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Lipid profile in breast cancer: From signaling pathways to treatment strategies

Hennrique Taborda Ribas [a, b], Mari C. Sogayar [c, d], Amalia M. Dolga [a], Sheila M.B. Winnischofer [b, e, f, **], Marina Trombetta-Lima [g, *]

[a] Faculty of Science and Engineering, Department of Molecular Pharmacology, Research Institute of Pharmacy (GRIP), University of Groningen, Groningen, Netherlands
[b] Postgraduate Program in Biochemistry Sciences, Sector of Biological Sciences, Federal University of Paraná, Curitiba, Brazil
[c] Cell and Molecular Therapy Center (NUCEL), Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil
[d] Department of Biochemistry, Chemistry Institute, University of São Paulo, São Paulo, Brazil
[e] Biochemistry and Molecular Biology Department, Federal University of Paraná, Curitiba, Brazil
[f] Postgraduate Program in Cellular and Molecular Biology, Biological Sciences Sector, UFPR, Curitiba, Brazil
[g] Faculty of Science and Engineering, Department of Pharmaceutical Technology and Biopharmacy, Research Institute of Pharmacy (GRIP), University of Groningen, Groningen, Netherlands

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ABSTRACT

Breast cancer is the most prevalent cancer in women. Metabolic abnormalities, particularly increased lipid synthesis and uptake, impact the onset and progression of the disease. However, the influence of lipid metabolism in breast cancer varies according to the disease stage and patient's hormone status. In postmenopausal patients, obesity is associated with a higher risk and poor prognosis of luminal tumors, while in premenopausal individuals, it is correlated to BRCA mutated tumors. In fact, the tumor's lipid profile may be used to distinguish between HER2+, luminal and BRCA-mutated tumors. Moreover, drug resistance was associated with increased fatty acid synthesis and alterations in membrane composition, impacting its fluidity and spatial subdomains such as lipid rafts. Here, we discuss the subtype-specific lipid metabolism alterations found in breast cancer and the potentiality of its modulation in a clinical setting.

Contents

* Corresponding author. Department of Biomedical Sciences of Cells and Systems, Molecular Neurobiology Section, University of Groningen, University Medical Center Groningen, Antonius Deusinglaan 1, Groningen, Netherlands.
** Corresponding author. Biochemistry and Molecular Biology Department, Federal University of Paraná, Av. Cel. Francisco H. dos Santos, 100, CEP 81531-980, 19046, Curitiba, Paraná, Brazil.
E-mail addresses: sheilambw@ufpr.br (S.M.B. Winnischofer), m.trombetta.lima@rug.nl (M. Trombetta-Lima).

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Abbreviations list

HER	Human Epidermal Growth factor receptor
ACCA	Acetyl CoA carboxylase
ATM	Ataxia Telangiectasia Mutated
ATR	Ataxia Telangiectasia and Rad3-related
Cer	Ceramide
COSY	Correlated Spectroscopy
CK	Choline kinase
TNBC	Triple Negative Breast Cancer
HR	Hormone Receptor
HR-MAS MRS	High Resolution Magic Angle Spinning Magnetic Resonance Spectroscopy
ER	Estrogen Receptor
PR	Progesterone Receptor
BRCA	Breast cancer gene
IGF-I	Insulin-like growth factor I
FA	Fatty Acid
FASN	Fatty Acid Synthase
EGFR	Epidermal growth factor receptor
PI3K	Phosphatidylinositol-3-kinase
RAS	Rat sarcoma
MAPK	Mitogen-Activated Protein Kinase
MUFA	Monounsaturated fatty acid
DESI-MSI	Desorption Electrospray Ionization Mass Spectrometry Imaging
TKR	Tyrosine-kinase receptors
TCGA	The Cancer Genome Atlas
AKT	Protein Kinase B
RAF	Rapidly Accelerated Fibrosarcoma
TG	Triacylglycerols
PC	Phosphatidylcholine
PI	Phosphatidylinositol
PE	Phosphoethanolamine
PG	Phosphatidylglycerol
PUFA	Polyunsaturated fatty acid
WHO	World Health Organization
SFA	Saturated fatty acid
SCD1	Stearoyl-CoA desaturase 1
TNBC	Triple negative breast cancer
CPT1	Carnitine palmitoyltransferase I

1. Introduction

Breast cancer is the most prevalent cancer in women, leading to the greatest number of cancer-related deaths among this population. According to the World Health Organization (WHO) [1], in 2020, 2.3 million women were diagnosed with breast cancer and globally the disease was responsible for 685,000 deaths. Even though it is more prevalent in women, breast cancer also affects men, however, in a lower proportion [2].

Cancer cells show metabolic abnormalities, which impact cancer onset and progression [3]. Lipid metabolism (synthesis and enhanced uptake) has been shown to play an important role in tumorigenic phenotypes [3].

Obesity has been associated with breast cancer risk and poor prognosis, with obese women showing an increased risk of developing malignant stages and an increased death rate [4,5]. A population-based cohort study of 17,145 women showed that healthy lifestyle factors such as weight would improve breast cancer prevention and survival [6]. Visceral and peritumoral fat tissue plays an important role in promoting and sustaining mammary carcinoma, leading to shorter disease-free survival and higher probability of developing lymph node-positive breast cancer [7]. Moreover, it has been shown that adipocytes are able to transfer fatty acids to breast cancer cells. This transport was enhanced by adipocytes supplemented with high concentrations of fatty acids (FAs), leading to increased cell proliferation and migration [8,9]. The relation between adipose tissue, obesity and cancer is better described elsewhere [5,10–12].

Lipid metabolism is a complex, tightly regulated process that plays a crucial role in the structure, energy metabolism, and signaling of cells. Lipids are not only vital for cell membrane integrity but also serve as fundamental components in energy storage and cell signaling pathways and are deeply reviewed elsewhere [13,14]. Glycerophospholipids, such as phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine, as well as sphingolipids are important components of the cellular membrane [15,16]. Whereas the glycerophospholipid, phosphatidylinositol (4,5)-bisphosphate and some sphingolipids exhibit signaling properties, contributing to a diverse range of cellular pathways [15,17]. Additionally, sterol lipids, such as cholesterol, also play a pivotal role in important cellular mechanisms and influence membrane biophysics [18]. Finally, fatty acids (FAs) are the most important energy store and necessary lipid building blocks used to generate a range of different lipids [13].

FAs play an essential role in cancer progression and development, which reflects their role in modulating cell membrane composition, constituting an additional energy source, being involved in metabolic reprogramming, and acting as precursors of signaling molecules. FAs are necessary lipid building blocks used to generate several different lipids, with tumor cells shifting towards FA synthesis when compared to normal cells, which prefer FA from exogenous sources [3]. Limiting FA synthesis has been shown to control cancer cell proliferation and higher rates of FA synthesis have been implicated in breast cancer risk, progression and drug resistance [19]. Increased FA levels may also be achieved by increased FA uptake. In breast cancer, it has been described that the FA receptor CD36 is upregulated, being responsible for increased FAs uptake, leading to drug resistance [20].

Breast cancer tissues display a specific lipid signature, which is different from that of normal tissues. Hence, lipid profiling has been shown to allow the classification of breast tumors, being a helpful tool in breast cancer grading [21,22]. In the present review, we discuss how mammary cancer molecular subtypes differ regarding their lipid profiles and how this information could be used for diagnostic and therapeutic purposes.

2. Lipids and breast cancer signaling pathways

Breast cancer consists of a group of heterogeneous subtypes in which different pathways dysregulation are involved [23]. Lipid metabolism would be strictly related to these important pathways that rule oncogenic properties of the different breast tumor subtypes. Exploring the pathway perspectives may highlight potential lipid-based diagnostic tools and therapeutic targets. Here, we focus on three pathways that are particularly important to the development of the disease: epidermal growth factor, estrogen and progesterone receptors, and BRCA pathways. Our objective is to gain deeper insights into the roles of lipid metabolism and its interplay with the signaling pathways specific to each cancer subtype. Firstly, we will briefly describe the signal transduction processes of the important pathways related to breast cancer markers and subtypes. Subsequently, we will explore the modulation of lipid metabolism in the context of each pathway, examining their respective roles. Additionally, we will explore the lipid profiles that are implicated as potential new cancer markers.

2.1. Epidermal growth factor pathway

In epithelial mammary tumors there is an increased expression of epidermal growth factor receptors (EGFR), therefore, these receptors have become important therapeutic targets [24]. The EGFR family includes four members, namely: EGFR (also known as ErbB1, EGDR, or HER-1), HER-2 (or ErbB2); HER-3 (or ErbB3) and HER-4 (or ErbB4). Among them, HER-2 is overexpressed in about 20% of breast carcinoma, being associated with poor prognosis [25,26]. These receptors are tyrosine-kinase receptors (TKR) that become activated through association with a ligand, which induces a change in the receptor conformation and formation of a dimer [27]. This dimer leads to an auto- or transphosphorylation of the TK domain [27]. The activated receptors then bind to adaptative proteins, such as SHC and GRB2, activating different signaling cascades, such as RAS (Rat sarcoma)/RAF (Rapidly Accelerated Fibrosarcoma)/MAPK (Mitogen-Activated Protein Kinase) and PI3K (Phosphatidylinositol-3-kinase)/AKT (Protein Kinase B) (Fig. 2) [28]. The downstream PI3K/AKT and MAPK signaling pathway play an important role in modeling lipid metabolism by inducing FASN expression [29,30] (Fig. 1).

HER2 is primarily situated within lipid raft regions, characterized by cholesterol and sphingomyelin-enriched membrane microdomains. The HER2 sub-cellular localization is essential for its proliferative role [32,33]. Disruption of these membrane microdomains leads to proliferation arrest and apoptosis of breast cancer cells overexpressing HER2 [34,35]. An important role of membrane lipids in the HER2 cancer subtype was shown by the lipid profile clinical data. Breast cancer patient samples analyzed by DESI-MSI showed that the HER2 subtype cancer could be identified and distinguished from other types by the presence of four lipids with positive charges: i) one assigned as steroid or FA weighting (m/z 359.2720), ii) a phosphoethanolamine (PE) molecule (m/z 751.5530), iii) phosphatidylglycerol (PG) (36:3) (m/z 771.5280), and iv) a phosphatidylinositol (PI) (36:4) (m/z 857.5380) [31].

Disruption in microdomains has also demonstrated the ability to reverse Tamoxifen resistance mediated by HER2 in 2D in vitro cultures [36]. Furthermore, the HER2 surface location seems to be regulated by the physical properties of the membrane. Reduced cholesterol levels lead to decreased membrane fluidity, subsequently promoting HER2 degradation and inhibiting cell growth [37].

Lipidomic analysis of the membranes of breast cancer cell lines further reinforces these findings, highlighting increased levels of PI(34:1) and phosphatidylcholine (PC) (28:0) in HER2-overexpressing cells when compared to other subtypes [38]. It's important to note that the presence of these lipids, which are indeed abundant in all mammalian cells and cell membranes, can vary on species according to the length and unsaturation of their fatty acid chains. In this context, the (PC) (28:0) and PI(34:1) species would serve as a specific marker for the HER2+ cancer subtype. It is worth mentioning that phospholipid species have been extensively explored as disease biomarkers, emphasizing the clinical significance of these lipid profiles [39–41].

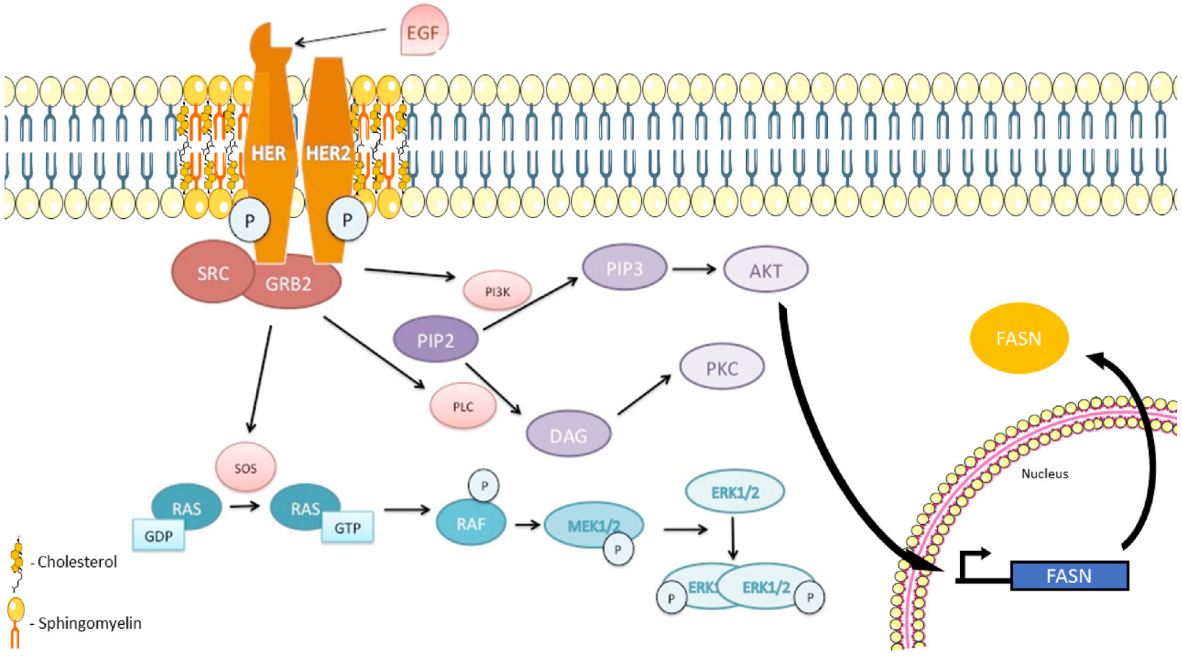

Fig. 1. Epidermal growth factor pathway. Ligand association leads to dimerization and auto- or transphosphorylation of the EGF receptors. Lack of binder domain is shown for the HER2 receptor. Receptors activation leads to the activation of several signaling pathways, such as that of AKT, leading to FASN transcriptional activation.

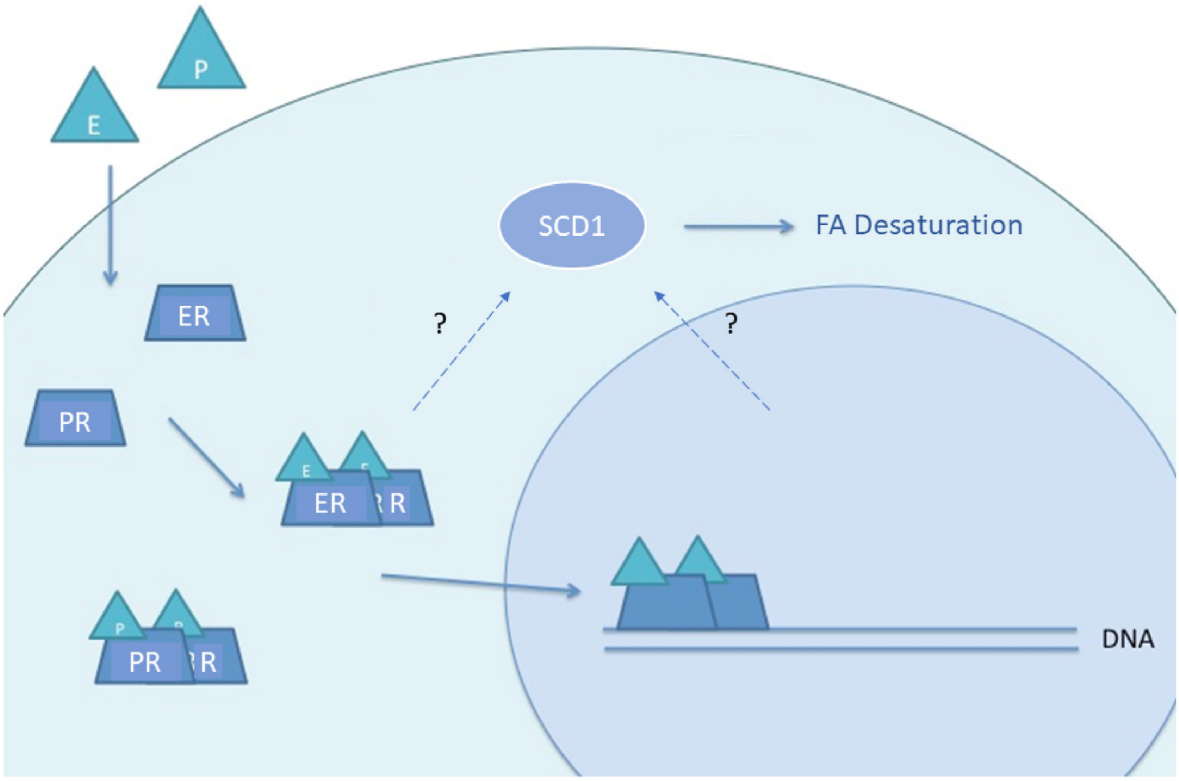

Fig. 2. Estrogen and progesterone receptors pathway. Binding of the steroidal hormone to its receptor leads to a conformational change, which results in dissociation of embedded chaperone complexes and dimerization of the ligand-receptor complexes. When the activated receptors are translocated to the nucleus, they act by recognizing responsive elements in the promoters of target genes, thereby modulating their expression. When present in the cytoplasm, these receptors interact with different protein partners. FA denaturation is one of the modulated pathways, although the exact molecular mechanism is still unclear.

While an elevated presence of these lipids, detected by clinical studies, would be promising as a diagnostic or prognostic marker, it also provides mechanistic evidence of the significance of these lipids and their metabolism in HER2+ breast cancer. Whole-cell lipidomic analysis of HER2+ cell lines revealed a distinct lipid profile. HER2+ cells exhibit elevated levels of triacylglycerols TG (C-46), PC, and PE containing short-chained (C-16) fatty acids and oleic acid (18:1); concomitantly displaying low polyunsaturated fatty acid and palmitic acid (C16:0) levels [42,43]. In HER2+ cells, palmitate (C16:0) treatment induces apoptosis accompanied by AMPK activation, inhibition of fatty acid synthesis and reduction of HER2 expression, while cells expressing normal levels of HER2 are not sensitive to this treatment [44,45]. This specific response illustrates the lipids' potential for the treatment of HER2+ breast tumors.

Interestingly, HER2 has been shown to modulate lipid metabolism. Clinical analysis of proteomic and transcriptomic co-expression networks revealed that HER2 is linked to lipid biosynthesis in breast cancer [46]. In HER2+ tumors, higher levels of proteins related to lipid metabolism, including FASN and CPT1, are observed compared to other breast cancer subtypes in patient samples [47].

Moreover, the overexpression of HER2 in breast cancer cell lines demonstrates the capacity to modulate lipid metabolism by upregulating the expression of genes involved in fatty acid synthesis and uptake, such as FASN and CD36 [48]. CD36 expression is linked to a poor prognosis in breast cancer patients undergoing anti-HER2 therapy and is upregulated in cells that develop resistance to lapatinib, a HER2 inhibitor. Remarkably, the inhibition of CD36 effectively suppresses the growth of lapatinib-resistant cells, both in vitro and in vivo [20].

HER2 was shown to increase *FASN* expression by activating its promoter through the PI3K pathway, whereas FASN inhibition is more effective on HER2-overexpressing breast epithelial cells [49,50]. Inhibition of PI3K/AKT suppresses HER2-overexpressing breast cancer cell proliferation and induces apoptosis, accompanied by reduction of HER2 and FASN expression [51,52]. Additionally, the application of a selective FASN inhibitor induces apoptosis in HER2-overexpressing breast cancer cells and reduces HER2+ tumors in in vivo models [53]. Notably, the overexpression of FASN has been demonstrated to increase the expression of HER1 and HER2, activating their respective receptors and contributing to the development of a breast cancer-like phenotype in human breast epithelial cells [54].

2.2. Estrogen (ER) and progesterone (PR) receptor pathways

The steroid hormones estrogen, and progesterone are involved in regulating proliferation, dedifferentiation, metabolism, and homeostasis of several tissues, such as the reproductive tissues [55,56]. These hormones activate intracellular receptors within target cells, which, in turn, function as ligand-dependent transcription factors, directly controlling gene expression (Fig. 2). The responsiveness of mammary tumors to steroids holds considerable clinical significance, as it enables the implementation of hormonal therapy strategies [57].

Hormone receptor-positive (HR+) breast cancers are associated with worse outcomes in obese patients, suggesting a connection between these types of cancer and metabolic disorders [58]. Compellingly, in a cohort study evaluating 337,327 women, it was observed that high total fat or saturated fat consumption is associated with a high risk of developing ER + PR + breast cancer [59].

Several studies have demonstrated a positive correlation between obesity and worsened outcomes in the luminal subtype [4,58,60–63], characterized by high levels of hormone receptors [23,64]. However, the increased risk of HR + breast cancer development with obesity is more evident in postmenopausal women, whereas in premenopausal patients, obesity-associated breast cancer is more associated with hormone-negative breast tumors [5,65,66]. Taken together, these results indicate that lipid metabolism plays different roles in cancer development according to the hormone status.

While saturated fat consumption and obesity may have a connection to the diagnosis and prognosis of hormone receptor-positive (HR+) breast tumors, adhering to diets rich in monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs), such as those in the Mediterranean diet, does not appear to reduce the risks of developing this cancer [67] However, recent findings from a multicenter case-control study by Lopes and collaborators emphasize the need to analyze the breast cancer risk associated with PUFAs and MUFAs individually. Their research indicates that higher levels of erucic acid, a monounsaturated fatty acid in plasma, are associated with a reduced risk for HR + breast cancer. Conversely, elevated levels of saturated pentadecanoic fatty acid are linked to an increased risk of HR + breast cancer [68].

Additionally, evaluation of Stearoyl-CoA desaturase 1 (SCD1) expression, the enzyme responsible for the conversion of PUFA into MUFA, showed that HR + samples present the highest levels of expression of this gene when compared to other subtypes [69]. Furthermore, MALDI-imaging mass spectrometry (IMS) revealed that ER + breast cancer patient tissues presented the ratio of MUFA-PC [PC(34:1)] to SFA-PC [PC(34:0)] higher than ER-lesions [70]. Considering the role of PUFAs in lipid peroxidation, it is observed that ER + plasma patients have higher levels of lipid peroxidation than other subtypes [71]. This suggests that despite the potential risk reduction associated with erucic acid, different endogenous MUFAs and PUFAs may play tumorigenic roles in hormone-positive breast cancer.

Furthermore, it has been demonstrated that de novo fatty acid synthesis is also modulated based on hormone status. The downregulation of SCD1 and FASN expressions through the knockdown of the resistance-associated splicing regulator factor ESRP1 disrupts lipid metabolism and reduces proliferation of endocrine-resistant breast cancer cells [72]. Metabolomic analysis of breast cancer patients showed that ER + tumors contain elevated levels of short- and medium-chain fatty acids, as well as increased carnitine derivative levels, compared to ER-, suggesting an elevated fatty acid transportation rate [73]. It has been shown that FASN further regulates the Erα signaling pathway in mammary carcinoma cells [74,75]. Taken together, these data suggest that SCD1 and FASN could play an important role in this subtype of cancer through the regulation of fatty acid metabolism; therefore, they constitute promising therapeutic targets. However, due to the dual role of MUFAs and PUFAs, more research is necessary to elucidate the role of specific fatty acids in HR + breast cancer.

Furthermore, other lipids may be associated with hormone status and could potentially serve as markers for this subtype of breast cancer. Lipidomic analysis of patient samples identified four key lipids essential for distinguishing the luminal A breast cancer subtype (ER+ and/or PR+): i) linoleic acid (*m/z* 279.2330), ii) ceramide (d40:1) (*m/z* 656.5760), and iii) two glycerophospholipids (*m/z* 765.5190 and *m/z* 772.5020). Additionally, two other glycerophospholipids, PG (32:3) (*m/z* 751.4860) and PI (36:2) (*m/z* 861.5330), were shown to play a crucial role in distinguishing the luminal B subtype (ER+ and/or PR+, as well as PR < 20% and HER2+) [31].

Although the presence of those glycerophospholipids was able to assign HR + breast cancers, other reports assessing patient samples and xenograft models by HRMASMRS (High Resolution Magic Angle Spinning Magnetic Resonance Spectroscopy) described that HR + samples presented lower levels of total glycerophosphocholine, while showing higher levels of phosphocholine due to alterations in choline metabolism [76–80]. Another lipidomic analysis in tissue samples, comparing ER + versus ER- patients, indicated alterations in several phospholipids and sphingolipids levels according to their ER status. In this study, ER + tumors presented higher levels of glycosylated ceramides and lower levels of phospholipids and sphingomyelins [81]. This data strongly suggested that the HR status is related to lipid membrane modulation, although there is still controversy and unclarity regarding its mechanism.

Metabolomic and transcriptomic approaches using breast cancer cells following estrogen stimulation demonstrated a reduction of glycerophosphocholine levels due to alteration of different Erα target genes expression, which, in turn, could impact choline metabolism [82]. It has already been described that alterations in choline metabolism and in the glycerophospholipid pathway are found in a variety of cancers [83,84]. However, regulation of choline phospholipid metabolism and membrane composition modulation would be more relevant to the hormone receptor-positive breast cancer subtype.

2.3. BRCA1 and BRCA2 pathways

The BRCA1 (BReast CAncer type 1 susceptibility protein) and BRCA2 (BReast CAncer type 2 susceptibility protein) are involved in genomic stability maintenance by mainly acting through the homologous recombination repair, and their malfunction could lead to mammary tumor development [85]. Homologous recombination is initiated by the concerted actions of two essential protein kinases, ATM (Ataxia Telangiectasia Mutated) and ATR (Ataxia Telangiectasia and Rad3-related). This process is crucial to the DNA double-strand break repair, in which the undamaged sister chromatid serves as the template for repairing the damaged DNA strand, ensuring the fidelity of the repair process [86].

Genetic studies have shown that *BRCA2* single nucleotide polymorphism is related to lipid metabolism and lipid serum levels [87,88]. Interestingly, diabetes risk is doubled among women diagnosed with breast cancers carrying *BRCA* mutations, suggesting a link between breast cancer *BRCA* carriers and metabolic disorders [89]. Although the association between breast cancer, obesity and diabetes is more evident in postmenopausal women [65,90], patients carrying *BRCA* mutations are more likely to be premenopausal [89]. Therefore, metabolism disorders, such as obesity, would be related to HR + breast tumor in postmenopausal women, whereas in premenopausal patients these disorders are more related to BRCA carriers.

Lipid modulation was described in breast tissues of BRCA mutation carriers by using two-dimensional (2D) correlation spectroscopy (COSY) in vivo analysis, showing that BRCA1 patients present higher levels of triglycerides and unsaturated lipids, while BRCA2 carriers present higher levels of cholesterol, also in addition to higher unsaturated lipids levels [91].

In vitro studies have shown that BRCA1 could modulate lipid synthesis by interacting with the phosphorylated form of Acetyl-CoA Carboxylase, preventing its dephosphorylation and activation, which is important for BRCA1-mediated tumor suppression (Fig. 3). When BRCA1 is downregulated, phospholipids, triglycerides, and fatty acid synthesis are increased [92,93]. These results were further confirmed by metabolomic analysis of TCGA (The Cancer Genome Atlas) subjects, demonstrating that *BRCA1* expression is positively correlated with increased fatty acid β-

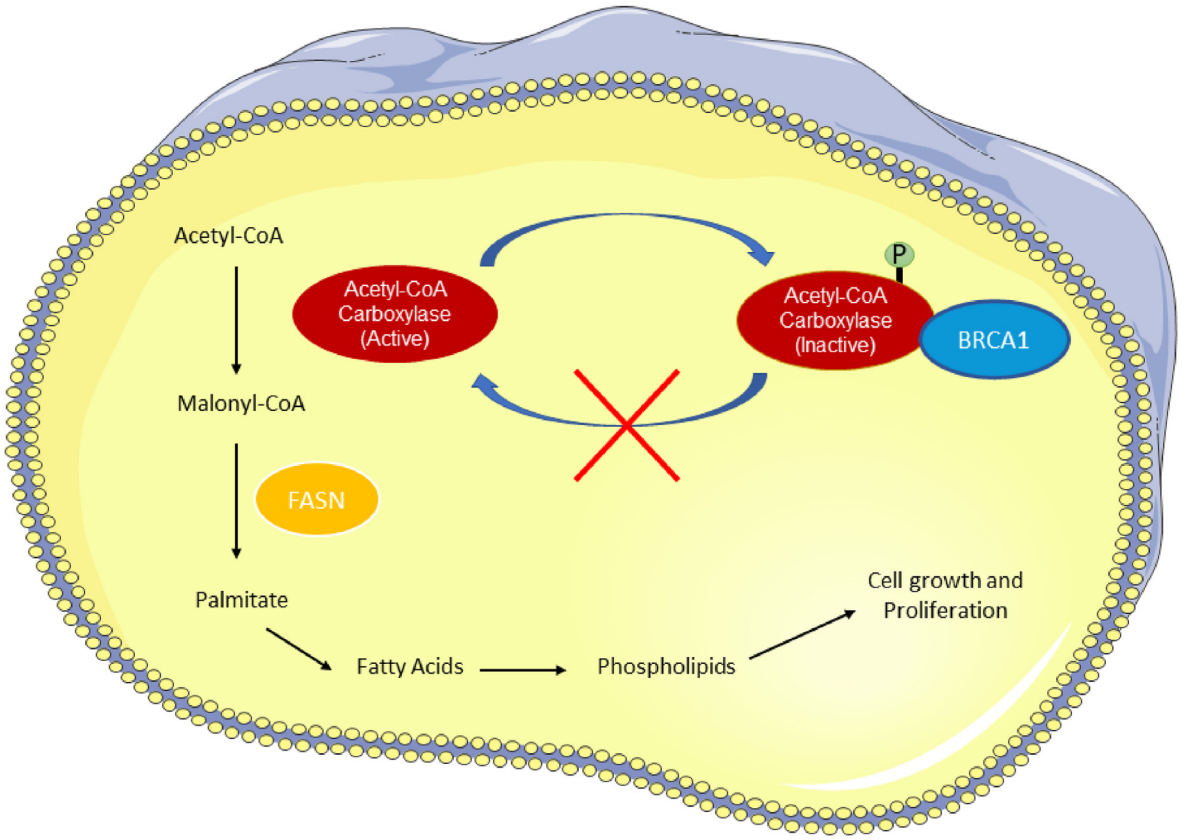

Fig. 3. Lipid metabolism regulated by BRCA1. BRCA1 modulates lipid metabolism by interacting with the inactive form of Acetyl-CoA Carboxylase thereby preventing it to be dephosphorylated and further activated.

oxidation and it is inversely correlated with membrane components and long-chain fatty acids levels [57]. Furthermore, *BRCA1* transfection promotes an increased level of MUFA, together with decreased levels of free fatty acids and of saturated fatty acids [78]. The lipogenic effects of BRCA1 were further investigated showing that BRCA1 modulates lipid metabolism by inhibiting the action of the insulin-like growth factor I (IGF-I) [94,95].

Commonly, tumors showing deletion mutations in *BRCA1* lack expression of *EGF2* (Epidermal Growth Factor 2), as well as of the estrogen and progesterone receptors. On the other hand, tumors that show deletion mutations in *BRCA2* generally exhibit the expression of estrogen and progesterone receptors. Some mutations in BRCA1 and 2 are considered risk factors for mammary or ovary cancer development; therefore, they are described as highly penetrant genes for those types of cancers.

Increased lipogenesis has been described in several cancer types as being important for breast cancer progression and growth [96,97]. These pieces of evidence suggest that lipid metabolism is a key player in the tumorigenic process in patients harboring *BRCA* mutations.

2.4. Triple negative breast cancer (TNBC)

The triple negative breast cancer subtype is distinguished by the lack of ER and PR expression, as well as the lack of HER2 expression and the absence or low expression of BRCA1 (which may be inherited or sporadic) [98]. Furthermore, the neoplastic cells of those tumors show a high proliferation index and similar characteristics of basal/myoepithelial normal cells, such as EGFR expression, p63, and P-cadherin (a protein involved in cell-cell adhesion and a marker of worse prognosis in mammary cancers). The absence or low expression of BRCA1 -which may be inherited or sporadic - is another characteristic of this class of tumors. Commonly, necrotic areas in the tumor and the presence of lymphocyte infiltration are observed. Due to these characteristics, these tumors display worse prognosis, and lower overall and disease-free survival [99].

Elevated choline metabolism, leading to an increase in choline-containing species, has been linked to increased tumor malignancy and a positive correlation with higher tumor grades in breast cancer [83,100]. Since TNBC is commonly associated with a more aggressive behavior, increased levels of choline metabolites are expected to play an important role in this subtype [101].

Clinical analysis has shown that TNBC displays higher levels of choline metabolites, as demonstrated by lipidomic analysis of TNBC patient samples. Plasma analysis indicates that choline and glycerophospholipid levels are associated with this cancer subtype [102,103]. Breast cancer H-MRS (Proton Magnetic Resonance Spectroscopy) showed that TNBC patients display higher concentrations of total choline [104,105]. Whereas lipid extracts from tumor tissues have shown that TNBC subtype presents a higher glycerophosphocholine to phosphocholine ratio and elevated levels of phosphatidylcholine PC (32:0) and PC (32:1) [21,76,80,106]. Elevated levels of PC (32:1) were also correlated to TBNC recurrence and they could be used as TBNC recurrence predictors [107].

Cellular models also confirm the important role of choline metabolism in TNBC. Those cells also display an increased amount of phosphatidylcholine compared to other subtypes [43]. The elevated levels of phosphatidylcholine are attributed to high choline kinase α (CKα) expression, with the MDA-MB-231 TNBC cell

line showing the highest CKα protein levels among breast cancer cell lines [38,83]. CKα downregulation by RNAi reduces the amount of total choline-containing compounds and decreases MDA-MB-231 proliferation, suggesting that choline metabolism is important for TNBC malignancy [108].

Phosphatidylcholine could also be important in TNBC therapy resistance since increased amounts of this phospholipid were also described in TNBC cells after radio-resistant acquirement [109]. The most abundant lipid in the membranes is phosphatidylcholine, suggesting that cellular membrane modulation could play an important role in TNBC [110].

Other cell membrane constituents were also correlated to TNBC. The lipidomic profile of TNBC demonstrated that sphingolipid metabolism is disrupted in this subtype, with elevated levels of several very long chain ceramides, Cer 36:1, Cer 42:2, Cer 43:1, Cer 44:2, Cer 42:3, and Cer 38:1 in the plasma of patients [102]. It has been shown that the length of ceramide chain may play different roles in cancer, suggesting that very long chain ceramides could promote breast cancer cell proliferation [111]. Furthermore, it has been demonstrated that the elongase ELOVL1 is important for the synthesis of very long ceramides [112]. Interestingly, higher gene expression of ELOVL1 was described in TNBC patient tissues, compared to other subtypes [113]. Lipidomic analysis of breast cancer tissues further linked another sphingolipid (sphingomyelin) to TNBC tumor, however, this study showed that higher levels of this lipid are correlated with a better prognosis, suggesting that sphingomyelin could be used as a prognosis marker in TBNC [114]. Taken together, these data highlight long-chain ceramides's role in TNBC.

Although all of these clinical and cellular data suggested that constituents of the cell membrane are important to the TBNC tumor biology, this subtype of breast cancer is very heterogeneous, which would result in different metabolic regulation according to specific TNBC subgroups [115]. Using multi-omics approaches, Gong et al. suggested a sub-classification of TBNC based on metabolic pathway features, leading to the three specific subtypes, one of which is lipid related, presenting upregulation of genes involved in lipid synthesis [116]. Therefore, modulating lipid metabolism would be only relevant to this subgroup of TNBC. More studies are necessary to better understand the correlation of membrane composition and organization with TNBC biology.

3. Modulation of lipid metabolism as a tool for subtype-specific cancer treatment

Targeting lipid metabolism has been described as a potential therapeutic strategy for cancer treatment [117]. Therefore, according to the lipid profiles of the different mammary cancer molecular subtypes, we would indicate specific therapeutic strategies (Fig. 4).

FASN expression has been associated with different types of cancer and is particularly high in breast cancer, therapies targeting this protein have gained more attention over the last few years. Therefore, several FASN inhibitors have been developed [118–120]. However, the only clinical FASN inhibitor available is TVB-2640, which is currently in phase II clinical trial, and recruiting candidates for HER2-positive metastatic breast cancer treatment (NCT03179904) following promising results from the phase I trials [121].

As previously discussed, the crosstalk between FASN and HER2 expression plays an important role in HER2+ tumors, therefore, inhibiting FASN activity represents a potential therapeutic strategy for this subtype of breast cancer. Several pre-clinical studies have shown that FASN inhibitors present antitumor activity in HER2+ breast cancer, as reviewed elsewhere [122]. In addition, FASN plays an important role in synthesizing phospholipids that integrate lipid rafts modeling the membrane fluidity, and its inhibition could impair HER2 activity by impacting lipid raft formation [123–125]. Disrupting lipid rafts by other mechanisms also induces apoptosis in breast cancer cells overexpressing HER2 [126]. As the lipidomic analysis suggests, membrane lipids might play an important role in the HER2 sub-type; therefore, drugs that affect the membrane composition and fluidity would also be promising for HER2 breast cancer therapy.

FASN inhibition would also be a promising therapeutic strategy to treat this breast cancer subtype. Considering the roles of MUFAs and SCD1 in HR + breast cancer, regulating saturated fatty acid levels by controlling SCD1 activity with SCD1 inhibitors would lead to potential therapeutic strategies. Inhibition of SCD1 has shown an antitumor effect in several cancer models; however, further studies are necessary to investigate its specific impact on HR + breast cancer [30].

Another key enzyme for lipid biosynthesis is acetyl CoA carboxylase (ACCA) which catalyzes a rate-limiting step to produce malonyl-CoA, a precursor of fatty acids synthesis [127]. Inhibitors of ACCA have shown antitumor activity in different tumor models [128,129]. Since BRCA1 interacts with and modulates ACCA activity, which could explain the lipid metabolism alterations that patients carrying *BRCA* mutations present, this enzyme would be a potential target to treat this sub-type of breast cancer [92]. However, additional studies are required to investigate this possible therapeutic approach.

Targeting choline kinase also constitutes a potential anti-cancer therapeutic strategy [130,131]. Preclinical studies have shown that different choline kinase inhibitors present antitumor activity in breast cancer [130,132–134]. The promising inhibitor TCD-717 is also in phase I clinical trial for solid tumors treatment (NCT01215864). In particular, targeting choline kinase would be an excellent strategy for TNBC treatment since the choline metabolism was shown to influence malignancy displayed by this breast cancer sub-type.

Together with the plethora of serum biomarkers discussed in this review, exploring the modulation of lipid metabolism has great potential not only for sub-type-specific strategies but also for patient-tailored strategies.

4. Conclusion

Through an exploration of clinical data, experimental studies, and epidemiological findings, we have discussed the role of lipid metabolism and its relationship with the distinctive signaling pathways that characterize different breast cancer subtypes.

The heterogeneity observed in lipid profiles, coupled with the specific alterations in various lipid species, highlights the relevance of lipid metabolism on each breast cancer subtype. From the epidermal growth factor pathway in HER2+ cancers to the hormone receptor-positive subtypes, lipidomic analyses have shown potential diagnostic and prognostic markers that would be promising for breast cancer diagnosis and treatment.

It is important to acknowledge that the lipid metabolism and breast cancer crosstalk field is continuously evolving. There remains a need for further research to elucidate the precise mechanisms by which lipids influence tumor development and progression. Additionally, while the utilization of lipid metabolism as a therapeutic target is still limited, the emerging therapeutic strategies hold great promise. As new therapeutic strategies emerge, the potential for targeting specific lipid-related processes opens exciting possibilities for the development of more effective treatments.

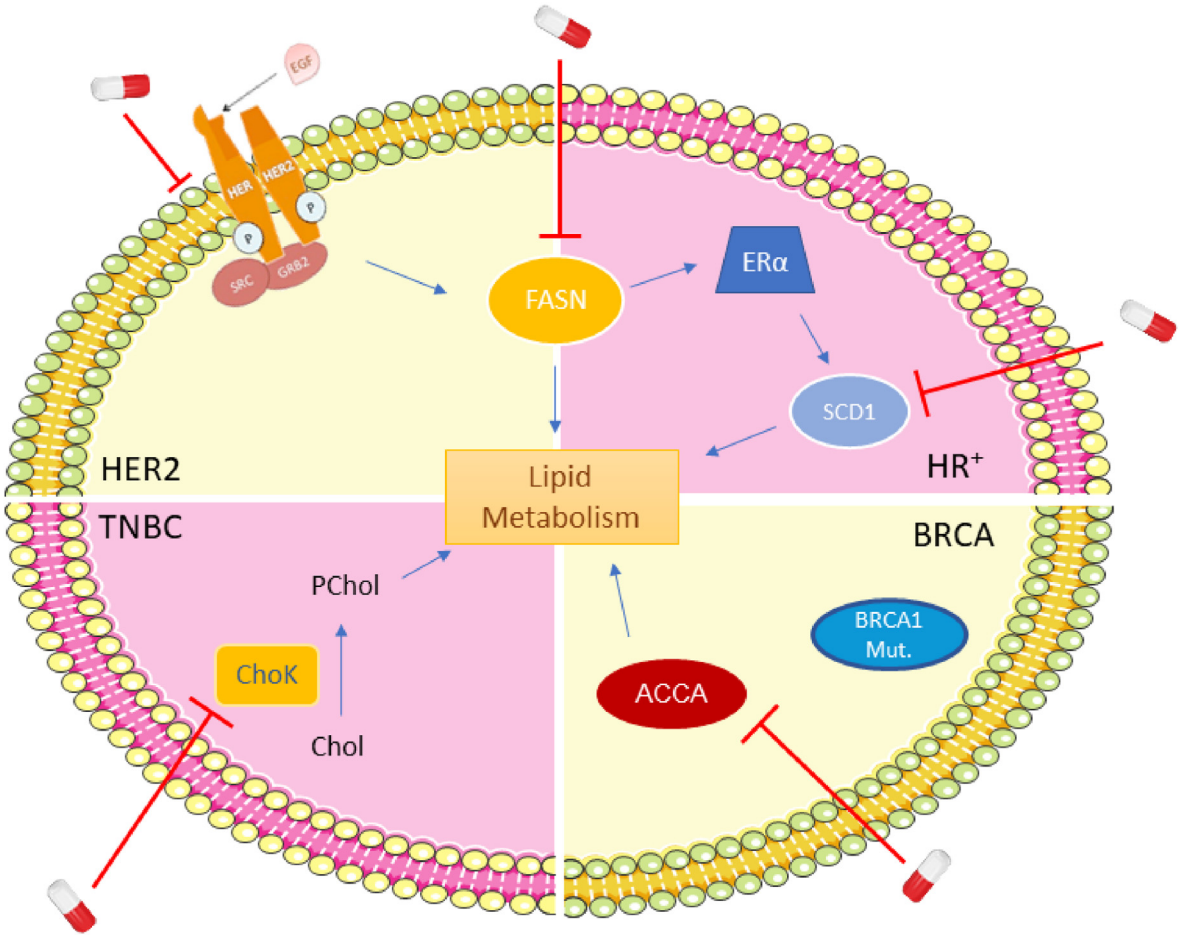

Fig. 4. Modulation of lipid metabolism as a tool for subtype-specific cancer treatment. Subtype-specific druggable targets for breast cancer. HER2 subtype: modulation of membrane composition, FASN inhibition. HR + subtype: FASN inhibition, SCD1 inhibition. BRCA subtypes: ACCA inhibition. TNBC subtype: Choline Kinase (ChoK) inhibition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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