Targeting Metabolic Pathways Improves TNBC Therapy

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Abstract. Breast cancer (BC) accounts for a significant proportion of female tumor cases globally. Triple-negative breast cancer (TNBC) is its most difficult variant, which is defined by the absence of the estrogen receptor, progesterone receptor, and HER2 expression. Aerobic glycolysis (Warburg effect) plays a pivotal role in TNBC, influencing both tumor microenvironment and immune responses. TNBC cells undergo metabolic reprogramming, favoring glycolysis over oxidative phosphorylation for energy production, leading to lactate accumulation and extracellular acidification in the tumor milieu, which exacerbates tumor proliferation, metastasis, and immunosuppression. This review delves into key glycolytic enzymes and regulators, including hexokinase, phosphofructokinase, pyruvate kinase M2, lactate dehydrogenase, and monocarboxylate transporters, as potential therapeutic targets. Highlighting promising preclinical evidence and clinical studies utilizing glycolytic pathway modulators, the review underscores their potential to reduce TNBC cell viability, curb growth, inhibit metastasis, and enhance chemosensitivity. Chemotherapy is still the most commonly used systemic treatment for TNBC, although immunotherapy, especially employing PD-1 and PD-L1 inhibitors, has advanced despite obstacles in the metastatic setting due to TNBC heterogeneity and changed immunogenicity. This review underscores the urgent need for tailored, effective therapies for TNBC patients, especially those with metastatic disease, shedding light on strategies to harness glycolysis for improving treatment outcomes.

Keywords: Breast cancer; Glucose metabolism; Cancer treatment; Triple-negative breast cancer.

1. Introduction

The most frequent kind of cancer among women is breast cancer. Breast cancer accounted for around 11.6% of all cancers in women in 2018, with nearly 2 million new cases globally [1]. Triple-negative breast cancer is a kind of breast cancer in which the primary targets for hormonal and therapeutic treatment, the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) are not present. TNBC is the most aggressive subtype of breast cancer with the worst prognosis, which contributes to 15-20% of all breast cancers and is more frequent in younger individuals, African Americans, and BRCA1 mutation carriers. TNBC has a high risk of invasiveness, recurrence, and mortality, making it the most lethal subtype of breast cancer. As demonstrated by statistics, the median survival time for patients with metastatic TNBC is 13.3 months and the mortality rate in the first five years after diagnosis is 40% [2]. TNBC is also highly heterogeneous in terms of its histology, molecular profile, and therapeutic response [3].

A possible technique for treating TNBC is to target aerobic glycolysis metabolic pathways. TNBC cells exhibit metabolic reprogramming. TNBC cells can increase metabolic pathways such as glycolysis, lipid synthesis, and nucleotide synthesis while inhibiting oxidative phosphorylation metabolic pathways. TNBC cells share the metabolic trait of aerobic glycolysis enhancement (Warburg effect), which enables them to produce ATP from glucose when oxygen is present [4]. Aerobic glycolysis causes lactate buildup and extracellular acidity, worsening tumor cell proliferation, metastasis, angiogenesis, and immunosuppression. Therefore, targeting aerobic glycolysis metabolic pathways may impair TNBC cell survival and growth by disrupting their energy supply and altering their microenvironment. Several glycolytic enzymes and regulators have been recognized as potential targets for TNBC therapy, such as hexokinase (HK), phosphofructokinase (PFK), pyruvate kinase M2 (PKM2), lactate dehydrogenase (LDH), monocarboxylate transporters (MCT). In preclinical or clinical investigations, certain inhibitors or modulators of these targets were explored, where

encouraging findings have been presented in lowering TNBC cell survival, proliferation, migration, invasion, metastasis, and chemosensitivity.

Despite the recent advances in TNBC research, systemic treatment for TNBC currently relies heavily on chemotherapy. However, patients are inclined to develop resistance and may undergo intense side effects when given cytotoxic agents, worsening the treatment outlook. Immunotherapy has been accessible in recent years and has helped improve the prognosis for TNBC, in either monotherapy or in conjunction with chemotherapy. The approved immunotherapy drugs for TNBC are atezolizumab and pembrolizumab, which target the PD-L1 and PD-1 pathways, respectively. However, there is still a significant gap in TNBC immunotherapy, especially in the metastatic setting, as demonstrated in Impassione130 where the overall survival between the two groups did not show significant differences [5]. This may be due to the heterogeneity of TNBC subtypes and the low immunogenicity of some tumors, which limit the efficacy of immune checkpoint blockade. As a result, more effective and precise targeted therapy for TNBC patients, particularly those with metastatic illness, is urgently needed.

Glycolysis stands as a metabolic process converting glucose into energy, concurrently yielding lactate as a byproduct. This review dives into the ramifications of glycolysis on the tumor microenvironment and the immune response concerning breast cancer, with a particular highlight on triple-negative occurrences. Enzymes of significance, along with regulatory components dictating glycolytic processes, are expounded upon, alongside the potential therapeutic avenues they provide. Moreover, strategies aimed at amplifying the effectiveness of glycolytic modulation are also discussed.

2. The expression and function of the main glycolytic enzymes in TNBC cells

During the metabolic process of glycolysis, glucose is converted to pyruvate, which then uses ATP and NADH to produce energy. The process of glycolysis is separated into two phases, the preparatory and the payoff, together ten steps. Initially, glucose is transformed into glyceraldehyde-3-phosphate by consuming two ATP molecules. The payoff phase makes four ATP molecules and two NADH molecules by changing G3P into pyruvate. The cellular process of glycolysis yields two ATP molecules and two NADH molecules per glucose molecule.

Based on the Warburg effect, tumor cell has enhanced glycolysis even when oxygen is present. In addition to being able to fulfill their increased need for energy and biosynthetic precursors, this also enables tumor cells to adjust to their environment, which is acidic and hypoxic. Glycolysis also confers several advantages to tumor cells in terms of proliferation, invasion, metastasis, and resistance to apoptosis and therapy. Therefore, targeting glycolysis or its key enzymes may be a promising strategy for cancer therapy. Common targets for glycolysis focus on key enzymes such as HK, PFK, PK, and LDHA [6]. Monocarboxylate channels are also targeted to control the acidity of the tumor microenvironment (Fig 1).

2.1. Hexokinase

The first restricting enzyme in glycolysis is hexokinase (HK), which has four isoforms (HK1-4) and catalyzes the phosphorylation of glucose [7]. HK2 is present in TNBC cells at higher levels and has been associated with a poor outlook. The control of this mechanism is influenced by various cancer-causing genes including c-Myc, p53, and PTEN. C-Myc, for example, stimulates HK2 expression by attaching to its promoter region. The TP53-induced glycolysis and apoptosis regulator, which dephosphorylates G6P and decreases HK2 activity, is expressed more frequently when p53 inhibits the production of HK2. By turning on AMP-activated protein kinase (AMPK), which phosphorylates and degrades HK2, PTEN prevents the synthesis of HK2.

Several inhibitors of HK have been developed and undergoing clinical tests in TNBC and other cancer cohorts (Table 1). 3-bromopyruvate (3BP) is an alkylating agent that covalently ties to the catalytic location of HK and represses its action, actuating apoptosis and necrosis of the TNBC cells

by depleting ATP levels and expanding responsive oxygen species (ROS) generation. In TNBC xenografts, 3-BP also prevents tumor development and metastasis. The chemical 3BrPA reduced c-Myc activity in BC cells, increasing TXNIP and decreasing HK2 as a result. 2-DG is a glucose analog that can lower ATP levels while increasing ROS generation in TNBC cells, causing apoptosis and autophagy. In the TNBC model, inhibition of glycolysis by 2-DG inhibits G-CSF and GM-CSF synthesis and restricts MDSC growth. 2-DG also sensitizes TNBC cells to drugs such as doxorubicin, paclitaxel, MDIVI-1, and metformin, providing potential for combination therapy discipline [8]. LND is an antitumor agent that inhibits HK by disrupting its binding to mitochondria. LND induces apoptosis in TNBC cells by decreasing ATP levels and increasing ROS production. LND also enhances the antitumor effects of chemotherapy drugs such as cisplatin and gemcitabine. DCA is a pyruvate analog that inhibits PDK, phosphorylating, and pyruvate dehydrogenase. DCA activates PDH and shifts the metabolism from glycolysis to oxidative phosphorylation (OXPHOS) in TNBC cells. DCA induces tumor apoptosis by upregulating ROS production and downregulating mitochondrial membrane potential, thereby inhibiting tumor metastasis in TNBC xenografts.

2.2. Phosphofructokinase

The second speed-limiting enzyme in glycolysis, phosphofructokinase (PFK), catalyzes the transformation to fructose-1,6-bisphosphate using ATP as a substrate. The glycolytic flow is primarily regulated by PFK-1, the primary isoform, whereas PFK-2 and PFK-3 are also engaged in other metabolic pathways. PFK is important in tumor progression. In TNBC cells, PFK is overexpressed and correlated with poor prognosis by promoting glycolysis and providing ATP and biosynthetic precursors for TNBC cells [9]. Additionally, PFK controls additional necessary metabolic pathways for TNBC cells' survival, including glutaminolysis, pentose phosphate pathway, and fatty acid synthesis.

Several inhibitors or modulators of PFK have been developed and tested in TNBC models. CTZ is a synthetic compound that inhibits PFK-1 and PFK-2, respectively and has been shown to inhibit glycolysis and induce apoptosis in various cancers. A bifunctional enzyme called PFKFB3i produces and degrades fructose 2,6-bisphosphate, which has been used to inhibit cancer proliferation malignancies such as glioblastoma, prostate cancer, and colon cancer. RSV and QUE are natural compounds found in fruits that inhibit PFK and modulate glycolysis and oxidative phosphorylation by binding to its allosteric site and preventing its activation by fructose 2,6-bisphosphate.

2.3. Pyruvate kinase

The last speed-controlling enzymatic molecular in glycolysis, pyruvate kinase M2 (PKM2), catalyzes the conversion into pyruvate with ATP releasing. The majority of four pyruvate kinase isoforms, including PKM2, are expressed in malignant, proliferative, and embryonic cells. PKM2 exists in two forms. A highly active tetramer that promotes glycolysis and a less active dimer that diverts glucose metabolism to other pathways. PKM2 is important in the Warburg effect, a condition identified in many cancer cells that prefers aerobic glycolysis to oxidative phosphorylation for energy and lactic acid production. PKM2 regulates the Warburg effect by switching between its tetrameric and dimeric forms, depending on the signals and conditions of the tumor microenvironment. PKM2 also has non-metabolic functions, such as acting as a protein kinase, a transcriptional coactivator, and a histone modifier, which contribute to tumorigenesis. Increased glycolysis and PKM2 activity in TNBC are linked to poor prognosis and treatment resistance. PKM2 is involved in modulating the immune response and the tumor microenvironment in TNBC by affecting the pH, hypoxia, and inflammation.

Several inhibitors targeting PKM2 have been developed or investigated as potential anticancer agents. These inhibitors aim to disrupt the Warburg effect and induce metabolic stress in cancer cells. The mechanism of PKM2 inhibitors varies depending on their structure and specificity. PKM2 inhibitors such as oxamate, galloflavin, and gossypol connect to PKM2's active domain lowering its capacity to catalyze. Other PKM2 inhibitors, such as FX11, attach to PKM2's allosteric location and

prevent it from dimerizing, which is essential for its non-metabolic actions. Some PKM2 inhibitors also affect the expression or stability of PKM2 by interfering with its transcriptional regulation or post-translational modifications. In preclinical or clinical research, PKM2 inhibitors have demonstrated encouraging outcomes for tumors like lung cancer, breast cancer, and leukemia.

2.4. Lactate dehydrogenase

The enzyme lactate dehydrogenase (LDH) interconverts NADH and NAD+ as well as turning pyruvate into lactate and lactate into pyruvate. LDH regulates the balance between glycolysis and oxidative phosphorylation, the main cellular energy pathways. LDH facilitates the Warburg effect and converts pyruvate to lactate. TNBC cells have high glycolysis and LDH activity, which correlate with poor prognosis and therapy resistance. LDH also modulates the immune response and the tumor microenvironment in TNBC by affecting pH, hypoxia, and inflammation.

Numerous LDH inhibitors have been created or are being investigated as possible anticancer drugs. GF, a synthetic substance that competes with NADH and inhibits LDH action, is one type of LDH inhibitor. GP, a naturally occurring substance derived from cotton seeds, binds to the active site of LDH and prevents it from working. OXA is a synthetic substance that suppresses LDH-A and LDH-B and competes with pyruvate. VIT C is a naturally occurring substance found in fruits and vegetables that turns NAD+ into NADH. An effective and specific inhibitor of lactate dehydrogenase A (LDHA), which plays a part in the metabolism of tumors, GSK2837808A has been proven to stop the generation of lactic acid and trigger apoptosis in cancer cells [10]. These inhibitors have different mechanisms of action and effects on glycolysis, oxidative phosphorylation, cell death, gene expression, tumor growth, angiogenesis, and hypoxia in various cancer models.

2.5. Monocarboxylate transporters

Aerobic glycolysis is implemented by tumor cells to generate lactate, which is subsequently expelled via monocarboxylic acid transporters (MCTs). The SLC gene family produces a group of 14 proteins known as MCTs. MCT1 and MCT4 are the most investigated, as they serve a vital function in pH homeostasis, glycolysis regulation, and oxidative phosphorylation. MCT1 and MCT4 expression status in tumors is influenced by estrogen receptor status, miRNAs, and STAT3 signaling. For example, MCT1 is upregulated in TNBC cells without estrogen receptor expression due to the absence of miP-342-3p and miP-124, which normally target MCT1 mRNA. This allows TNBC cells to avoid intracellular acidosis and apoptosis and gain a competitive advantage in their progression and proliferation. Regardless of the subtype of BC, MCT1 status is also related to unfavorable outcomes [11].

Inhibitors for MCT include Quercetin, AZD3965, and Kaempferol (KEM). Quercetin (QUE) is a natural compound that can inhibit MCT1 and reduce the efflux of lactic acid from tumor cells. This can impair lactic acid metabolism and alleviate the immunosuppressive effect since lactic acid can stabilize HIF-1α [12]. AZD3965 also shows significant anti-cancer potential and ongoing clinical trials are testing the efficacy in patients under advanced cancer diagnosis. In diffuse large B-cell lymphoma (DLBCL) patients, combination therapy of AZD3965 and mitochondrial inhibitor IACS-010759 shows synergy and exacerbates cell death in DLBCL [13].

3. The limitations and future development of targeting glycolysis in TNBC cells

Targeted glycolysis in TNBC is a potential strategy to exploit their metabolic vulnerabilities and impair their growth and survival. However, this strategy faces several challenges and limitations yet to be addressed before implementation in clinical practice, one of which is the heterogeneity of TNBC. TNBC consists of different molecular subtypes with different metabolic profiles and treatment responses. For example, some TNBC subtypes may rely more on oxidative phosphorylation (OXPHOS) than glycolysis and thus may be resistant to glycolysis inhibitors, and it is important to identify biomarkers that can predict the metabolic phenotype of TNBC cells and sensitivity to

glycolysis inhibitors. This would allow for a personalized and precise approach to target glycolysis in TNBC. Chaturvedi used metformin to inhibit the mitochondrial respiration of cells, making the cells dependent on glycolysis and then added LDH inhibitors to treat melanoma, and achieved a good therapeutic effect [14]. Another challenge is the off-target effects and toxicity of glycolytic inhibitors, which may affect normal cells that also rely on glycolysis, such as immune cells, neurons, and erythrocytes. For instance, 2-DG may inhibit T cell and NK cell function and stifle antitumor immunity [12]. Therefore, it is crucial to optimize the delivery, dosage, and timing of glycolytic inhibitors to minimize their adverse effects on normal cells and maximize their therapeutic effects on TNBC cells. This would require a careful evaluation of the pharmacokinetics, pharmacodynamics, and safety profile of glycolytic inhibitors in preclinical and clinical studies.

Drug resistance that TNBC cells may develop to glycolytic inhibitors also remains a major challenge and requires more research. This resistance may result from genetic or epigenetic changes that affect the expression or activity of glycolytic enzymes or regulators. For example, some TNBC cells may acquire mutations in hexokinase 2 or pyruvate kinase M2 that make them resistant to 3-bromopyruvate or dichloroacetate, respectively. As a result, it's critical to track the molecular alterations brought on by glycolytic inhibition in TNBC cells and to create innovative, targeted inhibitors that can overcome resistance mechanisms. This requires a comprehensive understanding of the molecular mechanisms and pathways involved in glycolysis regulation and modulation in TNBC. The single-use of glycolysis-targeted drugs cannot eliminate tumor cells with metabolic heterogeneity. Instead, drug-induced metabolic stress can lead to metabolic reprogramming of tumor cells, such as relying more on glutamine metabolism, leading to drug resistance. Faced with this dilemma, a potential strategy is making the metabolic patterns of diverse cell subpopulations in TME relatively homogeneous, and then uniformly inhibit this relatively homogeneous metabolic pattern. For example, giving anti-angiogenic drugs before glycolysis makes the tumor more dependent on glycolysis, leading to better therapeutic outcomes [15,16].

4. Optimizing the effectiveness of glycolysis targeted treatment

Targeting tumor metabolism, including glycolysis, is a complex task. While inhibiting glycolysis could potentially starve cancer cells of energy, it might also affect normal cells' metabolism, which is the off-target effect. Balancing the specificity and effectiveness of these drugs while minimizing side effects is a challenge in drug development. In one study, bio-reducible exosomes were developed as a mitochondria-targeted delivery system for the sound sensitivity enhancer T-Ce6 and the glycolytic inhibitor FX11 [17]. In line with the tumor microenvironment, bio-reducible exosomes demonstrated increased release of medication and sonodynamic effects. T-Ce6 accumulation induces mitochondrial damage under ultrasonic irradiation, whereas FX11 inhibits tumors from consuming energy (Figure 2). The use of targeted therapy and sonodynamic therapy with mitochondria in cancer treatment has shown promising results in stopping tumor growth without causing harmful effects throughout the body. This discovery suggests that using exosomes with sonosensitizers could be a safe and effective method for treating cancer using sound waves. Targeting glycolysis utilizing nanocarriers also provides potential metabolic circuits for treating cancer. For example, liposomal 3-BP nanocarriers have been developed to inhibit aerobic glycolysis and tumor energy supply [18,19].

Personalized medicine has emerged as a pivotal paradigm in the landscape of cancer treatment, signifying a shift away from the conventional one-size-fits-all approach. This transformative strategy acknowledges the inherent variability among patients, recognizing that responses to therapies can diverge significantly even within the same cancer subtype. This is particularly pertinent in the context of TNBC and other malignancies. Within this framework, the potential efficacy of glycolysis-targeted treatments becomes intricately intertwined with the unique genetic and molecular profiles of individual patients. The intricate interplay between a patient's genomic makeup, metabolic characteristics, and tumor microenvironment can influence the degree of sensitivity or resistance to glycolysis-targeted interventions. By comprehensively evaluating these intricate attributes and

identifying biomarkers for determining treatment threshold, patients who might derive greater benefits from glycolysis-targeted treatments could be discerned. As research into the molecular underpinnings of cancer continues to deepen, the potential to refine glycolysis-targeted therapies based on individualized parameters heralds a new era of therapeutic precision, empowering oncologists to optimize treatment regimens and ultimately improve patient outcomes.

Combination therapy involving glycolysis-targeted treatments is a dynamic strategy in cancer treatment, capitalizing on the intricate vulnerabilities of cancer cells through the simultaneous targeting of multiple cellular pathways. This approach seeks to enhance treatment efficacy beyond the scope of single-agent therapies. By synergistically integrating glycolysis inhibition with established treatment modalities like chemotherapy, immune checkpoint inhibitors, and radiotherapy, researchers aim to disrupt cancer cells' survival mechanisms and potentially overcome resistance. Immune checkpoint inhibitors have shown remarkable success by promoting immunity to recognize and clear tumor cells. Combining glycolysis-targeted therapies with immune checkpoint inhibitors might enhance the immunogenicity of cancer cells, making them more recognizable by the immune system. The vulnerability of MPS2 TNBC cells lies in their sensitivity to drugs targeting glycolysis for cellular energy production. Therefore, preventing lactate dehydrogenase from functioning could result in an improved reaction of tumors to anti-PD-1 immunotherapy. Moreover, targeting additional metabolic and signaling pathways such as mTOR pathway, etc. offers a comprehensive approach to treatment [20]. However, the complexity of interactions and potential side effects necessitates rigorous evaluation through preclinical studies and clinical trials. In effect, combination therapies present a promising avenue to address the multifaceted nature of cancer, offering the potential for improved patient outcomes in the quest for effective cancer management.

5. Literature References

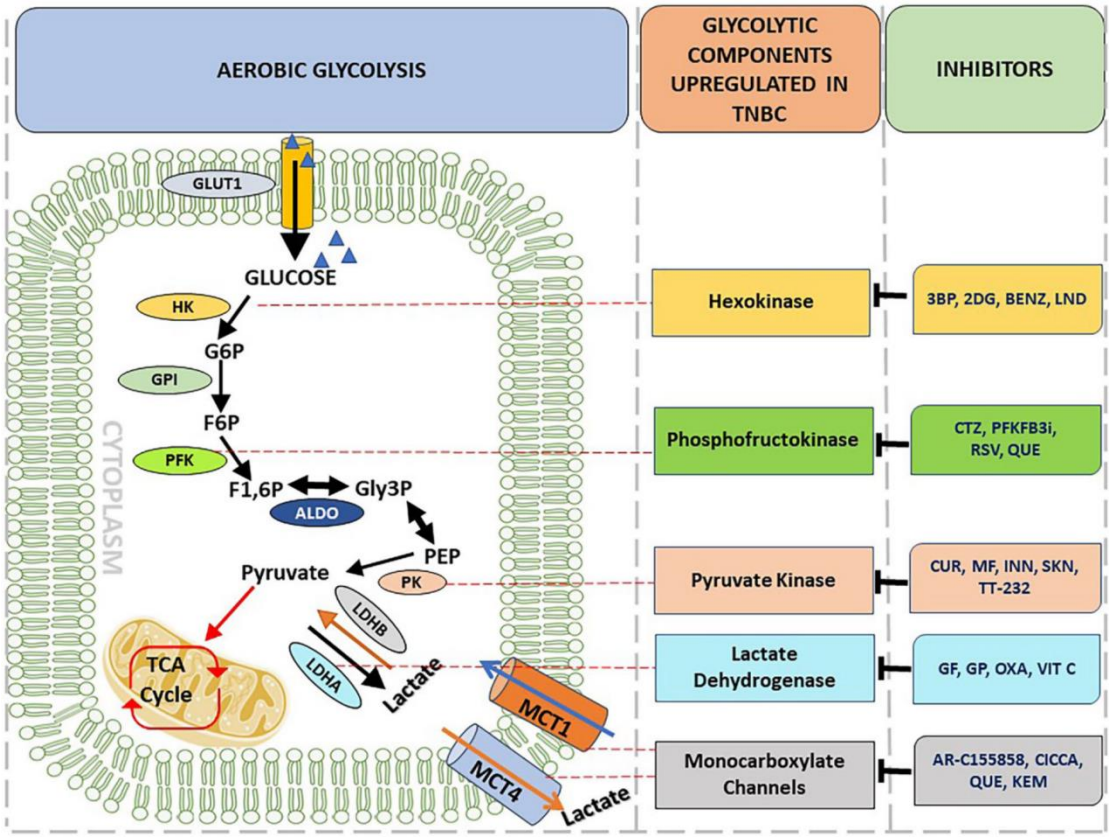

Fig. 1 Diagram of glycolysis and key enzyme regulators [6].

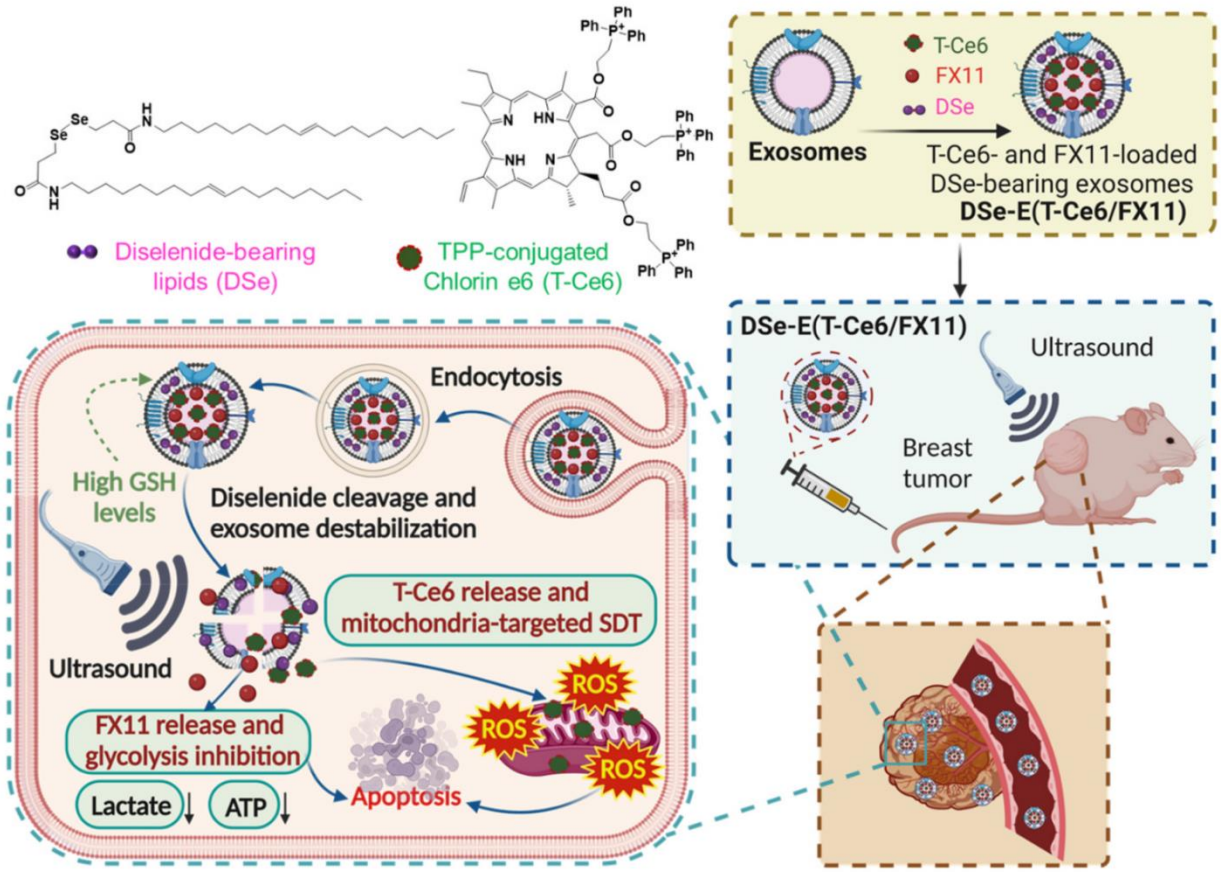

Fig. 2 Mechanistic of improving targeting efficiency through exosome-mediated drug delivery [17].

Table 1. Ongoing clinical trials for aerobic glycolysis pathway inhibitors

Target	Drugs	Sample size	Phase	Estimated Completion	ClinicalTrials.gov
Hexokinase	2-deoxyglucose (2DG)	45	I	Sep-23	NCT05314933
		4	I	Sep-23	NCT00864110
Phosphofructokinase	Benserazide (Benz)	36	Ib	Dec-23	NCT04432623
	Resveratrol (RSV)	25	II	Oct-22	NCT03253913
		0	II	Aug-22	NCT04266353
Pyruvate Kinase	Quercetin (QUE)	200	I	Jan-24	NCT05680662
		60	II	Dec-25	NCT04733534
		55	II	Sep-25	NCT03476330
	Curcumin (CUR)	100	II	Dec-23	NCT05456022
		22	I	Dec-23	NCT03980509
		40	II	Jan-25	NCT02944578
		291	III	Jan-26	NCT03769766
		608	III	Jun-26	NCT02064673
		60	II	Sep-22	NCT05045443
		3649	III	Aug-23	NCT01101438
		151	III	Nov-25	NCT01905046
		50	III	Sep-23	NCT05921942
		408	III	Aug-24	NCT01864096
	Metformin (MF)	40	II	Jun-26	NCT04741945
		87	I	Jun-24	NCT01529593
		23	II	Jun-23	NCT02874430
		49	II	Oct-25	NCT03379909
		77	III	Mar-24	NCT04792749
		90	II	Sep-25	NCT04275713
		23	II	Dec-22	NCT01980823
		76	Ib	Oct-25	NCT05036226
		24	II	Jan-25	NCT03800602
		24	I	Dec-23	NCT02339168
		55	Ib	Jun-27	NCT01638676
		200	I	Nov-36	NCT05515978
		67	II	Jul-27	NCT04758000
		74	II	Apr-32	NCT04114136
		62	II	Oct-23	NCT01797523
		100	II	Jun-23	NCT03238495
		256	I	Nov-24	NCT03006172
		27	II	Jun-23	NCT02874430
		68	II	Jul-24	NCT04300790
		30	II	May-24	NCT04248998
		120	II	Nov-25	NCT05023967
		5000	II	Dec-31	NCT01042379
		40	II	Feb-25	NCT01273610
		301	II	Dec-23	NCT03500380
		257	III	Sep-25	NCT01104571
	Lapatinib (INN)	23	II	Dec-24	NCT02158507
		608	III	Sep-24	NCT03523585
		339	III	Jun-24	NCT05122494
		128	II	Jan-24	NCT00999804
		87	II	Dec-23	NCT00470704
Lactate Dehydrogenase		30	II	Dec-22	NCT04033107
		16	Ib	Aug-24	NCT04046094
		109	II	Sep-25	NCT03682029
	Vitamin C (VIT C)	13	I	Dec-24	NCT01752491
		65	II	Dec-25	NCT02905578
		90	II	Dec-27	NCT02344355
		16	I	Jan-24	NCT02344355
		46	II	Dec-27	NCT02905591
		25	Ib	Jun-24	NCT03508726
Monocarboxylate Channels	AZD3965	53	1	Nov-20	NCT01791595

6. Conclusion

Triple-negative breast cancer presents a significant challenge within the realm of breast cancer, which is characterized by its aggressiveness, heterogeneity, and deficiency in effective targeted therapies. TNBC cells undergo metabolic reprogramming, notably exhibiting the Warburg effect.

This metabolic shift confers several advantages to TNBC cells, including rapid energy production, macromolecule biosynthesis, resistance to hypoxia and oxidative stress, evasion of apoptosis, and the promotion of invasion and metastasis. Consequently, targeting aerobic glycolysis has emerged as a promising strategy to impede TNBC growth and progression. Inhibiting key glycolytic enzymes or transporters, including hexokinase, phosphofructokinase, pyruvate kinase, lactate dehydrogenase, and glucose transporters, has been shown in numerous studies to effectively suppress TNBC cell migration, proliferation, and survival. Additionally, glycolysis-targeted therapy has the potential to overcome chemoresistance and enhance the efficacy of conventional chemotherapy in TNBC. However, clinical application faces challenges, including the need for specificity in glycolysis inhibitors and the optimization of delivery, dosage, and combination with other therapies. Future perspectives for advancing TNBC therapy through glycolysis targeting involve elucidating molecular mechanisms and biomarkers specific to glycolysis regulation in TNBC subtypes, developing nanotechnology-based delivery systems, synergizing glycolysis inhibitors with immunotherapy or radiotherapy, and personalizing treatment based on patients' metabolic profiles. These avenues offer hope for improving the prognosis of TNBC patients, especially those facing the complexities of metastatic disease, by harnessing the potential of glycolysis-targeted therapy while addressing its associated challenges and limitations.

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