Crosstalk between ferroptosis, metabolic reprogramming and antitumor immunity in the hypoxic breast cancer microenvironment (Review)

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Abstract. Hypoxia-driven metabolic reprogramming in the breast cancer (BC) tumor microenvironment (TME) notably influences tumor progression and immune evasion. However, the mechanistic links among hypoxia, tricarboxylic acid (TCA) cycle dysregulation, ferroptosis and natural killer (NK) cell dysfunction remain poorly defined. The present review delineates a unified framework in which hypoxia-induced hypoxia-inducible factor 1α stabilization disrupts TCA cycle flux, triggering mitochondrial reactive oxygen species overproduction and dual glutathione depletion (through electrophilic oncometabolite quenching and nutritional competition for cystine), thereby executing ferroptosis via lipid peroxidation. Critically, the same metabolic cascade propagates immunosuppressive oxidized lipids into the TME, potentially inducing bystander ferroptosis in NK cells, impairing their infiltration, and silencing their cytotoxic functions through receptor downregulation and metabolic paralysis. The present review further discusses the therapeutic paradox that ferroptosis induction kills tumor cells yet simultaneously compromises the immune effectors required for sustained antitumor responses. Breaking the hypoxia-TCA cycle-ferroptosis-immune suppression circuit represents a conceptual prerequisite for advancing NK cell-based immunotherapy in BC. Strategies that selectively sensitize tumor cells to ferroptosis while enhancing the role of NK cells against oxidative death may ultimately overcome this metabolic checkpoint and improve clinical outcomes.

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Contents

1. Introduction
2. Molecular regulatory mechanism of ferroptosis in BC
3. Metabolic and redox regulation of ferroptosis in BC
4. Paradoxical interplay: Ferroptosis and antitumor immunity in the BC microenvironment
5. Evolving paradigm of the TCA cycle in cancer biology
6. Trap-Kill-Disarm model: From TCA dysfunction to ferroptotic execution and NK cell immune paralysis in BC
7. Hypoxia-TCA cycle-ferroptosis axis as a metabolic checkpoint of NK cell surveillance in breast cancer
8. Conclusions

1. Introduction

Breast cancer (BC) remains the most commonly diagnosed cancer among women worldwide, with an estimated 2.3 million new cases and 666,000 associated deaths in 2022, accounting for 23.8% of all female cancer cases and 15.4% of cancer-associated deaths (1). Despite substantial progress in surgical intervention, chemotherapy, targeted therapy and immunotherapy, tumor metastasis and therapeutic resistance still pose notable clinical challenges (2). The complex tumor microenvironment (TME) critically regulates malignant progression in BC, indicating that exploring metabolic reprogramming, regulated cell death and immune mechanisms is crucial for developing novel therapeutic strategies (3). Hypoxia, metabolic reprogramming, ferroptosis and antitumor immunity closely interact in BC, but the regulatory networks underlying this crosstalk remain unclear (2,4).

Accumulating evidence indicates that TME remodeling is strongly associated with BC progression, metastasis and chemoresistance (2,4). The tumor immune microenvironment constitutes a complex ecological system comprising tumor cells, natural killer (NK) cells, other immune cells, fibroblasts, endothelial cells and extracellular matrix components (3). Tumor immune editing and immune escape severely limit current immunotherapy efficacy, highlighting the necessity of restoring and enhancing endogenous antitumor immune responses (5). As a core component of innate immunity, NK

cells are essential for maintaining TME homeostasis and tumor immune surveillance. NK cells recognize and eliminate malignant cells through stress-induced ligands and altered self-ligands, thereby exerting critical antitumor effects (6,7). NK cells not only directly kill tumor cells but also modulate adaptive immune responses, which highlights their potential use in tumor immunotherapy (6). However, NK cell infiltration, proliferation and cytotoxic activity are frequently suppressed within the BC TME (7). Importantly, hypoxia-driven metabolic reprogramming and ferroptosis signaling profoundly modulate NK cell function, forming a core regulatory axis that merits systematic review.

Hypoxia is a prominent metabolic hallmark of the TME and serves as a key driver of tumor progression (8,9). Under hypoxic conditions, normal cells typically reduce proliferation to adapt to oxygen deficiency. By contrast, cancer cells undergo oncogenic activation, tumor suppressor mutations and metabolic reprogramming to adapt to hypoxic stress and maintain proliferation (9). Hypoxia-related signaling cascades regulate tumor cell proliferation, migration, invasion and angiogenesis, ultimately affecting therapeutic responses and clinical prognosis (9).

Ferroptosis is an iron-dependent form of regulated cell death, and is characterized by glutathione (GSH) depletion, glutathione peroxidase 4 (GPX4) inactivation, iron overload and excessive lipid peroxidation (10,11). Ferroptosis acts both as a tumor-suppressive mechanism and as a promising therapeutic target in BC (3,12,13). Core regulatory pathways of ferroptosis, including the GSH/GPX4 axis, iron-dependent Fenton reaction and phospholipid peroxidation metabolism, are tightly controlled by hypoxic signaling in the TME (8,10).

Metabolic reprogramming is a well-established hallmark of cancer, supporting tumor proliferation, survival and immune escape (14). The tricarboxylic acid (TCA) cycle occupies a central role in cancer metabolic rewiring (15-17). In BC, TME hypoxia and metabolic enzyme abnormalities disrupt TCA cycle homeostasis, leading to the accumulation of oncometabolites such as succinate, fumarate and 2-hydroxyglutarate (15,17,18). These TCA-derived metabolites further stabilize hypoxia-inducible factor (HIF)-1α, remodel intracellular redox states and epigenetically promote malignant progression (8,15).

The present review aims to summarize the regulatory mechanisms by which hypoxia modulates ferroptosis in BC, and further elaborate on how TCA cycle reprogramming influences NK cell biological functions. Clarifying the crosstalk among metabolic reprogramming, ferroptosis and NK cell immune activity within the hypoxic TME could offer novel mechanistic insights and potential combination strategies for BC therapy.

2. Molecular regulatory mechanism of ferroptosis in BC

Ferroptosis is a distinct form of regulated cell death governed by multiple core mechanisms, including iron-dependent reactive oxygen species (ROS) generation, the GSH-centered redox system and GPX4-mediated lipid peroxide detoxification (10,19). These molecular processes serve critical roles in regulating biological behavior and cell death in BC (12,13).

GPX4 is a selenoprotein that catalyzes the reduction of phospholipid hydroperoxides, thus acting as the principal inhibitor of ferroptosis in mammalian cells (10,11). Its enzymatic activity depends on the selenocysteine-containing active site, with GSH acting as the essential electron donor (11,20). As the central guardian against lipid peroxidation, GPX4 is indispensable for regulating ferroptosis and BC malignant progression (11,12,20).

Targeting ferroptosis has emerged as a promising therapeutic strategy for BC. Modulating GPX4 activity, altering intracellular ROS levels or manipulating lipid peroxidation pathways offers potential approaches to reverse therapeutic resistance and improve clinical outcomes in BC (12,13,21).

Multiple cellular sources contribute to intracellular ROS generation in BC cells. The mitochondrial respiratory chain and endoplasmic reticulum oxidoreductases, such as cytochrome P450 oxidoreductase and cytochrome B5 reductase 1, facilitate electron transfer to molecular oxygen, producing ROS and driving phospholipid peroxidation during ferroptosis (22,23). NADPH oxidase (NOX) family proteins also represent important ROS sources, collectively influencing ferroptotic sensitivity (10,24). Notably, the tumor suppressor p53 inhibits ferroptosis by blocking the assembly of the NOX1-dipeptidyl peptidase 4 (DPP4) complex in colorectal cancer cells, thereby reducing ROS production and ferroptotic cell death (24). Whether this p53-NOX1-DPP4 axis operates similarly in BC requires further investigation, given the complexity of p53-mediated ferroptosis regulation in cancer (25,26).

3. Metabolic and redox regulation of ferroptosis in BC

Ferroptosis in BC is tightly regulated by the interplay between cellular metabolism and redox homeostasis (27,28). Key pathways involving iron, lipid and amino acid metabolism, together with redox signaling networks, jointly determine intracellular redox status. Dysregulation of these metabolic processes disrupts the balance between ROS generation and clearance, thereby altering ferroptotic sensitivity in BC cells (19,27).

Iron metabolism reprogramming and ferroptosis regulation. Iron metabolism is essential for ferroptosis induction. Excess labile iron directly triggers ROS production via the Fenton reaction, initiating lipid peroxidation (19,28). BC cells alter iron metabolism pathways to maintain ferroptosis resistance and support malignant progression, involving the regulation of iron uptake, storage and efflux (12,28). Targeting iron metabolic homeostasis effectively increases ferroptosis sensitivity in BC (29,30), particularly in triple-negative subtypes (21,31).

Lipid metabolism and ferroptosis susceptibility. Lipid metabolic reprogramming is a key determinant of ferroptosis vulnerability in BC. Polyunsaturated fatty acid (PUFA)-containing phospholipids are critical substrates for lethal lipid peroxidation during ferroptosis (32,33). Lipid metabolic enzymes involved in PUFA synthesis and membrane incorporation, such as acyl-CoA synthetase long-chain (ACSL) family members, are dysregulated in BC cells, altering membrane lipid composition and ferroptosis sensitivity (32,33). BC cells also activate antioxidant pathways to scavenge lipid peroxides and develop ferroptosis

resistance (34). Targeting lipid metabolic enzymes has thus become a promising strategy to enhance ferroptosis-mediated tumor suppression in BC (21,35).

Amino acid metabolism and redox homeostasis in ferroptosis. Amino acid metabolism, particularly involving cystine and glutamate, controls GSH synthesis and redox balance, thereby influencing ferroptosis (10,36). The cystine/glutamate antiporter system Xc^- antiporter mediates cystine uptake to support GSH biosynthesis, and its abnormal expression is closely associated with ferroptosis resistance and poor prognosis in BC (12,36). Glutamine metabolism also contributes to GSH precursor supply and redox regulation, affecting ferroptotic cell death in BC (27). However, glutamine metabolism in the TME represents a double-edged sword: Beyond serving as a GSH precursor, glutamine is a major bioenergetic fuel for numerous cancer cells, and its restriction has been proposed as a therapeutic strategy to target tumor glutamine addiction (30). While glutamine depletion can suppress cancer cell proliferation *in vitro*, *in vivo* evidence suggests that systemic glutamine deprivation may have unintended immunosuppressive consequences. Enzymatic depletion of circulating glutamine in syngeneic mouse models of BC increased intratumoral infiltration of myeloid-derived suppressor cells (MDSCs) and failed to inhibit tumor growth, with The Cancer Genome Atlas analyses confirming that glutamine depletion signatures correlate with poor clinical outcomes and MDSC accumulation (37). Conversely, oral glutamine supplementation in rat BC models enhanced NK cell activity through GSH-mediated suppression of prostaglandin E2 (PGE2) synthesis, leading to ~40% reduction in tumor growth (29). Thus, the net effect of glutamine modulation depends on the balance between tumor cell dependence on glutamine and the metabolic requirements of antitumor immune cells, a balance that may vary across BC subtypes and TME contexts.

Redox signaling pathways in ferroptosis regulation. Redox signaling centered on ROS and GSH forms the core mechanism driving ferroptosis (10). The pentose phosphate pathway maintains intracellular NADPH levels to support GSH regeneration and redox balance, influencing ferroptosis progression (14). Redox-sensitive transcription factors such as nuclear factor erythroid 2-related factor 2 (NRF2) are aberrantly activated in BC, upregulating antioxidant and ferroptosis-related genes to enhance stress tolerance and ferroptosis resistance (37). Modulating redox signaling pathways can effectively disrupt metabolic adaptation and increase ferroptosis sensitivity in BC cells (37). The key ferroptosis regulators in BC, their expression alterations and functional impacts are summarized in Table I (11,12,15,20,24,26,28,31-33,36-40).

4. Paradoxical interplay: Ferroptosis and antitumor immunity in the BC microenvironment

The BC immune microenvironment is a complex ecosystem involving diverse immune cells throughout tumor initiation and progression (5,41). Metabolic stress within the TME alters functional programs of infiltrating immune cells, impairing effective antitumor immune responses (5,42). Understanding these immune regulatory networks is essential to restore endogenous antitumor immunity in BC.

Ferroptosis serves a paradoxical role in tumor immunity. On the one hand, this iron-dependent regulated cell death exerts direct tumor-suppressive effects through cytotoxicity against cancer cells (28,43). On the other hand, ferroptosis induces immunosuppressive effects within the TME. Notably, ferroptotic cell death may compromise immune surveillance by affecting the viability and function of tumor-infiltrating immune cells (44,45). Furthermore, ferroptosis in tumor neutrophils promotes immune suppression by releasing lipid peroxidation products that impair T-cell activity (46).

Conversely, ferroptosis can enhance antitumor immune responses. Ferroptotic cancer cells release damage-associated molecular patterns (DAMPs) and tumor antigens that stimulate innate and adaptive immunity, offering opportunities for combined therapeutic strategies (43,47). The interaction between ferroptosis signaling and the tumor immune microenvironment is increasingly recognized as a critical determinant of therapeutic response in cancer (48,49). The tumor suppressor p53 further illustrates this interplay (15,50): Besides its role in ferroptosis regulation, p53 also enhances NK cell-mediated immune surveillance against tumor cells (38).

The intricate balance between the pro- and antitumor immunomodulatory effects of ferroptosis highlights it as a clinically relevant target for optimizing BC immunotherapy. Therapeutic strategies must carefully consider both direct cytotoxic effects on malignant cells and broader consequences for tumor immunity (44). Combination approaches integrating ferroptosis inducers with immunotherapy have demonstrated promising synergy (43,49).

5. Evolving paradigm of the TCA cycle in cancer biology

The TCA cycle acts as a central metabolic hub controlling energy supply, redox equilibrium and biosynthesis in normal cells. In malignant conditions, the canonical TCA cycle flux is substantially reprogrammed, providing tumor cells with metabolic plasticity beyond basic bioenergetic demands (15-17).

Within the BC TME, hypoxic stress and oncogenic aberrations disrupt key TCA cycle enzymes, causing abnormal accumulation of oncometabolites such as succinate, fumarate and 2-hydroxyglutarate (15,17,18). These metabolites stabilize HIF-1α, perturb intracellular redox status and trigger epigenetic alterations, thereby promoting BC cell proliferation, invasion and immune escape (15,17).

Dysregulated TCA cycle signaling is closely linked to BC progression, metastasis and therapeutic resistance (18). Enzyme mutations and abnormal expression reshape metabolic phenotypes, enabling BC cells to adapt to nutrient limitation and hypoxic stress within the TME (15,16). Furthermore, TCA cycle reprogramming mediates metabolic interactions between cancer, stromal and infiltrating immune cells, influencing the tumor immunological landscape (15,17).

Rather than merely serving as energy-generating machinery, the TCA cycle is increasingly recognized as a dynamic signaling node integrating metabolism, epigenetics and oncogenic pathways (15,18). Elucidating TCA cycle remodeling and its downstream molecular events in BC provides a mechanistic

Table I. Key ferroptosis regulators and their alterations in BC.

Category	Regulator	Alteration in BC	Effect on Ferroptosis	(Refs.)
Core suppressor	GPX4	Upregulated in therapy-resistant BC; downregulated in sensitive subtypes	Central inhibitor of lipid peroxidation; its inactivation triggers ferroptosis	(11,12,20)
	GSH	Depleted by oncometabolites (fumarate) and cystine competition	Obligate substrate for GPX4; depletion disables lipid peroxide detoxification	(15,36)
Iron metabolism	TfR1	Upregulated in BC	Enhances iron uptake, expanding labile iron pool for Fenton reaction	(28)
	NCOA4	Activated in TNBC	Autophagic ferritin degradation releases free iron, sensitizing cells to ferroptosis	(31)
	DMT1	Upregulated in BC	Mediates iron uptake from endosomes into cytoplasm, increasing labile iron pool	(41)
Lipid metabolism	ACSL4	Upregulated in BC	Activates PUFAs for membrane incorporation, increasing peroxidation-prone phospholipids	(32,33)
	LPCAT3	Upregulated	Catalyzes PUFA insertion into membrane phospholipids	(33)
	SCD1	Dysregulated in BC	Converts saturated to monounsaturated fatty acids; downregulation promotes ferroptosis susceptibility	(39)
Amino acid/GSH	SLC7A1 (xCT)	Upregulated, especially in TNBC	Mediates cystine uptake for GSH synthesis; high expression confers ferroptosis resistance	(12,36)
Redox signaling	NRF2	Aberrantly activated in BC	Upregulates GPX4, SLC7A11 and GSTs; promotes ferroptosis resistance	(37)
	p53	Frequently mutated/lost in BC	Loss diminishes ferroptosis execution and impairs NK cell recognition	(24,26,38)

BC, breast cancer; GPX4, glutathione peroxidase 4; GSH, glutathione; TfR1, transferrin receptor 1; NCOA4, nuclear receptor coactivator 4; DMT1, divalent metal transporter 1; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; SCD1, stearoyl-CoA desaturase 1; SLC7A11, solute carrier family 7 member 11; NRF2, nuclear factor erythroid 2-related factor 2; TNBC, triple-negative breast cancer; GST, glutathione S-transferase ; PUFA, polyunsaturated fatty acid.

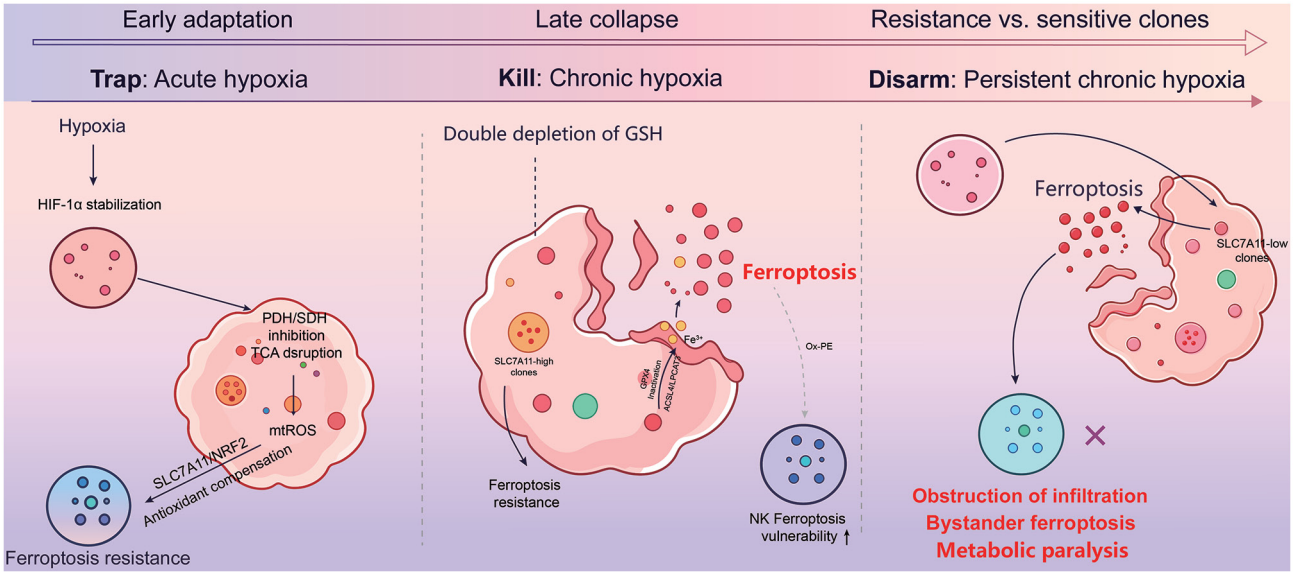


Figure 1. Temporal progression of the Trap-Kill-Disarm cascade linking tumor ferroptosis to NK-cell immune dysfunction in hypoxic breast cancer microenvironment. This schematic depicts step-wise biological events across acute, chronic and persistent chronic hypoxia. In Phase I (Trap), HIF-1α-driven TCA-cycle disruption triggers a mtROS burst; breast cancer cells activate SLC7A11/NRF2-dependent ferroptosis resistance, whereas infiltrated NK cells only develop mild mitochondrial stress. In Phase II (Kill), dual GSH-depleting pathways (fumarate-mediated consumption and cystine competition) break antioxidant defense, driving ferroptosis in SLC7A11-low tumor subclones. The dashed line denotes a hypothesized bystander oxidized-lipid signal targeting NK cells, which awaits experimental validation in breast cancer. NK cells gradually exhaust GSH and become vulnerable to ferroptosis. In Phase III (Disarm), sustained metabolic stress impairs NK infiltration, induces bystander NK ferroptosis, and triggers receptor down-regulation together with metabolic paralysis, ultimately abolishing anti-tumor surveillance. Late-stage modulators HIF-2α, FSP1-CoQ10 and GCH1-BH4 are labelled. This figure was created using Adobe Illustrator (Version 24.0; Adobe Systems, Inc.). mtROS, mitochondrial reactive oxygen species; NK, natural killer; HIF, hypoxia-inducible factor; TCA, tricarboxylic acid; GSH, glutathione; SLC7A11, solute carrier family 7 member 11; FSP1, ferroptosis suppressor protein 1; CoQ10, coenzyme Q10; GCH1, GTP cyclohydrolase 1; BH4, tetrahydrobiopterin; NRF2, nuclear factor erythroid 2-related factor 2; PDH, pyruvate dehydrogenase complex; SDH, succinate dehydrogenase.

foundation to further explore its crosstalk with ferroptosis and NK cell immune functions in the hypoxic TME.

Beyond their intracellular metabolic and redox functions, succinate and fumarate also act as extracellular signaling molecules that directly modulate immune cell behavior within the TME. Succinate is a ligand of succinate receptor 1 (SUCNR1; also known as GPR91), a G protein-coupled receptor expressed in various immune cells, including macrophages, dendritic cells and T cells. Engagement of SUCNR1 by tumor-derived succinate promotes macrophage polarization toward an M2-like tumor-promoting phenotype via PI3K-Akt and HIF-1α activation, leading to increased secretion of IL-6 and vascular endothelial growth factor (VEGF) as well as enhanced immunosuppression. Succinate also modulates dendritic cell maturation and T-cell differentiation, with previous evidence suggesting that SUCNR1 signaling can polarize $CD4^+$ T cells toward T helper 17 responses, which are frequently associated with pro-tumor inflammation and T-cell exhaustion (15,51). Fumarate, in addition to its electrophilic GSH-depleting function, covalently modifies cysteine residues on proteins through a process termed succination (15,50). This post-translational modification has been shown to target Kelch-like ECH-associated protein 1, thereby activating NRF2 and promoting anti-inflammatory phenotypes in immune cells. Furthermore, fumarate directly suppresses prolyl hydroxylase activity via cysteine succination, stabilizing HIF-1α and sustaining pro-inflammatory gene programs (38). Thus, beyond functioning as intracellular metabolic intermediates, succinate and fumarate serve as paracrine signaling metabolites that shape the immune landscape, an aspect that merits further investigation in the BC context, where direct evidence remains limited. It is important to note that the effects of TCA metabolites, including fumarate-mediated GSH depletion and succinate-associated ROS/HIF-1α signaling, are highly context-dependent and should not be generalized to all hypoxic breast cancers without sufficient evidence. For example, fumarate raises ROS without depleting GSH. In hypoxic breast tumor-repopulating cells, fumarate accumulation elevates ROS mainly by forming succinic glutathione and lowering the NADPH/$NADP^+$ ratio, not by direct GSH depletion, so the 'fumarate-mediated GSH depletion' pathway does not hold universally (15,20). Succinate stabilizes HIF-1α without requiring ROS. In breast cancer, TAM-derived TGF-β suppresses SDH in tumor cells, causing succinate accumulation and HIF1α stabilization; in bone metastasis, succinate acts via SUCNR1 to activate HIF1α and the YTHDF1/YAP-CXCL5 axis. Neither route depends on ROS as an obligatory mediator (15,51).

6. Trap-Kill-Disarm model: From TCA dysfunction to ferroptotic execution and NK cell immune paralysis in BC

The Trap-Kill-Disarm model is structured into three sequential phases that integrate the core molecular mechanisms and temporal dynamics of hypoxia-driven tumor ferroptosis and NK cell dysfunction (Figs. 1 and 2). Fig. 1 illustrates the comprehensive spatial signaling network linking TCA cycle disturbance, antioxidant collapse, lipid peroxidation

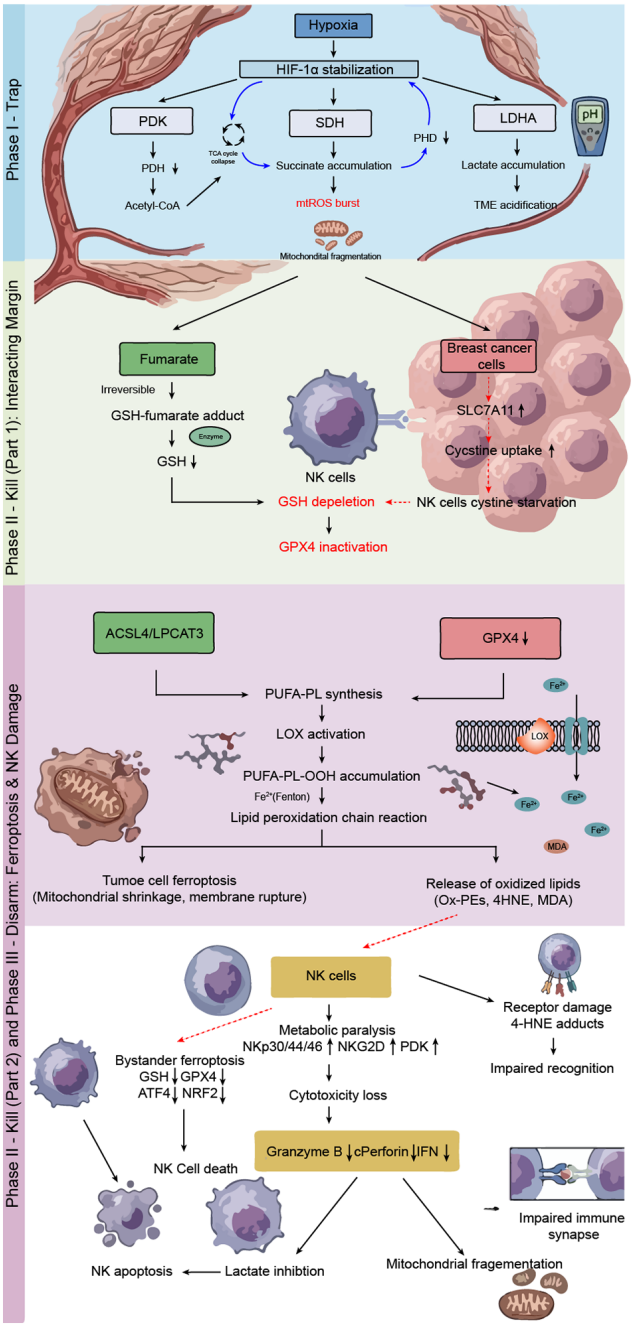


Figure 2. Hypoxia-driven TCA cycle dysregulation links tumor ferroptosis and NK cell immune paralysis in the breast cancer microenvironment. The schematic illustrates the three-phase Trap-Kill-Disarm model. Phase I (Trap) depicts hypoxia-induced TCA cycle disruption and mtROS overproduction. Phase II (Kill) comprises GSH/GPX4 axis collapse and lipid peroxidation-driven ferroptotic execution. Phase III (Disarm) depicts NK cell dysfunction, including impaired infiltration, survival and cytotoxicity. Solid black arrows denote experimentally supported pathways; dashed red arrows denote hypothesized connections requiring direct validation in breast cancer; the dashed blue arrow denotes the positive feedback loop of succinate accumulation → PHD inhibition → HIF-1α stabilization → further TCA suppression. This figure was created using Adobe Illustrator (Version 24.0; Adobe Systems, Inc.). TCA, tricarboxylic acid; HIF-1α, hypoxia-inducible factor 1α; mtROS, mitochondrial reactive oxygen species; GSH, glutathione; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; PUFA, polyunsaturated fatty acid; NK, natural killer; PHD, prolyl hydroxylase; PDK, pyruvate dehydrogenase kinase; PDH, pyruvate dehydrogenase complex; LDHA, lactate dehydrogenase A; SDH, succinate dehydrogenase; LOX, lipoxygenase; Ox-PEs, oxidized phosphatidylethanolamines; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde.

and subsequent NK cell immune impairment in hypoxic BC. Fig. 2 further depicts the stepwise temporal progression of this three-stage cascade. Phase I, Trap, establishes oxidative stress through TCA cycle disruption and mitochondrial ROS (mtROS) overproduction (as explained in the next subsection). Phase II, Kill, executes ferroptosis via GSH/GPX4 axis collapse and lipid peroxidation. Phase III, Disarm, describes the consequences of NK cell infiltration, survival and cytotoxicity. In addition, several modulating factors, including subtype heterogeneity, HIF-2α, compensatory antioxidant pathways and crosstalk with other cell death pathways, shape the activity and sensitivity of this axis (as discussed in subsequent subsections).

Phase I, Trap: TCA cycle disruption and mtROS overproduction. Mitochondrial oxidative phosphorylation is a primary intracellular source of ROS, relying on the TCA cycle to supply the essential electron donors nicotinamide adenine dinucleotide (NADH) and flavine adenine dinucleotide ($FADH_2$) to the electron transport chain (ETC) (15). In the hypoxic BC microenvironment, HIF-1α stabilization orchestrates a complex, multi-layered disruption of TCA cycle integrity, ultimately leading to excessive mtROS production (8,9).

Under hypoxic conditions, HIF-1α directly activates pyruvate dehydrogenase kinase (PDK), which phosphorylates and inhibits the pyruvate dehydrogenase complex, thereby preventing pyruvate conversion into acetyl-CoA (51,52). This mechanism blocks the primary route by which glucose-derived carbon enters the TCA cycle. Concurrently, HIF-1α upregulates lactate dehydrogenase (LDH)A and monocarboxylate transporter 4, diverting pyruvate toward lactate production and extracellular export, further restricting TCA cycle substrate availability (9).

Under hypoxia, the activity of succinate dehydrogenase (SDH), a key TCA cycle enzyme, is markedly reduced, causing substantial accumulation of succinate (15). Excess succinate drives SDH to operate in reverse, producing substantial mtROS at complex II (15,17). Critically, succinate accumulation inhibits PDH activity, thereby preventing HIF-1α ubiquitination and subsequent proteasomal degradation. This mechanism establishes a self-amplifying feedback loop ('succinate accumulation → HIF-1α stabilization → further TCA cycle suppression → increased succinate accumulation') that maintains pathologically high mtROS levels (15,53).

Defects in TCA cycle metabolism directly induce aberrant mitochondrial morphology, which is characterized by fragmented mitochondrial networks (54). Fragmented mitochondria display disrupted cristae structures and impaired assembly of ETC supercomplexes, increasing electron leakage from complexes I and III directly to molecular oxygen, generating superoxide anions. Zheng *et al* (54) demonstrated that mitochondrial fragmentation notably impairs NK cell-mediated tumor immune surveillance. Thus, within the hypoxic BC TME, infiltrating NK cells are not passive bystanders but directly experience mitochondrial fragmentation and oxidative stress resulting from TCA cycle disruption. This interpretation is supported experimentally by Hernansanz-Agustín *et al* (55), who showed that acute hypoxia induces a marked superoxide burst in cells dependent on intact mitochondrial ETC function.

Collectively, hypoxia employs a three-pronged strategy, enzyme inhibition, electron transport disruption and mitochondrial fragmentation, to convert the TCA cycle from a bioenergetic hub into a prominent ROS source. This oxidative stress establishes the biochemical foundation necessary for subsequent depletion of the GSH/GPX4 axis and the initiation of lipid peroxidation (10,27).

Phase II, Kill: Dual depletion of the GSH/GPX4 axis. The GSH/GPX4 axis is the primary cellular defense system against ferroptosis, with GPX4 catalyzing the reduction of phospholipid hydroperoxides using GSH as its essential electron donor (11,20). Within the hypoxic BC TME, TCA cycle disruption undermines this axis through two complementary mechanisms: i) Direct chemical depletion of GSH by electrophilic oncometabolites; and ii) competitive depletion of nutrients required for GSH synthesis.

Dysregulation of the TCA cycle results in pathological accumulation of electrophilic metabolites, particularly fumarate, which contains an α,β-unsaturated carbonyl group (15,18). These electrophilic compounds rapidly react via Michael addition with the nucleophilic thiol group of GSH, forming stable covalent adducts and irreversibly diminishing intracellular GSH reserves (15). Such chemical sequestration directly limits GSH availability for GPX4, leaving cells vulnerable to lipid peroxidation (11,20). This mechanism functions independently of transcriptional regulation, representing a rapid, metabolically embedded pathway to ferroptosis sensitization. While certain TCA cycle intermediates have been reported to confer antioxidant effects in neuronal contexts (56), the chronic hypoxia-induced accumulation of electrophilic metabolites in BC clearly shifts the intracellular environment toward pronounced GSH depletion (15).

In addition to direct chemical consumption, hypoxia-driven remodeling of the TCA cycle initiates nutritional competition, depriving infiltrating immune cells of critical GSH precursors. BC cells, particularly of the triple-negative subtype, upregulate solute carrier family 7 member 11 (SLC7A11), the cystine-specific subunit of the system Xc^- antiporter, to fulfill increased cystine demands for GSH synthesis (36). This transcriptional response, which is partly regulated by HIF-1α and NRF2, enables tumor cells to robustly resist ferroptotic cell death (12,37). However, the increased cystine uptake by tumor cells substantially reduces cystine availability in the TME, thereby restricting cysteine (the rate-limiting precursor for GSH) for NK cells (36). Consequently, NK cells experience progressive GSH depletion, GPX4 dysfunction and elevated lipid peroxide accumulation, ultimately succumbing to ferroptotic death (11,20).

This nutrient competition is exacerbated further by glutamine addiction. To replenish TCA intermediates depleted via cataplerosis, an effect intensified under hypoxia, BC cells markedly elevate glutamine uptake (15,27). Glutamine metabolism contributes doubly to GSH maintenance: Its breakdown directly provides glutamate, a necessary precursor for GSH synthesis, and glutamate also functions as the exchange substrate required for cystine import via system Xc^- (27,36). Thus, increased glutamine consumption by tumor cells simultaneously diminishes both the glutamate and cystine pools available to NK cells, critically impairing GSH biosynthesis. The importance of this pathway is underscored by previous evidence indicating that glutaminase inhibition enhances ferroptosis susceptibility in cancer cells by restricting GSH production (27). Within the hypoxic BC TME, coordinated metabolic disruptions, including electrophilic GSH depletion, cystine scarcity and glutamine exhaustion, collectively disrupt the NK cell GSH/GPX4 axis, creating conditions favorable for ferroptosis (10,44).

It should be emphasized that the HIF-1α/NRF2-driven upregulation of SLC7A11 represents an early adaptive response to hypoxic stress, conferring transient ferroptosis resistance to BC cells during the initial phase of TCA cycle remodeling. This is consistent with previous pan-cancer analyses demonstrating that SLC7A11 upregulation is tightly associated with drug resistance (57,58). However, this compensatory mechanism is not infinite. With prolonged chronic hypoxia, progressive accumulation of electrophilic oncometabolites and intensifying nutrient competition gradually overwhelm the GSH biosynthetic capacity, converting the protective adaptation into a state of metabolic exhaustion. Consequently, the GSH/GPX4 axis eventually collapses, shifting the balance from ferroptosis resistance to execution in a time-dependent manner. Furthermore, this transition may be further shaped by intratumoral heterogeneity: Although direct evidence in BC is lacking, previous studies in renal cell carcinoma and lung adenocarcinoma have demonstrated the coexistence of SLC7A11-high and -low subclones with differential ferroptosis susceptibility (59,60). By extrapolation, it is plausible that analogous heterogeneity exists in BC, where SLC7A11-high subclones maintain resistance while SLC7A11-low or metabolically compromised counterparts undergo ferroptosis, releasing oxidized lipids that exert paracrine immunosuppressive effects (as discussed in subsequent subsections). The regulatory network governing this transition has been comprehensively reviewed elsewhere (45,50).

Beyond direct metabolic effects, TCA cycle defects that lead to fumarate and D-2-hydroxyglutarate (D-2HG) accumulation have been shown to suppress antitumor immunity. D-2HG, produced by mutant isocitrate dehydrogenase (IDH) enzymes, can be released into the TME and impair $CD8^+$ T-cell function through multiple mechanisms, including inhibition of LDH activity, and disruption of T-cell metabolism and epigenetic reprogramming (61). Similarly, fumarate accumulation has been linked to impaired T-cell activation and cytokine production (50). These findings extend the immunosuppressive consequences of TCA cycle dysregulation beyond NK cells to other immune effectors, suggesting that oncometabolite-mediated immune suppression is a broad phenomenon in hypoxic TMEs.

Phase II, Kill: Lipid peroxidation and ferroptotic execution. While the preceding subsection described ferroptosis resistance in BC cells via the HIF-1α/NRF2/SLC7A11 axis, the current subsection addresses the subsequent phase, namely when chronic hypoxia and TCA cycle dysfunction reach a critical threshold. At this late stage, protective mechanisms are overwhelmed, and lipid peroxidation executes ferroptosis preferentially in metabolically vulnerable tumor subclones and, more critically, in infiltrating NK cells with already compromised GSH/GPX4 systems. Enzymatically, ACSL4 and

lysophosphatidylcholine acyltransferase 3 (LPCAT3) enrich membrane phospholipids with PUFAs, generating substrates highly susceptible to oxidative damage. Although direct evidence in BC is currently lacking, multi-omics analyses in hepatocellular carcinoma have revealed that ACSL4 enrichment correlates with ferroptosis sensitivity in cancer cells and is also highly expressed in NK cells (45). By extrapolation, it is plausible that a similar ACSL4-driven lipid peroxidation axis may be operational in the BC immune microenvironment. Thus, the transition from 'resistance' to 'execution' is not contradictory but reflects a temporal hierarchy and cell-type specificity within the evolving hypoxic TME (58). Specifically, this paradox can be resolved by defining the spatiotemporal conditions: i) Temporally, SLC7A11 upregulation confers early adaptation (resistance), whereas prolonged chronic hypoxia leads to late collapse (execution); and ii) spatially, intratumoral heterogeneity dictates that SLC7A11-high subclones exhibit resistance, while SLC7A11-low subclones undergo execution.

The convergence of mtROS accumulation and the collapse of the GSH/GPX4 axis culminates in ferroptosis via membrane phospholipid peroxidation. In BC, this process results from the coordinated induction of lipid metabolic enzymes that facilitate lipid peroxidation and the concurrent failure of lipid peroxide detoxification mechanisms (10,33).

Cellular susceptibility to ferroptosis primarily depends on the abundance of PUFA-containing phospholipids within membranes, as their bis-allylic hydrogens readily undergo abstraction during lipid peroxidation (32,33). BC cells upregulate ACSL4, an enzyme that converts PUFAs, particularly arachidonic acid, into activated PUFA-CoA derivatives (32). LPCAT3 subsequently incorporates these activated fatty acids into membrane phospholipids, enriching membranes with substrates highly susceptible to oxidative damage (33). Thus, the ACSL4/LPCAT3-mediated enrichment of PUFA-phospholipids predisposes BC cells to ferroptosis, creating a latent vulnerability with therapeutic implications (35).

Lipoxygenases, non-heme iron-dependent dioxygenases, catalyze the initiation of lipid peroxidation in the presence of PUFA-containing phospholipids (10,33). Under normal physiological conditions, GPX4 continually reduces phospholipid hydroperoxides generated by basal lipoxygenase activity, thereby maintaining lipid homeostasis (11,20). However, when GSH/GPX4-dependent detoxification mechanisms collapse, as occurs through the aforementioned dual depletion mechanisms, lipoxygenase-driven lipid peroxidation proceeds unchecked. This results in extensive phospholipid hydroperoxide formation, which, in the presence of ferrous iron (Fe^{2+}), triggers uncontrolled lipid autoxidation through Fenton chemistry (10,19). The resulting excessive lipid peroxide accumulation disrupts membrane integrity, leading to characteristic ferroptotic morphological features such as mitochondrial shrinkage and outer membrane rupture (10,28).

In BC, the Fe^{2+} required for lipid peroxidation is abundantly available due to the iron-rich TME. Tumor cells enhance iron uptake through transferrin receptor 1 upregulation and release labile iron via ferritinophagy, the autophagic degradation of ferritin (28,31). This combination of enriched PUFA-phospholipids, uncontrolled lipoxygenase activity and high labile iron levels creates a precarious biochemical state restrained solely by GPX4 function. Consequently, pharmacological inhibition of GPX4, either directly or through GSH depletion, has emerged as a promising therapeutic strategy, particularly against treatment-resistant BC subtypes (12,13,21).

Beyond direct cytotoxicity, lipid peroxidation products generated during ferroptosis exert notable immunomodulatory effects, particularly relevant to NK cell biology. Kim *et al* (46) demonstrated that ferroptotic neutrophils release oxidized phospholipids that functionally suppress T-cell responses within the TME. This key finding establishes that lipid peroxidation products can act as paracrine immunosuppressive mediators, a concept readily applicable to the interactions between ferroptotic BC and NK cells. Oxidized PUFA-phospholipids released by dying tumor cells can integrate into the plasma membranes of adjacent NK cells, potentially initiating secondary lipid peroxidation cascades (44). This bystander ferroptotic propagation model is supported by evidence from ferroptotic neutrophils suppressing T-cell responses (46) and from ovarian cancer models demonstrating activating transcription factor 3 (ATF3)-mediated NK cell ferroptosis (62). However, whether this mechanism operates similarly in the BC TME remains a hypothesis that requires direct experimental validation, and the extent to which tumor-derived oxidized lipids directly trigger NK cell ferroptosis in BC warrants further investigation. Given their already compromised GSH/GPX4 systems, NK cells within the hypoxic TME may be particularly vulnerable to such bystander effects. However, it should be noted that the majority mechanistic insights into ferroptosis sensitivity in immune cells have been derived from $CD8^+$ T cell studies, and T cells differ fundamentally from NK cells in metabolic features and ferroptosis susceptibility (63). Whether this bystander propagation operates with comparable kinetics or magnitude in NK cells within the BC TME requires direct validation using NK-cell-specific models. However, a previous ovarian cancer study provides direct evidence that tumor-infiltrating NK cells undergo ATF3-mediated ferroptosis (52), supporting the relevance of this pathway in NK cell biology, albeit in a different tumor context. Due to their already compromised GSH/GPX4 systems, NK cells within the hypoxic TME are vulnerable to this 'bystander' ferroptotic propagation. Recent findings further support this mechanism, revealing that tumor-infiltrating NK cells undergo ferroptosis mediated by ATF3-dependent suppression of the NRF2 antioxidant response, implicating the integrated stress response in NK cell susceptibility to ferroptosis (62).

Additionally, lipid peroxidation products, such as 4-hydroxynonenal (4-HNE) and malondialdehyde, form covalent adducts with proteins on the NK cell surface, impairing receptor functionality and downstream signaling (10). Activating NK receptors, including NKp30, NKp44 and NKp46, which are already downregulated by hypoxia (64), are particularly susceptible to oxidative modification, further diminishing NK cell-mediated cytotoxicity.

Overall, lipid peroxidation driven by TCA cycle dysfunction and GSH/GPX4 impairment not only executes tumor cell death but also initiates an immunosuppressive cascade of oxidized lipid mediators, creating an environment of immune exclusion within the BC TME (43-46,57-60).

Modulating factors of the Trap-Kill-Disarm axis

Subtype heterogeneity in ferroptosis regulation and NK cell dysfunction. The aforementioned mechanistic framework may not uniformly apply across all BC subtypes, as key ferroptosis regulators exhibit substantial inter-subtype heterogeneity (65).

Triple-negative BC (TNBC) displays heightened ferroptosis sensitivity due to elevated ACSL4 expression and cystine metabolism dependence (12,66). However, intra-TNBC heterogeneity exists: The mesenchymal subtype resists ferroptosis via solute carrier family 22 member 3 (SLC22A3)-driven serotonin metabolism (67), whereas the luminal androgen receptor subtype shows vulnerability associated with GPX4 dependency (12). Ferroptosis potential in TNBC correlates with immunotherapy response, and enhancing ferroptosis improves anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) efficacy (66). Human epidermal growth factor receptor 2 (HER2)-positive BC features SLC7A11 upregulation as an adaptive resistance mechanism, and SLC7A11 inhibition resensitizes trastuzumab-resistant cells (67). Hormone receptor-positive (luminal) tumors exhibit lower ferroptosis sensitivity, likely due to lower ACSL4 expression, although the basis remains unclear (65). BReast CAncer susceptibility gene (BRCA)-mutant tumors may harbor ferroptosis susceptibility, but direct evidence is limited (67). NK cell infiltration also displays subtype-specific patterns: SLC7A11 upregulation correlates with reduced NK cell infiltration; however, whether this association holds equally across subtypes is unknown (66).

These differences have therapeutic implications: TNBC is suitable for ferroptosis inducers combined with immunotherapy (66), whereas HER2-positive disease may require overcoming SLC7A11-mediated resistance (67). Systematic characterization of ferroptosis landscapes across BC subtypes is needed to enable precision approaches (12,65).

HIF-2α dimension: A complementary but distinct hypoxic axis. While the preceding subsections have focused on HIF-1α as the primary mediator of hypoxia-driven TCA reprogramming and ferroptosis regulation, it is important to acknowledge the complementary and potentially opposing roles of HIF-2α in the BC TME. HIF-1α and HIF-2α, although sharing high sequence homology in their DNA-binding and dimerization domains, exhibit distinct expression patterns, temporal dynamics and non-redundant functions in cancer (68). HIF-1α is stabilized and most active during acute hypoxia (<24 h), whereas HIF-2α predominates under chronic hypoxic conditions (>48 h) (68). This temporal switch has important implications for NK cell function, as chronic hypoxia, the hallmark of established tumors, may be governed more by HIF-2α than by HIF-1α.

In BC, the roles of the two HIF isoforms markedly diverge. Previous research has shown that HER2 overexpression in BC cells leads to a specific increase in HIF-2α, but not HIF-1α, expression even under normoxic conditions, along with an enhanced upregulation of HIF-2α under hypoxia (69,70). Global gene expression analysis revealed that HER2 overexpression promotes an exaggerated transcriptional response to both acute and chronic hypoxia, with increased expression of numerous hypoxia-responsive genes (70). Notably, HIF-2α expression is frequently higher in HER2-overexpressing tumors and is associated with worse disease-specific survival in patients with HER2-positive BC (70). These findings suggest that HER2-driven HIF-2α upregulation may contribute to the aggressive behavior and immune evasion of HER2-positive breast tumors. Furthermore, HER2-overexpressing cell lines demonstrated increased sensitivity to targeted HIF-2α inhibition (70).

Regarding NK cell biology, the HIF-2α-inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) axis has been identified as a critical mechanism of tumor resistance to NK-mediated killing. In clear cell renal carcinoma, HIF-2α directly upregulates ITPR1, which activates autophagy in target cells and protects them from NK cell lysis (71,72). Silencing ITPR1 markedly increases granzyme B activity in target cells and enhances NK-mediated tumor regression *in vivo* (71,72). Importantly, both ITPR1 and Beclin-1 silencing inhibit NK-induced autophagy and subsequently increase target cell susceptibility to NK-mediated cytotoxicity (71). Whether a similar HIF-2α-ITPR1-autophagy axis operates in BC remains to be investigated, but this mechanism raises the possibility that HIF-2α may exert opposing effects to HIF-1α on NK cell-mediated immune surveillance. Additionally, both HIF-1α and HIF-2α contribute to immune evasion through upregulation of immunosuppressive molecules, and HIF-1α-driven epigenetic modifications have been shown to impair immune effector functions in TNBC (73).

These observations suggest that the hypoxia-TCA cycle-ferroptosis-NK cell axis described in the present review may be modulated by the relative balance of HIF-1α and HIF-2α activity, which is influenced by the duration of hypoxia, tumor subtype (particularly HER2 status) and the specific cellular context. Given that HIF-1 and HIF-2 serve complementary roles in numerous cancer types, targeting both HIF isoforms for inhibition may provide greater therapeutic benefit than targeting either one alone (73). Future studies should systematically dissect the distinct and overlapping roles of HIF-1α and HIF-2α in regulating ferroptosis and NK cell function in BC.

Compensatory antioxidant pathways: Ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10) and GTP cyclohydrolase 1 (GCH1)/tetrahydrobiopterin (BH4). Beyond the canonical GSH/GPX4 axis, cells employ additional GPX4-independent antioxidant systems that compensate when GPX4 is inhibited. Two such pathways, the FSP1/CoQ10 and GCH1/BH4 axes, serve as critical parallel defense mechanisms against ferroptosis (74).

The FSP1/CoQ10 pathway regenerates CoQ10, a lipid-soluble antioxidant that terminates lipid peroxidation chain propagation (74). Notably, FSP1 is upregulated in chemotherapy-resistant BC cells, particularly in TNBC, where acquired resistance to GPX4 inhibition is associated with adaptive FSP1 upregulation (75,76). The GCH1/BH4 pathway, with GCH1 as the rate-limiting enzyme for BH4 synthesis, provides another independent defense; BH4 acts as a radical-trapping antioxidant protecting phospholipid membranes (75,77).

The activity of both pathways varies across BC subtypes: TNBC shows adaptive FSP1 upregulation, while luminal tumors may rely more on BH4 (2,4,6). This differential activity has therapeutic implications: Combining GPX4 inhibitors with FSP1 or GCH1 blockade may overcome

subtype-specific compensatory resistance and enhance ferroptosis induction (74,75).

However, the efficacy of such combination strategies is critically constrained by the emergence of ferroptosis resistance. Tumor cells can acquire resistance through at least three parallel antioxidant systems that operate independently of or in concert with the canonical GSH/GPX4 axis (78). First, GPX4 itself can acquire resistance-conferring mutations; a patient-derived homozygous GPX4 R152H variant has been shown to destabilize the active site and substantially reduce enzymatic activity. However, this variant exhibits altered degradation kinetics that may affect therapeutic vulnerability (79). This raises the possibility that GPX4-targeted inhibitors may select for such mutant clones, necessitating combination approaches that bypass GPX4 dependency altogether. Second, adaptive upregulation of SLC7A11, the cystine-specific subunit of system Xc^-, represents a well-characterized resistance mechanism in tumors with high oxidative stress (80). Notably, this adaptive SLC7A11 upregulation creates a metabolic vulnerability: Under glucose-restricted conditions, NADPH insufficiency prevents cystine-to-cysteine conversion, leading to disulfide stress and a distinct cell death modality termed disulfidptosis (79). This suggests that combining ferroptosis inducers with glucose transport inhibition could exploit this resistance-induced vulnerability to achieve synergistic cytotoxicity. Third, the aforementioned FSP1/CoQ10 and GCH1/BH4 pathways can functionally compensate for GPX4 loss when pharmacologically targeted (79).

These resistance mechanisms profoundly shape the proposed combination strategy. In TNBC, where adaptive FSP1 upregulation limits GPX4 inhibitor efficacy (75), simultaneous targeting of FSP1 [with FSP1 inhibitor (iFSP1) or iron-dependent condensation FSP1 inhibitor (icFSP1)] and GPX4 is necessary to overcome compensatory resistance (78). In HER2-positive or luminal subtypes, where BH4 may serve as the dominant compensatory pathway, GCH1 inhibition (with methotrexate) should be considered alongside GPX4 blockade (81). Furthermore, the temporal dynamics of resistance acquisition must be considered: While early adaptive responses (SLC7A11 upregulation) may be reversible, late-stage resistance involving genetic GPX4 mutations or stable pathway activation may require sequential or alternating combination regimens. Finally, the observation that SLC7A11-high cells are vulnerable to disulfidptosis under glucose deprivation offers an additional therapeutic angle: Combining ferroptosis inducers with glycolysis inhibitors could simultaneously trigger ferroptosis and disulfidptosis, overcoming resistance in tumors with high SLC7A11 expression (79). These considerations underscore the importance of real-time monitoring of resistance markers and subtype-specific stratification in the clinical deployment of ferroptosis-based combination therapies.

Crosstalk between ferroptosis and other regulated cell death pathways. Ferroptosis engages in complex crosstalk with apoptosis, autophagy and necroptosis in hypoxic TMEs (82,83). Ferroptosis and apoptosis can be co-induced by shared signals (such as ROS and p53), while apoptosis may antagonize ferroptosis via caspase-mediated cleavage of key ferroptosis regulators (83). Autophagy serves a dual role, since it promotes ferroptosis through ferritinophagy (releasing labile iron), while hypoxia-adapted tumors may exploit mitophagy to limit ROS and resist ferroptosis (84,85). Necroptosis serves as a backup death pathway when apoptosis is impaired, sharing crosstalk with ferroptosis through receptor-interacting protein kinase 1 (RIPK1) and ROS signaling (82). These pathways converge through shared stressors (namely oxidative stress, iron accumulation and metabolic reprogramming), suggesting that simultaneous activation of multiple death pathways may overcome resistance to single agents (83).

Phase III, Disarm: NK cell dysfunction in the hypoxic BC TME. The biochemical cascade involving TCA cycle disruption, GSH/GPX4 axis collapse and lipid peroxidation converges upon a critical immunological target: NK cells. Within the hypoxic BC TME, NK cells experience coordinated suppression that impairs their infiltration, survival and cytotoxic functions (6,7).

NK cell infiltration. Hypoxia impedes NK cell infiltration into the tumor parenchyma via two complementary mechanisms. First, HIF-1α-driven alterations in chemokine expression and TCA metabolite-induced VEGF production result in structurally abnormal tumor vasculature, creating physical barriers to NK cell extravasation (9,85). Second, hypoxia directly modifies NK cell migratory capabilities. Nawafleh *et al* (86) demonstrated that hypoxia alters sialic acid-binding immunoglobulin (Ig)-like lectin (Siglec)-7 and Siglec-9 expression on NK cells, thereby disrupting their adhesion and migration. Furthermore, Parodi *et al* (87) showed using transcriptomic analyses that hypoxia broadly reprograms NK cell gene expression, modifying chemokine receptor profiles and subset-specific migration patterns. Together with metabolic obstacles such as lactate accumulation in the tumor core (88), metabolic obstacles, particularly lactate accumulation in the tumor core, further impede NK cell infiltration and function.

Beyond the well-characterized acidification of the TME, recent evidence has uncovered a more direct and mechanistic pathway: Lactate serves as a substrate for histone lactylation, a novel epigenetic modification that markedly impairs NK cell effector functions. Specifically, lactate accumulation in hypoxic tumor regions drives histone H3 lysine 18 lactylation at the promoter of insulin-like growth factor binding protein 2 (IGFBP2), upregulating its transcription, and promoting the emergence of a dysfunctional $IGFBP2^+$ NK cell subset with impaired cytotoxicity and poor patient prognosis (89). Furthermore, lactylation has been shown to suppress interferon-γ (IFN-γ) transcription in NK cells, reduce the expression of cytotoxic molecules (including perforin and granzyme B) and upregulate inhibitory receptors such as T cell immunoreceptor with Ig and ITIM domains and NK group 2 (NKG2) member A, collectively diminishing NK cell-mediated antitumor immunity (90,91). Thus, lactate acts not merely as a metabolic waste product causing acidosis, but also as a signaling molecule that epigenetically reprograms NK cell function through histone lactylation, providing a mechanistic link between tumor glycolysis and immune evasion. These mechanisms collectively prevent NK cell entry into the tumor parenchyma and severely compromise their cytotoxic capacity.

NK cell survival. NK cells that successfully infiltrate tumors immediately encounter severe ferroptotic stress. The TME is enriched in lipid peroxides released from ferroptotic

tumor cells. Kim *et al* (46) established that ferroptotic neutrophils release oxidized phospholipids, suppressing T-cell functions via paracrine signaling, a concept directly applicable to NK cells. These oxidized lipids incorporate into NK cell membranes, initiating secondary lipid peroxidation events (59). Given that NK cells already experience notable GSH depletion due to cystine competition and electrophilic metabolite-induced GSH quenching (as aforementioned), their GPX4 defenses are critically impaired, increasing their susceptibility to ferroptotic death. Direct evidence provided by Chen *et al* (62) demonstrated that tumor-infiltrating NK cells undergo ferroptosis via ATF3-mediated suppression of NRF2 signaling. This vulnerability is further exacerbated by the iron-rich BC TME, where labile iron intensifies lipid peroxidation through Fenton chemistry (28,30).

NK cell cytotoxicity. Surviving NK cells encounter severe functional impairment. Balsamo *et al* (64) demonstrated that hypoxia downregulates critical activating receptors, including NKp30, NKp44, NKp46 and NKG2D, thereby notably impairing tumor recognition. Parodi *et al* (87) confirmed these observations at the transcriptional level. Metabolically, NK cells in the hypoxic TME experience what is termed 'metabolic paralysis', a state of profound bioenergetic insufficiency characterized by impaired oxidative phosphorylation due to PDK-mediated restriction of mitochondrial metabolism, forced reliance on glycolysis and consequent ATP depletion in a glucose-deprived microenvironment (52,92). In the glucose-deprived TME, this metabolic shift results in profound energy deficits, impairing essential cytotoxic processes such as lytic granule polarization and exocytosis (6). Harmon *et al* (88) demonstrated that lactate accumulation directly inhibits NK-cell IFN-γ production and perforin/granzyme B secretion. Additionally, Zheng *et al* (54) showed that mitochondrial fragmentation due to metabolic stress directly restricts NK cell-mediated tumor immune surveillance. Finally, breast tumors characterized by loss of p53 may simultaneously develop resistance to ferroptosis and reduced NK cell recognition (38,93).

In summary, the hypoxic BC TME systematically dismantles NK cell-mediated antitumor immunity through a coordinated 'Trap-Kill-Disarm' paradigm, reducing infiltration, inducing bystander ferroptosis and impairing cytotoxic functionality. This conceptual framework explains the limited success of NK cell monotherapies in solid tumors and underscores the rationale for integrating metabolic-targeted interventions with NK cell-based treatments (6,94). Mechanisms underlying NK cell dysfunction in the hypoxic BC TME, along with potential therapeutic intervention strategies, are summarized in Table II.

7. Hypoxia-TCA cycle-ferroptosis axis as a metabolic checkpoint of NK cell surveillance in breast cancer

The framework presented in the present review places TCA cycle dysregulation at the core of a metabolic network that links hypoxia, ferroptosis and NK cell dysfunction in BC. Instead of viewing these processes as separate phenomena, a unified 'metabolic Trap-Kill-Disarm' model can be proposed. In this model, TCA cycle collapse simultaneously sensitizes tumor cells to ferroptosis and incapacitates immune cells responsible for tumor elimination. This reciprocal vulnerability, where identical biochemical conditions threaten tumor viability and undermine antitumor immunity, may explain the paradox of extensive tumor cell death coexisting with profound immune suppression in aggressive breast tumors.

An important unresolved issue concerns the context-dependent regulation of NK cells under hypoxia. Lim *et al* (94) reported that pre-activated NK cells exposed to hypoxia acquire enhanced effector functions through HIF-1α-ERK/STAT3 signaling, including increased NKp44 expression. This observation aligns with another study (95) demonstrating that pre-existing proliferative signals enable HIF-1α-mediated NK cell adaptation toward highly proliferative and cytolytic phenotypes under hypoxic conditions. However, the majority of evidence supports a predominantly suppressive role of hypoxia on NK cell function. In glioblastoma models, CRISPR-Cas9-mediated HIF-1α knockout in NK cells actually enhanced their cytotoxicity under hypoxia, suggesting that HIF-1α itself may be a key driver of NK cell dysfunction in the hypoxic TME (95). Furthermore, hypoxia-induced mitochondrial fragmentation via dynamin-related protein 1 (DRP1) activation reduces NK cell mitochondrial content and membrane potential while increasing mtROS, leading to impaired cytotoxic function, a defect reversible by DRP1 inhibition or knockout (96). These divergent observations are not necessarily contradictory; rather, they likely reflect differences in NK cell activation states, the duration of hypoxic exposure and the specific cellular context.

The majority of NK cells infiltrating breast tumors are functionally exhausted and not pre-activated (6,7), making them particularly susceptible to the aforementioned metabolic suppression. By contrast, pre-activated NK cells may retain sufficient metabolic reserves and NRF2 activity to resist oxidative stress (62,94). This distinction has direct therapeutic implications, suggesting that *ex vivo* expansion and pre-activation of NK cells prior to adoptive transfer may confer resistance against TME-induced ferroptosis. Although detailed *ex vivo* activation protocols fall outside the scope of the present review, several promising metabolic preconditioning strategies are briefly highlighted. For instance, hypoxic preconditioning (such as culturing NK cells at 1-5% O_2 for 12-24 h) can stabilize HIF-1α and enhance mitochondrial fitness. Short-term cytokine cocktails (such as IL-2, IL-12, IL-15 and IL-18 for 16-48 h) can boost cytotoxicity, while pre-treatment with NRF2 agonists (such as sulforaphane or dimethyl fumarate) may mitigate lipid peroxidation and ferroptosis. However, maintaining NK cell activation post-infusion remains a major challenge, as the hypoxic TME, nutrient competition and oxidative stress can rapidly reverse these *ex vivo* metabolic gains, leading to exhaustion and bystander ferroptosis. Therefore, optimizing the durability of these preconditioning effects *in vivo* is a critical direction for future research. The absence of detailed procedural protocols for *ex vivo* NK cell activation is a limitation of the present review.

The interplay between ferroptosis and immunity also reveals a therapeutic paradox. Inducing ferroptosis in tumor cells is an established anticancer strategy (12,21); however, the present model raises the hypothesis that ferroptotic debris may simultaneously compromise the immune microenvironment through bystander lipid peroxide transfer, a mechanism suggested by previous studies in other tumor types (44,47) but not yet directly verified in BC. This dual

Table II. Mechanisms of NK cell dysfunction in the hypoxic breast cancer tumor microenvironment and potential interventions.

Functional deficit	Mechanism	Key mediators	Consequence	Potential intervention	(Refs.)
Impaired infiltration	Chemokine dysregulation and abnormal vasculature	HIF-1α → VEGF, altered chemokines	Physical barrier to NK extravasation	Anti-VEGF therapy; chemokine normalization	(9,85)
	Siglec receptor modulation	Siglec-7, Siglec-9	Reduced NK adhesion and migration	Siglec blockade	(87)
	Transcriptomic reprogramming	Global gene expression shift	Altered chemokine receptor profile	Epigenetic modulation	(44,46)
Compromised survival	Bystander ferroptosis	Ox-PEs, 4-HNE from ferroptotic tumor cells	Secondary lipid peroxidation in NK cells; NK cell ferroptotic death	GPX4 augmentation; iron chelation	(44,46)
	GSH depletion	Cystine competition (SLC7A11 ↑); electrophilic fumarate	GPX4 inactivation; lipid peroxide accumulation	NRF2 stabilization; GSH supplementation	(15,36)
	ATF3-driven ISR	ATF3 ↑ → NRF2 ↓	Suppressed antioxidant defense; ferroptosis execution	ATF3 inhibition; ISR targeting	(62)
Suppressed cytotoxicity	Activating receptor downregulation	NKp30, NKp44, NKp46, NKG2D ↓	Impaired tumor cell recognition	Pre-activation (IL-2/IL-15); *ex vivo* expansion	(64)
	Metabolic energy crisis	PDK activation → glycolysis dependence; glucose shortage	Failed lytic granule polarization and exocytosis	Metabolic reprogramming of NK cells	(51,92)
	Lactate-mediated suppression	Lactate accumulation	Reduced IFN-γ, granzyme B, perforin release	LDH inhibition; pH normalization	(91)
	Mitochondrial fragmentation	TCA defect → mitochondrial fission	Defective immune synapse; impaired surveillance	Promotion of mitochondrial fusion	(54)
	p53 loss	Mutant p53 in tumor cells	Diminished NK recognition; ferroptosis resistance	Pharmacological p53 reactivation	(38,93)

NK, natural killer; HIF-1α, hypoxia-inducible factor 1α; VEGF, vascular endothelial growth factor; Siglec, sialic acid-binding immunoglobulin-like lectin; GPX4, glutathione peroxidase 4; GSH, glutathione; SLC7A11, solute carrier family 7 member 11; NRF2, nuclear factor erythroid 2-related factor 2; ATF3, activating transcription factor 3; ISR, integrated stress response; NKp30/44/46, natural killer cell receptors p30/p44/p46; NKG2D, natural killer group 2 member D; PDK, pyruvate dehydrogenase kinase; LDH, lactate dehydrogenase; TCA, tricarboxylic acid; 4-HNE, 4-hydroxynonenal; Ox-PEs, oxidized phosphatidylethanolamines.

effect implies that ferroptosis-inducing therapies should be strategically combined with measures protecting NK cells from secondary ferroptosis. Possible protective interventions include stabilizing NRF2 signaling in adoptively transferred NK cells (37,62), pharmacological enhancement of GPX4 activity or iron chelation to limit Fenton reactions in the TME (28). Beyond the GSH/GPX4 axis, the FSP1/CoQ10 and GCH1/BH4 pathways represent critical GPX4-independent compensatory antioxidant mechanisms (74,75). FSP1 is upregulated in chemotherapy-resistant BC cells, particularly in TNBC, where adaptive FSP1 upregulation limits the efficacy of GPX4 inhibition (75,77). The activity of these pathways varies across subtypes: TNBC shows adaptive FSP1 upregulation, whereas luminal tumors may rely more on BH4 (75,76). This subtype-specific dependency suggests that effective ferroptosis-based therapies may require combination strategies targeting GPX4 alongside FSP1 or GCH1 to overcome compensatory resistance (74,75). Additionally, the recent identification of ATF3 as a mediator of NK cell ferroptosis (62) suggests that targeting the integrated stress response may selectively protect NK cells without impairing tumor cell sensitivity to ferroptosis. Furthermore, emerging evidence indicates that GPX4 inhibition may sensitize BC cells to cyclin-dependent kinases 4 and 6 inhibitors, revealing a potential therapeutic synergy between ferroptosis induction and cell cycle-targeted therapies (97). This intersection between ferroptosis and cell cycle regulation adds another dimension to the therapeutic landscape and warrants further investigation, particularly in the context of combination strategies with NK cell-based immunotherapy.

The aforementioned subtype heterogeneity underscores a critical caveat for therapeutic translation. While TNBC appears optimally positioned for ferroptosis-based combination strategies due to its inherent vulnerability and immunologically 'hot' phenotype, caution is warranted in luminal or HER2-positive subtypes where baseline ferroptosis sensitivity may be lower. Furthermore, within TNBC, ferroptosis resistance in the mesenchymal subtype suggests that, even within a single clinical subtype, stratification by molecular features (such as SLC22A3 expression and Equipment Monitoring Control System integrity) may be necessary to identify patients most likely to benefit from ferroptosis-targeted therapies (98). This precision approach could avoid unnecessary toxicity in non-responsive patients while maximizing therapeutic benefit in those with ferroptosis-vulnerable tumors (98,99).

While TNBC exhibits increased ferroptosis sensitivity, the mechanistic landscape in luminal, HER2-positive and BRCA-mutant subtypes remains largely unexplored. The HER2-HIF-2α axis adds further complexity: HER2-overexpressing tumors show elevated HIF-2α expression associating with worse survival (69), and HIF-2α has been shown to protect tumor cells from NK-cell killing through ITPR1-dependent autophagy (70,71). Thus, HIF-2α may exert opposing effects to HIF-1α on NK cell surveillance. Dual targeting of both HIF isoforms may offer greater benefit than inhibiting either alone (73). From a broader perspective, the TCA cycle emerges as more than a bioenergetic pathway: It serves as a metabolic-immunological signaling node. Succinate, fumarate and other TCA metabolites function as intercellular messengers coordinating tumor, stromal and immune cell behaviors (15,17). Their capacity to simultaneously induce tumor cell ferroptosis and suppress NK cells via metabolic and oxidative stress highlights evolutionary trade-offs within the TME. Unraveling how individual TCA metabolites selectively modulate distinct immune subsets remains an important goal.

Another critical dimension that shapes the therapeutic response to ferroptosis-based combination strategies is the baseline immunological state of the tumor, namely the 'hot' vs. 'cold' immune microenvironment (100). Ferroptosis-related gene signatures in TNBC have been shown to stratify patients into distinct subtypes that correlate with differential immune infiltration and immunotherapy responsiveness (101,102). TNBC tumors classified as immunologically 'hot' exhibit abundant NK and T-cell infiltration (101). In such tumors, ferroptosis induction could exert a dual-edged effect. On the one hand, ferroptotic cancer cells can stimulate immune responses by releasing oxidized phospholipids and DAMPs that serve as *in situ* adjuvants, further 'heating' the TME and enhancing antitumor immunity (100,102). On the other hand, the abundant NK cells in 'hot' tumors face an enhanced risk of bystander ferroptosis, given that ferroptotic cancer cells release immunosuppressive mediators, including PGE2, oxidized lipids and 8-hydroxy-2'-deoxyguanosine, which impair NK cell cytotoxicity and may propagate secondary lipid peroxidation cascades to adjacent immune effectors (100,103). This vulnerability underscores the importance of combining ferroptosis inducers with NK cell-protective strategies (such as NRF2 stabilization and GPX4 augmentation) specifically in 'hot' tumors (103).

Conversely, immunologically 'cold' tumors, characterized by limited immune cell infiltration and immune exclusion, may respond poorly to ferroptosis induction alone (101). In such tumors, the release of immunostimulatory DAMPs by ferroptotic cancer cells is unlikely to generate meaningful antitumor immunity because the requisite effector cells are absent (103,104). Thus, the therapeutic priority in 'cold' tumors must first be NK cell recruitment. Strategies capable of remodeling the TME, such as metformin-induced immunomodulation, have been shown to simultaneously enhance NK cell infiltration and potentiate ferroptosis, establishing a positive-feedback loop between ferroptosis and immune activation (104). Additionally, epigenetic modulators targeting histone deacetylase 3 can convert immunologically 'cold' tumors into 'hot' tumors by restoring NK cell cytotoxicity and dendritic cell maturation (105). These observations suggest a bifurcated therapeutic algorithm: In 'hot' tumors, ferroptosis inducers combined with NK cell protection, while, in 'cold' tumors, NK cell recruitment (via immunomodulators or epigenetic agents) followed by ferroptosis induction may be used. Given that the 'hot' vs. 'cold' classification is itself governed by ferroptosis-related gene expression (101,102), these immune states are not fixed, but may be dynamically modulated by ferroptosis-inducing therapies, offering opportunities for sequential or combination strategies that exploit this bidirectional interplay.

Beyond the ferroptosis-immunity crosstalk, ferroptosis also engages in complex interplay with apoptosis, autophagy and necroptosis (83,84). Apoptosis can co-occur or antagonize ferroptosis; autophagy serves dual roles via ferritinophagy and

mitophagy; and necroptosis shares crosstalk through RIPK1 and ROS (84). These converging pathways suggest that combination strategies engaging multiple death machineries may overcome resistance in the hypoxic BC TME (83,84).

NK cell subset heterogeneity adds further complexity. Peripheral blood and tumor-infiltrating NK cells differ profoundly in phenotype, metabolism and ferroptosis susceptibility. Single-cell transcriptomic analyses in BC have identified two functionally distinct tumor-infiltrating NK subsets: Cytotoxic NK_fibroblast growth factor binding protein 2 (NK_FGFBP2; also known as NKcyto), which highly express granzyme B and natural killer cell granule protein 7 and chemokine-secreting lymhotactin (NK_XCL1), which promote dendritic cell recruitment (106). Critically, these subsets exhibit distinct mitochondrial reserves and metabolic programs (6). In the hypoxic TME, tumor-infiltrating NK cells experience mitochondrial fragmentation and elevated ROS, defects exacerbated by TCA cycle dysfunction (96,107). Tumor-derived metabolites such as L-kynurenine have been shown to induce ferroptotic death in NK cells, while GPX4 overexpression or NRF2 activation confers protection (107).

These observations have therapeutic implications: Adoptively transferred NK cells may resist TME-induced ferroptosis if their metabolic fitness and antioxidant capacity are preserved *ex vivo* (54). Furthermore, ferroptosis-inducing therapies may differentially affect NK subsets, potentially depleting cytotoxic NK_FGFBP2 while sparing chemokine-secreting NK_XCL1, thus underscoring the need for subset-specific monitoring in clinical trials (6).

In conclusion, the hypoxia-TCA cycle-ferroptosis axis constitutes a critical metabolic checkpoint that determines the effectiveness of NK cell-mediated tumor surveillance in BC. Overcoming this checkpoint will require therapeutic strategies that disrupt the 'metabolic trap', simultaneously exploiting tumor cell ferroptosis vulnerability while protecting NK cells from immunosuppressive consequences. Such approaches, informed by the aforementioned mechanistic insights, may substantially enhance NK cell-based immunotherapies in BC and other malignancies.

8. Conclusions

BC progression relies not only on uncontrolled proliferation but also on alteration of the surrounding immune microenvironment. The present review proposes a mechanistic framework in which hypoxia-induced TCA cycle dysregulation simultaneously triggers ferroptosis in tumor cells and undermines NK cell-mediated antitumor immunity, revealing a fundamental metabolic conflict central to the TME.

The proposed model is based on three interconnected components: First, hypoxia-driven TCA cycle collapse transforms mitochondria from bioenergetic centers into sources of excessive ROS, creating oxidative conditions essential for ferroptosis initiation. Second, coordinated GSH depletion, through electrophilic oncometabolite-mediated quenching and nutritional competition for cystine, impairs the GPX4 antioxidant defense in both tumor and NK cells. Third, the resulting lipid peroxide surge not only executes tumor cell ferroptosis but also propagates through bystander mechanisms to induce NK cell death, while simultaneously suppressing surviving NK cells through receptor downregulation and metabolic impairment. This 'Trap-Kill-Disarm' sequence offers a unified explanation for the paradoxical observation that highly immunogenic, ferroptosis-prone tumors often evade effective immune destruction (39,40).

The translational implications are evident but challenging. Ferroptosis induction represents a double-edged therapeutic approach, capable of killing tumor cells but simultaneously harming immune effectors essential for sustained responses. Future therapeutic strategies must therefore selectively sensitize tumor cells to ferroptosis while safeguarding NK cells against oxidative death. Recent insights into NK cell ferroptosis via the ATF3-NRF2 axis, together with evidence of context-dependent hypoxia effects on NK cell activation, offer potential molecular targets to achieve this therapeutic specificity.

Ultimately, the TCA cycle functions beyond simple metabolism: It acts as an immunological regulator whose dysregulation notably impacts the tumor ecosystem. Clarifying how specific TCA metabolites distinctly influence tumor cells, NK cells and other immune subsets will be critical for developing the next generation of metabolism-informed cancer immunotherapies. Disrupting the hypoxia-metabolite-ferroptosis-immune suppression circuit is therefore not merely an attractive therapeutic approach, but imperative for overcoming current limitations of BC immunotherapy.

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Authors' contributions

MS wrote the original draft of the manuscript. BW and NW conducted reference investigations, were involved in funding

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Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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