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REVIEW

Breast Cancer Progression by the FGF/FGFR Axis: A Metabolic Perspective

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Abstract
Fibroblast growth factor receptors (FGFRs) are critical mediators of cellular signaling involved in development, tissue repair, and metabolic homeostasis. Dysregulated FGFR signaling is also a common feature in multiple cancer types, including breast cancer. In breast cancer, aberrant FGFR signaling can occur by amplification, mutation, isoform switching, or gene fusion and has emerged as a driver of tumor progression, metastasis, and therapeutic resistance. Beyond its canonical roles in proliferation and survival, recent evidence highlights FGFRs as key regulators of cancer cell metabolism. This review summarizes current findings on how FGFR signaling reprograms metabolic pathways in breast cancer, specifically glycolytic and lipid metabolism. We explore the interplay between FGFR activity and metabolic enzymes, transcription factors, and nutrient-sensing pathways, emphasizing subtype-specific metabolic vulnerabilities. Furthermore, we discuss how FGFR-mediated metabolic plasticity contributes to tumor heterogeneity and resistance to targeted therapies. Understanding the metabolic functions of FGFR signaling offers new opportunities for therapeutic intervention and biomarker development in breast cancer.

Keywords Breast Cancer · Cancer Biology · Cell Signaling · Metabolism

Background

Breast cancer is the most commonly diagnosed malignancy in women and the second leading cause of cancer-related deaths [1]. Breast cancer can be broadly classified by the expression of the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2). Breast cancers that do not express these receptors are referred to as triple-negative breast cancer (TNBC). Patients with ER-positive or HER2-positive tumors benefit from targeted therapies. While chemotherapy has long been the standard of care for TNBC, the use of immunotherapy, antibody-drug conjugates, and PARP inhibitors have shown promise in improve TNBC outcomes [2–5]. Despite vast improvements in breast cancer treatment, nearly 20% of patients will have relapsing disease [6], indicating the need for continued improvement. Fibroblast growth factors (FGFs) and their receptors (FGFR) regulate a wide range of cellular processes including morphogenesis, proliferation, differentiation, and migration. During mammary gland development [7], FGFR signaling is essential for ductal outgrowth and terminal end bud branching [8]. Consequently, components of FGFR signaling are frequently dysregulated in breast cancers. The oncogenic functions of the FGF/FGFR signaling axis range from driving oncogenesis to promoting therapeutic resistance. While these mechanisms of FGFR-driven tumorigenesis are well understood [9, 10], aspects of FGFR signaling, namely metabolic regulation, have remained largely unexplored in the cancer field. Recent studies indicate that the FGF/FGFR signaling axis regulates cellular metabolism in breast cancer cells, indicating a previously unknown tumor promoting role of FGFR signaling. This review highlights the known roles of FGFR signaling in regulating metabolism and in

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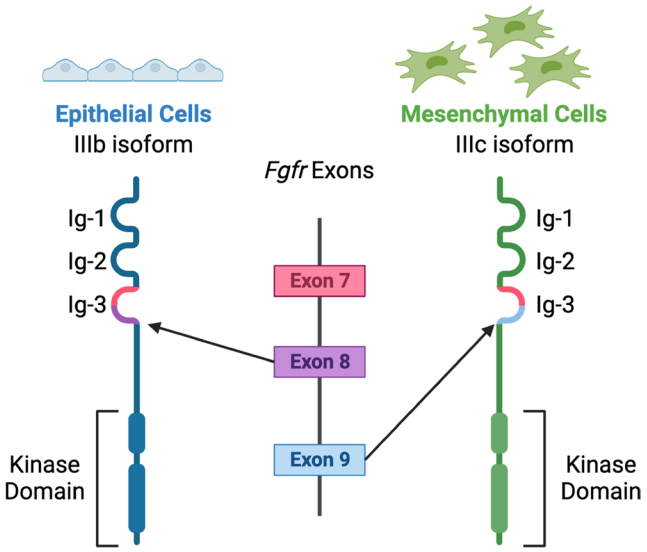

Fig. 1 FGFR alternative splicing. FGFR1-3 undergo alternative splicing in the Ig-3 domain, resulting in the IIIb and IIIc isoforms of FGFR

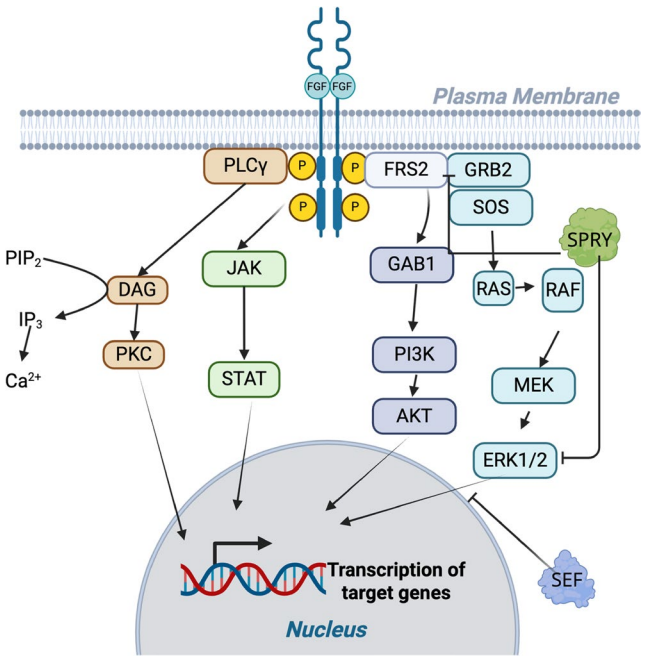

Fig. 2 The FGFR signaling pathway. FGF ligands bind to FGFR to induce receptor dimerization. This dimerization leads to autophosphorylation of the intracellular kinase domains. FRS2 binds to the phosphorylated kinase domains and serves as a scaffold for ERK and AKT signaling. PLCγ also binds to the phosphorylated kinase domain, ultimately leading to the activation of protein kinase C (PKC)

breast cancer progression and presents emerging evidence that the FGF/FGFR axis plays a critical role in regulating cellular metabolism in breast cancer [11], uncovering a previously unrecognized tumor-promoting function of FGFR signaling.

The FGF/FGFR Signaling Axis

FGFRs are transmembrane receptor tyrosine kinases (RTKs) made up of three extracellular immunoglobulin (Ig)-like domains, an acidic box, a transmembrane domain, and a split intracellular tyrosine kinase domain. In mammals, there are four FGFRs and 22 ligands, 18 of which are found extracellularly and can bind to multiple FGFRs [12]. To help control signaling specificity, FGFR1-3 are alternatively spliced in the third Ig-like domain to generate a IIIb or IIIc isoform [13]. Typically, IIIb isoforms are expressed on epithelial cells and IIIc isoforms are expressed on mesenchymal cells (Fig. 1) [14].

Heparan sulfate proteoglycans (HSPGs) are co-factors necessary to facilitate the binding of FGFs to FGFRs [15]. This binding event leads to receptor dimerization and transphosphorylation of the intracellular tyrosine kinase domains. The adaptor proteins FGFR substrate 2 (FRS2) and phospholipase Cγ (PLCγ) bind the phosphorylated kinase domains and facilitate signaling through downstream pathways including phosphoinositide-3 kinase (PI3K)/AKT, extracellular signal-regulated kinase 1/2 (ERK1/2), signal transducer and activator of transcription (STAT) proteins, and protein kinase C (PKC) [16–19]. Extracellular and membrane-associated co-regulators also dictate FGFR signaling specificity. In addition to HSPGs, syndecans and glypicans influence ligand–receptor clustering and local ligand availability [20].

FGFR activation is tightly regulated by multiple mechanisms that modulate the magnitude, duration, and spatial distribution of the signal. Following activation, FGFRs undergo clathrin-mediated endocytosis, a process that both sustains signaling from early endosomes and limits it by routing receptors toward recycling or degradation pathways [21]. Ubiquitination of FGFRs by the E3 ligase CBL, recruited through GRB2, targets receptors for lysosomal degradation and constitutes a major attenuation mechanism [22]. Negative feedback loops provide additional control. Induction of Sprouty (SPRY) proteins by ERK activity inhibits FRS2-GRB2 interactions and attenuates MAPK signaling [23]. Similar Expression to FGF genes (SEF) functions as another feedback regulator by limiting ERK nuclear translocation or interacting directly with FGFRs to restrict signaling output [24]. Dual-specificity phosphatases (DUSPs) deactivate ERK and other MAPKs [25], while PKC-dependent phosphorylation can reduce receptor responsiveness and facilitate signal termination [26]. Figure 2 provides an overview of the structure of FGFRs and the FGFR signaling pathway.

Metabolic Roles of Endocrine FGFs

Three FGFs, FGF19 (and its mouse orthologue FGF15), FGF21, and FGF23, do not bind to HSPGs, which allows them to enter and travel through the body's circulation [27, 28]. These aptly named endocrine FGFs require the transmembrane protein Klotho, with FGF23 binding α-Klotho and FGF15/19 and FGF21 binding β-Klotho, to activate FGFR signaling [29, 30]. FGF15/19 is unique due to its unusually strong affinity for FGFR4; FGF15/19 is able to bind and activate FGFR4 signaling in the absence of any co-factors [31].

FGF15/19 is produced in the small intestine in response to bile acids. FGF15/19 primarily acts in the liver to decrease bile acid synthesis and increase glycogen synthesis and in adipose tissue to decrease lipolysis and increase insulin sensitivity (Fig. 3) [32]. Systemic administration of FGF19 results in weight loss and decreased blood glucose in mouse models of obesity and diabetes [33]. The majority of FGF21 is produced in the liver and then travels to adipose tissue to regulate glucose metabolism and enhance insulin sensitivity (Fig. 3). Systemic administration of FGF21 also promotes weight loss and lowers blood glucose and triglyceride levels [34]. FGF21 also plays a role in bone homeostasis and promotes osteoporosis by decreasing osteogenesis and increasing bone resorption [35], though this relationship is not fully understood. The metabolic functions of FGF23 differ from the other endocrine FGFs as its primary functions do not occur in adipose tissue. FGF23 is primarily produced by osteoblasts and osteocytes and primarily acts in the kidney where it inhibits phosphate reuptake, stimulates uptake of calcium and sodium, and regulates vitamin D metabolism [36]. The variety of functions performed by the endocrine FGFs illustrates the complex range of roles held by all FGF ligands.

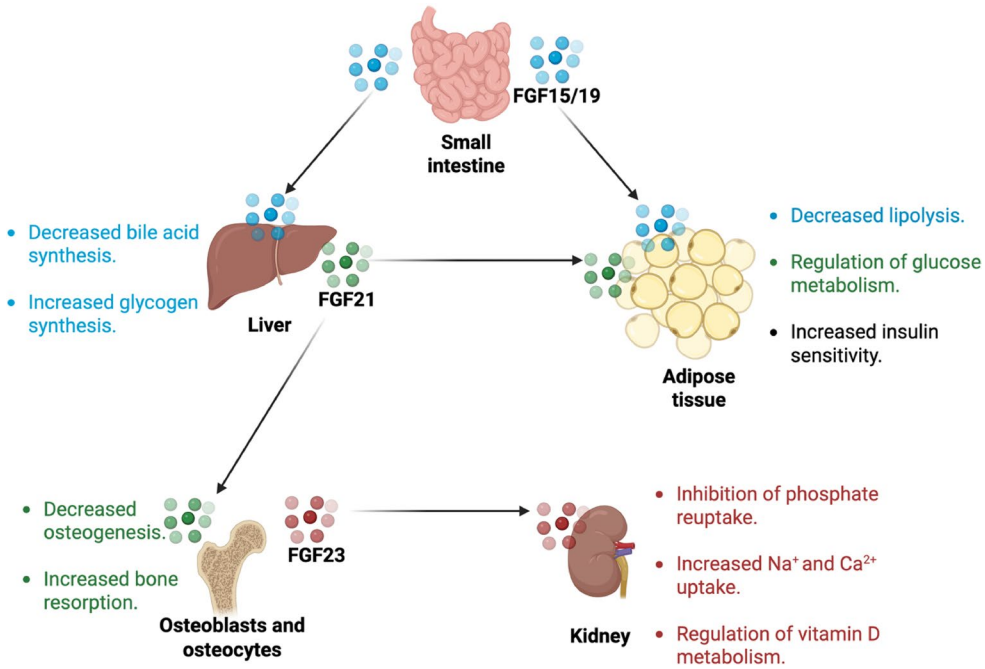

Fig. 3 The normal physiological functions of the endocrine FGFs

Metabolic Roles of Paracrine FGFs

While the endocrine FGFs are the primary FGFs associated with metabolism, there are several paracrine FGFs with known metabolic functions. Multiple FGFs can regulate blood glucose levels and insulin sensitivity. Systemic administration of FGF1, FGF2, FGF4, FGF8, and FGF9 lowers blood sugar and improves insulin sensitivity [37]. Despite these known roles, the physiological relevance of these functions remains unclear because the activity of these FGFs is limited to the tissues in which they are expressed. Several paracrine FGFs are expressed in adipose tissue and contribute to adipose tissue homeostasis, these functions are outlined below.

FGF1

FGF1 is critical for maintaining metabolic homeostasis through its role in initiating adipogenesis [38]. Expression of FGF1 in adipose tissue is heavily induced by a high fat diet. Additionally, FGF1 expression is induced by peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ signaling is essential for adipogenesis and is required for adipose tissue remodeling and insulin sensitivity. In white adipose tissue, loss of FGF1 attenuates these PPARγ-driven effects, resulting in insulin resistance and improper adipose tissue architecture, ultimately leading

to systemic inflammation [39]. FGF1 in the brain has also been implicated in whole-body metabolic regulation [40]. Delivery of FGF1 to the brain displays efficacy in treating diabetes mellitus by increasing glucose clearance from the bloodstream [41]. Overall, both adipose and brain derived FGF1 are capable of metabolic regulation.

FGF2

FGF2 is expressed in both white adipose tissue and preadipocytes. FGF2 enhances the survival and proliferation of preadipocytes in vitro [42]. Interestingly, FGF2 expression in adipocyte-derived stem cells regulates expression of the transcription factor CCAAT/enhancer binding protein beta (C/EBPβ) in a biphasic manner, stimulating its expression at low doses and inhibiting its expression at higher doses [43]. These results outline conflicting roles for FGF2 in adipocyte development and represent an area for further investigation.

FGF10

FGF10 is expressed in preadipocytes of white adipose tissue [44] and is necessary for adipogenesis [45]. The expression and secretion of FGF10 by preadipocytes controls the expression of transcription factors PPARγ and C/EBPβ, both of which are essential in adipocyte development. Loss of FGF10 expression in preadipocytes results in loss of lipid accumulation in white adipose tissue and impaired development of subcutaneous white adipose tissue [46].

In addition to these FGFs, FGF7, FGF9, FGF13, and FGF18 are expressed in subcutaneous white adipose tissue [47, 48], but their functions here remain poorly understood. Interestingly, FGF13 is an intracellular FGF that is not secreted, indicating that it may play a biological role distinct from the secreted FGFs [49]. Further research is needed to elucidate the specific roles these FGFs play in subcutaneous white adipose tissue function and regulation.

The FGF/FGFR Axis in Breast Cancer

Aberrant activation of FGFR and many of its downstream signaling pathways, such as AKT, ERK1/2, and STAT3, is associated with higher tumor grade and shorter overall survival in breast cancer patients [50–52]. FGFR activation in breast cancer cells can be enhanced through mechanisms including FGFR gene amplification, gain of function mutations, isoform switching, single nucleotide polymorphisms, and oncogenic gene fusions.

FGFR Gene Amplifications

Amplification of the *FGFR1* gene is present in approximately 10% of breast cancers and is most common in ER + cancers [53]. *FGFR1* amplification promotes anchorage-independent growth and contributes to endocrine therapy resistance. High FGFR1 expression is also associated with ligand-independent signaling and enhanced downstream signaling through ERK and AKT [54]. Amplification of *FGFR2* is observed in approximately 2% of treatment-naïve breast cancers, but the frequency of *FGFR2* amplification increases to nearly 7% in endocrine-resistant, metastatic ER + tumors [55], further implicating FGFR signaling as a major driver of therapy resistance.

Gain of Function Mutations

Mutations in the kinase domain of FGFRs may lead to constitutive, ligand-independent signaling. These activating mutations are most commonly observed in urothelial carcinoma, of which 15% of cases harbor FGFR3 activating mutation [56]. Although less commonly observed in breast cancer, mutations of FGFR1, FGFR3, or FGFR4 are able to drive cellular transformation by sustaining proliferative signaling pathways including PI3K/AKT and ERK [57]. Additionally, in a small cohort of women receiving ER-targeted therapy, approximately 15% of patients developed an *FGFR2* activating mutation during the course of treatment [55].

Isoform Switching and Autocrine Activation

Normally, FGFR activation is controlled by cell type-specific isoform expression of FGFRs and binding specificity of FGFs. In this way, cells will secrete ligands that bind to FGFRs on other cell types, preventing autocrine activation. An important process in cancer cells is the epithelial-mesenchymal transition (EMT). In many cancer types, including breast cancer, EMT is associated with FGFR2 isoform switching from FGFR2-IIIb to FGFR2-IIIc. This isoform switching also results in an autocrine activation loop which further promotes the invasive and metastatic properties of malignant cells [58]. FGF8 is one of the ligands found to be significantly increased in malignant breast cells compared to normal breast epithelial cells [59]. FGF8 binds and activates FGFR2-IIIc, FGFR3-IIIc, and FGFR4 [15]. FGF8 is typically produced by epithelial cells and acts on mesenchymal cells that express the appropriate receptors. In cancer however, FGF8-producing epithelial cells may undergo EMT and FGFR isoform switching. This offers the possibility of an FGF8 autocrine loop in breast cancer cells to further promote their proliferation [59]. Isoform switching by

FGFR2 also drives resistance to HER2-targeted therapies in HER2 + breast cancer [60]. FGF5 is secreted by tumor-associated fibroblasts which leads to persistent activation of the FGFR2-IIIc isoform on surrounding breast cancer cells [61]. FGFR2 activation leads to transactivation of HER2 through the activation of c-Src. The activation of both FGFR2 and HER2 result in cancer cells with increased survival and migration and resistance to HER2 therapy [60, 62].

Single Nucleotide Polymorphisms

Single nucleotide polymorphisms (SNPs) in the FGFR genes are able to regulate breast cancer susceptibility. SNPs in the *FGFR2* gene have been strongly associated with an increased risk of breast cancer. Genome-wide association studies have identified several common SNPs within intron 2 of the *FGFR2* genes, such as rs2981582, that are significantly correlated with ER + breast cancer [63]. These SNPs increase *FGFR2* expression and promote tumorigenesis through enhanced cell proliferation and survival signaling [64]. Additionally, two SNPs in the *FGFR4* gene have been identified and correlate with an increased risk for lymph-node positive breast cancer [65]. Conversely, an *FGFR1* SNP, rs17182023, reduces the overall risk of breast cancer by approximately 20% and results in lower FGFR1 protein expression [66]. The identification of SNPs may serve as a tool to identify patients who are at higher risk for developing breast cancer.

Oncogenic Gene Fusions

Fusion genes are formed when two previously independent genes are rearranged. These fusions can form by chromosomal translocation, deletion, inversion, or duplication. There are several well-characterized fusion proteins that play a role in cancer initiation and progression. Perhaps the best-known protein fusion is the Philadelphia chromosome, present in all chronic myeloid leukemia (CML) cells, which contains a gene fusion of the *Bcr* gene and the *Abl1* gene [67]. The BCR-ABL1 fusion protein is a valuable drug target in the treatment of CML, which indicates that the fusion proteins in cancer could be very valuable drug targets.

While somewhat uncommon, several FGFR gene fusions have been identified in breast cancer. FGFR2 fusions with ALF transcription elongation factor 3 (AFF3), Caspase 7 (CASP7), and coiled-coil domain containing 6 (CCDC6) have all been observed in breast cancer patients. In all of these fusions, the FGFR2 kinase domain remained intact, suggesting that receptor activity and downstream signaling pathways remain active [68]. These FGFR2 protein fusions display increased receptor dimerization and ligand-independent signaling, but a more specific role in breast cancer progression has not been studied.

In TNBC, a fusion between FGFR3 and transforming acidic coiled-coil containing protein 3 (TACC3) functions as an oncogenic driver. TACC3 regulates mitotic spindle organization, and in some TNBC cases, the FGFR3-TACC3 fusion protein caused defects in chromosomal segregation. Like the FGFR2 fusions, the FGFR3-TACC3 fusion protein demonstrates increases levels of ligand-independent FGFR activation and increased signaling through downstream pathways including AKT and ERK. Importantly, TNBC cells that express the FGFR3-TACC3 fusion protein are sensitive to RTK inhibitors. RTK inhibitors preferentially decrease proliferation and induce apoptosis in TNBC cells harboring this FGFR3-TACC3 fusion [69]. Despite being found in less than 1% of cases, the presence of FGFR fusions in breast cancer may help identify patients who will respond well to FGFR-targeted therapies.

FGFs in Breast Cancer

While amplification of FGFRs is relatively uncommon in breast cancer, the overexpression of FGFs is seen much more frequently. *FGF3*, *FGF4*, and *FGF19* are all located on chromosome 11q13 which is amplified in 15% of breast cancers. *FGF10* is also amplified in approximately 10% of breast cancers [70]. Apart from FGF19, all these ligands bind and activate FGFR1 and FGFR2, which both play roles in breast cancer initiation, progression, and therapeutic resistance. Of note, both FGF10 and FGF19 have known metabolic functions and are expressed by, or travel to, adipose tissue, respectively.

Increased copy numbers of *FGF3*, *FGF4*, and *FGF19* were found in HER2-amplified breast cancers with acquired resistance to HER2 blockade [62]. These resistant tumors with FGF amplification also had higher levels of active FGFR, compared to treatment-responsive tumors. Like FGFR, HER2 is also an RTK and both receptors signal through downstream effectors including ERK and AKT. Therefore, inhibition of HER2 should abrogate signaling through these downstream effectors. However, Hanker et al., found that FGF4 was able to stimulate ERK activation even in the presence of HER2 inhibitors [62]. These findings describe a mechanism by which FGFs promote therapeutic resistance in breast cancer.

The overexpression of FGFs plays a cancer-promoting role in all subtypes of breast cancer. Increased expression of FGF2 was found in over 60% of basal-like breast cancers. This increase in FGF2 likely comes from the cancer cells, as TNBC cells have been shown to secrete FGF2 in culture [71]. As mentioned above, FGF8 is also overexpressed in breast cancers and can be produced by breast cancer cells

in culture [59]. The mechanisms leading to FGF overexpression in TNBC are not well understood but may offer new insights into the drivers behind TNBC initiation and progression.

In ER + breast cancers, treating cells with estrogen increases the expression of FGF2, FGF4, FGF6, FGF7, and FGF9 [72]. FGF9 signaling can induce a more aggressive cancer stem cell-like phenotype in these cells and promote faster tumor growth. Interestingly, these authors found that FGFR inhibition suppresses the ability of estrogen to initiate tumor growth [72]. Taken together, these findings all indicate the importance of FGF expression in breast cancers, regardless of subtype. This suggests that the FGFs or their downstream pathways may be valuable therapeutic targets in breast cancer.

In addition to the increase in FGF19 discussed above, we have previously demonstrated that the endocrine FGFs FGF21 and FGF23 are elevated in breast cancer cell lines [73]. Interestingly, both α- and β-klotho generally act as tumor suppressors, and are expressed at lower levels in cancer cells compared to normal mammary epithelial cells [74]. The expression of klotho in breast cancer cells reduces cellular oxygen consumption and rates of glycolysis, outlining its role as a tumor suppressor [75]. Despite these known functions of klotho, the roles of the endocrine FGFs in cancer progression have not been extensively studied.

FGFR and the Hallmarks of Cancer

During tumor development, normal cells acquire characteristics that permit tumor formation. These biological and enabling capabilities, better known as the hallmarks of cancer, encompass the complex process of tumorigenesis [76–78]. Active FGFR signaling in cancer cells contributes to most of these cancer hallmarks, further illustrating the tumorigenic role of FGFR signaling. These actions are described below; however, further work needs to be done to define the roles of specific FGFRs in these processes. To support primary tumor growth, cells can engage sustained proliferative signaling through FGFR via receptor isoform switching and establishment of an autocrine signaling loop [71, 76]. Receptor isoform switching and other genetic alterations in FGFR (discussed above) also illustrate the contribution of FGFR to both genome instability and phenotypic plasticity in cancer [77, 78]. Sustained signaling by FGFR also confers resistance to cell death and aids in the evasion of growth suppressor signals [71, 76, 79].

FGFR signaling supports multiple hallmarks of cancer associated with metastasis, most prominently EMT and angiogenesis. Breast cancer patients with ER/PR-positive disease and *FGFR* genetic aberrations have significantly higher rates of brain, lung, and liver metastases compared to patients without *FGFR* aberrations [80]. Sustained FGFR activation promotes EMT by driving transcriptional programs that reduce epithelial adhesion and enhance cellular motility and invasiveness. For example, N-cadherin- mediated upregulation of FGFR activity increases the expression of EMT transcription factors such as Snail and Slug, thereby facilitating cytoskeletal reorganization and metastatic dissemination [81]. In parallel, FGFR signaling strongly supports tumor angiogenesis, both by inducing the production of pro-angiogenic ligands like FGF2 and VEGF [82] and by directly stimulating endothelial cell proliferation, migration, and survival [83]. This results in the formation of an abnormal yet highly supportive vascular network that supplies nutrients, enables tumor expansion, and provides routes for tumor cell intravasation [84]. Together, these FGFR-driven processes create an environment conducive to metastatic spread and underscore the central role of FGFR signaling in promoting advanced and aggressive disease.

The effects of sustained FGFR signaling in tumor cells also impacts the surrounding tumor microenvironment. Generally, active FGFR signaling in tumor cells favors "cold tumors" illustrated by exclusion of CD4 + and CD8 + T cells and increased infiltration of myeloid-derived suppressor cells in the tumor [77]. Additionally, our previous work demonstrated a role for FGFR1 signaling in tumor cells in promoting macrophage recruitment to the tumor [85, 86]. In accordance with these findings, FGFR inhibition leads to enhanced infiltration of CD4 + and CD8 + T cells into the tumor and results in decreased metastatic burden [87–89]. Building on these observations, recent studies have begun to uncover how FGFR signaling intersects with cancer metabolism, revealing a potential link between metabolic reprogramming and the immunosuppressive tumor microenvironment.

Metabolic Dysregulation in Breast Cancer

In order to understand how FGFR impacts cancer metabolism, it is important to understand key aspects of metabolic dysregulation in breast cancer. While changes in glucose consumption are perhaps the most well-known metabolic feature of transformed cells, cancer cells alter other metabolic pathways to support their growth. To keep up with rapid proliferation, cancer cells demonstrate increased rates of protein and DNA synthesis [77]. Another important metabolic pathway with growing relevance in the cancer field is lipid metabolism. Most adult cells procure lipids from the circulation and do not make their own. These lipids are derived from dietary sources or from lipid-synthesizing tissues like the liver or adipose tissue [90]. Another metabolic

phenotype of aggressive cancer cells is an increase in *de novo* fatty acid synthesis.

Glycolytic Metabolism in Breast Cancer

The concept of altered metabolism in cancer cells is certainly not a new one with Dr. Otto Warburg publishing his original work nearly 100 years ago. The "Warburg hypothesis" states that cancer cells will preferentially metabolize glucose via aerobic glycolysis regardless of oxygen availability [91] (Fig. 4). This phenomenon is, in part, mediated by a change in isoform expression of the enzyme lactate dehydrogenase from lactate dehydrogenase B (LDHB) to lactate dehydrogenase A (LDHA), which plays a key role in aerobic glycolysis. This isoform switching is mediated by methylation of the *LDHB* gene promoter in many cancers, including breast cancer [92].

The switch to glycolytic metabolism confers several benefits to tumor cells. Along with faster production of ATP, the glycolytic pathway also produces intermediates that feed amino acid, nucleotide, and lipid synthesis [93]. This shift also helps cells survive in the hypoxic regions of the tumor [94]. Additionally, the resulting lactate export acidifies the microenvironment in ways that promote invasion, angiogenesis, and immune evasion [95]. Overall, heightened glycolysis is a metabolic strategy that supports growth, survival, and competitive advantage within the tumor niche.

Glycolytic metabolism by breast cancer cells also varies slightly by subtype. TNBC tumors typically exhibit high levels of glycolysis with elevated GLUT1 expression and lactate production compared to other breast tumors [96]. This high level of glycolysis also promotes chemoresistance in TNBC [97]. In HER2-positive disease, glycolytic metabolism, as detected by tumoral lactate levels, is correlated with increased HER2 transcript number and susceptibility to anti-HER2 therapies [98, 99]. In contrast, ER-positive tumors tend to rely more on oxidative phosphorylation at baseline [100] although they can become more glycolytic when they acquire resistance to endocrine or PI3K-targeted therapies [101]. These differences influence tumor behavior, metabolic imaging patterns, and potential responsiveness to metabolism-targeted therapies.

Fatty Acid Metabolism in Breast Cancer

Fatty acids (FAs) provide the building blocks for cell membranes and signaling molecules. As mentioned, normal cells typically take up fatty acids from exogenous sources while cancer cells shift to *de novo* fatty acid synthesis [102]. Biosynthesis of fatty acids is catalyzed by the enzyme fatty acid synthase (FASN). In tumors, almost all of the fatty acids, up to an estimated 93%, are produced from *de novo* synthesis [103]. In the early 1990's, Pasternack and colleagues found that the expression of the molecule OA-519 was associated with worsened prognosis in breast cancer patients. Through sequence homology, this group found that OA-519 was FASN. Additionally, they found that inhibition of FASN led to growth inhibition in breast cancer cells [104].

The role of FAs and lipid metabolism in breast cancer differs depending on breast cancer subtype. Among the breast

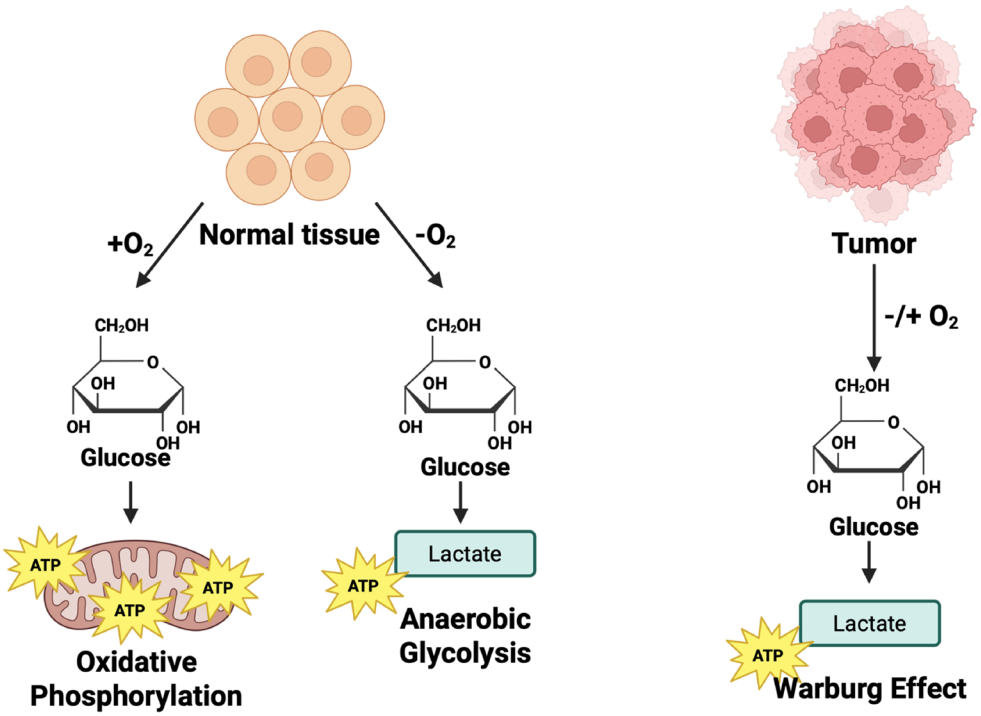

Fig. 4 The metabolic differences between normal and malignant tissue, as described in the Warburg Hypothesis. In normal tissue in the presence of oxygen, cells will undergo oxidative phosphorylation to generate ATP. In the absence of oxygen, normal tissue uses anaerobic glycolysis to generate ATP. The Warburg Hypothesis states that cancer cells will generate ATP via aerobic glycolysis regardless of oxygen availability

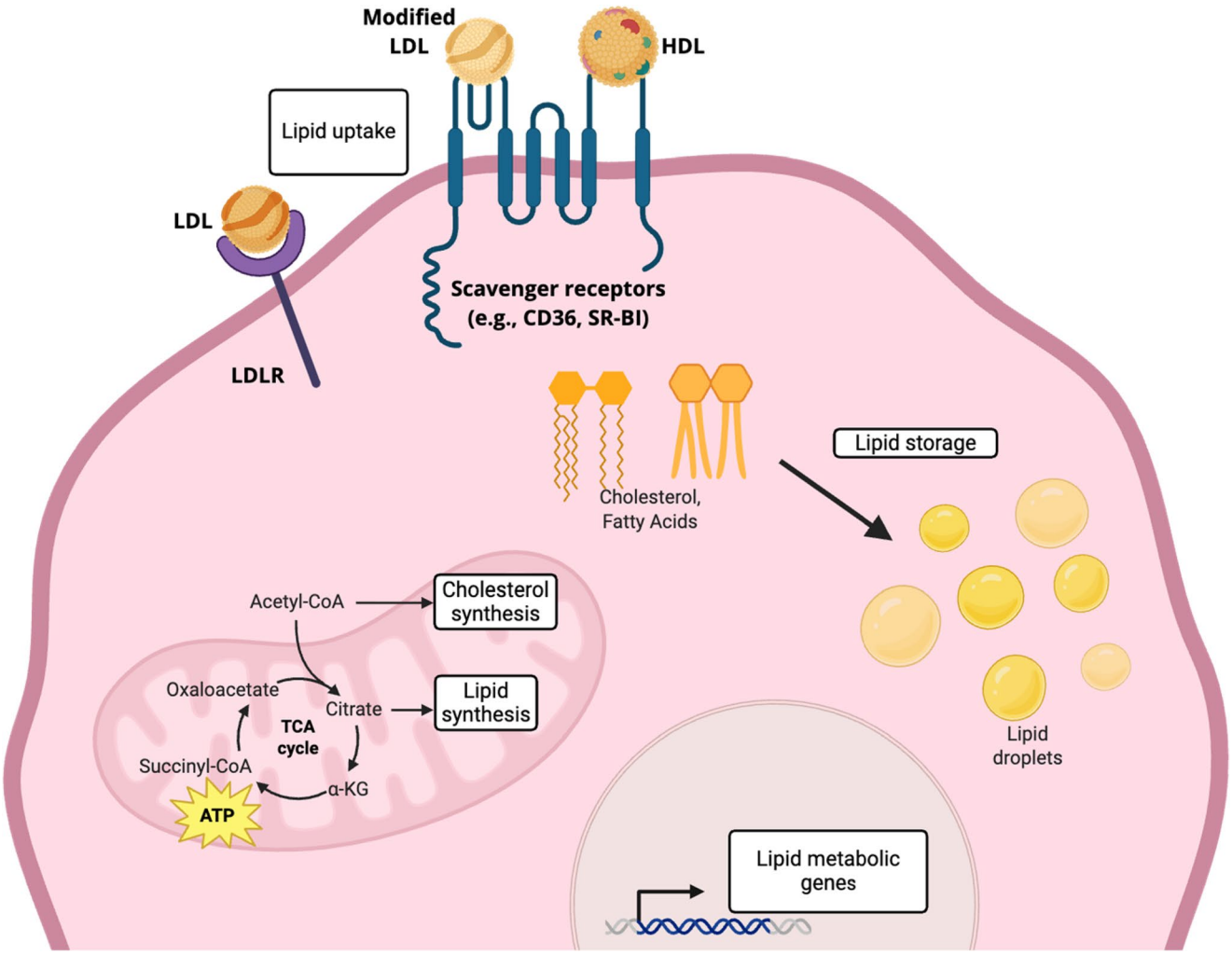

Fig. 5 An overview of lipid metabolic processes in cancer cells

cancer subtypes, HER2-positive tumors express the highest levels of lipid-related genes including FASN [105]. In these cases, HER2 amplification or overexpression directly leads to FASN upregulation via activation of the PI3K pathway [106]. Additionally, when considering the expression of fatty acid binding protein 4 (FABP4), there is no correlation between protein expression and overall survival or disease-free survival in breast cancer. However, when considering only TNBC, FABP4 expression is significantly correlated with worse overall and disease-free survival [105]. Fatty acids are not the only class of lipid present in cancer cells. Cholesterol and its metabolites also play a large role in cancer cell behavior and may serve as the connection between the metabolic and oncogenic roles of the FGF/FGFR signaling axis. Figure 5 provides an overview of lipid metabolic processes in cancer cells.

Cholesterol Metabolism in Breast Cancer

The role of cholesterol in breast cancer has remained somewhat controversial, specifically in terms of the influence of serum cholesterol levels on breast cancer risk and severity of disease. The most widely used class of cholesterol-lowering drugs are the statins, which inhibit the enzyme HMG-CoA reductase and therefore inhibit cholesterol biosynthesis. Many studies have examined the link between statin use and breast cancer risk and have found no association between the use of statins pre-diagnosis and the likelihood of developing breast cancer [107, 108]. However, patients in remission from non-metastatic breast cancer are less likely to experience disease recurrence when taking statins. This is true for all subtypes of breast cancer, but statins more effectively prevent recurrence in ER + breast cancers [109]. These effects of statins indicate that cholesterol plays an important role in breast cancer growth and progression.

Cholesterol is a major component of cellular membranes and strongly influences membrane permeability. There are also cholesterol-rich microdomains known as lipid rafts present in the cell membrane which mediate cell signaling [110]. In cancer cells, lipid rafts are enriched at invadopodia, membrane protrusions through which cancer cells degrade extracellular matrix. In breast cancer, these regions are required for invadopodia-mediated ECM degradation [111]. They also mediate oncogenic signaling, including pro-survival signaling by AKT and Src family kinases [112]. The role of these membrane domains varies across breast cancer subtypes. For example, they are required for signal transduction by HER2 and their disruption can resensitize HER2-overexpressing breast cancers to treatment by trastuzumab [113]. Extracellularly, ERs are also found in these domains, where their increased presence accelerates phosphorylation of nuclear ER targets, promoting cell proliferation [114]. Cholesterol also plays an intracellular role in breast cancer progression, and, unsurprisingly, this role varies by breast cancer subtype.

In the cell, cholesterol can be oxidized into a class of molecules known as oxysterols. Most oxysterols are generated from cholesterol by autooxidation or by oxidation reactions catalyzed by cytochrome P-450 enzymes [115]. When cholesterol is metabolized by the enzyme CYP27A1, the metabolite 27-hydroxycholesterol (27HC) is formed. 27HC is a selective estrogen receptor modulator and, in breast cancer cells, acts as an ER agonist to promote estrogen-independent growth [116, 117]. 27HC levels are higher in malignant breast tissue compared to normal tissue, and higher protein levels of CYP27A1 are associated with higher tumor grade. Additionally, 27HC strongly mediates metastasis in ER + breast cancers through interactions with T cells and myeloid cells [118].

Cholesterol also has well-characterized roles in the promotion of ER- breast cancers. Increased cholesterol biosynthesis is a frequent feature of TNBCs and aids in the metastasis of these cancers. One cholesterol metabolic enzyme, NAD(P)H steroid dehydrogenase-like protein (NSDHL), is highly expressed in breast cancers and is associated with poor prognosis. In TNBC, NSDHL expression promotes cancer cell migration and metastasis. Furthermore, knockdown of NSDHL expression induces cell cycle arrest and reduces metastasis in TNBC models [119]. While multiple roles for cholesterol in breast cancer progression and metastasis have been described, the mechanisms that drive these changes remain somewhat elusive. Although largely unstudied in the context of cancer, the FGF/FGFR axis may, in part, contribute to the alterations in cholesterol metabolism seen in breast cancer.

An Emerging Role for FGFR-Mediated Metabolic Dysregulation in Cancer

While the roles of FGFRs in metabolism are well established, the intricate connections between FGFR signaling, metabolic regulation, and cancer development have only recently begun to emerge. Seminal work in the field demonstrates that patients with ER-positive breast cancer and obesity have increased FGF1 expression, leading to increased FGFR1 signaling, accelerated tumor growth, and therapy resistance [120]. These results indicate that the FGF/FGFR signaling axis may exert control over tumor growth through metabolic mechanisms. This section highlights recent studies exploring the role of FGFR regulation of metabolism in breast cancer, as well as other cancer types.

Glycolytic Metabolism

A growing body of work has implicated aberrant FGFR signaling with dysregulated metabolism in cancer. In cholangiocarcinoma, oncogenic FGFR2 signaling drives a glycolytic phenotype in a NF-κB-dependent manner [121]. Similarly, FGFR activation by FGF1 and FGF2 has also been shown to drive a glycolytic phenotype in prostate cancer, specifically by activating LDHA and repressing LDHB expression [122, 123]. In FGFR1-amplified lung cancer, glucose uptake and glycolytic rate are elevated via activation of the AKT/mTOR pathway by FGFR1 [124]. Similar findings have been reported in breast cancer models. In ER-positive disease, FGF1 drives tumor growth in the absence of estrogen. Consequently, FGF1 drives these breast cancer cells towards a highly glycolytic phenotype [125]. Further studies in chemotherapy-resistant breast cancer cells identify an increased reliance on glycolysis driven by FGFR4 activation [126]. Additional mechanisms of regulation by FGFR have also emerged. For example, long non-coding RNA (lncRNA) FGF13-AS1 is expressed at lower levels in malignant breast tissue compared to benign tissue, and its reduced expression is associated with enhanced stemness and glycolytic activity in breast cancer cells [127]. Collectively, these studies highlight glycolytic reprogramming as a downstream consequence of aberrant FGFR signaling.

Lipid Metabolism

Signaling by FGFR has also been related to the dysregulation of lipid metabolism in several cancer models. This relationship was first identified in bladder cancer when Du et al. found that aberrant signaling by FGFR3 promotes activation of the transcription factor sterol regulatory element-binding protein 1 (SREBP1). This leads to induced expression of genes related to cholesterol. and fatty acid metabolism

and promotes fatty acid synthesis, ultimately leading to increased cellular proliferation and survival [128]. These findings are further corroborated by King et al. who demonstrate that FGFR inhibition potentiates cell death, in part, by disrupting cellular cholesterol metabolism [129]. Recently published work in FGFR-dependent gastric cancer illustrates changes in cholesterol metabolism that occur during the development of resistance to FGFR inhibitors (FGFRi). FGFRi resistant cells demonstrate higher expression of cholesterol biosynthesis genes and higher levels of cellular cholesterol compared to FGFRi sensitive cells. These FGFRi resistant cells are also less sensitive to cell death by ferroptosis and depletion of cellular cholesterol levels resensitizes cells to death by ferroptosis [130]. This growing body of work indicates that FGFR signaling plays a role in regulating lipid metabolism in several cancer models.

In breast cancer, the FGF/FGFR signaling axis has been implicated in tumor progression in tumor cell intrinsic and extrinsic mechanisms. First, in TNBC, the activation of FGFR4 and downstream signaling through AKT has been linked to lipid accumulation, biosynthesis, and lipolysis [131]. Next, breast cancer cells were found to produce and secrete high levels of FGF21 into the tumor microenvironment. FGF21 activates FGFR1 on T cells and eventually leads to the upregulation of several cholesterol biosynthetic genes. The increased levels of cellular cholesterol in T cells drives T cell exhaustion and impaired cytotoxic function, leading to impaired immunosurveillance and tumor progression [132]. Finally, we have recently demonstrated that FGFR1 activation in breast cancer cells promotes the intracellular storage of cholesterol in lipid droplets. This increased cholesterol storage leads to increased tumor cell invasion and metastasis in mouse models [133]. These findings add to a growing recognition that FGFR signaling is not only a potent regulator of proliferation and survival pathways, but also a key orchestrator of cancer metabolism. In particular, metabolic rewiring toward lipid synthesis, storage, and utilization has emerged as a hallmark of aggressive tumors [134], enabling cells to meet heightened energetic demands, maintain membrane integrity, and produce pro-invasive lipid signaling molecules. By coupling receptor activation to cholesterol sequestration in lipid droplets, FGFRs effectively link growth factor signaling with a metabolic state that supports cellular plasticity, cytoskeletal remodeling, and metastasis. Overall, this expanding body of work positions metabolic regulation as an additional and underappreciated mechanism through which FGFR signaling promotes tumor progression.

Concluding Remarks

Emerging evidence highlights the pivotal role of FGFR signaling in reprogramming metabolic pathways that support breast cancer initiation, progression, and therapeutic resistance. FGFR alterations, including gene amplifications and mutations, not only drive oncogenic signaling but also reshape cellular metabolism by promoting glycolysis and altering lipid metabolism. This metabolic plasticity enables tumor cells to adapt to nutrient stress and evade anti-cancer therapies. Understanding the intricate crosstalk between FGFR pathways and metabolic networks offers valuable insights into the metabolic vulnerabilities of FGFR-driven breast cancers. As such, co-targeting FGFR signaling and key metabolic nodes holds promise for more effective and durable therapeutic strategies. Future research should aim to dissect subtype-specific metabolic dependencies and validate combinatorial approaches in preclinical and clinical settings to translate these findings into meaningful clinical benefit.

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Declarations

Competing Interests Dr. Schwertfeger is a member of the Editorial Board of the Journal of Mammary Gland Biology and Neoplasia.

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