GLUT1 is positively regulated by HIF1 [122]. Moreover, HIF1 can regulate 8 of 9 types of enzymes involved in glycolysis (Table 2), including HK2, GAPDH, PFK1, ALDOA, TPI, PGK1, ENO1, and PKM2 [123–126]. Although the evidence of a regulatory relationship between PGM and HIF1 is unclear, hypoxia increases the PGM levels [127]. Pyruvate is further metabolized to lactate, but not acetyl coenzyme A, through glycolysis by LDHA in cancer cells. The high expression level of LDHA is associated with HIF1 [128]. Furthermore, HIF1 can reduce OXPHOS by activating the pyruvate dehydrogenase kinase 1 (PDK1) expression, which partly explains the Warburg effect in breast cancer.

Although the relationship between HIF1 and glucose metabolism has been extensively studied, the HIF1 function on lipid metabolism is nearly the focus of recent research. HIF1 upregulates the expression of sterol regulatory element binding protein (SREBP) 1 under hypoxia. SREBP1 can upregulate lipid synthesis genes, such as ACLY, ACC1, and FASN [129]. The SREBP1 activity has recently been shown to be controlled by the Akt/mTOR signaling, which are potently activated by the oncogenic HER2 signaling [130,131]. In addition, HIF1 directly activates the expression of transcription factor PPARγ, which regulates the expression of genes involved in lipid storage and mobilization [132].

HIF1 can enhance exogenous FA uptake by promoting the FABP expression in cancer cells under hypoxia. Given the extremely low level of FA oxidation without oxygen, cells can convert FAs to neutral TAGs to avoid the lipotoxicity of accumulated free FAs [133]. The TAG biosynthesis pathway enzymes acylglycerol-3-phosphate acyltransferase 2 and lipin-1, the two direct targets of HIF1, regulate the lipid droplet accumulation [134,135]. HIF1 also supports the lipid accumulation under hypoxia by inhibiting the expression of enzymes involved in FA degradation [136–138]. Considering that HIF1 has not been shown to have a direct effect on the inhibition of the transcription of these genes, the expression of these enzymes may be regulated indirectly through HIF1 target genes [139].

**Table 2** Hypoxia-inducible factor 1 (HIF1) downstream targets that regulate metabolism

| Metabolism | Genes | Functional category of genes | Role of HIF1 in metabolism | Reference |
|---|---|---|---|---|
| Glycometabolism | GLUT1 | Glucose uptake | Increase | [140] |
| | GLUT3 | | | [141] |
| | HK2 | Glucose phosphorylation | Increase | [142] |
| | PGI | Glycolysis | Increase | [143] |
| | PFK1 | | | [143] |
| | ALDOA | | | [143] |
| | TPI | | | [143] |
| | GAPDH | | | [143] |
| | PGK1 | | | [143] |
| | ENO1 | | | [143] |
| | PKM2 | | | [143] |
| | LDHA | | | [143] |
| | PFKFB3 | | | [144] |
| | MCT4 | Lactate excretion | Increase | [145] |
| | PDK1 | OXPHOS inhibition | Increase PDK1 expression | [143] |
| | MXI1 | | | [143] |
| Lipid metabolism | PPARγ | Lipid uptake | Increase | [132] |
| | FABPs | | | [139] |
| | LRP1 | | | [146] |
| | VDLR | | | [147] |
| | SREBP-1 | Lipid synthesis | Increase | [148] |
| | FASN | | | [148] |
| | Lipin-1 | | | [134] |
| | AGPAT2 | | | [135] |
| | HIG2 | Lipid accumulation | Increase | [149] |
| | CPT1 | FA β-oxidation | Decrease | [138] |
| | PGC-1α | | | [138] |
| | LCAD | | | [137] |
| | MCAD | | | [137] |
| Glutamine metabolism | GLS1 | Glutaminolysis | Increase | [150] |

*c-Myc*

The c-Myc encoded by the Myc oncogene is over-expressed in 30%–50% of advanced breast cancers [151,152]. As a transcription factor controlling cell growth and metabolism, c-Myc plays an important role in tumorigenesis and drug resistance.

LDHA is the first glucose metabolism gene that is found directly regulated by c-Myc [153]. In addition, Zhang *et al*. have found that inhibiting LDHA expression can reversely elevate c-Myc mRNA level, indicating that LDHA has a negative feedback effect on the c-Myc expression [154]. Many other genes involved in glucose metabolism, such as GLUT1, HK2, GPI, GAPDH, PFK, ENO1, PGK, and PDK1, have been found to be activated by c-Myc (Table 3) [155,156].

In terms of glucose metabolism, complex interactions exist between c-Myc and HIF1. In hypoxia, HIF1 can inhibit the activity of c-Myc by stimulating the degradation of MYC and interrupting the complex of MYC–MAX [157,158]. However, intermittent hypoxia occurs all the time in tumor cells. Therefore, elevated c-Myc levels still work in tumor cells without the HIF1 inhibition of c-Myc [159]. Overall, HIF1 regulates many glucose metabolism genes under hypoxic conditions, whereas c-Myc elevates several genes under normal conditions [160]. For example, PDK1, which inhibits pyruvate oxidation in mitochondria under hypoxia, is elevated by HIF1 and c-Myc [161]. However, c-Myc transactivates glycolytic genes and several key genes involved in TCA. Therefore, the overall role of c-Myc in glucose metabolism remains to be investigated.

In addition, glutamine utilization is increased along with the Warburg effect [162]. A key function of c-Myc in cancers is the regulation of expression of genes involved in the absorption and the metabolism of glutamine, such as GLS [163]. N-Myc also contributes to the conversion of glutamine to glutamate via transactivating the GLS2 expression directly in neuroblastoma cells [164]. Moreover, the lncRNA GLS–AS, which binds to and decreases GLS mRNA, is downregulated by c-Myc in pancreatic cancer with glucose and glutamine deprivation [165]. In breast cancer, c-Myc increases glutamine and glucose uptake by regulating the glutamine transporter alanine serine cysteine transporter 2 and excitatory amino acid transporters 2 for cell growth [94]. In the luminal B breast cancer subtype, c-Myc protects the cell from oxidative damage and maintains survival by regulating the glutamine–proline regulatory axis [166]. A recent study has identified that HER2 activation also stimulates the expression of GLS1 in breast cancer cells [167,168].

*SIX1*

SIX1, the most studied SIX family member, plays a role in the development of tumors, including breast cancer [173]. SIX1 is active in the sustained proliferative signaling by activating cyclin A and cyclin D [174,175]. The SIX1 overexpression is positively correlated with the malignant biological properties of tumors, including invasion and metastasis, evasion of growth suppressors, malignant transformation of nontumorigenic cells, and resistance of cell death [176–178].

SIX1 promotes breast cancer growth *in vitro* and *in vivo* by regulating aerobic glycolysis [179]. This study shows that the miR-548a-3p/SIX1 axis acts as an essential regulatory pathway in the Warburg effect. SIX1 can enhance aerobic glycolysis by upregulating the expression of almost all of glycolysis genes, including GLUT1, HK2, PFKL, ALDOA, GAPDH, PGK1, ENO1, pyruvate kinase M2 (PKM2), and LDHA. Mechanistically, SIX1 increases

**Table 3** c-Myc downstream targets that regulate metabolism

| Metabolism | Genes | Functional category of genes | Role of c-Myc in metabolism | Reference |
|---|---|---|---|---|
| Glycometabolism | Glut1 | Glucose uptake | Increase | [169] |
| | Glut2 | | | [170] |
| | Glut4 | | | [170] |
| | HK2 | Glucose phosphorylation | Increase | [171] |
| | PGI | Glycolysis | Increase | [172] |
| | PFK1 | | | [170] |
| | ALDOA | | | [170] |
| | PGK1 | | | [170] |
| | ENO1 | | | [170] |
| | PKM2 | | | [171] |
| | LDHA | | | [171] |
| | PDK1 | OXPHOS inhibition | Increase PDK1 expression | [170] |
| Lipid metabolism | FASN | Lipid synthesis | Increase | [170] |
| Glutamine metabolism | GLS1 | Glutaminolysis | Increase | [171] |
| | ASCT2 | Glutamine uptake | Increase | [171] |

the glycolytic gene expression through histone acetyltransferases HBO1 and AIB1. miR-548a-3p can reduce the SIX1 expression, thus affecting tumor metabolism and growth.

*p53*

p53 mutations are found in almost 30% of breast cancers and is highly associated with various breast cancer subtypes [180]. Women with p53 mutations have an 85% risk of developing breast cancer by age 60 years [181]. In addition to its traditional role as a tumor suppressor, p53 suppresses glycolysis and accelerates oxidative phosphorylation in glucose metabolism. In aerobic glycolysis, p53 limits glucose uptake by downregulating GLUT family genes (Table 4) [182,183]. p53 can compromise glycolysis by downregulating HK2 and PDK2 transcriptionally [142,184] and promoting PGM degradation [185]. Moreover, p53 accelerates the accumulation of intracellular lactate by downregulating the monocarboxylate transporter 1 (MCT1), leading to the shift from glycolysis to oxidative phosphorylation [186,187]. p53 prevents the active dimer formation of G6PD through binding, thus suppressing PPP and reducing glucose consumption and NADPH production and biosynthesis [188]. However, studies report that p53-inducible glycolysis and apoptosis regulator (TIGAR), one of p53 downstream genes, is overexpressed and promotes cell oxidative resistance by reducing the Warburg effect and promoting PPP in breast cancer cells [189,190]. Moreover, TIGAR may contribute in the enhancement of the mitochondrial functions of cancer cells [191]. The function of TIGAR on glycometabolism is paradoxical to p53, which is supposed to be a tumor suppressor gene in breast cancer. However, elevated TIGAR expression is dependent on tumor and not dependent on p53 in breast cancer, and p53 can slightly regulate the TIGAR expression [192].

In addition, p53 contributes to the survival during serine starvation and oxidative stress. When serine is scarce, p53 blocks cell cycle and promotes remaining serine to join in glutathione synthesis [193]. Recently, the p53 family member p73 is reported to affect serine biosynthesis. p73 tends to promote the conversion of glutamine to glutamate by transcriptionally regulating GLS2, thus increasing the intracellular levels of serine and glycine. Therefore, the combined action of p73 and p53 maintains glutamine balance against the oxidative stress [194].

## Post-translational modifications of proteins (PTMs) involved in glucose, lipid, and amino acid metabolism

PTMs are the covalent bindings of functional molecules to proteins and play essential roles in regulating the activities and the functions of proteins involved in the malignant transformation of various cancer types. The common PTMs mainly include phosphorylation, acetylation, and ubiquitination. Previous research shows that PTMs are closely related to energy metabolism in breast cancer [197–199].

For instance, many rate-limiting enzymes involved in glucose metabolism, such as HK2, PFK1/2, PKM2, and LDHA, are all regulated by reversible phosphorylation (Table 5). The Tyr10 phosphorylation of LDHA facilitates the formation of its tetramers and enhances the LDHA activity [200]. By contrast, the Lys5 acetylation degrades LDHA via the HSC70 transport to lysosomes, thus inhibiting the LDHA activity [201]. A sharp increase in ROS concentration inhibits PKM2 through the oxidation of Cys358 [202]. For lipid metabolism, PPARγ is an essential regulator of adipogenesis. Mitogen-activated

**Table 4** p53 downstream targets that regulate metabolism

| Metabolism | Genes | Functional category of genes | Role of p53 in metabolism | Reference |
|---|---|---|---|---|
| Glycometabolism | GLUT4 | Glucose uptake | Decrease | [43] |
| | PGM1 | Glycolysis | Decrease | [43] |
| | TIGAR | Decrease glycolysis and promote PPP | Increase TIGAR expression | [195] |
| | SCO2, Acad11 | OXPHOS | Increase | [195] |
| | HK2 | Glucose phosphorylation | Decrease | [43] |
| | G6PD | PPP | Decrease | [196] |
| Lipid metabolism | Caveolin1 | Lipid homeostasis and endocytosis | Decrease | [196] |
| | SREBP1 | Lipid synthesis | Decrease | [195] |
| | DHR53, Lipin1, MCD | Lipid accumulation | Increase | [196] |
| | AMPK | Promote FA β-Oxidation and inhibit lipid synthesis | Increase AMPK expression | [196] |
| Glutamine metabolism | GLS2 | Glutaminolysis | Increase | [195] |

protein kinase-mediated phosphorylation at Ser112 inhibits the PPARγ function [203]. SUMOylation and ubiquitination can decrease the stabilization and the activity of PPARγ [204,205]. Although the deacetylation of PPARγ may induce the browning of white adipose tissue, complex and unknown regulatory mechanisms between acetylation and PPARγ function [206]. SREBP, another essential transcriptional regulator of lipid metabolism, is degraded by phosphorylation-dependent ubiquitination [207]. In glutamine catabolism, the phosphorylation at the Ser95 of GLS decreases its activity in breast cancer cells [208]. However, the Ser314 phosphorylation of GLS has the opposite effect, indicating that phosphorylation can enhance the GLS activity [209]. These contradictory phenomena show that the same PTM at different sites may have different functions.

## Targeting abnormal metabolism in the treatment of breast cancer

In recent years, numerous and comprehensive research have been conducted on the mechanisms of abnormal metabolism in breast cancer. At the same time, various targeted drugs for metabolism have been developed.

For instance, obese women have higher incidence and mortality rates of breast cancer compared with nonobese women. The overactivation of insulin-like growth factor-1 (IGF1) system plays a vital role in carcinogenesis in obese women [228]. MEDI-573, a monoclonal antibody (mAb) blocking the binding of IGF1 and IGF1R, has shown excellent anticancer activity and tolerability in a phase I clinical trial in patients with breast cancer [229]. AMPK, a key protein kinase for maintaining metabolic homeostasis, is activated and sustains cell survival in the case of glucose depletion. However, the overactivated AMPK promotes cell apoptosis instead [230]. Several clinical drugs, such as metformin, demethoxycurcumin, and fluoxetine, are thought to overactivate the AMPK pathway to inhibit breast cancer cells [231]. Over the last decade, several different FASN inhibitors have been developed. First-generation FASN inhibitors are not applicable in clinical practice because of critical defects, such as poor cell permeability and severe weight loss in mice [232]. TVB-2640 is the first clinically available new-generation FASN inhibitor and needs to be further explored in the treatment of breast cancer. Glutamylcyclotransferase (GGCT), one of

**Table 5** Post-translational modifications of proteins involved in metabolism

| Proteins | Modification | Site | Functional category | Reference |
|---|---|---|---|---|
| HK2 | Phosphorylation | Thr473 | Enhancing activity | [210] |
| PFK1 | Oxidation | Ser529 | Decreasing activity | [211] |
| PFK2 | Phosphorylation | Ser466, Ser483 | Enhancing activity | [212] |
| PGAM1 | Phosphorylation | His11, Tyr26 | Enhancing activity | [213] |
| | Acetylation | Lys251, Lys253, Lys254 | Enhancing activity | [214] |
| PKM2 | Phosphorylation | Ser37, Tyr105 | Enhancing activity | [215,216] |
| | Acetylation | Lys305, Lys433 | Degradation | [217] |
| | Oxidation | Cys358 | Decreasing activity | [202] |
| PDP1 | Phosphorylation | Tyr381 | Enhancing activity | [218] |
| | Acetylation | Lys202 | Decreasing activity | [218] |
| LDHA | Phosphorylation | Tyr10, Tyr 83 | Enhancing activity | [200,219] |
| | Acetylation | Lys5 | Degradation | [201] |
| PDK1 | Phosphorylation | Tyr243, Tyr244 | Enhancing activity | [220] |
| PDHA1 | Phosphorylation | Ser293, Tyr301 | Decreasing activity | [221,222] |
| | Acetylation | Lys321 | Decreasing activity | [218] |
| p53 | Phosphorylation | Ser15 | Stabilization | [223] |
| | Ubiquitylation | Lys237, Lys338 | Degradation | [20] |
| | Acetylation | Lys | Stabilization | [224] |
| HIF1α | Ubiquitylation | Lys709, Lys532 | Degradation | [225] |
| PPARγ | Phosphorylation | Serine112 | Decreasing activity | [203] |
| | SUMOylation | Lys63, Lys94, Lys98, Lys107 | Decreasing activity | [195] |
| | Acetylation | Lys268, Lys293 | Decreasing activity | [206] |
| | Ubiquitylation | Lys184, Lys185 | Degradation | [204,205] |
| SREBP1 | Phosphorylation | Thr402, Thr426 | Degradation | [207] |
| | Acetylation | Lys324, Lys333 | Stabilization | [207,226] |
| GLS | Phosphorylation | Ser95 | Decreasing activity | [208] |
| | Phosphorylation | Ser314 | Stabilization | [209] |
| | Acetylation | Lys320 | Decreasing activity | [227] |

the main catalytic enzymes in glutathione metabolism, contributes to cell proliferation, invasion, and migration of breast cancer [233]. Pro-N-glutaryl-l-alanine (pro-GA), the first cell membrane-permeable GGCT inhibitor, has evident inhibitory effects on the proliferation of breast and other cancer cells. Moreover, the anticancer effect and the favorable tolerability of pro-GA *in vivo* have been demonstrated [234]. Folic acid metabolism plays a key role in nucleotide synthesis, whose fluxes are elevated in breast cancer cells. Pemetrexed disodium is an anticancer drug that targets thymidylate synthase and several folate-dependent enzymes. Pemetrexed has remarkable effects on the clinical treatment of breast cancer [235]. In addition to the drugs mentioned above, a number of anticancer drugs targeting normal metabolism are being developed. However, the effectiveness and the adverse side effects of these drugs deserve further exploration and evaluation.

## Breast cancer and immune therapy

Immune evasion is an emerging hallmark of cancer. In 1909, Ehrlich has put forward the notion of "immune surveillance" and brought the cancer researchers' attention to the connection between cancer and the host's immune response. In 1970, Burnet has refined the concept and suggested that malignant genetic mutations occur constantly in the body and that the host immune system eliminates these cells with dangerous mutants all the time [236]. Gradually, "immune surveillance" has evolved into a theory termed "immunoediting," which can be divided into three phases, namely, elimination, equilibrium, and escape [237]. At present, the most in-depth research is the "Escape" phase. In the "Escape" phase, cancer cells have established an immunosuppressive tumor microenvironment and proliferate rapidly [238]. In the tumor microenvironment, poor cellular immunogenicity, lymphocyte infiltration, and immunosuppression are considered the reasons for the low efficacy of breast cancer immunotherapy. Thus, scientists have found a couple of potential directions for breast cancer treatment, which will be introduced below.

### Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) in breast cancer

The T cell activation plays an important role in tumor immunity. The proper activation of T cells requires antigens and costimulatory signals. The CD28/B7 family, known as "immune checkpoints," is a main part of costimulatory signals [239,240]. T cells are activated if the B7 on antigen-presenting cells (APCs) binds to the CD28 on the T cell. However, T cells sometimes need to be properly inactivated to prevent excessive autoimmunity. The CTLA-4 on the T cell surface has been termed a negative regulator of naive T cell activation. Considering that the affinity of B7 binding to CTLA-4 is greater than that to CD28, B7 preferentially interacts with CTLA-4, resulting in an inhibitory signal to the T cell nucleus [241].

Aside from the negative costimulation signals to T cells, regulatory T (Treg) cell-mediated immunosuppressive activity is promoted by CTLA-4 [242]. Interestingly, the expression of CTLA-4 is found in cancer cells. The presence of cytoplasmic CTLA-4 may represent the poor prognosis of breast cancers [243]. Another study has found that the secretion of an alternatively spliced soluble CTLA-4 isoform can be increased during the healthy human T cell immune responses, and this isoform has potent inhibitory ability on T cell proliferative responses. This soluble CTLA-4 isoform is derived from Treg cells [244].

The anti-CTLA-4 mAb ipilimumab has been approved by FDA for advanced melanoma treatment. Ipilimumab inhibits the CTLA-4 signaling via the enhancement of T cell response and mediates the antibody-dependent cytotoxicity reaction [245]. Ipilimumab and tremelimumab (another anti-CTLA-4 mAb) are clinically evaluated in other solid tumors, including breast cancer with limited symptomatic effects [246,247].

### Programmed cell death (PD)-1 in breast cancer

CTLA-4 suppresses T cell responses in the initiation of T cell activation process, and PD-1 attenuates T cell activity in the later process [248]. PD-1, an immunosuppressive molecule, is expressed on the T cell surface, which then binds to the PD ligand 1 (PD-L1) on the tumor tissue, resulting in T cell inactivation [249,250]. PD-1 is thought to interact with peripheral tissues directly, and the inhibition of this process can also promote antitumor immunity [251,252]. Compared with normal breast samples, the expression of PD-L1 is upregulated in 20% of clinical samples and 38% of basal tumor and has positive correlation with poor prognosis [253].

The expression levels of PD-1 and PD-L1 are upregulated by certain cytokines, including interferon (IFN) γ and interleukin 4, through the activation of IFN/signal transducer and activator of transcription (STAT) pathway [254–256]. Tumor cells can induce the expression of PD-L1 directly through constitutive oncogenic pathways or indirectly with the help of T cells [257]. This finding explains in part the phenomenon that PD-L1 expression level has linear correlation with inflammatory genes, including IFNγ in breast cancer [258]. Moreover, PD-L1 is overexpressed in breast cancers with treatment of some antitumor drugs, such as etoposide, paclitaxel, and 5-fluorouracil [259], suggesting that chemotherapy resistance may involve cancer immunity. Doxorubicin has the opposite effect (PD-L1 expression declines).

PD-1 and PD-L1 are regarded as vital targets of tumor

immunotherapy. Pembrolizumab is a mAb against PD-1. Several clinical trials have suggested that pembrolizumab has certain anticancer activity in patients with early and PD-L1-positive TNBC [260]. Moreover, pembrolizumab is well tolerated in patients with breast cancer, and its toxicities are similar to those in other disease cohorts [259]. The combination of nivolumab (another anti-PD-1 mAb) and ipilimumab (anti-CTLA-4 mAb) has been demonstrated to have considerable antitumor effects on melanoma and needs further evaluation in the clinical therapy of breast cancer [261]. Atezolizumab is a mAb against PD-L1 and the first immune checkpoint inhibitor approved by FDA for breast cancer. The combination of atezolizumab with paclitaxel has been approved by FDA for PD-L1-positive advanced or metastatic TNBC. In a phase III study, this combination therapy improves the progression and the prognosis for patients with TNBC [262].

## Lymphocytic infiltration in breast cancer

Massive lymphocyte infiltration is an important characteristic of breast cancer. A growing body of literature has demonstrated that the infiltration of leukocytes into the neoplastic stroma is enhanced, functionally contributing to the progression of most solid tumors, including breast cancer [263].

In general, tumor-infiltrating lymphocytes (TILs) are composed of T cells and a minority of NK or B cells. B cells only represent predominant lymphocytes by secreting immunoglobulins during early breast cancer progression [6]. However, $CD8^+$ T cells are generally in a state of inactivation in breast tumors and activated in one-third of the patients after chemotherapy [264].

The mechanisms of TILs in the clinical oncology of breast tumors are a matter of debate. For example, one study suggests that a high percentage of $CD4^+$ T cells implies the development of metastases in breast cancers [265]. However, other studies have the opposite argument that lymphocyte infiltration presents a favorable prognosis in breast cancer [266,267]. For example, Aaltomaa *et al*. have studied the predictive value of TILs in 489 patients with breast cancer followed for more than 10 years and found that the presence of TILs are correlated with low malignancy of tumors, showing efficient immune defense mechanisms [268]. Moreover, the high level of stromal TILs is a favorable factor in the chemotherapy response in TNBC [269,270]. However, the assessment of TILs still lacks sufficient standardization in the clinical treatments of breast cancer.

TILs may enhance the antitumor effect of chemotherapy with improved clinical response [271]. Interestingly, the level of TILs may increase from low to high after chemotherapy in patients with TNBC [272,273]. In patients with TNBC, tumors with high TILs after chemotherapy have a lower risk of recurrence than those with low TIL levels [274,275]. Overall, in TNBCs, an activated immune microenvironment with high TILs is positively correlated with improved effectiveness of chemotherapy.

## Vaccine-based therapies for breast cancer

Vaccine-based therapies are effective immunotherapies used to build antitumor immune system by submitting tumor-associated antigens (TAAs, Fig. 4). In the vaccine-based therapeutic process of breast cancer, the most striking example is HER-2 applied in several types of breast cancer vaccines [276].

### *Autologous cell-based vaccines*

Early autologous cell-based vaccines submit almost all tumor antigens through the use of whole autologous tumor cells or tumor cell lysates indiscriminately [277]. Scientists also use genes encoding costimulatory signals in combination with the vaccine to achieve T cell activation [278]. However, considering that T cells may preferentially process other antigens instead of TAAs, autologous cell-based vaccines are less effective than vaccines presenting specific antigens [279]. This type of vaccine requires to generate individualised vaccines for each patient, which is not a convenient method. Most of all, autologous cell-based vaccines contain normal somatic cell antigens that may induce an autoimmune response [280]. Lapuleucel-T, an autologous cell-based vaccine, has antigen constructs that consist of HER2 protein sequences. The vaccine therapy is well tolerated with no major adverse effect in the phase I clinical trial in breast cancer. This study suggests that autologous cell-based vaccines are feasible and opens an avenue to further investigation in tumor immunotherapy [281].

### *Dendritic cell (DC)-based vaccines*

DCs are efficient APCs that can activate the host immune system, making them an ideal vehicle for tumor vaccines [282]. Most of DC vaccines are made by generating DCs, loading TAAs, or transfecting associated genes [283]. Although DC vaccines have many advantages, several main challenges associated with *ex vivo* DC vaccine preparation have limited development, such as lacking a good manufacturing practice facility and a relatively simple process.

However, a large number of DC vaccines are used in solid tumor with inconsistent results [284–286]. In animal studies, scientists have injected DCs with a nonsignaling neu oncogene (i.e., HER-2) into mice with the overexpression of HER2. This result shows that compared with

all mice in the control groups, only 35% of vaccinated mice have developed breast tumors after 28 weeks [287].

*Peptide-based vaccines*

Peptide vaccines are divided into single- and long-peptide vaccines. Single-peptide vaccines play a role in cellular immunity via the major histocompatibilty complex class I (MHC I). However, the vaccine is only effective for certain patients because of the MHC I restriction [280]. Besides, the immune response activated by single-peptide vaccines may be short lasting and easy to tolerate [288]. Peptide vaccines are generally used with adjuvants or designed as DC vaccines to defeat these drawbacks.

The long-peptide vaccines, which elicit intense immune reactions and MHC II-restricted T cell activation, are being investigated. Protein vaccines containing whole HER2 protein have appeared. These vaccines contain MHC I and MHC II epitopes and activate most $CD4^+$ T cells and relatively few $CD8^+$ T cells in patients with breast cancer [289].

*DNA-based vaccines*

DNA-based vaccines are typically provided as plasmids either with viral vectors or naked. Once these vaccines are injected, plasmids are integrated to APCs for protein translation and submission to immune cells. Hence, DNA-based vaccines can overcome weak immunogen and tolerance, which occur when peptide or cell-based vaccines are used. Vaccinia and other pox viruses are the most appropriate viral vectors because they have enough size to accommodate numerous genes coding TAAs and costimulatory molecules [290,291]. Although DNA vaccines are easy and inexpensive to construct, their performance is unsatisfactory. This finding may be because of the difficulty in expressing enough exogenous genes to activate effective immune responses in APCs [292].

HER2 DNA vaccines are used in clinical trial without serious adverse toxicity in patients with breast cancer after therapy. This result shows that these HER2 DNA vaccines are safe and effective to activate long-lasting immune responses in patients with breast cancer [293].

## Role of cancer stem cells (CSCs) in metabolism and immunity

### CSCs and metabolism

CSCs may represent an important mechanism of tumor recurrence and metastasis. Two main viewpoints exist on the glucose metabolism of CSCs. On the one hand, many studies suggest that the glycolytic switch plays a critical role in CSCs. CSCs are more dependent on the Warburg

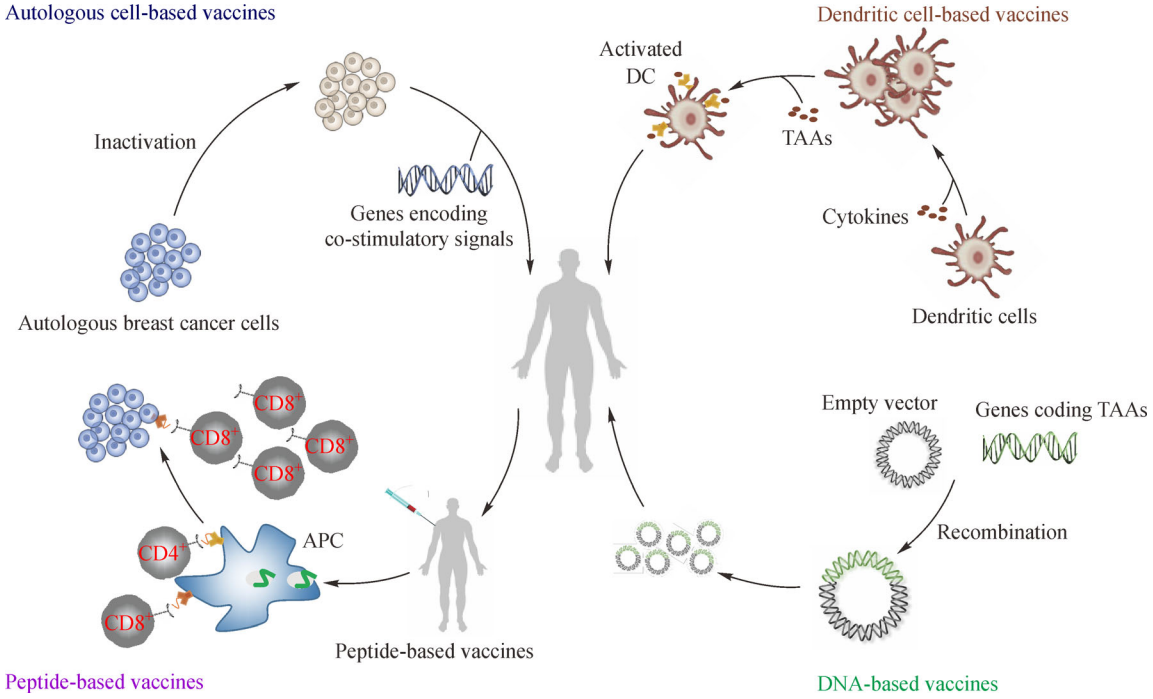


**Fig. 4** Vaccine-based therapies for breast cancer. The autologous cell-based vaccines uses the whole autologous tumor cells, which can submit almost all tumor antigens. Dendritic cell-based vaccines are finished following DC generation, TAA loading, or associated gene transfection. Peptide-based vaccines contain MHC I and MHC II epitopes and activate most $CD4^+$ T cells and relatively few $CD8^+$ T cells. DNA-based vaccines are usually delivered in the form of plasmids. Abbreviations: TAAs, tumor-associated antigens; APC, antigen-presenting cells.

effect than normal cancer cells [294]. CD44, a marker of CSCs, enhances the glycolytic phenotype by interacting with PKM2 in breast cancer [295,296]. In turn, glucose increases the population of CSCs by inhibiting the ATP-mediated AMPK pathway suppression and activating the Akt pathway [297]. On the other hand, several lines of evidence demonstrate that quiescent CSCs rely heavily on mitochondrial respiration rather than glycolysis [298,299]. In TNBC, oxidative phosphorylation may confer CSC resistance to chemotherapy, which is regulated by MYC and MCL1 [300].

CSCs also have a reliance on glutamine- and lipid-associated pathways in addition to glucose metabolism. High lipid droplets are observed in colorectal CSCs and BCSCs and confer CSCs with high tumorigenic potential [301]. In addition, blocking FAO resensitizes breast cancers to chemotherapy by decreasing BCSCs, suggesting that FAO is an important mechanism for CSC maintenance and chemotherapy resistance in breast cancer [302].

### CSCs and immunity

Besides the alteration of tumor microenvironment, the antitumor immunity is suppressed by CSCs. Glioblastoma multiforme (GBM) is a rapidly growing malignant brain tumor, and its CSCs are the classic models for the research of CSCs. GBM CSCs can modulate the immune cells in the tumor microenvironment to support the malignant phenotype of the tumor. For instance, GBM CSCs mediate the recruitment of TAMs and the suppression of T cell activation during chemotherapy [303]. Notably, TAMs can directly enhance the tumor-initiating capacity of CSCs by activating the transcription factor STAT3 [304].

CSCs avoid immune-mediated rejection *in vivo* by reducing immunogenicity. CSCs are found to express less MHC-I, MHC-II, and natural killer group 2 member D ligand molecules compared with normal stem cells [305,306]. In addition, CSCs express PD-L1 instead of the costimulatory molecules [307]. Moreover, PD-L1 can raise the expression of embryonic stem cell factors in BCSCs by activating the PI3K/AKT pathway. The decreased expression of PD-L1 impairs the ability of BCSCs to self-renewal *in vitro* and *in vivo* [308].

## Interplay between metabolism and immunity in cancer

### The metabolic microenvironment suppresses tumor immunity

Recent studies reveal that the dysfunctional immunity is closely associated with abnormal metabolism in various cancer types (Fig. 5). The abnormal metabolism of cancer cells creates an extreme environment characterized by acidity, hypoxia, and immunosuppressive metabolites. In this abnormal metabolic microenvironment, immune cells are deprived of nutrients and undergo metabolic changes that influence their activation.

Macrophages play a crucial role in cancer progression. Under the influence of inflammatory tumor microenvironment, the phenotype of macrophages varies from M1 (antitumor phenotype) to M2 (promoting tumor phenotype) [309,310]. The M1 phenotype is characterized by microbicidal functions by producing inflammatory cytokines and reactive oxygen intermediates. By contrast, the M2 phenotype is characterized by immunosuppression and tissue remodeling by producing anti-inflammatory cytokines. In metabolism, M1 maintains energy metabolism through anaerobic glycolysis, PPP, and FA biosynthesis, whereas M2 relies on OXPHOS [311]. Most of tumor-associated macrophages (TAMs) are generally regarded as the M2 phenotype. Macrophages are sensitive to changes in oxygen supply. M2 macrophages are concentrated in hypoxic tumor areas, and M1 macrophages are concentrated in normoxic areas. Mechanistically, hypoxia recruits TAMs in the hypoxia region by triggering the phosphorylation of the vascular endothelial growth factor (VEGF) receptor [312]. HIF1 is overexpressed and essential to regulate glycolysis in macrophages to support their phenotype and function in hypoxic areas [313,314]. In addition, lactic acid plays a critical role in inducing macrophages to transform into TAMs [315]. In turn, hypoxic TAMs express HIF1 and secrete proteolytic enzymes, thus promoting cell proliferation and metastasis [316]. The arginase 1 expressed by lactate-induced macrophages can promote tumor growth. Furthermore, the accumulation of lactate can decrease the production of type I IFN to suppress tumor-associated immunity [317].

Besides macrophages, T cells also play vital roles in the host immune response to cancer cells. Naive T cells ingest small amounts of glucose and utilize OXPHOS to meet their energy needs, whereas effector T cells upregulate glycolysis and glutaminolysis to support rapid proliferation and function [309]. The glycolysis enzyme GAPDH binds to AU-rich elements in the 3′ UTRs of IFNγ and inhibits its expression. The increase in the Warburg effect can eliminate the GAPDH function of inhibiting translation [318]. AMPK, which is activated by the increased AMP/ATP ratio in the absence of nutrients, also suppresses the IFNγ mRNA translation [319]. The high metabolism of tumor cells and the poor vascular system within tumors lead to the deficiency of nutrients in the microenvironment. This microenvironment prevents T cells from increasing glycolysis and impairs TCR signaling, thus suppressing their function. However, Treg cells gain energy through FAO rather than glycolysis, whose characteristic helps Treg cells survive and exert their immunosuppressive effect on abnormal metabolic microenvironment [320]. In

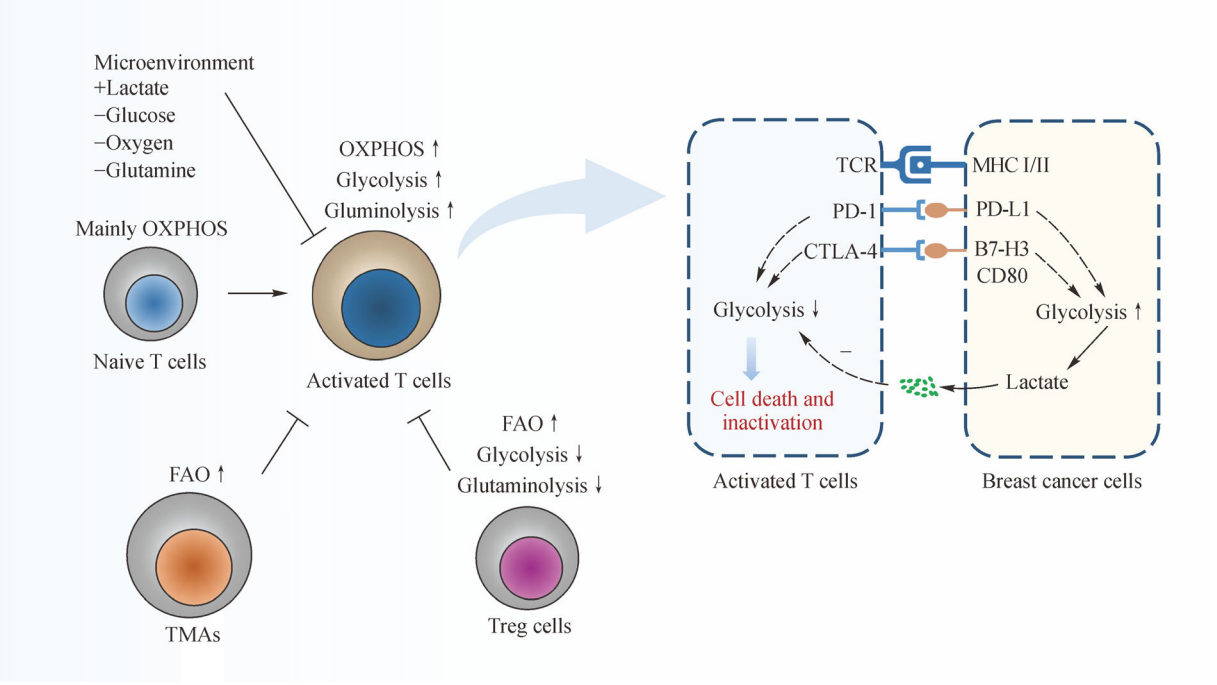


**Fig. 5** Interplay between metabolism and immunity in cancer. On the one hand, abnormal metabolism in cancer cells creates a tumor microenvironment characterized by hypoxia, nutrient depletion, and acidic pH. This microenvironment can prevent T cells from increasing glycolysis and impair TCR signaling, thus suppressing their function. However, TAMs and Treg cells gain energy through fatty acid oxidation rather than glycolysis, whose characteristic helps them survive and exert their immunosuppressive effect. On the other hand, PD-1 and CTLA-4 can inhibit glycolysis in T cells, thus promoting cell death and inactivation. Furthermore, the expression levels of B7-H3 and PD-L1 promote glucose uptake, glucose utilization, and lactate production in breast cancer cells. Abbreviations: OXPHOS, oxidative phosphorylation; FAO, fatty acid oxidation; TCR, T cell receptor; MHC, major histocompatibilty complex class; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4.

addition, the accumulation of metabolites, such as lactic acid and amino acid metabolites, contributes to inhibiting T cell activation and promoting Treg cells [321]. Furthermore, HIF1α can induce the proliferation of Treg cells and PD-L1-overexpressing cancer cells [322].

### The immune system adjusts T cell and cancer cell metabolism

Aside from directly killing cancer cells, the effect of immune system on the abnormal metabolism of cancer cells is emerging. The CD28/B7 family plays an important role in regulating tumor and T cell metabolism.

CD28 plays a key role in increasing glucose uptake and glycolysis via the PI3K/AKT serine/threonine kinase (AKT) signaling pathways, allowing T cells to sustain active response [323]. Recent studies demonstrate that the PD-1 signaling pathway is involved in the FAO in T cells [324]. In response to PD-1 signals, T cells utilize increased FAO to generate the energy required for activation instead of glycolysis, glutaminolysis, or another metabolism. PD-1 promotes FAO and lipolysis by increasing the expression of CPT1A and ATGL. CTLA-4 can inhibit glycolysis without augmenting FAO [324]. Antibodies against PD-1 or CTLA-4 can restore the glucose concentration in the tumor microenvironment, which promotes T cell glycolysis and immune factor production [325]. However, this phenomenon still cannot be fully explained by molecular mechanisms.

The function of PD-L1 in breast cancer also needs to be further explored. The depletion of PD-L1 can reduce the glycolysis rate by decreasing the mTOR activity and the glycolytic enzyme expression, suggesting that PD-L1 may play a crucial role in the glucose utilization in cancer cells [325,326]. Moreover, the overexpressed B7-H3 promotes glucose uptake and lactate production in breast cancer. One of the mechanisms may be that B7-H3 can upregulate the levels of HIF-1α and its target genes, namely, LDHA and PDK1 [327].

## Conclusions and prospects

In conclusion, recent breakthroughs have tremendously refreshed our understanding of the interaction between reprogramming metabolism and the antitumor immune system during breast cancer development. Although the abnormal metabolism and immunity of cancer has emerged

as two revolutionary strategies in breast cancer, most of the related pathways between them remain unknown.

In the aspect of metabolism, breast cancer cells have a high level of energy metabolism. Breast cancer cells enhance the Warburg effect to produce energy and lactate for sustaining proliferation and tumor microenvironment. Breast cancer cells also utilize lipid metabolism and other glucose metabolism, such as TCA and PPP, to gain vital compounds for sustaining the organism. Glutamine is also elevated and protects cells from ROS elevation and apoptosis in breast cancer cells. As for immune changes associated with breast cancer, CTLA4, PD-1/PD-L1, and TILs have been studied deeply, and novel and effective clinical treatments have been developed for patients with breast cancer. In addition, BCSCs have distinctive metabolism and immune response compared with breast cancer cells. In general, the unique tumor microenvironment caused by abnormal metabolism suppresses the antitumor immunity. The effect of immunity on metabolism is still largely unknown but is becoming the hot spot.

With the gradual research of immunotherapy and metabolic therapy, the next generation of anticancer drugs should obtain the dual effect of remodeling tumor metabolism and activating host immunity [328]. For example, metformin possesses multiple mechanisms of restraining breast cancer [329,330]. Metformin promotes the HIF1α degradation by increasing the cellular oxygen content, thus inhibiting cancer cell growth [331]. Furthermore, metformin maintains the activity of antitumor immunity by inhibiting PD-L1 expression in endometrial and breast cancers. This phenomenon is dependent on the mechanism that activated AMPK by metformin directly phosphorylates PD-L1. The phosphorylation of PD-L1 leads to its glycosylation and subsequent degradation through the endoplasmic reticulum-associated protein degradation pathway [332,333]. However, the actual clinical effect is not as effective as the expected theoretical mechanism. The treatment of breast cancer still lacks an ideal and more effective drug than metformin.

Overall, metabolism and immunity share certain oncogenes, signal pathways, tumor microenvironment, important related functions, and further elucidation is needed.

## Compliance with ethics guidelines

Deyu Zhang, Xiaojie Xu, and Qinong Ye declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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