REVIEW

Breast cancer therapy: from the perspective of glucose metabolism and glycosylation

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Abstract

Breast cancer is a leading cause of mortality and the most prevalent form of malignant tumor among women worldwide. Breast cancer cells exhibit an elevated glycolysis and altered glucose metabolism. Moreover, these cells display abnormal glycosylation patterns, influencing invasion, proliferation, metastasis, and drug resistance. Consequently, targeting glycolysis and mitigating abnormal glycosylation represent key therapeutic strategies for breast cancer. This review underscores the importance of protein glycosylation and glucose metabolism alterations in breast cancer. The current research efforts in developing effective interventions targeting glycolysis and glycosylation are further discussed.

Keywords Breast cancer · Glucose metabolism · Glycosylation · Glycolysis

Introduction

In 2020, the global incidence of cancer reached 19.3 million new cases, resulting in nearly 10 million deaths. Among these cases, breast cancer is the most prevalent type of malignant tumor [1, 2] and remains a prominent cause of mortality among women worldwide, posing significant threats to their well-being [3]. Physiologically, normal breast ducts consist of basal membrane, luminal epithelial cells, and myoepithelial cells. However, the onset of breast cancer is marked by myoepithelial cell shrinkage, stromal cell proliferation, and basement membrane degradation [4–6]. As the

basement membrane and myoepithelial cells diminish, cancer cells can invade neighboring tissues. The mortality in most breast cancer cases is attributed to metastasis to critical organs such as the brain, liver, lungs, and bones, leading to compromised organ function and eventual demise [7]. Breast cancer is characterized by heterogeneity, comprising various subtypes with distinct morphological and clinical characteristics. Among these, ductal carcinoma arising from breast epithelial cells is the predominant subtype [8, 9]. Clinically, breast cancer cells are classified into four subtypes according to their expression levels of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), commonly known as Luminal A, Luminal B, HER2-positive, and triple-negative breast cancer (TNBC) [10]. Among these subtypes, Luminal A breast cancer patients constitute the largest number with the most favorable prognosis, whereas TNBC patients exhibit the worst prognosis [11].

Carbohydrates provide nutrients and calories for the body. When carbohydrates are digested, they are converted to glucose. Previous studies have found altered glucose metabolism and abnormal glycosylation in breast cancer cells [12, 13]. On the one hand, the modified glucose metabolism in these cells primarily occurs via the glycolytic pathway, which provides cells with sufficient energy and promotes their proliferative capacity, thus contributing to the development of breast cancer. On the other hand, abnormal glucose metabolism or aerobic glycolysis may

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also alter the glycosylation profile of cancer cells, which in turn affects tumor growth, invasion, and metastasis [14, 15]. This review elucidates the impact of glucose metabolism and glycosylation in breast cancer cells and discuss potential therapeutic interventions targeting these alterations.

Glucose metabolism in breast cancer cells - Warburg effect

Glucose serves as a vital nutrient essential for cell growth. In normal breast cells, glucose metabolism predominantly involves the tricarboxylic acid (TCA) cycle in mitochondria, the glycolysis pathway, and the pentose phosphate pathway (PPP) in the cytoplasm. A critical step in glucose metabolism is the phosphorylation of glucose to glucose-6-phosphate by hexokinase (HK). The resulting glucose-6-phosphate not only participates in glycolysis but also intersects with the PPP, glycogen synthesis, and hexosamine biosynthesis pathway (HBP) [16]. In addition, glycolytic intermediates may participate in other metabolic pathways, such as the serine pathway, to provide the energy and substances necessary for cell proliferation [17].

Cancer development and progression represent intricate processes [18]. The alteration of the genome in a cell disrupts the normal processes of apoptosis and aging [19]. Cells proliferate indefinitely and autonomously change various metabolic pathways to satisfy their own and biosynthetic demands for large amounts of nutrients and energy [20]. The onset, progression, and metastasis of breast cancer are linked to metabolic reprogramming in tumor cells [21]. The energy metabolism of normal breast cells is mainly generated by oxidative phosphorylation, with only a small percentage coming from glycolysis [22].

Breast cancer cells exhibit heightened glucose uptake. Glucose metabolism is mainly dependent on glycolysis

and produces lactate (Fig. 1). This phenomenon is commonly referred to as the "Warburg effect" [23]. Worth noting, although glycolysis is an extremely important process in tumor cell metabolism, the metabolic reprogramming induced by increased glycolysis is uncommon in all cancers types, including various subtypes of breast cancer. For instance, analysis of gene expression signatures revealed significant variations in glycolysis scores among different cancer types. Some cancers exhibit elevated glycolysis levels, such as kidney renal clear cell carcinoma, head and neck squamous cell carcinoma, lung squamous cell carcinoma, and colon adenocarcinoma, while others, such as the thyroid carcinoma, prostate adenocarcinoma, stomach adenocarcinoma, and thymoma, demonstrate lower glycolysis levels [24].

Glycolysis

Glycolysis is an oxygen-independent metabolic pathway converting glucose to pyruvate, which occurs in the cytoplasm of most organisms [22, 25]. After being transported into the cytoplasm by glucose transporters, glucose is subsequently converted into fructose-1,6-bisphosphate by HK, glucose-6-phosphate isomerase, and phosphofructokinase. Aldolase then breaks down the 6-carbon skeleton of fructose-1,6-diphosphate to yield dihydroxyacetone phosphate and glyceraldehyde-3-phosphate. In addition, these two molecules can be transformed by triphosphate isomerase. After a series of reactions catalyzed by glyceraldehyde-3-propionate dehydrogenase, phosphoglycerate kinase, phosphoglycerate mutase, enolase, and pyruvate kinase, the glyceraldehyde-3-phosphate is metabolized into pyruvate and produces ATP.

In normal breast cells with adequate oxygen and functional mitochondria, pyruvate generated from glycolysis undergoes oxidation to form acetyl-CoA catalyzed by

Fig. 1 Comparing glucose metabolism between normal breast cells and breast cancer cells. Created with BioRender. com. GLUT: Glucose transporter; TCA: tricarboxylic acid; MCT4: monocarboxylate transporter 4
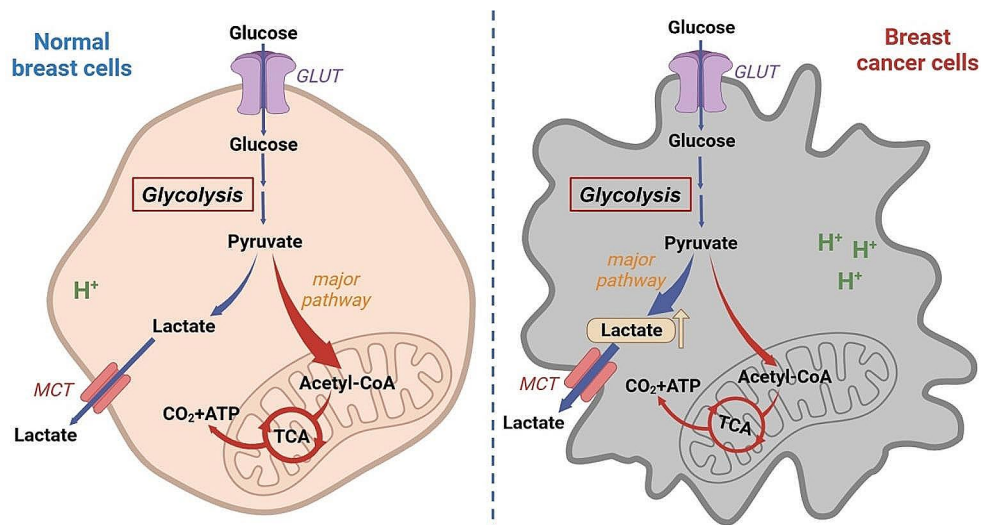
pyruvate dehydrogenase. Acetyl-coenzymes then enter the tricarboxylic acid (TCA) cycle, participating in oxidative phosphorylation (OXPHOS) to yield carbon dioxide and ATP. Conversely, OXPHOS is impeded under hypoxic conditions, leading to the conversion of pyruvate to lactate by lactate dehydrogenase (LDH). In addition, when mitochondria are defective, OXPHOS is reduced, and lactate production is increased.

For breast cancer cells, pyruvate generated from glycolysis is often converted to lactate even in the presence of oxygen, instead of entering the TCA cycle, which is referred to as "aerobic glycolysis" [26–28]. The lactate produced is extruded from the cell by the monocarboxylate transporter (MCT) to maintain intracellular pH stability [29].

Other glucose metabolic pathways

Pentose phosphate pathway (PPP)

The PPP is a metabolic route that occurs in conjunction with glycolysis [30], providing pentose phosphate for nucleic acid synthesis and NADPH for fatty acid synthesis and cell survival. Therefore, it plays a key role in cell growth [31]. It comprises two branches, an oxidative branch and a non-oxidative branch. The oxidative branch involves three irreversible reactions of glucose-6-phosphate, leading to the production of NADPH and ribulose 5-phosphate. Enzymes in this branch include 6-phosphogluconate dehydrogenase and glucose 6-phosphate dehydrogenase. The non-oxidizing branch produces pentose phosphate after a series of reactions, which is used in the synthesis of ribonucleotides. Additionally, this branch yields glycolytic intermediates like fructose 6-phosphate and glyceraldehyde 3-phosphate, crucial for amino acid synthesis. Enzymes in the non-oxidative branch include ribulose-5-phosphate epimerase, ribose 5-phosphate isomerase, transketolase, and transaldolase [32].

Hexosamine biosynthesis pathway (HBP)

HBP converts glucose into uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) through a six-step procedure. The final product UDP-GlcNAc can participate in protein modification [33]. Initially, glucose-6-phosphate from glycolysis is converted to fructose-6-phosphate by glucose-6-phosphate isomerase (GPI). Then, via fructose-6-phosphate amidotransferase (GFAT), glucosamine-6-phosphate N-acetyltransferase 1 (GNA1), phosphoglucomutase 3 (PGM3) and UDP-N-acetylhexosamine pyrophosphorylase (UAP), fructose-6-phosphate is converted to UDP-GlcNAc. UDP-GlcNAc is important substrate for not only N-glycan synthesis but also the formation of other monosaccharides

and eventually glycans. At the same time, UDP-GlcNAc plays a crucial role in promoting glycosylation as a key regulatory metabolite.

Research progress of glycolysis inhibitors in the treatment of breast cancer

Compared to normal breast cells, the energy metabolism of breast cancer cells increases. However, cells produce less ATP per glucose molecule, and cancer cells need to take up more glucose to meet their basic metabolic needs. Glycolysis serves as the main pathway of sugar metabolism in tumor cells, and the use of this process to develop anticancer drugs has been recognized as a viable approach [27]. Therefore, targeting glucose uptake characteristics of tumor cells to impede glucose utilization and consequently disrupt energy supply represents a therapeutic strategy for breast cancer. At present, research has identified several anti-glycolysis drugs for breast cancer treatment, targeting glucose transporters (Table 1) or enzymes involved in glycolysis (Table 2).

Inhibitors targeting glucose transporters (SGLTs and GLUTs)

The transportation of glucose into cancer cells requires glucose transporters. Two major glucose transporters have been identified including glucose transporters (GLUTs) and sodium-glucose cotransporters (SGLTs) [34]. Among them, GLUTs transport glucose along the concentration gradient, while SGLTs use the electrochemical gradient of Na^+ to actively transport glucose. It is noteworthy that the magnitude of extracellular glucose concentration is independent of glucose transport by SGLTs [35].

SGLT1 and SGLT2 are expressed in breast cancer cells compared to normal breast cells. For SGLT1, in vitro experiments have shown that down-regulating of SGLT1 levels inhibits cell growth in breast cancer cell lines of TNBC [36] or HER2-positive [37]. It has been reported that KGA-2727 [38] and mizagliflozin [39] are two specific SGLT1 inhibitors. Tsunokake et al. evaluated the impact of mizagliflozin and KGA-2727 on breast cancer MCF-7 and MDA-MB-468 cells, respectively, and found an inhibition of cell proliferation by these two inhibitors. In addition, mizagliflozin also exhibited inhibitory effects on MCF-7 cell proliferation under low glucose conditions [35]. For SGLT2, canagliflozin [40], dapagliflozin [40] and ipragliflozin [41] have been reported to serve as specific inhibitors of SGLT2, which have been applied to clinical treatment of type 2 diabetes. All these SGLT2 inhibitors can effectively suppress the growth of MCF-7 breast cancer cells.

The GLUT family consists of 14 members, including GLUT1-GLUT12, GLUT14 and the H^+/myo-inositol transporter [42]. Some of these members, such as GLUT1,

Table 1 Glucose transporters (GLUTs and SGLTs) inhibitors

Method		Inhibitor	Mode of action	Breast cancer type	State of development	Reference
Inhibitors of SGLTs	SGLT1 inhibitors	KGA-2727	Inhibited the proliferation of MCF-7 and MDA-MB-468 cells	Luminal A TNBC	Preclinical	[38]
		Mizagliflozin	Reduced the phosphorylation of VEGF R2 and inhibits glucose uptake	Luminal A TNBC	Phase II	[39]
	SGLT2 inhibitors	Canagliflozin	Decreased glucose uptake, activated AMPK signaling, inhibited mTOR pathway	Luminal A	marketed	[35]
		Dapagliflozin	Affected AMPK/mTOR signaling pathway, blocked cell cycle in G1/G0 phase and induced MCF-7 cell apoptosis	Luminal A	marketed	[40]
		Ipragliflozin	The proliferation of MCF-7 cells was reduced by membrane hyperpolarization and mitochondrial membrane instability	Luminal A	marketed	[41]
Inhibitors of GLUTs	Competitive indirect inhibition	2-deoxy-D-Glucose (2-DG)	Competing with glucose for transport of GLUT1 and GLUT4	Luminal A TNBC	Phase II	[45]
	Inhibition of GLUTs expression	Silibinin	Inhibition of GLUT1 expression	Luminal A	Phase III	[49]
		Quercetin	GLUT1 inhibitor, Inhibition of glycolysis through autophagy induction mediated by the Akt-mTOR pathway	Luminal A HER2 positive TNBC	Phase III	[51, 52]
		BAY-876	Decrease glucose uptake in triple negative breast cancer cell lines	TNBC	Preclinical	[53]
		Phloretin	GLUT2 inhibitor, inhibits cell growth in MDA-MB-231 cells and arrests the cell cycle in a p53 mutation-dependent manner	TNBC	Preclinical	[55]
		Kaempferol	Down-regulated GLUT1 mRNA expression	Luminal A	Phase I	[56]
		Indinavir	Inhibit GLUT4 uptake of glucose	TNBC	marketed	[57]
		Sorafenib	Inhibit mTORC1 pathway and reduce the expression level of GLUT1 protein	Luminal A HER2 positive TNBC	Phase I	[58]
		STF-31	GLUT1 inhibitor	TNBC	Preclinical	[59]
	Binds directly to glucose transporters	WZB117	Blocking glucose transport by binding to GLUT1 glucose binding sites	Luminal A	Preclinical	[62]

Table 2 Glycolytic enzyme inhibitors and MCTs inhibitors

Inhibitors of HK	2-DG	Interfere with glucose phosphorylation		Luminal A TNBC	Phase II	[63]
	Lonidamine (LN)	Inhibit HK, induce endoplasmic reticulum stress response, downregulate apoptosis inhibition protein, promote caspase-8 activation, reduce ATP levels		Luminal TNBC	Phase II	[64]
	3-Bromopyruvate (3-BrPA)	A HK inhibitor that inhibits glycolysis leading to ATP depletion and leads to apoptosis of MDA-MB-231 breast cancer cell line		TNBC	Phase I	[66]
	Genistein-27 (Gen-27)	Decreased the expression of HK2		TNBC	Preclinical	[67]
Inhibitors of GAPDH	3-BrPA	Selective inhibition of GAPDH leads to significant energy depletion and redox imbalance		TNBC	Phase I	[66]
Inhibitors of LDH	Gossypol	LDH-A inhibitor, induction of MCF-7 cell autophagy and promotion of apoptosis		Luminal A	Phase III	[72]
	Oxamate	LDH-A inhibitor		TNBC	Preclinical	[73]
Inhibitors of MCTs	AZD3965	MCT1 inhibitor		Luminal A	Phase I	[76]

GLUT2 and GLUT4, are overexpressed in breast cancer cells. Therefore, GLUTs are promising target for breast cancer treatment. By developing GLUT inhibitors to block the GLUT-mediated transportation of glucose into cells, the growth of cancer cells is inhibited or apoptosis is activated, so as to achieve therapeutic effect.

It is important to note that GLUT inhibitors function in diverse ways. For example, 2-deoxy-D-glucose (2-DG) is a glucose analog and indirect inhibitor that interferes with GLUTs by competing with glucose. 2-DG serves as a glycolysis inhibitor in glucose metabolism [43]. It inhibits glucose uptake by cells through competitive binding with GLUTs, thereby reducing glucose transport efficiency [44]. Although 2-DG exerts anti-proliferative activity in breast cancer cells (MCF-7, MDA-MB-231), the inhibitory effect of 2-DG alone was not significant. Studies have shown that the use of 2-DG in combination therapy can enhance the chemical sensitivity of breast cancer cells [45]. Andrad-vieira et al. inhibited the mechanistic target of rapamycin (mTOR) pathway and glycolytic metabolism after combined administration of AZD8055 and 2-DG, thereby reducing the growth of breast cancer cells [46]. The addition of 2-DG makes tumor cells more sensitive to the inhibition of mTOR signaling pathway. In addition, although 2-DG is overall safe, previous study has shown that high doses of 2-DG can reduce blood pressure and respiratory rate in animals [47].

There are inhibitors and drugs that inhibit GLUTs expression. Silibinin is a GLUT inhibitor and a natural flavonoid with diverse biological activities [48]. Studies have shown that Silibinin inhibits GLUT1 expression through up-regulation of Bak, P53 and p21 and down-regulation of Bcl-xl, affects the proliferation of Luminal A (MCF7) breast cancer cells, induces apoptosis, and halts the cell cycle in the G0/G1 phase [49]. However, due to the poor bioavailability of Silibinin, high doses are required to exert significant inhibitory effects, halting it in the phase I clinical trial stage [50]. Quercetin is another natural polyphenolic compound with GLUT inhibiting effect. Studies have found that Quercetin can reduce the level of GLUT in MCF-7 and MDA-MB-231 cells and reduce glucose uptake [51]. Compared with other glucose transport proteins, BAY-876, an inhibitor with high selectivity for GLUT1, is currently in the preclinical research stage [53]. Wu et al. found that there was a RB1 protein in TNBC cell line, and the expression level of the protein was related to GLUT1. The experiment showed that BAY-876 could block the expression level of RB1 protein [54]. In addition, Phloretin [55], Kaempferol [56], Indinavir [57], Sorafenib [58], and STF-31 [59] have also been found to inhibit GLUTs.

In addition to the inhibitors described above, there are some drugs that bind directly to GLUTs, thereby blocking GLUTs from functioning. WZB117 is a specific GLUT1 inhibitor, which can effectively block the transportation of glucose and reduce the level of intracellular ATP, thus achieving anti-proliferation effect [60]. However, WZB117 alone was not effective in inducing apoptosis. De et al. adopted the combined treatment method, and the prepared polymer (WZB117-OCMC-MET) could double target GLUT1 and mammalian target of rapamycin pathway to change the metabolism of breast cancer cells and improve the therapeutic effect [61].

Drugs targeting the glycolysis process

When glucose enters cancer cells, glycolysis and other pathways occur. The initial enzyme involved in the glycolysis process is HK, which catalyzes the rate-limiting phosphorylation of glucose to produce glucose 6-phosphate, which activates and carries out subsequent glycolysis or PPP. 2-DG is not only a GLUT inhibitor, but also a representative HK inhibitor. It interferes with glucose phosphorylation by competing with glucose-6-phosphate after entering the cell via GLUTs. In addition, 2-DG phosphorylated by HK, the product 2-deoxyglucose-6-phosphate, cannot be further metabolized by cells and gradually accumulates in cells, reducing the production of ATP [63]. Lonidamine (LN), an indole derivative and HK inhibitor, shows promise in breast cancer treatment. Studies have shown that LN can inhibit HK, induce endoplasmic reticulum stress response, down-regulate apoptosis inhibitory proteins, and reduce ATP levels [64]. LN was found in early clinical trials to have significant toxicities on the hepatic and pancreatic [65]. This prevents it from being formally used in the clinic. Therefore, in order to reduce the damage of LN to the liver, the research focus has been on the modification and local targeted delivery of LN. 3-Bromopyruvate (3-BrPA) can selectively inhibit HK and DAPDH, thereby inhibiting the glycolysis process, leading to ATP consumption and ultimately apoptosis [66]. Genistein-27 (GEN-27), an HK inhibitor, has been found to down-regulate HK2 expression in MDA-MB-231 breast cancer cells, inhibit glycolysis and promote apoptosis [67].

LDH includes two subtypes, LDH-A and LDH-B. LDH-A catalyzes the conversion of pyruvate to lactate during glycolysis. Cancer cells undergo glycolysis to produce excess lactate, which is associated with the upregulation of hypoxia-inducible factor-1α and c-Myc. This up-regulation subsequently increases LDH-A and MCT expression [68, 69]. Gossypol, an inhibitor of LDH-A, is a complex polyphenolic compound that occurs naturally in various parts of cotton plants, particularly in the seeds [70, 71]. There is evidence that gossypol can induce autophagy of MCF-7 cells and promote apoptosis [72].

The task of transporting lactate molecules outside the cell during glycolysis is performed by MCTs. Studies have

found that human breast cancer generally has high MCT1 expression [74, 75]. AZD3965 is a promising selective inhibitor of MCT1 and is currently in clinical trials. Previously, it has been shown that AZD3965 has a strong anti-cancer effect in breast cancer models [74]. Moreover, Benyahia et al. used representative Luminal A breast cancer cells (T-47D and MCF-7) and non-malignant cells (MCF-10 A and human BJ fibroblasts) and several behavioral tests in mice to determine the anti-cancer effects and safety of AZD3965 [76]. Phenotypic characterization of mice focusing on metabolism, muscle and brain physiology found partial and transient memory retention defect as the only side effect of AZD3965. At present, AZD3965 is still in the clinical trial stage and certain side effects have been reported. However, it is believed that the clinical safety of AZD3965 in inhibiting MCT1 can be established through continuous trials.

Although some of these drugs are still in the clinical trial stage, and some have been terminated due to adverse reactions. Nonetheless, these drugs serve as valuable references for the future discovery and development of effective and selective anti-breast cancer agents.

Abnormal glycosylation in breast cancer

Glycans and glycosylation

Glycans are important constituent of cells, mainly composed of monosaccharides, oligosaccharides or polysaccharides, and are key components of glycoproteins, glycosaminoglycans, proteoglycans and glycolipids on cell surfaces [77]. The synthesis of glycans in cells is promoted by hundreds of enzymes, including glycosyltransferase, glycosidase, and enzymes involved in sugar modification, metabolism, and transportation [78]. These enzymes attach specific sugar residues to new glycans, so the synthesis of glycans is not templated, which gives them a specific structure [79]. During protein synthesis, the presence of glycans ensures the stability of endoplasmic reticulum folding and participates in the distribution of newly synthesized proteins [80]. Characteristics of different cancers can be associated with aberrant glycan structure, including tumor cell growth, survival, migration, immune evasion, and drug resistance [81–83]. In addition, as tumors develop and progress, certain glycans covering the surface of cells will also change. So, we can monitor tumor progression based on changes in glycans.

Alterations in glycosylation represent a well-established hallmark of cancer [84]. Glycosylation not only influences cell migration, proliferation, adhesion and apoptosis but also plays an important role in cell matrix interactions, protease activities, and immune recognition [85]. Glycosylation

refers to the enzymatic process of attaching glycans to proteins, lipids or other sugars to produce glycoproteins, glycolipids, and proteoglycans. Glycosylation occurs in the endoplasmic reticulum and Golgi apparatus. When abnormal glycosylation occurs in the body, it induces a variety of pathological changes. In particular, aberrant glycosylation occurs in association with pathological changes occurring in epithelial-mesenchymal transition in tumor diseases [86]. Glycosylation is among the most prevalent forms of post-translational modifications of proteins [84]. According to the nature of glycosidic bond formation, protein glycosylation can be classified into O-glycosylation, N-glycosylation and GPI [87]. Among them, O-glycosylation and N-glycosylation are the two main types. O-glycosylation is also called mucin glycosylation [88]. O-glycosylation in which the attachment of glycans to the side chains of serine and threonine, and N-glycosylation refers to the attachment of polysaccharides to the side chain of asparagine [89]. The presence of glycosyltransferases and glycosidases plays a regulatory role in the glycosylation process.

Proteins undergo glycosylation to form glycoproteins. Therefore, glycosylation plays an important role in modifying protein and regulating protein function. On one hand, glycosylation does not affect the spatial structure of the protein. Studies have shown that protein glycosylation has little effect on the secondary structure of proteins [90, 91]. For example, Kajihara et al. used a semi-synthetic approach to obtain erythropoietin (EPO). The CD spectral analysis showed that glycoylation has no significant impact on the secondary structure of EPO [92]. In addition, experimental results showed that glycosylation does not cause major conformation changes of Fractalkine at room temperature [93]. On the other hand, glycosylation promotes the correct folding of protein, makes it more stable, and also impact its thermal stability and aggregation. Raines et al. recently evaluated the effect of N-glycosylation on ribonuclease 1 (RNase 1) and found that N-glycosylation of RNase 1 at any location can enhance the thermal stability of the protein and inhibit its hydrolysis [94].

Role of glycosylation in breast cancer

Glycosylation affects not only the proliferation but also the metastasis and survival of cancer cells. Firstly, abnormal glycosylation regulates glucose metabolism in breast cancer cells and accelerates the growth of tumor cells. Unlike normal cells, whose proliferation is regulated by precise signals, cancer cells can multiply indefinitely. The reason is that signal regulation in cancer cells is disrupted, which allows cancer cells to autonomously change metabolic pathways to obtain the energy needed for their own proliferation. For example, The final product of HBP pathway UDP-GlcNAc

can participate in O-linked/N-linked glycosylation and can also participate in O-GlcNAcylation as a substrate of O-GlcNAc transferase (OGT) [95]. A study has shown that the enhanced binding of O-GlcNAc acylated DNA topoisomerase IIα (TOP2A) to DNA enhances the interaction between TOP2A and cycle regulators such as CDK1 and UPF1, affecting the cell cycle process and ultimately promoting the proliferation of breast cancer cells [96]. In addition, OGT expression levels catalyzing O-GlcNAc acylation were elevated in breast cancer cells [97]. There is an ER-independent link between OGT and the transcription factor FOXA1, which promotes oglcn acylation at three FOXA1 sites (Thr^{432}, Ser^{441}, and Ser^{443}), thereby promoting breast cancer metastasis [98]. Therefore, the growth of tumor cells can be inhibited by reducing the level of OGT. In addition, by comparing the effects of OGT inhibition on the proliferation and survival of different subtypes of breast cancer cells, it was found that TNBC cell lines were more dependent on OGT [99].

Secondly, the glycosylation modifications affect cell-cell adhesion and mediates cell-matrix interactions. Tumor cells disrupt intercellular adhesion and invade surrounding tissues to promote breast cancer progression [100]. The transmembrane glycoprotein mucin 1 (MUC1) is the most easily identifiable transmembrane protein in the mucin family with a highly glycosylated extracellular domain. Normally, MUC1 forms a tight mesh structure and covers the surface of epithelial cells to protect the cells from extreme conditions [101–103]. However, in cancer cells, MUC1 expression is upregulated, leading to altered protein structure, glycosylation patterns, and spatial distribution. These changes in MUC1 are pivotal in the onset and progression of breast cancer and other malignancies. Abnormal glycosylation in the MUC1 makes the O-chain truncation, increased expression of Tn and STn, formation of new side chains, induction of carcinogenic characteristics of cells, and promotion of cell growth and invasion by disrupting intercellular adhesion contact [104]. Extracellular matrix (ECM) is a complex network composed of glycoproteins, glycosaminoglycans, collagen and proteoglycans, which influence tumor development and cancer progression [105]. Notably, integrins, pivotal cell surface adhesion glycoproteins, play a crucial role in ECM interactions and metastasis [106]. Evidence suggests that alterations in integrin glycosylation can modulate the adhesive properties of cancer cells [107]. It can be concluded that the alteration of integrin glycosylation may affect cell adhesion to ECM, and thus play a role in cell migration. Singh et al. examined the differential expression of integrins avb3 and avb6 in breast cancer cells and untransformed breast cells at two different disease stages. The results suggest the necessity of N-glycosylation on integrins for cell-ECM interactions [108].

Thirdly, glycosylation plays a role in the metastasis of breast cancer cells. More and more evidence has revealed the important role of abnormal glycosylation in malignant transformation and metastasis of tumors. Abnormal N-glycosylation can alter the three-dimensional structure of MUC1 and promote cancer cell migration [109]. However, there are also some glycoproteins that possess inhibitory effects on breast cancer metastasis. SGK196 is a transmembrane protein that is commonly expressed in skeletal muscle, brain, heart and kidney tissues. Studies have shown that SGK196 is mainly modified by N-glycosylation in breast cancer cells, and is a glycosylated specific kinase, which plays a role in inhibiting cell metastasis and invasion in breast cancer. Li et al. found that N-glycosylated SGK196 can inhibit the metastasis of BLBC cells. Through mechanism studies, it was found that N-glycosylated SGK196 plays a regulatory role through the PI3K/AKT/GSK3β signaling pathway [110]. This finding provides new insights into the function of SGK196 in breast cancer.

Drugs for treating breast cancer by inhibiting abnormal glycosylation

At present, breast cancer treatment mainly includes conventional therapy, immunotherapy and small-molecule inhibitors [111]. Conventional therapies refer to radiation therapy, chemotherapy and surgery, which have certain side effects and lack of specificity. Immunotherapy has clinical significance for the treatment of triple-negative breast cancer and HER2 positive breast cancer. In immunotherapy, the clinical application of therapeutic antibodies, including PD-L1 [112], CAR-T cell therapy [113], trastuzumab [114], and other clinical applications, has improved the survival rate of breast cancer patients. However, immunotherapy also has many disadvantages, such as high heterogeneity, laborious production and treatment resistance. Meanwhile, the use of small-molecule inhibitors also has the above disadvantages. It is considered that altered glycans play a role in the occurrence, progression, and metastasis of breast cancer. Therefore, targeted glycosylation has become one of the options to develop therapeutic agents for breast cancer.

Targeted glycosylation therapy for breast cancer can be divided into the following three categories, as shown in Table 3. The first category is synthetic monosaccharide analogs. Because cell membranes and secretory proteins are glycoproteins, small changes in the glycan chains may affect the function of the glycoconjugate, affecting cell adhesion, immune recognition, and the growth and metastasis of tumor cells [115]. Monosaccharide analogs with active groups are glycosylated after uptake by cells, and can then act as inhibitors to interfere with the formation of oligosaccharide chains [116, 117]. Currently, synthesized

Table 3 Targeted glycosylation inhibits breast cancer progression

Classification		Inhibitor	Mode of action	Breast cancer type	State of development	Reference
Monosaccharide analogs	Glucose analog	2-DG	Influencing the HBP pathway, blocking glucose-6-phosphate isomerase and playing an anti-cancer role in MCF7 and MDA-MB-231 breast cancer cells	Luminal A TNBC	Phase II	[121]
	GalNAcanalog	2-KetoGal	Change the structure of O-GalNAc to inhibit the spread of cancer cells	—	Preclinical	[119]
	Fucose analog	6-Azidofucose			Preclinical	[120]
glycosyltransferase/ glycoprotein inhibitors		FR054	Induces the decrease of intracellular UDP-GlcNAc, reduces N-glycan, and reduces the adhesion and migration of MDA-MB-231 cells	TNBC	Preclinical	[122]
		H89	Inhibit N-glycosylation, activate protein kinase A (PKA), and inhibit breast cancer cell migration	TNBC	Preclinical	[123]
Antibody drugs for glycosylation		Tunicamycin (TM)	Blocking the N-glycan formation step, that is, preventing the transfer of GlcNAc-1-P to dolichol-P	HER2 positive	Preclinical	[124]
		Erbitux	Inhibition of EGFR glycosylation, ERK1/2 signal pathway, significant downregulation FUT4 expression	HER2 positive	Phase II	[125]
		EGCG	Interfere with MUC1 production and inhibit O-glycosylation	Luminal A TNBC	Phase III	[127, 128]
		Ginsenoside Rg3	Inhibition of fucosylation	Luminal A TNBC	Preclinical	[130]
		NAC	Inhibition of fucosylation	TNBC	marketed	[131]

monosaccharide analogs include glucose analog 2-DG [118], GalNAc analog 2-KetoGal [119], and focusing analog 6-Azidofucose [120]. Among them, 2-DG is a monosaccharide analog that not only inhibits glycolysis, but also interferes with glycosylation [121]. In terms of glycosylation, 2-DG exerts anticancer effects in Luminal A (MCF7) and TNBC (MDA-MB-231) breast cancer cell lines by blocking glucose-6-phosphate isomerase. The second category involves glycosyltransferase/glycoprotein inhibitors. Because glycosylation refers to the process of attaching glycans to protein under the catalysis of enzymes. Therefore, enzymes or protein-related inhibitors involved in the glycosylation can compete with glycosyltransferase to participate in protein glycosylation, block the abnormal glycosylation process, and thus inhibit tumor cell metastasis. PGM3 is an enzyme involved in the HBP pathway which can be targeted by inhibitors. As a competitive inhibitor of PGM3, FR054 induces a decrease in intracellular UDP-GlcNAc, resulting in a decrease in N-glycans. Treatment of breast cancer cells with FR054 can induce apoptosis and reduce TNBC (MDA-MB-231 cells) adhesion and migration [122]. The third category is antibodies against glycosylation. Tunicamycin is an antibiotic. HER2 positive (SKBR-3 cells) can prevent the transfer of GLNAC-1-p to dolichol-P under tunicamycin. This is an important step in the production of N-glycans. Therefore, tunicamycin reduces cell responsiveness to growth factors by inhibiting N-glycosylation, thereby inhibiting cancer cell growth [124]. Erbitux is a lgG1 monoclonal antibody targeting EGFR. In Luminal breast cancer cell lines, EGFR was competitively blocked from binding to other ligands, EGFR glycosylation was inhibited, ERK1/2 signaling pathway was inhibited, and FUT4 expression was significantly down-regulated [125]. In summary, Erbitux plays an anticancer role by inhibiting fucosylation. Epigallocatechin gallate (EGCG) is the monomer with the highest content and biological activity in green tea [126]. In breast cancer cells, MUC1 expression is upregulated and protein glycosylation is altered. EGCG can interfere with the production of MUC1 and inhibit O-glycosylation. Studies have found that EGCG inhibits the expression of miR-25 in Luminal A (MCF-7 cells), induces cell cycle arrest in G2/M phase, and thus plays a role in apoptosis and inhibition of cell proliferation [127]. In addition, EGCG can inhibit the growth of TNBC (MDA-MB-231) cells and can be used as a potential therapeutic agent for TNBC patients [128]. Due to its low bioavailability and lack of targeting, the use of EGCG in clinical practice has been limited. However, EGCG can be used as a chemotherapy adjuvant to enhance the sensitivity of tumors to drugs [129]. Ginsenoside Rg3 [130] and N-acetylcysteine (NAC) [131] inhibited fucosylation in Luminal A (MCF7) and TNBC (MDA-MB-231) cell lines.

Links between glucose metabolism and glycosylation in breast cancer

The specific changes and effects of glucose metabolism and glycosylation in breast cancer have been described in the previous chapters. This also brings to light a question worth

pondering: Is there a link between altered glucose metabolism, or aerobic glycolysis, and abnormal glycosylation in cancer cells? There is evidence that these two processes can influence each other (Fig. 2). The HBP links glucose metabolism with abnormal glycosylation. An intermediate product of the glycolysis pathway (fructose-6-phosphate) is a critical reactant of HBP and a substrate for UDP-GlcNAc. The activation of GlcNAc forms UDP-GlcNAc, and UDP-GlcNAc is a metabolic precursor of UDP-GalNAc and CMP-sialic acid [132], which is used for the synthesis of N- and O-linked protein glycosylation and modification of O-GlcNAcylation [84, 133, 134]. Therefore, the UDP-GlcNAc concentration is critical for the glycosylation process. In addition, O-GlcNAC modifies PFK activity, thereby blocking glycolysis in cancer cells. This suggests that important metabolic reprogramming in cancer cells is carried out via O-GlcNAC [135]. It can be concluded that metabolism and glycosylation are interrelated and abnormal changes in cancer cells, providing the characteristic microenvironment of proliferation and metastasis for cancer cells.

In normal cells, HBP can strictly maintain UDP-GlcNAc levels in response to material fluctuations in cells, which establishing cell homeostasis [136]. In cancer cells, altered HBP fluxes lead to changes in glucose metabolism and abnormal glycosylation [137]. The level of enzymes involved in the HBP are often elevated in cancer cells [138]. GFAT is the main rate-limiting enzyme involved in HBP. When GFAT expression is up-regulated, HBP increases. Therefore, GFAT activity can regulate HBP flow [139]. Chanmee et al. found that GFAT expression is upregulated in breast cancer patients and is associated with overexpression of a cancer-related hyaluronan (HA) [140]. Chokchaitaweesuk et al. further demonstrated through animal experiments that HA overexpressing breast cancer cells rapidly progress to invasive breast cancer [139]. However, it is worth noting that GFAT inhibitors can also inhibit the synthesis of amino acids and so are not specific. In addition, some substances

that affect metabolism can also have an impact on the HBP pathway. For example, the glycolysis inhibitor 2-DG can also inhibit the phosphorylation of GFAT and reduce the generation of UDP-GlcNAc, thus affecting the glycosylation pathway [141]. How to design and use metabolic inhibitors to regulate HBP and play a therapeutic role needs to be further studied.

Conclusion and future perspectives

At present, breast cancer is still the main disease threatening women's life and health, affecting their quality of life. Glucose serves as the primary energy substrate for cancer cells, and a series of changes in the cell are worth studying. Existing studies have shown that alterations in glucose metabolic pathways (especially increased glycolysis) and abnormal glycosylation are associated with breast cancer progression. In addition, the HBP pathway links glucose metabolism to the process of glycosylation. Therefore, the inhibition of HBP pathway can also be considered in the future discovery and development of breast cancer drugs from the perspective of glucose changes. Moreover, although there are limited studies on the development of therapeutic agents for breast cancer by targeting glycolysis and inhibiting glycosylation, the existing studies still provide implications for the future development of novel agents against breast cancer. Much more importantly, considering the genetically heterogeneous nature of breast cancer involving complex heritable and somatic factors, future studies should focus on exploring different signaling networks associated with various breast cancer subtypes. This effort aims to clarify sensitivity to therapeutic agents and provide personalized benefits against breast cancer.

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Fig. 2 The HBP pathway links glycolysis and glycosylation. Created with PowerPoint. GLUT: Glucose transporter; HK: hexokinase; GPI: glucose-6-phosphate isomerase; GFAT: ructose-6-phosphate amidotransferase; GNA1: glucosamine-6-phosphate N-acetyltransferase 1; PGM3: phosphoglucomutase 3; UAP: UDP-N-acetylhexosamine pyrophosphorylase
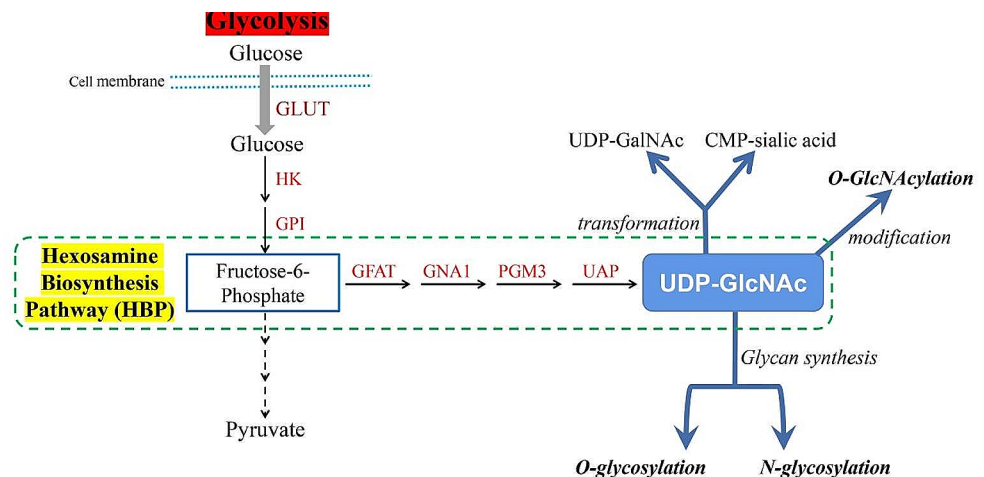
Declarations

Ethical approval Not applicable.

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