

Lipid Metabolic Reprogramming in Breast Cancer: Mechanisms and Emerging Therapeutic Strategies

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Abstract: Breast cancer remains the most commonly diagnosed malignancy among women worldwide, with a steadily increasing incidence. Lipid metabolic reprogramming is increasingly recognized as both a hallmark and a fundamental driver of breast cancer progression. Breast cancer cells exhibit enhanced lipid uptake, de novo fatty acid synthesis, fatty acid oxidation, and lipid storage, which collectively support membrane biosynthesis, energy production, and oncogenic signaling. In addition to cancer cell-intrinsic effects, lipid metabolic alterations reshape the tumor microenvironment by modulating immune responses, stromal activation, and angiogenesis. Key metabolic enzymes, including FASN, ACC, ACLY, SCD, and FABP4, play central roles in these processes and represent promising therapeutic targets. Emerging evidence from preclinical and clinical studies highlights the therapeutic potential of targeting lipid metabolism, particularly in aggressive subtypes such as triple-negative breast cancer. Despite these advances, challenges such as therapeutic resistance, metabolic compensation, and lack of predictive biomarkers remain major barriers to clinical translation. Overall, targeting lipid metabolic vulnerabilities offers a promising strategy for precision therapy in breast cancer.

Keywords: breast cancer, lipid metabolism, fatty acid metabolism, FASN, FABP4, metabolic reprogramming, triple-negative breast cancer, tumor microenvironment, targeted therapy, spatial metabolomics

Introduction

Cancer is increasingly recognized as a disease driven not only by genetic alterations but also by profound metabolic reprogramming.^{1,2} As a hallmark of cancer, metabolic adaptation enables tumor cells to sustain proliferation, survive under stress, and evade therapeutic interventions.³ Over the past decades, cancer treatment strategies have evolved from non-specific cytotoxic therapies to targeted therapies, and more recently toward metabolism-oriented approaches.^{4,5} However, despite these advances, therapeutic resistance remains a major clinical challenge, highlighting the need to better understand how cancer cells dynamically adapt to treatment pressure.⁶

Emerging evidence suggests that metabolic plasticity plays a central role in this adaptive process.⁷ Under therapeutic stress, cancer cells reprogram multiple metabolic pathways to maintain energy supply, biosynthetic capacity, and redox homeostasis.⁸ Among these pathways, lipid metabolism has attracted increasing attention due to its unique role in integrating energy production, membrane biosynthesis, and signal transduction.⁹ Importantly, lipid metabolic reprogramming is not merely a bystander effect but represents a key adaptive mechanism that enables tumor cell survival and evolution under therapeutic pressure.¹⁰

From a broader biological perspective, metabolic reprogramming is not unique to cancer but represents a conserved cellular strategy for adapting to environmental stress.¹¹ Although lipid metabolism has been extensively studied in diverse biological contexts—including kidney injury, immune regulation, and cancer—it is highly context-dependent. Nevertheless, growing evidence indicates that certain cellular responses to lipid metabolic dysregulation are conserved across tissues.^{12,13} For example, studies in acute kidney injury (AKI) have shown that impaired fatty acid oxidation (FAO) leads to lipid accumulation, lipid peroxidation, and the formation of a lipotoxic inflammatory milieu.^{14,15} These

alterations trigger mitochondrial dysfunction, endoplasmic reticulum stress, and inflammatory signaling, ultimately resulting in tissue injury and maladaptive repair. Importantly, this conserved framework provides a valuable perspective for understanding lipid metabolism in cancer. Unlike non-malignant tissues, where lipid accumulation often leads to cellular dysfunction or death, breast cancer cells actively reprogram lipid metabolism to buffer lipotoxic stress.¹⁶ By coordinately regulating lipid uptake, synthesis, storage, and oxidation, tumor cells maintain metabolic flexibility and sustain survival under both therapeutic and microenvironmental stress. Therefore, lipid metabolism in cancer should be interpreted not as an isolated tumor-specific phenomenon, but as an adaptive reconfiguration of conserved metabolic stress responses, conferring a selective advantage for tumor progression and evolution.^{17,18} Within this framework, breast cancer represents a highly heterogeneous disease in which metabolic adaptation is particularly pronounced. It remains one of the most common malignancies among women worldwide and a leading cause of cancer-related mortality.^{19,20} Based on the expression of molecular markers such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67, breast cancer can be classified into distinct subtypes, including luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC).²¹ Among these, TNBC is characterized by high invasiveness, frequent recurrence, and a lack of effective targeted therapies, making it a major clinical challenge.

In breast cancer, lipid metabolism is profoundly reprogrammed. Unlike most normal cells, which primarily rely on exogenous lipid uptake, cancer cells exhibit enhanced *de novo* lipogenesis, increased fatty acid uptake, and activated fatty acid oxidation (FAO). These metabolic changes support rapid proliferation, membrane biosynthesis, and oncogenic signaling.^{22,23} In addition, lipid metabolism actively reshapes the tumor microenvironment (TME) by modulating immune cell function, stromal interactions, and metabolic crosstalk, thereby promoting tumor progression.^{22,24} Importantly, accumulating evidence indicates that lipid metabolic reprogramming is closely associated with therapeutic resistance. Breast cancer cells can exploit lipid metabolism to maintain redox homeostasis, resist oxidative stress, and adapt to nutrient deprivation and treatment-induced stress.^{25,26} Therefore, lipid metabolism represents not only a key driver of tumor progression but also a critical vulnerability under therapeutic intervention.

Based on these considerations, this review aims to provide a systematic overview of the role of dysregulated lipid metabolism in breast cancer development and progression, with a particular focus on key regulators such as fatty acid synthase (FASN) and fatty acid-binding protein 4 (FABP4). We further discuss the therapeutic potential of targeting lipid metabolism and its implications for precision oncology.

Abnormal Fatty Acid Metabolism and Dysregulation of Breast Cancer Cells

An increasing body of evidence indicates that the malignant phenotype of tumor cells depends on highly active fatty acid synthesis and metabolism.¹⁶ In breast cancer, *de novo* fatty acid synthesis is markedly upregulated, and pathways involved in fatty acid uptake, storage, and oxidation are also enhanced and activated (Figure 1).²⁷ These changes provide membrane components, energy, and lipid-derived signaling molecules, thereby strongly promoting malignant proliferation and survival of tumor cells.²⁷ Invasion and metastasis are among the most aggressive features of cancer cells. During the metastatic process, tumor cells frequently experience metabolic stress, including hypoxia and nutrient deprivation, and must increase fatty acid uptake and lipid storage to generate sufficient energy for survival.²⁸ The drug sensitivity of tumor cells is also influenced by the composition and degree of saturation of membrane lipids, which are in turn governed by fatty acid synthesis and desaturation.²⁹ In this section, we focus on how enzymes and genes involved in fatty acid metabolism contribute to the molecular pathology underlying malignant phenotypes in breast cancer, including proliferation, migration, invasion, autophagy, epithelial–mesenchymal transition (EMT), remodeling of the tumor microenvironment, and mitochondrial metabolism.

Proliferation, Invasion, and Migration of Breast Cancer Cells

During breast cancer progression, fatty acid metabolism activates multiple processes that provide essential substrates for membrane biogenesis, signaling molecules, and energy production.³⁰ a) Proliferation Dysregulation of the nuclear receptor Nur77 suppresses the transcription of its downstream targets CD36 and FABP4, leading to reduced fatty acid

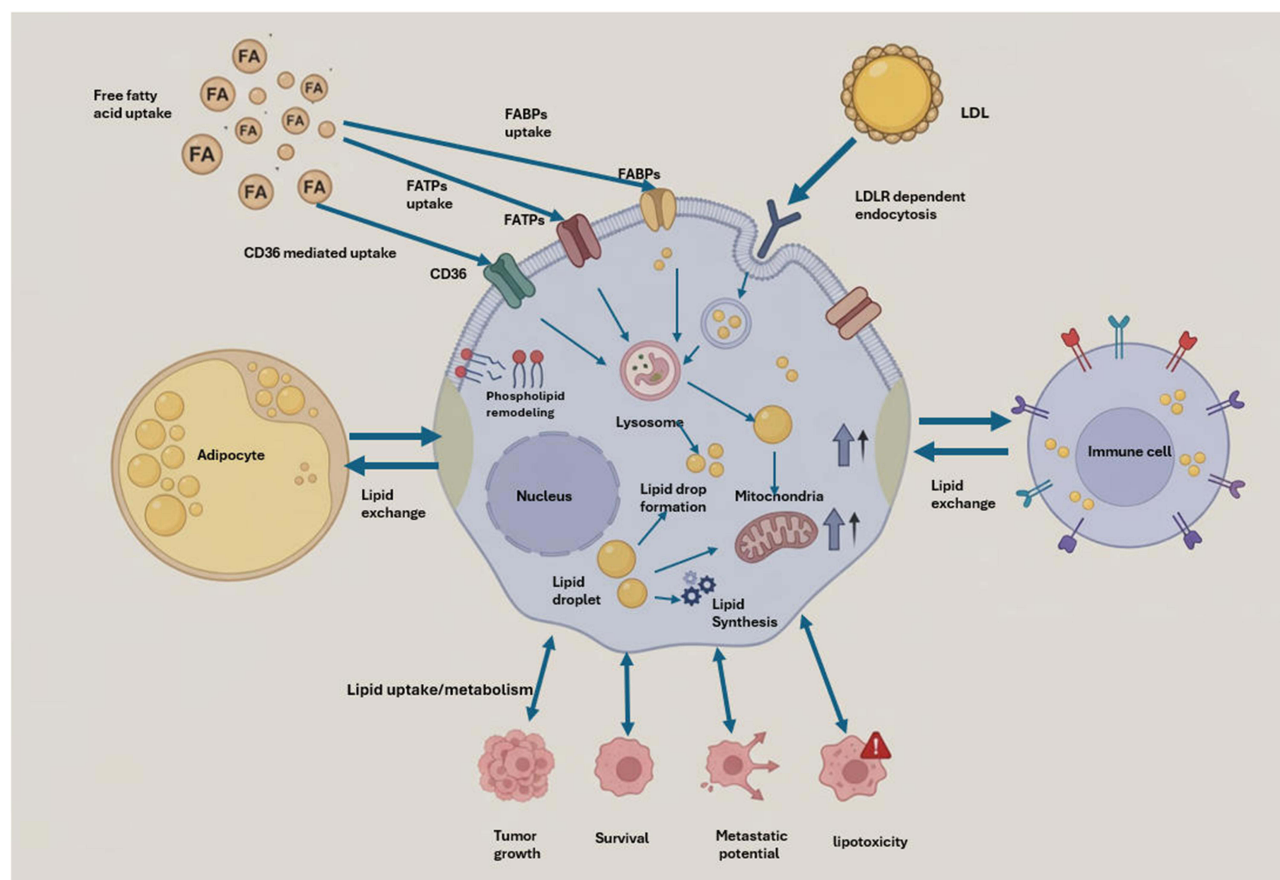


Figure 1 Integrated mechanisms of lipid uptake, metabolic reprogramming, and bidirectional lipid exchange in the breast tumor microenvironment. This schematic illustrates the dynamic processes of lipid acquisition, redistribution, and utilization in breast cancer cells within the peritumoral adipose niche. Tumor cells obtain lipids through multiple mechanisms, including direct fatty acid uptake mediated by transporters such as CD36, FATPs, and FABPs, as well as receptor-driven lipoprotein internalization via LDLR-dependent endocytosis. In addition, cholesterol trafficking is regulated by ATP-binding cassette (ABC) transporters, enabling sterol exchange and redistribution across cellular compartments. Once internalized, lipids are processed through lysosomal pathways and subsequently contribute to membrane phospholipid remodeling, lipid droplet formation, and energy storage. These lipids are further mobilized to support biosynthesis and fatty acid oxidation, thereby sustaining tumor growth, survival, and metabolic flexibility. The balance between lipid storage and mobilization allows cancer cells to buffer lipotoxic stress while maintaining bioenergetic and biosynthetic demands. Importantly, lipid metabolism within the tumor microenvironment is highly dynamic and involves bidirectional lipid exchange among cancer cells, adipocytes, and immune cells. This metabolic crosstalk not only fuels tumor progression but also reshapes the microenvironment, influencing immune cell function, metastatic potential, and therapeutic response.

uptake and consequently attenuated proliferation of breast cancer (BC) cells.³¹ This inhibitory effect can be reversed by activation of peroxisome proliferator-activated receptor γ (PPAR γ). In addition, the chromatin-remodeling enzyme BRG1 has been shown to regulate fatty acid production and thereby control the proliferation of triple-negative breast cancer (TNBC) cells.³²

Invasion and migration: Fatty acids primarily promote breast cancer invasion through upregulation of fatty acid oxidation (FAO)-related signaling pathways.³³ Tumor-associated adipocytes enhance FA uptake and invasiveness of breast cancer cells by secreting the fatty acid transporter CD36; conversely, CD36 inhibition reduces lipid droplet accumulation and diminishes invasive capacity.³⁴ Silencing of integrin $\alpha 2$ (ITGA2) on the cell surface suppresses breast cancer metastasis by downregulating genes involved in cell-cycle regulation and lipid metabolism, such as cyclin D1 (CCND1) and ATP-citrate lyase (ACLY).³⁵ Moreover, monoglyceride lipase (MAGL), which is highly expressed in breast cancer tissue, promotes the release of intracellular fatty acids and thereby increases tumor invasiveness.³⁶

Apoptosis

Studies on lipid metabolism-related regulation of apoptosis in breast cancer cells have mainly focused on FASN, monounsaturated fatty acids (MUFA), and acetyl-CoA carboxylase α (ACC α).³⁷ Inhibition of FASN has been shown

to induce breast cancer cell apoptosis or tumor shrinkage, at least in part by markedly upregulating BNIP3 expression, which triggers apoptotic signaling.³⁸ In lipid-deprived cancer cells, suppression of MUFA synthesis leads to pronounced endoplasmic reticulum stress and apoptosis.³⁹ Furthermore, knockdown of ACC α expression induces apoptosis, which can be reversed by supplementation with palmitate esters or the antioxidant vitamin E. These findings collectively demonstrate that lipogenesis is a critical determinant of breast cancer cell survival and susceptibility to apoptosis.³⁹

Autophagy

Fatty acid levels are known to regulate autophagy in various tissues and cell types.⁴⁰ High concentrations (at least 500 μ M) of unsaturated fatty acids (UFAs), such as oleic acid, can robustly promote autophagy in breast cancer cells. Similarly, the polyunsaturated fatty acid-containing monoacylglycerol docosahexaenoic acid (DHA) has been shown to induce both apoptosis and autophagy in breast cancer cells.^{41,42} In contrast, when high levels of saturated fatty acids (SFAs), such as palmitic acid, cannot be efficiently converted into triglycerides stored within lipid droplets, autophagy is significantly inhibited.⁴² Taken together, the dual regulatory role of lipid metabolism in autophagy is largely determined by the type of fatty acid, the degree of lipotoxicity, and the specific cellular context.

Epithelial–Mesenchymal Transition (EMT)

It is well established that most breast cancers arise from epithelial cells. Under specific conditions, epithelial cells can undergo EMT, a process that drives multiple phenotypic changes, including altered cell morphology, loss or reduction of cell–cell adhesion, and acquisition of stem cell–like properties.⁴³ These changes are closely associated with tumor initiation, invasion, metastasis, and the development of chemoresistance. Differences in fatty acid metabolic demands between epithelial and mesenchymal cells may be a key factor enabling the EMT phenotype.⁴⁴ Notably, expression of elongation of very long-chain fatty acids protein 5 (Elovl5) is significantly downregulated in metastatic estrogen receptor–positive breast cancer and is positively associated with EMT, invasiveness, and lung metastasis. Mechanistically, reduced Elovl5 expression promotes upregulation of TGF- β receptor signaling, which is mediated by Smad2 acetylation in a lipid droplet–dependent manner.^{45,46}

Tumor Microenvironment

The tumor microenvironment (TME), composed of diverse cellular and extracellular matrix components, plays a decisive role in the progression and metastasis of breast cancer.^{47,48} In TNBC, dysregulated lipid metabolism is considered a key driver of TME “reprogramming.” By altering immune cell fate, promoting immunosuppression, and modifying stromal cell behavior, aberrant lipid metabolism helps establish an ecosystem that facilitates tumor dissemination.²⁶

Fatty acids and their metabolic byproducts can profoundly reshape immune cell phenotypes.⁴⁹ For example, excess lipids promote the polarization of macrophages from a pro-inflammatory, antitumor M1 phenotype toward an immunosuppressive M2 phenotype, thereby altering cytokine profiles and weakening antitumor immunity.⁵⁰ Tumor cells also exploit the scavenger receptor CD36 to increase lipid uptake, which not only contributes to lipid peroxidation but also induces CD8⁺ T-cell dysfunction.⁵¹ In addition, lipid peroxidation products such as 4-hydroxynonenal (4-HNE) can directly trigger apoptosis of T cells and B cells, further compromising local antitumor immune responses.⁵²

Lipid metabolism also amplifies immunosuppression by supporting the expansion of regulatory T cells (Tregs).⁵³ In the TNBC microenvironment, enhanced fatty acid synthesis increases Treg survival and differentiation, thereby suppressing effector T cells and cytotoxic lymphocytes and facilitating immune evasion.²² Conversely, pharmacologic activation of PPAR- α , which promotes peroxisomal fatty acid β -oxidation—for example, by using fenofibrate—has been shown to partially restore antitumor immunity in metabolically dysregulated TNBC microenvironments.⁵⁴

Beyond immune modulation, altered lipid metabolism reshapes tumor stroma and promotes angiogenesis and distant metastasis.⁵⁵ TNBC cells rely on lipid metabolism–related enzymes to modulate vascular structure and permeability; increased MT1-MMP activity, for instance, is closely associated with vascular invasion and enhanced metastatic potential. At the same time, cancer-associated fibroblasts (CAFs) with elevated fatty acid uptake tend to adopt a pro-tumorigenic phenotype and secrete multiple factors that stimulate tumor cell proliferation, migration, and invasion.⁵⁶ Importantly, TNBC cells exhibit site-specific lipid metabolic adaptations in certain metastatic organs, such as the brain.

For example, downregulation of RARRES2 disrupts the PTEN–PI3K–SREBP1 axis, leading to altered glycerophospholipid and triglyceride profiles and conferring metabolic advantages for survival and colonization in distant microenvironments.⁵⁷

Mitochondrial Function

Lipid metabolism is tightly coupled to mitochondrial energy production, with fatty acid oxidation (FAO) serving as a central pathway for meeting the metabolic demands of TNBC cells.⁵⁸ After massive uptake of fatty acids, TNBC cells rely on carnitine palmitoyltransferase 1 (CPT1) to convert fatty acids into acylcarnitines and transport them into the mitochondrial matrix.⁵⁹ There, fatty acids undergo successive rounds of β -oxidation to generate acetyl-CoA and reducing equivalents (NADH/FADH₂), which fuel the TCA cycle and oxidative phosphorylation.⁶⁰ In addition to driving ATP synthesis, FAO regulates mitochondrial membrane potential and reactive oxygen species (ROS) homeostasis, thereby enhancing metabolic plasticity under conditions of nutrient deprivation or therapeutic stress.⁶¹ Multiple studies have shown that metastatic TNBC cells are particularly dependent on elevated FAO to maintain high-energy states. For example, mitochondrial fusion models and multi-omics analyses indicate that increased FAO activity supports sustained ATP production in metastatic TNBC cells, while downregulation of ANXA6 similarly enhances FAO and accelerates mitochondrial energy output.⁶²

Chemotherapeutic stress can further remodel lipid metabolism and mitochondrial function.⁶³ Neoadjuvant chemotherapy has been reported to induce the expression of key lipid metabolic enzymes and increase oxidative phosphorylation (OXPHOS) activity, promoting lipid droplet accumulation as an energy reservoir in chemical resistant TNBC cells.⁶⁴ Overall, TNBC cells boost mitochondrial ATP generation by upregulating fatty acid uptake and oxidation, thus supporting proliferation, survival, and drug resistance.

In addition, fatty acids and their precursors directly influence the composition and stability of mitochondrial membranes. As essential substrates for phospholipid and sphingolipid synthesis, fatty acids are critical for maintaining membrane integrity in rapidly dividing tumor cells.⁶⁵ Studies have demonstrated that inhibiting FASN disrupts mitochondrial phospholipid synthesis and induces cell death.⁶⁶ Conversely, strategies that enhance lipid metabolism or increase ROS production—such as nicotinamide supplementation—can exacerbate mitochondrial damage and ultimately trigger apoptosis in TNBC cells.^{67,68}

Cross-Regulation of Metabolic Pathways

Lipid metabolism is intricately interconnected with oncogenic signaling pathways and other metabolic processes, forming a dynamic regulatory network that supports tumor initiation and progression.^{12,69} A representative example is the bidirectional interaction between fatty acid synthase (FASN) and HER2 signaling. FASN promotes the formation of lipid rafts, which facilitate the membrane localization and activation of HER2 and other receptor tyrosine kinases, thereby amplifying downstream oncogenic signaling. Conversely, HER2 overexpression enhances FASN expression and activity, establishing a feed-forward loop that sustains tumor growth and metabolic reprogramming.⁷⁰ Similarly, fatty acid-binding protein 4 (FABP4) functions as a key metabolic–signaling hub linking lipid metabolism to intracellular signaling pathways. By facilitating lipid transport and activating pathways such as PI3K/Akt, FABP4 promotes cell survival, proliferation, and tumor progression. These findings highlight that lipid metabolism is not merely a source of energy but also a critical regulator of signal transduction.⁷¹

Beyond oncogenic signaling, lipid metabolism is highly integrated with other metabolic networks. For instance, glucose metabolism provides essential substrates, such as acetyl-CoA, to drive *de novo* lipogenesis, thereby linking the Warburg effect to lipid metabolic reprogramming.¹ In addition, lipid metabolism plays a pivotal role in maintaining redox homeostasis. Elevated oxidative stress in tumor cells can modulate lipid metabolic enzyme activity, while lipid synthesis and remodeling help buffer reactive oxygen species (ROS)-induced damage and prevent ferroptosis.^{72,73} Collectively, lipid metabolism functions as a central hub that integrates oncogenic signaling, energy metabolism, and redox balance, thereby driving tumor progression and contributing to therapeutic resistance.

Immune Reprogramming

Lipid metabolic reprogramming in breast cancer is not confined to tumor cells but also reshapes the immune landscape of the tumor microenvironment. Different immune cell subsets rely on distinct metabolic programs, and alterations in lipid availability can significantly influence their differentiation, activation, and effector functions.^{16,74} As a result, lipid-rich or metabolically stressed microenvironments may impair antitumor immune populations, such as CD8⁺ T cells and NK cells, while promoting immunosuppressive or tumor-supportive phenotypes, including tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells.^{52,74,75} These immune-metabolic alterations are highly relevant to breast cancer progression and treatment outcomes, as they determine whether the tumor microenvironment supports immune surveillance or shifts toward immune evasion and therapeutic resistance.

Th17 cells provide a representative conceptual framework linking lipid metabolism to immune cell behavior. Th17 differentiation is tightly coupled to de novo lipid biosynthesis and cholesterol-associated metabolic flux, which regulate the activity of the master transcription factor ROR γ t through endogenous lipid ligands.^{76,77} Thus, lipid metabolism functions not only as a bioenergetic pathway but also as a determinant of immune cell fate and inflammatory programming. In the context of breast cancer, tumor-driven changes in lipid availability may skew immune responses in ways that sustain chronic inflammation, suppress effective antitumor immunity, and promote therapeutic resistance.^{78,79} Accordingly, immune lipid metabolism should be considered an integral component of tumor metabolic reprogramming rather than a secondary downstream effect.

Extracellular Vesicles and Metastasis

Extracellular vehicles (EVs) should not be viewed merely as passive intercellular messengers but rather as selective lipid bilayer-delimited carriers that package biologically active cargo, including DNA, RNA, miRNAs, proteins, glycans, and lipids. Through this selective cargo loading, EVs can reshape the phenotype of recipient cells and enhance metastatic competence.⁸⁰

In breast cancer, EVs are involved in multiple steps of tumor progression, including tumor microenvironment remodeling, epithelial–mesenchymal transition (EMT), pre-metastatic niche formation, and organ-specific metastasis. Importantly, the biological function of EVs is tightly linked to lipid metabolism.^{81,82} As membrane-bound structures, their biogenesis, stability, and uptake are highly dependent on lipid composition, while their cargo can actively reprogram lipid handling in recipient cells. Studies have shown that breast cancer-derived EVs are enriched in specific lipid classes, such as sphingolipids and glycerophospholipids, and that their lipid composition can distinguish malignant from non-malignant mammary cells as well as reflect different breast cancer subtypes.⁸³ Moreover, EVs released from highly metastatic breast cancer cells exhibit distinct lipid signatures, suggesting that EV-associated lipids are not merely structural components but may play functional roles in promoting metastasis.⁸⁴

Beyond lipid transport, EVs carry genetic and metabolic regulators that modulate stromal activation, extracellular matrix remodeling, immune evasion, and metabolic adaptation.⁸⁵ Furthermore, therapy-induced EV release may facilitate the spread of resistance traits among tumor cell populations.⁸⁶ Therefore, EVs represent a critical interface where lipid metabolism, genetic signaling, and micro environmental adaptation converge, linking lipid reprogramming to metastasis and therapeutic resistance in breast cancer.

Research Progress on Therapeutic Interventions Targeting Fatty Acid Metabolism in Breast Cancer

Given the central role of fatty acids in cancer pathogenesis, developing therapies that target metabolic reprogramming of fatty acid pathways has gained substantial clinical significance. Most currently available inhibitors focus on enzymes involved in de novo fatty acid synthesis or exogenous lipid uptake, and several related drug candidates have been developed.⁸⁷ (see [Supplementary Table](#)).

Statins

Breast cancer cells display remarkable metabolic plasticity, enabling them to adjust fatty acid synthesis, storage, and utilization according to microenvironmental stress to sustain rapid proliferation and invasive behavior.⁴⁵ Consequently, metabolic modulation of lipid pathways has become an increasingly important focus in breast cancer therapy research.⁸⁸ Multiple preclinical studies registered in global clinical trial databases have demonstrated that inhibition of cholesterol biosynthesis or disruption of key lipid metabolic nodes weakens breast cancer cell viability.⁸⁹

Among these strategies, statins—which inhibit HMG-CoA reductase and block the mevalonate (MVA) pathway—have attracted particular attention.⁸⁸ Previous studies reveal that by lowering membrane cholesterol content, statins disrupt several oncogenic signaling cascades, including the KRAS-driven PI3K/TBK/AKT axis, ultimately inducing apoptosis in breast cancer cells.⁹⁰

Furthermore, combining statins with other targeted agents can significantly enhance antitumor activity. For example, co-administration of a ROR γ antagonist with statins produces strong synergistic effects against triple-negative breast cancer (TNBC).⁹¹ Simvastatin reduces GPX4 expression by suppressing HMGCR and the MVA pathway, thereby promoting ferroptosis in TNBC cells.⁹² Additionally, simvastatin combined with metformin suppresses endothelin-1 and downstream HIF signaling, alleviates tumor hypoxia, and reduces angiogenesis.⁹³ Overall, targeting lipid metabolism—particularly cholesterol biosynthesis via statins—provides a promising metabolic intervention strategy for breast cancer, with potentially high value in refractory subtypes such as TNBC.⁹⁴

FASN Inhibitors

Fatty acid synthase is aberrantly overexpressed in many tumor types, with particularly strong activation in breast cancer, making it a major metabolic therapeutic target.⁹⁵ Although numerous FASN inhibitors have been developed, only one agent—TVB-2640—has advanced to clinical evaluation. TVB-2640 has completed a Phase I clinical trial (NCT03179904), demonstrating a favorable safety profile and pharmacokinetics, and is currently undergoing Phase II testing in patients with HER2-positive metastatic breast cancer.⁹⁶ Extensive evidence indicates functional cross-talk between FASN and HER2, suggesting that metabolic–signaling coupling mediated by FASN plays an essential role in HER2-driven breast cancer biology. Consequently, FASN inhibition has emerged as a novel therapeutic strategy for this subtype, showing robust antitumor activity across multiple preclinical models.^{97,98}

Mechanistically, FASN is essential for de novo phospholipid synthesis, generating lipid components required for lipid raft formation—structures that maintain HER2 localization and activation. FASN inhibition alters membrane lipid composition and destabilizes lipid rafts, thereby diminishing HER2 signaling output.⁹⁹ Experimental evidence shows that disrupting lipid raft integrity—through pharmacological or genetic approaches—induces apoptosis in HER2-overexpressing breast cancer cells.¹⁰⁰ Lipidomic profiling further suggests that membrane lipid remodeling is highly relevant to HER2-positive breast cancer, indicating that targeting membrane structure or fluidity may represent an innovative therapeutic avenue.^{63,101}

Acetyl-CoA Carboxylase (ACCA/ACAC) Inhibitors

In the de novo fatty acid synthesis pathway, conversion of acetyl-CoA to malonyl-CoA is the rate-limiting step, catalyzed by acetyl-CoA carboxylase (ACAC).¹⁰² ACAC consists of two isoforms, ACACA and ACACB, both of which are significantly upregulated in various cancers, particularly in breast cancer.¹⁰³ Immunohistochemical analyses show markedly higher ACAC expression in breast cancer tissues compared to normal breast tissue, with further elevation as tumors progress.¹⁰⁴ Importantly, ACACA has been shown to interact functionally with BRCA1, broadening the recognized role of BRCA1 in metabolic regulation in breast cancer.¹⁰⁵ ACACA inhibition not only suppresses breast cancer cell proliferation but also induces apoptosis, underscoring its importance in tumor growth.¹⁰⁶ Because ACAC governs the rate-limiting step of malonyl-CoA production, inhibition of ACACA/ACACB is considered a promising metabolic therapeutic strategy.¹⁰² Studies further indicate that BRCA1-mediated modulation of ACAC activity is consistent with lipid metabolic abnormalities observed in BRCA-mutated patients, providing theoretical support for metabolic targeting of BRCA-related breast cancer.¹⁰⁷ Although

ACAC inhibitors have demonstrated antitumor efficacy in several cancer models, their clinical relevance in breast cancer—particularly BRCA-mutant subtypes—requires further validation.¹⁰⁸

Choline Kinase Inhibitors

Choline kinase, a key enzyme in the phosphatidylcholine biosynthesis pathway responsible for generating phosphocholine (PCho), is frequently overactivated in several cancers and is therefore considered an attractive metabolic target.¹⁰⁹ Over the past decades, numerous ChoK inhibitors have been developed, many of which have shown significant antiproliferative effects against breast cancer cells in preclinical studies.¹¹⁰ The most advanced candidate, TCD-717, has entered a Phase I clinical trial for solid tumors (NCT01215864), providing early support for the clinical translation of ChoK-targeted therapy.¹¹¹

Notably, ChoK inhibition may offer particular therapeutic advantages in TNBC, where dysregulated choline metabolism is recognized as a key metabolic feature driving tumor aggressiveness.⁹² By disrupting ChoK activity and limiting the availability of phospholipid precursors, this strategy may effectively restrain the growth and invasiveness of TNBC, offering a new therapeutic option for this highly challenging subtype.¹¹²

Development of Therapeutic Strategies Targeting Enzymes in the Fatty Acid Biosynthetic Pathway in Breast Cancer

Targeting FASN

Fatty acid synthase (FASN), a key enzyme in *de novo* fatty acid synthesis, is markedly overexpressed in breast cancer and is closely associated with tumor proliferation, invasion, epithelial–mesenchymal transition (EMT), malignant progression, and multiple forms of therapeutic resistance.¹¹³ Identified early as the breast cancer tumor antigen OA-519, FASN has been confirmed as a major metabolic driver in several molecular subtypes of breast cancer.¹¹⁴ Upregulation of FASN supplies tumor cells with membrane lipids, energy, and biosynthetic precursors, and also enhances the activity of critical signaling pathways, including those mediated by HER2 and ER α , thereby promoting tumor cell survival.¹¹⁵ Inhibition of FASN downregulates HER2 expression, interferes with MAPK/ER α and AKT/ER α crosstalk, and increases the sensitivity of cancer cells to chemotherapeutics such as paclitaxel.¹¹⁶ These findings highlight FASN as a promising target for breast cancer therapy. Although early FASN inhibitors (such as C75, cerulenin, and orlistat) showed significant potential in preclinical models by suppressing tumor growth and increasing vulnerability to oxidative stress, their severe systemic side effects—including rapid weight loss—hindered clinical translation.⁹⁹ To overcome these limitations, a new generation of selective inhibitors (eg., TVB-3166 and TVB-2640) has been developed. These agents avoid the undesirable activation of CPT1 and peripheral β -oxidation observed with earlier compounds, resulting in markedly improved tolerability and strong antitumor activity in breast and colorectal cancer models.¹¹⁷

HER2-positive breast cancer represents a particularly important therapeutic context, given the strong functional connection between FASN and HER2 downstream signaling.¹¹⁸ Current clinical development of FASN inhibitors is therefore focused primarily on this patient population. TVB-2640, which demonstrated favorable tolerability in Phase I trials, is currently being tested in Phase II studies (NCT03179904) in combination with chemotherapy for HER2-positive metastatic breast cancer.¹¹⁹ As research advances, metabolic or HER2-based patient stratification may further enhance the clinical benefit of FASN-targeted therapies.¹²⁰

The Target of FABP4 in Breast Cancer Cell Signaling Pathways

Fatty acid-binding protein 4 (FABP4), a member of the fatty acid-binding protein (FABP) family, plays a central role in lipid metabolism and intracellular signaling. FABP4 is primarily expressed in adipocytes and macrophages, where it facilitates fatty acid transport and regulates various biological processes, including inflammation and insulin sensitivity.¹²¹ FABP4 is functionally linked to several critical signaling pathways across different malignancies, including PI3K/Akt, ROS/ERK/mTOR, Wnt, and NOTCH cascades.¹²² In various tumor types, FABP4 promotes proliferation and migration by activating the ERK/mTOR pathway, suppressing the NF- κ B–IL1 α axis via ubiquitination-mediated mechanisms, or enhancing Wnt10b signaling.¹²³ In breast cancer, FABP4 regulates cell-cycle progression by modulating

key Cyclin/CDK components required for G1/S and G2/M transitions.¹²⁴ It can also increase tumor stemness and invasiveness through activation of the IL-6/STAT3/ALDH1 pathway. Moreover, FABP4 enhances pERK and NRF2 activity, leading to the induction of antioxidant genes that help tumor cells alleviate oxidative stress.¹²⁵ Through these mechanisms, FABP4 drives breast cancer toward more aggressive and therapy-resistant phenotypes, positioning it as a critical metabolic and signaling hub with therapeutic potential.¹²⁶

FABP4 is largely derived from adipocytes and macrophages and is typically upregulated within the breast tumor microenvironment. Studies have shown that FABP4 promotes polarization of tumor-associated macrophages (TAMs) toward the protumorigenic M2 phenotype, which is characterized by enhanced angiogenesis, immunosuppression, and metastatic capability.¹²⁷ Upregulation of FABP4 therefore remodels the tumor immune landscape, supporting tumor growth. In obesity-associated breast cancer, FABP4 is closely linked to increased angiogenesis.¹²⁸ Inhibition of FABP4 in tumor endothelial cells suppresses VEGFA-driven angiogenic responses, increases fatty acid oxidation and ROS accumulation, and ultimately reduces neovascular formation.^{129,130} Taken together, the dual roles of FABP4 in immune modulation and angiogenesis underscore its value as a potential therapeutic target in breast cancer.

Advances in structural biology have enabled detailed characterization of FABP4's ligand-binding cavity and inhibitory sites, facilitating the development of highly selective small-molecule inhibitors.¹³¹ For instance, compounds based on the 4-aminopyrazin-3(2H)-one scaffold exhibit strong inhibitory activity. Additionally, antibody screening has identified a FABP4-specific monoclonal antibody, clone 12G2, capable of reducing circulating FABP4 levels and suppressing breast tumor growth and metastasis by disrupting mitochondrial metabolism.¹³² These discoveries suggest that targeting FABP4 may represent a novel therapeutic strategy for breast cancer and other lipid metabolism-driven malignancies, particularly those with a microenvironment heavily influenced by lipid signaling.

Targeting ACLY and ACSS2

ATP-citrate lyase (ACLY) is a metabolic hub linking glucose metabolism to de novo fatty acid synthesis. ACLY converts citrate—derived from glucose or glutamine metabolism—into acetyl-CoA, fueling lipid synthesis, cholesterol biosynthesis, and membrane construction.¹³³ In breast cancer, ACLY is broadly overexpressed and associated with tumor proliferation, invasion, and metabolic plasticity.¹³⁴ Genetic silencing or pharmacological inhibition of ACLY significantly impairs breast cancer cell proliferation and malignant behavior.¹³⁵ ACLY also forms complexes with the low-molecular-weight isoform of Cyclin E, enhancing lipogenesis and promoting oncogenic transformation and metastatic potential.¹³⁶ Notably, ACLY expression is particularly elevated in HER2-enriched breast cancer, suggesting strong metabolic dependence in this subtype.¹³³

Because ACLY is the key enzyme regulating acetyl-CoA production, ACLY-targeted strategies have been successful in metabolic diseases, exemplified by the LDL-lowering agent ETC-1002, which has shown strong efficacy and tolerability in clinical trials.¹³⁷ This provides indirect evidence supporting the safety of ACLY inhibition. Preclinical breast cancer studies similarly demonstrate that ACLY inhibitors (such as SB-204990 and hydroxycitrate) can suppress tumor growth, especially in highly glycolytic cells that rely heavily on acetyl-CoA for lipogenesis.¹³⁸ This finding suggests that metabolic phenotyping may improve precision and therapeutic response to ACLY-targeted treatment.

The therapeutic relevance of ACLY inhibition extends beyond lipid synthesis, impacting epigenetic regulation. Reduced acetyl-CoA availability alters histone acetylation patterns, thereby affecting transcriptional programs involved in proliferation and drug resistance.¹³⁹ Under environmental stressors such as nutrient deprivation or hypoxia, breast cancer cells may compensate by upregulating ACSS2, enabling the conversion of acetate into acetyl-CoA and partially bypassing ACLY blockade.^{140,141}

Recent studies are developing ACSS2 inhibitors to shut down this acetate compensation pathway, potentially enhancing the efficacy of ACLY-targeted therapies. Overall, ACLY represents an upstream master regulator of lipid metabolic reprogramming in breast cancer.¹⁴² With improved tolerability of ACLY inhibitors and the emergence of metabolic stratification strategies, ACLY targeting is poised to become a promising therapeutic approach, particularly in metabolically active subtypes such as HER2-enriched breast cancer.¹⁴³

Targeting SCD: Inhibiting Fatty Acid Desaturation

Stearoyl-CoA desaturase (SCD) is a rate-limiting enzyme in the fatty acid synthesis pathway responsible for converting saturated fatty acids into monounsaturated fatty acids (MUFA).¹⁴⁴ MUFAs constitute essential components of membrane phospholipids, sphingolipids, and glycerophospholipids, and are required for organelle membrane integrity, fluidity, and the membrane biogenesis necessary for rapidly proliferating tumor cells.¹⁴⁵ In breast cancer and other malignancies, lipid utilization is generally elevated, and increased SCD activity further enhances membrane remodeling, tumor invasiveness, and metabolic adaptability.¹⁴⁶

Importantly, the degree of membrane lipid unsaturation affects cardiolipin composition, thereby modulating the interaction between cytochrome c and the mitochondrial inner membrane, ultimately influencing respiratory chain stability and apoptotic signaling.¹⁴⁷

Inhibition of SCD significantly reduces MUFA levels, alters cardiolipin composition, induces mitochondrial stress, and increases cancer cell sensitivity to chemotherapeutic or oxidative insults—making SCD a compelling therapeutic target for lipid-dependent tumors.¹⁴⁸ Preclinical studies in breast cancer show that SCD inhibition suppresses EMT, reduces invasiveness, and triggers multiple cell death pathways, including ER stress, mitochondrial dysfunction, and depletion of cancer stem-like cell populations.¹⁴⁹ Several small-molecule inhibitors, such as SSI-4, betulinic acid (BetA), and MF-438, have demonstrated these effects in a variety of cancer models.¹⁵⁰

However, some cancers are resistant to SCD inhibition because they activate compensatory desaturation pathways via FADS2, enabling continued processing of palmitic acid to fulfill membrane lipid requirements.¹⁵¹ In such cases, SCD inhibition alone is insufficient to disrupt tumor growth; only dual blockade of SCD and FADS2 yields significant antitumor effects, as shown in hepatocellular carcinoma models. These findings indicate that the success of SCD-targeted therapy depends on understanding the broader network of fatty acid synthesis, including available lipids in the microenvironment, FADS2 substrate preferences, and tumor cell adaptations to maintain unsaturated fatty acid pools.¹⁵¹ Overall, SCD plays a central role in lipid metabolic reprogramming in breast cancer. Its inhibition disrupts membrane lipid biogenesis and enhances therapeutic sensitivity through mitochondrial and ER stress pathways, making it a promising therapeutic strategy for metabolically active breast cancers, particularly TNBC and other highly aggressive subtype.¹⁵²

Discussion

Abnormal reprogramming of fatty acid metabolism is a fundamental drive that sustains the proliferation, survival, and invasive capacity of breast cancer cells. Multiple classes of inhibitors targeting fatty acid synthesis, fatty acid oxidation, and lipid uptake pathways have demonstrated antitumor potential in breast cancer models, effectively suppressing tumor growth and reducing metastasis. Therefore, restricting fatty acid availability or pharmacologically targeting key metabolic enzymes is emerging as a promising therapeutic strategy for breast cancer. In addition, ferroptosis inducers—such as sulfasalazine, siramesine, erastin, and curcumin—further enhance therapeutic sensitivity by disrupting lipid homeostasis and weakening antioxidant defenses, suggesting that combining metabolic targeting approaches with conventional anticancer agents may produce superior therapeutic outcomes.¹⁵³

Breast cancer cells exhibit pronounced metabolic vulnerabilities owing to their dependence on lipid metabolism. Dysregulation of specific metabolic pathways profoundly influences the tumor immune microenvironment, for instance by impairing cytotoxic T lymphocytes (CTLs) and natural killer cells, thereby diminishing the efficacy of immunotherapies. Consequently, identifying metabolic weaknesses across different breast cancer subtypes is of great importance. High-throughput approaches such as siRNA, shRNA, or CRISPR-based screens may reveal cell type-specific metabolic dependencies, while certain oncogenic mutations may confer unique lipid utilization patterns. Compared with single-pathway interventions, combinatorial strategies—integrating lipid metabolic inhibitors, antiproliferative agents, statins, and even dietary interventions—are more likely to elicit synergistic and durable antitumor responses.

The malignant phenotypes of breast cancer, including uncontrolled proliferation, migration, invasion, and therapeutic resistance—are closely linked to upregulate *de novo* fatty acid synthesis, lipid droplet accumulation, fatty acid uptake, and enhanced FAO. Inhibiting these processes or silencing core metabolic enzymes significantly suppresses tumor

progression in various preclinical models, and these strategies hold promise for tumors arising in lipid-rich environments such as breast tissue.

Continuous advances in analytical technologies are reshaping our understanding of breast cancer lipid metabolism. Single cell lipidomic and spatial metabolomics provide unprecedented resolution for dissecting metabolic heterogeneity and microenvironmental interactions. These approaches permit the mapping of lipid flux dynamics across distinct TNBC subpopulations, reveal spatial co-localization patterns between lipid metabolites and immune cells (such as tumor-associated macrophages or tumor-infiltrating lymphocytes), and—when integrated with spatial transcriptomics—allow the construction of region-specific associations between gene expression and lipid metabolic states. The integration of multi-omics datasets will enable the development of dynamic regulatory networks of lipid metabolism in TNBC and support the design of precision metabolic therapies, with the potential to improve outcomes for patients who are refractory to conventional treatments.

Despite significant advances in understanding lipid metabolic reprogramming in breast cancer, the translation of these findings into effective clinical therapies remains challenging. Among the major obstacles, metabolic plasticity-driven resistance represents a central barrier that limits the efficacy of lipid metabolism-targeted strategies. For example, inhibition of stearoyl-CoA desaturase 1 (SCD1) can induce tumor cell death through lipid imbalance; however, compensatory pathways such as fatty acid desaturase 2 (FADS2) can restore lipid homeostasis via bypass mechanisms, thereby attenuating therapeutic effects.¹⁵¹ In addition, cancer cells exhibit remarkable metabolic flexibility, allowing dynamic switching between de novo lipogenesis and exogenous lipid uptake. This metabolic redundancy substantially reduces the effectiveness of single-target interventions. At the same time, lipid metabolism plays a critical role in maintaining redox homeostasis in tumor cells. Lipid synthesis and remodeling help buffer reactive oxygen species (ROS)-induced damage and support tumor cell survival under stress conditions.¹⁵⁴ As a result, inhibition of lipid metabolic pathways alone often fails to produce durable antitumor responses, highlighting the need for combinatorial therapeutic strategies.

Another major limitation is the lack of reliable predictive biomarkers for patient stratification. Although key metabolic regulators such as fatty acid-binding protein 4 (FABP4) have shown promising potential in preclinical studies, their clinical efficacy remains uncertain. This inconsistency is partly due to the high degree of metabolic heterogeneity across breast cancer subtypes and metastatic sites, which significantly influences treatment response. Collectively, these challenges underscore that the future development of lipid metabolism-targeted therapies will require integrated strategies that account for metabolic plasticity, tumor heterogeneity, and microenvironmental influences. Multi-target combination approaches, together with biomarker-guided precision medicine, are likely to be essential for achieving more durable and clinically meaningful therapeutic outcomes.

Conclusions

Targeting key metabolic enzymes, such as FASN and FABP4, represents a promising therapeutic strategy for breast cancer, particularly in metabolically adaptive and treatment-resistant subtypes.

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