Molecular Cancer

REVIEW

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Lipid metabolic reprograming: the unsung hero in breast cancer progression and tumor microenvironment

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Abstract

Aberrant lipid metabolism is a well-recognized hallmark of cancer. Notably, breast cancer (BC) arises from a lipid-rich microenvironment and depends significantly on lipid metabolic reprogramming to fulfill its developmental requirements. In this review, we revisit the pivotal role of lipid metabolism in BC, underscoring its impact on the progression and tumor microenvironment. Firstly, we delineate the overall landscape of lipid metabolism in BC, highlighting its roles in tumor progression and patient prognosis. Given that lipids can also act as signaling molecules, we next describe the lipid signaling exchanges between BC cells and other cellular components in the tumor microenvironment. Additionally, we summarize the therapeutic potential of targeting lipid metabolism from the aspects of lipid metabolism processes, lipid-related transcription factors and immunotherapy in BC. Finally, we discuss the possibilities and problems associated with clinical applications of lipid-targeted therapy in BC, and propose new research directions with advances in spatiotemporal multi-omics.

Keywords Breast cancer, Lipid metabolism, Cancer progression, Tumor microenvironment, Metabolism-based therapies

Introduction

Breast cancer (BC) has emerged as the most commonly diagnosed malignancy worldwide. Representing 31% of all cancer diagnoses in women, the global incidence is anticipated to escalate by an additional 40% by the year 2040 [1]. Despite advancements in survival rates, the overall disease burden attributable to BC remains substantial, and it continues to be a predominant cause of mortality among women aged 30–60 in China [2]. BC has historically been classified into three primary subtypes based on receptor and protein expression: hormone receptor-positive (HR+, approximately 70%), HER2-positive (HER2+, approximately 20%), and triple-negative (approximately 10%). Each subtype exhibits distinct clinical and molecular characteristics, necessitating tailored diagnostic and therapeutic strategies [3, 4]. Recent advancements in molecular biology have facilitated the

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development of platforms such as Oncotype, which offer prognostic and predictive insights to guide the selection of patients for adjuvant chemotherapy [5]. At the same time, novel classes of therapeutics, such as immune checkpoint blockade (ICB), have been developed to explicitly target the tumor microenvironment (TME) rather than the tumor cells themselves. This approach offers a new paradigm in targeted therapy, particularly in cases where tumor cells lack actionable targets [6]. Consequently, it is imperative to deepen our understanding of the molecular mechanisms underlying BC to identify novel hallmarks of signaling pathways.

Metabolic reprogramming has emerged as a critical hallmark of cancer. In addition to the extensively studied reprogramming of glucose and glutamine metabolism, lipid metabolism has gained increasing recognition as a significant pathway in cancer cells over recent years [7, 8]. Lipids are primarily categorized into fatty acids (FAs), cholesterol, and phospholipids [9]. Lipids are structurally essential, functioning as key components of the phospholipid bilayer, and may be conjugated to proteins to serve as lipid anchors. Furthermore, lipids can also act as potent signaling molecules and fulfill energetic roles, facilitating the long-term storage of energy in the form of triglycerides [10]. Lipid metabolism is gaining research interest due to its vital role in tumor initiation, progression, and metastasis [11]. BC cells frequently undergo lipid metabolic reprogramming, which is marked by enhanced lipid uptake, lipid synthesis, fatty acid oxidation, and lipid storage. These adaptations enable BC cells to survive and proliferate under hypoxic and nutrient-deficient conditions [12, 13], which will be discussed in subsequent sections. Given their involvement in numerous critical cellular processes, elucidating the role of lipid metabolism in the development and progression of BC is of paramount importance.

In addition to mediating the biological characteristics of tumor cells, substantial evidence suggests that lipids influence the function and status of immune cells within the TME [14]. Tumor cells actively modify the TME by secreting signaling molecules and metabolites, thereby affecting the functions of non-tumor cells within the TME [15]. Concurrently, lipid metabolic reprogramming in non-tumor cells drives the environment toward an immunosuppressive phenotype, which supports tumor progression [16]. Understanding the alterations in lipid metabolism induced by various cell types within the TME and their reciprocal interactions with lipids is critical for developing more effective cancer treatments. Given the significant role of lipid metabolism in BC progression and the substantial influence of lipids on the TME, this review provides a comprehensive summary of recent advancements in lipid metabolism reprogramming in BC. Furthermore, we also summarize potential therapeutic targets, offering insights for future research and clinical applications.

Dysregulation of lipid uptake and transport in BC

Recent observations indicate that the capacity of cancer cells to assimilate fatty acids from their environment serves as a significant metabolic marker [17]. Notably, BC arising in tissues with abundant adipocyte populations preferentially absorbs exogenous fatty acids to promote tumor development [18, 19]. Previous studies have demonstrated that heightened extracellular lipid availability enhances fatty acid transport in breast cancer cells under a lipid-rich extracellular environment [20]. Several membrane-associated transport proteins are involved in FAs uptake and transport, including CD36, fatty acid transport proteins (FATPs), and fatty acid binding proteins (FABPs) [21, 22]. Among them, CD36 has been the most extensively studied in cancer. The transmembrane protein CD36 belongs to the class B scavenger receptor type 2. It is a receptor for a variety of ligands, including lipid-related ligands (e.g., long-chain fatty acids) and protein-related ligands (e.g., thrombospondins, collagens I and IV) [23]. In regard to BC, CD36 exhibited the highest levels in HER2 + lapatinib-resistant BC cells, and its ablation may induce apoptotic cell death. Meanwhile, the administration of an anti-CD36 antibody to xenografts originating from lapatinib-resistant BC cells increased their susceptibility to lapatinib [24]. Additionally, Feng et al. also observed a significant increase in the expression of CD36 in lapatinib-resistant breast cancer cells. Notably, increased CD36 facilitated fatty acid uptake to compensate for reduced fatty acid synthesis caused by HER-2 inhibition [25]. The role of CD36 in tamoxifen treatment was associated with the CD36-facilitated absorption of fatty acids to satisfy the increased metabolic requirements of tumor cells [26]. In the lipid-rich microenvironment, breast-associated adipocytes release molecules that facilitate tumor growth by enhancing CD36 expression and fatty acid absorption in breast cancer cells [27, 28]. Platelets with elevated levels of CD36 were found to release a diverse range of growth factors and cytokines, particularly high levels of PDGF-B. The PDGF-B subsequently activated the PDGFR-β/COX-2 signaling pathway, resulting in an elevation of many pro-inflammatory factors, hence intensifying tumor metastasis [29]. In terms of clinical application, CD36 was identified as an independent prognostic indicator, predicting responses to trastuzumab-based neoadjuvant therapy in early-stage HER2 + breast cancer [30]. Collectively, CD36 has been implicated as a crucial regulator of drug resistance and tumor microenvironment remodeling in BC.

FABPs are recognized for their role in mediating lipid homeostasis, membrane-protein interactions, and metabolic and inflammatory processes [31]. Recent investigations have identified abnormal FABP expression as a possible mediator of tumorigenesis [32, 33]. In the case of BC, FABP4 establishes a molecular connection between tumor-associated macrophages, adipocytes, and tumor cells [34]. The abrogation of FABP5 markedly diminished the aggressiveness of BC cells in co-culture with adipocytes, underscoring the critical function of FABP5 in the interaction between adipocytes and BC cells. [35]. In vivo studies demonstrated that mice deficient in FABP4 exhibited retarded tumor development and enhanced survival in a mouse breast cancer model [36]. Moreover, FABP5 deletion also demonstrated a reduction in tumor development and lung metastasis in animals orthotopically injected with murine BC cells. Molecular studies have revealed that FABP5 knockdown decreases EGFR expression in triple-negative breast cancer (TNBC) cells, and FABP5 serves as a crucial modulator of EGF-induced metastatic signaling [37–39]. Several studies have demonstrated that the presence of fatty acid transporters in the tumor-adipose microenvironment is closely associated with macrophage function and has prognostic implications in BC. FABP4 was found to exhibit preferential expression within a distinct subset of macrophages characterized by the $CD11b+F4/80+MHCII-Ly6C-$ phenotype. The intracellular presence of FABP4 in macrophages results in the downregulation of miR-29b through NF-κB, subsequently inhibiting the IL-6/STAT3 signaling pathway and ultimately promoting tumor growth [40]. Liu et. identified a specific group of macrophages termed lipid-associated macrophages, distinguished by elevated expression of fatty acid transporters and lipid receptors, as well as demonstrating immunosuppressive properties and heightened phagocytic activity [41]. At the individual study level, elevated levels of FABP4 in the bloodstream contribute to the progression of BC. The upregulation of FABP4 has been noted in recurrent breast cancer and correlates with a worse outcome in individuals with different tumor types [42]. Elevated levels of circulating FABP4 and FABP5 have been detected in individuals with breast cancer, with particular emphasis on the potential of circulating FABP4 levels as a novel independent biomarker [43]. Of note, FABP4 levels were significantly higher in obese women with BC, regardless of menopausal status, which correlated with larger tumor sizes and poorer outcomes [44]. In summary, FABPs serve as a mechanism by promoting interactions among cancer cells, adipocytes, and tumor-associated macrophages, especially in obesity-related breast carcinogenesis.

Cholesterol, an essential lipid component of the mammalian cell membrane, is crucial for maintaining membrane integrity and fluidity, as well as for the creation of membrane microstructures [45]. The role of cholesterol in cancer has garnered increasing attention, with substantial evidence indicating a dysregulated cholesterol balance within tumors. Disruption of cholesterol homeostasis influences various tumor hallmarks, thereby facilitating tumorigenesis, metastasis, and treatment resistance through the reprogramming of multiple microenvironments [46]. Cholesterol in humans is derived from food consumption and de novo production inside endogenous cells. Cholesterol is usually acquired by cells via low-density lipoprotein receptor (LDLR)-mediated endocytosis, wherein LDLR binds to low-density lipoprotein (LDL) in the bloodstream. The resulting LDL-LDLR complex is subsequently transported to lysosomes for degradation [47]. Furthermore, ATP-binding cassette (ABC) transporters are also involved in cholesterol transport and have been regarded as key players in BC chemoresistance [48]. Notably, a majority of tumor tissues in cancer patients exhibit overexpression of LDLR, which supports the rapid proliferation of cancer cells. Moreover, abnormalities in blood cholesterol levels are significantly correlated with an increased risk of various cancers [49]. Regarding BC, multiple lines of evidence suggest that dysregulation of cholesterol uptake contributes to carcinogenesis. Specifically, the expression of LDLR and the uptake of LDL-cholesterol are elevated in BC cell lines, with LDL being crucial for fulfilling the energy demands of BC cell motility [50, 51]. Furthermore, reducing LDLR expression in triple-negative and HER2-overexpressing breast cancer cells has been shown to increase cell death and reduce tumor growth in the context of hyperlipidemia [52, 53].Antalis et al. demonstrated that LDLR and cholesterol levels are elevated in metastatic BC cells compared to non-metastatic cancer cells. Furthermore, they found that inhibiting PKC and MEK expression in MDA-MB-231 cells reduces LDLR expression and impedes cell migration [54]. Mechanistic studies revealed that EGF-mediated stimulation of the EGFR signaling pathway leads to augmented cholesterol absorption and elevated LDLR expression in MDA-MB-468 and Mvt1 BC cells [55]. Clinically, the overexpression of LDLR and the accumulation of cholesterol esters have been correlated with increased proliferation and aggressiveness of BC, as well as with unfavorable clinical outcomes [56]. The subsequent section offers a comprehensive overview of lipid uptake and transport in BC (Fig. 1).

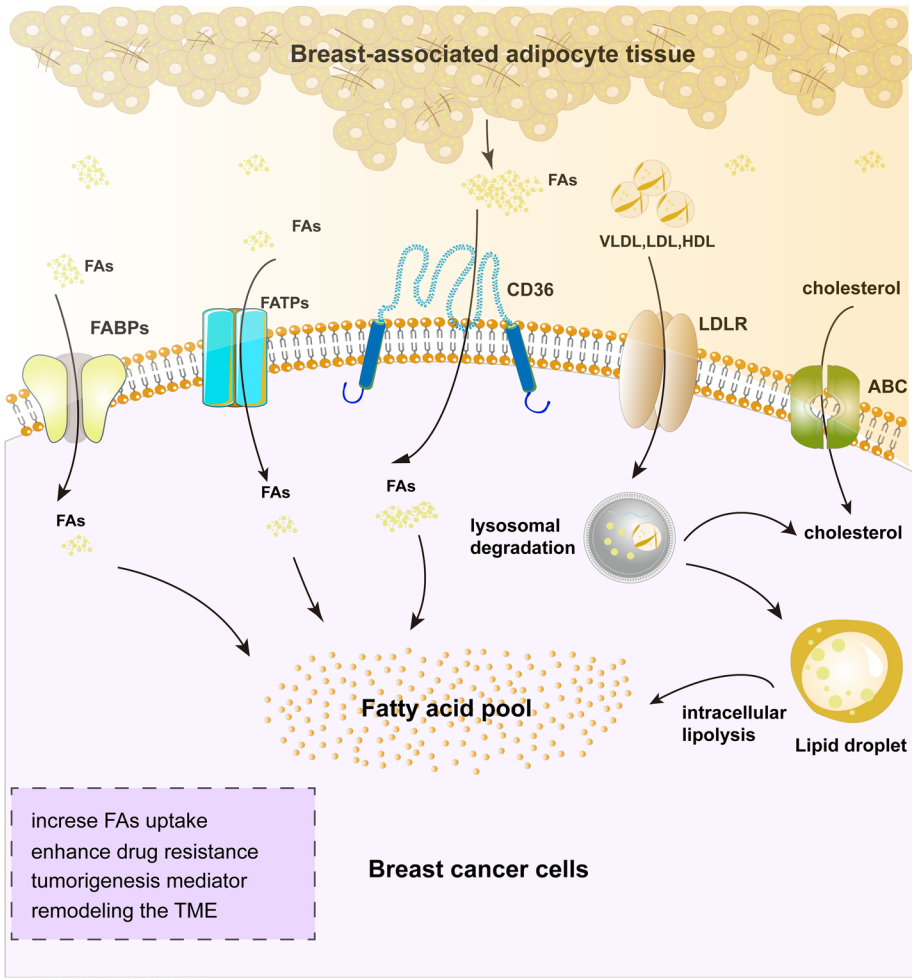

Fig. 1 An overview of lipid uptake and transport in BC. Due to its proximity to adipose tissues, adipocytes are major constituents of mammary stroma and play an important role in lipid metabolic reprogramming of BC. Extracellular lipids released from adipose tissues were acquired by BC cells through specialized receptors (CD36, FATPs, FABPs, ABC transporters, and LDLR). Cellular acquisition of cholesterol typically occurs through LDLR-mediated endocytosis, and the LDL-LDLR complex is subsequently transported to lysosomes for degradation. BC cells often exhibit elevated activity of these transport receptors, which facilitate the uptake of FAs, promote malignant biological behaviors, and reshape the TME through lipid trafficking among BC cells, adipocytes, and immune cells. Abbreviations: FAs, fatty acids; CD36, fatty acid translocase; FATPs, fatty acid transport proteins; FABPs, fatty acid-binding proteins; LDL, low-density lipoprotein; VLDL, Very-low-density lipoprotein; HDL, high-density lipoprotein; LDLR, low-density lipoprotein receptor; ABC, ATP-binding cassette transporter; TME, tumor microenvironment

Dysregulation of lipid synthesis in BC

The main steps of FAs biosynthesis

In typical physiological conditions, only specialized lipogenic cells, including those found in the liver, adipose tissue, and lactating mammary glands, participate in de novo fatty acid synthesis. In contrast, most normal cells depend on the uptake of exogenous lipids [57]. To meet the increased demand for lipids and cholesterol, cancer cells often upregulate their internal fatty acid synthesis pathways, which are crucial for membrane formation, energy production, and the creation of signaling molecules [58]. Elevated lipogenesis is recognized as a key metabolic marker of cancer cells. Research indicates that the activation of fatty acid production plays a significant role in oncogenesis and the survival of tumor cells [58]. Elevated lipogenesis has also been associated with the enhanced expression and activity of enzymes involved in the lipogenic pathway [59]. Consequently, lipid reprogramming is acknowledged as a significant factor in the progression of cancer.

Fatty acid synthesis occurs in the cytosol, utilizing acetyl-CoA as the main precursor. Acetyl-CoA is generated through the catabolism of glucose, fatty acids, ketone bodies, and proteins [60]. Because acetyl-CoA is produced in the mitochondria and cannot cross the membrane, it first forms citrate with oxaloacetate.

Citrates are then carried into the cytosol via the citrate transporter (SLC25A1), where ATP-citrate lyase (ACLY) transforms it into acetyl-CoA and oxaloacetate [61]. In the cytosol, acetyl-CoA is carboxylated by acetyl-CoA carboxylase (ACC) to produce malonyl-CoA [62]. Malonyl-CoA is crucial for the elongation of fatty acid chains, which also represents the rate-limiting stage of the entire process [63]. The fatty acid synthase complex (FASN) catalyzes a sequence of events involving one molecule of acetyl-CoA and seven molecules of malonyl-CoA, hence driving fatty acid production [64]. This sequence of reactions (transfer, condensation, hydrogenation, dehydration, and re-hydrogenation) is repeated seven times, each cycle adding two carbon units to the growing chain. The outcome is the synthesis of a 16-carbon fatty acid, palmitoyl-ACP, which is subsequently cleaved by thioesterase to yield free palmitic acid. The process outlined above, starting from acetyl-CoA, is referred to as de novo lipogenesis [65]. Palmitic acid can be further elongated or desaturated by stearoyl-CoA desaturase (SCD) to produce other fatty acids. Several key enzymes drive fatty acid synthesis, including ACLY, ACC, and FASN [66]. In normal human cells, de novo fatty acid synthesis occurs at relatively low levels, with minimal expression of the corresponding enzymes. However, in tumor cells, up to 90% of lipid synthesis is driven by de novo fatty acid synthesis, with significantly elevated enzyme activity [67]. For instance, FASN expression is significantly elevated in several types of cancer, including breast, colorectal, liver, and lung cancers [68–70]. De novo lipogenesis is a meticulously regulated metabolic pathway that supports cancer progression through the activation of various signaling pathways in proliferating cells. This process not only supplies energy but also supports the malignant phenotype by promoting proliferation, angiogenesis, metastasis, and drug resistance [71]. Given the critical role of de novo fatty acid synthesis in tumor initiation and progression, increasing research is being directed toward this pathway to uncover potential therapeutic targets for cancer treatment.

FAs have diverse effects on tumor growth in BC

Fatty acids exhibit diverse functions influenced by their carbon chain length, saturation degree, and structural characteristics, each contributing uniquely to human health, metabolism, and dietary sources [72]. A significant amount of preclinical and clinical evidence indicates that specific fatty acids, including monounsaturated fatty acids (MUFAs), saturated fatty acids, and trans fatty acids, exhibit pro-carcinogenic properties [73]. Palmitic acid, a saturated fatty acid, significantly enhances the tumorigenic capacity of HR-negative breast cancer cells through the regulation of key transcription factors [74]. Oleic acid facilitates the migration of BC cells via the EGFR and AKT-dependent signaling pathways [75]. Free fatty acids (FFAs) also regulate carcinogenesis through their interaction with specific free fatty acid receptors that belong to the G-protein-coupled receptor superfamily [76]. Notably, GPR120, a receptor for long-chain fatty acids, has been favorably correlated with chemosensitivity in BC patients. Activation of GPR120 signaling can enhance the expression of ABC transporters and promote de novo fatty acid synthesis [77]. Conversely, polyunsaturated fatty acids (PUFAs), especially omega-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), demonstrate significant anti-cancer properties [78]. Research indicates that PUFAs inhibit the growth of BC cells and impede tumor progression in xenograft models [79]. Increasing the intake of omega-3 fatty acids has been associated with a reduced risk in high-risk BC populations [80]. Additionally, alpha-linolenic acid (ALA), an essential omega-3 fatty acid, along with EPA and DHA, has been shown to improve the effectiveness of treatments for HER-2 positive BC [81]. Furthermore, the balance between saturated fatty acids (SFAs) and MUFAs has been identified as a potential indicator for evaluating the risk of BC. An imbalance in this ratio is significantly linked to an increased risk of BC [82, 83]. In summary, FAs play an essential and complex role in BC development, involving a variety of molecular mechanisms, including cellular metabolism, and pro- and anti-inflammatory signaling pathways.

Key enzymes of fatty acid synthesis pathway in BC

Fatty acid synthase

Fatty acid synthase (FASN) is a crucial biosynthetic enzyme and the primary regulator of endogenous FAs production [84]. Under normal physiological conditions, FASN primarily serves two functions: the storage of surplus energy as triglycerides in adipose tissue and the synthesis of phospholipid constituents for cellular and organelle membranes [85]. In healthy cells, FASN has a limited function; nevertheless, in cancer cells, it mostly facilitates de novo fatty acid synthesis [86]. Dysregulation of FASN activity has been implicated in several metabolic disorders and cancers, highlighting its importance as a therapeutic target [87, 88]. Studies from clinical samples suggest that FASN is significantly associated with the aggressiveness, metastatic potential, and patient prognosis of BC. FASN has been regarded as an early indicator in human BC. For instance, studies found that blood FASN levels are raised in breast cancer patients, and those with high FASN expression have increased serum fatty acid levels [89, 90]. In early-stage breast cancer patients, FASN expression is significantly associated with menopausal status, body mass index, and pathological

stage [91]. Furthermore, aberrant expression of FASN has been shown to be associated with the metastatic properties of BC. The expression of FASN was elevated in lymph node metastases relative to non-lymph node metastases [92]. Notably, FASN expression was significantly elevated in BC that metastasized to the brain compared to primary breast tumors or those metastasized to other locations, suggesting that brain metastasis in HER2 + breast cancer depends on FASN activity [93]. FASN expression also correlates with advanced disease stages and poor clinical outcomes. In the TCGA-BC cohort, elevated FASN expression is associated with reduced overall survival (OS), recurrence-free survival (RFS), and distant metastasis-free survival (DMFS) [94]. A meta-analysis revealed that elevated FASN expression correlates with tumor size and HER2 positivity, although it does not significantly influence the overall prognosis of BC [95]. FASN is overexpressed in TNBC tissue, which was significantly higher than that in adjacent tissues. The positive expression of FASN correlated with lymph node metastases, TNM stage, histological grading, diabetes, and body mass index [96, 97]. Overall, the evidence suggests that FASN plays a critical role in BC malignancy and metastasis, underscoring its potential as a prognostic biomarker and a target for therapeutic intervention.

In preclinical studies, FASN expression correlated with a more aggressive phenotype in breast cancer cells. Studies have demonstrated that inhibition of FASN activity resulted in decreased cell viability and proliferation, implying that targeting FASN could serve as a therapeutic approach for BC [98, 99]. FASN overexpression results in increased long-chain FAs production, which enhances the expression of ligands such as VEGF, ultimately inducing epithelial-mesenchymal transition (EMT) and therapy resistance [100]. Studies have shown that the FASN inhibitor psoralen can reverse EMT, decreasing cell dispersion, migration, and invasion in MCF-7 cells [101]. FASN may play a role as an intrinsic factor in the transition to endocrine resistance in ER + /HER2 + BC. And pharmacological inhibition of FASN activity might overcome HER2-determined tamoxifen resistance in animal models [102, 103]. Mechanistically, FASN inhibition decreased the growth of tamoxifen-resistant breast tumors by reducing ERα levels and changing its subcellular localization [104]. In TNBC, FASN serves as a potential anti-apoptotic protein, and inhibiting FASN expression may improve CDDP-induced apoptosis and overcome chemoresistance [105]. FASN was hyperactivated in stem cell-enriched TNBC samples, and pharmacological FASN inhibition might reduce stemness and prevent 3D BC stem cell expansion [106]. In HER2-overexpressing BC cells, FASN phosphorylation has been identified as a critical factor that enhances signaling pathways associated with tumor progression [107]. In conclusion, FASN could serve as a key biomarker of aggressive BC.

FASN is generally regulated by intracellular kinase pathways and lipid-associated transcription factors. In SK-BR-3 and BT-474 cells, FASN expression was higher in HER2-overexpressing cells compared to those with low or no HER2 expression [108]. Furthermore, high FASN expression is positively correlated with HER2 overexpression, with HER2 signaling believed to drive this increase in FASN levels [109]. MAPK and PI3K-AKT pathways are also central regulators of FASN expression in BC cells [110]. Specifically, FASN gene expression is activated downstream of the PI3K-AKT-mTOR signaling cascade in response to metabolic and growth signals. Furthermore, HER2 overexpression enhances the activity of the FASN gene promoter, thereby promoting endogenous fatty acid synthesis via the activation of the MAPK and PI3K-AKT pathways [103]. Studies have shown that α-mangostin downregulates PI3K-AKT levels in BC cell lines, which decreases FASN activity and reduces intracellular fatty acid levels, ultimately inducing apoptosis [111]. Moreover, inhibitors targeting mTOR and PI3K have been shown to impede HER2-induced FASN expression [107]. Additionally, FASN is regulated by several transcription factors, with Sterol Regulatory Element-Binding Protein 1 (SREBP-1) serving a pivotal function in fatty acid synthesis. SREBP-1 directly regulates FASN expression in BC [112, 113]. Beyond FASN, SREBP-1 also regulates other key enzymes involved in fatty acid synthesis, including ACC and SCD1. Notably, SREBP-1 is strongly associated with EMT, driving breast cancer growth and metastasis [114, 115]. Peroxisome Proliferator-Activated Receptors (PPARs) are nuclear receptors that regulate lipid metabolism and inflammatory responses via the regulation of FASN transcription [116]. The PPARα agonist, clofibrate, has been shown to effectively treat breast cancers with high FASN expression, drastically diminishing FASN bioactivity in clofibrate-treated breast cancer cells [116]. The role of FASN-mediated lipid metabolism signaling pathways in BC is attracting growing attention. The interplay between FASN expression and other oncogenic pathways further underscores its potential as a novel therapeutic intervention for aggressive BC.

ATP-citrate lyase

ATP-citrate lyase (ACLY) functions as a crucial enzyme in glucose metabolism and lipid biosynthesis, acting as an essential connection between these two primary metabolic pathways [117]. ACLY is essential in FAs metabolism, and its aberrant expression has been noted in several immortalized cell lines and malignancies [118]. In

BC, the enzymatic activity of ACLY is approximately 150 times higher than in normal breast tissue [119]. ACLY overexpression is associated with clinical stage and lymph node metastases, but not with age or tumor size. ACLY and its phosphorylated variant are markedly increased in BC tissues relative to surrounding normal tissues, with phosphorylated ACLY exhibiting a positive connection with lymph node metastasis [120]. Additionally, elevated ACLY expression in BC tissues correlates with ER status, PR status, and lymph node metastasis. The expression of ACLY has been associated with RFS and is regarded as an independent prognostic factor for breast cancer recurrence [121]. Survival analysis demonstrated that BC patients with high ACLY expression had shorter OS and DMFS, underscoring the significance of ACLY in BC prognosis [122]. In preclinical studies, silencing ACLY expression diminishes cell viability and induces apoptosis in BC cells [120].Kimberly S et al. discovered ACLY as a new binding partner of cyclin E and demonstrated that this interaction enhances ACLY function, contributing to the aggressiveness of BC [123]. As a key enzyme in cellular metabolism, ACLY also serves as an important signaling molecule, playing a crucial role in various pathways, much like FASN. As a downstream effector of the PI3K-AKT-mTOR pathway, ACLY is activated by AKT phosphorylation at serine 455 [124, 125]. As an upstream regulator of genes encoding enzymes involved in fatty acid synthesis, transcription factors including SREBP-1c and SIX1 are shown to directly increase the expression of ACLY in BC cells [126, 127]. ACLY participates in multiple signaling pathways; however, its specific role in the development of BC within these pathways is not well understood.

Acetyl-CoA carboxylase

Acetyl-CoA carboxylase (ACC) converts acetyl-CoA to malonyl-CoA [128], a critical and rate-limiting step in FAs synthesis. ACC has two isoforms: ACC1 and ACC2. ACC1 resides in the cytoplasm, utilizing malonyl-CoA for de novo FAs synthesis [129]. In contrast, ACC2 is linked to the mitochondrial membrane, producing malonyl-CoA that inhibits carnitine palmitoyltransferase 1 (CPT1), thus blocking fatty acid entry into the mitochondria for β-oxidation [130]. Recent studies have highlighted the role of ACC in various cancers, notably colorectal, ovarian, liver, gastric, and breast cancers [131–134]. ACC is a key factor for BC cells survival, metastasis, and treatment resistance. An in vitro study on BC cells indicated that knocking down ACC reduced cell viability, increased apoptosis, and significantly inhibited cell migration [135]. Consistent with these results, silencing ACC1 with shRNA or inhibiting it with non-specific small-molecule inhibitors consistently resulted in cell death [136, 137]. Genome-wide CRISPR-Cas9 loss-of-function screenings have revealed ACC1 as a predominant cancer-associated isozyme. Inhibition of ACC by small molecules reduced BC viability in vitro and inhibited tumor development in vivo [138]. Bacci et al. reported that ACC1 mobilized lipids in estrogen-deprived BC cells, causing anti-estrogen treatment resistance. Pharmacologically inhibiting ACC1 in patient-derived xenograft models decreased tumor growth and enhanced animal survival, suggesting that ACC1 might better sensitize ER + breast cancer to endocrine therapies [139]. However, the role of ACC in BC remains a topic of debate. While targeting ACC is widely recognized as a strategy to inhibit fatty acid synthesis, some studies suggest that activating ACC1 may also help prevent BC metastasis [140]. A previous study has shown that ACC inhibition is pivotal in the development of the pre-metastatic niche in lung metastasis of BC. Specifically, pathological downregulation of ACC in lung fibroblasts leads to lipid metabolism abnormalities, fibroblast senescence, and inflammatory factors that collectively contribute to promoting BC metastasis [141]. Meanwhile, down-regulation of ACC1 increases acetyl-CoA levels, leading to Smad2 acetylation and EMT in BC cells. Mechanistically, leptin and TGFβ suppressed ACC1 function through inhibitory phosphorylation mediated in part by the TAK1 kinase. Significantly, they discovered that inactive ACC1 phosphorylation levels were associated with the metastatic potential of BC [142]. Viewed together, these studies indicate that ACC acts as a double-edged sword in BC, and the mechanism behind it needs to be clarified further.

Stearoyl-CoA desaturase

Stearoyl-CoA desaturase (SCD) is a membrane protein located in the endoplasmic reticulum that catalyzes the conversion of SFAs into MUFAs. The MUFAs generated by SCD are vital constituents of cellular membrane phospholipids, triglycerides, and cholesterol esters, rendering SCD essential for energy storage, membrane fluidity maintenance, and regulation of cellular metabolism [143]. Lipid desaturation is a crucial mechanism for the survival of cancer cells. Thus, targeting SCD might effectively restrict tumor growth, particularly in the metabolically challenged circumstances of the tumor microenvironment [144]. Overexpression of SCD1 has been reported in various human cancers and carcinogen-induced tumors, leading to increased membrane fluidity [145], which in turn facilitates the migration of malignant cells [146]. At the patient level, SCD1 is markedly increased in breast adipose tissue adjacent to malignant tumors in comparison to benign tumors [147]. SCD1 expression has been found to be elevated in recurrent human BC samples, correlating with poorer prognoses

[42]. BC patients with high SCD1 levels had significantly shorter RFS and OS. Since SCD1 was significantly lower in TNBC, SCD1 might only be useful as a target in HR + and HER2 + breast cancers [148].

Furthermore, elevated cytoplasmic levels of SCD1 serve as a predictor of residual disease in patients with HER2-positive BC who have undergone trastuzumab-based neoadjuvant treatment [149].

Studies have shown that SCD1 is involved in malignant phenotypes, recurrence, and therapy resistance of BC. Several studies have revealed that silencing SCD1 in BC cells produces the strongest inhibitory effect on cell proliferation, underscoring the critical role SCD1 plays in malignant progression [144, 150, 151]. Reciprocally, upregulation of the SCD1 gene accelerates cell proliferation and migration, significantly enhancing tumorigenic potential [143].

Additionally, SCD1 and its catalytic product, oleic acid, are pivotal in facilitating the migration and invasion of ErbB2-overexpressing BC cells [152]. Alterations in SCD1 activity are correlated with modifications in the migratory characteristics of TNBC cells, including variations in speed, direction, and cell morphology [153]. The major signaling pathways involved in SCD1 activity are the PI3K/AKT and Wnt signaling pathways. SCD1 silencing has been reported to impede GSK3 phosphorylation, resulting in reduced β-catenin translocation to the nucleus, hence diminishing the expression of its target genes [154]. MUFAs products generated by SCD1 can bind to Wnt-related proteins, facilitating their intracellular transport [155]. SCD1 is also a key target of the PI3K-AKT-mTOR pathway, which contributes to resistance to ferroptosis in TNBC [156, 157]. In summary, while the molecular mechanisms involving SCD in BC are beginning to be elucidated, there is a critical need for clinical studies to evaluate how inhibition of SCD improves the prognosis of BC.

Dysregulation of cholesterol synthesis in BC

Overview of cholesterol synthesis metabolism

Cholesterol, a crucial lipid component, serves as an essential structural element of cell membranes, affecting substance transport, controlling membrane fluidity and stability, and engaging in membrane signaling events, including the formation of lipid rafts. Additionally, cholesterol acts as a precursor for steroid hormones, bile acids, vitamin D, and oxysterols, making it essential for cellular development and function [158–160]. Cells can synthesize cholesterol de novo or acquire it from dietary sources via lipoproteins. However, organisms primarily rely on the uptake of exogenous cholesterol to reduce the energy costs of cholesterol biosynthesis. In humans, cholesterol is mainly transported through low-density lipoprotein (LDL) and high-density lipoprotein (HDL). LDL is taken up by cells through LDL receptors (LDLR) and hydrolyzed by lysosomal enzymes into FAs and cholesterol [161]. Tumor cells exhibit an increased lipid requirement for activities such as supporting membrane synthesis, maintaining membrane rigidity, and sustaining the high growth rate and functionality of cancer cells [162]. The intracellular cholesterol accumulation in tumor cells can be increased by reducing cholesterol efflux and enhancing cholesterol uptake through receptor-mediated LDL endocytosis, but it is largely met by de novo cholesterol biosynthesis [163]. Cholesterol synthesis primarily takes place in the endoplasmic reticulum (ER) and is subsequently transported to other cellular membranes through various cellular mechanisms [164]. Endogenous cholesterol synthesis begins with acetyl-CoA and proceeds through the mevalonate pathway, generating intermediates such as 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), mevalonate (MVA), and squalene [165]. Acetyl-CoA reacts to form HMG-CoA, which is subsequently reduced to MVA by HMG-CoA reductase (HMGCR). HMGCR functions as the principal rate-limiting enzyme in the cholesterol biosynthesis pathway, assuming a pivotal role in the process [166]. Another critical step in cholesterol synthesis involves the oxidation of squalene monooxygenase (SQLE) to form 2,3-oxidosqualene, which is then cyclized into lanosterol. SQLE is recognized as the second rate-limiting enzyme in cholesterol synthesis. Studies indicated that SQLE was found to be highly expressed in aggressive BC and served as an independent prognostic factor for poor outcomes in BC patients [167].

Cholesterol biosynthesis is tightly regulated by transcription factors, primarily including sterol regulatory element-binding proteins 1 and 2 (SREBP-1 and SREBP-2) and nuclear receptors such as the liver X receptor (LXR) [168]. Among these, SREBP-2 plays a central role in controlling cholesterol biosynthesis. Intracellular cholesterol levels are modulated by the coordinated actions of SREBPs and LXRs [169]. In the nucleus, these factors bind to sterol response elements (SREs) to activate the expression of cholesterol biosynthetic enzymes such as HMGCR and SQLE. SREBPs have also been identified as downstream targets and effectors of oncogenic signaling pathways, including the pRb, Myc, PI3K-AKT, and mTORC-1 pathways [170]. Activated LXR induces the expression of ABC transporters, which facilitate cholesterol efflux and reduce cholesterol synthesis [171]. In cancer cells, elevated SREBP activity supports high intracellular cholesterol levels, which are essential for sustaining rapid cell proliferation [172]. Furthermore, it is important to highlight that cholesterol metabolism is intricately associated with tumor proliferation, invasion,

metastasis, immune evasion, and resistance to chemotherapeutic agents. Since cholesterol plays a key role in membrane formation and elevated cholesterol levels increase membrane rigidity, reducing drug permeability and leading to resistance, while lower cholesterol levels enhance membrane fluidity, making cancer cells more prone to invasion and metastasis [173, 174]. Therefore, therapeutic strategies targeting cholesterol metabolism may provide new ideas for the treatment of cancer.

Associations between serum cholesterol levels and BC incidence

Metabolic syndrome and obesity are recognized as significant risk factors for BC [175, 176]. Similarly, elevated levels of cholesterol, very-low-density lipoprotein (VLDL), and LDL, which are common comorbidities of obesity, are also considered risk factors for BC. However, the relationship between serum cholesterol levels and BC incidence remains inconclusive in epidemiological studies [177]. Some studies suggest an inverse correlation between cholesterol levels and BC risk, indicating that higher serum cholesterol levels may reduce the risk of BC, particularly for total cholesterol and LDL cholesterol levels [178–181]. A large retrospective longitudinal cohort study revealed that women over 40 years old with high cholesterol had a 45% reduced probability of developing BC compared to women without high cholesterol. Notably, BC patients with elevated cholesterol levels had a 40% decreased chance of mortality [182]. Additionally, a meta-analysis also reported a slight negative correlation between total cholesterol and breast cancer risk, particularly prominent in premenopausal women [183]. In contrast, several studies have shown a strong positive association between blood total cholesterol levels and BC risk [184]. For instance, a large prospective study in Korea found that high total cholesterol levels were positively correlated with prostate cancer, male colorectal cancer, and female BC, while showing an inverse correlation with the overall risk of liver, stomach, and lung cancer [185]. Furthermore, a meta-analysis has revealed a significant positive correlation between high dietary cholesterol intake and breast cancer risk [186]. However, numerous studies have not successfully shown a definitive correlation between blood cholesterol levels and the risk of BC [187–192]. Studies investigating the impact of cholesterol levels on BC risk in premenopausal and postmenopausal women have also yielded mixed results. A study reported that overweight and obese postmenopausal women were at an increased risk of BC, and those with high cholesterol intake had a 48% higher risk of developing BC [193]. Similarly, a prospective study in Korea also indicated that postmenopausal women with higher serum total cholesterol levels had an increased risk of BC compared to those with lower levels [184]. However, after adjusting for body mass index, the impact of elevated cholesterol became less significant, indicating that obesity is a more essential risk factor than elevated cholesterol levels. In summary, while much evidence indicates a correlation between blood cholesterol levels and BC risk, the results are contradictory across studies. The above variations may be affected by demographic traits, lifestyle factors, and dietary choices, highlighting the complexity of this relationship. This inconsistency underscores the need for further research to clarify the potential mechanisms and interactions involved in this relationship, particularly considering the influence of other factors such as diet and metabolic health.

The role of oxidized low-density lipoprotein and its receptors in BC

Oxidized low-density lipoprotein (ox-LDL) represents a modified form of LDL that arises from oxidative processes. Aberrant lipid metabolism within cells can lead to lipotoxicity, subsequently inducing oxidative stress and significantly increasing reactive oxygen species levels. This increase of oxidative stress facilitates the gradual oxidation of LDL to ox-LDL intracellularly [194]. Ox-LDL has traditionally been investigated as a biomarker for cardiovascular diseases [195, 196]. However, recent studies have increasingly focused on its potential association with cancer. Elevated levels of Ox-LDL and its receptors, such as oxidized low density lipoprotein receptor 1 (OLR1) and CD36, have been associated with an elevated risk of various malignancies, including colorectal, breast, esophageal, prostate, and pancreatic cancers [197–202]. With regard to breast cancer, elevated ox-LDL levels have been detected in the plasma of BC patients, and there is a positive correlation between increased plasma ox-LDL levels and BC risk [203]. OLR1 is overexpressed in 70% of human BC, and it has been shown to be positively correlated with tumor grade and stage [204]. Current studies demonstrate that ox-LDL and its receptor participate BC progression through regulation of immune microenvironment and pro-inflammatory reactions. In breast epithelial cells, ox-LDL induces the upregulation of miR-21, which subsequently activates the PI3K/Akt pathway, thereby promoting cell proliferation and inhibiting apoptosis [205]. OLR1 also significantly influences the infiltration levels of M2 macrophages and is implicated in the metastasis and invasion of BC cells [206, 207]. Ox-LDL can stimulate tumor proliferation and progression by participating in various pro-inflammatory signaling pathways. Studies have shown that OLR1 is involved in activating the TNFα/NF-κB pro-inflammatory signaling pathway, leading to the inhibition of apoptosis and stimulation of proliferation in BC cells [208]. Furthermore,

TNFα can upregulate the expression of OLR1, promoting the adhesion and trans-endothelial migration of BC cells. Blocking the function of OLR1 significantly reduces the migration of BC cells [209]. Notably, Yu et al. found that tamoxifen could downregulate CD36 expression in macrophages by inactivating the PPARγ signaling pathway, thereby reducing the cellular levels of ox-LDL [210]. Overall, the involvement of ox-LDL and its receptor in BC progression underscores the complex interplay between lipid metabolism, inflammation, and the immune microenvironment in cancer. Targeting these pathways may offer new therapeutic strategies for managing BC and improving patient outcomes.

The role of cholesterol metabolism-related genes in BC

In cancer cells, intracellular cholesterol is often elevated through the upregulation of key enzymes or transcription factors involved in cholesterol biosynthesis, such as HMGCR, SQLE, SR-BI and SREBPs [211]. The mevalonate pathway, in which HMGCR plays a pivotal role, has been demonstrated to serve a crucial role in the initiation and progression of BC. Overexpression of metabolic genes in this pathway, including HMGCR, has been associated with adverse prognostic outcomes of BC [212, 213]. In contrast, studies focusing on different BC subtypes revealed that patients exhibiting elevated HMGCR expression had enhanced RFS and OS, indicating that HMGCR may function as a beneficial prognostic biomarker [214–216]. In preclinical experiments, HMGCR is frequently upregulated, resulting in increased cholesterol synthesis that promotes tumorigenesis and lung metastasis of BC [217]. Additionally, HMGCR promotes a stem cell-like phenotype in epithelial BC cells, consequently affecting tumor initiation and progression [218]. The expression of HMGCR is a crucial factor in statin resistance in BC cells, and targeting HMGCR with statins and its transcriptional regulation may effectively address statin resistance in tumor cells [219, 220]. In addition to HMGCR, SQLE is another key rate-limiting enzyme in cholesterol biosynthesis that has gained attention for its role in BC. SQLE expression was markedly elevated in BC, and elevated SQLE expression levels were substantially correlated with a poor prognosis [167, 221]. In vitro experiments demonstrated that SQLE accelerates BC progression by promoting tumor cell proliferation and migration. The inhibition of SQLE significantly reduced the survival rate of cells and prolonged their cell cycle [222, 223]. These findings offer significant insights into the role of HMGCR and SQLE in the pathogenesis of BC and indicate their potential as therapeutic targets for its treatment.

Scavenger receptor class B type I (SR-BI) acts as the receptor for HDL that facilitates selective uptake of HDL-C into cells. Overexpression of SR-BI in tumors enhances the uptake of HDL-C by cancer cells [224]. SR-BI is highly expressed in BC tissues, and overexpression of SR-BI is associated with increased tumor invasiveness, higher risks of recurrence, and poorer OS [225–227]. HDL promotes BC cells proliferation and exhibits anti-apoptotic effects in an SR-BI-dependent manner. Inhibiting SR-BI reduced HDL uptake and subsequently suppressed BC cells migration and tumor growth [228]. Furthermore, in vitro studies indicate that SR-BI facilitates tumor progression via the AKT and ERK1/2 signaling pathways in BC. The knockdown of SR-BI reduced the activation of the MAPK and PI3K/Akt pathways induced by HDL [228]. Sterol regulatory element-binding proteins (SREBPs) are a class of transcription factors that primarily regulate the expression of genes involved in cholesterol and lipid metabolism [229]. Among them, SREBP-2 primarily regulates genes associated with cholesterol synthesis and is activated in response to low intracellular cholesterol levels. The expression of SREBP-2 is significantly higher in invasive BC tissues compared to normal breast tissues. Knockdown of SREBP-2 significantly reduces the expression of key matrix-degrading enzymes involved in tumor invasion and metastasis, suggesting that SREBP-2 may contribute to BC tumorigenesis and metastasis [230]. Similarly, the mRNA and protein levels of SREBP-1 are significantly overexpressed in BC compared to adjacent non-cancerous tissues. SREBP-1 correlates with unfavorable prognostic characteristics, whereas the knockdown of SREBP-1 inhibits the migration and invasion of BC cells [231]. Multiple signaling pathways regulate SREBP-2 activation to control the mevalonate pathway. For example, the tumor suppressor gene p53 can block SREBP-2 activation by mediating the transcriptional upregulation of ABCA1, which reduces the transcription of mevalonate pathway genes [232]. In contrast, mutant p53 enhances SREBP-2 activity by recruiting it to the promoters of genes encoding enzymes of the mevalonate pathway, thereby increasing the activity of multiple oncogenic pathways and promoting cancer progression [232]. Thus, targeting SREBPs to inhibit the mevalonate pathway has been explored as a therapeutic strategy for various cancers.

The role of cholesterol-driven signaling pathways in BC

Cholesterol not only serves as an energy source for cells but also acts as a precursor for the synthesis of numerous essential cellular components. One critical structure formed by cholesterol is the lipid raft. Lipid rafts are highly dynamic, detergent-resistant microdomains within the plasma membrane that are enriched in cholesterol and sphingolipids [233]. Lipid rafts, which are

rich in signaling molecules, play a crucial role in regulating signal transduction by modulating phosphorylation cascades associated with various physiological processes [234, 235]. Lipid rafts provide essential platforms for growth factors, receptor tyrosine kinases, and their downstream mediators, promoting cell proliferation and survival [236]. The MAPK pathway and the activation of EMT are known to be critical pathways for cell migration and invasion [237], with MAPK activation being highly dependent on the integrity of lipid rafts [238]. In addition to the MAPK pathway, cholesterol accumulation mediated by PI3K/Akt through the activation of SREBP proteins can lead to therapeutic resistance [239, 240]. Furthermore, loss of PTEN results in hyperactivation of the PI3K signaling pathway, leading to increased expression of SQLE and other cholesterol synthesis enzymes, thereby promoting tumor progression [241]. Cholesterol is also a key regulator of EGFR signaling pathways to drive proliferation, invasion, and therapy resistance. LDL cholesterol enhances the invasiveness of TNBC cells by activating EGFR and its downstream Src and ERK signaling pathways [55]. Studies on the therapeutic effects of targeted tyrosine kinase inhibitors (TKIs) in BC have demonstrated that cholesterol localized in lipid rafts promotes resistance to EGFR-TKIs by activating EGFR-associated pathways [242]. Depleting cholesterol from lipid rafts not only inhibits EGFR signaling but also significantly alters ERK phosphorylation and mitochondrial apoptosis pathways [243]. In conclusion, cholesterol, as a key component of lipid rafts, plays an important role not only in the structure and function of cell membranes, but also participates in multiple signaling pathways that contribute to BC progression.

Cholesterol is a key component in hormone synthesis and serves as a precursor for estrogen production, which is crucial for the maintenance of the female reproductive system [244]. Among estrogens, estradiol is the most active form and can regulate the activity of the smoothened (SMO) protein. In BC, increased cholesterol synthesis promotes excessive estradiol production, which enhances SMO activity. Activated SMO stimulates the Sonic Hedgehog (SHH) signaling pathway in the nucleus, leading to uncontrolled cell proliferation [245, 246]. In ER-positive BC, estrogen and ER activation stimulate the proto-oncogene Src, subsequently activating downstream pathways such as RAS-MAPK, PI3K/AKT, and mTOR. These pathways promote the expression of cholesterol biosynthesis-related genes, further enhancing cancer cell proliferation and migration [247]. Furthermore, the activation of the mevalonate pathway diminishes the inhibitory function of the Hippo pathway, resulting in enhanced YAP/TAZ activity. YAP/TAZ further translocate to the nucleus and activate downstream target genes, promoting the growth and metastasis of BC cells [248]. Estrogen-related receptor α (ERRα) is a transcription factor that does not bind estrogen directly. ERRα is expressed in most types of BC cells, and increased ERRα activity correlates with unfavorable prognoses in BC patients [249]. Both in vitro and in vivo studies have demonstrated that knockdown of ERRα significantly inhibits the growth of ER + BC and TNBC [250, 251]. Notably, cholesterol acts as an endogenous ligand for ERRα, enhancing its transcriptional activity [252]. Studies have shown that cholesterol increases the interaction between ERRα and peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) and further activates ERRα-related target genes, which ultimately promotes BC cells proliferation and migration [253]. In addition, cholesterol was reported to promote the maintenance of cancer stem cell-like (CSC) populations and therapy resistance through the activation of the ERRα pathway [254]. In summary, cholesterol promotes malignant progression of BC through various signaling pathways. The synergistic interplay among these pathways makes cholesterol metabolism as a crucial regulatory element in BC, underscoring the potential of targeting cholesterol-related signaling pathways as an innovative approach for treatment. In this section, we systematically describe the lipid synthesis in BC involved in metabolic pathways, key enzymes, ligand-receptor interactions, and signaling pathways (Fig. 2).

Dysregulation of lipid catabolism in BC

Landscape of fatty acid oxidation in BC

Fatty acid oxidation (FAO) is a complex metabolic mechanism that transforms long-chain fatty acids into acetyl-CoA in the mitochondria [255]. Subsequently, acetyl-CoA is fully oxidized via the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC) to generate adenosine triphosphate (ATP) [256]. CPT1 catalyzes the conversion of fatty acyl-CoA to fatty acylcarnitine at the outer mitochondrial membrane. Acylcarnitine is then carried into the mitochondrial matrix via carnitine/acylcarnitine translocase, located on the inner mitochondrial membrane [257, 258]. The CPT2 enzyme, located on the matrix side of the inner membrane, is mainly responsible for converting acylcarnitine into acyl-CoA [259]. The cleavage of acyl-CoA into acetyl CoA within the mitochondrion is executed through a cyclic sequence of four steps, involving the sequential actions of acyl-CoA dehydrogenase, hydroxyacyl-CoA dehydrogenase, enoyl-CoA hydratase, and 3-ketoacyl-CoA thiolase [260, 261].

Finally, acetyl-CoA is transferred into the TCA cycle for oxidative phosphorylation to generate ATP. Besides ATP, FAO also produces cytosolic NADPH, which provides

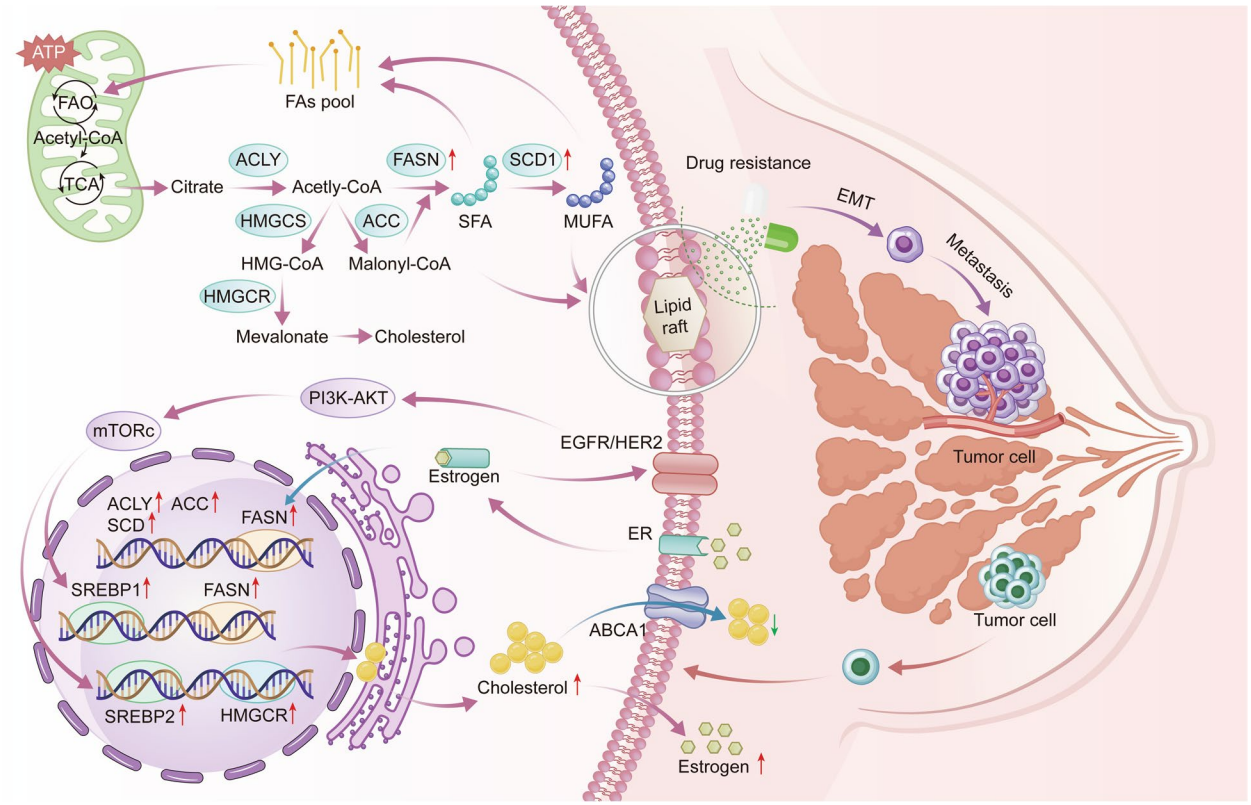

Fig. 2 The dysregulation of lipid synthesis and related pro-oncogenic signaling pathways involved in BC development. The mitochondrial TCA cycle produces Ac-CoA, which is transformed to citrate and delivered to the cytoplasm. Citrate is transformed to Ac-CoA by ACLY, entering the lipid synthesis pathway. ACC and FASN convert Ac-CoA to SFA in the cytoplasm, constituting the basic structure of cellular membranes. Some of these SFAs are converted to MUFAs by SCD1, which increases membrane fluidity and flexibility. The Ac-CoA is converted to cholesterol through the mevalonate pathway. HMGR and HMGCS further synthesize cholesterol, which forms lipid rafts in the cell membrane. Lipid rafts provide aggregation platforms for receptors like EGFR/HER2 and ER, facilitating the clustering and activation of signaling molecules. Additionally, synthesized FAs serve not only structural roles but are also stored in the cytoplasmic FA pool. Under high energy demands, FAs are transported into mitochondria for β-oxidation, generating steady energy for BC cells metabolism. The lipid metabolic pathway is regulated by multiple signaling pathways particularly the mTOR and PI3K/AKT pathways. These pathways activate transcription factors, including SREBP1/2 to upregulate ACLY, ACC, SCD1, and FASN, maintaining BC cells lipid and energy production efficiency. In hormone-dependent BC, estrogen activates the PI3K/AKT pathway via ER, boosting lipid production and imparting cancer cells greater proliferative potential and drug resistance. Lipid synthesis is a crucial metabolic pathway, promoting BC cells proliferation, EMT, and drug resistance, particularly exacerbating malignant traits in hormone-dependent BC. Abbreviations: TCA, Tricarboxylic Acid Cycle; Ac-CoA, Acetyl-Coenzyme A; ACLY, ATP Citrate Lyase; SFA, Saturated fatty acids; MUFA, Monounsaturated fatty acids; ACC, Acetyl-CoA Carboxylase; FASN, Fatty Acid Synthase; SCD, Stearoyl-CoA Desaturase 1; HMGCS, 3-Hydroxy-3-Methylglutaryl-CoA Synthase; HMGCR, 3-Hydroxy-3-Methylglutaryl-CoA Reductase; ER, Estrogen Receptor; EMT, Epithelial-mesenchymal transition

cancer cells with redox power to combat oxidative stress [262]. Even though FAO produces significant amounts of ATP, the Warburg effect has been the focus of most previous studies on cancer bioenergetics [263]. However, the roles of FAO in cancer cells have gained more and more attention recently.

FAO activity is significantly elevated in several cancers, including gastric cancer, breast cancer, colorectal cancer, renal cell carcinoma, acute myeloid leukemia, and esophageal squamous cell carcinoma [264–268]. It has been demonstrated that FAO is crucial for sustaining malignant cancer phenotypes [269]. Tumor cells are able to evade death by developing resistance to chemotherapy, which is a primary factor contributing to treatment failures [270]. Notably, the level of FAO is increased in chemoresistant MDA-MB-231 cells, and FAO is implicated in the resistance of TNBC to chemotherapy [271]. In addition, tumor cells in metastatic lymph node are critically dependent on FAs as an energy source due to the lipid-rich microenvironment of lymph nodes [272, 273]. It has been observed that FAO can accelerate the homing of circulating tumor cells to lymph nodes [274]. Moreover, FAO contributes to the metastatic phenotype by potentially influencing the regulation of cancer stem

cells, and disrupting FAO pathways can lead to depletion of the stem cell population [275]. Therefore, the regulation of FAO plays a crucial role in the progression of cancer, and focusing on this mechanism may present a viable therapeutic strategy for cancer treatment.

When viewed as a whole, different BC cells exhibit heterogeneous metabolic preferences and energy dependencies [20]. Bulk and single-cell transcriptome profiling uncovered that BC tumors were classified into two energy-related metabolic subtypes. And subtype 2 exhibits a dependency on FAO, which predicts a better survival prognosis [276]. Several studies highlighted that transcription factors served as important regulators for driving FAO in BC. MYC, as a known regulator of metabolic reprogramming, is sufficient to stimulate FAO in human mammary epithelial cells [277].Camarda et al. reported that FAO was upregulated in a mouse model of MYC-overexpressing TNBC, as well as in tumors from patients with BC. Inhibition of FAO, using the CPT1 inhibitor etomoxir, blocked tumor growth in both a MYC-driven transgenic TNBC mouse model and in a patient-derived xenograft model of MYC-overexpressing TNBC [278]. Furthermore, obesity-induced metabolic reprogramming to FAO and mitochondrial oxidative phosphorylation, which was accompanied by coordinated activation of YAP signaling [279]. In addition, blocking JAK/STAT3 signaling downregulated several key lipid metabolism genes in breast cancer stem cells, including the rate-limiting enzyme CPT1 for FAO [271]. Overall, the intricate network of transcription factors regulating FAO in BC underscores the importance of these molecular players in cancer metabolism.

The role of FAO in BC resistance and metastasis

Although treatments for BC have progressed in recent decades, resistance and metastases still remain the most common reasons for treatment failures [280]. Recently, FAO has received prominent attention for its critical role in resistance. ER + endocrine-resistant cancer cells exhibit greater dependence on FAO than primary cells. Meanwhile, a synergistic effect was also observed when endocrine therapy and FAO inhibitors were combined in vitro [281–283]. Jiang et al. observed that the FAO rate and ATP production increased in tamoxifen-resistant ER-positive BC cells. Mechanistically, c-Jun recruits CBP/P300 to the CPT1A promoter, initiating CPT1A transcription in ER-positive BC cells [284]. Wang et al. demonstrated that leptin from mammary adipocytes activated STAT3, leading to increased CPT1B expression and FAO in BC stem cells. Thus, blocking FAO and leptin re-sensitizes them to chemotherapy and inhibits BC stem cells in mouse breast tumors [271]. Li et al. found that FAO reprograms phospholipid biosynthesis through acetylated STAT3-mediated upregulation of ACSL4, which increases mitochondrial membrane potential and counteracts the mitochondrial apoptotic pathway in chemoresistant TNBC cells [285]. Moreover, radioresistant BC cell lines exhibit higher activity mitochondrial FAO metabolism, which is accompanied by increased levels of CPT1A/CPT2 [286]. As research continues to unravel the complexities of cancer metabolism, FAO emerges as a critical player in the resistance mechanisms of BC, warranting further investigation into its therapeutic targeting.

The role of FAO in the metastasis of BC is still a matter of intense research. BC brain metastases cause significant mortality and remain an important clinical challenge [287]. Latent brain metastatic cells survive the lipid-rich brain milieu by mitochondrial FAO, and targeting mitochondrial plasticity suppressed the growth of latent metastatic cells in BC preclinical models [288]. Another study found that metastatic TNBC maintained high levels of ATP through FAO, and inhibition of FAO could reduce metastatic characteristics in patient-derived xenografts [289]. EMT-associated genes such as TGF-β and snail were reported to promote the survival and motility of BC cells by enhancing catabolic FAO activity [290, 291]. One of the main mechanisms is that mesenchymal cells channel FAs toward FAO for energy production, and acetyl-CoA is made from the production of FAO, which epigenetically regulates EMT target genes, indicating that FAO is a metabolic "gateway" for cell state transitions in BC [292]. Besides, increasingly more studies have recognized the critical factors influencing BC metastasis via FAO. CDCP1 promotes TNBC metastasis by reducing lipid droplets abundance and enhancing lipid accumulation in mitochondria for FAO. Mechanistically, CDCP1 regulates these processes, in part, by directly inhibiting ACSL activity [293]. Furthermore, the ZEB2/ACSL4 axis is a novel metastatic metabolic pathway that leads to increased BC invasion and metastasis through the stimulation of lipogenesis and FAO [294]. In summary, these findings suggest the critical roles of FAO in BC resistance and metastasis, and molecular mechanisms are revealed from different directions. However, whether targeting FAO has a promise for clinical applications in BC depends on the results of reliable clinical trials.

Carnitine palmitoyltransferases in BC

Carnitine palmitoyltransferases (CPTs) convert carnitines into fatty acyl carnitines in the FAO process and are regarded as a crucial enzyme [295]. CPT1A levels in serum are positively correlated with BC progression, potentially serving as a disease-monitoring indication [296]. Furthermore, clinical evidence supports the association of elevated CPT1C levels with poor outcomes in

terms of OS, disease-free survival (DFS), progression-free survival (PFS), and disease-specific survival (DSS) among basal-like breast cancer patients (BLBC) [297]. From cellular and animal experiments, the CPT1A-mediated FAO has a cancer-promoting effect in BC cells. Overexpression of CPT1A promotes proliferation of ER-positive BC cells through FAO [298]. CPT1A was also reported to regulate breast cancer-associated invasion and lymphangiogenesis via regulating VEGFR-3 signaling. [299]. Cancer-specific nuclear CPT1A variant 2 interacts with HDAC1 to regulate epigenetic regulation of genes related to cell death and invasion in cancer, offering a promising direction for improving BC treatment strategies [300]. Recently, the role of CPT1C, an isoform of CPT1, in BC has been gradually emphasized. Silencing CPT1C in BC cells leads to lipid remodeling characterized by enhanced phospholipid saturation and chain length, which contributes to increased drug impermeability and chemoresistance [301]. The expression of CPT1C in BC xenografts correlates inversely with activation of the mTOR pathway and rapamycin sensitivity [302].The inhibition of CPT1C expression has been shown to hinder tumor growth and pulmonary colonization of BLBC cells in vivo [297]. In summary, the investigation of CPTs in BC is still in its infancy stage, and the molecular mechanism of CPT1A-mediated FAO in BC biology still needs further exploration.

Lipid peroxidation and ferroptosis in BC

Lipid peroxides, derived from PUFAs, are detrimental to cells and tissues [303]. Lipid peroxidation is implicated in various forms of cell death, such as apoptosis, necroptosis, ferroptosis, and pyroptosis, which are linked to inflammation, neurodegenerative diseases, and cancer [304]. Recent years have seen an increased scholarly emphasis on lipid peroxidation, especially regarding ferroptosis, a cell death mechanism defined by iron-dependent lipid peroxidation [305]. Ferroptosis is triggered by dysregulation of intracellular redox homeostasis, which triggers lipid peroxidation and eventually disrupts membrane integrity, leading to cell death [306].Ferroptosis exerts an important inhibitory effect on tumor progression, and targeting ferroptosis may lead to a major breakthrough in cancer therapy. Breast tumors contain high levels of lipid and iron, suggesting that inducing ferroptosis in breast cancer may be a viable treatment strategy [307]. Ferroptosis susceptibility varied markedly among various BC subtypes. GPX4 is specifically elevated in luminal BC, with luminal BC cell lines showing high sensitivity to GPX4 inhibitors [308]. TNBC subtypes also display unique features concerning ferroptosis, particularly the luminal androgen receptor (LAR) subtype, which demonstrates an upregulation of ferroptosis-related pathways, indicating a possible vulnerability to ferroptosis [309]. Both basal and TNBC tumors exhibit high levels of CD274 and key regulators of ferroptosis, including IFNG, TNFAIP3, and IDO1. Thus, the potential synergistic effects of combining ferroptosis inducers with anti-PD-L1 immunotherapy are proposed for the treatment of TNBC [310]. Additionally, the status of the ferroptosis regulators ACSL4/GPX4 was identified as a potential independent predictive factor for achieving pathological complete response (pCR) for BC patients undergoing neoadjuvant chemotherapy [311]. In summary, the rich lipid and iron content of breast tumors presents a unique opportunity for the application of ferroptosis as a therapeutic strategy.

Recent evidence has suggested that BC cells are inhibited by Fer-1 or deferoxamine, and increased ROS and death of BC cells are caused by ferroptosis inducers erastin and RSL3 [312]. Moreover, inhibition of the xCT ferroptosis signaling pathway using erastin and SAS promotes ferroptosis, resulting in increased ROS accumulation in TNBC cells [313, 314]. Fatty acid desaturases 1 and 2 (FADS1/2) are the key enzymes involved in the biosynthesis of PUFAs. Notably, a novel study also reported that TNBC with high FADS1/2 expression was susceptible to ferroptosis-inducing agents, and that ablation of FADS1/2 resulted in a decrease in the PUFA/MUFA ratio and rendered TNBC insensitive to pro-ferroptosis agents [315]. Recent studies indicate a strong link between ferroptosis and chemotherapy resistance in BC. Ferroptosis markers were elevated in BC tissues relative to normal tissues, and resistance to Adriamycin in BC is linked to the modulation of iron ion-mediated ferroptosis [316]. Ferroptosis has been shown to efficiently target breast cancer stem cells (BCSCs), a cell subpopulation recognized for its resistance to conventional treatments. Treatment-induced ferroptosis, especially with salinomycin, has shown increased effectiveness and specificity in eradicating BCSCs by promoting the accumulation and sequestration of iron in lysosomes [317, 318]. Beyond that, inhibiting Gpx4 expression can reduce TNBC resistance to DOX and enhance chemotherapy's therapeutic effect by inducing ferroptosis [319]. Ferroptosis in BC cells is influenced by the tumor microenvironment (TME), in particular immune cells. Oleic acid secreted from adipocytes inhibited lipid peroxidation and ferroptosis through its interaction with ACSL3 in TNBC [320]. Interferon-γ produced by CD8 + cytotoxic T cells suppresses cystine uptake by cancer cells through the downregulation of SLC7A11, leading to lipid peroxidation and ferroptosis in BC [321]. Overall, as an emerging research hotspot in tumor research, inhibiting ferroptosis could be a promising therapeutic strategy for BC. However, the

identification of this vulnerable BC population and the best candidate drugs underscores the need for developing highly specific ferroptosis inhibitors. In this part, we explore the effect of FAO on BC metastasis and resistance, and we also discuss the role of ferroptosis in BC progression and TME (Fig. 3).

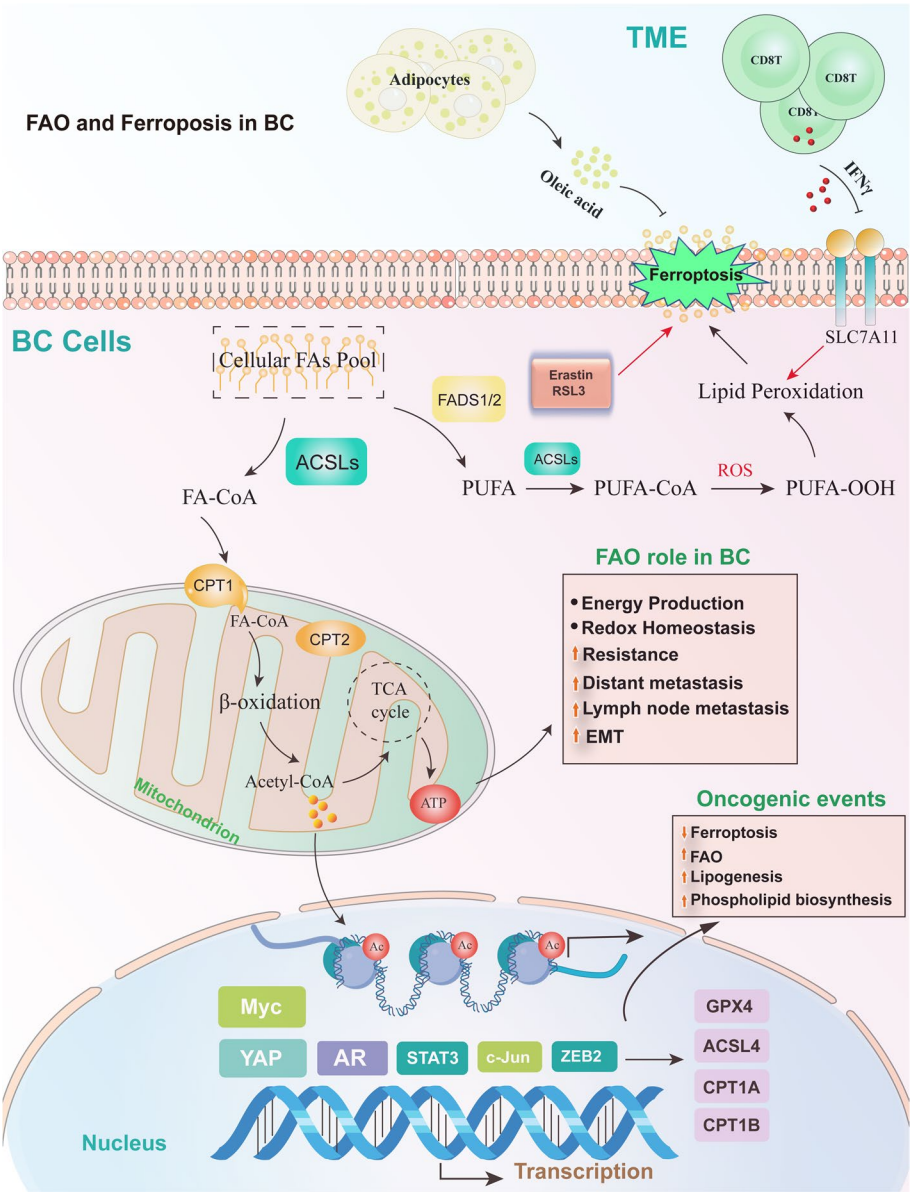

Fig. 3 FAO signaling pathway and ferroptosis in BC. 1) FAs are catalyzed by ACSLs to produce acyl-CoA, which is subsequently converted to CPT1 on the outer mitochondrial membrane. The cleavage of acyl-CoA into acetyl CoA in mitochondrion is aided by β-oxidation. FAO is involved in various facets of malignant behaviors in BC, encompassing energy production and redox equilibrium for cancer cell proliferation, drug resistance, metastasis, and the EMT. 2) Transcription factors such as Myc, AR, and STAT3 serve as significant regulators in BC. Modifications in these genes subsequently enhance the expression of crucial enzymes implicated in fatty acid oxidation and ferroptosis. Furthermore, acyl-CoA generated by fatty acid oxidation serves as a crucial cofactor in the post-translational acetylation of histones. Transcriptional and posttranscriptional regulatory mechanisms result in lipid metabolic changes in BC. 3) Ferroptosis is an acknowledged kind of programmed cell death induced by reactive oxygen species-mediated lipid peroxidation, which directly leads to cell death characterized by the degradation of lipid membranes. Ferroptosis inducers erastin and RSL3 elevate ROS and iron levels and induce the mortality of BC cells. In TME, oleic acid released from adipocytes prevented lipid peroxidation and ferroptosis. Interferon-γ generated by CD8 + cytotoxic T lymphocytes causes the downregulation of SLC7A11, resulting in lipid peroxidation and ferroptosis in BC. Abbreviations: FAs, fatty acids; TME, tumor microenvironment; BC, breast cancer; ROS, reactive oxygen species; PUFA, polyunsaturated fatty acids; FAO, fatty acid oxidation; EMT, epithelial–mesenchymal transition

Fatty acid storage

Lipid droplets (LDs), which are composed of neutral lipids, are essential for maintaining lipid homeostasis, signaling, and energy equilibrium inside the cell [322]. One notable characteristic of cancer cells is their abundance of cellular LDs, indicative of heightened lipid metabolic activity in comparison to normal cells [323].The lipid metabolism in tumor cells is evidenced by elevated rates of lipid uptake and synthesis, as well as activation of the de novo fatty acid synthesis pathway, resulting in the production of significant quantities of FAs. These FAs are subsequently converted into glycerides by acyltransferases and stored within LDs [10, 324]. Due to their ability to act as phospholipid reservoirs, LDs can also provide phospholipid membranes so that cancer cells can synthesize membranous organelles fast enough to sustain rapid proliferation [325]. In addition, LDs accumulate in cancer cells under hypoxic conditions, potentially serving as a metabolic energy source and intermediates to mitigate oxidative stress, thereby promoting growth and invasiveness upon reoxygenation [326, 327]. Additionally, LDs are essential for supplying energy and maintaining the survival of CSCs via activating pathways linked to cancer stemness [328]. Existing evidence suggests that CSCs exhibit elevated LD levels compared to non-stem cancer cells [329]. Thus, to sum up, LDs play a significant role in cancer progression by providing resistance to cell death through maintenance of redox homeostasis, provision of energy for proliferation, metastasis, and facilitation of communication between cancer cells and TME.

The role of LDs in BC is becoming increasingly clear. First, LDs are dynamic cytoplasmic organelles that provide energy metabolism substrates as well as a lipid reservoir for BC cells. Exogenous unsaturated fatty acids are often required for the survival of cancer cells under stressful conditions [330]. Previous data showed that LDs serve as transient reservoirs for unsaturated fatty acids, such as ω−3 and ω−6 PUFAs, offering protection against lipotoxicity and nutrient deprivation by releasing these FAs gradually as required for TNBC cells survival [331]. Likewise, BC cells absorb extracellular fatty acids from the surrounding adipose tissue and store them in LDs [332, 333]. Secondly, the dysfunction of LDs is now recognized as a contributing factor to BC's development and progression. Aggressive BC cells with ras oncogenic mutations demonstrate increased lipid droplet production when exposed to low concentrations of monounsaturated or polyunsaturated fatty acids in nutrient-rich environments [334]. Another study found that LDs were enriched and active in estrogen-deprived ER + BC cells, which are essential for maintaining redox equilibrium and facilitating metabolic adaptability in resistant tumors [139]. Furthermore, dysregulated LDs contributed to CSCs and drug resistance. High LDs numbers were enriched in the breast CSCs pool, suggesting a key role for lipid metabolism in maintaining the breast CSCs population [335]. The doxorubicin-resistant TNBC cells were characterized by smaller but functional mitochondria, as well as numerous lipid droplets [336]. Meanwhile, tamoxifen-resistant T-47D cells exhibit a rapid increase in neutral lipids in lipid droplets and free cholesterol accumulation in lysosomes [337, 338]. Of note, inhibiting LDs biosynthesis inhibited tumorigenesis, potentiated BC cell radiosensitivity, and improved radiotherapy efficacy [339, 340]. In summary, LDs significantly influence BC progression by regulating redox balance, transmitting signaling molecules, supporting cellular energy demands for growth and spread, and enabling intercellular communication within the TME.

Lipid metabolism reprogramming in BC microenvironment

Rather than growing independently, cancer cells exist within a complex TME. Besides serving as a vital energy source, lipids also serve as a fundamental substrate for the growth of membrane remodeling and function as signal transduction molecules in a variety of intracellular and extracellular information transmission pathways [341].Tumor cells produce the metabolites and lipid-associated signaling molecules to form an immunosuppressive TME. Meanwhile, altered lipid metabolic patterns of TME cells can affect the growth of cancer cells, facilitating tumor immune escape [342, 343]. Lipid metabolism reprogramming can activate or suppress various immune cell functional states and immune factors in TME, ultimately leading to BC development [344]. Therefore, both BC cells and TME cells undergo lipid metabolic rewiring to evade the adverse conditions (Fig. 4, Table 1).

Notably, lipid metabolism and inflammatory signals are tightly linked, and their coordinated activity is essential for sustaining metabolic equilibrium [345]. Obesity, a condition involving low-grade chronic inflammation and aberrant lipid metabolism, has been related to the risk of developing estrogen receptor–positive BC [346]. In obesity, metabolic dysregulation within adipose tissue results in the release of numerous pro-inflammatory cytokines, growth factors, and hormones. These factors collectively contribute to the establishment of the TME and facilitate the progression of BC [347]. Several studies have demonstrated that lipid mediators such as 27-hydroxycholesterol [348],leptin [349], and lysophosphatidic acid [350] have emerged as important players in obesity-driven BC progression. Therefore, the strong associations between lipid metabolism and inflammatory signaling in the progression of obesity-driven BC highlights the necessity for comprehensive therapeutic strategies that simultaneously target the metabolic and inflammatory aspects of the disease.

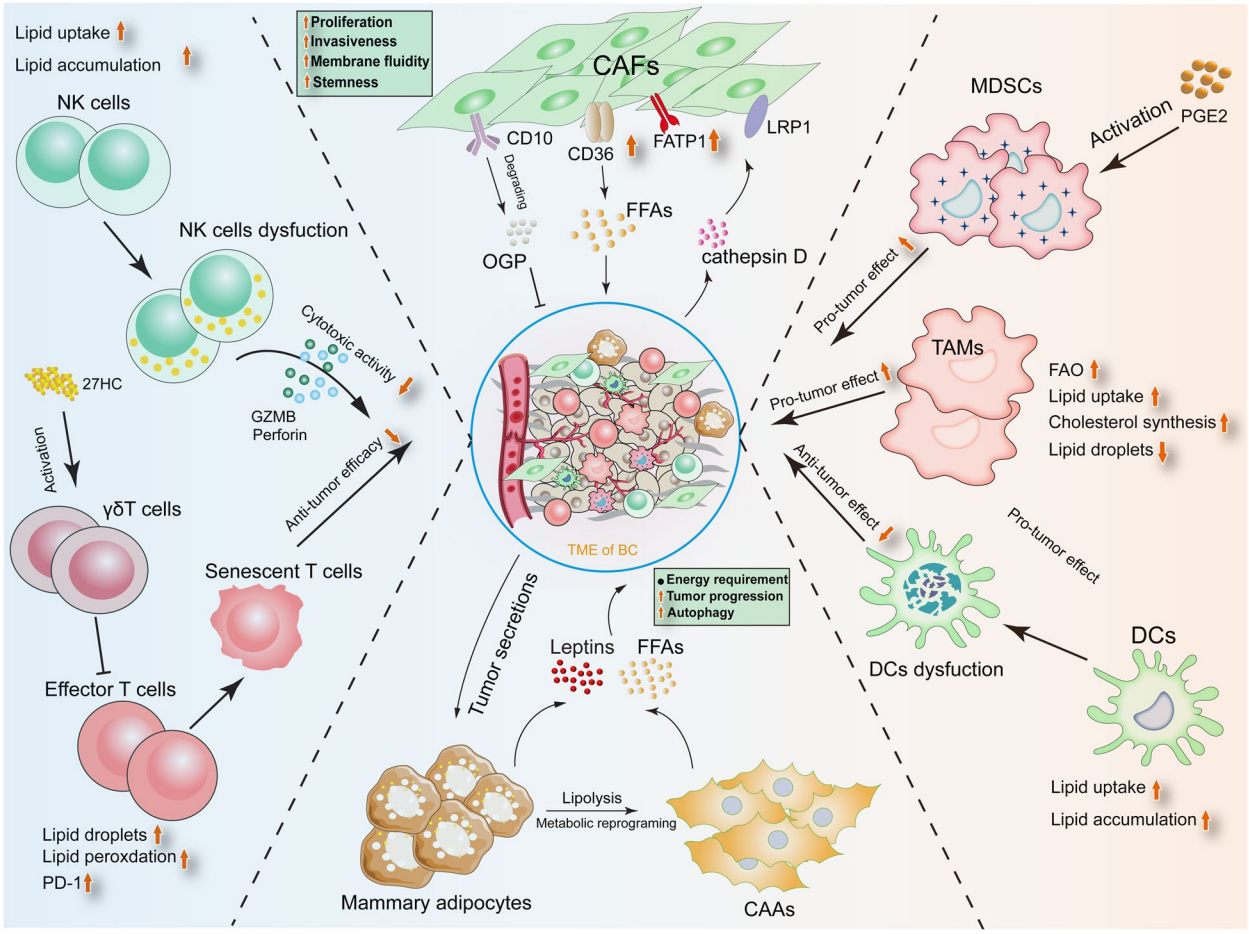

Fig. 4 The dysregulation of lipid metabolism landscape in the TME of BC. Abnormal lipid metabolism in BC cells can educate surrounding stromal cell, and immune cells into a pro-tumor phenotype. For instance, adipocytes experience a shift in lipid metabolism and differentiation, leading to a transformation into cells with characteristics resembling myofibroblasts and macrophages. BC-associated fibroblasts can secrete signaling molecules such as FFAs and OGP to promote tumor progression. Furthermore, dysregulation of lipid metabolism in TAMs, characterized by increased FAO, lipid uptake, and cholesterol synthesis, can further enhance pro-tumorigenic effects. Similarly, the activation of lipid peroxidation in effector T cells can reduce their anti-tumor activity. Taken together, lipid metabolic reprogramming enhances crosstalk between BC cells and TME cells, thereby supporting tumor cell growth and altering the functional phenotypes of TME cells. Abbreviations: FFAs, free fatty acids; CAFs, cancer-associated fibroblasts; OGP, osteogenic growth peptide; CAAs, cancer-associated adipocytes; TAM, tumor-associated macrophages; MDSCs, marrow derived suppressor cells; DCs, dendritic cells; PGE2, prostaglandin E2; FAO, fatty acid oxidation; 27HC, 27-hydroxycholesterol; NK, natural killer

Cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) play a crucial role in modifying the extracellular matrix, enabling tumor cell infiltration into the TME and promoting interactions with cancer cells and other stromal cells through the secretion of diverse signaling molecules, including growth factors, cytokines, and chemokines. These interactions facilitate the metastasis, angiogenesis, immunosuppression, and treatment resistance of BC cells [213, 351]. Recent findings indicate that the co-culture of BC cells with cancer-associated CAFs might enhance the overexpression of FATP1 and the down-regulation of FASN, hence facilitating the proliferation of BC cells [352, 353]. Notably, BC-associated fibroblasts and BC cells are markedly stimulated to express and activate FASN by G protein-coupled estrogen receptors, facilitating cancer growth [354]. Conversely, BC cells secrete cathepsin D that binds to low-density lipoprotein receptor-associated proteins in the microenvironment and stimulates fibroblast growth [355]. BC cells are able to modify the metabolic characteristics of fibroblasts, leading to the formation of a pre-metastatic niche that facilitates lung metastasis. Additionally, heightened secretion of CXCL1 by lung fibroblasts diminishes immune response in the lung microenvironment by attracting G-MDSCs [141]. Furthermore,

Table 1 The lipid metabolism in the breast cancer tumor microenvironment

Cells	The role in lipid metabolism	Mechanisms	Effects on BC	Potential therapeutic targets	References
CAFs	Promote lipid desaturation	Overexpresse FATP1 and SCD1 Downregulate FASN Degrade OGP	Promote metastasis Facilitate angiogenesis Induce immunosuppression Enhance therapeutic resistance	FATP1 SCD1 OGP	[213, 351–356]
CAAs	Enhance FAO Increase TAG uptake	Enhance CPT1A expression Enhance JARID2 expression Secrete lysophospholipids	Promote proliferation and invasion Induce autophagy Facilitate therapeutic resistance	CPT1A JARID2 AMPK pathway	[357–370]
TAMs	Increase lipid uptake Promote CS Enhance FAO	Upregulate SREBP2 pathways Upregulate FABP4 pathways Activate Caspase 1 Suppress immunity	Inhibit T cell activation Promote tumor proliferation	FABP4, SREBP2 CXCL12-CXCR4 Caspase 1 TREM2 + TAMS	[41, 371–378]
DCs	Enhance TG synthesis	Activate CD8 + T cells Induce ER stress	Facilitate immune escape	XBP1 splicing factor	[14, 379, 380]
NK cells	Promote lipid accumulation	Downregulate perforin Downregulate granzyme Reduce IFN-γ levels	Promote the proliferation of ER + BC cells	CD36 PPARs IFN-γ	[381–385]
MDSCs	Increase lipid uptake	Activate PGE2 Suppress T cells	Promote tumor progression	PGE2	[386, 387]
T cells	Enhance FAO Increase lipid droplet accumulation	Activate p38 MAPK	Promote immune evasion T-cell degeneration promotes tumor progression	ILT4 PD-1 MAPK-ERK1/2 pathway LXR	[388–397]

Abbreviations: *CAFs* Cancer-associated fibroblasts, *CAAs* Cancer-associated adipocytes, *TAGs* Triacylglycerols, *TAMs* Tumor-Associated Macrophages, *DCs* Dendritic cells, *NK cells* Natural killer cells, *MDSCs* Myeloid-derived suppressor cells, *T cells* T lymphocytes, *FATP1* Fatty Acid Transport Protein 1, *SCD1* Stearoyl-CoA Desaturase 1, *FASN* Fatty Acid Synthase, *OGP* osteogenic growth peptide, *TAG* Triacylglycerols, *CPT1A* Carnitine Palmitoyltransferase 1A, *JARID2* Jumonji AT-Rich Interactive Domain 2, *CS* Cholesterol Synthesis, *SREBP2* Sterol Regulatory Element-binding Proteins 2, *FABP4* Fatty Acid Binding Protein 4, *TG* Triglyceride, *ER* Endoplasmic Reticulum, *XBP1* X-box binding protein 1, *PPARs* Peroxisome Proliferator-Activated Receptors, *IFN-γ* Interferon-gamma, *PGE2* Prostaglandin E2, *ILT4* Immunoglobulin-like transcript 4, *PD-1* Programmed Cell Death Protein 1; LXR, liver X receptor

CAFs play a role in modulating the membrane fluidity of tumor cells, leading to increased invasiveness. Specifically, contact between CAFs and BC cells specifically stimulates the overexpression of the desaturase enzyme SCD1, resulting in enhanced synthesis of MUFAs and subsequently elevating cell membrane fluidity and migratory capabilities of BC cells [143]. Moreover, CD10 expressed in a subset of CAFs promotes tumor progression by degrading the anti-tumoral peptide osteogenic growth peptide (OGP). OGP functions to suppress the expression of the rate-limiting desaturase SCD1, hence obstructing lipid desaturation essential for breast cancer stem cells [356]. Therefore, targeting lipid metabolism alterations in the crosstalk of CAFs and BC cells presents a promising therapeutic strategy to enhance anti-tumor immunity, and improve treatment outcomes in BC patients.

Adipocytes

The stroma of the breast is largely composed of adipocytes, and recent studies have demonstrated that stromal adipocytes and BC cells exhibit a reciprocal metabolic adaptation [13]. Cancer-associated adipocytes (CAAs) are abnormal adipocytes whose phenotypic alterations are affected by tumor cells. CAAs are characterized by reduced cell volume, lower LDs, changes in fibroblast-like alterations, and reduced lipid differentiation [357, 358]. Zhu et al. have reported that within mammary tumors, adipocytes undergo alterations in lipid metabolism and differentiation, resulting in their metamorphosis into cells resembling myofibroblasts and macrophages. This phenomenon, known as "adipocyte mesenchymal transition," alters the TME through extracellular matrix remodeling and immune response activation, potentially playing a role in tumor progression [359]. CAAs were reported to drive BC cells lipid metabolic reprogramming to promote tumor progression. The intake of triacylglycerols (TAGs) by adipocytes rises when cocultured with BC cells, leading to elevated CPT1A levels and enhanced fatty acid metabolism in cancer cells [360, 361]. As well, BC cells exhibited lipid accumulation when cocultured with primary human omental adipocytes [362]. Interestingly, oleic acid released by adipocytes stimulates AMPK-mediated FAO in highly metastatic BC cells, but it suppresses the growth of metastatic BC cells in low-metastatic MCF-7 cells [363]. Furthermore, leptin

produced by adipocytes enhances JARID2 expression, which physically interacts with the NuRD complex and modulates lipid metabolism-related genes, hence facilitating the proliferation and invasion of BC cells [364].

Meanwhile, altered phospholipid metabolism of tumor–adipocytes interactions also exerts a profound influence on the progression of BC. Lysophospholipids secreted by adipose tissue have been shown to promote the proliferation of tumor cells in the mammary glands of mice. The pharmacological or genetic suppression of the G-protein-coupled lysophosphatidic acid receptor diminished the proliferation of tumor cells induced by lysophospholipids, suggesting a lipid-specific mechanism that influences the role of adipocytes in BC cell biology [365]. Bellanger et al. have reported that adipocytes trigger autophagy in breast cancer cells by altering membrane phospholipid composition, hence boosting cancer cell survival in nutrient-deficient settings [366]. Intriguingly, diet-induced obesity has been shown to reduce the effectiveness of doxorubicin in TNBC tumors through the modulation of phospholipid profiles in mammary and tumor tissue, therefore enabling cancer cells to sustain their survival and energy demands [367]. In addition to CAAs being able to modify BC cell behaviors, BC cells are also capable of modulating CAAs behaviors. Exosomal miR-155 derived from BC cells has been shown to inhibit lipogenesis in preadipocytes and promote the browning of white adipose tissues [368]. Analysis of primary human samples indicates that adipocytes in close proximity to tumor exhibit smaller size and reduced TAGs stores compared to adipocytes distal to the tumor. Additionally, studies using co-culture and conditioned media models have demonstrated that human BC cells decrease TAG stores in adipocytes [369, 370]. In conclusion, BC cells and stromal adipocytes exhibit reciprocal lipid metabolic adaptations, which may be able to develop and implement novel therapies in the long term by repurposing existing drugs or using new compounds targeted at the interaction between CAAs and BC cells.

Tumor-associated macrophages

Macrophages constitute a major immune cell population in the tumor microenvironment, accounting for up to fifty percent of the cellular composition and significantly influencing all phases of BC growth [371]. Tumor-associated macrophages (TAMs) often exhibit enhanced FAO and lipid uptake, which supports their pro-tumorigenic functions [41, 372]. On the one hand, alterations of lipid metabolism in TAMs exert immunosuppressive effects that facilitate BC progression. TAMs may absorb various lipids, with unsaturated fatty acids being preferentially collected in macrophages. TAMs with lipid accumulation promote BC growth via FABP4-dependent lipolysis and lipid consumption pathways [373]. Timperi E et al. identified a specific subset of high-lipid TAMs originating from monocytes characterized by increased lipid uptake, which stimulate the inflammatory CXCL12-CXCR4 pathway to recruit monocytes in TNBC, ultimately altering monocyte function to inhibit T cell activation [374]. Furthermore, the downregulation of lactate dehydrogenase B decreased fatty acid synthesis by activating SREBP2 in TAMs, thereby promoting cholesterol biosynthesis in macrophages and facilitating BC cells proliferation [375]. In a murine model of BC, the activation of caspase 1 in TAMs leads to the upregulation of medium-chain acyl-CoA dehydrogenase, which inhibits the accumulation of lipid droplets and facilitates the acquisition of tumorigenic properties by TAMs [376]. On the other hand, altered lipid metabolism of BC cells also exerts a profound influence on the interactions of tumor–macrophages. TNBC cells treated with docosahexaenoic ethanolamine acid exhibit reduced recruitment of human THP-1 cells and downregulation of genes associated with the TAM phenotype by decreasing CCL5 expression and secretion [377]. Sun et al. discovered that the presence of ceramide metabolites leads to the alteration of macrophage function towards immune-suppressive TREM2 + tumor-associated macrophages, ultimately contributing to CD8 T cell exhaustion in BC [378]. Therefore, understanding these lipid metabolic changes and their implications for TAM function is crucial for developing novel therapeutic strategies aimed at reprogramming TAMs to enhance anti-tumor immunity for BC.

Dendritic cells, natural killer cells and marrow derived suppressor cells

Dendritic cells (DCs) serve as the principal antigen-presenting cells responsible for activating CD8 + T cells and orchestrating anti-tumor immune responses. Lipid metabolic changes in DCs can diminish their ability to present antigens effectively, thereby promoting immune evasion by tumors [14, 379]. The accumulation of lipids triggers endoplasmic reticulum stress in DCs, leading to the activation of the X-box binding protein 1 splicing factor and the subsequent enhancement of triglyceride biosynthesis. This process ultimately hinders antigen presentation by DCs, thereby facilitating immune evasion by BC cells [380]. Natural killer (NK) cells are essential components of the immune response against tumors and viral infections, as they utilize perforin and granzyme to eliminate infected or tumor cells [381]. In murine BC models, lipid accumulation in NK cells mediated by CD36 and peroxisome proliferators has been shown to downregulate the expression of perforin and granzyme, leading to impaired metabolic function and transport

processes [382]. Additionally, research has demonstrated that dietary fat can promote the proliferation of estrogen receptor-positive BC cells by reducing the number and cytotoxic activity of splenic NK cells [383]. NK cells have the ability to internalize lipid-rich extracellular vesicles released by lung mesenchymal cells, resulting in intracellular lipid accumulation [384]. This lipid-laden state in NK cells leads to reduced production of granzyme B and IFN-γ, ultimately impairing their anti-tumor efficacy and promoting BC lung metastasis [384, 385]. Myeloid-derived suppressor cells (MDSCs) play a significant role in modulating the immunosuppressive tumor microenvironment. The bioactive lipid PGE2 has been identified as a key factor in activating MDSCs within the TME in a mouse model of BC [386]. MDSCs induced by E-prostanoid receptor exhibit stronger inhibitory activity on T cells, inhibiting antigen-specific activation of CD4 + T cells and CD8 + T cells, thereby promoting BC progression [387].

T cells

The primary T cell subsets depend closely on lipid metabolism to adjust their functions in response to altered TME. Tumor-infiltrating T cells often undergo metabolic alterations due to the hypoxic, glucose-deficient, and lipid-rich TME. This metabolic adaptation includes a shift from glycolysis to FAO to enhance their functionality and sustain their anti-tumor capabilities [388]. However, an excessive elevation in lipid metabolism may lead to lipid peroxidation and the formation of ROS inside cells, thereby reducing their anti-tumor potency [389]. For instance, the activation of fatty acid metabolism was noted in both tumor cells and T cells within the male BC microenvironment. T cells in male BC exhibit activation of p38 MAPK and lipid oxidation pathways, indicating a state of malfunction [390]. Furthermore, in a murine model of obesity-related BC, CD8 + tumor-infiltrating lymphocytes have shown the ability to inhibit glycolytic activity while enhancing FAO [391]. A high-fat diet affects the formation of PD-1 + CD8 + fatigued T lymphocytes in breast tumors, and these cells contribute to obesity-induced tumorigenesis [392].

The emergence of senescence in T cells within the tumor microenvironment of BC is a significant pathological condition. Senescent T cells have increased glucose metabolism but show dysregulated lipid metabolism. This dysregulation of lipid metabolism leads to alterations in the expression of lipid metabolic enzymes, subsequently impacting lipid species and the accumulation of lipid droplets within T cells [276]. Previous research has shown that immunoglobulin-like transcript 4, an immunosuppressive molecule present in tumor cells, can activate the MAPK-ERK1/2 signaling pathway to enhance fatty acid synthesis and lipid accumulation in tumor cells, resulting in effector T cell senescence and the inhibition of specific T cell senescence expression [393]. Additionally, it has been shown that cholesterol and its metabolites contribute to the immunosuppressive tumor microenvironment [394]. The primary cholesterol metabolite 27-hydroxycholesterol (27HC) has been demonstrated to enhance the activation and recruitment of γδ T cells and polymorphonuclear leukocytes (PMNs), resulting in a reduction of CD8 + cytotoxic T cell populations and modifying the immune profile of estrogen receptor-positive BC [395, 396]. Furthermore, the activation of liver X receptor (LXR) in TNBC impedes the mitochondrial metabolism of CD8 + T lymphocytes and alters cholesterol distribution on the cell membrane. Inhibiting LXR activation increases the cytotoxicity of CD8 + T lymphocytes, hence facilitating more efficient tumor eradication [397]. In conclusion, although studies on the relationship between T cell lipid metabolism and the BC microenvironment are still in their infancy, existing findings suggest that abnormalities in lipid metabolism of T cells may play an important role in BC immune escape and tumor progression.

Current and future therapeutics by targeting lipid metabolism for BC treatment

Given the extensive insights into lipid metabolism within BC and the TME, targeting lipid metabolism emerges as a promising, multifaceted strategy. Targeting lipid dysmetabolism has the potential to impact both tumor cells and TME cells, ultimately improving the effectiveness of therapies. Remarkably, recent studies have shown that lipid-targeted agents can enhance anti-tumor efficacy when combined with chemotherapy and targeted therapy in BC. Furthermore, therapeutic medicines targeting lipid metabolism, in conjunction with immunotherapy, have shown encouraging outcomes in augmenting anti-tumor immunity. Here, we describe small-molecule compounds and other agents targeting lipid metabolism that might be employed or have been tested in clinical trials not only in BC but also in other tumor types (Fig. 5).

Targeting lipid uptake and transport

Tumor cells have an enhanced capacity for lipid absorption, facilitating their metabolic functions, energy generation, and lipid accumulation. Thus, the inhibition of lipid uptake has gained attention as a potential therapeutic strategy in oncology. Notably, targeting the fatty acid receptor CD36 has shown effectiveness against several cancer types in numerous preclinical investigations [282, 398–400]. However, the advancement of CD36-targeted inhibitors is currently in the preliminary phase. CD36-blocking antibodies, including FA6.152 and JC63.1,

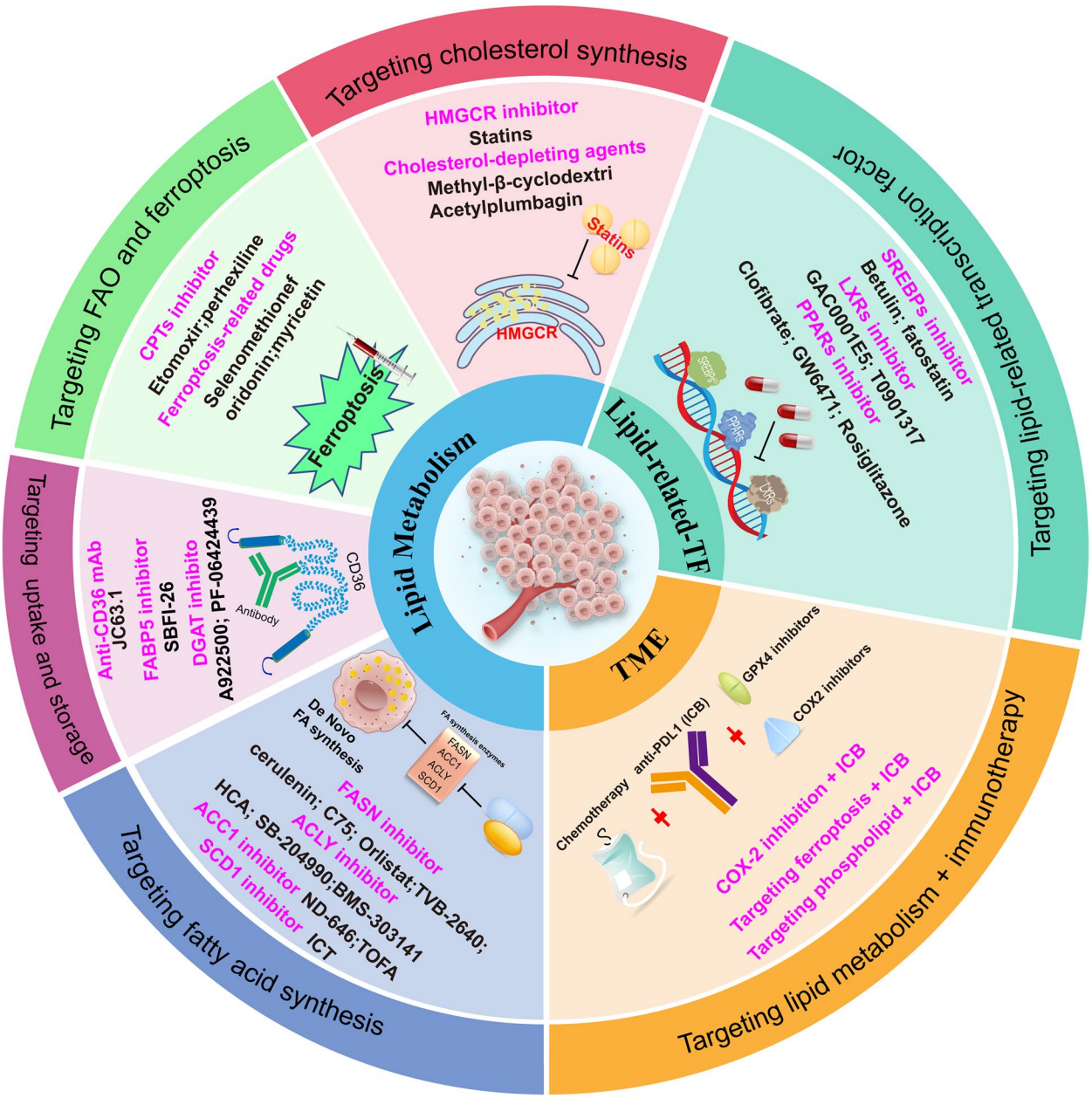

Fig. 5 Lipid-targeted therapy in BC. Lipid metabolism reprogramming not only promotes BC progression but also plays a crucial role in shaping the immunosuppressive microenvironment. Thus, targeting lipid dysmetabolism has the potential to impact both tumor cells and TME cells and enhance therapeutic efficacy. Inhibitors of lipid metabolism have shown promising antitumor efficacy combined with standard treatment in numerous preclinical studies. Overall, lipid-targeted therapy in BC includes targeting lipid metabolism process, targeting lipid-related transcription factors, and targeting TME. The potential therapeutic targets of lipid-targeted therapy include lipid uptake and storage (CD36, FABP5, DGATs), lipid synthesis (FASN, ACLY, SCD, ACC), FAO and ferroptosis (CPTs, ferroptosis inducers), lipid-related transcription factors (SREBPs, PPAR and LXRs) and TME regulators (COX2, GPX4 and phospholipase). Abbreviations: FAO, fatty acid oxidation; FA, fatty acid; TF, transcription factor; TME, tumor microenvironment; ICB, immune checkpoint blockade

have shown benefits in many preclinical murine models by significantly slowing tumor progression [399, 401]. JC63.1C, an anti-CD36 monoclonal antibody, has been shown to sensitize lapatinib-resistant xenograft tumors to HER2-targeted therapy, suggesting a new avenue for combined treatment approaches in BC [25]. Furthermore, CD36-targeting antibodies have demonstrated efficacy in various cancer models. For instance, JC63.1 has

been shown to decrease the stemness and malignancy of bladder cancer cells induced in vitro by oxLDL, as well as inhibit in vivo tumor growth promoted by a high-fat, high-cholesterol diet [402]. Antibody-mediated blockage of CD36 has been found to reduce the viability of pancreatic cancer cells, inhibit clonogenic survival in pancreatic cancer-derived organoids, and suppress de novo lipogenesis in human pancreatic cancer-derived organoids [400]. Nipin et al. demonstrated that the interaction of the small chemical nobiletin with CD36 in BC cells impedes tumor angiogenesis, metastasis, and sphere formation via regulating the CD36/STAT3/NF-κB signaling pathway [403]. In addition, several studies have highlighted CD36 as a potential immunotherapeutic target, with evidence suggesting that its blockade on CD8 + T cells can enhance ICB-based immunotherapy by impairing anti-tumor immune responses across multiple cell types [282, 404].

Similar to CD36-targeted inhibitors, targeting FABPs is currently limited to animal tumor models. BMS309403, initially identified as a drug for targeting FABP4, has been shown to effectively inhibit tumor growth and metastases in various mouse models by targeting both tumor and stromal cells [405, 406]. Inhibition of FABP5 using the small molecule SBFI-26 has demonstrated reduced proliferation and invasiveness of prostate cancer in vitro and in vivo by decreasing fatty acid uptake and PPARγ levels [407]. In BC, SBFI-26-mediated downregulation of FABP5 protein expression has been shown to increase the sensitivity of MCF-7/ADR cells to doxorubicin and reduce intracellular calcium, PPARγ, and autophagy levels [408]. In addition, SBFI-26 disrupts the equilibrium of the FAs pool by impeding the transport function of FABP5, resulting in lipid peroxidation and the initiation of ferroptosis in TNBC cells [409].Taken together, these observations indicate that targeting fatty acid uptake and transport represents a viable new strategy for mitigating tumor progression in BC therapy.

Targeting fatty acid synthesis

Targeting FASN

FASN, a key player in fatty acid metabolism in BC, was first examined as a prognostic indicator of recurrence in stage I breast cancer patients by Alo et al. in 1996 [410]. Since that initial study, research on the role of FASN in BC and its potential as a therapeutic target has steadily expanded. Over the past two decades, investigations into FASN's involvement in BC have deepened, leading to the development of an increasing number of FASN-targeted drugs, some of which have entered clinical trials. Cerulenin was the first chemical identified to block FASN function, demonstrating the capacity to suppress BC cell growth in vitro and cause apoptosis [411, 412]. Notably, treatment of BC cells with cerulenin restored epithelial traits, since FASN inhibition was shown to reverse EMT, hence diminishing invasiveness and metastasis [413]. Due to cerulenin's chemical instability, a semisynthetic compound called C75 was developed [414]. Studies have demonstrated that C75 inhibits FASN activity by directly blocking HER2 and FASN phosphorylation, showing significant antitumor effects in BC cells [107]. Another FASN inhibitor, orlistat, which has a structure similar to cerulenin, was synthesized and is primarily used to treat obesity. In HER2-overexpressing BC cells, orlistat was found to reduce cell proliferation and promote apoptosis [415]. Further research led to the development of TVB-2640, an oral FASN inhibitor, making it the first small-molecule FASN inhibitor to enter clinical trials [416]. Other compounds, such as TVB-3166 and TVB-3664, have been developed and are now undergoing examination. TVB-3166 specifically inhibits de novo fatty acid manufacture, disrupts lipid raft structures, and impedes membrane-associated molecules, finally triggering death in tumor cells [417]. Alpha-mangostin diminishes the viability of BC cells, causing apoptosis via the inhibition of FASN activity and the downregulation of its expression [418]. Additionally, the FASN inhibitor G28-UCM, either alone or with trastuzumab, markedly improved anticancer efficacy against trastuzumab-resistant HER2 + breast cancer [419]. FASN inhibitors can independently suppress de novo fatty acid synthesis, effectively inhibiting the growth of BC cells. Moreover, when combined with other drugs, FASN inhibitors create a synergistic effect that enhances overall anticancer efficacy. This combination not only boosts treatment effectiveness but also increases the sensitivity of chemotherapy or targeted therapy in BC cells [420, 421]. In summary, FASN inhibitors not only target the metabolic vulnerabilities of BC cells but also improve the overall effectiveness of existing therapies, paving the way for more effective treatment strategies in the clinic.

Targeting ACLY

ACLY is crucial for fatty acid synthesis, and its blockage disrupts both fatty acid synthesis and oxidation, resulting in energy depletion and eventually cell death [120]. Studies have demonstrated that ACLY inhibitors impede fatty acid elongation in the endoplasmic reticulum, thereby inhibiting tumor development associated with ACLY activity [422]. Hydroxycitric acid (HCA) was one of the first ACLY inhibitors discovered [423]. HCA, structurally analogous to citrate, has a much greater affinity for ACLY, functioning as a competitive inhibitor by binding to ACLY and diminishing its action [424]. In tamoxifen-resistant BC cells, treatment with HCA increased sensitivity to tamoxifen, which was directly attributed to ACLY inhibition. The combination of TAM/HCA

treatment led to reduced ACLY protein levels compared to tamoxifen alone [425]. Another ACLY inhibitor, bempedoic acid (BA), has gained attention for its ability to reduce fatty acid and sterol synthesis. In 2019, the Food and Drug Administration (FDA) authorized BA for the reduction of LDL cholesterol in individuals [426]. BA functions as a prodrug, activated in the liver to inhibit ACLY activity. In mouse models, it has been shown to significantly suppress glucose-dependent hepatic de novo fatty acid synthesis [427]. Inhibition of ACLY using BA in combination with palbociclib was reported to diminish cell viability and invasiveness in BC cells and a three-dimensional cell culture model [125]. Additionally, cucurbitacin B (CuB) and guggulsterone (Gug), two natural compounds, have also been identified as ACLY inhibitors. CuB suppresses ACLY phosphorylation and inhibits tumor growth in prostate cancer [428], while guggulsterone, a plant steroid, reduces angiogenesis in prostate cancer cells by inactivating the Akt signaling pathway and lowering phosphorylated ACLY levels [429]. While these inhibitors have shown effectiveness in prostate cancer, further study is necessary to explore their potential effects on BC. In summary, while the research on ACLY inhibitors in BC is still in its infancy, the initial findings are encouraging and suggest that these inhibitors could play a significant role in future therapeutic strategies against BC.

Targeting ACC and SCD

ACC is a key enzyme in lipid metabolism, catalyzing the conversion of acetyl-CoA to malonyl-CoA, a crucial step in fatty acid biosynthesis. Thus, inhibiting ACC is considered an effective strategy to block the lipid supply to tumor cells [430, 431]. ND-646, one of the most promising ACC inhibitors in preclinical research, has shown remarkable efficacy by inhibiting ACC1 and ACC2 activities, thereby reducing fatty acid synthesis and storage in tumor cells [432]. Additionally, the successful application of ND-646 in non-small cell lung cancer further highlights its potential therapeutic value in other cancer types [433]. Another commonly used ACC inhibitor is TOFA, which blocks fatty acid synthesis by inhibiting ACC activity. Although TOFA has primarily been utilized in preclinical research, it has been shown to significantly reduce fatty acid storage in BC cells and induce apoptosis [434–436]. Additionally, studies have demonstrated that TOFA, when combined with chemotherapy, can significantly enhance anti-cancer effects, particularly in tumor types with high metabolic activity [437]. In addition to monotherapy, the combination of ACC inhibitors with other anti-cancer agents has demonstrated synergistic effects. For example, when combined with PI3K/AKT pathway inhibitors, ACC inhibitors can significantly enhance tumor growth suppression [438]. Furthermore, studies suggest that combining ACC inhibitors with immune checkpoint inhibitors may improve anti-tumor immune responses, offering potential for future research [431]. Drugs such as ND-646 have demonstrated promising safety and efficacy in animal models, but further clinical studies are needed to validate their application in humans, particularly regarding potential side effects and the safety of long-term use. For instance, some studies have indicated that long-term use of ACC inhibitors may lead to metabolic disorders or hepatotoxicity, highlighting the need for additional research to mitigate these risks [439].

Several small-molecule inhibitors targeting SCD1, such as T-3764518, CAY-10566, and MF-438, have been developed and shown significant antitumor effects. However, in vivo investigations of these inhibitors have shown significant harmful side effects, hindering their advancement to clinical trials [150]. Icaritin (ICT), an isopentenyl flavonoid extracted from the traditional Chinese medicinal Epimedium, has shown anticancer effects [440]. Research indicates that ICT induces cell cycle arrest and apoptosis in BC cells through sustained activation of the ERK pathway [441]. Building on this, Chen Yang et al. developed a new ICT derivative, IC2, specifically targeting SCD1 and inducing apoptosis in BC cells by inhibiting SCD activity [440]. Given the critical role of SCD in promoting cancer cell metastasis, brain-penetrant SCD inhibitors have been developed to specifically target SCD1 in metastatic brain tumor cells. These inhibitors can induce lipotoxicity in tumor cells, impair DNA damage repair, and simultaneously enhance the antitumor response within TME [442]. Although ACC and SCD inhibitors have shown significant potential in preclinical studies for cancer, their application in BC remains at an early stage. As research continues to evolve, the integration of ACC or SCD inhibitors into the therapeutic landscape for BC may become more feasible.

Targeting FAO

FAO is a crucial mechanism of energy metabolism in cancer cells, and several studies indicate that the suppression of FAO may significantly impede the proliferation and expansion of tumor cells [443]. Etomoxir, a commonly used inhibitor of CPT in preclinical research, has shown considerable effectiveness in blocking mitochondrial FAO [444]. Likewise, several in vitro preclinical studies have shown possible therapeutic use of etomoxir in BC therapy [445, 446]. In vivo studies have further shown that etomoxir effectively suppresses the growth of estrogen receptor-positive (ER+) BC cells and tumors, thereby restoring sensitivity to tamoxifen in tamoxifen-resistant ER+ cells [283, 284]. Furthermore, the combination of

endocrine therapy with the FAO inhibitor etomoxir has been shown to synergistically inhibit the growth of both primary and endocrine-resistant BC cells [281]. Notwithstanding encouraging outcomes, human clinical studies were halted owing to the elevated incidence of hepatotoxicity in the therapy of congestive heart failure [447]. Another CPT1 inhibitor, perhexiline, has received approval from the FDA and foreign regulatory agencies for the treatment of severe angina pectoris [448]. Preclinical investigations of pancreatic cancer indicate that the combination of perhexiline and chemotherapy may have potential clinical applicability [449]. Ren et al. revealed that perhexiline effectively ablated HER3 through the promotion of HER3 internalization and degradation, presenting a potential treatment approach to improve survival rates in BC patients [281]. Nonetheless, clinical trials investigating the efficacy of CPT inhibitors in antitumor treatment have not yet been undertaken. Metformin, at therapeutic doses, has shown a reduction in FAO in an in vitro model of BC cells, resulting in elevated intracellular triglyceride levels, independent of AMPK activation [450, 451]. This suggests that metformin, at clinically relevant doses, may specifically target FAO in cancer cells, with potential implications for patient stratification and combination therapy approaches. Furthermore, experimental data indicated that GPCR-mediated signaling was closely related to tumor FAO. Specifically targeting GRP78 inhibits mitochondrial beta-oxidation through CPT1A inhibition in BC cells. Metabolic analysis indicates that silencing GRP78 leads to increased intracellular concentrations of linoleic acid, which in turn promotes macrophage infiltration and impacts innate immunity [452]. Targeting GPR81 and FAO offers a potential treatment strategy, since the GPR81 agonist and CPT1 inhibitor etomoxir substantially reduce ER + BC cell and tumor proliferation in vivo, restoring sensitivity to tamoxifen in tamoxifen-resistant ER + cells [283]. Additionally, several natural compounds (e.g., bergamot, eugenol) have also been shown to inhibit FAO in vitro and in vivo to prevent BC progression [453, 454]. In conclusion, FAO inhibitors show good anti-tumor potential in pre-clinical studies of BC, and future studies will further promote their clinical application.

Targeting ferroptosis

Lipids are essential in the regulation of ferroptosis, and a comprehensive understanding of their mechanisms can offer valuable insights for developing therapeutic approaches for diseases associated with ferroptosis. [455]. Indeed, ferroptosis offers potential therapeutic use in breast cancer therapy because of its distinctive inhibitory impact on tumor proliferation [456, 457]. Furthermore, the successful targeting of ferroptosis inhibitors such as GPX4 or ACSL4 using nanoparticle agents or nanoparticles has demonstrated effective inhibition of TNBC tumor growth in mouse models with minimal adverse effects [458, 459]. Firstly, ferroptosis has been shown to have synergistic effects with targeted therapies in BC treatment. Resistance to poly (ADP-ribose) polymerase inhibitors (PARPi) restricts the therapeutic efficacy of PARP inhibition in treating BRCA1-deficient malignancies [460]. Lei et al. revealed that xenograft tumors derived from BRCA1-mutant BC patients exhibiting PARPi resistance had diminished GPX4 expression and increased susceptibility to concurrent inhibition of PARP and GPX4. Their study demonstrated that BRCA1 deficiency resulted in increased vulnerability to ferroptosis when PARP and GPX4 were co-inhibited, indicating a possible treatment strategy to address PARPi resistance in BRCA1-deficient malignancies [461]. Ma et al. conducted a study illustrating the synergistic anticancer impact of siramesine and lapatinib via the ferroptosis pathway in BC. Mechanistically, lapatinib alone or in conjunction with siramesine upregulated transferrin expression, promoting iron influx into cells, augmenting cellular iron levels, and stimulating iron-dependent Lip-ROS generation [462]. Zhu et al. demonstrated that inhibition of BRD4 resulted in increased cell-cycle arrest and elevated levels of GPX4. Consequently, the co-targeting of CDK4/6 inhibitors and BRD4 also enhanced senescence and vulnerability to ferroptosis in pancreatic and BC cells [463]. A recent study indicated that depletion or inhibition of GPX4 enhances sensitivity to palbociclib and giredestrant in ER + and potentially TNBC, indicating a strategy to improve the efficacy of CDK4/6 and ER inhibition [464].

Second, ferroptosis-related drugs are expected to minimize the toxic side effects of BC treatments. Selenomethionine, a glutathione GPX4 activator, exhibited antitumor effects in BC models treated with doxorubicin, concurrently offering cardiac protection without detectable toxicities in the same animal subjects. Therefore, the pharmacological activation of GPX4 offers a potential strategy to reduce the cardiotoxic effects linked to doxorubicin [465]. Iron-dependent ferroptosis is involved in the pathogenesis of herceptin-induced cardiomyopathy, indicating that targeting ferroptosis may provide cardioprotective benefits in in vitro models against Herceptin-induced toxicity [466]. Additionally, the co-administration of ER or AR antagonists with ferroptosis inducers demonstrated a notable inhibitory effect on the proliferation of ER-positive breast cancer and AR-positive prostate cancer, particularly in cases of resistance to singular hormonal treatments [467]. Interestingly, various natural extracts (e.g., boswellia carterii, myricetin, oridonin, Sculponeatin A) have also exhibited the ability

to induce ferroptosis via the GPX4 pathway in preclinical models of BC, thereby enhancing the effectiveness of chemotherapy in treating this disease [319, 468–472]. Put together, targeting ferroptosis demonstrates potential as a strategy to improve treatment efficacy and overcome the challenges posed by BC.

Targeting cholesterol synthesis and lipid Storage

Cholesterol accumulation in cancer cells is intricately linked to the signaling pathways involved in tumor progression, suggesting that cholesterol reduction may serve as a viable therapeutic target for BC treatment. Current targeting cholesterol synthesis research, both in clinical and preclinical trials, is primarily focused on two approaches: inhibiting intracellular cholesterol synthesis and depleting excess cholesterol from cancer cells. Statins, which inhibit the rate-limiting enzyme HMGCR, are the most extensively studied drugs for reducing cholesterol synthesis [473]. Previous experimental and epidemiological data indicated that statins might inhibit tumor progression and decrease the incidence of BC [474]. Studies indicated that BC patients utilizing statins experienced a 30–60% decrease in recurrence rates, with the extent of risk reduction associated with the duration of statin use [475–477]. Several FDA-approved statins, such as simvastatin, were reported to promote PTEN transcription through the modulation of NF-κB activity, consequently suppressing the proliferation of BC cells [478]. Lovastatin inhibited tumor growth and metastasis in mouse models of BC by enhancing apoptosis and decreasing DNA synthesis [479]. Additionally, many studies have explored combination therapies to enhance the efficacy of statins. Studies indicated that lovastatin markedly improved the inhibitory effects of HER2 kinase inhibitors, including lapatinib and neratinib [480]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein that plays a role in the degradation of LDLR, leading to elevated plasma cholesterol levels [481]. Statins have been shown to increase PCSK9 expression, and the combination of statins with PCSK9 inhibitors may lead to a greater reduction in plasma cholesterol levels [482]. Furthermore, statin-induced depletion of intracellular cholesterol can activate the processing of the inactive precursor of SREBP-2 into its active nuclear form, leading to the transcription of MVA pathway genes, such as HMGCR and upstream enzymes like HMGCS1 [483]. Thus, inhibiting SREBP-2 through RNA interference or employing agents like dipyridamole to obstruct SREBP-2 processing can markedly improve the therapeutic efficacy of statins [484].

Elevated cholesterol levels in tumor cells have prompted the development of therapeutic strategies focused on decreasing intracellular cholesterol as a treatment for cancer. Cholesterol-depleting agents, such as acetylplumbagin (AP) and methyl-β-cyclodextrin (MβCD), have been shown to induce cancer cell death [485]. By depleting cholesterol, these agents reduce the cholesterol content in lipid rafts and disrupt the structural integrity of lipid rafts [486]. Additionally, decreased membrane cholesterol enhances membrane permeability, thereby affecting drug uptake. In tamoxifen-resistant BC, MβCD improves tamoxifen efficacy by facilitating increased cellular uptake [487]. Studies have shown that tamoxifen-resistant BC cells exhibit increased levels of cholesterol-enriched lipid rafts in comparison to tamoxifen-sensitive cells, as well as heightened expression of growth factor signaling mediators [488]. Thus, targeting cholesterol-enriched lipid rafts presents a promising therapeutic strategy for the treatment of tamoxifen-resistant BC. As for targeting lipid storage in BC, PF-06424439, a selective DGAT2 inhibitor, coupled with X-ray exposure, might potentiate BC cell radiosensitivity and potentially improve the radiotherapy effectiveness [340]. A922500, a selective DGAT1 inhibitor, coupled to ACLY inhibition, partly ameliorated 4-hydroxytamoxifen-induced cell death in BC cells [489]. However, to date, no inhibitors designed to target DGAT have been tested in clinical trials in cancer patients. The potential of drugs and targets associated with lipid metabolic processes are summarized in Table 2.

Targeting transcriptional regulators of lipid metabolism

SREBP, a transcription factor that regulates FAs, cholesterol, and phospholipid metabolism genes, has three isoforms (SREBP-1a, SREBP-1c, and SREBP-2) produced from two genes (SREBF1 and SREBF2) in mammals [490]. These isoforms exhibit overlapping transcriptional programs for the biosynthesis of FAs and cholesterol [491]. In BC, the PI3K-AKT-mTOR pathway dominantly regulates SREBP expression and activity. The inhibition of SREBP1 was reported to increase the susceptibility of cancer cells with PI3K pathway mutations to ferroptosis [157, 492]. Betulin, an SREBP1 inhibitor, might treat metabolic problems and improve the anti-tumor effects of Sorafenib in hepatocellular carcinoma [493, 494]. The inhibition of SREBP-2 by fatostatin, a selective SCAP inhibitor that obstructs SREBP activation, led to a reduction in breast cancer-induced osteolysis and tumor proliferation in vivo [230, 495]. Furthermore, the addition of Fatostatin demonstrates enhanced inhibition of proliferation in ER-positive BC cells in comparison to tamoxifen monotherapy, suggesting a synergistic effect of Fatostatin in combination with tamoxifen [496, 497]. Liver X receptors (LXRs) are nuclear receptor transcription factors that regulate genes related to lipid and cholesterol

Table 2 The treatment drugs and targets related to lipid metabolism in breast cancer

Treatment	Mechanism	Effects on BC	Combined treatment	Study Progress/ Status	References
FA6.152 (anti-CD36)	Blocks CD36	Suppress tumor lipid uptake and progression	N/A	Preclinical	[399, 401]
JC63.1C (anti-CD36)	Targets CD36	Sensitize HER2-positive BC therapy	Lapatinib	Preclinical	[24, 25, 399–402]
Nobiletin	Regulates CD36/STAT3/ NF-κB pathway	Inhibit tumor angiogenesis and metastasis	N/A	Preclinical	[403]
BMS309403	Targets FABP4	Inhibit tumor growth and metastasis	N/A	Preclinical	[405, 406]
SBFI-26	Targets FABP5	Induce lipid peroxidation and ferroptosis in TNBC	Doxorubicin	Preclinical	[407–409]
Cerulenin	Inhibits FASN	Reverse EMT and induce apoptosis	N/A	Preclinical	[411–413]
C75	Blocks HER2 and FASN phosphorylation	Activate immunity, induce apoptosis	PI3Kα inhibitor (CYH33)	Preclinical	[107, 402, 414]
Orlistat	Inhibits FASN	Inhibit proliferation, promotes apoptosis in HER2 + BC	N/A	Phase II	[415]
TVB-2640	Oral FASN inhibitor	Induce apoptosis	Chemotherapy and immunotherapy	Phase II	[416]
TVB-3166	Inhibits FASN	Disrupt lipid rafts and induce apoptosis	PI3K inhibitor	Preclinical	[417]
α- mangostin	Downregulates PI3K-AKT signaling and reduces FASN activity	Induce apoptosis	N/A	Preclinical	[111, 418]
G28-UCM	Inhibits FASN	Enhance efficacy in HER2 + and trastuzumab-resistant BC	Trastuzumab	Preclinical	[419]
Psoralen	Inhibits FASN	Reverse EMT and induce apoptosis	N/A	Preclinical	[101]
Clofibrate	Activates PPARα and inhibits FASN	Reduce FASN activity	N/A	Preclinical	[116]
HCA	Competitively inhibits ACLY	Increase tamoxifen sensitivity in resistant BC	tamoxifen	Preclinical	[424, 425]
BA (FDA approved for LDL cholesterol reduction)	Inhibits ACLY	Reduce tumor invasiveness	palbociclib	Preclinical	[125, 426, 427]
CuB	Suppresses ACLY phosphorylation	Inhibit tumor growth in PC	N/A	Preclinical	[428]
Gug	Blocks Akt pathway and reduce phosphorylated ACLY	Reduce angiogenesis in PC	N/A	Preclinical	[429]
ND-646	Inhibits ACC1/ACC2	Reduce tumor lipid supply	PI3K/AKT inhibitor ICIs	Preclinical	[431–433]
TOFA	Inhibits ACC	Reduce FA storage and induce apoptosis	Chemotherapy	Preclinical	[434–437]
Icaritin (ICT)	Activates the ERK pathway	Induce cell cycle arrest and apoptosis	N/A	Preclinical	[440, 441]
IC2	Targets SCD1	Induce apoptosis	N/A	Preclinical	[440]
Etomoxir	Inhibits CPT1A/B	Block FAO and enhance drug sensitivity in ER + BC	Tamoxifen (Endocrine therapy)	On hold	[281, 283, 284, 444–447]
Perhexiline	Inhibits CPT1	N/A	Chemotherapy	Preclinical	[281, 448, 449]
Metformin	Reduces FAO	Induce apoptosis	N/A	Preclinical	[450, 451]
Erastin RSL3 SAS	Induces ferroptosis	Increase ROS in TNBC	Adriamycin Salinomycin	Preclinical	[312–318]

Table 2 (continued)

Treatment	Mechanism	Effects on BC	Combined treatment	Study Progress/ Status	References
Siramesine Lapatinib	Induces ferritin deposition	Induce apoptosis	CDK4/6 inhibitors	Preclinical	[462, 464]
Salinomycin	Induces ferroptosis	Eliminate BCSC	N/A	Preclinical	[317, 318]
Selenomethione	Activates GPX4	Reduce doxorubicin cardiotoxicity, anti-tumor in BC	DOX	Preclinical	[465]
PF-06424439	Inhibitors DGAT2	Increase BC sensitivity to radiotherapy	Radiotherapy	Preclinical	[340]
A922500	Inhibitors DGAT1	Induce apoptosis	ACLY inhibitors	Preclinical	[489]
Statins (e.g. simvastatin, lovastatin)	Inhibits HMGCR	Reduce cholesterol, inhibits growth signaling	PCSK9 inhibitors, PTX, HER2 kinase inhibitors (e.g. lapatinib, neraparib)	Phase I	[473–484, 520]
MβCD	Consumes cholesterol	Enhance tamoxifen uptake in resistant BC	Tamoxifen	Preclinical	[487]
AP	Consumes cholesterol	Disrupt lipid rafts, induce cancer cell death	N/A	Preclinical	[485]

Abbreviations: *BC* Breast Cancer, *TNBC* Triple-negative Breast Cancer, *EMT* Epithelial-Mesenchymal Transition, *FASN* Fatty Acid Synthase Complex, *PPARα* Peroxisome Proliferator-Activated Receptor α, *CuB* Cucurbitacin B, *Gug* guggulsterone, *ACLY* ATP-citrate Lyase, *PC* prostate cancer, *ACC1* Acetyl-CoA Carboxylase 1, *ACC2* Acetyl-CoA Carboxylase 2, *ICIs* Immune Checkpoint Inhibitors, *FA* Fatty Acids, *SCD1* Stearoyl-CoA Desaturase 1, *FAO* Fatty acid oxidation, *BCSC* Breast Cancer Stem cells, *DOX* Doxorubicin, *HMGCR* 3-Hydroxy-3-Methylglutaryl-CoA Reductase, *PCSK9* Proprotein Convertase Subtilisin/Kexin type 9, *PTX* Paclitaxel, *MβCD* Methyl-β-cyclodextrin, *AP* Acetylplumbagin, *DOX* Doxorubicin, *CPT1A/B* Carnitine Palmitoyltransferase 1A/B, *FABP4* Fatty Acid Binding Protein 4, *FABP5* Fatty Acid Binding Proteins 5, *LDL* Low-density Lipoprotein, *GPX4* Glutathione Peroxidase 4, *DGAT2* Diacylglycerol O-acyltransferase 2, *DGAT1* Diacylglycerol O-acyltransferase 1

metabolism [498]. The compound GAC0001E5, an LXR inverse agonist, disrupts glutaminolysis, resulting in increased oxidative stress and reduced HER2 expression. This indicates a possible therapeutic approach for addressing HER2 overexpression and related metabolic alterations in HER2-positive BC [499, 500]. Additionally, the LXR agonist T0901317 has demonstrated inhibitory effects on proliferation and metastasis in a mouse model of butylated hydroxytoluene-induced BC [501]. Vitamin D3 and T0901317 effectively reduced cholesterol levels and promoted apoptosis in a preclinical model, suggesting their combined use may significantly mitigate the progression of estrogen receptor-positive BC [502].

PPARs are nuclear transcription factors in the steroid hormone receptor family that act as biosensors for lipid metabolism changes [503]. Fenofibrate and clofibrate, as PPARα agonists, have been widely utilized in research and clinical settings. Clofibrate has been shown to inhibit the activation of NF-κB and ERK1/2, leading to apoptosis and ultimately impeding the proliferation of BC cells [116]. Fenofibrate has also demonstrated cytotoxic effects on BC cells in vivo and in vitro, with a favorable safety profile and tolerable side effects [504, 505]. Furthermore, the PPARα antagonist GW6471 was found to reduce cell proliferation and spheroid formation in BC stem cells, leading to metabolic dysfunction and apoptosis [506]. Notably, the clinical drug rosiglitazone, a specific agonist of PPARγ, is currently available on the market as an insulin sensitizer for the management of diabetes [507]. A preliminary investigation showed that short-term administration of rosiglitazone does not significantly affect tumor cell proliferation, indicating limited efficacy for treating BC as a standalone therapy [508]. Conversely, the combination of doxorubicin or cisplatin with rosiglitazone demonstrated a significant enhancement in therapeutic effectiveness against cancer cells [509, 510]. Pioglitazone, a PPARγ agonist, was found to augment the efficacy of cisplatin viability when compared to chemotherapy alone [511, 512]. In addition, other PPAR agonists or inhibitors (e.g., GW501516, GW0742, GW9662) have also demonstrated antitumor effects in preclinical BC models [398, 513, 514]. However, to date, clinical trials involving targeting PPARs have not yet been conducted in cancer patients. In conclusion, although drug development targeting transcription factors for lipid metabolism is progressing, more research and validation are needed to achieve its clinical application in BC. Table 3 summarizes the regulatory effects of lipid-related transcription factors in BC and their small molecule inhibitors.

Targeting lipid metabolism combined with immunotherapy

The progress of immunotherapy in the treatment of BC has shown significant expansion during the last two

Table 3 Transcriptional regulation of lipid metabolism in breast cancer

Transcription factors	Target genes	The role in Lipid metabolism	Signaling pathways	Inhibitor/Activator	References
SREBP-1	FASN SCD1 ACC ACLY	Promotes fatty acid synthesis and storage	PI3K-AKT-mTOR, pRb, Myc, MAPK	Inhibitor: Betulin	[112, 113, 126, 157, 170, 492–494]
SREBP-2	HMGCR SQLE	Regulates cholesterol synthesis and lipid storage	PI3K-AKT-mTOR	Inhibitor: Fatostatin, Tamoxifen, Dipyridamole	[169, 230, 232, 483, 484, 494, 496, 497]
LXR	ABCA1 SREBP-1	Regulates cholesterol metabolism and fatty acid synthesis	PI3K-AKT	Activator: T0901317, GAC0001E5	[169, 171, 397, 499–501]
MYC	CPT1A	Promotes FAO and energy metabolism	JAK/STAT3 MAPK	Inhibitor: Etomoxir	[277, 278]
PPARα	FASN SCD1	Promotes FAO and reduces lipid storage	MAPK NF-κB ERK1/2	Activator: Fenofibrate, Clofibrate Inhibitor: GW6471	[116, 506, 507]
PPARγ	FASN ATGL	Regulates fatty acid synthesis and catabolism	MAPK NF-κB	Activator: Rosiglitazone, Pioglitazone	[507, 508, 511, 512]

Abbreviations: *SREBP-1* Sterol Regulatory Element-binding Proteins 1, *SREBP-2* Sterol Regulatory Element-binding Proteins 2, *LXR* liver X receptor, *MYC* Myelocytomatosis Viral Oncogene Homolog, *PPARα* Peroxisome Proliferator-Activated Receptors α, *PPARγ* Peroxisome Proliferator-Activated Receptors γ, *FASN* Fatty Acid Synthase, *SCD1* Stearoyl-CoA Desaturase 1, *ACC* Acetyl-CoA Carboxylase, *ACLY* ATP-citrate Lyase, *HMGCR* 3-Hydroxy-3-Methylglutaryl-CoA Reductase, *SQLE* Squalene monooxygenase, *ABCA1* ATP-binding Cassette Sub-family A member 1, *CPT1A* Carnitine Palmitoyltransferase 1A, *ATGL* Adipose Triglyceride Lipase, *FAO* Fatty acid oxidation

decades. The explosion of clinical studies using antibody–drug conjugates (ADCs) and immune checkpoint inhibitors (ICIs) has greatly improved outcomes for many BC patients [515] However, observations from clinical settings underscore the pivotal influence of TIME composition on the efficacy of immunotherapy [516]. Lipid metabolic reprogramming has the potential to influence the activation or suppression of diverse immune cell functional states, thereby contributing to the progression of BC [517]. This concept offers a theoretical foundation for modifying the tumor microenvironment via the targeting of lipid metabolism. Therefore, combination with metabolism-regulating agents and immunotherapy is probably an attractive treatment modality for BC. Lipid synthesis plays a critical role in tumor-associated immune cells, making it a potential target for combination immunotherapy. SREBP activity was significantly elevated in tumor-regulating T lymphocytes of human breast carcinomas. Furthermore, the deletion of the SREBP cleavage activator protein resulted in the inhibition of tumor growth and improved the therapeutic response to PD-L1 inhibitors [518]. Additionally, the combination of the PI3Kα inhibitor CYH33 and the FASN inhibitor C75 was shown to boost immunological activation and enhance anti-tumor immunity, suggesting a potential strategy for simultaneous targeting of PI3K and FASN in BC treatment [402]. Bell et al. illustrated that the presence of prostaglandin E2 (PGE2) derived from dying cancer cells hinders the T cell-mediated immune response. Therefore, the incorporation of pharmacological COX-2 inhibition in conjunction with immunotherapy and cytotoxic therapy has the potential to enhance the effectiveness of the combination of chemotherapy and PD-1 blockade [519]. Cholesterol synthesis inhibitor statins play a role in facilitating the transition from cold to hot tumors. The combination of lovastatin and paclitaxel boosts CD8 + T-cell activity, improving their tumor-killing efficacy and resulting in more favorable prognostic outcomes for BC patients [520].

Targeting ferroptosis and phospholipid metabolism also represents a promising approach to improving immunotherapy treatment outcomes in BC. The LAR subtype of TNBC exhibits increased susceptibility to ferroptosis inducers, specifically GPX4 inhibitors. Notably, the combination of GPX4 inhibitors with immune checkpoint blockade shows promising preclinical effectiveness [309]. Inhibition of group IVA phospholipase A2 was reported to modify effector T cell lipid metabolism, mitigate T cell senescence in vitro, and enhance antitumor immunity and immunotherapy efficacy in murine models of melanoma and BC [276, 521]. Furthermore, neutral sphingomyelinase 2 (nSMase2) catalyzes the hydrolysis of sphingomyelin to produce ceramide, an anti-oncometabolite. Enhanced expression of wild-type nSMase2 has been shown to improve the efficacy of anti-PD-1 treatment in murine models of melanoma and BC, corresponding with an elevated Th1 immune response [522]. These preclinical findings indicate that combining lipid metabolism with immunotherapy strategies may provide new therapeutic options for BC patients. With insights

into the role of lipid metabolism in the TME, future studies may develop more effective combination treatment regimens to improve the therapeutic efficacy of BC.

Conclusions and perspectives

Research conducted over the past two decades has unequivocally identified altered lipid metabolism as a significant metabolic phenotype of cancer cells. Due to the specific characteristics of the tumor microenvironment, particularly the infiltration of adipocytes surrounding BC, an increasing number of studies have recognized the role of lipid metabolism on tumor growth and TME. Metabolic heterogeneity represents a key characteristic of BC, reflecting the significant energy demands, membrane compositions, and signaling molecules necessary for tumor cell proliferation. Current studies indicated that distinct lipid metabolism pathways are present across various BC subtypes, marked by enhanced lipid uptake, lipid synthesis, fatty acid oxidation, and lipid storage, facilitating tumor cell survival under hypoxic and nutrient-deprived conditions. Lipid metabolic reprogramming plays multifaceted roles in remodeling the BC microenvironment, influencing both lipid metabolism and the functional phenotypes of TME cells. Lipid metabolic reprogramming in adipocytes, CAFs, TAMs, T cell subsets, and other myeloid lineage immune cells plays a critical role in shaping the BC TME. Therefore, precise regulation of lipid metabolism and a comprehensive understanding of the plasticity within the BC microenvironment have considerable promise for the development of targeted therapeutic strategies against this disease.

Lipid metabolism can be conceptualized as an intricate network of pathways characterized by plasticity, feedback loops, and crosstalk, which collectively ensure the fitness and survival of tumor cells [523]. Consequently, it is somewhat unexpected that few targeted compounds directed at this pathway have progressed to clinical trials in BC. One plausible explanation for this limited progress is the challenge of selectively inhibiting lipid metabolism in cancer cells without inducing significant systemic effects [524]. Another limitation arises from the metabolic flexibility of cancer cells, which may swiftly transition from de novo synthesis to lipid uptake in the presence of inhibitory compounds [525]. Furthermore, many lipids metabolic enzymes have various isoforms, each potentially associated with distinct lipid metabolic pathways and exhibiting varied cellular localizations or tissue distributions. Given the limited efficacy of certain metabolic drugs, it is evident that the integration of therapies, including targeted inhibitors, standard-of-care treatments, and dietary interventions, may effectively enhance existing strategies for BC treatment.

A multifaceted and dynamic network of interactions exists between BC cells and the non-cancerous constituents of the TME. Each component of the TME possesses the capacity to influence cancer immunity. Presently, the majority of lipid-related research focuses on CAFs, CAAs, and the metabolic interactions between immune cells and tumor cells. Nevertheless, the metabolic susceptibilities of non-cancerous cells within the TME warrant significant attention. Secondly, the TME undergoes substantial alterations during tumor progression and in response to therapeutic interventions [516]. Consequently, it is imperative to meticulously monitor these changes within the TME and adjust treatment strategies in a timely manner. To effectively observe the dynamic processes of lipid metabolites associated with TME modifications, it is essential to expand the detection scope of lipid-related proteins and small molecules, as well as to enhance the precision of detection at both the single-cell and spatial levels. Current single-cell and spatial detection technologies serve as potent methodologies for elucidating the metabolic vulnerabilities of cancer within the BC microenvironment [526, 527]. Future research should focus on tracking tumor cells dynamic metabolic adaptations and translating those findings into clinical practice.

The plasticity of lipid metabolism warrants significant attention. Increasing evidence suggests that distinct histological types of BC and individual patients exhibit unique metabolic profiles [305, 528, 529]. Future research should focus on identifying lipid metabolic molecules that are predominant during specific developmental stages of various BC subtypes, which holds promise for uncovering potential diagnostic and therapeutic targets. The findings suggest that a single metabolic drug may demonstrate efficacy exclusively within a specific subgroup of tumor cells. Therefore, rather than implementing a uniform metabolic treatment for all cancer patients, it is advisable to adopt personalized metabolic therapy. Further research is warranted to elucidate the contextual roles of specific lipids in each subtype of BC. Additionally, the adaptability of lipid metabolism during tumor progression and treatment presents a significant challenge that must be addressed. Tumor cells exhibit metabolic flexibility and plasticity to circumvent metabolic constraints during tumor progression. Similarly, these cells demonstrate metabolic adaptability and reprogram metabolic networks to acquire more malignant phenotypic characteristics. To effectively counteract metabolic adaptation, it is imperative to dynamically monitor metabolic alterations and adjust metabolic treatment strategies in a timely manner.

Given the temporal and spatial metabolic heterogeneity of BC, personalized lipid metabolic therapy represents a promising future direction. Consequently, the efficacy of

such therapies may depend on a comprehensive understanding of the specific lipid metabolic abnormalities associated with particular BC subtypes. Initially, it is crucial to implement subtype-specific metabolic therapies tailored to the distinct lipid metabolic profiles of various BC tumors. Furthermore, lipid metabolic therapy must be dynamically adjusted in response to metabolic adaptations occurring at different stages of BC progression and treatment. In the future, pharmacological agents targeting lipid metabolism may be integrated with conventional therapies or immunotherapies for the treatment of BC. We are inclined to believe that the incorporation of tumor genomic testing with the classification of FAs, the TME, and patients' dietary modifications will facilitate the development of more comprehensive precision medicine strategies for BC treatment.

Abbreviations

BC	Breast Cancer
TNBC	Triple-negative Breast Cancer
HR +	Hormone Receptor-positive
HER2 (ErbB2)	Human Epidermal Growth Factor Receptor
ATP	Adenosine Triphosphate
ICB	Immune Checkpoint Blockade
TME	Tumor Microenvironment
FAs	Fatty Acids
FATPs	Fatty Acid Transport Proteins
FABPs	Fatty Acid Binding Proteins
CD36	Cluster of Differentiation 36
COX-2	Cyclooxygenase-2
EGFR	Epidermal Growth Factor Receptor
IL-6	Interleukin-6
LDLR	Low-density Lipoprotein Receptor
LDL	Low-density Lipoprotein
ABC	ATP-binding Cassette
FASN	Fatty Acid Synthase Complex
ACLY	ATP-citrate Lyase
ACC	Acetyl-CoA Carboxylase
SCD	Stearoyl-CoA Desaturase
ACP	Acyl Carrier Protein
MUFAs	Monounsaturated Fatty Acids
PUFAs	Polyunsaturated Fatty Acids
SFAs	Saturated Fatty Acids
FFAs	Free fatty Acids
DHA	Docosahexaenoic Acid
EPA	Eicosapentaenoic Acid
ALA	Alpha-linolenic Acid
OS	Overall Survival
RFS	Recurrence-free Survival
DMFS	Distant Metastasis-free Survival
EMT	Epithelial-Mesenchymal Transition
ER	Estrogen Receptor
SREBP-1	Sterol Regulatory Element-binding Proteins 1
SREBP-2	Sterol Regulatory Element-binding Proteins 2
PPARs	Peroxisome Proliferator-Activated Receptors
PR	Progesterone Receptor
CPTs	Carnitine Palmitoyltransferases
HDL	High-density Lipoprotein
ER	Endoplasmic Reticulum
HMG-CoA	3-Hydroxy-3-methylglutaryl-CoA
HMGCR	3-Hydroxy-3-Methylglutaryl-CoA Reductase
MVA	Mevalonate Pathway
SQLE	Squalene monooxygenase (squalene epoxidase)
VLDL	Very-Low-Density Lipoprotein
SR-BI	Scavenger Receptor Class B Type I
HDL-C	High-Density Lipoprotein Cholesterol
SMO	Smoothened
SHH	Sonic Hedgehog Signaling Pathway
ERRα	Estrogen-related Receptor Alpha
PGC-1	Proliferator-activated receptor gamma coactivator 1
FAO	Fatty acid oxidation
TCA	Tricarboxylic Acid
ACSL	Acyl-CoA Synthetase Long-Chain
DFS	Disease-Free Survival
PFS	Progression-Free Survival
DSS	Disease-Specific Survival
BLBC	Basal-Like Breast Cancer
LAR	Luminal Androgen Receptor
IFNG	Interferon gamma
ROS	Reactive Oxygen Species
BCSCs	Breast Cancer Stem cells
DOX	Doxorubicin
LDs	Lipid droplets
CSCs	Cancer stem cells
CAFs	Cancer-associated fibroblasts
OGP	Osteogenic growth peptide
CAAs	Cancer-associated adipocytes
TAGs	Triacylglycerols
TAMs	Tumor-Associated Macrophages
DCs	Dendritic cells
NK	Natural killer
IFN-γ	Interferon-gamma
MDSCs	Myeloid-derived suppressor cells
PGE2	Prostaglandin E2
PMNs	Polymorphonuclear leukocytes
27HC	27-Hydroxycholesterol
LXR	Liver X receptor
FDA	Food and Drug Administration
HCA	Hydroxycitric acid
BA	Bempedoic acid
BRCA1	Breast Cancer 1
AR	Androgen Receptor
SCAP	SREBP Cleavage Activating Protein
ADCs	Antibody-drug Conjugates
PGE2	Prostaglandin E2
ox-LDL	Oxidized low-density lipoprotein
ROS	Reactive Oxygen Species
OLR1	Low-Density Lipoprotein Receptor 1
LOX-1	Lectin-like Oxidized Low-Density Lipoprotein Receptor 1
TNFα	Tumor Necrosis Factor-alpha

Authors' Contributions

Jinguo Zhang, Xinghua Han and Yueyin Pan were involved in design of the work and the figures. Mengting Wan, Shuaikang Pan and Benjie Shan performed the literature search and wrote the draft. Hongwei Jin, Wei Wang, Haizhou Diao and Ziqi Wang prepared the figures and provided the critical revisions. Zihan Zheng, Shuya Han, Wan Liu and Jiaying He provided the critical revisions and contributed to editing the manuscript. All authors were involved in manuscript writing, read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
This manuscript has been read and approved by all the authors to publish and is not submitted or under consideration for publication elsewhere.

Competing interests
The authors declare no competing interests.

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