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# Dysregulation of Fatty Acid Metabolism in Breast Cancer and Its Targeted Therapy

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**Abstract:** Breast cancer has become the number one cancer worldwide, there are challenges in its prevention, diagnosis and treatment, especially the pathogenesis of triple negative breast cancer has not been clear and the treatment dilemma of metastatic breast cancer. Metabolic reprogramming is currently considered to be one of the hallmarks of cancer, and metabolic alterations in breast cancer, including enhanced glycolysis, tricarboxylic acid cycle activity, glutamine catabolism, and fatty acid biosynthesis, are manifested differently in different breast cancer subtypes and have a complex relationship with tumor growth, metastasis, death, and drug resistance. At present, inhibitors of fatty acid synthesis and oxidation related enzymes have a certain effect in the treatment of breast cancer. In this paper, we review the studies on fatty acid metabolism in breast cancer to better understand the mechanism of fatty acid metabolism in breast cancer pathogenesis and hope to provide new ideas for targeting fatty acid metabolism in the treatment of breast cancer.

**Keywords:** breast cancer, fatty acid metabolism, metabolic reprogramming, targeted therapy

## Introduction

Breast cancer (BC) is the most common cancer in women and the leading cause of cancer-related deaths. According to the World Health Organization (WHO),[1] by 2020, 2.3 million women worldwide will be diagnosed with BC and the disease will cause 685,000 deaths worldwide. The female breast is rich in adipose tissue, so the development of BC in women may be strongly linked to lipid metabolism. It is now known that fatty acid (FA) metabolism plays a critical role in cancer progression and development, reflecting its role in regulating cell membrane composition, providing an additional source of energy, participating in metabolic reprogramming, and acting as precursors of signaling molecules.[2] Cancer cells disrupt normal lipid metabolism by increasing exogenous lipid (dietary) uptake, FA and cholesterol synthesis from scratch. Obesity is one of the major risk factors for BC patients and is associated with poor patient prognosis, and obese women have an increased risk of developing malignant tumors and increased mortality rates.[3,4] A population-based cohort study of 17,145 women suggests that healthy lifestyle factors such as weight may improve prognosis and survival in BC.[5] Visceral and peritumoral adipose tissue play an important role in promoting BC, leading to shorter disease-free survival and an increased likelihood of developing lymph node-positive BC.[6] In addition, studies have shown that adipocytes are capable of transferring FA into BC cells. Adipocytes supplemented with high concentrations of FA enhanced this translocation, thereby increasing cell proliferation and migration.[7,8]

However, the mechanism of the role of abnormal FA metabolism in the pathogenesis of BC has not been elucidated. Meanwhile, limiting FA synthesis has been shown to control cancer cell proliferation, and higher rates of FA synthesis have been associated with the risk of BC development, progression, and drug resistance.[9] It has been reported that upregulation of the FA receptor CD36 leads to increased FA uptake and thus drug resistance.[10] Therefore, this paper reviews the role and regulatory mechanisms of abnormal FA metabolism in BC, starting from abnormal tumor metabolism, in the hope of exploring novel metabolism-targeted therapies.

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## Molecular Subtypes of Breast Cancer and Their Therapeutic Rationale

BC can be classified into four subtypes based on marker expression, namely luminal type A, luminal type B, human epidermal growth factor receptor 2 (HER2) overexpression, and triple-negative type.[11] The luminal type is positive for estrogen receptor alpha (ER-α) due to the activation of the oncogenic growth pathway by ER-α to induce cancer, luminal type B are of higher grade, and worse prognosis compared to luminal type A, because they are ER positive and can be progesterone receptor (PR) negative with Ki67>20%; The HER2 overexpression type is negative for both ER-α and PR and positive for HER2 due to the overactivity of the oncogenic gene, ERBB2, which encodes the ERBB2 receptor tyrosine kinase of the EGFR family, leading to the development of BC; The triple-negative type is a subtype of breast cancer, namely the luminal A, luminal B, HER2 overexpression type and the triple-negative type. Occurrence; triple-negative breast cancer (TNBC) is negative for ER-α, PR, and HER2, and the mechanism of its invention has not been clarified, which can be caused by a variety of causes.[11]

The metabolic pathways and metabolite levels are categorized as Mc1 (high levels of glycerophosphorylcholine and phosphorylcholine), Mc2 (high levels of glucose), and Mc3 (high levels of lactate and alanine).[12] Recent studies have shown that there are three distinct metabolic phenotypes in TNBC: a. MPS1 lipid synthesis subtype, characterized by upregulation of metabolism and synthesis of lipids, such as FA and cholesterol, in cancer cells; b. MPS2 glycolysis subtype, which is characterized by the upregulation of carbohydrate and nucleotide metabolism in cancer cells; and C. MPS3 mixed subtype, which is characterized by the characteristics of both of the above two subtypes.[12] This study suggests targeting different metabolic phenotypes as a potential strategy for the precision treatment of TNBC. For non-metastatic BC, the main goal of treatment is to eradicate the tumor in the breast and regional lymph nodes to prevent metastatic recurrence. Local treatment for non-metastatic BC includes surgical excision and sampling or removal of axillary lymph nodes, with consideration of postoperative radiotherapy.[13] Systemic therapy may be given preoperatively (neoadjuvant), postoperatively (adjuvant), or both. For patients with metastatic BC, who have a poor prognosis and are currently difficult to treat, the goal of treatment is to prolong life and relieve symptoms. Local therapeutic modalities (eg, surgery and radiation) are usually used only for palliative treatment of metastatic disease.[14]

## Abnormal Fatty Acid Metabolism in Breast Cancer

Dysregulated FA metabolism is thought to play an important role in the malignant transformation of many different cancers, including BC. Key metabolic enzymes involved in FA synthesis and oxidation play a critical role in BC cell proliferation, migration, and invasion.FA metabolism includes a variety of pathways, such as FA transport, storage in lipid droplets as triglycerides and cholesteryl esters, mobilization from phospholipids and triglycerides, and FA oxidation. The differential importance of FA ab initio pathways in normal versus cancerous tissues makes them an attractive therapeutic target.[15] In addition to synthesizing FA de novo, cancer cells can obtain the fatty acids they need by consuming dietary lipids or by ingesting exogenous FA released from cancer-associated adipocytes. This section focuses on the aberrant roles of genes regulating enzymes involved in fatty acid metabolism in BC and related research advances (Figure 1).

### Fatty Acid Synthesis and Acquisition

The biological characteristics and energy metabolism mechanisms of tumor cells are different from those of normal cells, and FA is derived from both exogenous dietary intake and endogenous ab initio synthesis. It has been found that the FA required for the growth and proliferation of malignant tumors is mainly derived from the ab initio pathway, and that important enzymes related to synthesis and oxidative metabolism are overexpressed in tumor tissues but not in normal tissues or are lowly expressed in normal tissues.[16](Figure 1)

BC cells enhance FA uptake through multiple pathways, including enhanced CD36/fatty acid translocase, low-density lipoprotein (LDL)-mediated endocytosis, and increased expression of fatty acid transport protein (FATP) and fatty acid-binding protein (FABP).[15] BC cells exhibit increased ab initio FA synthesis, such as increased expression of various enzymes involved in ab initio FA synthesis, including acetyl CoA carboxylase (ACC) and fatty acid synthase (FASN), to promote cancer cell survival. Depletion of ACC decreases FA synthesis and induces apoptosis in BC cells, but not in

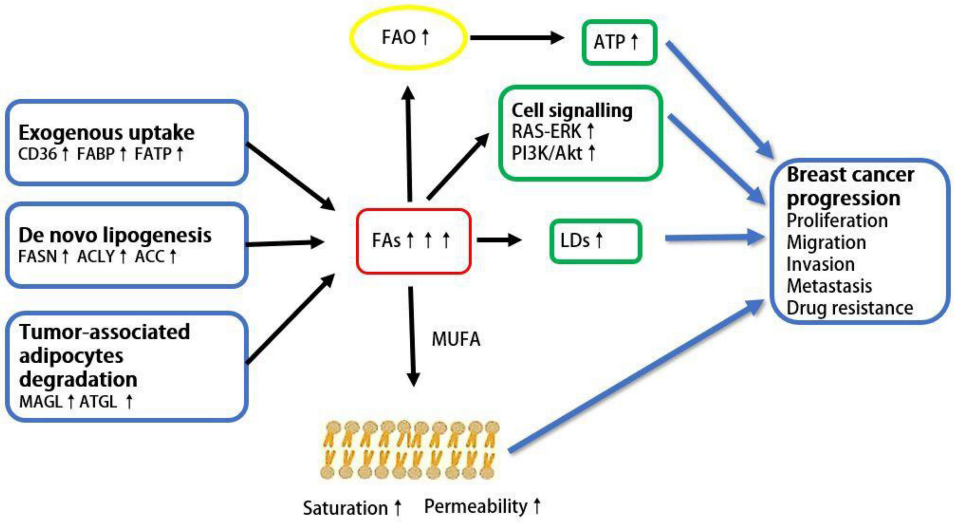


**Figure 1** Metabolic disorders of FA in breast cancer.

non-malignant cells. In contrast, recent studies have shown that FASN expression is necessary for lipid synthesis and maintenance of palmitate levels, especially in the absence of exogenous lipids. Perhaps FASN could be a potential therapeutic target for BC brain metastasis. Enhanced ab initio FA synthesis properties of cancer cells confer membrane saturation, favoring antagonism of apoptosis against lipid peroxidation, as well as altered lateral membrane dynamics to limit drug uptake, making cancer cells more resistant to treatment.[17] Cancer cells convert FA into diacylglycerol (DAG) and triacylglycerol (TAG), which bud through the endoplasmic reticulum to form lipid droplets (LDs), which serve as energy reservoirs, and the increased storage of LDs facilitates high tumor invasiveness (Figure 1).

The luminal subtype has been shown to rely on de novo lipogenesis (DNL) as a source of bioenergetic requirements, but TNBC cell overexpression is involved in the utilization of exogenous fat.[18] DNL is often shown to be activated in approximately 85% of HER2+ BC, and in particular, FASN is often overexpressed/activated in HER2+ BC, but less so in TNBC.[19] Cancer cells typically exhibit high glucose uptake for aerobic glycolysis to produce lactate, and this metabolic reprogramming results in reduced conversion of pyruvate to acetyl coenzyme A. Thus, cancer cells exhibit different metabolic adaptations for FA synthesis, manifested as a dependence on glutamine or acetate as alternative substrates.[20] For example, compared to luminal types, TNBC is usually more dependent on glutamine metabolism to produce acetyl coenzyme A.[21] Under hypoxic conditions, BC upregulates enzymes that convert acetate to acetyl coenzyme A (eg, acetyl coenzyme A synthetase) to increase acetate uptake.[22]

Cancer cells can also induce the metabolism of extracellular matrix components, BC cells are co-cultured with adipocytes, and BC cell secretion induces adipocytes to catabolize and release FA, which is converted to LDs for storage, and then BC cells upregulate the adipose triglyceride lipase (ATGL)-dependent lipolysis pathway and the fatty acid oxidation (FAO) pathway to degrade FA to enhance their invasive capacity.[23] The FA uptake pathway is a major component of the FA oxidation pathway. Therefore, transporter proteins such as fatty acid translocase and fatty acid binding proteins in the FA uptake pathway may be potential targets for cancer therapy, and inhibition of exogenous FA sources or induction of LDs degradation serve as therapeutic targets.

The CD36 molecule regulates lipid uptake and is involved in FA uptake at the membrane surface of a variety of metastatic tumor cells, including melanoma, BC, bladder, lung, and ovarian cancers. Knocking down CD36 expression completely halted the invasive metastatic behavior of tumor cells in a mouse model.[24] CD36 was expressed at higher levels in tumor-infiltrating regulatory T cells, and inhibition of CD36 blocked regulatory T cell adaptation to the tumor microenvironment and enhanced anti-tumor activity.[25] In conclusion, the abnormal FA metabolism-specific phenotype of tumor cells has gradually attracted great attention, and the exploration of the role of abnormal FA metabolism in the

development of BC and the strategy of treating malignant tumors by targeting FA metabolic pathways are attracting much attention.

## Fatty Acid Oxidation and Utilization

FA is involved in cancer progression in two main ways: by participating in the synthesis of membrane phospholipid structures and feeding tumor growth via FAO, and by participating in the synthesis of important intracellular lipid signaling molecules. BC cells enrich cancer cell membranes with saturated and/or monounsaturated fatty acids (MUFA) through de novo synthesis increase the expression of enzymes that convert saturated FA to MUFA, such as sterol CoA desaturase (SCD1), and increase the number of lipid rafts in the cell membrane to affect membrane fluidity to counter oxidative and drug resistance. Polyunsaturated fatty acids (PUFA) such as docosahexaenoic acid (DHA) prevent the development of BC and increase the chemosensitivity of cancer cells (Figure 1).

Beta-oxidation is an FA modification process by which long-chain FA can be converted to FA of a length appropriate for the metabolic needs of the body. Acyl coenzyme A oxidase 2 (ACOX2) is the rate-limiting enzyme in the β-oxidation process of branched, long-chain FA that occurs in peroxisomes. Expression and translation of a variant transcript, ACOX2-i9 is regulated by estrogen in ER-positive BC cell lines, and knockdown of this enzyme results in decreased cell viability.[26] Carnitine palmitoyltransferase 1B (CPT1B) is a key enzyme that encodes FAO.JAK/STAT3 regulates lipid metabolism, and inhibition of JAK/STAT3 prevents self-renewal and expression of various lipid metabolism genes, including the CPT1B gene, in BC stem cells. The STAT3-CPT1B-FAO pathway promotes stemness and chemoresistance in cancer cells, and blockade of FAO can re-sensitize cancer cells to chemotherapy and inhibit cancer stem cells in mouse mammary tumors in vivo.[27] Metastatic TNBC maintain high levels of ATP through fatty acid oxygenation and promote metastasis through activation of SRC oncoproteins by autophosphorylation at Y419.[28] BC subtypes exhibit differential FA utilization, and it was found that TNBC cells preferentially dope palmitate into storage TAG, whereas luminal-type cells preferentially shunt palmitate to FAO.[29]

Other FA-derived lipids such as arachidonoids are involved in the synthesis of inflammatory substances to promote tumorigenesis, and prostaglandin E2 activates signaling pathways such as rat sarcomeric protein/extracellular signal-regulated protein kinase (RAS-ERK), induces BC cell proliferation by increasing aromatase expression in stromal adipocytes, and promotes cancer cell metastasis to lymph nodes by upregulating chemokine expression[30](Figure 1).

# Dysregulation of Fatty Acid Metabolism Leads to Aberrant Behavior of Breast Cancer Cells

The functional and biological behavior of BC cells is influenced by state transitions characterized by lipid metabolism reprogramming (LMR). FA metabolism is extensively upregulated at different stages of BC and serves as both an energy source for tumor cells and a trigger for specific signaling pathways and aberrant cellular activity.

## Cancer Cell Proliferation, Invasion, and Migration

There is evidence that the nuclear receptor Nur77 inhibits CD36 and FABP4 transcription and inhibits FA uptake and thus BC proliferation, but this effect can be reversed by peroxisome proliferator-activated receptor γ (PPARγ) ubiquitination of Nur77.[31] The chromatin repair enzyme BRG1 regulates TNBC proliferation by modulating FA production. Compound C in combination with aspirin enhances oncogenic effects by inhibiting FA synthesis gene expression.[32]

FA promotes BC invasion through the FAO pathway. Co-culture of adipocytes with BC cells showed upregulation of the FAO pathway, and such cancer cells enhanced tumor metastasis in vivo.[33] Tumor-associated adipocytes enhanced FA uptake and invasiveness of BC through secretion of the FA uptake protein CD36, and inhibition of CD36 showed reduced accumulation of LDs and decreased invasive capacity.[34] A recent study showed that silencing cell membrane surface integrin α2 (ITGA2) inhibits BC metastasis by repressing genes involved in cell cycle regulation and lipid metabolism, such as cell cycle protein D1 (CCND1) and ATP citrate lyase (ACLY), thereby inhibiting BC metastasis.[35] Monoacylglycerol lipase (MAGL) is upregulated in BC, and the MAGL pathway controls the release of intracellular FA, the hyperactivation of which enhances tumor invasiveness.[36]

## Apoptosis and Autophagy in Cancer Cells

Tumor cells rely on increased SREBP transcription to activate FASN, ACLY, and ACC1 expression.[37] Studies have shown that pharmacological inhibitors of FASN result in BC cell apoptosis or tumor cell shrinkage.[38] Inhibition of FASN upregulated the expression of the pro-apoptotic gene BNIP3 and induced apoptosis.[39] In vitro In cancer cells cultured under lipid depletion conditions in vitro, inhibition of desaturase-catalyzed MUFA synthesis leads to endoplasmic reticulum stress and apoptosis.[40] Studies have reported that acetyl coenzyme A carboxylase α (ACCα) gene silencing led to BC cell apoptosis, and ACCα and FAS siRNA-induced apoptosis could be rescued by supplementing the culture medium with palmitate or the antioxidant vitamin E, indicating the importance of lipogenesis in BC cell survival.[41]

Emerging evidence suggests that LMR optimizes lipid structure for biosensors related to tumor autophagy. Studies have shown that upregulation of FA levels increases autophagy in a variety of tissues or cells. For example, high concentrations (at least 500 μM) of unsaturated fatty acids (UFA, eg oleic acid) show significant promotion of autophagy. The PUFA glycerol monoester docosahexaenoate induces apoptosis and autophagy in BC cells. Here, autophagy is an inhibitor of apoptosis.[42] However, autophagy is inhibited in the presence of high concentrations of SFA (eg palmitic acid), probably because they are not efficiently converted to triglycerides stored in the LD. The regulation of tumor cell autophagy by the desaturase SCD1 has a dual role that may be related to FA type, lipotoxicity, and cell type.[43] SCD1 converts SFA to UFA and protects tumor cells from lipotoxic damage. From the perspective of autophagy as a protective mechanism, a decrease in SCD1 levels leads to a moderate accumulation of SFA, which triggers the AMPK-mediated compensatory resistance mechanism, accelerates autophagy, and prevents further FA accumulation, thereby escaping cytotoxicity induced by an increase in SFA and maintaining cell survival.[44] However, high levels of lipotoxicity, excessive autophagy, and consumption of MUFA through inhibition of SCD1 lead to cell death.[45] Breast cancer stem cells (BCSC) have a higher autophagic flux than differentiated cells, and inhibition of SCD1 renders them susceptible to autophagic hyperactivation leading to cell death.[46] In conclusion, SCD1 exerts a strong directional effect on autophagy through a specific balance between saturated and unsaturated FA.

Activation of ovarian cancer G protein-coupled receptor 1 (OGR1), an acid-sensitive receptor highly expressed in BC, triggers the accumulation of LD derived from ketogenic amino acids during autophagy. Given its involvement in endoplasmic reticulum stress-induced autophagy under acidic conditions, depletion of OGR1 not only reduces acid-induced lipid accumulation but also inhibits cell proliferation in the acidic microenvironment while impairing the endoplasmic reticulum stress response and the initiation of autophagy.[47] Aberrant expression of CAV1, a marker of lipid rafts/cholesterol-rich membrane microregions (CEMM), was also observed in BC with reduced expression levels. CEMM acts as a barrier to restrict the activity of the v-SNARE protein vesicle-associated membrane protein 3 (VAMP3) during autophagy-vesicle fusion. Deletion of CEMM results in dissociation of VAMP3 from STX6, which triggers autophagy and leads to resistance to adriamycin (DOX) in BC cells.[48] Sphingosylcholine (SPC), a lipid mediator present in the blood, mediates autophagy and apoptosis in TNBC cell lines; however, autophagy is a negative regulator of SPC-induced apoptosis. SPC induces apoptosis by activating the autophagy/AKT/p38 signaling pathway and antagonizing c-JNK signaling.[49]

## Epithelial-Mesenchymal Transformation (EMT)

It is well known that most BC cells are derived from epithelial cells. Epithelial cells play a critical role in mediating various phenotypic changes, including altered cell morphology, reduced or loss of adhesion, and enhanced stem cell-like properties, during their transformation to a mesenchymal phenotype under certain conditions. These changes are closely associated with BC initiation, invasion and metastasis, and the development of chemoresistance. Phenotype reversal through EMT is possible. The complex diversity of lipid metabolic pathways and intermediates results in a complex mechanism of EMT in BC. SREBP1 downregulates E-cadherin expression through recruitment of the Snail/HDAC1/2 complex, and miR-18a-5p has been identified as a potential target of SREBP1 regulation. Overexpression of SREBP1 and inhibition of miR-18a-5p can significantly induce metastasis.[50] In addition, sphingosine synthase 2, which is overexpressed in BC, is a key regulator affecting sphingomyelin (SM) homeostasis and activates the TGF-β/Smad

signaling pathway, which promotes invasion and metastasis by initiating EMT through increasing TGF-β1 activity levels.[51]

Differences in FA metabolic requirements between epithelial and mesenchymal cells may be a key factor in achieving the EMT phenotype. Notably, expression of very long chain fatty acid elongation protein 5 (Elovl5) was significantly downregulated in metastatic estrogen receptor-positive BC, which was positively correlated with EMT, invasion, and lung metastasis. Mechanistically decreased Elovl5 expression promotes upregulation of TGF-β receptor signaling, which is mediated by Smad2 acetylation dependent on LD accumulation.[52] Extracellular vesicles derived from TNBC cells stimulated with PFA enhanced the expression of a variety of EMT-related genes, including Snail1, waveform protein, MMP-2, and −9 secretion.[53] In addition, mesenchymal cells are associated with elevated levels of FAO, which promotes histone acetylation modifications in EMT genes through an acetyl coenzyme A-dependent pathway, thereby affecting epigenetic regulation of EMT. Alterations in FAO promote a more pronounced epithelial cell phenotype by redirecting FA to lipid stores in the epithelium via RXR/RAR signaling, while inhibition of the key enzyme disrupts EMT.[54]

As a component of the cytoplasm and cell membrane, cholesterol plays a direct or indirect role in regulating molecular markers of EMT. In addition, it affects EMT by regulating cell membrane fluidity. ZMYND8 acts as an epigenetic enhancer and is partially expressed in BCSC. ZMYND8 enhances intracellular cholesterol accumulation and oxidation while inhibiting the catabolism of 27-HC. Elevated levels of 27-HC activate LXR and inhibit the expression of E-calmodulin and β-linker protein. This leads to the upregulation of Snail1, waveform protein, fibroblast activation protein α, MMP9, and STAT3 at the transcriptome level and activity.[55–57] Apo C1 adopts a similar mechanism and is involved in the EMT of BC by inhibiting E-calmodulin and promoting waveform protein expression. Upregulation of nicotinamide N-methyltransferase in TNBC downregulates protein phosphatase 1A activity, which activates the MEK/ERK/c-Jun/ABCA2 signaling pathway, promotes cholesterol efflux, increases cell membrane fluidity, and ultimately induces EMT and TNBC translocation. The coenhibitor CtBP is highly expressed in BC and regulates intracellular cholesterol homeostasis by inhibiting SREBF2 and HMGCR activities. Decreased cholesterol levels impair the stability of TGF-β receptors on the cell membrane, which triggers EMT and promotes cancer cell metastasis.[58]

## Iron Death

Abnormalities in tumor lipid metabolism are closely associated with iron death. Recent studies have shown that lipid peroxidation (LPO) induced by high levels of reactive oxygen species (ROS) can mediate an iron-dependent form of programmed cell death known as iron death. Unlike other forms of cell death, which are susceptible to resistance, its unique features include iron accumulation and LPO, making targeted intervention and induction a promising avenue for the development of BC therapies. Iron accumulation subsequently triggers LPO via a non-enzymatic iron-dependent Fenton reaction and activation of iron-containing enzymes such as lipoxygenase.[59,60]

In BC, the cell death mode of the antioxidant system results in decreased expression of GPX4, a key regulator that oxidizes glutathione, reduces cytotoxic lipid peroxides and inhibits lipid peroxide production and iron death. The mevalonate (MVA) pathway biomolecules isopentenyl pyrophosphate (IPP) and coenzyme Q10 play a role in resistance to iron death, with IPP being required for GPX4 biosynthesis.[61] GPX4 induces the expression of the pentameric transmembrane protein prominin-2, which promotes the formation of ferritin-containing exosomes. This mechanism promotes iron death resistance in mammary epithelial cells and breast cancer cells.[62] Notably, GPX4 expression has shown significant predictive value in the neoadjuvant treatment of BC, and high GPX4 expression is positively correlated with distant metastasis-free survival.[63] Glycogen synthase kinase-3β (GSK-3β) has been shown to disrupt cellular antioxidant defenses by regulating nuclear factor erythroid-related factor 2 (Nrf2), and reduced expression of GSK-3β in BC leads to upregulation of GPX4 and downregulation of arachidonic acid 15-lipoxygenase, which in turn leads to reduced levels of ROS and malondialdehyde (MDA). Nrf2 attenuates iron death induced by GSK-3β overexpression, suggesting that targeting the GSK-3β/Nrf2 axis may be promising for inhibiting tumor growth.[64] This suggests that targeting the GSK-3β/Nrf2 axis may be expected to inhibit tumor growth. In addition, heme oxygenase (HO), a major target of Nrf2, plays a critical role in heme catabolism and is closely associated with iron release. Notably, HO-1 has bidirectional effects on tumors; therefore, inhibition of HO-1 is widely considered to be an effective strategy for tumor

therapy. The emerging correlation between HO-1 expression and iron death suggests that cells with lower HO levels are more susceptible to iron death. Iron supplementation and enzyme induction accelerated Erastin-induced iron death.[65]

Activation of the PI3K-AKT-mTOR pathway promotes cell migration through downstream SREBP1 upregulation of SCD1 expression, mediates increased MUFA synthesis (increased MUFA/ PUFA ratio), and protects BC cells from ROS-induced iron death.[66] Unlike PUFA, MUFA inhibits LPO and iron death by displacing PUFA from phospholipids in the cell membrane. Interferon secreted by CD8+ T cells and arachidonic acid induction within the tumor microenvironment promotes iron death via ACSL4-dependent LMR.[67] Fascin actin-binding protein 1 was significantly upregulated in tamoxifen-resistant BC cells, thereby enhancing their sensitivity to elastin-induced iron death.[68] Thus, targeting the induction of iron death in drug-resistant cells may represent a novel strategy to overcome drug resistance. TNBC is more sensitive to iron death than other types of BC, and the application of iron death to TNBC therapy has shown promising results.

## Multidrug Resistance (MDR)

In addition to indirectly contributing to chemoresistance by promoting EMT in breast cancer, the development of the MDR phenotype is a direct result of altered levels of lipid metabolites that create favorable conditions for breast cancer cell survival. Changes in cell membrane lipid composition, activation of FAO, fatty acid synthesis, increased uptake, and abnormal accumulation of lipids may render breast cancer cells resistant to stressors,[69] involving complex mechanisms: 1) Cell membranes contain large amounts of tightly arranged long-chain saturated fatty acids. Elevated cholesterol levels reduce membrane fluidity and may limit drug uptake. For example, sphingomyelin, phosphatidylinositol, cholesterol, and cholesteryl ester concentrations in the lipids of drug-resistant BC cell membranes are higher than those of sensitive cell membranes, and reduced cholesterol levels in the cell membranes of MCF-7 BC cells enhance DOX uptake.[70] 2) Altered lipid distribution in the plasma membrane of drug-resistant cells and interconversion between the plasma membrane and organelle membranes result in altered organelle lipid profiles in drug-resistant cells to maintain MDR, including mitochondrial membrane lipid profiles.[71] Cardiolipin (CL) is primarily found in mitochondrial membranes and is susceptible to oxidation by reactive oxygen species, leading to cytochrome A-dependent apoptosis. CL that is less susceptible to oxidation reduces apoptosis. It has been found that an increase in CL in DOX- or cisplatin-resistant MCF-7 cells leads to increased resistance to LPO, possibly due to the presence of CL species that are more resistant to LPO (eg higher saturated/unsaturated fatty acyl ratio).[72] 3) Increased exogenous fatty acid intake leads to elevated LD and triglyceride levels. Hydrophobic cytotoxic drugs (eg, docetaxel and tamoxifen) can be readily isolated within lipid microspheres.[73] In addition, upregulation of the fatty acid transporter protein CD36 was observed in cells resistant to the HER2 inhibitor lapatinib.[10] 4) Specific precursors of certain lipid components act as second messengers, activating multiple signaling cascades and inducing transcriptional expression of drug efflux transporter protein genes. A variety of ligands (including stearic acid, docosahexaenoic acid, docosapentaenoic acid, and dehydroepiandrosterone) are elevated in BC for free fatty acid receptor 4 (FFAR4). These ligands induce tamoxifen resistance in hormone receptor-positive BC through activation of the ERK and AKT pathways.[74]

Drug resistance has become a major obstacle to the treatment of BC. HER+BC cells upregulate FAO and increase autophagy to produce tamoxifen resistance.[75] Studies on HER+BC resistant to trastuzumab found that AGAP2-AS1 induced by co-culture with mesenchymal stem cells caused stemness and drug resistance by promoting CPT1 expression and inducing FAO.[76] Bidirectional interference between HER-2 and FASN inhibits FASN, which triggers compensatory cell uptake of exogenous FA. Therefore, the upregulation of FA uptake in the extracellular environment is becoming a potential mechanism of primary or acquired resistance to anti-HER-2 therapy.[10] Several key genes involved in drug resistance can interact with specific lipids, particularly those highlighted by important secondary messenger molecules in the sphingomyelin pathway. Reprogramming sphingomyelin metabolism in DOX-resistant cells tends to decrease ceramide (Cer) levels and increase SM levels, thereby evading ceramide-induced apoptosis by activating the SM synthesis pathway. Increased SM levels recruit and functionalize ABCB1, promoting a partial multidrug-resistant state in the cell, as well as the accumulation of glucose ceramide and sphingolipids.[77] The Cer derivative sphingosine has been identified as a potential molecular target for characterizing sphingosine metabolism chemoresistance in BC, as its activity level is regulated by sphingosine kinase 1.[78] In addition, MCF-7 and MDA-MB-231 cell lines resistant to paclitaxel

(TAX) show a similar pattern of PC biosynthesis and have a worse prognosis compared to the sensitive cell lines MCF-7, BT474 and HER2+.[79] Different subtypes of BC exhibited differences in lipid metabolism in drug-resistant cells characterized by different patterns of gene expression: activation of JAK/STAT3-regulated FAO enhanced paclitaxel resistance in mouse mammary stem cells.[27] In HER2+ and hormone receptor-positive BC, the activity levels of FASN and CPT1A were positively correlated with chemoresistance.[80]

## Pathways Regulating Fatty Acid Metabolism in Breast Cancer

### LKB1/AMPK/mTOR

LKB1 kinase is a tumor suppressor, and low LKB1 protein levels are associated with poor BC prognosis;[81] under energy deprivation, cancer cells activate the AMPK pathway to inhibit early biosynthesis, which coordinates the activation of catabolic processes, such as FAO and autophagy, and the inhibition of anabolic processes, such as fatty acid synthesis and the mTOR pathway.[82] Under oxidative stress conditions, LKB1/AMPK is activated to produce more NADPH by decreasing FA synthesis and increasing FAO.[83]

### PI3K/AKT/mTOR

Widespread activation of the PI3K/AKT/mTOR pathway in BC inhibits oxidative stress and iron death-induced lipid peroxidation through up-regulation of SREBP1/SCD1-mediated MUFA synthesis.[66] The IGF1R/PI3K/AKT/mTOR pathway is a classic growth and metabolic regulatory pathway in cancer cells.[84] mTOR acts as a regulator and effector of lipid metabolism mainly by regulating SREBP expression.[85] mTORC1 is an important regulator of lipid metabolism. It has been shown that mTORC1 can inhibit SREBP transcription by negatively regulating phosphatidic acid phosphohydrolase 1 activity.[86] Rapamycin (mTORC1 inhibitor) can block SREBP nuclear aggregation and FAS-related gene expression.[87]

### Jak/Stat3

STAT3 is a key regulator of cell survival and metabolism.[88] Recent studies have shown that STAT3 regulates lipid metabolism by mediating fatty acid synthesis and β-oxidation, for example, adipokines such as leptin and IL-6 produced by adipose tissue activate STAT3 and thus upregulate the expression of CPT1B, FASN, and CD36.[89] Recent studies have shown that the maintenance and function of BC stem cells (BCSCs) are dependent on FAO.[90] Inhibition of the JAK/STAT3 pathway to block CPT1B inhibits the stemness of BCSCs and re-sensitizes BCSCs to chemotherapy.[91]

### Foxo3-Foxm1

Fatty acid-binding protein (FABP4) can inhibit FOXO3 through the PI3K/AKT and MAPK/ERK signaling pathways to upregulate the expression of FOXM1. The FOXO3-FOXM1 axis is affected by FA synthesis and β-oxidation, respectively. FA inhibits the PI3K/AKT pathway, which induces protein degradation and activation of FOXO3, which activates endoplasmic reticulum stress. On the other hand, FOXO3 can inhibit oxidative stress generated by the β-oxidation pathway, which is upregulated by carnitine palmitoyltransferase 1 (CTP1).[92] FOXO3 and FOXM1 have antagonistic roles in the regulation of their target genes and can modulate chemotherapy resistance.[93] FOXO3 and FOXM1 have antagonistic effects in the regulation of their target genes and can modulate chemotherapy resistance. A recent study showed that ACSL4 regulates FOXM1, which mediates breast BC radioresistance by enhancing the DNA damage response and inhibiting apoptosis.[94]

### PGC-1α Signaling Pathway

Peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1α) regulates metabolic processes such as FAO by interacting with various transcription factors. Several studies have elucidated the role of PGC-1α in BC metastasis.[95] It has been shown that tumor metastasis depends on higher levels of PGC-1α to coordinate mitochondrial respiration and ATP production.[96] PGC-1α mediates the transformation of normal adipocytes into tumor-associated adipocytes to provide metabolites to cancer cells.[97]

Reprogramming of lipid metabolism alters oncogenic signaling pathways in breast cancer cells and affects neighboring normal cell populations through secreted components including lipids. Different signaling pathways interact together to regulate breast cancer cell stemness, cancer cell proliferation, and lipid accumulation through lipid metabolism. This complexity suggests the need to study not only the lipid metabolic network in breast cancer cells, but also the impact of lipid metabolic reprogramming in the tumor microenvironment on breast cancer progression and treatment response. Deeper exploration of the tumor-specific regulation of lipid metabolic reprogramming in breast cancer is still needed to find potential new targets for breast cancer diagnosis and treatment.

## Progress in Research Related to Fatty Acid Metabolism Intervention in the Treatment of Breast Cancer

Some drugs have been developed to target fatty acid metabolism in breast cancer, which can be summarized as follows (Table 1).

### Statins

Given the complex role of lipid components in the BC microenvironment, BC cells exhibit plasticity in lipid synthesis, storage, and catabolism. Preclinical studies from the Global Trial Identification website and the WHO International Clinical Trials Registry platform suggest that targeting these processes is a promising therapeutic approach for BC. Clinical trials have explored the use of statins as anticancer agents by selectively intervening in cholesterol anabolism in patients with BC. Laboratory models suggest that statins reduce membrane cholesterol levels through cytokine binding and disruption of KRAS-mediated PI3K/TBK/AKT signaling, ultimately inducing apoptosis in BC cells.[98] The combination of nuclear receptor RORγ antagonists with statins has shown synergistic antitumor effects, particularly against TNBC.[99] Simvastatin inhibits HMGCR expression, downregulates MVA pathway and GPX4 expression, and promotes iron apoptosis in TNBC cells. Simvastatin in combination with metformin inhibits endothelin-1 expression, thereby inhibiting hypoxia-inducible factors and alleviating hypoxia while reducing angiogenesis, a potential application in BC therapy.[100]

### FASN Inhibitors

FASN expression is associated with several types of cancer and is particularly high in BC, and therapies targeting this protein have received increased attention in recent years. As a result, several FASN inhibitors have been developed.[101–103] However, the only clinically available FASN inhibitor is TVB-2640, which is currently in a Phase II clinical trial and is recruiting candidates for the treatment of HER2-positive metastatic BC following favorable results from a Phase I trial (NCT03179904).[104] Studies have shown that crosstalk between FASN and HER2 expression plays an important role in HER2+ tumors. Therefore, inhibition of FASN activity represents a potential therapeutic strategy for this BC subtype. Several preclinical studies have shown that FASN inhibitors exhibit antitumor activity in HER2+ BC, as reviewed elsewhere.[105] In addition, FASN plays an important role in the synthesis of phospholipids that form lipid rafts that mimic membrane fluidity, and its inhibition may impair HER2 activity by interfering with lipid raft formation.[106] Disruption of lipid rafts by other mechanisms also induces apoptosis in BC cells overexpressing HER2.[107] Lipidomic analysis suggests that membrane lipids may play an important role in HER2 subtypes; therefore, drugs that affect membrane composition and fluidity would also be expected to be used in HER2 BC therapy.

FASN inhibition would also be a promising therapeutic strategy for the treatment of this BC subtype. Considering the role of MUFA and SCD1 in HR+ BC, regulation of saturated fatty acid levels by controlling SCD1 activity using SCD1 inhibitors would lead to potential therapeutic strategies. SCD1 inhibition has shown antitumor effects in several cancer models; however, further studies are needed to investigate its specific effects on HR+ BC.[108]

### Acetyl Coenzyme a Carboxylase (ACCA) Inhibitors

Another key enzyme in lipid biosynthesis is ACCA, which catalyzes the rate-limiting step to produce the precursor of fatty acid synthesis, malonyl coenzyme A. ACCA inhibitors have shown antitumor activity in several tumor models.[109]

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**Table 1** Drug Development Targeting Lipid Metabolism in Breast Cancer

| Categories | Name of Drug/ Intervention | Research Organization or Staff | Research Topics | Molecular Mechanism | Research Phase (Clinical Trial Registration Number) |
|---|---|---|---|---|---|
| **Statins** | Drug: Simvastatin 40mg<br>Drug: Placebo | Indonesia University | Vimentin Expression-based Therapeutic Response in Triple Negative Breast Cancer Receiving Combination of Simvastatin and NAC: A Randomized, Double-Blind, Placebo-Controlled Trial | Statins can help inhibit the EMT process in metastases | NCT05550415 |
| | Drug: Simvastatin<br>Other: Laboratory Biomarker Analysis | Michael Simon | The Effect of Statins on Markers of Breast Cancer Proliferation and Apoptosis in Women With Early Stage Breast Cancer | Simvastatin may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth and reduce the aggressiveness of breast cancer cells | NCT03454529 |
| | Drug: Letrozole<br>Drug: Simvastatin | Emory University | A Randomized Window of Opportunity Study of Preoperative Letrozole and Simvastatin Versus Letrozole Alone in Stage I–III Hormone Receptor Positive, HER2 Negative Breast Cancer | Letrozole and simvastatin may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth | NCT05464810 |
| | Drug: Simvastatin 40mg<br>Drug: Placebo oral capsule | Indonesia University | Cancer: A Window-of-Opportunity Study Combination of CAF and Simvastatin Improves Response to Neoadjuvant Chemotherapy and Increases Tumor-Free Margin in Locally Advanced Breast Cancer:<br>A Randomized, Double-Blind, Placebo-Controlled Trial | Simvastatin acts synergistically with doxorubicin against MCF-7 cells, through downregulation of the cell cycle or induction of apoptosis | NCT04418089 |
| | Drug: Atorvastatin | Lund University Hospital | A Phase II Study of Neo-Adjuvant Statin Therapy in Postmenopausal Primary Breast | Effects of statins on tumor proliferation | NCT00816244 |
| | Drug: Rosuvastatin | Duke University | Dose Optimization of Rosuvastatin in Early Stage and Metastatic Estrogen Receptor Positive Breast Cancer Patients on Endocrine Therapy | A statin in the treatment of estrogen receptor positive breast cancer | NCT02483871 |
| | Drug: Placebo, metformin and atorvastatin | Tanta University | Comparative Clinical Study Evaluating the Anti-tumor Effect of Metformin Versus Atorvastatin as an Adjuvant Therapy With Chemotherapy in Patients With Non-metastatic Breast Cancer | The anti-tumor effects of metformin and statins (hydroxyl-methyl-glutaryl-CoA reductase inhibitors) in patients with non-metastatic breast cancer | NCT05507398 |
| | Drug: Atorvastatin 80mg<br>Other: placebo | Beni-Suef University | Study of the Therapeutic Effect of Atorvastatin on the Clinical Outcomes in HER2 Negative Breast Cancer Patients | Statin has lipid independent effects include inhibition of inflammatory responses, immunomodulatory actions, apoptotic and antiproliferative effects, which might contribute to the suggested anti-tumoral effects of these agents | NCT05103644 |

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|---|---|---|---|---|---|
| | Drug: Pitavastatin<br>Drug: placebo | Mansoura University | Efficacy of Statin Addition to Neoadjuvant Chemotherapy Protocols for Breast Cancer | Statins have been reported to have possible advantages as anticancer, and control of cancer progression. Moreover, they can sensitize cancer cells for radiotherapy | NCT04705909 |
| | Drug: Metformin/ Simvastatin/ Fulvestrant | National University Hospital, Singapore | Single Arm Phase 2 Study of Metformin and Simvastatin in Addition to Fulvestrant in Metastatic Estrogen Receptor Positive Breast Cancer | Simvastatin, a lipophilic HMGCoA reductase inhibitor, has been shown to interrupt oncogenic signaling by prenylation-dependent proteins including the RAS oncogene family, and attenuate PI3K signaling | NCT03192293 |
| | Drug: Atorvastatin<br>Drug: Capecitabine | M.D. Anderson Cancer Center | Atorvastatin in Triple-Negative Breast Cancer (TNBC) Patients Who Did Not Achieve a Pathologic Complete Response (pCR) After Receiving Neoadjuvant Chemotherapy, a Multicenter Pilot Study | Atorvastatin is used for the treatment of high cholesterol and may reduce the risk of triple negative breast cancer from coming back | NCT03872388 |
| | Drug: atorvastatin calcium<br>Other: laboratory biomarker analysis | National Cancer Institute (NCI) | A Phase I Prevention Study of Atorvastatin in Women at Increased Risk for Breast Cancer | Chemoprevention is the use of certain drugs to keep cancer from forming. The use of atorvastatin (Lipitor) may prevent breast cancer | NCT00637481 |
| | Drug: simvastatin | Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins | A Phase II Study of Simvastatin in Women at High Risk for a New Breast Cancer | The use of simvastatin may keep cancer from coming back in women who are at high risk for a new breast cancer after undergoing surgery for ductal carcinoma in situ or stage I, stage II, or stage III breast cancer | NCT00334542 |
| | Drug: Metformin<br>Drug: Atorvastatin | Columbia University | Pre-Surgical "Window of Opportunity" Trial of the Combination of Metformin and Atorvastatin in Newly Diagnosed Operable Breast Cancer | Metformin, a biguanide, results in activation of AMPK which consequently inhibits mTOR through phosphorylation of TSC2, as well as anti-proliferative effects through reduction in insulin receptor mediated mitogenesis and inhibition of cyclin dependent kinases. And Statin has been shown to interrupt oncogenic signaling by prenylation-dependent proteins including the RAS oncogene family, and attenuate PI3K signaling | NCT01980823 |
| | Drug: Zoledronate<br>Drug: Atorvastatin 80mg Drug: Standard neoadjuvant cht | Mario Negri Institute for Pharmacological Research | Multicenter, Randomized, Phase II Study of Neoadjuvant Chemotherapy Associated or Not With Zoledronate and Atorvastatin in Triple Negative Breast Cancers - YAPPETIZER Study | Statin, a first-class of lipid-lowering medications that inhibit the enzyme HMG-CoA reductase, inhibit the sterol biosynthesis via the mevalonate pathway | NCT03358017 |

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**Table 1** (Continued).

| Categories | Name of Drug/ Intervention | Research Organization or Staff | Research Topics | Molecular Mechanism | Research Phase (Clinical Trial Registration Number) |
|---|---|---|---|---|---|
| | Drug: statins Behavioral: Dietary intervention group (control group) | Peking Union Medical College Hospital | Survival Benefits of Statins in Breast Cancer Patients With Abnormal Lipid Metabolism | Statin, a first-class of lipid-lowering medications. The clinical trial was conducted to compare the survival benefits of statins in breast cancer patients with dyslipidemia (low and medium risk of ASCVD) | NCT03971019 |
| **FASN inhibitors** | Drug: TVB-2640 | Sagimet Biosciences Inc | A Phase 1, First-In-Human Study of Escalating Doses of Oral TVB-2640 in Patients With Solid Tumors | TVB-2640 belongs to a class of drugs called fatty acid synthase inhibitors (FASN inhibitors). This means that they interfere with the body's (and the tumor's) ability to use a substance called fatty acid synthase (FASN). Research has shown that some tumors appear to need FASN to keep growing | NCT02223247 |
| | Drug: Anastrozole Drug: FASN Inhibitor, TVB-2640 Drug: Exemestane | Mayo Clinic | Phase II Trial to Evaluate the Efficacy of the FASN Inhibitor, TVB-2640, in Combination With Trastuzumab Plus Paclitaxel or Endocrine Therapy in Patients With HER2+ Metastatic Breast Cancer Resistant to Trastuzumab-Based Therapy | FASN inhibitor TVB-2640 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth | NCT03179904 |
| **ACCA inhibitors** | A series of novel chroman derivatives | Department of Medicinal Chemistry, China Pharmaceutical University | Design, synthesis and biological evaluation of novel chroman derivatives as non-selective acetyl-CoA carboxylase inhibitors | Recent research reveals that Acetyl-CoA carboxylases (ACCs) are tightly relevant to many kinds of metabolic diseases and cancers. In this study, we synthesized a series of chroman derivatives and evaluated their ACCs inhibitory activities, obtaining compound 4s with IC50 value of 98.06 nM and 29.43 nM of binding activities in ACC1 and ACC2, respectively | The China National Key HiTech Innovation Project for the R&D of Novel Drugs (No.2013ZX09301303-002) Research link: https://doi.org/10.1016/j.bioorg.2020.103943 |
| | Spiroketopyrazoles | Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, Xuzhou Medical University | Synthesis and in vitro evaluation of novel spiroketopyrazoles as acetyl-CoA carboxylase inhibitors and potential antitumor agents | Acetyl-CoA carboxylase (ACC) is a rate-limiting enzyme in de novo fatty acid synthesis, which plays a critical role in the growth and survival of cancer cells. In this study, a series of spiroketopyrazole derivatives bearing quinoline moieties were synthesized, and in vitro anticancer activities of these compounds as ACC inhibitors were evaluated | National Natural Science Foundation of China (81671744) Research link: https://doi.org/10.1016/j.ejmech.2020.113036 |
| | An investigational drug, PF-05221304 (PF'1304) | Columbia University | Effects of ACC Inhibitor on Lipid and Lipoprotein Metabolism | Acetyl-CoA carboxylases (ACCs) are the rate-limiting enzymes in the de no lipogenesis, which play an important role in the synthesis and oxidation of fatty acid. | NCT04395950 |

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| **Choline kinase inhibitors** | Drug: TCD-717 | Translational Cancer Drugs Pharma, SL | Study of Intravenous TCD-717 in Patients With Advanced Solid Tumors | TCD Pharma has developed TCD-717, a novel drug that is a specific inhibitor of the enzyme choline kinase alpha (ChoKα), involved in the synthesis of phosphatidylcholine, which constitutes the major phospholipid in eukaryotic cell membranes and has been described as a potent oncogene when overexpressed in human cells | NCT01215864 |
| **Aromatase inhibitors** | Steroidal AI group: Exemestane; Non-steroidal AI group: Letrozole or anastrozole | The First Hospital of China Medical University | Effects of aromatase inhibitors on blood lipids in postmenopausal patients with hormone receptor-positive breast cancer in northern China and prognosis of treatment with different lipid-lowering drugs: study protocol for a prospective, multi-center, open-label, randomized, parallel-group, controlled, two-phase trial | Exemestane reduces the risk of breast cancer by blocking the effect of estrogen, which is related to lipid metabolism. Therefore, after using exemestane, the estrogen in the body decreases, which may lead to dyslipidemia and dyslipidemia | ChiCTR1900024790 |
| | Drug: Letrozole Drug: Tamoxifen | Novartis Pharmaceuticals | A Study to Evaluate the Effect of Letrozole and Tamoxifen on Bone and Lipids in Postmenopausal Women With Breast Cancer | Estrogen is known to be a regulator of bone and lipid metabolism. Letrozole is a potent inhibitor of estrogen synthesis | NCT00171704 |
| | Drug: Exemestane Drug: Letrozole Drug: Anastrozole | Chinese Academy of Medical Sciences | Effects of Adjuvant Endocrine Therapy With Aromatase Inhibitors on the Postoperative Lipid Levels in Postmenopausal Breast Cancer Patients | Steroidal aromatase inhibitor (AI) exemestane and non-steroidal AIs on the lipid levels of breast cancer patients | NCT02765373 |
| **Ketogenic and Low Carbohydrate Diets** | A personalized nutritional strategy (diet + supplementation) | AZTI - Member of the Basque Research & Technology Alliance | Personalised nutrition intervention for breast cancer survivors based on individual molecular analyses (nutrigenetics, lipidomics and microbiomics) | Secondary compounds in low animal fat and polyunsaturated fatty acids reduce tumor cell immune escape and angiogenesis | ISRCTN13901439 |
| | Dietary Supplement: Fish oil + EPO | University of Belgrade | Fish Oil and Evening Primrose Oil in the Treatment of Breast Cancer | Fish oil is the richest source of anti-inflammatory n-3 PUFAs. Evening primrose oil (EPO) is rich in 18:3 n-6, the only n-6 fatty acid with an anti-inflammatory effect. Dietary intake of fish oil or EPO has been shown to decrease inflammation and improve PUFAs status in patients with cancers | NCT03516253 |
| | Behavioral: Mediterranean diet | Gangnam Severance Hospital | Effects of Mediterranean Diet Based Intervention in Postmenopausal Women With Breast Cancer Receiving Adjuvant Hormone Therapy: the Randomized Controlled Trial | Adherence to the Mediterranean diet may directly or indirectly inhibit proliferation, induce cell cycle arrest and apoptosis | NCT04045392 |
| | Dietary Supplement: Omega-3 fatty acid supplement | University of Michigan Rogel Cancer Center | Omega-3 Fatty Acids, Oxylipins, and Tolerance of Aromatase Inhibitor Therapy | Research has shown that over half of patients who had joint pain and stiffness when taking an aromatase inhibitor had an improvement in their symptoms when they took omega-3 fatty acid supplements | NCT04268134 |

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**Table 1** (Continued).

| Categories | Name of Drug/ Intervention | Research Organization or Staff | Research Topics | Molecular Mechanism | Research Phase (Clinical Trial Registration Number) |
|---|---|---|---|---|---|
| **Others** | Procedure: Lipidomic analysis for breast cancer patients | Fondazione Policlinico Universitario Agostino Gemelli IRCCS | Lipidomic Characterization in Non-metastatic Breast Cancer Women Undergoing Surgery: a Pilot Study | Breast cancer lipidome signature in patients waiting for surgery with different Body Mass Index | NCT06026631 |
| | Drug: ceramide | Alliance for Clinical Trials in Oncology | A Phase II Study Of Topical Ceramide Lipids As Treatment For Cutaneous Breast Cancer | Drugs used in chemotherapy use different ways to stop tumor cells from dividing so they stop growing or die | NCT00008320 |
| | Drug: tamoxifen Drug: Goserelin | Zhejiang Cancer Hospital | The Effects of Adjuvant Zoladex Plus Tamoxifen on Breast Density in Pre- or Peri-menopausal Women With Early-stage Breast Cancer | Tamoxifen as adjuvant hormonal therapy in pre- or perimenopausal women with early-stage breast cancer | NCT00827307 |
| | Drug: Letrozole Drug: Atezolizumab | Universitaire Ziekenhuizen KU Leuven | Investigating Atezolizumab in Newly Diagnosed Endocrine Receptor Positive Breast Cancer | Endocrine therapy for breast cancer using aromatase inhibitors | NCT04630210 |
| | Dietary Supplement: Fasting-mimicking diet Drug: Metformin Drug: Preoperative chemotherapy | Fondazione IRCCS Istituto Nazionale dei Tumori, Milano | Targeting Triple Negative BREAst Cancer Metabolism With a Combination of Chemotherapy and a Diet Mimicking FASTing Plus/Minus Metformin in the Preoperative Setting: the BREAKFAST Trial | Preclinical studies indicate that cycles of fasting or calorie-restricted, low-carbohydrate, low-protein diets, also known as fasting-mimicking diets (FMDs), have synergistic cytotoxic effects when combined with chemotherapy agents, such as doxorubicin or cisplatin, in several in vitro and in vivo tumor models, including murine TNBC models | NCT04248998 |
| | Drug: Metformin | Oxford University Hospitals NHS Trust | A Phase 2 Single Arm Study to Examine the Effects of Metformin on Cancer Metabolism in Patients With Early Stage Breast Cancer Receiving Neoadjuvant Chemotherapy | There is now growing evidence from in vitro laboratory and animal work that metformin has anticancer properties. In addition a retrospective clinical study in a diabetic population has demonstrated evidence of markedly increased pathological response rates (a typically robust surrogate clinical endpoint of efficacy) to pre-surgical chemotherapy in early breast cancer for patients that were also taking metformin as part of their diabetes treatment. | NCT01266486 |
| | Drug: Dasatinib Dietary Supplement: Icosapent Ethyl | National Cancer Institute (NCI) | Phase Ib/II Study of EPA-Based EphA2 Targeted Therapy for Patients With Metastatic Triple-Negative Inflammatory Breast Cancer | Dasatinib is in a class of medications called tyrosine kinase inhibitors. It works by blocking the action of an abnormal protein that signals cancer cells to multiply, which may help keep cancer cells from growing. Icosapent ethyl is an omega-3 fatty acid and in a class of medications called antilipemic or lipid-regulating agents. | NCT05198843 |

Since BRCA1 interacts with ACCA activity and regulates ACCA activity, which could explain the altered lipid metabolism seen in patients harboring BRCA mutations, this enzyme would be a potential target for the treatment of this subtype of BC.[110,111] However, further studies are needed to explore this potential therapeutic approach.

## Choline Kinase Inhibitors

Targeting choline kinase is also a potential anticancer therapeutic strategy.[112] Preclinical studies have shown that several choline kinase inhibitors have antitumor activity in BC.[113] The promising inhibitor TCD-717 is also in phase I clinical trials for the treatment of solid tumors (NCT01215864). In particular, targeting choline kinase would be an excellent strategy for the treatment of TNBC, as choline metabolism has been shown to influence the degree of malignancy exhibited by this BC subtype.

## Ketogenic and Low-Carbohydrate Diets

Lipids have emerged as a key nutrient contributing to the progression of BC, and the effect of dietary lipids on the response to BC therapy has received considerable attention in numerous clinical trials. Epidemiologic evidence suggests that adherence to the Mediterranean diet may potentially benefit BC by directly or indirectly inhibiting proliferation,[114] inducing cell cycle arrest and apoptosis, and reducing immune evasion and angiogenesis through secondary compounds in olive oil and n-3/n-6 polyunsaturated fatty acids.

The ketogenic diet has been identified as a therapeutic anticancer agent that inhibits tumor progression and lung metastasis by lowering serum insulin levels through upregulation of β-hydroxybutyric acid levels in a BC mouse model; it exhibits favorable antitumor effects when combined with rapamycin, an mTOR inhibitor.[115] Intervention studies have shown that both ketogenic and low-carbohydrate diets significantly improve body mass, muscle/fat ratio, and quality of life in patients recovering from BC, and these diets are considered safe and beneficial.[116] In addition, a large prospective cohort study showed that participants who consumed fatty fish weekly had an increased risk of developing BC.[117] A large prospective cohort study showed an increased risk of BC among participants who consumed fatty fish weekly. Plant sterols, which occur naturally in vegetable oils, nuts, and seeds, play an important role in reducing p-AKT expression and markers associated with BC metastasis (alkaline phosphatase and matrix metalloproteinases) and angiogenesis (VEGF and CD67).[118] In conclusion, the future development of multiple intervention strategies targeting the different stages of BC based on the dynamic regulation of lipid metabolism will be a new challenge.

# Summary

In conclusion, dysregulation of FA metabolism is critical for maintaining BC cell proliferation and survival. Current inhibitors targeting FA synthesis and FAO-related enzymes have been effective in BC therapy, demonstrating inhibition of tumor growth and metastasis, so limiting FA uptake and synthesis of other key proteins in the FAO process may be an emerging aspect of inhibiting BC progression. Ferroptosis inducers such as sulfasalazine, siramesine, erastino and curcumin have been shown to be helpful in the anticancer treatment of BC. In the future, we need to find more valuable targets and combine ferroptosis inducers with traditional anti-BC drugs to induce ferroptosis, thereby increasing the sensitivity of anti-tumor drugs in BC. Combining BC fatty acid metabolism with anti-BC drugs is an emerging therapy. Precise targeting of specific lipid metabolites or enzymes may interfere with the anti-tumor effects of immune cells in the BC microenvironment. Indeed, metabolic inhibition of immune cells (eg, cytotoxic T lymphocytes and natural killer cells) may attenuate the effects of other anti-tumor modalities. Candidate approaches can be used to identify the metabolic vulnerability of cells. For example, siRNA, shRNA, and CRISPR-Cas9 gene editing screens can reveal cell type-specific vulnerabilities based on cell source, while specific oncogenic mutations can create selective metabolic vulnerabilities in tumor cells. Furthermore, targeting a single lipid pathway or a specific target may not completely eradicate BC cells, but a combination of therapies such as targeted inhibitors, cytostatic known organic compounds, statins, and dietary interventions can effectively complement existing BC treatment strategies.

## Abbreviations

ACAT1, Acetyl-CoA acetyltransferase 1; ACC, Acetyl-CoA carboxylase; ACLY, ATP citrate lyase; ACOX2, Acyl-coa oxidase 2; ACSL4, Acyl-coasynthase 4; ACSS2, Acetyl-CoA synthase 2; AMPK, AMP-activated protein kinase; ATGL, Adipose triglyceride lipase; BC, Breast cancer; BCSC, Breast cancer stem cell; CAA, Cancer-associated adipocyte; CAF, Cancer-associated fibroblast; CEMM, Cholesterol-rich membrane microdomains; Cer, Ceramide; CL, Cardiolipin; CPT1A, Carnitine lipoacyltransferase 1A; DC, Dendritic cell; DHEA, Docosahexaenoic acid; DOX, Doxorubicin; Elovl5, Elongation of very long-chain fatty acids protein 5; EMT, Epithelial-Mesenchymal Transition; FABP, Fatty acid binding protein; FAO, Fatty acid oxidation; FASN, Fatty acid synthetase; FFAR4, Free fatty acid receptor 4; FFA, Free fatty acid; GPX4, Glutathione peroxidase 4; GSK-3β, Glycogen synthase kinase-3β; HIF-1α, Hypoxia-inducing factor 1α; HMGCR, Hydroxymethylglutarate monoacyl-CoA reductase; HO, Heme oxygenase; HSL, Hormone-sensitive lipase; IGF-1, Insulin-like growth factor 1; IPP, Isopentenyl pyrophosphate; LD, Lipid droplet; LMR, Lipid metabolic reprogramming; LPO, Lipid peroxidation; LXR, Liver X receptor; MAGL, Monacylglycerol lipase; MDA, Malondialdehyde; MDR, Multidrug Resistance; MDSC, Marrow derived suppressor cell; MET, Mesenchymal-epithelial transition; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; MUFA, Monounsaturated fatty acid; MVA, Mevalonate; NK, Natural killer; Nrf2, Nuclear factor erythroid 2-associated factor 2; OGP, Osteoblastic growth peptide; OGR1, Ovarian cancer G protein-coupled receptor 1; OXPHOS, Oxidative phosphorylation; PC, Phosphatidylcholine; PG, Prostaglandin; PPAR, Peroxisome proliferator-activated receptor; PUFA, Polyunsaturated fatty acid; ROS, Reactive oxygen species; SCD1, Stearoyl-CoA desaturase 1; SFA, Saturated fatty acid; SM, Sphingomyelin; SPC, Sphingodylcholine; SQLE, Squalene monooxygenase; SREBP1, Sterol regulatory element binding protein 1; TAM, Tumor-associated macrophage; TAX, Paclitaxel; TCA, Tricarboxylic acid cycle; TME, Tumor micro-environment; TNBC, Triple-negative breast cancer; Treg cell, Regulatory T cell; UFA, Unsaturated fatty acid; VAMP3, v-SNARE protein vesicle-associated membrane protein 3; 27-HC, 27-hydroxycholesterol.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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