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Regulation of Acid-Base Homeostasis in Breast Cancer Cells: Therapeutic Strategies Based on Hexose and Citrate Derivatives

Rauash Mangazbayeva,[1] Ayaz Belkozhayev,[1,*] Laura Agibayeva,[2] Anel Mun,[3] Bayana Yermukhambetova,[2,4,*] Mubarak Yermaganbetov,[1,4] Adilet Alikulov[2,4] and Grigoriy Mun[2,4]

Abstract

Breast cancer is the most common malignancy among women and a leading cause of cancer-related mortality worldwide. A critical but often underappreciated hallmark of this disease is dysregulated acid–base homeostasis within the tumor microenvironment (TME). Driven by the Warburg effect, cancer cells preferentially utilize aerobic glycolysis, producing excessive lactate and protons. This results in extracellular acidification while maintaining a neutral-to-alkaline intracellular pH, a state that promotes proliferation, invasion, immune evasion, and resistance to therapy. Central to pH regulation are transporters and enzymes such as monocarboxylate transporters (MCT1/4), Na^+/H^+ exchanger (NHE1), vacuolar H^+-ATPases, and carbonic anhydrases, which coordinate proton efflux and buffering. Therapeutic strategies targeting these pathways include hexose derivatives (*e.g.*, 2-deoxy-D-glucose, D-mannose) that inhibit glycolytic flux, and citrate-based agents that buffer acidity and restore metabolic feedback inhibition. Additional approaches encompass lactate transport inhibition, bicarbonate therapy, and pH-responsive drug delivery systems. Preclinical evidence supports the efficacy of these interventions, and early clinical exploration suggests translational potential, particularly in aggressive subtypes such as triple-negative breast cancer. By disrupting the pH balance that supports tumor growth and survival, these strategies offer promising avenues for improved outcomes. This review provides a comprehensive overview of the molecular mechanisms and therapeutic opportunities for targeting acid–base regulation in breast cancer.

Keywords: Breast cancer, Acid–base homeostasis, Tumor microenvironment, Warburg effect, pH-targeted therapy.
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1. Introduction

Breast cancer is the most diagnosed malignancy among women and remains one of the leading causes of cancer-related mortality worldwide.[1] According to global cancer statistics, approximately 2.3 million women were newly diagnosed with breast cancer in 2020, and nearly 685,000 deaths were attributed to the disease.[1,2] This global burden underscores the urgent need for more effective therapeutic strategies, especially for aggressive and treatment-resistant subtypes.[3] Despite significant advances in treatment modalities, certain aggressive subtypes of breast cancer such as triple-negative breast cancer (TNBC)exhibit therapeutic resistance, frequently leading to recurrence and metastasis.[4,5] TNBC lacks expression of estrogen receptor (ER), progesterone receptor (PR), and HER2, leaving patients with limited targeted therapy options and making systemic chemotherapy the mainstay of treatment.[6-8] One of the hallmarks of cancer is the metabolic reprogramming of tumor cells, characterized by increased glucose uptake and a predominant reliance on aerobic glycolysis for energy production, even in the presence of sufficient oxygen.[9,10] This phenomenon, first observed by Otto Warburg in the 1920s, is now widely known as the Warburg effect. Instead of undergoing complete oxidative phosphorylation, cancer cells preferentially convert glucose into lactate, resulting in the accumulation of lactate and protons in the tumor microenvironment (TME).[11,12] Consequently, while the extracellular milieu becomes acidic, the intracellular pH of cancer cells remains neutral to slightly alkaline.[13,14]

The acidification of the TME plays a pivotal role in tumor progression. Acidic conditions damage surrounding normal

[1]*Satbayev University, 22 Satpayev street, Almaty, 050013, Kazakhstan*
[2]*Al-Farabi Kazakh National University, 71 Al-Farabi avenue, Almaty, 050040, Kazakhstan*
[3]*Nazarbayev University, 53 Kabanbay batyr avenue, Astana, 010000, Kazakhstan*

tissues, facilitating tumor invasion, and suppress immune cell function, thereby impairing immune surveillance.[15,16] Notably, excessive lactate production by cancer cells has been shown to inhibit cytotoxic T lymphocyte activity and enhance the immunosuppressive function of regulatory T cells (Tregs).[17,18] Furthermore, the acidic extracellular pH can diminish the efficacy of certain chemotherapeutic agents particularly weakly basic drugs such as vincristine and doxorubicin through a process known as ion trapping, where protonation prevents these drugs from crossing the cell membrane.[19,20] Thus, the acidic microenvironment provides cancer cells with an evolutionary advantage, enabling them to thrive under hostile conditions while promoting aggressive phenotypes, including rapid proliferation, metastasis, and multidrug resistance.[21,22] The maintenance of intracellular pH within a physiological range (~7.2–7.4) is critical for cancer cell survival. To achieve this, cancer cells upregulate a variety of ion transporters and enzymatic systems that facilitate proton efflux and maintain pH homeostasis more effectively than normal cells.[23] Key players in this process include the Na^+/H^+ exchanger (NHE1), vacuolar H^+-ATPases, monocarboxylate transporters (MCTs), and carbonic anhydrases, which together form an integrated pH-regulatory network.[24,25] In recent years, the concept of targeting tumor metabolism and pH regulation has emerged as a novel therapeutic strategy aimed at exploiting the vulnerabilities of cancer cells.[26] Interventions designed to inhibit aerobic glycolysis or neutralize the acidic TME are being actively investigated. Among these, metabolic modulators such as hexose derivatives can interfere with glycolytic flux, while citrate-based agents can influence both energy metabolism and acid–base balance, offering a dual mechanism of action.[27,28] This review provides a comprehensive analysis of the molecular mechanisms underlying acid–base homeostasis in breast cancer cells, with a particular focus on therapeutic approaches based on hexose and citrate derivatives.

2. Metabolic reprogramming and acidic microenvironment in cancer

A hallmark of cancer metabolism is the Warburg effect preferential reliance on aerobic glycolysis for ATP production despite adequate oxygen.[29,30] Instead of fully oxidizing pyruvate, cancer cells convert most of it to lactate, supplying intermediates for nucleotide, amino acid, and lipid synthesis. This metabolic reprogramming provides a proliferative advantage by coupling energy production with the demands of rapid cell division.[31,32] Such alterations in glycolytic flux and pH regulation are detected in various breast cancer subtypes but are particularly prominent in highly aggressive forms such as triple-negative breast cancer (TNBC), which display elevated glucose uptake, enhanced lactate secretion, and stronger extracellular acidification compared to luminal and HER2-positive tumors.[33,34]

Oncogenic signaling pathways, including PI3K/AKT/mTOR, c-MYC, and hypoxia-inducible factor 1-alpha (HIF-1α), play central roles in upregulating key glycolytic enzymes such as hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDHA).[35] As a result, even under normoxic conditions, glycolytic flux remains elevated, sustaining high rates of lactate and proton production. To prevent intracellular acidification which can trigger apoptosis cancer cells actively export lactate and H^+ ions via monocarboxylate transporters (MCT1 and MCT4), the Na^+/H^+ exchanger (NHE1), and vacuolar-type H^+-ATPases (V-ATPases). This maintains intracellular pH in a neutral to slightly alkaline range (~7.2–7.4), while the tumor microenvironment (TME) becomes progressively more acidic, with extracellular pH values dropping to ~6.5–7.0 in many solid tumors.

This acidic TME profoundly influences cancer progression. Low pH induces stress that selectively kills nearby normal cells while favoring the survival of acid-resistant tumor clones, which often display enhanced aggressiveness. Chronic acidosis promotes genomic instability, increases mutagenesis, and accelerates tumor evolution.[36] Moreover, prolonged exposure to acidic conditions has been shown to enhance the invasive and migratory capacities of tumor cells, in part through epithelial-to-mesenchymal transition (EMT) and extracellular matrix remodeling. Acidosis also contributes to immune evasion. Elevated extracellular lactate suppresses the cytotoxic activity of $CD8^+$ T lymphocytes and natural killer (NK) cells while enhancing the immunosuppressive function of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).[17] Lactic acid further modulates immune function by stabilizing HIF-1α, activating NF-κB, and inducing PD-L1 expression on tumor and immune cells.[37] Additionally, lactic acid can reprogram tumor-associated macrophages toward a pro-tumor, immunosuppressive phenotype.[38]

The acidic TME also diminishes the efficacy of anticancer therapies. Weakly basic chemotherapeutic agents such as vincristine and doxorubicin undergo protonation in acidic conditions, reducing their ability to cross cell membranes a phenomenon known as ion trapping.[39,40] Furthermore, acidic pH stimulates the activity of membrane drug-efflux pumps, including P-glycoprotein (P-gp), contributing to multidrug resistance. These effects highlight the dual role of tumor acidosis in both tumor progression and therapeutic failure.[41-43] Recent research has focused on exploiting the metabolic-acidic vulnerability of tumors for therapeutic gain. Strategies

[4]*National Engineering Academy of Republic of Kazakhstan, 67 Khodzhanov street, Almaty, 050060, Kazakhstan*
**Email:* a.belkozhayev@satbayev.university (Ayaz Belkozhayev), baya_yerm@mail.ru (Bayana Yermukhambetova)

include inhibiting glycolytic enzymes (HK2, LDHA), blocking lactate transport (MCT inhibitors), or targeting proton pumps (V-ATPase inhibitors) to disrupt pH regulation.[44] pH-responsive drug delivery systems are also being developed to selectively release cytotoxic agents in acidic tumor regions, thereby improving specificity and minimizing systemic toxicity. Innovative diagnostic tools, such as pH-sensitive magnetic resonance imaging and optical pH sensors in 3D tumor models, are emerging to monitor tumor acidosis and predict treatment responses.[45,46] In summary, metabolic reprogramming through the Warburg effect generates an acidic microenvironment that fosters cancer cell survival, aggressiveness, immune suppression, and drug resistance. Understanding the interplay between altered metabolism and pH regulation provides a strong rationale for targeting this axis in breast cancer. Fig. 1 illustrates the key molecular mechanisms of acid–base regulation in the tumour microenvironment, including the role of glucose transporters (GLUT1/2), monocarboxylate transporters (MCTs), Na^+/H^+ exchangers (NHE), and carbonic anhydrases (CAIX/CAII) in maintaining intracellular alkalinity and extracellular acidity.

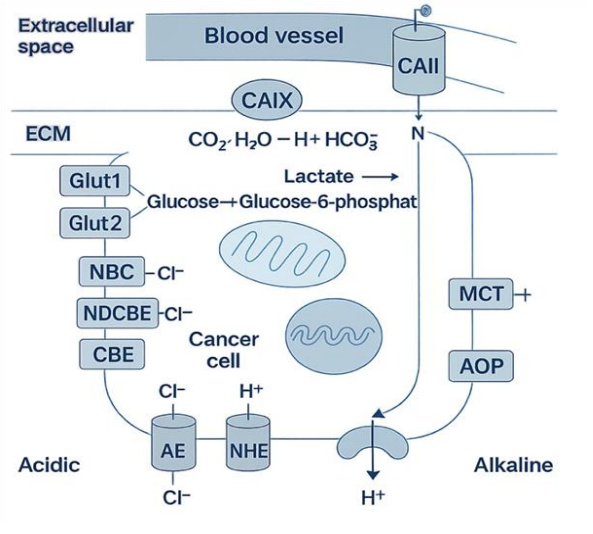

Fig. 1: Schematic representation of acid–base regulation in the tumour microenvironment. Cancer cells maintain a neutral-to-alkaline intracellular pH while exporting protons (H^+) and lactate through transporters such as NHE, AE, and MCT, resulting in extracellular acidification. Carbonic anhydrases (CAII and CAIX) contribute to CO_2 hydration and bicarbonate buffering, while glucose transporters (Glut1, Glut2) and metabolic enzymes sustain glycolytic flux. This coordinated acid–base regulation supports tumour survival and progression.

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3. Therapeutic targeting of acid–base homeostasis in breast cancer

Breast cancer cells survive and thrive in an acidic microenvironment by upregulating key pH-regulating mechanisms. These include proton export pumps and transporters such as NHE1 (Na^+/H^+ exchanger), NBCn1 (Na^+/HCO_3^- cotransporter), monocarboxylate transporters (MCT1/4 for lactate–H^+ co-transport), and V-type H^+-ATPases.[47] Carbonic anhydrase enzymes (especially CAIX in hypoxic regions) further facilitate acid removal by converting CO_2 to bicarbonate and protons.[48] The net effect is efficient extrusion of excess protons into the extracellular space, maintaining a slightly alkaline intracellular pH favorable for cancer cell proliferation.[49,50] This pH dysregulation promotes invasion, immune evasion, and therapy resistance in breast tumors. Targeting acid–base homeostasis has therefore emerged as an innovative approach to disrupt the cancer cells' survival strategy.[39]

3.1 Hexose derivatives as glycolytic inhibitors

One strategy to counter tumor acidity is to cut off its source: excessive glycolytic flux. Hexose derivatives modified sugars that interfere with glucose metabolism can drastically reduce lactic acid generation in cancer cells. A prominent example is 2-deoxy-D-glucose (2-DG), a glucose analog taken up by tumor cells via GLUT transporters but unable to proceed through glycolysis. 2-DG competitively inhibits hexokinase and traps glucose in a non-metabolizable form, thereby starving cancer cells of energy and biosynthetic intermediates.[51,52] In aggressive breast cancer models, 2-DG treatment led to significant anti-migratory and anti-invasive effects. For instance, O'Neill *et al.* showed that 2-DG inhibited the migration and invasion of highly metastatic triple-negative breast cancer (TNBC) cells and reduced their ability to resist anoikis (detachment-induced cell death).[51] Notably, 2-DG also depleted the subpopulation of cancer stem-like cells in these cultures, indicating it can target the tumor cells that drive recurrence and metastasis.[53,54] These findings underscore that blocking glycolysis not only impacts tumor growth but also its metastatic and stemness traits.

Beyond cell culture, glycolytic inhibition has shown promise in vivo, although clinical translation of 2-DG has faced challenges. Early-phase trials of 2-DG in solid tumor patients demonstrated that tolerable dosing is feasible.[55,56] However, 2-DG alone has limited potency, and high doses can cause hypoglycemia or fatigue. Current research is therefore exploring combination therapies using hexose analogs. One recent approach combined 2-DG with the anti-inflammatory drug diclofenac, achieving synergistic cytotoxic effects in breast cancer cell lines.[57] This combination amplified oxidative stress in cancer cells and improved cell killing compared to either agent alone.[58] Such synergy suggests that glycolytic blockers may be most effective when paired with drugs targeting complementary vulnerabilities (*e.g.* aberrant inflammation or mitochondrial function).

Another intriguing hexose-based therapy is the use of D-mannose, a simple sugar and C-2 epimer of glucose. Mannose is normally metabolized only in small amounts, but cancer cells with low levels of the enzyme phosphomannose isomerase (MPI) are exquisitely sensitive to mannose

supplementation.[59] Excess mannose is phosphorylated to mannose-6-phosphate, which accumulates and allosterically inhibits phosphoglucose isomerase – a critical enzyme that converts glucose-6-phosphate to fructose-6-phosphate in glycolysis.[60] Consequently, mannose can dampen the Warburg effect and deprive tumor cells of both energy and anabolic precursors. Follow-up studies confirmed that only tumors with low MPI (hence unable to effectively metabolize mannose) respond to this strategy. This implies a potential precision-medicine angle assaying a patient's tumor for MPI expression could predict responsiveness to mannose therapy.[59,61] Early preclinical evidence also indicates mannose can act as a radiosensitizer in cancers with the appropriate metabolic profile.[62] Thus, mannose and similar hexose analogues represent a promising class of metabolic therapeutics to curb tumor acid production at its source. Table 1 summarizes key hexose-based agents and their mechanisms and status.

Table 1: Selected therapeutic approaches targeting acid–base homeostasis in breast cancer, with their mechanisms and current development status.

Therapy Class	Example Agent	Mechanism of Action	Preclinical Efficacy	Clinical Status	Ref.
Hexose Analogues	2-Deoxy-D-glucose (2-DG); mannose	Glucose analogues taken up by tumor cells; inhibit glycolytic enzymes (*e.g.*, hexokinase), leading to ATP depletion and reduced lactic acid production	2-DG slowed breast tumor growth and sensitized cancer cells to chemo- and radiotherapy in models. Mannose also showed tumor-suppressive effects by perturbing glycosylation.	Investigational – tested in phase I trials for advanced solid tumors, but not yet an approved therapy.	[63,64]
Citrate-Based Therapies	Sodium citrate; Hydroxycitrate (HCA)	Systemic alkalization and metabolic inhibition: citrate buffers extracellular pH, while HCA inhibits ATP citrate lyase (blockade of lipid synthesis)	HCA (a competitive ACLY inhibitor) reduced breast tumor cell proliferation and reversed tamoxifen resistance by blocking lipid metabolism.	No dedicated cancer clinical trials to date; HCA is a common dietary supplement (weight-loss agent) with known safety, but its anticancer use remains experimental.	[65]
Targeted pH Regulators	CAIX inhibitors (SLC-0111); Proton Pump Inhibitors (*e.g.*, omeprazole)	Inhibit tumor proton exporters: CAIX inhibitors block carbonic anhydrase IX, preventing H⁺ conversion to CO₂ (disrupting intracellular pH homeostasis), and PPIs block vacuolar H⁺-ATPases, reducing proton efflux	CAIX inhibition impaired survival, migration and invasion of breast cancer cells in models. For example, novel CAIX inhibitor compounds reduced 3D invasion and lung metastases in breast xenografts.	CAIX inhibitors: SLC-0111 completed a phase I trial in solid tumors with no dose-limiting toxicity.	[66,67]
Bicarbonate Therapy	Oral/IV sodium bicarbonate	Systemic pH buffering: bicarbonate raises extracellular pH in tumors, neutralizing acidity and offsetting the Warburg effect's acid load	Elevating tumor pH with bicarbonate reduced metastases and improved drug response in breast cancer models. n mice, oral NaHCO₃increased tumor pH, curbed invasive growth, and enhanced immune cell infiltration.	Experimental – no large trials yet. Case studies and early-phase studies report slowed tumor progression and improved therapy when using buffer therapy (*e.g.*, ascites tumor treated with intraperitoneal NaHCO₃showed tumor marker decline.	[68,69]
Lactate Transport Inhibitors	MCT1 inhibitor AZD3965; MCT1/4 inhibitor syrosingopine	Blockade of lactate export via monocarboxylate transporters (MCT1/4), forcing intracellular lactic acid accumulation and tumor cell acidification. This disrupts glycolysis and can alleviate lactate-mediated immunosuppression.	AZD3965 (MCT1 inhibitor) showed anti-tumor activity in preclinical breast cancer models, slowing 4T1 tumor growth and enhancing radiosensitivity and immune T-cell infiltration	AZD3965 has completed a phase I/II trial in advanced cancers, demonstrating tolerability and target engagement	[37]

Therapy Class	Example Agent	Mechanism of Action	Preclinical Efficacy	Clinical Status	Ref.
NHE1 Inhibitors	Cariporide (HOE-642); Amiloride analogs (*e.g.*, EIPA)	Inhibition of Na⁺/H⁺ exchanger-1, the key proton extruder on cancer cell membranes. Blocking NHE1 prevents H⁺ efflux in exchange for Na⁺, leading to intracellular acid accumulation and reduced extracellular acidification. This can trigger cancer cell apoptosis and impair migration.	NHE1 blockade has shown anticancer effects in vitro and in vivo. Cariporide significantly improved doxorubicin efficacy against breast cancer cells and tumors	No cancer clinical trials to date. Cariporide reached Phase III for cardiac ischemia but was never repurposed for oncology due to side effects. NHE1 inhibitors remain at the preclinical stage in cancer, under investigation as potential adjuncts to enhance chemosensitivity	[70-72]
pH-Responsive Nanoparticle Systems	pH-sensitive liposomes (*e.g.*, TS-DOX liposome); polymeric micelles	Nanocarriers engineered to release therapeutic payloads in acidic environments. They remain stable at physiological pH ~7.4 and undergo structural changes or bond cleavage in the acidic tumor microenvironment (pH ~6.5), triggering localized drug release. This improves drug concentration in tumors and spares normal tissue.	pH-sensitive liposomal doxorubicin showed enhanced intratumoral drug accumulation and antitumor activity in breast cancer models.	In development – several pH-responsive nanodrugs are in preclinical testing, and a few have entered early clinical trials (no approvals yet). For example, a urease-based pH-targeting immunoconjugate (Helicase-DOS47) is in Phase I/II for solid tumors.	[68,73,74]
Combination Therapy (Glycolysis Inhibitors + Checkpoint Blockade)	3-BrPA (HK2 inhibitor) + anti–PD-1/PD-L1; 2-DG + anti–CTLA-4	Dual targeting of tumor metabolism and immune checkpoints. Inhibiting glycolysis (*e.g.*, hexokinase-2 with 3-bromopyruvate) reduces lactate production and tumor acidity, relieving immunosuppression, while checkpoint inhibitors reinvigorate T cells. The combination aims to create a more favorable (less acidic, more "immunogenic") TME for T-cell attack.	Blocking tumor glycolysis has shown synergy with immunotherapy in preclinical studies. HK2 inhibition by 3-BrPA decreased myeloid suppressor cells and enhanced CD8⁺ T-cell activity, resulting in improved anti–PD-L1 therapeutic outcomes in TNBC models.	Concept under investigation – no clinical trial results yet. The approach is supported by strong rationale (Pilon-Thomas *et al*., 2016 showed bicarbonate + checkpoint cures in mice.	[75,76]

3.2 Citrate derivatives and tumor acid neutralization

Another complementary approach exploits the tumor's dependence on an acidic environment by directly neutralizing or perturbing acid–base balance using citrate, a central metabolic buffer. Citrate is a tricarboxylic acid cycle (TCA) intermediate that, in their natural state, cancer cells paradoxically keep at low levels.[77,78] Rapid turnover of citrate in cancer cells avoids feedback inhibition of glycolysis – low citrate relieves suppression of phosphofructokinase, thus sustaining high glycolytic flux.[79,80] It also promotes acetyl-CoA utilization and histone deacetylation, changes associated with greater tumor aggressiveness and apoptosis resistance. Researchers have posited that raising intracellular or extracellular citrate could reverse these effects and impair cancer cell survival.[79,81] In support of this, Icard *et al*. reported that high-dose citrate can reinstate the feedback brake on glycolysis and simultaneously serve as a buffer of tumor acidity.[80]

Preclinical studies have demonstrated notable anti-cancer effects of citrate-based therapies. For example, injecting citrate into tumor-bearing mice was found to significantly inhibit tumor growth. In a gastric cancer model, intraperitoneal citrate administration led to slower tumor progression, suggesting that citrate can act as a therapeutic agent in vivo.[77,82] Parallel in vitro experiments showed that citrate enhances the potency of chemotherapy drugs: adding citrate increased cancer cell sensitivity to platinum-based chemotherapeutics, resulting in greater cell death than chemo

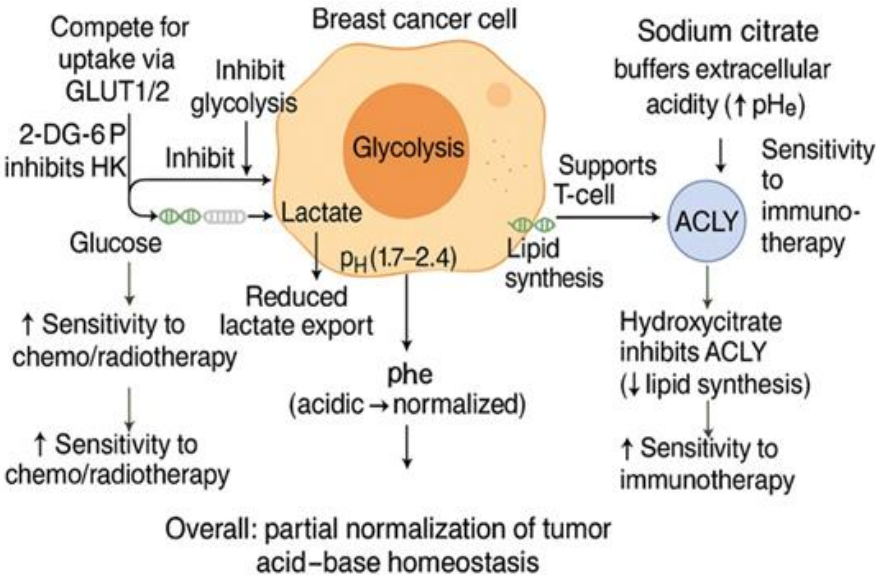

Fig. 2: Mechanistic overview of hexose (2-DG, mannose) and citrate (sodium citrate, hydroxycitrate) derivatives in regulating tumor acid–base homeostasis.

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alone.[83] These findings align with the idea that neutralizing tumor acidity can improve drug uptake and reduce the acid-mediated drug resistance often seen in tumors. Another avenue has been to pharmacologically increase intracellular citrate by inhibiting ATP citrate lyase (ACLY), the enzyme that cleaves citrate for lipid synthesis. Hydroxycitrate (a natural derivative of citric acid from Garcinia fruit) is an ACLY inhibitor that has shown anti-tumor activity. In mouse models, hydroxycitrate administration led to reduced tumor growth, presumably by raising citrate levels and curtailing the cancer cell's ability to generate acetyl-CoA for fatty acid synthesis.[84] Several clinical trials have investigated the therapeutic potential of metabolic modulators targeting tumor acidity. 2-deoxy-D-glucose (2-DG) has advanced to phase II clinical testing in solid tumors and breast cancer, demonstrating safety and partial metabolic efficacy.[85,86] Citrate-based interventions, including oral sodium citrate and hydroxycitrate, are being evaluated in early clinical trials for their buffering effects and synergy with chemotherapeutic agents.[87,88] Collectively, these ongoing studies underscore the translational relevance of targeting acid–base balance in breast cancer therapy. Taken together, these data highlight the need to examine the mechanistic basis through which hexose and citrate derivatives modulate tumor pH homeostasis and therapeutic sensitivity.[89,90] Hexose analogs (2-deoxy-D-glucose, mannose) inhibit glycolysis via hexokinase blockade and reduce lactate and proton export through MCT transporters, thereby contributing to intracellular pH normalization and enhanced chemo/radiosensitivity. Conversely, citrate-based agents (sodium citrate, hydroxycitrate) act through distinct yet complementary mechanisms: sodium citrate buffers extracellular acidity, supporting T-cell function, while hydroxycitrate inhibits ATP-citrate lyase, reducing lipid synthesis and metabolic adaptability.[91,92] Overall, these coordinated actions partially restore tumor acid–base equilibrium and sensitize cancer cells to therapeutic intervention (Fig. 2).

3.3 Synergistic strategies and combination therapies

Given the complex network of pH regulation in breast cancer, current research emphasizes combining metabolic therapies with other treatments to maximize anti-tumor effects. Both hexose and citrate derivative strategies can potentiate standard therapies. For example, glycolytic inhibition (2-DG or mannose) tends to lower ATP and can push cancer cells into metabolic crisis when combined with agents that induce oxidative stress or DNA damage, thereby lowering the threshold for apoptosis.[51,60] As mentioned, 2-DG combined with diclofenac (an NSAID that also acidifies the cytosol by inhibiting proton efflux via MCTs) showed enhanced cancer cell kill rates relative to either monotherapy. Likewise, mannose's ability to enforce a glycolytic brake has been shown to sensitize cells to radiation therapy and genotoxic chemotherapy.[62] On the other hand, buffering approaches using citrate could synergize with immunotherapies: an acidic microenvironment is known to impair T cell activation and facilitate immune evasion.[93,94] By raising pH, citrate or related buffers may improve T cell infiltration and function, as suggested by preclinical models where neutralization of tumor acidity boosted checkpoint inhibitor efficacy.[75,95] Comparatively, hexose analogues such as 2-deoxy-D-glucose and mannose primarily suppress glycolysis and lactic acid production, leading to intracellular energy depletion and metabolic stress.[96,97] In contrast, citrate derivatives (sodium citrate and hydroxycitrate) act by buffering extracellular acidity and inhibiting ATP citrate lyase, thereby reducing lipid

synthesis and improving tumor pH balance.[98,99] While hexose-based therapies directly target acid generation at its source, citrate-based strategies stabilize the tumor microenvironment, suggesting their complementary efficacy when combined in integrated treatment approaches.

It is increasingly clear that no single intervention fully reverses the tumor's pH dysregulation, due to redundant mechanisms (multiple transporters, metabolic plasticity). Therefore, rational combinations are a focal point of ongoing studies.[100,101] Researchers are investigating tandem blockade of lactate export (MCT inhibitors) along with glycolysis inhibitors to "trap" acid inside cancer cells, forcing lethal acidification. Others are exploring merging pH-targeted drugs with nanocarriers that release cytotoxins specifically in low-pH environments, thereby turning the tumor's own acidity against it.[102,103] Clinically, several drugs targeting tumor acid–base regulation are under evaluation. Proton pump inhibitors such as omeprazole and lansoprazole have demonstrated tumor-neutralizing and chemosensitizing effects in early clinical studies. Similarly, carbonic anhydrase IX inhibitors (*e.g.*, SLC-0111) have completed phase I trials, showing safety and preliminary efficacy in solid tumors. Systemic bicarbonate therapy has also been explored as a buffering strategy to elevate tumor pH and enhance treatment response. These findings indicate that pharmacological modulation of tumor acidity holds translational promise for breast cancer therapy.[104,105]

Pharmacokinetic aspects are also crucial for assessing the therapeutic potential of these compounds. Hexose analogues such as 2-deoxy-D-glucose exhibit rapid cellular uptake through glucose transporters but display a short plasma half-life and limited bioavailability due to metabolic degradation. Mannose shows favorable oral absorption, though its tissue distribution depends on phosphomannose isomerase (PMI) activity.[105-107] In contrast, citrate derivatives demonstrate good systemic tolerance and rapid renal clearance, while hydroxycitrate maintains moderate bioavailability and effective tissue penetration.[108,109] These pharmacokinetic features highlight the need for improved formulations or nanocarrier-based delivery systems to enhance efficacy and tumor selectivity.

4. Conclusion

Dysregulated acid–base homeostasis is a hallmark of breast cancer, shaping tumor biology and therapeutic resistance. The Warburg-driven acidic TME confers survival advantages, promotes invasion, and impairs immune surveillance. Strategies aimed at reducing acid production, enhancing proton buffering, and disrupting pH-regulatory transporters show considerable preclinical promise. Hexose analogues and citrate derivatives emerge as leading candidates, acting via complementary mechanisms to impair tumor metabolism and modulate the TME. Combination regimens linking pH-targeted agents with chemotherapy, radiotherapy, or immunotherapy may offer synergistic benefits by addressing both metabolic vulnerabilities and immune suppression. However, translating these approaches into routine clinical practice requires overcoming challenges in drug delivery, specificity, and patient selection. Biomarker-guided trials, particularly those assessing glycolytic enzyme expression or citrate metabolism, will be crucial for identifying responsive patient subsets. Future studies should focus on integrating pH-modulating therapies with immune checkpoint inhibitors to restore anti-tumor immunity and on developing reliable biomarkers of tumor acidity to enable personalized treatment selection. Such combined approaches may reveal new therapeutic windows and improve clinical outcomes in resistant breast cancer phenotypes. As our understanding of tumor acid–base regulation deepens, the integration of metabolic and pH-focused interventions into breast cancer management holds significant potential for improving survival and quality of life, especially in aggressive, treatment-resistant subtypes such as triple-negative breast cancer.

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Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

CRediT Statement

Rauash Mangazbayeva: Investigation, Data curation, Formal analysis, Visualization. **Ayaz Belkozhayev:** Conceptualization, Methodology, Writing - Original draft, Writing - Review & editing, Supervision, Project administration, Funding acquisition. **Laura Agibayeva:** Methodology, Validation, Resources, Writing - Review & editing. **Anel Mun:** Formal analysis, Data curation, Visualization. **Bayana Yermukhambetova:** Investigation, Methodology, Validation, Writing - Review & editing. **Mubarak Yermaganbetov:** Software, Data curation, Formal analysis, Visualization. **Adilet Alikulov:** Methodology; Resources, Validation, Writing - Review & editing. **Grigoriy Mun:** Supervision, Conceptualization, Writing - Review & editing.

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