Metabolic Reprogramming Strategy Targeting Glucose Metabolism

Subjects: Biochemistry & Molecular Biology

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Diabetes is not only a risk factor for breast cancer but also worsens its prognosis. Patients with diabetes usually show hyperglycemia and hyperinsulinemia, which are accompanied by different glucose, protein, and lipid metabolism disorders. Metabolic abnormalities observed in diabetes can induce the occurrence and development of breast cancer. The changes in substrate availability and hormone environment not only create a favorable metabolic environment for tumorigenesis but also induce metabolic reprogramming events required for breast cancer cell transformation. Metabolic reprogramming is the basis for the development, swift proliferation, and survival of cancer cells. Metabolism must also be reprogrammed to support the energy requirements of the biosynthetic processes in cancer cells. In addition, metabolic reprogramming is essential to enable cancer cells to overcome apoptosis signals and promote invasion and metastasis.

diabetes breast cancer cancer metabolism

1. Background

Diabetes mellitus (DM) has always been one of the most common health conditions. In 2022, more than 11% of the US population was diagnosed with DM [1]. Meanwhile, breast cancer (BC) has the highest incidence among women's cancers [2]. Epidemiology studies have shown that DM increased BC risk in women by up to 20% [3] and raised its mortality rate significantly [4]. There are two main types of DM: Type 1 and Type 2. T1DM, also known as insulin-dependent DM, is caused by a lack of insulin production which hinders glucose uptake in the body. On the other hand, T2DM is described as insulin independent. It usually happens later in life when cells develop insulin resistance due to a sedentary lifestyle and poor dietary habits. Between 90% and 95% of DM belongs to T2DM.

The insulin resistance in DM causes hyperinsulinemia and hyperglycemia, further disrupting the body's regular metabolism. On the other hand, metabolic reprogramming occurs in cancer cells to enhance nutrient absorption, hence supporting their rapid proliferation rate. Recent therapeutic target research has focused on the similarities between the metabolic reprogramming of DM and BC, with the three main focuses being glucose, amino acid, and lipid metabolism [5]. Given the high prevalence of both diseases and the evident metabolic linkage between them, it is essential to discover a breakthrough treatment for this patient group.

2. MRS Targeting Glucose Metabolism

It is shown that hyperglycemia and hyperinsulinemia in DM promote BC progression [5]. Hyperglycemia supports BC cell growth by providing sufficient glucose for aerobic glycolysis, known as the “Warburg effect”. Under aerobic glycolysis, a large amount of lactate is produced to generate enough ATP to support rapid cancer cell proliferation [6]. Hyperinsulinemia in DM also promotes BC cell growth. Besides inducing glucose uptake, insulin plays a vital role in activating mTOR via the PI3K/AKT pathway. Activating mTORC1/2 increases mRNA translation, cellular growth, and cell proliferation and enhances cell survival [7]. Within the pathway, Akt and phospholipase Cγ play a key role in BC patient with diabetic conditions [8]. Many components of the metabolic pathway, such as transporters and kinases, have been found to have significant therapeutic potential as MRS targets for DM-associated BC. The possible target in glucose metabolism pathway for metabolic reprogramming of breast cancer is summarized in **Figure 1**.

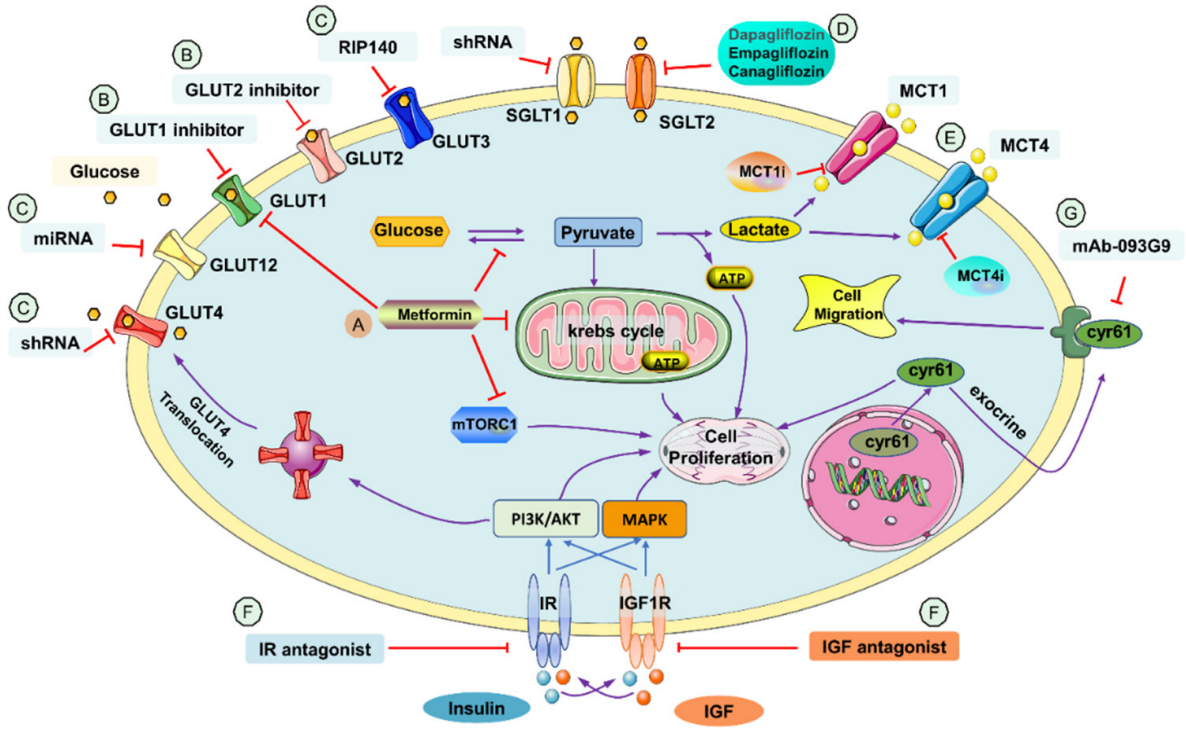

Figure 1. Potential targets of glucose metabolism pathway in metabolic reprogramming of breast cancer. Ⓐ Metformin’s mechanism of action in BC includes inhibiting GLUT1, inhibiting mTORC1, and shifting mitochondrial oxidative phosphorylation to aerobic glycolysis to increase the effect of MCT4i. Ⓑ GLUT1 and GLUT2 inhibitors inhibit the glucose influx to cancer cells. Ⓒ Downregulation of the transporter using transcriptional co-regulator RIP140, shRNA, and miRNA. There are no inhibitors of GLUT3, GLUT4 and GLUT12 suitable for BC yet. Ⓓ SGLT2 inhibitors inhibit the influx of glucose into BC cells. There is no selective SGLT1 inhibitor for BC yet but downregulation of the transporter by siRNA is found to be effective to inhibit BC growth. Ⓔ MCT1i inhibits the bidirectional transport of lactate. MCT4i inhibits lactate export, triggers intracellular acidification, and inhibits cell growth. Ⓕ IR and IGF-1R antagonists inhibit binding of insulin and IGF, thus inhibiting the mTOR signaling pathway which induces tumorigenesis. They also inhibit glucose uptake in cells. Ⓖ IGF1R triggers the PI3K/AKT and MAPK pathway which induces Cyr61 transcription and promotes BC growth. Antibody 093G9 is a potential therapy inhibiting Cyrs61.

2.1. Metformin

Metformin is best known as a diabetic drug, but it has also been proved useful as a treatment in BC. It has two main mechanisms to carry out its anti-diabetic and anti-tumorigenic effect: the AMPK-dependent and -independent pathway. In the AMPK-dependent pathway, AMPK increases glucose uptake and reduces gluconeogenesis, thus improving glycemic control. Moreover, it inhibits mTORC1, which induces BC cell proliferation. For the AMPK-independent pathway, metformin regulates oncogenes and tumor suppressor genes. Anti-tumorigenic effects targeting the reactive oxygen species, NF-kB, and cell cycle regulatory proteins are also carried out [9]. However, despite the encouraging results of metformin on BC from preclinical research, several clinical trials on BC patients without DM show no significant improvement in patient survival [10][11]. Further clinical trials are required on DM-associated BC patients to better understand its therapeutic potential.

Recent studies have shown that when metformin is used in combination with other therapeutic drugs, its effectiveness will be improved. For example, glucagon-like peptide-1 receptor agonist exendin-4 (Ex-4), another anti-diabetic drug, has been proven to be effective for BC when used in combination with metformin [12] by inhibiting NF-κB [13] and modulating different RNA gene expression [12].

MCT4 inhibitor is another potential drug candidate that can be used in combination with metformin. As lactate is produced from aerobic glycolysis in cancer cells, MCT4 maintains intracellular pH balance by exporting lactate out of cells. A novel MRS uses metformin and NF-κB inhibitor to further enhance the rate of aerobic glycolysis and increase the amount of lactate produced. With the addition of an MCT4 inhibitor, lactate accumulation decreases intracellular pH and achieves cytotoxicity by intracellular acidification [14]. Another study has shown that BC chemotherapies, such as paclitaxel and doxorubicin, have a lower efficacy in diabetic patients under metformin treatment as a large amount of lactate produced is pumped out of cells by MCT4, hence inducing extracellular acidosis, which inhibits doxorubicin's uptake. MCT4 inhibitors can potentially improve chemotherapy response in DM-associated BC patients by regulating the extracellular pH [15].

2.2. GLUT Inhibitor

Glucose is one of the most important energy sources of BC cells, especially under the hyperglycemic condition in DM patients. Therefore, regulating glucose transporters is another research direction for DM-associated BC. Fourteen glucose transporters have currently been discovered [16].

GLUT1 is well known to be upregulated in BC cell lines [17] and plays a significant role in glucose uptake in BC tissues. The oncogenic factors in DM, such as insulin, glucose, INF-γ, and oxidative stress, are found to be mediated by GLUT1 to produce its effect [18]. A recent study has confirmed the effectiveness of GLUT1 inhibitors in hindering the growth of triple-negative breast cancer (TNBC), one of the deadliest subtypes of BC, by inhibiting glucose influx to undergo glycolysis [19]. Given the great potential of a GLUT1 inhibitor in BC, there are numerous ongoing studies about the inhibition of GLUT1, involving both synthetic agents, natural compounds and registered drugs such as metformin [20].

GLUT2, as a low-affinity glucose transporter, works well in high glucose concentrations [21]. It is also found to be present in some BC cell lines. Natural compounds, including phloretin and cytochalasin B, are effective as GLUT2 inhibitors to reduce glucose uptake in BC cell lines such as MDA-MB-231 [22] and MCF-7 [23].

GLUT3 is also a transporter in numerous cancer cells, especially under hypoxic conditions [17]. New findings have pointed out that downregulation of it can inhibit glycolysis and proliferation of BC [24]. It is a poor prognostic factor of BC [25].

GLUT4 is an insulin-dependent transporter [26]. It translocates to the membrane only in the presence of insulin. GLUT4 inhibition induces metabolic reprogramming, shifts glycolysis to oxidative phosphorylation, and lowers BC's proliferation rate under hypoxic conditions [27]. However, studies have shown that the downregulation of GLUT4 worsens DM progression as it hinders glucose uptake and causes peripheral insulin resistance and poorer glycemic control [28]. Recent studies have shown that, different from BC, it is important to increase the expression of GLUT4 via pharmaceutical and dietary means to improve the diabetic condition [29]. Therefore, despite the success of GLUT4 inhibition therapy in BC, GLUT4 may not be a suitable drug target for BC patients with concurrent DM.

GLUT12, an insulin and glucose-sensitive transporter, was first found in BC cell lines [30]. Lowering the expression of GLUT12 has been proven to inhibit TNBC cell proliferation by decreasing glucose uptake and inhibiting aerobic glycolysis [31]. More importantly, GLUT12 plays an essential role in BC progression under hyperglycemic conditions by detecting high glucose environments and assisting in the migration of MCF-7 cells [32]. However, GLUT12, the same as GLUT4, is an insulin-sensitive glucose transporter. A high level of GLUT12 is essential to maintain insulin sensitivity in diabetic patients [33], contraindicating the fact that inhibiting GLUT12 helps treat BC cells. Therefore, GLUT12 may not be a suitable target for DM-associated BC.

2.3. SGLT Inhibitor

Sodium-glucose cotransporter-2 (SGLT2) is a key transporter located in the proximal convoluted tubules of the kidneys [34]. It is responsible for glucose reabsorption and plays an essential role in the glycemic control of our body [34]. As its name suggests, the transporter exports glucose from the cell to circulation with the help of sodium ions to create an electrochemical gradient [35]. Given its importance in glycemic control, several SGLT2 inhibitors are already approved by FDA and used in DM patients, including canagliflozin, ipragliflozin, empagliflozin, dapagliflozin, and ertugliflozin. They work by inhibiting glucose reabsorption in the kidney and increasing renal glucose excretion [36].

SGLT2 inhibitors are also found to be effective in treating BC via various mechanisms. Although SGLT2s are typically expressed in renal cells, several studies have discovered their presence in BC cells [37][38]. Ipragliflozin can inhibit glucose and sodium influx into cells, hyperpolarize cancer cells' membranes, and hinder cancer cell growth [37]. Other SGLT2 inhibitors, Canagliflozin and Dapagliflozin, can inhibit BC proliferation by inducing nutrient deficiency and cell cycle arrest [38]. Dapagliflozin is also an effective agent in ameliorating hyperinsulinemia, which

causes BC progression in DM patients [39]. However, the inhibitors' effect is limited to BC with a specific mutation, namely Pten-driven EMT6 tumors and HRAS-driven Ac711 tumors [40]. Several clinical trials are ongoing to determine the safety and efficacy of SGLT2 inhibitors when used in combination with other BC chemotherapy (**Table 1**). Although more preclinical and clinical research is required, SGLT2 inhibitors have considerable potential as MRS for DM-associated BC.

Table 1. Ongoing clinical trials of SGLT2 targeting BC.

	Title	Status	Study Results	Conditions	Interventions	Phases	NCT Number
1	Alpelisib, Fulvestrant and Dapagliflozin for the Treatment of HR+, HER2-, PIK3CA Mutant Metastatic Breast Cancer	Recruiting	No Results Available	Metastatic BC HER2-negative BC	Dapagliflozin 10 Mg Tab	Phase 2	NCT05025735
2	A Phase 1b/2 Study of Serabelisib in Combination with Canagliflozin in Patients with Advanced Solid Tumors	Unknown status	No Results Available	BC Endometrial Cancer Lung Cancer Colorectal Cancer Head and Neck Cancer	Serabelisib Canagliflozin 300 mg	Phase 1 Phase 2	NCT04073680
3	Preventing High Blood Sugar in People Being Treated for Metastatic Breast Cancer	Recruiting	No Results Available	BC BC Stage IV Metastatic BC	Dietary Supplement: Ketogenic Diet Dietary Supplement: Low Carbohydrate Diet Drug: Alpelisib Drug: Fulvestrant Drug: Canagliflozin	Phase 2	NCT05090358
4	Study of Safety and Efficacy of Dapagliflozin + Metformin XR Versus Metformin XR in Participants	Recruiting	No Results Available	BC	Alpelisib Fulvestrant Metformin XR Dapagliflozin + metformin	Phase 2	NCT04899349

Title	Status	Study Results	Conditions	Interventions	Phases	NCT Number
With HR+, HER2-, Advanced Breast Cancer While on Treatment with Alpelisib and Fulvestrant				XR Dapagliflozin		[41]

should not
ed to the
ic control [34]. However, the SGLT1 inhibitor is a beneficial agent in enhancing the SGLT2 inhibitors' effect in glycemic control of diabetic patients [41]. There are several dual inhibitors of SGLT1 and SGLT2, including LX4211 and Sotagliflozin. LX4211 shows satisfactory results in improving glycemic control in phase 1 clinical trials [42]. In phase 3 studies of Sotagliflozin, although it has been proven to be a safe drug, an insignificant anti-diabetic effect is shown [43]. When it comes to BC, overexpression of SGLT1 is found in tamoxifen-resistant ER-positive BC. The transporter increases glycolytic flux and lactate production via aerobic glycolysis which induces a tumor-associated macrophage. The macrophage then promotes cell growth via EGFR/PI3K/Akt signaling, releasing immunosuppressive factors [44]. In line with the previous study, there is other evidence suggesting that high expression of SGLT1 correlates to a high growth rate of TNBC [45]. Knocking down SGLT1 is proven effective in inhibiting BC growth, including subtypes such as TNBC [45] and HER2+ BC [46]. SGLT1 is a potential therapeutic target for DM-associated BC. However, discovery of more selective SGLT1 inhibitors against BC cells is required. More in-depth studies are necessary to determine the safety and efficacy of using SGLT1 and SGLT2 inhibitors in combination.

2.4. MCT Inhibitor

Monocarboxylate transporter (MCT) 1 & 4 are one of the leading research directions of BC therapy. Due to the Warburg effect, cancer cells shift their metabolism from oxidative phosphorylation to aerobic glycolysis, producing lactate for energy production. Under the hyperglycemic condition of DM, MCT plays a crucial role in maintaining the balance of lactate and the pH of cells [47]. Both MCT1 & 4 are upregulated in BC [48][49].

MCT1 is a bidirectional lactate transporter. A few MCT1 inhibitors (MCT1i) have already undergone phase I/II clinical trials for solid tumors. As a sole agent, MCT1 is found to have no direct toxicity toward BC cells. The blockage of the lactate import of MCT1 is more effective under glucose deprivation, as cancer cells will switch back to glucose for energy production when there is a lack of lactate [50]. It is also shown that MCT1i's effect may be compromised by the upregulation of MCT4, a lactate exporter. Therefore, combination therapy may be required to improve MCT1i's efficacy [51]. A recent study suggests that inhibiting lactate import by MCT1i while depleting BACH1 proteins, which increases lactate catabolism, is effective as a TNBC therapy. As DM-associated BC cells rely heavily on aerobic glycolysis and lactate metabolism, the combination therapy forces cells to reprogram their metabolism to oxidative phosphorylation, which is less favorable for the rapid proliferation rate [52].

The MCT4 inhibitor (MCT4i) is also a popular candidate for DM-associated BC. As mentioned above, upregulation of MCT4 compromises the efficacy of MCT1i; therefore, a combination of MCT1i and MCT4i may be required [50]. As a lactate exporter, it is essential to note that MCT4 regulates intracellular and extracellular pH. It can be demonstrated that under the hyperglycemic condition, it can be used in combination with metformin and NF-κB

inhibitors to achieve intracellular acidification [14]. It can also prevent extracellular acidification and inhibit the expression of acidity-sensitive immune checkpoint protein, hence acting as immunotherapy [53]. Although MCT4i has excellent therapeutic potential, some studies have shown that inhibition of MCT4i will increase the risk of endothelial injury and cardiovascular complications [54]. MCT4 inhibition may also induce resistance toward traditional BC chemotherapy such as tamoxifen [55]. More research is required to ensure its safety and efficacy in DM-associated BC.

2.5. Insulin Growth Factor Receptor (IGF1R) Antagonist and Insulin Receptor (IR) Antagonist

Insulin-like growth factor (IGF) and insulin are peptide hormones that regulate the growth and metabolism. Subunits of their respective receptors, IGF-1R, IR-A, and IR-B, form heterodimeric hybrid receptors. With their similar amino acid sequence, they are known to bind to each other's receptors [56]. Besides glycemic controls, insulin could cause tumorigenesis and trigger the downward cascade involving the mTOR signaling pathway [57]. Therefore, insulin treatment in DM has always been controversial due to its potential risk of inducing cancer [58][59]. In more recent research, it can be found that the cysteine-rich 61 (Cyr61) elevation plays a key role in tumorigenesis. Once IGF-1 binds to IGF1R, it triggers the PI3K/AKT and MAPK signaling pathway, inducing the production of Cyr61. As IGF-1 is an essential growth factor, there are concerns that inhibiting IGF1R may affect other organs. It is suggested that targeting specific tumorigenic molecules along the IGF1 signaling pathway, such as Cyr61, will be a safer and more effective potential therapy [60]. Inhibition of Cyr61 signaling is proved to be effective in hindering BC growth [61]. An anti-Cyr61 antibody, 093G9, is proved to be an effective approach to inhibiting Cyr61 in vivo [62].

In DM-associated BC, hyperinsulinemia is one of the key factors which promotes cell proliferation and BC growth. IGF1R and IR are well-anticipated potential therapies for DM-associated BC. However, regulating IGF1R shows disappointing results in clinical trials. According to a review, most treatments show no improvement compared to the standard of care. Some hypothesized that an increase in insulin receptor expression compromises the drug's efficiency [63]. With an increasing number of BC MRS targeting IR, e.g., anti-idiotypic antibodies [64], combined therapy of IGF1R and IR antagonists may be able to optimize the therapeutic effect [65]. New findings indicated that combinations of IGF1R/IR with androgen receptor antagonist or anti-PD-L1, are effective in hindering migration and progression of TNBC cells [66][67]. However, IGF1R and IR therapies can cause worrying side effects. It is shown that low levels of IGF in the blood could lead to metabolic syndrome, insulin resistance, and glucose intolerance. Like insulin, IGF can also promote glucose uptake in many cell types. Antagonizing its receptor may further worsen the metabolic disturbance of DM patients [68]. IR also produces worrying side effects for DM patients. When IR antagonist S961 is used as a sole agent to treat BC, it results in hyperinsulinemia, hyperglycemia, and increased BC tumor size, possibly due to elevated amounts of insulin targeting the IGF1R that is not inhibited [65]. It is still unclear if the antagonist of IGF1R and IR is suitable for DM-associated BC. More research is required to investigate the potential side effects of IGF1R and IR antagonists on BC patients with DM.

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