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Mini-review

The lipid metabolism remodeling: A hurdle in breast cancer therapy

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ABSTRACT

Lipids, as one of the three primary energy sources, provide energy for all cellular life activities. Lipids are also known to be involved in the formation of cell membranes and play an important role as signaling molecules in the intracellular and microenvironment. Tumor cells actively or passively remodel lipid metabolism, using the function of lipids in various important cellular life activities to evade therapeutic attack. Breast cancer has become the leading cause of cancer-related deaths in women, which is partly due to therapeutic resistance. It is necessary to fully elucidate the formation and mechanisms of chemoresistance to improve breast cancer patient survival rates. Altered lipid metabolism has been observed in breast cancer with therapeutic resistance, indicating that targeting lipid reprogramming is a promising anticancer strategy.

1. Introduction

Breast cancer is the most common malignant tumor worldwide and the most common contributor to cancer-related deaths in women [1,2]. In developed countries, improvements in early detection and treatment have contributed to a decline in breast cancer mortality. However, in developing countries, mortality rates are increasing due to poor health care. Overall, the global breast cancer burden is rising [2]. Although there are many treatment options for breast cancer, including conventional chemotherapy, radiotherapy and surgery, drug or radiotherapy resistance often arises partly due to the heterogeneity and complexity of breast cancer, significantly reducing the effectiveness of treatment and posing a challenge for breast cancer patients [3–5]. Therefore, deepening the understanding of the mechanism of breast cancer drug resistance will provide new methods to improve the breast cancer survival rate.

Therapy resistance in breast cancer is closely linked to ferroptosis, autophagy, inflammation, etc. [6–8]. In recent years, studies have demonstrated that therapy resistance is closely related to metabolism, especially lipid metabolism. Breast cancer cells have abnormal metabolic characteristics including significantly remodeling the metabolism of glycolysis, amino acids and lipids. Many studies have reported the effects of glycolysis and glutamine metabolism on breast cancer, and the importance of lipid metabolism has been gradually revealed [9–11]. Lipids are mainly classified into fatty acids (FAs), cholesterol and phospholipids, and the elevated rate of lipid metabolism provides a reliable substrate for cancer cell invasion and migration during drug therapy, leading to the emergence of drug resistance [12,13]. In cancers, large amounts of lipid accumulation have been observed to play a significant role in tumor drug resistance through ferroptosis, the tumor microenvironment, endoplasmic reticulum (ER) stress, stemness and so on [14–18]. Studies have indicated that inhibitors targeting the lipid metabolism signaling pathway may reverse the chemoresistance of breast cancer. For example, statins, etomoxir (ETO), TVB-2640 and so on enhance the therapeutic effect of traditional anticancer drugs by affecting lipid metabolism [19–21]. Moreover, some free lipids, such as polyunsaturated fatty acids (PUFAs), may increase the effectiveness of traditional therapies for cancer treatment [22]. Here, we discuss the role played by fatty acid, cholesterol, and phospholipid metabolism in therapy-resistant breast cancer with the aim of contributing to the development of new treatment methods for breast cancer patients.

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Abbreviations

FA	fatty acids
BCSC	breast cancer stem cells
ER	endoplasmic reticulum
EMT	epithelial-mesenchymal transition
ETO	etomoxir
MUFAs	monounsaturated fatty acids
PUFAs	polyunsaturated fatty acids
CPT1	carnitine palmitoyl transferase 1
ACLY	ATP-citrate lyase
MSCs	mesenchymal stem cells
FASN	fatty acid synthase
MVA	mevalonate
SCD	stearoyl-CoA desaturases
HMGCR	HMG-CoA reductase
BRCA	breast cancer susceptibility gene
SQLE	squalene epoxidase
FAO	fatty acid oxidation
SERM	selective estrogen receptor modulator
TNBC	triple-negative breast cancer
LD	lipid droplets

2. De novo lipid biosynthesis

De novo synthesis of fatty acids occurs in the cytoplasm. ATP-citrate lyase (ACLY) is a critical enzyme linking gluconeogenesis and lipid metabolism, converting cytoplasmic citrate to acetyl-coenzyme A (acetyl-CoA) and providing precursors for lipid synthesis [23](Fig. 1). The de novo synthesis of lipids is initiated by the catalytic conversion of acetyl-CoA in the cytoplasm to malonyl coenzyme A (malonyl-CoA) by acetyl-CoA carboxylase (ACC), which is the first essential enzyme in the process [23]. Next, fatty acid synthase (FASN) catalyzes acetyl-CoA and malonyl-CoA to long-chain saturated fatty acids/palmitate in the presence of NADPH. Finally, palmitate is modified by elongase and desaturases [e.g., stearoyl-CoA desaturases (SCDs) and FA desaturases (FADS)] to produce fatty acids with various lengths and saturations [24].

Relative to adjacent normal tissue, breast cancer tissue displayed a high level of de novo lipogenesis-related enzymes. ACLY is highly expressed in breast cancer tissues of patients and negatively correlated with stage and prognosis, while inhibition of ACLY increases apoptosis, inhibiting tumor growth [25–28]. In addition to ACLY, acetyl-CoA can be catalyzed by acetyl-CoA synthetase 2 (ACSS2) under hypoxia or nutrition deficiency, resulting in a lipogenesis-dependent response in breast cancer [29].

As the first essential enzyme, ACC, which is activated by breast cancer susceptibility gene (BRCA) is critical to the survival of breast cancer cells [30,31]. Moreover, the expression of FASN, which is also of

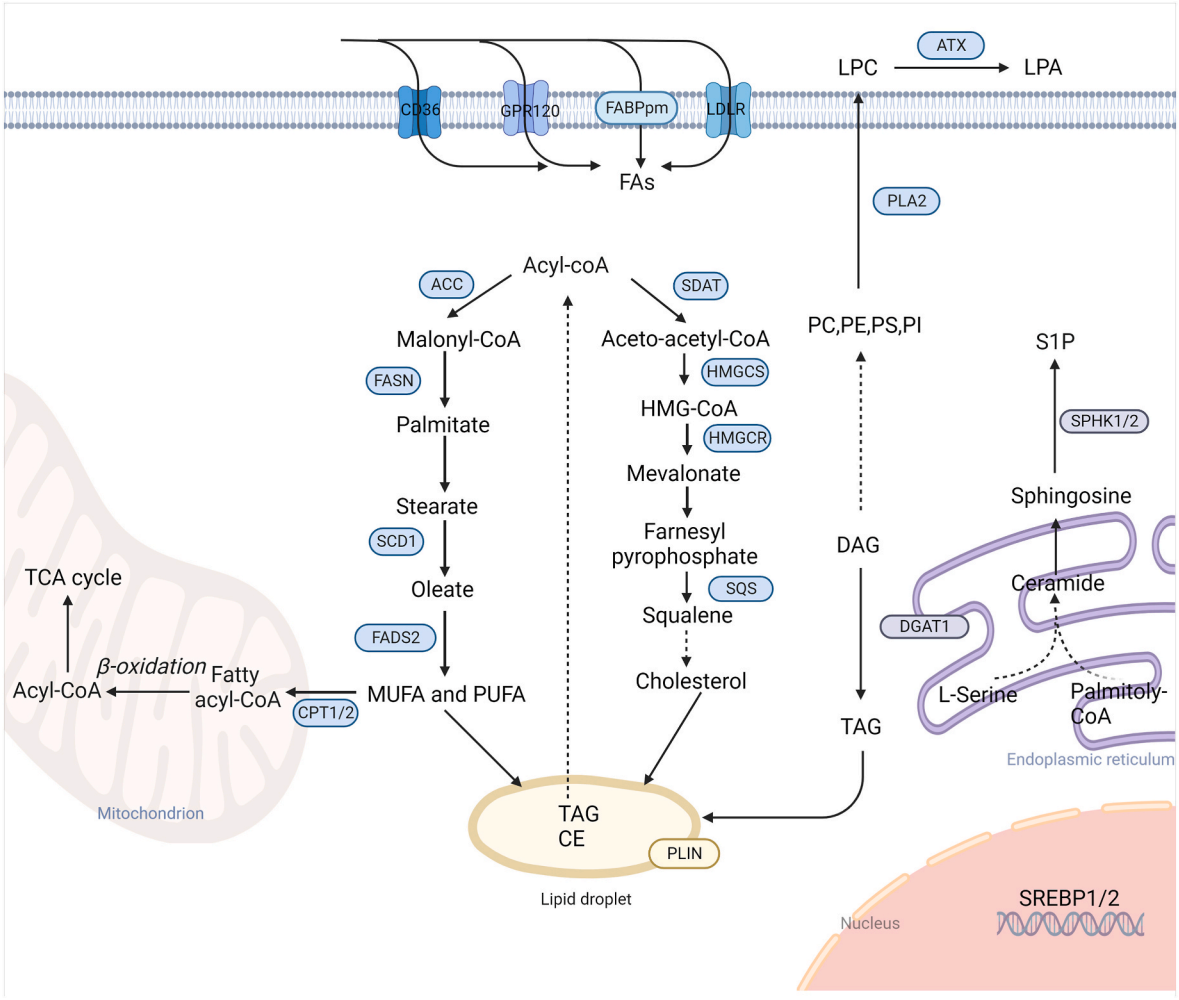

Fig. 1. Overview of lipid metabolism in breast cancer cells. The figure shows key lipid metabolism pathways in breast cancer cells. Intracellular lipids are mainly derived from uptake from the outside and de novo synthesis. Cholesterol and fatty acids can be stored in lipid droplets. Created with BioRender.com.

interest, is thought to be an early event in the progression of breast cancer, and HER2+ regulates FASN activity [26,32] (Fig. 2). More importantly, most researchers have confirmed that, in breast cancer, the increased expression and activity of lipid biosynthesis enzymes or the large accumulation of metabolites are the leading causes of chemoresistance.

2.1. De novo lipid biosynthesis and therapeutic resistance

Abnormal accumulation of FA can interfere with breast cancer treatment by providing energy to tumor cells, forming triglycerides that are involved in the composition of lipid droplets, remodeling cell membrane structure or acting as signaling molecules [24]. Breast tissue is rich in adipocytes, and some molecules secreted by adipocytes have regulatory effects on tumor cells. Adipocytes can inhibit FA release from tumor cells induced by doxorubicin treatment, thereby promoting drug resistance [33]. Clinical studies have shown that G protein-coupled receptor 120 (GPR120) levels in breast cancers are positively correlated with the side effects of drugs [34]. Interestingly, FA can act as a GPR120 ligand and activate the GPR120-induced de novo synthesis of fatty acids. Moreover, the upregulated fatty acids act as a positive feedback mechanism that activates GPR120 to induce the expression of ABC transporters (ABCC1 and ABCG2), thereby reducing the accumulation of epirubicin in breast cancer cells and leading to drug resistance. Given the importance of FA in the drug resistance of breast cancer, the role of related enzymes in its synthetic pathway has attracted much attention (Fig. 3).

2.1.1. ACLY

As the first rate-limiting enzyme in lipid synthesis, ACLY has been confirmed to function as an oncogene whose upregulation is closely related to therapeutic resistance [35–37]. In breast cancer, ACLY is upregulated in the gene expression profile of tamoxifen-resistant cells, revealing its potential role in tamoxifen resistance. Mechanistically, an ACLY inhibitor (hydroxycitric acid) promotes apoptosis of tamoxifen-resistant cells, leading to a return of sensitivity to tamoxifen in resistant cells [38,39]. Resistance to CDK4/6 inhibitor, palbociclib, resistance is mediated by protein kinase B (AKT) activation. As a downstream target of AKT, ACLY is also involved in the development of acquired resistance, and targeting ACLY (bempedoic acid) could help improve the efficacy of palbociclib [40]. The above mechanism may be that ACLY inhibition affects fatty acid prolongation in the ER and fatty acid oxidation (FAO) in mitochondria, altering fatty acid composition and affecting triglyceride (TG) accumulation, leading to cell growth inhibition and/or apoptosis [41]. In addition, clinical studies have also shown that ACLY promotes ABCB1/ABCG2 expression leading to paclitaxel resistance in breast cancer [27].

2.1.2. FASN

Clinical studies have confirmed that FASN levels are associated with metastasis of triple-negative breast cancer (TNBC), and the mechanism may be that FASN promotes the synthesis of fatty acids to provide raw materials for cell membrane synthesis as well as intermediate metabolites such as palmitic acid or arachidonic acid to provide signaling molecules for migration [42–44]. Due to low lipid utilization in the brain environment, tumor cells rely on de novo lipid synthesis to supply energy, and patients with brain metastases from breast cancer also exhibited FASN overexpression [45]. FASN inhibition prevents tumor regeneration and metastasis after cessation of antiangiogenic treatments such as sunitinib or sorafenib treatment [46]. In preclinical models, FASN expression correlates with drug resistance [42,47].

Studies have shown that FASN prevents the activation of nuclear factor (NF)-κB and neutral sphingomyelinase (nSMase) via tumor necrosis factor (TNF)-α, thereby inhibiting apoptosis and leading to drug resistance of in breast cancer [48]. During endocrine therapy, although tamoxifen can inhibit estradiol-promoted FASN expression via the phosphatidylinositol 3-kinase (PI3K)-AKT-SREBP (sterol regulatory element binding protein) pathway in ER + breast cancer, HER2 activation of the PI3K/AKT pathway in HER2+ and ER + breast cancer promotes FASN expression while FASN can increase HER2 expression and activity in return, forming positive feedback and leading to tamoxifen resistance [49]. Furthermore, Menendez et al. found that HRG drives HER2:HER3 heterodimerization, which activates the PI3K/AKT and MAPK-ERK1/2 signaling pathways, promoting FASN

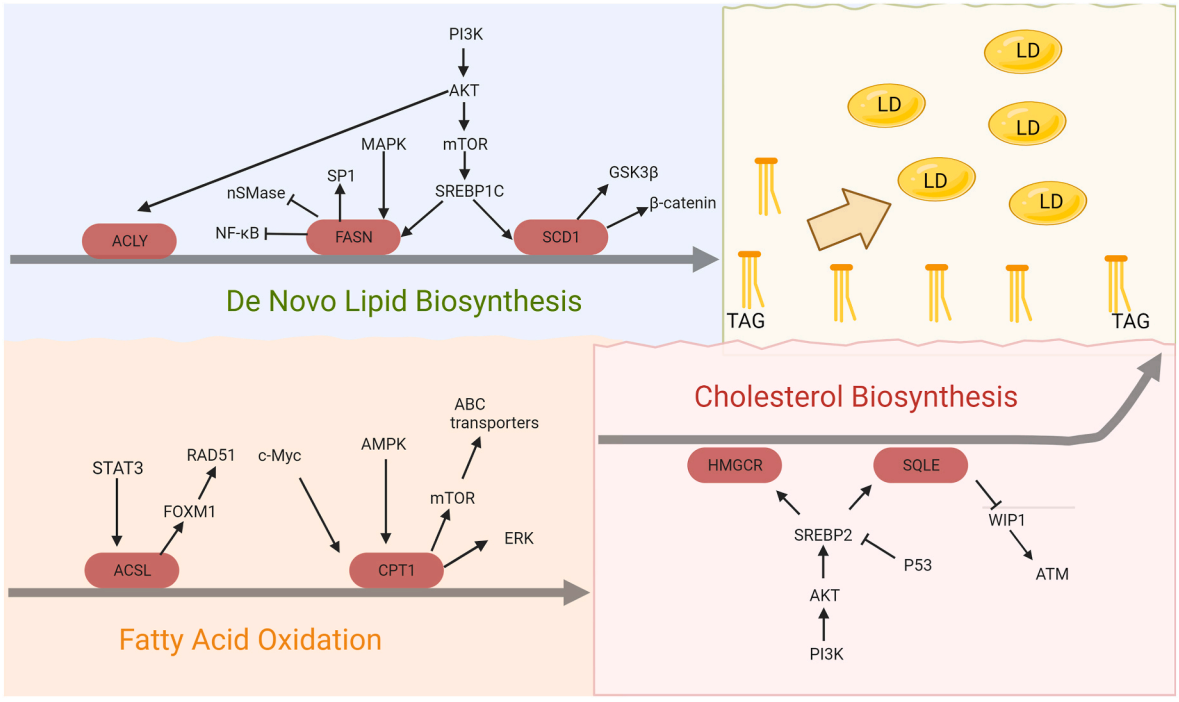

Fig. 2. The regulatory networks of lipid metabolism in breast cancer cells. The interplay of aberrant expression of enzymes in lipid metabolism with tumor-associated signaling pathways in breast cancer cells. Created with BioRender.com.

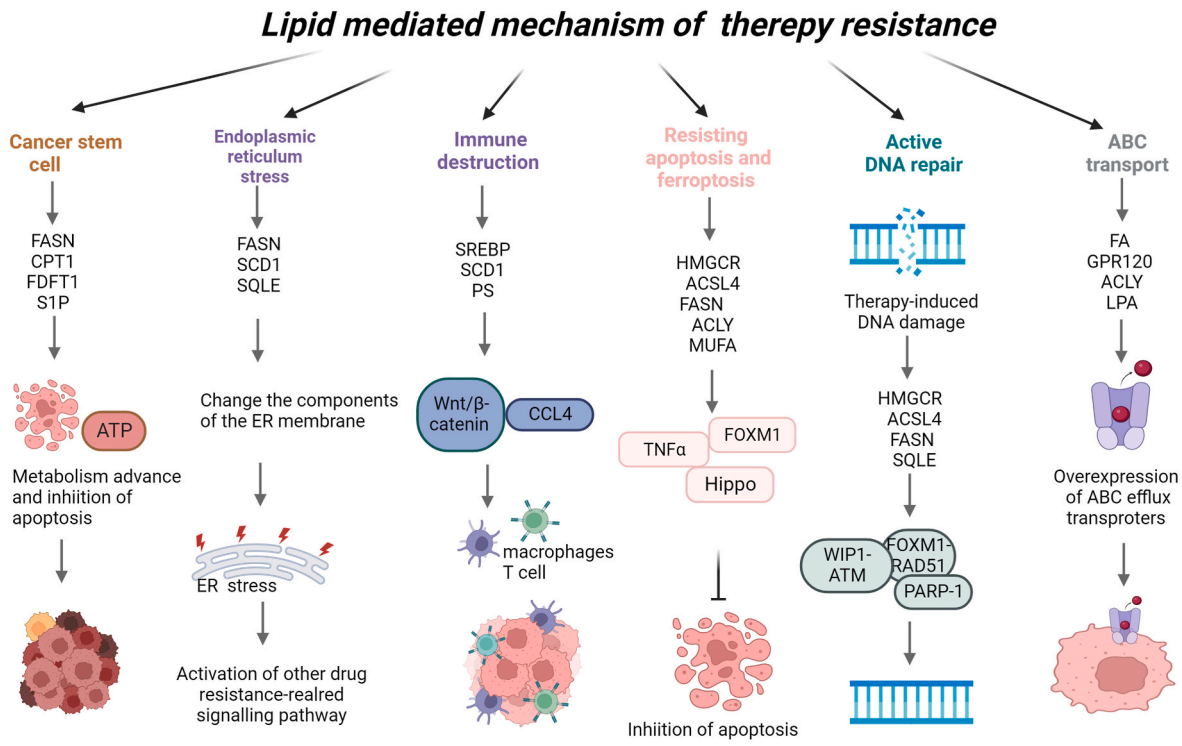

Fig. 3. Lipid-mediated mechanisms of therapy resistance in breast cancer. Lipid metabolism is involved in drug resistance mainly by affecting stemness, endoplasmic reticulum stress, immune microenvironment, cell death, DNA damage repair, and ABC transporter proteins in breast cancer cells. Created with BioRender.com.

expression and inducing endocrine therapy resistance [50]. Regarding other drug resistance factors, FASN increases poly(ADP-ribose) polymerase 1 (PARP-1) expression via NF-κB and specificity protein 1 (SP1), which affects Ku protein recruitment at the DNA double-strand break (DSB) terminus and ultimately promotes nonhomologous end-joining (NHEJ) repair, thereby targeting FASN to improve the drug and radiation sensitivity of breast cancer [51]. In the antitumor mechanism of resveratrol, downregulation of FASN was found to mediate drug-promoted apoptosis in breast cancer stem cells (BCSCs) [52]. In breast cancer mouse models, the FASN inhibitor Fasnall is synergistic in reducing tumor volume in combination with the platinum-based chemotherapeutic agent carboplatin and affects survival [53].

2.1.3. SCD1

Increasing evidence has shown that SCD1 is associated with breast cancer invasion and migration [45,54–57]. Oleic acid, the primary product of SCD1, activates phospholipase D 2 (PLD2) to promote phosphatidic acid production and finally upregulates the PLD-mammalian target of rapamycin (mTOR)/p70S6K pathway to promote cell invasion and migration [58]. Mauvoisin et al. found that reduced SCD1 expression promotes epithelial-mesenchymal transition (EMT) and metastasis by inhibiting glycogen synthase kinase 3 (GSK3) phosphorylation and the expression and transactivation capacity of β-catenin in the nuclear [59].

SCD1 is strongly associated with fatty acid saturation. Fatty acid saturation is closely related to ferroptosis. In ferroptosis, polyunsaturated fatty acids (PUFAs) are involved in producing toxic lipid reactive oxygen species (ROS) and promoting ferroptosis [60]. Monounsaturated fatty acids (MUFAs) can inhibit ferroptosis by displacing polyunsaturated fatty acids (PUFAs) from plasma membrane phospholipids. Thus, MUFAs are potent inhibitors of ferroptosis, protecting cells from ferroptosis and promoting breast cancer recurrence and chemoresistance towards tyrosine kinase inhibitors (TKIs) or cisplatin [17,61]. SCD1 also plays a vital role in immunotherapy. Through Wnt/β-catenin signaling and endoplasmic reticulum stress, SCD1 inhibitors increase the expression of C–C motif chemokine ligand 4 (CCL4) in tumor cells and T cells and promote dendritic cell (DC) recruitment to exert antitumor effects and have a synergistic effect with anti-PD-1 antibodies [62].

3. Fatty acid oxidation (FAO)

Before oxidation, exogenous and endogenous FAs are activated by acyl-CoA synthase (ACS) to fatty acyl-CoA, which then crosses the inner and outer mitochondrial membranes via carnitine palmitoyl transferase 1(CPT1), carnitine/acylcarnitine transporter(CACT) and carnitine palmitoyl transferase 2(CPT2) in that order [63] (Fig. 1). In this process, fatty acyl-CoA is catalyzed by CPT1 to fatty acylcarnitine, which is converted back to fatty acyl-CoA under the action of CPT2. Finally, fatty acyl-CoA undergoes four steps of β-oxidation to generate acyl-CoA, which provides raw materials for the tricarboxylic acid cycle [64]. In the above process, several enzymes control the speed of fatty acids across the mitochondria, which is important for oxidative catabolism.

In contrast to the role of lipid synthesis in cancer, FAO has only started to draw attention in recent years. Malonyl-CoA in lipid synthesis can act as a CPT1 inhibitor, coordinating the simultaneous occurrence of two mutually exclusive processes, de novo synthesis and FAO [23,64]. Under normal conditions, FAO is carried out in energy-consuming tissues such as the heart and skeletal muscle. However, a growing body of research suggests that both FAO and de novo synthesis are abnormally activated in cancer [65–68]. In breast cancers, c-Myc and AMPK signaling induces the expression of FAO-related enzymes such as CPT1, whose overexpression drives the onset, growth and metastasis of breast cancer [48,69–72] (Fig. 2).

3.1. FAO and therapeutic resistance

During treatment, breast cancer cells become resistant to chemotherapeutics by maintaining stem cell stemness, mitochondrial function or ATP production, which mainly rely on the upregulation of FAO pathway-related enzymes (Fig. 3).

3.1.1. ACSL

ACSL activates long-chain fatty acids to generate fatty acyl-CoA esters, which enter into fatty acid oxidation (FAO) to provide energy for cancer cell proliferation. ACSL in mammals includes types 1, 3, 4, 5 and 6. Among them, ACSL4 has been proven by many studies to be closely related to drug resistance in breast cancer. ACSL4 can promote the formation of fatty acyl-CoAs, which are essential for phospholipid synthesis. Since phospholipids are the main component of mitochondrial membranes, they can alter the membrane potential of mitochondria and regulate the mitochondrial apoptotic pathway [73,74]. In drug-resistant TNBC cells, acetyl-CoA in FAO activates STAT3, leading to elevated expression of ACSL4, which in turn promotes drug resistance by affecting phospholipid synthesis and thereby altering mitochondrial membrane potential and resisting the mitochondrial apoptotic pathway [75]. The overexpression of ACSL4 in ER + or HER2+ breast cancer cells has been proven to promote cell proliferation, inhibit apoptosis, and reduce sensitivity to tamoxifen, etoposide, and lapatinib [76]. ACSL4 can also promote resistance to cisplatin, doxorubicin, and paclitaxel in TNBC by upregulating the activity of ABCG2 and ABCC4 through the mTOR pathway, while inhibition of ACSL4 expression partially restores sensitivity to these agents [77].

Moreover, Kwon et al. found that ACSL4 also promotes radiotherapy resistance in HER2+ or ER + breast cancer by promoting the expression of the forkhead box protein M1 (FOXM1)-RAD51 pathway and further promoting DNA repair. In addition, it was found that ACSL4 can also mediate radiotherapy resistance by promoting antiapoptotic effects through FOXM1 [78]. Therefore, targeting ACSL4 may offer a new approach to breast cancer treatment.

3.1.2. CPT1 and CPT2

CPT1, a key enzyme for FAO, is closely associated with the stemness of breast cancer cells and can be detected in the serum of patients, indicating that CPT1 can function as a biomarker of breast cancer progression [72,79,80]. When cocultured with mesenchymal stem cells (MSCs), MSC-induced LincRNA AGAP2-AS1 increases stemness and drug resistance in tumor cells by regulating CPT1 transcription. Mechanistically, nuclear AGAP2-AS1 forms a complex with human antigen R (HuR) to enhance the stability of CPT1 mRNA, while AGAP2-AS1 in the cytoplasm functions as a ceRNA that binds to miR-15a-5p and releases downstream CPT1 mRNA. Ultimately, upregulated CPT1 mediates the onset of drug resistance [18]. Therefore, targeting AGAP2-AS1 may be one of the targets to overcome the chemoresistance induced by the overexpression of CPT1. In BCSCs, STAT3 promotes CPT1 expression and FAO by binding to its promoter. The increased FAO fosters the production of ATP, which acts as an electron carrier in the electron transport chain, providing a metabolic advantage for BCSCs and facilitating the maintenance of BCSC stemness and the development of drug resistance [16].

In addition to chemoresistance, the overexpression of CPT1 and CPT2 also plays a role in radiotherapy resistance. In radiation-resistant breast cancer cells and radiation-derived breast cancer stem cells, CPT1 and CPT2 increase FAO, providing ATP for ERK phosphorylation and promoting resistance to radiotherapy [20].

4. Cholesterol biosynthesis

The cholesterol synthesis pathway is also known as the mevalonate (MVA) pathway. As with fatty acid synthesis, the synthesis of mammalian 3-hydroxy-3-methylglutaryl (HMG)–CoA (HMG-CoA) first requires the involvement of acetyl-CoA. HMG-CoA is then reduced by HMG-CoA reductase (HMGCR) to mevalonate [81]. Next, mevalonate undergoes a series of enzymatic reactions to produce farnesyl pyrophosphate (FPP), which is subsequently catalyzed by squalene synthase (SQS) to produce squalene, which in turn produces cholesterol in the presence of squalene epoxidase (SQLE) (Fig. 1).

The key enzymes HMGCR and SQLE are highly expressed in breast cancer and are associated with a poorer prognosis by regulating different signaling pathways and disrupting some oncogenes (e.g, mTORC1, HIF-1α, WIP1) to accelerate tumorigenesis [82–84]. The production of cholesterol derivatives also increases due to the upregulation of related enzymes. For example, the CYP-dependent monooxygenase CYP2A1 promotes the conversion of cholesterol to 27-hydroxycholesterol (27-HC), which acts as a selective estrogen receptor modulator (SERM), and 27-HC has estrogenic activity to promote ER + breast cancer progression [85,86]. For example, in TNBC, upregulation of the mevalonate pathway leads to the activation of the Hippo pathway, which is needed for cancer cell proliferation and self-renewal [87]. Moreover, MVA, via the Hippo pathway, can upregulate receptor for hyaluronan-mediated motility (RHAMM) transcription, leading to extracellular signal-regulated kinase (ERK) activation in breast cancer metastasis. The addition of simvastatin inhibited the metastasis of cancer [88]. Mandal et al. found that simvastatin prevents skeletal metastasis of breast cancer by mutant p53 to suppress CD44 expression [89]. Moreover, cholesterol promotes breast cancer metastasis by affecting lipid rafts to promote the expression of the transmembrane protein CCDC25 and neutrophil extracellular trap formation [65]. Elevated cholesterol on the cell membrane surface also promotes invasion through invadopodia and extracellular matrix (ECM) degradation [90]. In addition, miRNA-195 could target HMGCR to inhibit EMT in breast cancer and reduce invasion and migration [91] (Fig. 2).

However, as an essential component of the cell membrane, cholesterol content negatively correlates with cell membrane fluidity and affects cell metastasis [92]. For instance, nicotinamide N-methyltransferase (NNMT) increases cholesterol efflux through ABCA1 and reduces cholesterol levels in cell membranes, increasing membrane fluidity and TNBC migration [93]. C-terminal binding proteins (CtBP) and zinc-finger E-box binding homeobox 1 (ZEB1) decrease intracellular cholesterol levels by inhibiting SREBP2 transcription, leading to activation of the TGF-β signaling pathway and promoting EMT and cell migration [94]. The two different roles uncover the complex function of cholesterol in breast cancer metastasis.

4.1. Cholesterol biosynthesis and therapeutic resistance

In aggressive breast cancer cells, cholesterol is important in cell stemness and tumorsphere formation, which play significant roles in drug resistance [33,95,96]. The metabolic intermediates of the MVA pathway are involved in chemoresistance in breast cancer (Fig. 3). For example, the cholesterol biosynthesis precursor mevalonate promotes BCSC proliferation through upregulation of estrogen receptor alpha (ERα) and related pathways, mediating the development of tamoxifen and doxorubicin resistance in breast cancer cells [97]. 27-HC leads to anti-programmed death-ligand 1 (αPD-L1) resistance in breast cancer by modulating the phenotype of macrophages, altering the secretion of certain molecules, and inhibiting T-cell expansion and cytotoxic function in a liver x receptor (LXR)-dependent manner [98]. 27-HC expression is elevated in ER + LTED (chronic estrogen deprivation) breast cancer cells and activates ER-mediated transcription to promote cell proliferation, providing a rationale for the role of 27-HC in endocrine drug resistance [99]. Moreover, upregulation of genes related to the MVA pathway is negatively correlated with the prognosis of breast cancer patients, and the role of cholesterol metabolism genes in therapeutic resistance has attracted widespread attention [96].

4.1.1. HMGCR

Statins are widely used in the clinical treatment of hypercholesterolemia. The mechanism of statins is to reduce intracellular cholesterol synthesis by competitively inhibiting the endogenous cholesterol synthesis rate-limiting enzyme HMGCR and blocking the intracellular hydroxymevalonate metabolic pathway [100]. Statins reduce recurrence and improve breast cancer survival and may improve the efficacy of antitumor therapy via the following two mechanisms [101]. On the

one hand, targeting cholesterol biosynthesis with statins delays DSB repair of cellular DNA after radiation exposure, thereby increasing cellular senescence and improving the efficacy of radiotherapy treatment [102]. On the other hand, the statin-targeted MVA pathway mediates resistance through apoptosis. When HER2 is blocked, the MVA pathway promotes cell survival and drug resistance through activation of Hippo-mTORC1-Survivin signaling and promotion of apoptosis. Statins can significantly inhibit the growth of drug-resistant cells [19]. However, because of the different levels of HMGCR expression, breast cancer cells also vary in their sensitivity to statins [103,104]. In addition, activation of SREBP, upregulation of cholesterol-synthesis genes, and elevation of LDLR on the cell surface after statin treatment affect the rate of metabolism and intracellular cholesterol level, ultimately affecting statin sensitivity [105,106]. Therefore, the clinical use of statins can be tailored according to the characteristics of each patient and the response after dosing.

4.1.2. SQLE

SQLE expression in breast cancer patients is associated with poor prognosis and resistance to radiotherapy, since squalene is involved in the composition of the endoplasmic reticulum membrane. Targeting SQLE (terbinafine/A8533 and NB-598/A3645) causes squalene accumulation and thus induces ER stress, activating the wild-type p53-induced phosphatase (WIP1)/ataxia-telangiectasia mutated (ATM) pathway to inhibit homologous recombination (HR) and repair pathways and improve radiotherapy sensitivity [107].

4.1.3. SREBP-transcriptional regulation

SREBP is a transcription factor involved in regulating most genes related to fatty acid, cholesterol, and phospholipid metabolism. Under high sterol content, SREBP forms an insulin-induced gene protein (INSIG)/SREBP cleavage-activating protein (SCAP)/SREBP complex in the ER membrane. When sterol levels decrease, SCAP/SREBP is transported to the Golgi apparatus [108,109], where site-1 protease (S1P) and site-2 protease (S2P) cleave SREBP, which re-enters the nuclear to bind to the promoters of metabolism-related target genes and regulate transcription [110]. SREBP is divided into SREBP1 and SREBP2, and SREBP1 has two isoforms, SREBP1A and SREBP1C. SREBP1A regulates all SREBP-related genes, SREBP1 for fatty acid synthesis and SREBP2 for cholesterol synthesis [111]. In breast cancer, the PI3K-AKT-mTOR pathway predominantly regulates SREBP expression and activity, leading to increased levels of both SREBP mRNA and protein [112–114]. Moreover, SREBP1 inhibits E-cadherin expression by forming a complex with SNAIL and histone deacetylase 1/2 (HDAC1/2), promoting EMT and breast cancer metastasis. Some noncoding RNAs, such as miR-18a-5p, can also target SREBP1 to inhibit breast cancer metastasis [14].

Recent studies have indicated that SREBP plays a key role in the chemoresistance of breast cancer. Perone et al. found that SREBP1 promotes the transcription of Keratin-80 and increases its expression, which is closely associated with cytoskeletal reprogramming and promotes the invasion of endocrine-resistant cells in breast cancer [115]. Moreover, the SREBP1 pathway plays a crucial role in resistance to PARP inhibitors, such as olaparib. In BRCA1-associated TNBC, olaparib can cause the metabolism of infiltrating macrophages to transition from glycolysis to lipid metabolism; this is because olaparib inhibits glycolysis via the PARP1-p38 pathway and regulates transcription factor-specific proteins to promote the expression of SREBP1, thereby enabling the differentiation of macrophages that depend on lipid metabolism with immunosuppressive effects [18]. Since maintenance treatment with olaparib has some disadvantages, such as lower absorption and utilization, olaparib in combination with SREBP may be a promising strategy for breast cancer treatment.

Importantly, some key enzymes are associated with essential pathways for developing drug resistance, which, although unexplored in breast cancer, are closely related to drug resistance in other tumors. For example, FDFT1 is the key enzyme for the synthesis of cholesterol. Silencing of FDFT1 in TNBC reduces the formation of mammospheres and this effect could be rescued by the addition of a downstream metabolite, illustrating that cholesterol biosynthesis is important for the growth of BCSCs [96]. There are few studies on FDFT1 resistance in breast cancer, but given the important role of FDFT1 in stem cells and its close association with drug resistance in other cancers, such as cisplatin resistance in bladder cancer, the potential of FDFT1 in breast cancer resistance warrants further exploration [116].

5. Lipid droplets and therapeutic resistance

Lipid droplets (LDs) are widely distributed in the cytoplasm and function as lipid reservoir organelles that consist of perilipin (PLIN) protein monolayers of phospholipids wrapped around neutral lipids. Neutral lipids are mainly triacylglycerols (TAGs) and sterol esters [117,118] (Fig. 1). TAGs are formed on the endoplasmic reticulum by adding FA to the backbone of glycerol catalyzed by a series of acyltransferases such as diacylglycerol acyltransferases 1/2 (DGAT1/2), while cholesteryl esters are produced by esterification of cholesterol via SOAT1/2. The catabolism of TAGs in lipid droplets is mainly catalyzed by three enzymes including adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MGL), and the end-product FA is finally catabolized in the mitochondria to produce ATP. Among these members, ATGL is reported to be elevated in breast cancer and provides energy for breast cancer progression [119].

ATGL can regulate lipid droplet catabolism and play an essential role in the tumor microenvironment. In premetastatic lung neutrophils and mesenchymal cells, ATGL inhibition allows lipid droplet accumulation, which is then delivered to immune cells, inhibiting the activation and function of antitumor immune cells. This promotes the formation of premetastatic ecological sites in the lung metastasis of breast cancer [120,121]. Increased ATGL in breast cancer cells promotes lipid droplet catabolism and free FA (FFA) release, providing FAO with raw materials and enhancing breast cancer invasion [119]. However, in TNBC, the researchers found that ATGL-mediated lipid droplet catabolism and increased FFAs finally cause lipotoxicity, affecting mitochondrial function and leading to tumor cell growth arrest [122]. Lipid droplet catabolism provides energy and raw material for cancer cell invasion and migration. However, excess FFAs inhibit tumor cells when subsequent catabolism cannot be accelerated together, suggesting that maintaining lipid homeostasis is crucial for antitumor therapy.

LDs can function as scavengers to scavenge the ROS produced by cells after radiation and protect cells from free radical attack. In cell survival from radiotherapy, elevated expression of the iron-heavy chain protein FTH1 leads to an imbalance of iron metabolism and increases LD, ultimately leading to increased cell viability and radiotherapy resistance [123]. Furthermore, since there exists lipid solubility of some drugs, such as docetaxel, LDs also play a role in chemoresistance by isolating the drug in lipid droplets where it cannot be effective [124].

Proteins involved in lipid droplet stabilization by covering its surface also play an essential role. Clinical studies have found shorter relapse-free survival in breast cancer patients with positive perilipin, suggesting a poor prognosis for TNBC patients [125]. Increased expression of PLIN4 was found in adriamycin-resistant TNBC, and silencing PLIN4 resulted in a significant decrease in viability and increased the death of drug-resistant cells. However, the specific molecular mechanisms of drug resistance described above still need to be studied [125,126].

6. Phospholipids and therapeutic resistance

Phospholipids (glycerophospholipids and sphingolipids) are the most essential components of cell membranes [127]. Glycerophospholipids consist of two fatty acid (FA) molecules esterified at the sn-1 and sn-2 positions in the glycerol moiety and further classified into phosphatidylcholine (PC), phosphatidylserinephos (PS),

phosphatidylethanolamine (PE), and phosphatidylinositol (PI) according to the moiety they carry. Abundant studies have indicated that glycerophospholipids are involved in the development of breast cancer through apoptosis, immunosuppression in the tumor microenvironment and focal adhesion dynamics [128–130] (Fig. 1).

Glycerophospholipid metabolism is involved in most cancer events, especially in chemoresistance. The anticancer agent dichloroacetate (DCA) can promote the formation of autophagic membranes by inducing an increase in PC synthesis, affecting the treatment efficacy [131]. The phospholipid metabolite LPA displaces paclitaxel from microtubules in a PI3K-dependent manner, allowing cells to escape paclitaxel-induced mitotic arrest and promoting drug resistance [132]. In doxorubicin-resistant cells, LPA promotes the expression of MDRTs such as ABCC1 and ABCG2 through nuclear factor erythroid 2-related Factor 2 (NRF2) and regulates the sphingosine 1-phosphate (S1P) signaling pathway to mediate drug resistance [132,133]. Chk-α is involved in TAM and 5-fluorouracil resistance in breast cancer by regulating autophagy and drug efflux [134,135].

Sphingolipids (SPLs) contain the long-chain amino alcohol sphingosine (instead of glycerol) esterified to a fatty acid and a phosphate group [136]. Among these, S1P and ceramide belong to the central bioactive sphingolipids, and S1P is generated from ceramide catalyzed by enzymes such as sphingosine kinase 1 (SPHK1) [137]. Clinical studies have shown the high expression of SPHK1 and S1P in breast cancer tissues, whose increases are closely associated with poorer prognosis and shorter survival rates [138–141]. In hormone-treated breast cancer cells, tamoxifen is an antagonist of estrogen receptor α (ERα66) but an agonist of the estrogen receptor spliceosome Erα36, which increases the production of S1P facilitated by SPHK1, leading to activation of downstream pro-oncogenic signaling pathways and tamoxifen resistance [142]. Hii et al. found that S1P also regulates CSC survival via STAT1 [143]. FTY720 is a functional antagonist of the S1P receptor, and the use of FTY720 in tamoxifen-resistant cells can reduce cell viability and promote CSC modulation. In addition, FTY720 combined with doxorubicin reduces the expression of IL6 and STAT3 inflammatory cytokines and attenuates obesity-induced inflammation, which improves the efficacy of breast cancer [143,144]. These findings suggest that phospholipid metabolism dysregulation exists in most breast cancers, and targeting phospholipid metabolism may be a prospective method to avoid invasion and chemoresistance.

7. Targeting therapy based on lipid metabolism

Lipid metabolism remodeling plays a vital role in chemoresistance. Studies have found the abnormal accumulation of lipid metabolism products in drug-resistant malignancies. For example, in refractory multiple myeloma (MM), the patients who showed remission and those who were nonremission showed different lipidomics after CAR-T treatment, which could be due to the dysregulation of LPCAT1 [145]. In colorectal cancer, patients with 5-FU resistance showed disordered lipid metabolites such as phospholipids, and polyunsaturated phospholipids can reverse the chemoresistance to 5-FU [146]. In breast cancer, exposing PS of tumor cell on the outside of the cell membrane induces immunosuppression by promoting macrophage polarization toward the pro-tumor subtypes, inhibiting dendritic cell antigen presentation and T-cell activation, and the PS-targeted drug bavituximab in combination with anti-PD-1 significantly increases its antitumor activity [147] (Fig. 4).

Therefore, targeting lipid metabolism has been deemed a promising strategy for patients to overcome drug-resistance. In breast cancer, some small-molecule inhibitors have also been developed to overcome therapeutic resistance via targeting lipid metabolism related enzymes (Table 1).

7.1. FASN

Inhibitors targeting FASN have been developed to reverse drug resistance and increase the curative effect. For example, C75 and EGCG enhance the effect of cetuximab by promoting apoptosis, thereby enhancing its therapeutic effect on TNBC [148]. Abnormal lipid

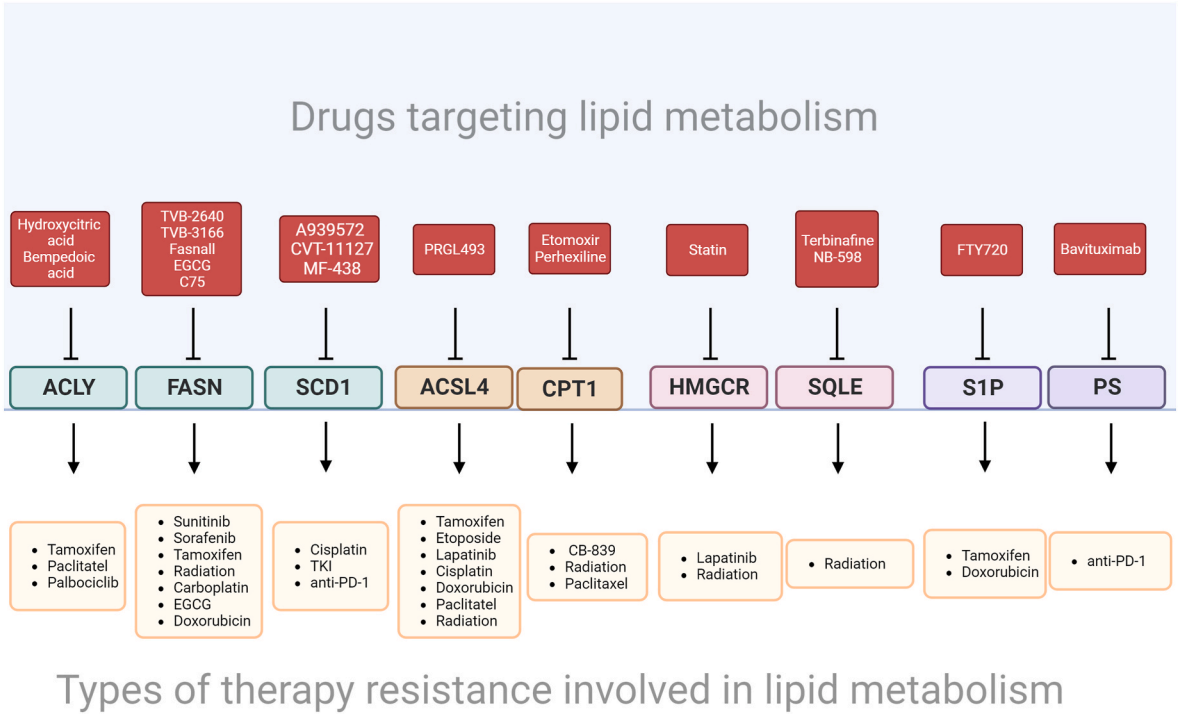

Fig. 4. Types of therapy resistance involving lipids and the corresponding targeted agents in breast cancer. Lipid metabolism in breast cancer cells is involved in the therapeutic resistance of conventional chemotherapeutic agents, endocrine therapy, targeted agents, and radiotherapy. Lipid-targeted drugs can improve the efficacy of the above therapy. Created with BioRender.com.

Table 1
Targeting lipid metabolism in breast cancer models. This table summarizes the aberrant expression of lipid metabolism components that participate in the therapy resistance of breast cancer cells and their potential targeted drug.

Target	Drugs	Development stage	References
ACLY	Hydroxycitric acid	preclinical	[38,39]
	Bempedoic acid	preclinical	[40]
FASN	TVB-2640	phase II	[21]
	TVB-3166	preclinical	[149]
	Fasnall	preclinical	[53]
	EGCG	preclinical	[148]
	C75	preclinical	[9,148]
SCD1	A939572	preclinical	[62]
	MF-438	preclinical	[56]
	CVT-11127	preclinical	[57]
ACSL4	PRGL493	preclinical	[150]
CPT1	Etomoxir	preclinical	[71,154]
	Perhexiline	preclinical	[16]
HMGCR	Statins	preclinical	[19,89,102]
SQLE	Terbinafine	preclinical	[107]
	NB-598	preclinical	[107]
S1P	FTY720	preclinical	[143,144]
PS	Bavituximab	preclinical	[147]

metabolism leads to reactive oxygen species (ROS)-mediated DNA damage, promoting cell survival and breast cancer recurrence. The use of FASN inhibitors C75 significantly reduces oxidative stress and improves therapeutic efficacy [9]. In addition, inhibitors targeting FASN (TVB-3166) were found to reduce the expression of ERα and improve the efficacy of tamoxifen. Mechanistically, as lipids are essential components of the endoplasmic reticulum membrane, FASN inhibition disrupts lipid metabolism and leads to endoplasmic reticulum stress, thereby leading to an increase in the phosphorylation level of transcription factors and a reduction in ERα translation [41–43,149]. The FASN inhibitor TVB-2640 has been shown to improve efficacy in combination with paclitaxel. In a phase II clinical trial, TVB-2640, in combination with paclitaxel, improved the partial response and disease control rate in breast cancer patients [21]. Furthermore, FASN inhibition with omeprazole improves the efficacy of neoadjuvant chemotherapy in patients with operable TNBC [48].

In addition to inhibitors targeting FASN directly, some clinical medicines have been proven to inhibit FASN and improve the efficacy of many classical therapies [47]. For example, the proton pump inhibitor PPI inhibits the FASN-regulated PARP1-mediated NHEJ repair pathway to promote doxorubicin and radiotherapy sensitivity, improving the overall survival of breast cancer patients [17].

7.2. ACSLs

PRGL493 is a selective and potent ACSL4 inhibitor whose tumor suppression function has been confirmed in breast and prostate carcinoma. Castillo et al. found that PRGL493 functions mainly by reducing ABCG2 in TNBC and promoting ER expression. More importantly, PRGL493 combined with either tamoxifen or paclitaxel is more effective than single agents [150]. However, given that the drug is being used for the first time in tumors, its safety still needs to be explored.

7.3. CPT1 and CPT2

ETO targeting CPT1 and restoring cellular sensitivity to conventional chemotherapeutic agents and radiotherapy has been demonstrated in various cancers [65,151–153]. In breast cancer, ETO deprives cells of nutrients and growth factors and promotes apoptosis [154]. In glutaminase inhibitor CB-839-resistant breast cancer cells, an activated AMK pathway was found to upregulate CPT1 and FAO. ETO, combined with CB-839, inhibited migration and promoted cell death of drug-resistant cells [71].

In addition to chemoresistance, targeting lipid metabolism also improves the sensitivity of breast cancer to radiotherapy. Since radiotherapy generates large amounts of ROS to cause cell death, reducing LD levels with DGAT2 inhibitors can enhance the radiotherapy sensitivity of breast cancer [122].

Targeting lipid metabolism may also reverse chemoresistance or radiotherapy resistance in other cancers. In colorectal cancer, targeting LPCAT2-mediated LD formation may be a therapeutic approach to restore cellular chemosensitivity [155]. Increased free PUFAs and their esterification to membrane phospholipids not only cause lipid peroxidation and contribute to ferroptosis of tumor cells but also modulate tumor sensitivity to chemotherapeutic agents with adjuvant chemotherapeutic potential [156]. In colorectal cancer, PUFAs not only enhance the sensitivity to 5-FU but are also used in combination with celecoxib and tamoxifen for the treatment of breast cancer or with cisplatin for the treatment of lung cancer [22]. In nasopharyngeal carcinoma, targeting CPT1 restores cellular sensitivity to radiotherapy by activating mitochondrial apoptosis [65]. Furthermore, clinical studies have shown that lipids in breast cancer patients treated with neoadjuvant chemotherapy are strongly associated with prognosis [157]. An increase in the oleic acid in serum TG is associated with a poor response to neoadjuvant chemotherapy [158]. In TNBC, high SPHK1 in tissues is associated with a poor response to 5-FU and doxorubicin in patients, suggesting a poorer prognosis [159]. Collectively, existing research has indicated the importance of lipid metabolism remodeling in cancers, and the combination of chemotherapy drugs and metabolic enzyme inhibitors provides an important guarantee for tumor patients to overcome chemotherapy resistance.

8. Discussion

Therapy resistance in breast cancer is a significant challenge in current treatment, and the vital role of lipid metabolism is gradually being recognized. At the same time, the activation of related oncogenic pathways eventually affects lipid metabolism and even other cells in the tumor microenvironment, forming a lipid metabolism regulatory network. Some lipid metabolism-targeting agents have obtained excellent synergistic effects in combination with conventional drugs. Targeting these critical factors of lipid metabolism can effectively inhibit the metastasis and drug resistance of cancer cells, which has significant prognostic benefits for patients. However, there is still some controversy in existing studies regarding the role of lipid metabolism. For example, although statins can improve efficacy, negative feedback regulation is induced when lipids are reduced to a certain extent due to the complex regulatory network of lipid metabolism, eventually decreasing the efficacy of drugs targeting lipids. Moreover, decreased cell membrane cholesterol promotes membrane fluidity, activates procarcinogenic pathways, and increases metastasis ability [93,94]. FASN was also found to have a drug-induced proapoptotic effect during cisplatin treatment. However, FASN exerts an antiapoptotic function in TNBC and a proapoptotic role in triple-positive breast cancer (TPBC). The opposite effect of FASN may be related to the difference in gene levels between the two cell types, whose specific regulatory mechanism remains to be investigated [160]. Moreover, due to the dialog between immune cells, adipocytes and tumor cells in the tumor microenvironment, it is still an issue of concern to find effective methods to avoid affecting normal immune cells and reduce the occurrence of side effects. In summary, although treatments targeting lipids face enormous challenges, they remain promising and attractive strategies for improving therapeutic outcomes in breast cancer patients.

CRediT authorship contribution statement

Qian Xiao: Writing – original draft, Conceptualization. **Min Xia:** Writing – review & editing. **Weijian Tang:** Writing – review & editing. **Hu Zhao:** Writing – review & editing. **Yajun Chen:** Writing – review & editing. **Jing Zhong:** Writing – review & editing, Funding acquisition,

Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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