Am J Cancer Res 2024;14(9):4172-4196
www.ajcr.us /ISSN:2156-6976/ajcr0155938

Review Article

Receptor tyrosine kinases in breast cancer treatment: unraveling the potential

Yu Qi[1*], Shu-Min Deng[1*], Kuan-Song Wang[1,2]

[1]*Department of Pathology, School of Basic Medical Sciences, Central South University, Changsha, Hunan, China;* [2]*Department of Pathology, Xiangya Hospital, Central South University, Changsha, Hunan, China.* [*]*Equal contributors and co-first authors.*

Received February 17, 2024; Accepted September 9, 2024; Epub September 15, 2024; Published September 30, 2024

Abstract: Breast cancer is a multifactorial disease driven by acquired genetic and epigenetic changes that lead to aberrant regulation of cellular signaling pathways. Receptor tyrosine kinases (RTKs), a class of critical receptors, are involved in the initiation and progression of breast cancer. RTKs are cell surface receptors with unique structures and biological characteristics, which respond to environmental signals by initiating signaling cascades such as the mitogen-activated protein kinase (MAPK) pathway, Janus kinase (JAK)/signal transducer, activator of transcription (STAT) pathway, and phosphoinositide 3-kinase (PI3K)/AKT pathway. The critical role of RTKs makes them suitable targets for breast cancer treatment. Targeted therapies against RTKs have been developed in recent years, evaluated in clinical trials, and approved for several cancer types, including breast cancer. However, breast cancer displays molecular heterogeneity and exhibits different therapeutic responses to various drug types, leading to limited effectiveness of targeted therapy against RTKs. In this review, we summarize the structural and functional characteristics of selected RTKs and discuss the mechanisms and current status of drug therapy involving different protein tyrosine kinases in breast cancer progression.

Keywords: Receptor tyrosine kinases, breast cancer, tyrosine protein kinase inhibitors, anti-RTK therapy, drug resistance, targeted therapy

Introduction

Breast cancer (BC) is the most prevalent and highly fatal tumor among women worldwide [1]. It can be classified into five distinct subtypes: luminal A/B, HER2-positive (HER+), basal-like, claudin-low, and normal breast-like, based on the expression levels of estrogen receptor (ER), progesterone receptor (PR), HER2, cytokeratin 5/6 (CK5/6), and claudins 3/4/7 [2-4]. Among these, triple-negative breast cancer (TNBC) accounts for 15-20% of breast cancer and shares remarkable similarities with basal-like breast cancer. TNBC lacks the expression of ER, PR, and HER2, and is characterized by its high metastatic capacity [5, 6].

Breast cancer is a consequence of dysregulation in multiple signaling pathways within the epithelial cells of the breast. The activation of growth factors and chemokines disrupts diverse signaling cascades in the tumor microenvironment, thereby contributing to cancer progression [7, 8]. Playing a crucial role in this process, receptor tyrosine kinases (RTKs) are a vital family of receptors that regulate essential biological processes, including cell proliferation, differentiation, metabolism, and survival [9]. They achieve this by initiating downstream signaling pathways.

RTKs are single-pass transmembrane proteins expressed in various cell types. Multiple RTKs, such as epidermal growth factor receptors (EGFRs), vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), insulin-like growth factor receptors (IGFRs), and fibroblast growth factor receptors (FGFRs), are expressed in different types of tumors, including breast cancer [9-11]. Elevated levels of RTKs have been associated with increased invasiveness of breast cancer and decreased overall and disease-free survival rates [12]. Ligand binding induces conforma-

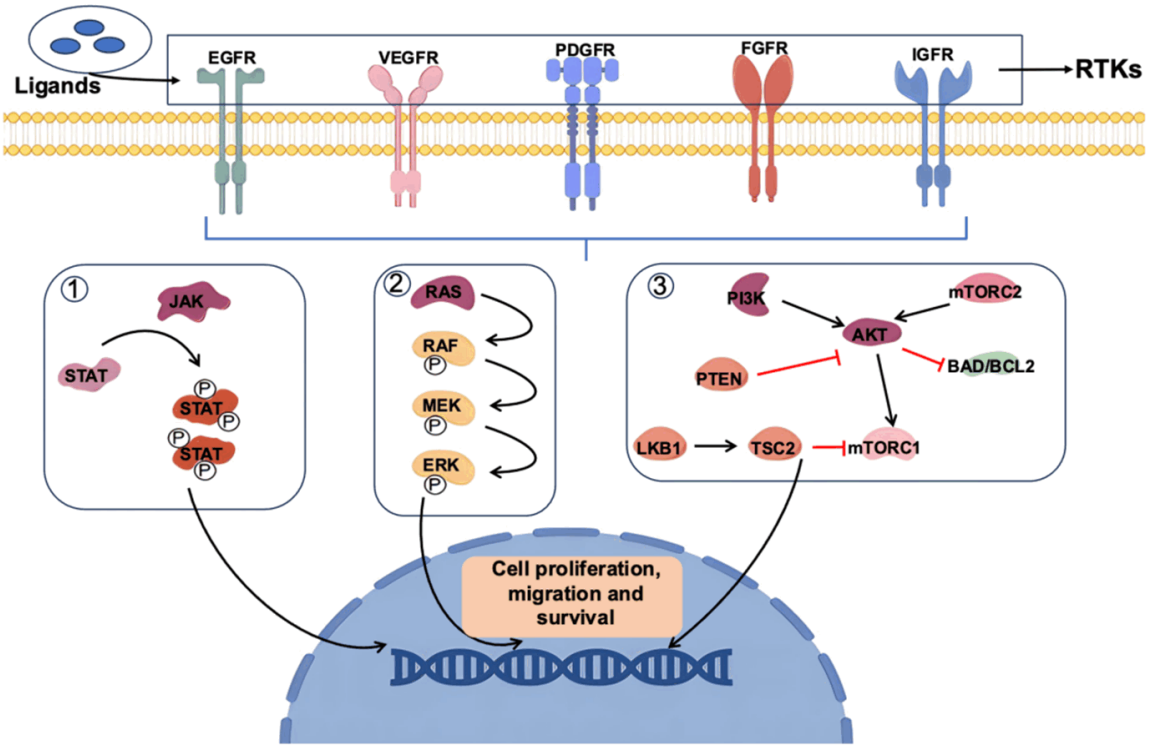

Figure 1. RTK-regulated important signaling in breast cancer progression. (1) Once a ligand binds to the receptor, two STAT proteins are phosphorylated by JAK forming a dimer that enters the nucleus, causing the transcription of target genes. (2) After the TKR is activated by a ligand, Ras dimerizes and binds Raf, promoting Raf activation. Active Raf phosphorylates and activates MEK1/2 which induces ERK1/2 activation, leading to transcription activation. (3) PI3K phosphorylates phosphatidyl inositol-bisphosphate (PIP2) to PIP3, a process that can be reversed by the action of PTEN. PIP3 causes the activation of Akt in the plasma membrane, thereby activating the mTOR complex, one of the major pathways involved in tumorigenesis. The above have represented the interaction between various signaling pathways activated through RTKs and involved in tumor proliferation.

tional changes in RTKs, subsequently activating downstream signals. Key pathways known to be activated by RTKs include the mitogen-activated protein kinase (MAPK), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), as well as phosphoinositide 3-kinase (PI3K)/AKT pathway [13-17]. These RTK-activated pathways play pivotal roles in various aspects of breast cancer progression (**Figure 1**).

Due to the significant role of RTKs in breast cancer progression, targeting RTKs may contribute to cancer treatment. Over the years, targeted therapies against RTKs, including small molecule inhibitors and monoclonal antibodies, have demonstrated efficacy in cancer treatment [18, 19]. Among them, drugs such as lapatinib, trastuzumab, and bevacizumab have gained approval from the U.S. Food and Drug Administration (FDA) for the clinical management of breast cancer. Furthermore, RTK inhibitors have shown promise in overcoming multidrug resistance and improving disease-free survival rates in patients with metastatic breast cancer [20]. Despite the clinical benefits of anti-RTK therapy for breast cancer, the primary and acquired resistance significantly limits the effectiveness of RTK-targeted treatments. Therefore, further research is essential to overcome this challenge and enhance the efficacy of RTK-targeted therapies [21]. In this review, we have delved into the intricate signaling cascades of EGFR, VEGFR, PDGFR, FGFR, and other key receptors implicated in breast cancer. Our exploration of the role of RTK inhibitors in breast cancer treatment offers valuable insights into the potential for targeted therapy. Understanding the underlying mechanisms and the potential benefits of RTK inhibitors can contribute to more effective and personalized treatment strategies for breast cancer patients, ultimately improving their clinical outcomes.

Functions and targeted drugs of RTKs

Features of RTKs

RTKs, integral membrane proteins, are activated through specific ligand interactions. These receptors consist of distinct domains, including extracellular ligand-binding regions, a transmembrane domain, and intracellular kinase domains [22]. Remarkably, each receptor class exhibits unique structural and sequence characteristics within their extracellular domains, defining their ligand specificity. Various protein motifs, such as immunoglobulin-like (Ig) domains, leucine-rich domains (L domains), cysteine-rich domains (CR domains), or fibronectin type III (Fn3) domains, are specifically present in different receptors. Conversely, the intracellular domains encompass the tyrosine kinase domain and the C-terminal region [23]. Some receptors possess insertions that separate the kinase domain when varying lengths of sequences are inserted [24]. Additionally, the C-terminal domains of RTKs differ among the family members, contributing to the specificity and diversity of downstream signaling. Their catalytic activity enables tyrosine residue phosphorylation, which is triggered by ligand binding to the extracellular domains of RTK proteins, thereby stabilizing the active state [25, 26].

Mechanism of RTK activation

RTKs, a superfamily of 58 members into 20 subfamilies [27, 28], share two key features: ligand-induced dimerization and auto-phosphorylation of tyrosine residues [29]. As for the first one, conformational changes occur in the monomeric or self-inhibited receptors. This enables the receptors to form dimers, which facilitates the enhancement of tyrosine kinase activity. Subsequently, the kinase domain and the C-terminal region of RTKs undergo auto-phosphorylation at specific tyrosine residues. This auto-phosphorylation plays a crucial role in the assembly of signaling molecules comprising Src homology 2 (SH2) and phosphotyrosine-binding domains [30].

RTKs primarily interact with soluble ligands, such as growth factors, cytokines, and hormones, to initiate signal transduction pathways [25, 27]. These ligands engage a repertoire of downstream signaling components, including kinases like PI3K and SRC, adaptor proteins like SHC and GRB2, transcription factors like STAT, ubiquitin ligases, and phospholipases such as phospholipase C-gamma (PLC-γ) [13-17]. These signaling cascades activate various pathways, including MAPK, PI3K/AKT/mammalian target of rapamycin (mTOR), PLC-γ/protein kinase C, and JAK/STAT pathways. It is important to note that RTK signaling can occur both intracellularly and at the cell surface, with distinct signaling pathways depending on the subcellular localization of the receptors [31]. Ultimately, the activation of RTKs leads to diverse biological responses, including cell growth, survival, inhibition of apoptosis, stimulation of angiogenesis, and promotion of cell motility (**Figure 2**) [32].

Development of RTKs-targeted drugs

RTKs have emerged as central players in regulating critical cellular processes, including cell growth, survival, organ morphogenesis, angiogenesis, and tissue regeneration [33, 34]. While RTK activity is intricately regulated in normal cells, dysregulated or constitutive activation of RTKs has been observed across a wide variety of cancers. Aberrant activation can stem from functional mutations, gene rearrangements, amplification, overexpression, or abnormal autocrine, endocrine, as well as paracrine signaling between receptors and ligands. Notably, these aberrations have been found to correlate with the progression of various human cancers [35-37].

Targeting RTKs has shown promising therapeutic benefits. In colorectal cancer, for instance, alterations in EGFR ligands [38], dual mutations in associated proteins, epidermal regulatory protein irregularities, and transforming growth factor-alpha (TGF-α) have been established as predictive biomarkers and prognostic indicators for the response to anti-EGFR antibodies, such as cetuximab or panitumumab [39]. Similarly, EGFR mutations, anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 (ROS1) translocations in non-small cell lung cancer (NSCLC), ret proto-oncogene (RET) mutations in medullary thyroid carcinoma (MTC), and HER2 amplification in breast cancer have been identified, paving the way for targeted therapeutic strategies [40, 41]. In fact, over the last decade, RTK-targeted therapies have demonstrated significant improvements in the

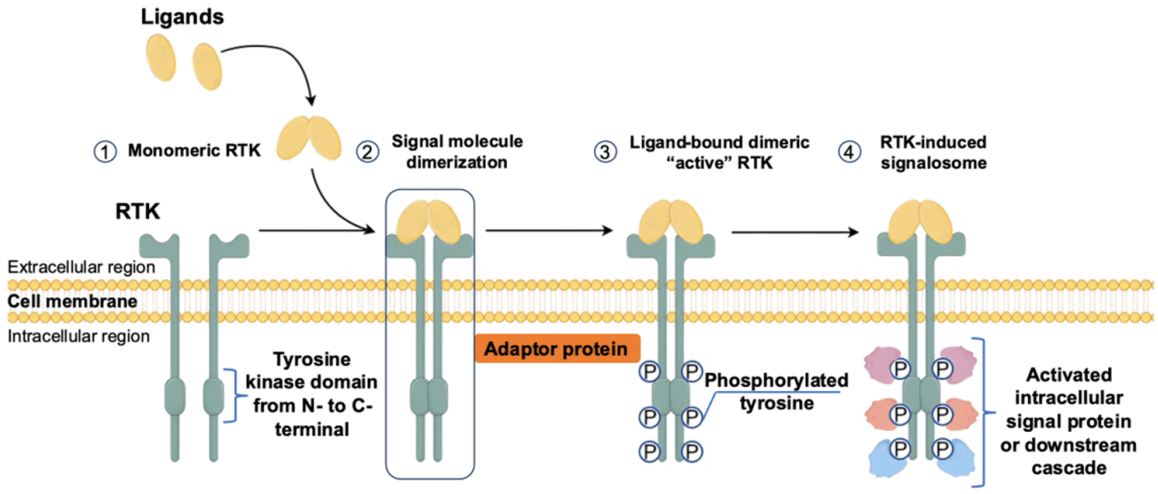

Figure 2. Classical Structure of receptor tyrosine kinase and activation mechanism. (1) At first, RTKs reside at the cell membrane as a monomer. (2) Upon ligand binding, RTKs are activated through the formation of inter-molecular dimerization in the presence of ligands, resulting in kinase activation and phosphorylation of the receptor C-terminal tail. (3) Phosphorylated RTK either serves as a docking site for adaptor proteins or may directly phosphorylate signaling molecules.

treatment of selected cancer patients [42-46]. Their ability to selectively inhibit constitutively activated RTKs within tumor cells holds promise as a novel approach for cancer treatment [47].

In summary, gaining insights into the mechanisms that drive the activation of RTKs, particularly within the context of specific RTKs, helps us understand crucial cellular processes with significant implications in cancer (**Table 1**) [48-52]. Moreover, advancements in targeting these aberrant signaling pathways have opened new possibilities for therapeutic interventions, bringing hope for improved outcomes in the treatment of cancer.

The drugs targeting tyrosine kinases can be categorized into antibody-based therapies and small molecule inhibitors. Currently, there are 87 approved small-molecule kinase inhibitors worldwide, with the majority of the 71 small molecule kinase inhibitors approved by the FDA being tyrosine protein kinase inhibitors (TKIs), which find their primary application in oncology [53-58] (**Table 2**).

In breast cancer, overexpression of HER2 occurs in approximately 25% of patients and is associated with lower survival rates [59, 60]. Similarly, EGFR is frequently upregulated in solid tumors and plays a role in various malignant characteristics such as proliferation, apoptosis resistance, and tumor cell mobility. These discoveries have paved the way for the development of antibodies targeting HER2 and EGFR, and the success of drugs like trastuzumab and cetuximab validates the efficacy of targeting these growth factor receptors [61, 62]. Moreover, successful interventions using RTK inhibitors include imatinib for the treatment of gastrointestinal stromal tumors harboring c-Kit mutations and gefitinib as well as erlotinib for NSCLC patients with EGFR mutations [49]. In addition to its inhibition of BCR-ABL and SRC, sunitinib also targets multiple RTKs such as PDGFR and VEGFR on endothelial cells, both of which play roles in tumor angiogenesis and proliferation [63].

Based on clinical trial data for small molecule kinase inhibitors (SMKIs) [64], there are currently approximately 110 novel kinases being investigated as potential targets [51, 52, 55, 56, 65-67]. The approved kinase inhibitors only cover around 30% of the human kinase, indicating that there are still numerous untapped areas within this kind of drugs waiting to be explored.

The role of RTK signaling in breast cancer progression

Under normal physiological conditions, the activity levels of RTKs are tightly balanced through the mechanisms mentioned above, as

Table 1. Classification and therapeutic applications of RTKs

Receptor family	Receptor	Applications
Epidermal growth factor receptor, EGFR	HER1, HER2, HER3, HER4	Non-small cell lung cancer, head and neck tumors, colorectal cancer, pancreatic cancer, breast cancer, ovarian cancer, cervical cancer
Insulin receptor, INSR	IGF-I, IGF-II, INSR, INSRR	Breast cancer, hematological malignancies, colorectal cancer, lung cancer, cervical cancer
Platelet-derived growth factor receptor, PDGFR	PDGFRα, PDGFRβ, CSF-1R, SCFR, FLK2, FLT3	Hypereosinophilic syndrome, mastocytosis, gastrointestinal stromal tumor, epithelial cell tumor, leukemia
Fibroblast growth factor receptor, FGFR	FGFR1, FGFR2, FGFR3, FGFR4	Angiogenesis
Vascular endothelial growth factor receptor, VEGFR	VEGFR1, VEGFR2, VEGFR3, VEGFR4	Hepatocellular carcinoma, lung cancer, ovarian cancer
Hepatocyte growth factor receptor, HGFR	HGFR, MSPR	Breast cancer, colorectal cancer, gastric cancer, prostate cancer, renal cell carcinoma
Angiopoietins receptor of Tie family	Tie1, Tie2, TEK	Hemangioblastoma, epithelial cell tumor, gastric cancer, hepatocellular carcinoma

Table 2. List of FDA-approved TKIs

Targeted kinase	Name of the drugs
ALK	Alectinib, Crizotinib, Brigatinib, Lorlatinib, Ceritinib
Bcr-Abl	Bosutinib, Dasatinib, Nilotinib, Ponatinib, Imatinib
BTK	Acalabrutinib, Ibrutinib, Zarubrutinib
C-Met	Crizotinib, Cabozantinib
EGFR	Erlotinib, Afatinib, Gefitinib, Dacomitinib, Osimertinib, Neratinib
JAKs	Ruxolitinib, Baricitinib, Tofacitinib
PDGFR	Lenvatinib, Nintedanib, Ponatinib, Regorafenib, Imatinib
RET	Lenvatinib, Regorafenib, Sunitinib, Vandetanib
SRC	Dasatinib, Bosutinib, Ponatinib
VEGFR	Axitinib, Lenvatinib, Regorafenib, Pazopanib, Nintedanib, Sorafenib, Sunitinib
FGFR	Nintedanib, Erdafitinib
c-Kit	Pexidartinib, Avapritinib
FLT3	Gelteritinib, Sunitinib

well as interactions with other molecules, including tyrosine phosphatases [68]. RTKs acquire activating capabilities through various mechanisms, such as gain-of-function mutations, genomic amplification, chromosomal rearrangements, and autocrine activation [9], ultimately resulting in the disruption of the balance between cell proliferation and cell death [22]. Moreover, when considering the intricate regulation of RTK signaling in terms of time and space, the dysregulation becomes even more intricate [69]. Constitutive activation of RTKs can endow normal cells with oncogenic properties, initiating tumorigenesis driven by these receptors [70].

The RTK pathway exhibits diverse mechanisms and clinical significance across different subtypes of breast cancer [25]. In HR+ (hormone receptor-positive) breast cancer, RTK pathways such as EGFR and HER2 contribute to tumor progression by promoting cell proliferation and survival [49]. The interplay between hormone receptor activation and RTK signaling pathways further enhances cellular dependence on hormones [71]. In HER2+ breast cancer, overexpression of HER2 leads to the activation of downstream signaling pathways, including PI3K/AKT and MAPK, thereby fostering cell proliferation and anti-apoptotic effects [72]. The RTK pathway plays a pivotal role in this subtype, and targeted therapies against HER2, like trastuzumab, have achieved remarkable success in improving patient outcomes [73].

TNBC (triple-negative breast cancer), characterized by the absence of HR and HER2 expres-

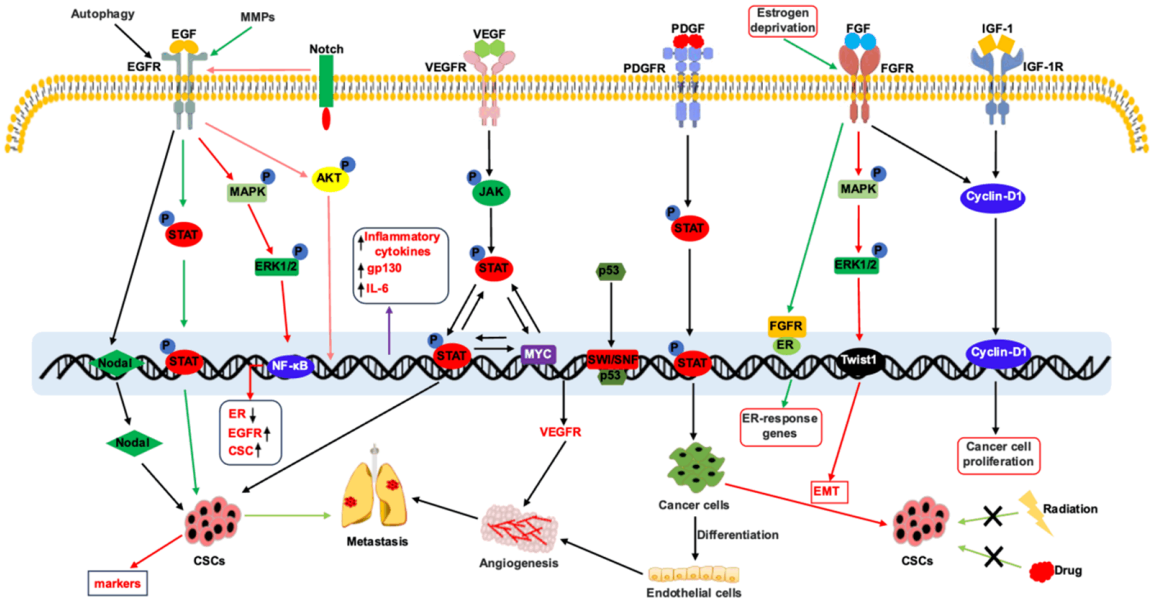

Figure 3. RTK-regulated signaling in breast cancer progression. (1) EGFR regulates the activation of JAK/STAT and MAPK signaling pathway to induce expression of stem cell markers leading to enrichment of cancer stem cells. EGFR induces Akt phosphorylation to promote inflammation. EGFR-regulated signaling also plays pivotal role in angiogenesis and metastasis. (2) VEGFR activates JAK/STAT signaling pathway to induce cancer stem cell phenotype through MYC expression. Mutant p53 induces the expression of VEGFR through the interaction with SWI/SNF complex. (3) PDGFR is expressed on stromal cells such as fibroblasts and is a marker of fibroblast activation. PDGFR-regulated STAT activation is involved the differentiation of cancer cells to endothelial cells leading to angiogenesis. (4) FGFR-activated MAPK pathway induces EMT and CSC phenotype. (5) Cooperation between the FGFR and IGF-1R regulates nuclear translocation of Cyclin D1 leading to enhanced cancer cell proliferation.

sion, may see RTK pathways like EGFR and FGFR facilitate tumorigenesis and progression through distinct signaling mechanisms [74-77]. The absence of specific targets renders TNBC treatment challenging, yet ongoing research into RTK pathways is exploring novel targeted therapeutic strategies [78-80]. Heterogeneity in mutations and expression levels of RTK pathways across different breast cancer subtypes influences tumor biology and treatment responses [81, 82].

Next, we delve into the specific mechanisms of RTK pathways across different breast cancer subtypes (**Figure 3**), as an understanding of these mechanisms holds the potential to enhance prognosis and quality of life for breast cancer patients [25, 73, 75, 77, 83-91].

EGFR: key regulator of cancer stem cell phenotype and metastasis

EGFR, a member of the ErbB family, is an RTK comprised of four closely related receptors: EGFR1 (EGFR, HER1, c-ErbB1), HER2 (EGFR2, c-ErbB2), EGFR3 (c-ErbB3, HER3), and EGFR4 (c-ErbB4, HER4). These receptors are situated on the cell membrane and consist of an extracellular ligand-binding domain, a transmembrane hydrophobic region, and an intracellular RTK domain [92, 93]. Activation of EGFR occurs upon binding with its ligand. Ligand binding induces conformational changes in the receptor, facilitating the formation of either homodimers or heterodimers with other ErbB receptors [94]. Dimerization leads to cross-phosphorylation of conserved tyrosine residues within the kinase domain, resulting in the activation of downstream signaling pathways such as MAPK/ERK1/2 and PI3K/AKT. These pathways regulate vital cellular processes including proliferation, survival, migration, differentiation, and metastasis [95, 96].

The EGFR signaling pathway is meticulously regulated in normal cells. However, alterations in EGFR expression and ligand overexpression in tumor cells can disrupt the balance, leading to abnormal autocrine or paracrine stimulation and increased activation of the tyrosine kinase

domain [97]. Consequently, this aberrant signaling promotes cell proliferation, differentiation, angiogenesis, and apoptosis suppression, ultimately facilitating tumor growth and metastasis [98]. Overexpression of EGFR is commonly observed in breast cancer tissues and is associated with heightened invasiveness and poor clinical outcomes [99]. Studies have revealed that EGFR and HER-2 are overexpressed in approximately 30% of invasive breast cancers and are correlated with tumor recurrence and overall survival. Furthermore, EGFR overexpression is observed in over half of TNBC cases, accounting for 15% of all breast cancers [100]. Research has revealed a positive correlation between EGFR expression and tumor pathological grade, while a negative correlation exists between EGFR expression and ER expression in breast cancer. Additionally, ER levels negatively correlate with cancer stem cell phenotype. These findings suggest that ER-negative TNBCs exhibit higher levels of EGFR expression and harbor a population of stem cells [98].

Inflammatory breast cancer (IBC) is an aggressive, fatal type marked by a significant number of chemo- and radio-resistant CSCs. Approximately 30% of IBC cases exhibit EGFR expression, rising to 40-50% in ER- and PR-negative cases [98, 100, 101]. High EGFR expression predicts worse prognosis and higher recurrence risk in IBC. Studies have demonstrated that using EGFR antibodies effectively reduces SUM149 cell proliferation, indicating the potential of targeting EGFR in IBC [102-104]. EGFR-HER2 heterodimers boost breast cancer metastasis. Moreover, EGFR inversely correlates with HER2 and ER. Research has shown that EGFR-HER2 heterodimers can promote the metastasis of breast cancer cells. In TNBC patients, EGFR expression is markedly elevated. Therefore, EGFR holds great potential as a therapeutic target in TNBC, warranting further investigation and development of targeted therapies [105, 106]. Recent studies conducted on various cell lines have highlighted the critical role of EGFR in promoting epithelial-mesenchymal transition (EMT). EMT involves cellular morphological changes, wherein epithelial cells transition to a mesenchymal fibroblast-like phenotype. This process is considered crucial for tumor infiltration and metastasis. While EMT is also implicated in normal mammary gland development, its significance becomes more prominent in breast cancer progression [107]. Multiple growth factors, including EGFR, hepatocyte growth factor, fibroblast growth factor, and insulin-like growth factor 1 or 2, have been shown to induce EMT in different epithelial cell lines. Among these, EGFR is particularly influential in EMT induction. For instance, EGFR activates the Ras-ERK pathway, which regulates EMT, thereby impacting tumor infiltration and metastasis. In cancer cells, the activation of RSK through ERK enhances mesenchymal activity and invasiveness [108-110]. Studies have explored the role of erlotinib, an EGFR-tyrosine kinase inhibitor, can inhibit cell viability, invasiveness, and the transition of IBC cells from a mesenchymal phenotype to an epithelial phenotype. Treatment with erlotinib resulted in increased expression of E-cadherin, an epithelial cell marker, and decreased expression of elastin, a component of the extracellular matrix. These findings suggest that erlotinib may exert its anti-metastatic effects by suppressing EMT [102-106]. Therefore, the strong correlation between EGFR and EMT indicates their potential as critical targets for inhibiting tumor metastasis. Further research in this area holds promise for providing valuable insights into the development of targeted therapies.

VEGFRs: key node in tumor angiogenesis and lymphatic genesis

VEGF, also known as vascular permeability factor or vasculotropin, plays a crucial role in regulating angiogenesis by exerting specific effects on vascular endothelial cells. The VEGF family comprises six homologues, including VEGF-A, -B, -C, -D, -E, and the placenta growth factor. Within the VEGF family, three receptors have been identified. VEGFR-1, encoded by the Flt-1 gene; VEGFR-2, encoded by the Flk-1/KDR gene; and VEGFR-3, encoded by the Flt-4 gene. These receptors are classified as transmembrane receptor tyrosine kinases [111]. VEGF expression varies among different tissues, including the heart, lymph nodes, placenta, and tumor tissues, during body development. The discovery of VEGF and its receptors in breast cancer cells indicates the presence of specific autocrine signaling pathways. These pathways can mediate the phosphorylation of VEGFR-1/2 or induce NRP1/2 signaling, pro-

moting tumor cell proliferation, survival, and migration. Understanding these pathways is crucial in developing strategies to target VEGF signaling for therapeutic intervention in breast cancer [111-113].

Numerous studies have demonstrated the involvement of VEGF-A in promoting the survival of breast cancer cells. Blocking VEGF-A transcription, either through using VEGF siRNA or neutralizing antibodies, has been shown to induce apoptosis in tumor cells under both normal and low oxygen conditions [114]. This apoptotic effect in breast cancer cells involves downregulation of Bcl-2 expression, increased protein misfolding, and disruption of the PI3K pathway [115]. Moreover, VEGF binding to VEGF-R1 and VEGF-R2 sustains cancer cell survival. In cell models such as MCF-7 or MDA-MB-231, downregulatingVEGF-R2 or NRP-1 inhibits AKT phosphorylation, suppressing VEGF-R1 and decreasing cancer cell survival [116]. These findings shed light on the complex interplay between VEGF-A and its receptors in breast cancer cell survival and provide crucial insights for the development of therapeutic strategies aimed at targeting the VEGF signaling pathway. VEGF-A, -C, and -D are simultaneously expressed in various types of tumor cells and bind to receptors VEGFR-1, VEGFR-2, and VEGFR-3. This binding serves to protect lymphatic endothelial cells from apoptosis induced by the immune system while promoting the growth, proliferation, and migration of these cells. Consequently, lymphatic vessel formation is stimulated, leading to lymphatic metastasis in tumors [117-120]. Notably, VEGF-C and VEGF-D exhibit specific affinity for VEGFR-3, which triggers receptor phosphorylation. VEGF-C demonstrates a high affinity for lymphatic endothelial cells, thus inducing their proliferation and the formation of lymphatic sinuses. In different cancer types, VEGF-A binds to VEGFR-1 and VEGFR-2 to induce tumor angiogenesis, while VEGF-C and VEGF-D interact with VEGFR-3 to promote lymphatic vessel generation [121]. Recent studies involving 50 breast cancer patients focused on investigating the expression of VEGF-C, VEGFR-3, and angiopoietin-1 in cancerous tissue, along with their associations with different clinical and pathological characteristics, including metastasis [122]. The results revealed a robust correlation between microlymphatic vessel formation and both lymph node metastasis and VEGFR-3 expression [123]. Moreover, microvessel and microlymphatic vessel densities in breast cancer are crucial for tumor progression and lymph node metastasis. Notably, microlymphatic vessel density in adjacent tissues independently predicts lymph node metastasis. VEGF-C expression in lymphatic endothelial cells strongly correlates with lymphatic vessel formation and metastasis, highlighting its role in promoting lymphatic metastasis in breast cancer [124, 125]. It is worth noting that although VEGF plays a vital role in promoting tumor angiogenesis, lymphangiogenesis, and immune modulation, the vessels and lymphatic vessels formed exhibit characteristics such as immaturity, leakiness, and inadequate support from the surrounding vasculature [126]. Targeting VEGF-C, VEGF-D, and their corresponding receptor VEGFR-3 shows promise in inhibiting tumor metastasis and improve prognosis in breast cancer [127, 128]. These targeted interventions can suppress tumor vessel growth or promote apoptosis [129], holding potential for managing metastatic breast cancer and enhancing patient outcomes.

PDGFR: crucial role in tumor-stroma interaction

PDGFRs, belonging to the RTK superfamily, consist of PDGFR-α and PDGFR-β. These receptors share similar functions and play significant roles in early hematopoiesis, blood vessel formation, and organ development [130]. Both PDGFRα and PDGFRβ are crucial in both physiological and pathological conditions. The diverse binding patterns of PDGF to its receptors involve five different homodimeric or heterodimeric forms: PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC, and PDGF-DD. PDGF-AA specifically activates PDGFRα, while PDGF-BB activates PDGFRα, PDGFRα/β, and PDGFRβ [131]. PDGF-AB and PDGF-CC activate PDGFRα and PDGFRα/β, whereas PDGF-DD selectively activates its receptor, PDGFR-β. The interaction between PDGF and its receptors leads to the assembly of PDGFR subunits into dimers, which activates the intrinsic tyrosine kinase activity of the receptors [132]. Upon activation, PDGFR phosphorylates tyrosine residues on its substrates, initiating downstream signaling cascades that regulate cellular responses. These downstream signaling pathways can be divided

into three categories based on their specific effects: (1) regulation of cell survival and growth, (2) regulation of cell invasion, blood vessel formation, and metastasis, and (3) regulation of EMT [133-135].

PDGF is derived from the stromal stem cells of the local tumor microenvironment. These stem cells generate various cytokines that interact with tumor cells, playing a crucial role in tumor initiation and progression [136]. PDGFs and PDGFRs are key regulators of cell growth and division, exerting significant impacts on malignant cells and the tumor microenvironment [124]. Dysregulation of PDGF signaling has been observed in various human malignancies, including prostate, lung, kidney, ovarian, brain, and pancreatic cancers. Overexpression of PDGF has been detected in the stromal cells of breast cancer, accompanied by the activation of the PI3K-AKT-mTOR signaling pathway [137]. Promising results have been demonstrated through combined treatment employing PDGFR tyrosine kinase inhibitors and mTOR inhibitors, showing potential in reducing stromal reactions and tumor proliferation, offering a novel therapeutic strategy for breast cancer [134]. PDGF plays a vital role in breast tumor invasion. Enhanced expression of PDGF promotes cell proliferation, inhibits apoptosis, and induces the expression of the CXCR4, thereby facilitating tumor growth and lymph node metastasis. Effective elimination of PDGF-induced lymph node metastasis can be achieved through blocking CXCR4 signaling pathway [138]. In breast cancer cells, there exists an interplay between PDGF, Notch, and NF-κB signaling pathways. Overexpressed PDGF leads to elevated NF-κB/Jagged-1 expression, where NF-κB activation influences Notch signaling, EMT, and tumor invasion. Downregulation of PDGFD can inhibit Notch and NF-κB pathways, partially reverse EMT, suppress cell growth, and induce apoptosis [135]. The interactions between tissue-resident stem cells and the cancer microenvironment also contribute to tumor progression. These stem cells secrete PDGF in a paracrine manner, inducing EMT in cancer cells. This PDGF-dependent mechanism promotes the expansion of cancer stem cell populations and facilitates tumor growth [139]. In summary, PDGF represents a promising therapeutic target for the treatment of breast cancer. The dysregulation of PDGF signaling in the tumor microenvironment and its interaction with tumor cells contribute to tumor initiation, progression, invasion, and metastasis [140]. Understanding the role of PDGF in breast cancer opens up opportunities for targeted therapeutic interventions aimed at disrupting PDGF signaling pathways and preventing tumor progression. Unveiling the crosstalk between PDGF, Notch, and NF-κB signaling pathways provides valuable insights into the mechanisms behind tumor invasion, EMT, and the regulation of cancer stem cells.

FGFR: aberrant expression in breast cancer

FGFRs are members of the RTK family. Encoded by the FGFR1, FGFR2, FGFR3, and FGFR4 genes, these receptors are primarily composed of single-chain glycoproteins [141]. Structurally, FGFRs consist of three main regions: an extracellular region, a transmembrane region, and an intracellular region with tyrosine kinase activity. FGFRs play a crucial role in regulating cell growth and division [142]. Upon binding with their specific ligands, FGFRs undergo receptor dimerization, leading to the activation of their tyrosine kinase activity. Activated tyrosine kinases serve as connection points between upstream signaling pathways and transmit signals to the intracellular environment, triggering various downstream signaling pathways [143]. These pathways include the MAPK, PI3K/AKT, STAT, and PLC-γ pathway. These pathways regulate gene expression and modulate cellular processes such as cell differentiation, proliferation, and the formation of tumors [144, 145]. Numerous studies have demonstrated that FGFs and FGFRs play a crucial role in promoting cancer progression through diverse mechanisms. These mechanisms encompass inducing mitotic and survival signals, promoting EMT, invasion, and angiogenesis. The dysregulation of FGFR signaling has been implicated in various types of cancer, highlighting its potential as a viable therapeutic target for cancer treatment [145-148].

FGFRs and FGFs play a crucial role in breast development and tissue homeostasis regulation. An array of studies have identified a close association between ectopic expression of the FGFR family and the development of breast cancer [147]. Notably, approximately 10% of breast cancer patients exhibit amplification of

the FGFR1 gene, a genetic alteration that has been linked with early recurrence and poor prognosis, particularly in ER-positive breast cancer [149]. Intriguingly, FGFR1 amplification is rarely observed in HER2-amplified breast cancer, suggesting a mutually exclusive activation of similar downstream signaling pathways between FGFR1 and HER2 [150]. FGFR1 amplification has been linked to endocrine therapy resistance. High rates of FGFR1 amplification are observed in breast cancer subtypes characterized by a high Ki-67 proliferation index and luminal B phenotype, emphasizing the significance of FGFR1 overexpression in predicting unfavorable outcomes. These findings provide a strong rationale for exploring targeted endocrine therapies against FGFR1 [151]. Recent research has increasingly associated FGFR2 with breast cancer, identifying it as one of the key non-inherited susceptibility genes, particularly in TNBC. Studies have reported FGFR2 gene amplification and overexpression in a specific subtype of TNBC, demonstrating its activation of the PI3K/AKT signaling pathway and subsequent inhibition of apoptosis. These findings underscore the potential of FGFR2 as a promising therapeutic target, especially in TNBC cases with FGFR2 amplification [152]. Besides, FGFR3 mutations have been implicated in various malignancies, such as multiple myeloma, cervical cancer, and bladder cancer, but their association with breast cancer remains limited [153]. Moreover, compelling evidence has pointed towards FGFR4 ectopic expression in human breast cancer, which is linked to chemoresistance in breast cancer. By using mouse breast cancer models has substantiated the role of FGFR4 in promoting tumor progression and metastasis [154]. Analyses of breast cancer cells that survived doxorubicin treatment have revealed an upregulation of FGFR4 expression, while interference with FGFR4 using antagonistic antibodies has demonstrated increased chemosensitivity in breast cancer cells expressing FGFR4. Collectively, these findings underscore FGFR4 as a significant factor influencing chemotherapy resistance and a promising therapeutic target for overcoming drug resistance [155]. Collectively, it is evident that FGFRs are mechanistically interlinked with the function and resistance of other RTKs, providing potential targets for breast cancer treatment.

IGFR: a high-risk factor for breast cancer

As a member of the IGFR family, IGF-1R is a ubiquitously expressed type 1 transmembrane heterotetrameric receptor consisting of two ligands, an extracellular α subunit and two β subunits, and ligand binding induces transphosphorylation of tyrosine within the TK domain by the dimeric subunit partner [156]. Phosphorylated residues act as docking sites for other signaling molecules, such as insulin receptor substrates 1 to 4 (IRS1 to IRS4) and adaptor protein SHC, which lead to the activation of the PI3K and MAPK pathways [157, 158]. Under normal physiological conditions, the IGF system is tightly regulated, allowing for homeostatic growth. In tumor cells, these molecules are activated by mutations, chromosomal translocations, abnormal stimuli (autocrine, endocrine, or paracrine), or loss of genomic imprinting [159]. IGF-1R gene amplification has been reported in a variety of malignancies [160]. High concentrations of IGF-1 are present in several common cancers, including prostate cancer and premenopausal breast cancer, and higher blood concentrations of IGF-1 are associated with a higher risk of breast cancer in nonmenopausal women [161]. Therefore, IGF-IR can be a promising protein for specific and targeted therapeutics.

Current application of tyrosine kinase inhibitors in breast cancer treatment

Breast cancer is a heterogeneous disease which has been characterized molecularly into different subtypes depending on expression of ER, PR and HER2. For hormone receptor-positive breast cancer (luminal A and B), hormone therapy consists of selective estrogen receptor modulators (tamoxifen and raloxifene) is routinely used as adjuvant therapy [32, 162]. Since TNBC or basal like and HER-enriched breast cancer do not express hormone receptors so that hormone therapy is not effective in these subtypes [53]. However, due to the prominent expression of RTKs in TNBC and HER2-enriched sub types, blocking the functions of RTKs is one of the promising approaches for management of TNBC and HER2-enriched breast cancer [42]. So far, various strategies have been adopted for inhibition of RTK-dependent signaling, and some are currently used in clinics (**Table 3**) [38, 39, 50, 55, 56, 66, 76, 77, 87, 163-178].

Table 3. Current anti-RTK therapy of breast cancer

Molecule	Type	Target	Phase of study	Mechanism
Trastuzumab	Humanized mAb	HER	In clinical use	Inhibits HFR2 and HER3 dimerization, induces ADCC
Cetuximab	Chimeric mAb	EGFR	Phase I, II	Induces NK cell mediated ADCC
Panitumumab	Humanized mAb	EGFR	Phase II	Enhances sensitivity to DNA-damaging agents in TNBC
Nimotuzumab	Humanized mAb	EGFR	Phase I	Induces NK cell mediated ADCC
Necitumumab	Humanized mAb	EGFR	Phase II	Inhibits downstream targets in EGFR pathway, induces ADCC
Gefitinib	Reversible TKI	EGFR	Phase I, II	Reverses TAM resistance by up-regulating the ERα
Erlotinib	Reversible TKI	EGFR	Phase I, II	Suppresses CDK2 activity
Lapatinib	Reversible TKI	EGFR, HER2	In clinical use	Used as an alternate therapy in HER2 positive breast cancer
Afatinib	Irreversible TKI	EGFR, HER2	Phase II	Inhibits EGFR and HER2 signaling irreversibly
Varlitinib	Reversible TKI	EGFR, HER2, ErbB4	Phase II	Inhibits HER/MAPK signaling in TNBC
Dacomitinib	Irreversible TKI	EGFR, HER2, ErbB4	Phase I, Solid tumors	Inhibits HER2, EGFR, HER4, Akt and ERK phosphorylation
Sapitinib	Reversible TKI	EGFR, HER2, ErbB3	Phase I, Solid tumors	Showed higher inhibitory potential in tamoxifen resistant breast cancer
Vandetanib	TKI	EGFR, VEGFR2-3, RET	Phase I, II	Targets angiogenesis by inhibiting VEGFR2 and 3 signaling along with EGFR pathway
Neratinob	Irreversible TKI	EGFR, HER2, ErbB4	Phase I, II, III	Irreversibly blocks EGFR and HER2 pathway
BMS-690514	Irreversible TKI	EGFR, HER2, ErbB4, VEGFR1-3	Phase I, Solid tumors	Irreversibly blocks EGFR and HER2 pathway
AEE788	Reversible TKI	EGFR, ErbB2, VEGFR	Phase I	Targets angiogenesis by inhibiting VEGFR2 and 3 signaling along with EGFR pathway
Lucitanib	TKI	FGFR1-2, PDGFRα/β, VEGFR1-3	Phase II	Show anti-angiogenic and anti-tumoral activity by targeting FGFR and VEGFR

Tyrosine kinase plays a pivotal role in tumor formation and progression. TKIs, which specifically target these kinases, have emerged as a focal point of cutting-edge research in molecular targeted therapy for combating tumors worldwide [47]. By effectively suppressing the biological activity of tyrosine kinases, TKIs disrupt the reparative mechanisms employed by tumor cells, leading to cell cycle arrest at the G1 phase, induction of apoptosis, inhibition of neovascularization, and the manifestation of anti-tumor effects through diverse signaling pathways [179, 180]. Currently, TKIs utilized in breast cancer treatment can be classified into three main groups based on their specific targets: EGFR-targeting TKIs, VEGFR-targeting TKIs, and non-receptor TKIs.

Inhibitors of tyrosine kinase targeting EGFR

EGFR tyrosine kinase inhibitors (EGFR-TKIs) are small-molecule compounds that specifically target the EGFR [181-186]. Currently, there are two main classes of drugs used to target the EGFR pathway in cancer treatment: 1) EGFR monoclonal antibodies, represented by trastuzumab, which targets HER2. Trastuzumab interferes with ligand binding to HER2, inhibiting receptor dimerization [187-189]. Trastuzumab has achieved significant breakthroughs in breast cancer treatment and is considered the standard therapy for HER2+ breast cancer. However, some patients develop primary or acquired resistance to trastuzumab, still posing significant challenges in clinical management [190]; 2) EGFR-TKIs can penetrate cells and competitively repress the tyrosine kinase domain of EGFR. By binding to ATP, they inhibit autophosphorylation of EGFR, thereby blocking downstream signaling pathways mediated by EGFR, ultimately exerting anti-tumor effects [191]. Currently, several EGFR-TKIs are being studied for breast cancer treatment, including lapatinib, afatinib, gefitinib, erlotinib, and neratinib [192].

Inhibitors of tyrosine kinase targeting VEGFR

VEGFR Tyrosine Kinase Inhibitors (VEGFR-TKIs) are small-molecule compounds designed to specifically target the tyrosine kinase domain of VEGFR. Since angiogenesis plays a crucial role in tumor growth, invasion, and metastasis, inhibiting tumor angiogenesis has emerged as a promising approach for cancer treatment [191]. Existing anti-angiogenic therapies primarily focus on inhibiting the VEGF pathway using strategies such as VEGF monoclonal antibodies like bevacizumab, as well as VEGFR-TKIs sorafenib, sunitinib, and others [192-200]. Notably, VEGF mRNA expression has been identified in various tumors, including breast cancer. Bevacizumab has demonstrated efficacy in treating breast cancer in previous studies. Several novel VEGFR-TKIs are currently under investigation and in different stages of clinical trials, which mainly include sorafenib, sunitinib, axitinib, pazopanib, vandetanib, and others [201, 202].

Non-receptor tyrosine kinase inhibitors

Among the non-receptor tyrosine kinase family, Src kinases have received significant attention. They could interact with various receptor proteins, regulating cell proliferation, differentiation, adhesion, motility, and angiogenesis. Blocking or regulating the binding of Src tyrosine kinases with these overexpressed receptors can keep tumor cell proliferation and invasion under control. Recently, TKIs such as dasatinib (BMS-354825), bosutinib (SKI-606), and saracatinib (AZD-0530) have emerged, working by competing for the ATP-binding site of Src tyrosine kinase. Numerous ongoing clinical studies hold the promise of offering a brighter future for targeted therapy in breast cancer [203].

Promising future development

Over the past two decades, a diverse range of RTKs targeted inhibitors have been developed and clinically evaluated to enhance cancer patient survival rates. In particular, the aberrant activation of RTKs has emerged as a potential therapeutic target, where molecular targeted inhibitors can hinder the activity of pathogenic tyrosine kinases. Further insights into genetics, cell biology, and structural biology have led to the development of novel treatment approaches. Disease-causing RTK mutations, deletions, translocations, and amplifications have been identified in breast cancer. Currently, therapies targeting RTKs involve both small molecule inhibitors and monoclonal antibodies, with ongoing research. The potential applications of RTKs in breast cancer treatment hold significant prospects for future advancements.

Targeting RTKs in TNBC treatment

TNBC is a highly heterogeneous subtype of breast cancer with the highest rates of recurrence and distant metastasis. Due to absence of both hormone receptors (HR) and HER2 protein, effective treatment for TNBC remain limited. Even immunotherapy has shown modest response rates of around 10-20% in patients. Particularly for patients with advanced-stage TNBC, chemotherapy remains the primary clinical treatment method. Therefore, the search for more effective breast cancer targets and treatment methods is of utmost importance.

Currently approved or clinically tested antibodies for breast cancer treatment can be classified into three main categories: 1) Monoclonal antibodies targeting tumor-surface antigens; 2) Immune checkpoint inhibitors represented by PD-1 and PD-L1 antibodies; 3) Antibody-drug conjugates (ADCs) [204]. Monoclonal antibodies targeting tumor-surface antigens primarily work by blocking the signaling pathways that promote tumor cell growth through binding to HER2 or other antigens on the tumor surface. This inhibits tumor growth or facilitates the destruction of tumor cells through antibody-dependent cellular cytotoxicity (ADCC). Various cell factor receptors such as EGFR, VEGFR, and FGFR are included in this category [205].

Research has shown that EGFR protein is frequently overexpressed in TNBC and serves as an independent prognostic indicator for disease-free and overall survival. EGFR can potentially be targeted using cetuximab and small-molecule TKIs [184]. Similarly, compared to non-TNBC patients, TNBC patients exhibit significantly higher levels of VEGF expression and have shorter disease-free survival periods [206]. Since angiogenesis is considered a key component driving tumor cell proliferation and survival, VEGF has emerged as a promising target for TNBC treatment [207]. A study evaluat-

ing bevacizumab, a monoclonal antibody targeting VEGF-A, as an adjunct therapy for TNBC showed improved immunotherapeutic effects [208]. Aberrant FGFR signaling, fueled by various genetic alterations including point mutations, activating mutations, fusions, rearrangements, and amplifications, plays a vital role in tumor progression. Therefore, FGFR is regarded as a potential target for breast cancer treatment [209]. While FGFR1 amplification is associated with poor prognosis in HR-positive breast cancer, its role in TNBC remains controversial. FGFR2 expression is correlated with poorer overall survival [210]. FGFR inhibitors have gained attention as one of the promising drugs. If TNBC patients can also benefit from FGFR inhibitors, it would significantly improve their survival rates. However, drug resistance in breast cancer patients to FGFR inhibitors is currently the major obstacle hindering clinical approval. Preclinical data have also investigated the efficacy of anti-FGFR isoform antibodies and FGFR inhibitors, showing promising results in Phase I clinical trials for solid tumors, including breast cancer [211].

Overall, targeting RTKs offers a potential therapeutic avenue for the treatment of TNBC. Further research and advancements in targeted therapies are crucial for enhancing the outcomes and survival rates of TNBC patients.

Alterations in RTKs in ER+ breast cancer with endocrine resistance

RTKs, including EGFR, HER2, IGFR, VEGFR, and FGFR, are activated upon ligand binding. These receptors are primarily involved in growth factors, cytokines, or hormones, and their activation or overexpression is associated with endocrine therapy resistance in ER+ breast cancer [212].

HER2 overexpression reduces the sensitivity to antiestrogen therapy, partly through activation of the PI3K-AKT-mTOR and MAPK pathways [213]. Additionally, HER2 expression depends on the NF-κB pathway, and in ERα-suppressed breast cancer circulating tumor cells, NF-κB signaling can increase HER2 expression. Thus, inhibiting the NF-κB pathway in combination with fulvestrant can restore the sensitivity of ER+/HER2- endocrine-resistant breast cancer cells to endocrine therapy [214]. The current treatment for ER+/HER2+ tumors involves combining estrogen targeting with HER2 inhibitors [215]. HER2 mutations are linked to acquired endocrine resistance and have been found in non-HER2 amplification metastatic breast cancer within 5% of endocrine therapy-resistant patients. ER+ breast cancer cells and xenografts that express HER2 mutations are resistant to estrogen deprivation or fulvestrant treatment and show poor response to HER2 TKI, lapatinib [216]. However, studies suggest that co-blocking HER2 and ER expression in breast cancer cells has a synergistic effect. Therefore, for patients with ER+ breast cancer and concurrent HER2 mutations, the combination of lapatinib and fulvestrant is a favorable choice [217].

EGFR amplification accounts for approximately 1.7% of endocrine-resistant metastatic breast cancer and can promote fulvestrant resistance. Co-administration of EGFR inhibitors can reverse this resistance [218-220]. In a cohort of 60 patients diagnosed with metastatic ER+ breast cancer, both before and after initiation of endocrine therapy, the comparison of whole exome sequencing data and circulating DNA analysis revealed that FGFR1 amplification accounted for 15%, FGFR2 amplification accounted for 5%, FGFR2 activating mutations accounted for 3.3%, and FGF3 amplification accounted for 28.3%. Immunohistochemical (IHC) staining and fluorescence in situ hybridization (FISH) showed that besides its typical membrane-bound intracellular signaling function, FGFR1 can also participate in endocrine resistance by regulating gene transcription in ER+ breast cancer [221]. The combination of FGFR inhibitors with fulvestrant can inhibit the growth of ER+/FGFR1-amplified cell lines and tumors. It was reported almost two decades ago that approximately 30% of breast tumors demonstrate elevated FGFR4 expression in comparison to normal tissues. Experimental studies suggest that FGFR4 may mediate acquired endocrine resistance in metastatic breast cancer [222]. Therefore, endocrine therapy in combination with novel FGFR inhibitors may offer new strategies for treating metastatic breast cancer.

Conclusion

Breast cancer is a multifactorial disease characterized by dysregulation of cellular signaling

pathways due to genetic and epigenetic alterations. Numerous growth factors and their receptors, known as RTKs, are involved in the development and progression of cancer. Overexpression or dysregulation of RTKs in breast cancer cells activates downstream signaling pathways such as MAPK, PI3K/AKT, and JAK/STAT, promoting tumor growth, angiogenesis, and metastasis. The multifaceted role of RTKs makes them attractive targets for breast cancer treatment. In recent decades, significant progress has been made in understanding RTKs and targeted therapies through genomic technologies. Several drugs, including small molecule inhibitors and monoclonal antibodies, have been developed and approved for treating cancer by targeting RTK activation. While approved TKIs have led to tumor regression or prolonged survival, the lack of selectivity for individual targets and the drug resistance remain challenges. Furthermore, structural mutations, gene amplification, and alternative pathway activation pose challenges to anti-RTK therapy.

Despite research findings supporting the significance of RTK signaling as a therapeutic target in breast cancer, existing clinical trial data show modest efficacy of RTK inhibitors. The reasons for the lack of efficacy of RTK inhibitors in breast cancer patients are still inconclusive, whether it is due to drug ineffectiveness, insufficient patient selection, or a lack of oncogenic potential in RTK genomic variations. Before considering RTK signaling as a therapeutic target in breast cancer, the following issues need to be addressed: precise definition of RTK signaling abnormalities and identification of predictive biomarkers for response to RTK inhibitors; optimization of combinational strategies of RTK inhibitors with endocrine drugs or other targeted agents to enhance efficacy and reduce resistance; and development of more effective RTK inhibitors.

In conclusion, RTK signaling plays a crucial role in the pathogenesis of breast cancer, and targeted strategies against RTK signaling show promising prospects for treatment. However, further exploration is needed to appropriately block this signaling pathway in breast cancer patients to achieve optimal efficacy. Therefore, further research on acquired resistance in breast cancer is of great significance for developing novel therapeutic strategies against tumor recurrence.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81972490) and the Fundamental Research Funds for the Central Universities of Central South University (No. 2022ZZTS0877).

Disclosure of conflict of interest

None.

Abbreviations

ADCC, Antibody-dependent cellular cytotoxicity; ADCS, Antibody-drug conjugates; ALK, Anaplastic lymphoma kinase; BC, Breast cancer; CXCR4, CXC chemokine receptor 4; EGFR, Epidermal growth factor receptor; EMT, Epithelial-mesenchymal transition; ER, Estrogen receptor; FDA, Food and Drug Administration; FGFR, Fibroblast growth factor receptor; FISH, Fluorescence in situ hybridization; HR, Hormone receptors; IBC, Inflammatory breast cancer; IGFR, Insulin-like growth factor receptor; IHC, Immunohistochemical; JAK, Janus kinase; MAPK, Mitogen-activated protein kinase; MTC, Medullary thyroid carcinoma; mTOR, Mammalian target of rapamycin; NSCLC, Non-small cell lung cancer; PDGFR, Platelet-derived growth factor receptor; PI3K, Phosphoinositide 3-kinase; PLC-γ, Phospholipase C-gamma; PR, Progesterone receptor; RTKs, Receptor tyrosine kinases; SH, Src homology; STAT, Signal transducer and activator of transcription; TGF-α, Transforming growth factor-alpha; TKI, Tyrosine kinase inhibitor; TNBC, Triple-negative breast cancer; VEGFR, Vascular endothelial growth factor receptor.

Address correspondence to: Kuan-Song Wang, Department of Pathology, School of Basic Medical Sciences, Central South University, Changsha, Hunan, China. ORCID: 0000-0002-7828-2648; E-mail: wangks001@csu.edu.cn

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.

[2] Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO and Botstein D. Molecular portraits of human breast tumours. Nature 2000; 406: 747-752.

[3] Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Lønning PE and Børresen-Dale AL. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001; 98: 10869-10874.

[4] Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, Deng S, Johnsen H, Pesich R, Geisler S, Demeter J, Perou CM, Lønning PE, Brown PO, Børresen-Dale AL and Botstein D. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003; 100: 8418-8423.

[5] Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO and Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 2010; 28: 1684-1691.

[6] Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012; 490: 61-70.

[7] Tomiguchi M, Yamamoto Y, Yamamoto-Ibusuki M, Goto-Yamaguchi L, Fujiki Y, Fujiwara S, Sueta A, Hayashi M, Takeshita T, Inao T and Iwase H. Fibroblast growth factor receptor-1 protein expression is associated with prognosis in estrogen receptor-positive/human epidermal growth factor receptor-2-negative primary breast cancer. Cancer Sci 2016; 107: 491-498.

[8] Palmieri D, Bronder JL, Herring JM, Yoneda T, Weil RJ, Stark AM, Kurek R, Vega-Valle E, Feigenbaum L, Halverson D, Vortmeyer AO, Steinberg SM, Aldape K and Steeg PS. Her-2 overexpression increases the metastatic outgrowth of breast cancer cells in the brain. Cancer Res 2007; 67: 4190-4198.

[9] Lemmon MA and Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell 2010; 141: 1117-1134.

[10] Yarden Y and Shilo BZ. SnapShot: EGFR signaling pathway. Cell 2007; 131: 1018.

[11] Chen MK and Hung MC. Proteolytic cleavage, trafficking, and functions of nuclear receptor tyrosine kinases. FEBS J 2015; 282: 3693-3721.

[12] Templeton AJ, Diez-Gonzalez L, Ace O, Vera-Badillo F, Seruga B, Jordán J, Amir E, Pandiella A and Ocaña A. Prognostic relevance of receptor tyrosine kinase expression in breast cancer: a meta-analysis. Cancer Treat Rev 2014; 40: 1048-1055.

[13] Wise R and Zolkiewska A. Metalloprotease-dependent activation of EGFR modulates CD44(+)/CD24(-) populations in triple negative breast cancer cells through the MEK/ERK pathway. Breast Cancer Res Treat 2017; 166: 421-433.

[14] Park J, Kim S, Joh J, Remick SC, Miller DM, Yan J, Kanaan Z, Chao JH, Krem MM, Basu SK, Hagiwara S, Kenner L, Moriggl R, Bunting KD and Tse W. MLLT11/AF1q boosts oncogenic STAT3 activity through Src-PDGFR tyrosine kinase signaling. Oncotarget 2016; 7: 43960-43973.

[15] Qian BZ, Zhang H, Li J, He T, Yeo EJ, Soong DY, Carragher NO, Munro A, Chang A, Bresnick AR, Lang RA and Pollard JW. FLT1 signaling in metastasis-associated macrophages activates an inflammatory signature that promotes breast cancer metastasis. J Exp Med 2015; 212: 1433-1448.

[16] Ibrahim SA, Gadalla R, El-Ghonaimy EA, Samir O, Mohamed HT, Hassan H, Greve B, El-Shinawi M, Mohamed MM and Götte M. Syndecan-1 is a novel molecular marker for triple negative inflammatory breast cancer and modulates the cancer stem cell phenotype via the IL-6/STAT3, Notch and EGFR signaling pathways. Mol Cancer 2017; 16: 57.

[17] Zhao D, Pan C, Sun J, Gilbert C, Drews-Elger K, Azzam DJ, Picon-Ruiz M, Kim M, Ullmer W, El-Ashry D, Creighton CJ and Slingerland JM. VEGF drives cancer-initiating stem cells through VEGFR-2/Stat3 signaling to upregulate Myc and Sox2. Oncogene 2015; 34: 3107-3119.

[18] Neal JW and Sledge GW. Decade in review-targeted therapy: successes, toxicities and challenges in solid tumours. Nat Rev Clin Oncol 2014; 11: 627-628.

[19] Remon J, Morán T, Majem M, Reguart N, Dalmau E, Márquez-Medina D and Lianes P. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in EGFR-mutant non-small cell lung cancer: a new era begins. Cancer Treat Rev 2014; 40: 93-101.

[20] He M and Wei MJ. Reversing multidrug resistance by tyrosine kinase inhibitors. Chin J Cancer 2012; 31: 126-133.

[21] Westover D, Zugazagoitia J, Cho BC, Lovly CM and Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol 2018; 29: i10-i19.

[22] Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell 2000; 103: 211-225.

[23] Robinson DR, Wu YM and Lin SF. The protein tyrosine kinase family of the human genome. Oncogene 2000; 19: 5548-5557.

[24] Ullrich A and Schlessinger J. Signal transduction by receptors with tyrosine kinase activity. Cell 1990; 61: 203-212.
[25] Esteban-Villarrubia J, Soto-Castillo JJ, Pozas J, San Román-Gil M, Orejana-Martín I, Torres-Jiménez J, Carrato A, Alonso-Gordoa T and Molina-Cerrillo J. Tyrosine kinase receptors in oncology. Int J Mol Sci 2020; 21: 8529.
[26] Hubbard SR. Crystal structure of the activated insulin receptor tyrosine kinase in complex with peptide substrate and ATP analog. EMBO J 1997; 16: 5572-5581.
[27] Choura M and Rebaï A. Receptor tyrosine kinases: from biology to pathology. J Recept Signal Transduct Res 2011; 31: 387-394.
[28] Grassot J, Mouchiroud G and Perrière G. RTK-db: database of Receptor Tyrosine Kinase. Nucleic Acids Res 2003; 31: 353-358.
[29] Yarden Y and Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001; 2: 127-137.
[30] Trenker R and Jura N. Receptor tyrosine kinase activation: from the ligand perspective. Curr Opin Cell Biol 2020; 63: 174-185.
[31] Yarden Y and Pines G. The ERBB network: at last, cancer therapy meets systems biology. Nat Rev Cancer 2012; 12: 553-563.
[32] Ebrahimi N, Fardi E, Ghaderi H, Palizdar S, Khorram R, Vafadar R, Ghanaatian M, Rezaei-Tazangi F, Baziyar P, Ahmadi A, Hamblin MR and Aref AR. Receptor tyrosine kinase inhibitors in cancer. Cell Mol Life Sci 2023; 80: 104.
[33] Arora A and Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther 2005; 315: 971-979.
[34] Li E and Hristova K. Role of receptor tyrosine kinase transmembrane domains in cell signaling and human pathologies. Biochemistry 2006; 45: 6241-6251.
[35] Paul MK and Mukhopadhyay AK. Tyrosine kinase - role and significance in cancer. Int J Med Sci 2004; 1: 101-115.
[36] Pytel D, Sliwinski T, Poplawski T, Ferriola D and Majsterek I. Tyrosine kinase blockers: new hope for successful cancer therapy. Anticancer Agents Med Chem 2009; 9: 66-76.
[37] Porter AC and Vaillancourt RR. Tyrosine kinase receptor-activated signal transduction pathways which lead to oncogenesis. Oncogene 1998; 17: 1343-1352.
[38] Siatis KE, Giannopoulou E, Manou D, Sarantis P, Karamouzis MV, Raftopoulou S, Fasseas K, Alzahrani FM, Kalofonos HP and Theocharis AD. Resistance to hormone therapy in breast cancer cells promotes autophagy and EGFR signaling pathway. Am J Physiol Cell Physiol 2023; 325: C708-C720.
[39] Takeda T, Tsubaki M, Matsuda T, Kimura A, Jinushi M, Obana T, Takegami M and Nishida S. EGFR inhibition reverses epithelial-mesenchymal transition, and decreases tamoxifen resistance via Snail and Twist downregulation in breast cancer cells. Oncol Rep 2022; 47: 109.
[40] Yamaoka T, Kusumoto S, Ando K, Ohba M and Ohmori T. Receptor tyrosine kinase-targeted cancer therapy. Int J Mol Sci 2018; 19: 3491.
[41] Miraghel SA, Ebrahimi N, Khani L, Mansouri A, Jafarzadeh A, Ahmadi A and Aref AR. Crosstalk between non-coding RNAs expression profile, drug resistance and immune response in breast cancer. Pharmacol Res 2022; 176: 106041.
[42] Sudhesh Dev S, Zainal Abidin SA, Farghadani R, Othman I and Naidu R. Receptor tyrosine kinases and their signaling pathways as therapeutic targets of curcumin in cancer. Front Pharmacol 2021; 12: 772510.
[43] Fleuren EDG, Terry RL, Meyran D, Omer N, Trapani JA, Haber M, Neeson PJ and Ekert PG. Enhancing the potential of immunotherapy in paediatric sarcomas: breaking the immunosuppressive barrier with receptor tyrosine kinase inhibitors. Biomedicines 2021; 9: 1798.
[44] Abella JV and Park M. Breakdown of endocytosis in the oncogenic activation of receptor tyrosine kinases. Am J Physiol Endocrinol Metab 2009; 296: E973-984.
[45] Kam KW, Wong PPY and Young AL. Tyrosine kinase inhibitor-induced corneal ulcers. Lancet Oncol 2019; 20: e65.
[46] Zhao Y, Zhang D, Guo Y, Lu B, Zhao ZJ, Xu X and Chen Y. Tyrosine kinase ROR1 as a target for anti-cancer therapies. Front Oncol 2021; 11: 680834.
[47] Abbaspour Babaei M, Kamalidehghan B, Saleem M, Huri HZ and Ahmadipour F. Receptor tyrosine kinase (c-Kit) inhibitors: a potential therapeutic target in cancer cells. Drug Des Devel Ther 2016; 10: 2443-2459.
[48] Xia L, Zheng Z, Liu JY, Chen YJ, Ding J, Hu GS, Hu YH, Liu S, Luo WX, Xia NS and Liu W. Targeting triple-negative breast cancer with combination therapy of EGFR CAR T cells and CDK7 inhibition. Cancer Immunol Res 2021; 9: 707-722.
[49] Yang L, Bhattacharya A, Peterson D, Li Y, Liu X, Marangoni E, Robila V and Zhang Y. Targeted dual degradation of HER2 and EGFR obliterates oncogenic signaling, overcomes therapy resistance, and inhibits metastatic lesions in HER2-positive breast cancer models. Drug Resist Updat 2024; 74: 101078.
[50] Boichuk S, Dunaev P, Mustafin I, Mani S, Syuzov K, Valeeva E, Bikinieva F and Galembikova A. Infigratinib (BGJ 398), a pan-FGFR inhibitor, targets P-glycoprotein and increases chemotherapeutic-induced mortality of multidrug-resistant tumor cells. Biomedicines 2022; 10: 601.

[51] Fernández-Nogueira P, Mancino M, Fuster G, López-Plana A, Jauregui P, Almendro V, Enreig E, Menéndez S, Rojo F, Noguera-Castells A, Bill A, Gaither LA, Serrano L, Recalde-Percaz L, Moragas N, Alonso R, Ametller E, Rovira A, Lluch A, Albanell J, Gascon P and Bragado P. Tumor-associated fibroblasts promote HER2-targeted therapy resistance through FGFR2 activation. Clin Cancer Res 2020; 26: 1432-1448.

[52] Kähkönen TE, Toriseva M, Petruk N, Virta AR, Maher A, Eigéliené N, Kaivola J, Boström P, Koskivuo I, Nees M, Tuomela JM, Ivaska KK and Härkönen PL. Effects of FGFR inhibitors TKI258, BGJ398 and AZD4547 on breast cancer cells in 2D, 3D and tissue explant cultures. Cell Oncol (Dordr) 2021; 44: 205-218.

[53] Rimel BJ, Crane EK, Hou J, Nakayama J, MacDonald J, Lutz K, Makker V and O'Cearbhaill RE. Tyrosine kinase inhibitor toxicities: a society of gynecologic oncology review and recommendations. Gynecol Oncol 2023; 174: 148-156.

[54] Kang J, Choi YJ, Seo BY, Jo U, Park SI, Kim YH and Park KH. A selective FGFR inhibitor AZD4547 suppresses RANKL/M-CSF/OPG-dependent ostoclastogenesis and breast cancer growth in the metastatic bone microenvironment. Sci Rep 2019; 9: 8726.

[55] Meric-Bernstam F, Bahleda R, Hierro C, Sanson M, Bridgewater J, Arkenau HT, Tran B, Kelley RK, Park JO, Javle M, He Y, Benhadji KA and Goyal L. Futibatinib, an irreversible FGFR1-4 inhibitor, in patients with advanced solid tumors harboring FGF/FGFR aberrations: a phase I dose-expansion study. Cancer Discov 2022; 12: 402-415.

[56] Morales-Guadarrama G, Méndez-Pérez EA, García-Quiroz J, Avila E, Ibarra-Sánchez MJ, Esparza-López J, García-Becerra R, Larrea F and Díaz L. The inhibition of the FGFR/PI3K/Akt axis by AZD4547 disrupts the proangiogenic microenvironment and vasculogenic mimicry arising from the interplay between endothelial and triple-negative breast cancer cells. Int J Mol Sci 2023; 24: 13770.

[57] Abdalla AN, Qattan A, Malki WH, Shahid I, Hossain MA and Ahmed M. Significance of targeting VEGFR-2 and cyclin D1 in luminal-a breast cancer. Molecules 2020; 25: 4606.

[58] Dong X, Ren J, Amoozgar Z, Lee S, Datta M, Roberge S, Duquette M, Fukumura D and Jain RK. Anti-VEGF therapy improves EGFR-vIII-CAR-T cell delivery and efficacy in syngeneic glioblastoma models in mice. J Immunother Cancer 2023; 11: e005583.

[59] Nahta R, Yu D, Hung MC, Hortobagyi GN and Esteva FJ. Mechanisms of disease: understanding resistance to HER2-targeted therapy in human breast cancer. Nat Clin Pract Oncol 2006; 3: 269-280.

[60] Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A and McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987; 235: 177-182.

[61] Laird AD and Cherrington JM. Small molecule tyrosine kinase inhibitors: clinical development of anticancer agents. Expert Opin Investig Drugs 2003; 12: 51-64.

[62] Yook S, Cai Z, Jeong JJ, Lu Y, Winnik MA, Pignol JP and Reilly RM. Dual-receptor-targeted (DRT) radiation nanomedicine labeled with (177)Lu is more potent for killing human breast cancer cells that coexpress HER2 and EGFR than single-receptor-targeted (SRT) radiation nanomedicines. Mol Pharm 2020; 17: 1226-1236.

[63] O'Farrell AM, Abrams TJ, Yuen HA, Ngai TJ, Louie SG, Yee KW, Wong LM, Hong W, Lee LB, Town A, Smolich BD, Manning WC, Murray LJ, Heinrich MC and Cherrington JM. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood 2003; 101: 3597-3605.

[64] Huang Y, Xiong W, Ma L and Wu H. A cross-sectional study of the FDA approved indications and supporting pivotal trials of small-molecular kinase inhibitors in cancer therapies with the biomarker of cancer driver gene. Int J Cancer 2022; 151: 2107-2114.

[65] Chen Z, Tong LJ, Tang BY, Liu HY, Wang X, Zhang T, Cao XW, Chen Y, Li HL, Qian XH, Xu YF, Xie H and Ding J. C11, a novel fibroblast growth factor receptor 1 (FGFR1) inhibitor, suppresses breast cancer metastasis and angiogenesis. Acta Pharmacol Sin 2019; 40: 823-832.

[66] Li Y, Qiu X, Wang X, Liu H, Geck RC, Tewari AK, Xiao T, Font-Tello A, Lim K, Jones KL, Morrow M, Vadhi R, Kao PL, Jaber A, Yerrum S, Xie Y, Chow KH, Cejas P, Nguyen QD, Long HW, Liu XS, Toker A and Brown M. FGFR-inhibitor-mediated dismissal of SWI/SNF complexes from YAP-dependent enhancers induces adaptive therapeutic resistance. Nat Cell Biol 2021; 23: 1187-1198.

[67] Liu Z, Zhang S, Wang T, Shao H, Gao J, Wang Y and Ge Y. Neferine inhibits MDA-MB-231 cells growth and metastasis by regulating miR-374a/FGFR-2. Chem Biol Interact 2019; 309: 108716.

[68] Ostman A and Böhmer FD. Regulation of receptor tyrosine kinase signaling by protein tyrosine phosphatases. Trends Cell Biol 2001; 11: 258-266.

[69] Casaletto JB and McClatchey AI. Spatial regulation of receptor tyrosine kinases in development and cancer. Nat Rev Cancer 2012; 12: 387-400.

[70] McDonell LM, Kernohan KD, Boycott KM and Sawyer SL. Receptor tyrosine kinase mutations in developmental syndromes and cancer: two sides of the same coin. Hum Mol Genet 2015; 24: R60-66.
[71] Wan G, Chen X, Gou R, Guan C, Chen J, Wang Q, Wu W, Chen H, Zhang Q and Wang H. Platelet membrane-based biochemotactic-targeting nanoplatform combining PDT with EGFR inhibition therapy for the treatment of breast cancer. Biomater Sci 2024; 12: 691-709.
[72] Szymczyk J, Czyrek A, Otlewski J and Zakrzewska M. FGF1 protects MCF-7 cells against taltobulin through both the MEKs/ERKs and PI3K/AKT signaling pathway. Biomedicines 2023; 11: 1856.
[73] Hagan ML, Mander S, Joseph C, McGrath M, Barrett A, Lewis A, Hill WD, Browning D, McGee-Lawrence ME, Cai H, Liu K, Barrett JT, Gewirtz DA, Thangaraju M and Schoenlein PV. Upregulation of the EGFR/MEK1/MAPK1/2 signaling axis as a mechanism of resistance to antiestrogen-induced BimEL dependent apoptosis in ER(+) breast cancer cells. Int J Oncol 2023; 62: 20.
[74] Russo GC, Crawford AJ, Clark D, Cui J, Carney R, Karl MN, Su B, Starich B, Lih TS, Kamat P, Zhang Q, Nair PR, Wu PH, Lee MH, Leong HS, Zhang H, Rebecca VW and Wirtz D. E-cadherin interacts with EGFR resulting in hyper-activation of ERK in multiple models of breast cancer. Oncogene 2024; 43: 1445-1462.
[75] Pellecchia S, Franchini M, Viscido G, Arnese R and Gambardella G. Single cell lineage tracing reveals clonal dynamics of anti-EGFR therapy resistance in triple negative breast cancer. Genome Med 2024; 16: 55.
[76] Ganesan K, Xu C, Wu J, Du B, Liu Q, Sui Y, Song C, Zhang J, Tang H and Chen J. Ononin inhibits triple-negative breast cancer lung metastasis by targeting the EGFR-mediated PI3K/Akt/mTOR pathway. Sci China Life Sci 2024; 67: 1849-1866.
[77] Cheung A, Chenoweth AM, Johansson A, Laddach R, Guppy N, Trendell J, Esapa B, Mavousian A, Navarro-Llinas B, Haider S, Romero-Clavijo P, Hoffmann RM, Andriollo P, Rahman KM, Jackson P, Tsoka S, Irshad S, Roxanis I, Grigoriadis A, Thurston DE, Lord CJ, Tutt ANJ and Karagiannis SN. Anti-EGFR antibody-drug conjugate carrying an inhibitor targeting cdk restricts triple-negative breast cancer growth. Clin Cancer Res 2024; 30: 3298-3315.
[78] Forte L, Turdo F, Ghirelli C, Aiello P, Casalini P, Iorio MV, D'Ippolito E, Gasparini P, Agresti R, Belmonte B, Sozzi G, Sfondrini L, Tagliabue E, Campiglio M and Bianchi F. The PDGFRβ/ERK1/2 pathway regulates CDCP1 expression in triple-negative breast cancer. BMC Cancer 2018; 18: 586.
[79] Chen L, Qi H, Zhang L, Li H, Shao J, Chen H, Zhong M, Shi X, Ye T and Li Q. Effects of FGFR gene polymorphisms on response and toxicity of cyclophosphamide-epirubicin-docetaxel-based chemotherapy in breast cancer patients. BMC Cancer 2018; 18: 1038.
[80] Camorani S, Hill BS, Collina F, Gargiulo S, Napolitano M, Cantile M, Di Bonito M, Botti G, Fedele M, Zannetti A and Cerchia L. Targeted imaging and inhibition of triple-negative breast cancer metastases by a PDGFRβ aptamer. Theranostics 2018; 8: 5178-5199.
[81] Koh SB, Ross K, Isakoff SJ, Melkonjan N, He L, Matissek KJ, Schultz A, Mayer EL, Traina TA, Carey LA, Rugo HS, Liu MC, Stearns V, Langenbucher A, Saladi SV, Ramaswamy S, Lawrence MS and Ellisen LW. RASAL2 confers collateral MEK/EGFR dependency in chemoresistant triple-negative breast cancer. Clin Cancer Res 2021; 27: 4883-4897.
[82] DiGiacomo JW, Godet I, Trautmann-Rodriguez M and Gilkes DM. Extracellular matrix-bound FGF2 mediates estrogen receptor signaling and therapeutic response in breast cancer. Mol Cancer Res 2021; 19: 136-149.
[83] Hassan RM, Ali IH, El Kerdawy AM, Abo-Elfadl MT and Ghannam IAY. Novel benzenesulfonamides as dual VEGFR2/FGFR1 inhibitors targeting breast cancer: design, synthesis, anticancer activity and in silico studies. Bioorg Chem 2024; 152: 107728.
[84] Diep CH, Spartz A, Truong TH, Dwyer AR, El-Ashry D and Lange CA. Progesterone receptor signaling promotes cancer associated fibroblast mediated tumorigenicity in ER+ breast cancer. Endocrinology 2024; 165: bqae092.
[85] Belli S, Esposito D, Ascione CM, Messina F, Napolitano F, Servetto A, De Angelis C, Bianco R and Formisano L. EGFR and HER2 hyper-activation mediates resistance to endocrine therapy and CDK4/6 inhibitors in ER+ breast cancer. Cancer Lett 2024; 593: 216968.
[86] Rajput PK, Varghese JF, Srivastava AK, Kumar U and Yadav UCS. Visfatin-induced upregulation of lipogenesis via EGFR/AKT/GSK3β pathway promotes breast cancer cell growth. Cell Signal 2023; 107: 110686.
[87] Li Y, Zhang MZ, Zhang SJ, Sun X, Zhou C, Li J, Liu J, Feng J, Lu SY, Pei-Jun L and Wang JC. HIF-1α inhibitor YC-1 suppresses triple-negative breast cancer growth and angiogenesis by targeting PlGF/VEGFR1-induced macrophage polarization. Biomed Pharmacother 2023; 161: 114423.
[88] Hao XS, Feng PP, Zhang YY, Wang FZ, Wang GL and Fei HR. Scutebarbatine A induces ROS-mediated DNA damage and apoptosis in breast cancer cells by modulating MAPK and EGFR/Akt signaling pathway. Chem Biol Interact 2023; 378: 110487.

[89] Guo CH, Wang SY, Chung CH, Shih MY, Li WC, Chen PC, Lee SY and Hsia S. Selenium modulates AR/IGF-1R/EGFR and TROP2 signaling pathways and improves anticancer efficacy in murine mammary carcinoma 4T1. J Nutr Biochem 2023; 120: 109417.
[90] Zhou L, Li H, Sun T, Wen X, Niu C, Li M, Li W, Hoffman AR, Hu JF and Cui J. HULC targets the IGF1R-PI3K-AKT axis in trans to promote breast cancer metastasis and cisplatin resistance. Cancer Lett 2022; 548: 215861.
[91] Nafie MS and Boraei ATA. Exploration of novel VEGFR2 tyrosine kinase inhibitors via design and synthesis of new alkylated indolyl-triazole Schiff bases for targeting breast cancer. Bioorg Chem 2022; 122: 105708.
[92] Lee HJ, Seo AN, Kim EJ, Jang MH, Kim YJ, Kim JH, Kim SW, Ryu HS, Park IA, Im SA, Gong G, Jung KH, Kim HJ and Park SY. Prognostic and predictive values of EGFR overexpression and EGFR copy number alteration in HER2-positive breast cancer. Br J Cancer 2015; 112: 103-111.
[93] Park HS, Jang MH, Kim EJ, Kim HJ, Lee HJ, Kim YJ, Kim JH, Kang E, Kim SW, Kim IA and Park SY. High EGFR gene copy number predicts poor outcome in triple-negative breast cancer. Mod Pathol 2014; 27: 1212-1222.
[94] Cicek E, Circir A, Oyken M, Akbulut Caliskan O, Dioken DN, Guntekin Ergun S, Cetin-Atalay R, Sapmaz A, Ovaa H, Sahin O and Erson-Bensan AE. EGF-SNX3-EGFR axis drives tumor progression and metastasis in triple-negative breast cancers. Oncogene 2022; 41: 220-232.
[95] Wilson KJ, Gilmore JL, Foley J, Lemmon MA and Riese DJ 2nd. Functional selectivity of EGF family peptide growth factors: implications for cancer. Pharmacol Ther 2009; 122: 1-8.
[96] Macdonald-Obermann JL and Pike LJ. Different epidermal growth factor (EGF) receptor ligands show distinct kinetics and biased or partial agonism for homodimer and heterodimer formation. J Biol Chem 2014; 289: 26178-26188.
[97] Weinberg F, Peckys DB and de Jonge N. EGFR expression in HER2-driven breast cancer cells. Int J Mol Sci 2020; 21: 9008.
[98] Witton CJ, Reeves JR, Going JJ, Cooke TG and Bartlett JM. Expression of the HER1-4 family of receptor tyrosine kinases in breast cancer. J Pathol 2003; 200: 290-297.
[99] Wang X, Semba T, Manyam GC, Wang J, Shao S, Bertucci F, Finetti P, Krishnamurthy S, Phi LTH, Pearson T, Van Laere SJ, Burks JK, Cohen EN, Reuben JM, Yang F, Min H, Navin N, Trinh VN, Iwase T, Batra H, Shen Y, Zhang X, Tripathy D and Ueno NT. EGFR is a master switch between immunosuppressive and immunoactive tumor microenvironment in inflammatory breast cancer. Sci Adv 2022; 8: eabn7983.
[100] Price JT, Tiganis T, Agarwal A, Djakiew D and Thompson EW. Epidermal growth factor promotes MDA-MB-231 breast cancer cell migration through a phosphatidylinositol 3'-kinase and phospholipase C-dependent mechanism. Cancer Res 1999; 59: 5475-5478.
[101] Silva CM. Role of STATs as downstream signal transducers in Src family kinase-mediated tumorigenesis. Oncogene 2004; 23: 8017-8023.
[102] Zheng Z, Shao N, Weng H, Li W, Zhang J, Zhang L, Yang L and Ye S. Correlation between epidermal growth factor receptor and tumor stem cell markers CD44/CD24 and their relationship with prognosis in breast invasive ductal carcinoma. Med Oncol 2015; 32: 275.
[103] Hance KW, Anderson WF, Devesa SS, Young HA and Levine PH. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. J Natl Cancer Inst 2005; 97: 966-975.
[104] Charafe-Jauffret E, Ginestier C, Iovino F, Tarpin C, Diebel M, Esterni B, Houvenaeghel G, Extra JM, Bertucci F, Jacquemier J, Xerri L, Dontu G, Stassi G, Xiao Y, Barsky SH, Birnbaum D, Viens P and Wicha MS. Aldehyde dehydrogenase 1-positive cancer stem cells mediate metastasis and poor clinical outcome in inflammatory breast cancer. Clin Cancer Res 2010; 16: 45-55.
[105] Van Laere SJ, Van der Auwera I, Van den Eynden GG, van Dam P, Van Marck EA, Vermeulen PB and Dirix LY. NF-kappaB activation in inflammatory breast cancer is associated with oestrogen receptor downregulation, secondary to EGFR and/or ErbB2 overexpression and MAPK hyperactivation. Br J Cancer 2007; 97: 659-669.
[106] Wang X, Reyes ME, Zhang D, Funakoshi Y, Trape AP, Gong Y, Kogawa T, Eckhardt BL, Masuda H, Pirman DA Jr, Yang P, Reuben JM, Woodward WA, Bartholomeusz C, Hortobagyi GN, Tripathy D and Ueno NT. EGFR signaling promotes inflammation and cancer stem-like activity in inflammatory breast cancer. Oncotarget 2017; 8: 67904-67917.
[107] Tian M and Schiemann WP. TGF-β stimulation of EMT programs elicits non-genomic ER-α activity and anti-estrogen resistance in breast cancer cells. J Cancer Metastasis Treat 2017; 3: 150-160.
[108] Yeo SK, Wen J, Chen S and Guan JL. Autophagy differentially regulates distinct breast cancer stem-like cells in murine models via EGFR/Stat3 and Tgfβ/Smad signaling. Cancer Res 2016; 76: 3397-3410.
[109] Holdman XB, Welte T, Rajapakshe K, Pond A, Coarfa C, Mo Q, Huang S, Hilsenbeck SG, Ed-

wards DP, Zhang X and Rosen JM. Upregulation of EGFR signaling is correlated with tumor stroma remodeling and tumor recurrence in FGFR1-driven breast cancer. Breast Cancer Res 2015; 17: 141.
[110] Yang J, Liao D, Chen C, Liu Y, Chuang TH, Xiang R, Markowitz D, Reisfeld RA and Luo Y. Tumor-associated macrophages regulate murine breast cancer stem cells through a novel paracrine EGFR/Stat3/Sox-2 signaling pathway. Stem Cells 2013; 31: 248-258.
[111] Shibuya M. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: a crucial target for anti- and pro-angiogenic therapies. Genes Cancer 2011; 2: 1097-1105.
[112] Alitalo K and Carmeliet P. Molecular mechanisms of lymphangiogenesis in health and disease. Cancer Cell 2002; 1: 219-227.
[113] Laakkonen P, Waltari M, Holopainen T, Takahashi T, Pytowski B, Steiner P, Hicklin D, Persaud K, Tonra JR, Witte L and Alitalo K. Vascular endothelial growth factor receptor 3 is involved in tumor angiogenesis and growth. Cancer Res 2007; 67: 593-599.
[114] Chakraborty G, Jain S and Kundu GC. Osteopontin promotes vascular endothelial growth factor-dependent breast tumor growth and angiogenesis via autocrine and paracrine mechanisms. Cancer Res 2008; 68: 152-161.
[115] Srabovic N, Mujagic Z, Mujanovic-Mustedanagic J, Softic A, Muminovic Z, Rifatbegovic A and Begic L. Vascular endothelial growth factor receptor-1 expression in breast cancer and its correlation to vascular endothelial growth factor a. Int J Breast Cancer 2013; 2013: 746749.
[116] Kosaka Y, Kataoka A, Yamaguchi H, Ueo H, Akiyoshi S, Sengoku N, Kuranami M, Ohno S, Watanabe M, Mimori K and Mori M. Vascular endothelial growth factor receptor-1 mRNA overexpression in peripheral blood as a useful prognostic marker in breast cancer. Breast Cancer Res 2012; 14: R140.
[117] Kapahi R, Guleria K, Sambyal V, Manjari M, Sudan M, Uppal MS and Singh NR. Association of VEGF and VEGFR1 polymorphisms with breast cancer risk in North Indians. Tumour Biol 2015; 36: 4223-4234.
[118] Bussard KM, Mutkus L, Stumpf K, Gomez-Manzano C and Marini FC. Tumor-associated stromal cells as key contributors to the tumor microenvironment. Breast Cancer Res 2016; 18: 84.
[119] Incio J, Tam J, Rahbari NN, Suboj P, McManus DT, Chin SM, Vardam TD, Batista A, Babykutty S, Jung K, Khachatryan A, Hato T, Ligibel JA, Krop IE, Puchner SB, Schlett CL, Hoffmman U, Ancukiewicz M, Shibuya M, Carmeliet P, Soares R, Duda DG, Jain RK and Fukumura D. PlGF/VEGFR-1 signaling promotes macrophage polarization and accelerated tumor progression in obesity. Clin Cancer Res 2016; 22: 2993-3004.
[120] Chen XW, Yu TJ, Zhang J, Li Y, Chen HL, Yang GF, Yu W, Liu YZ, Liu XX, Duan CF, Tang HL, Qiu M, Wang CL, Zheng H, Yue J, Guo AM and Yang J. CYP4A in tumor-associated macrophages promotes pre-metastatic niche formation and metastasis. Oncogene 2017; 36: 5045-5057.
[121] Guo S, Colbert LS, Fuller M, Zhang Y and Gonzalez-Perez RR. Vascular endothelial growth factor receptor-2 in breast cancer. Biochim Biophys Acta 2010; 1806: 108-121.
[122] Pfister NT, Fomin V, Regunath K, Zhou JY, Zhou W, Silwal-Pandit L, Freed-Pastor WA, Laptenko O, Neo SP, Bargonetti J, Hoque M, Tian B, Gunaratne J, Engebraaten O, Manley JL, Børresen-Dale AL, Neilsen PM and Prives C. Mutant p53 cooperates with the SWI/SNF chromatin remodeling complex to regulate VEGFR2 in breast cancer cells. Genes Dev 2015; 29: 1298-1315.
[123] Jahangiri A, Nguyen A, Chandra A, Sidorov MK, Yagnik G, Rick J, Han SW, Chen W, Flanigan PM, Schneidman-Duhovny D, Mascharak S, De Lay M, Imber B, Park CC, Matsumoto K, Lu K, Bergers G, Sali A, Weiss WA and Aghi MK. Cross-activating c-Met/β1 integrin complex drives metastasis and invasive resistance in cancer. Proc Natl Acad Sci U S A 2017; 114: E8685-E8694.
[124] Schoppmann SF, Bayer G, Aumayr K, Taucher S, Geleff S, Rudas M, Kubista E, Hausmaninger H, Samonigg H, Gnant M, Jakesz R and Horvat R. Prognostic value of lymphangiogenesis and lymphovascular invasion in invasive breast cancer. Ann Surg 2004; 240: 306-312.
[125] Wehrman T, He X, Raab B, Dukipatti A, Blau H and Garcia KC. Structural and mechanistic insights into nerve growth factor interactions with the TrkA and p75 receptors. Neuron 2007; 53: 25-38.
[126] Tutunea-Fatan E, Majumder M, Xin X and Lala PK. The role of CCL21/CCR7 chemokine axis in breast cancer-induced lymphangiogenesis. Mol Cancer 2015; 14: 35.
[127] Timoshenko AV, Chakraborty C, Wagner GF and Lala PK. COX-2-mediated stimulation of the lymphangiogenic factor VEGF-C in human breast cancer. Br J Cancer 2006; 94: 1154-1163.
[128] Lyons TR, Borges VF, Betts CB, Guo Q, Kapoor P, Martinson HA, Jindal S and Schedin P. Cyclooxygenase-2-dependent lymphangiogenesis promotes nodal metastasis of postpartum breast cancer. J Clin Invest 2014; 124: 3901-3912.

[129] Chen WS, Cao Z, Sugaya S, Lopez MJ, Sendra VG, Laver N, Leffler H, Nilsson UJ, Fu J, Song J, Xia L, Hamrah P and Panjwani N. Pathological lymphangiogenesis is modulated by galectin-8-dependent crosstalk between podoplanin and integrin-associated VEGFR-3. Nat Commun 2016; 7: 11302.
[130] Strell C, Folkvaljon D, Holmberg E, Schiza A, Thurfjell V, Karlsson P, Bergh J, Bremer T, Akslen LA, Wärnberg F and Östman A. High PDGFRb expression predicts resistance to radiotherapy in DCIS within the SweDCIS randomized trial. Clin Cancer Res 2021; 27: 3469-3477.
[131] Thies KA, Hammer AM, Hildreth BE 3rd, Steck SA, Spehar JM, Kladney RD, Geisler JA, Das M, Russell LO, Bey JF 4th, Bolyard CM, Pilarski R, Trimboli AJ, Cuitiño MC, Koivisto CS, Stover DG, Schoenfield L, Otero J, Godbout JP, Chakravarti A, Ringel MD, Ramaswamy B, Li Z, Kaur B, Leone G, Ostrowski MC, Sizemore ST and Sizemore GM. Stromal platelet-derived growth factor receptor-β signaling promotes breast cancer metastasis in the brain. Cancer Res 2021; 81: 606-618.
[132] Heldin CH. Targeting the PDGF signaling pathway in tumor treatment. Cell Commun Signal 2013; 11: 97.
[133] Carvalho I, Milanezi F, Martins A, Reis RM and Schmitt F. Overexpression of platelet-derived growth factor receptor alpha in breast cancer is associated with tumour progression. Breast Cancer Res 2005; 7: R788-795.
[134] Bhardwaj B, Klassen J, Cossette N, Sterns E, Tuck A, Deeley R, Sengupta S and Elliott B. Localization of platelet-derived growth factor beta receptor expression in the periepithelial stroma of human breast carcinoma. Clin Cancer Res 1996; 2: 773-782.
[135] Paulsson J, Sjöblom T, Micke P, Pontén F, Landberg G, Heldin CH, Bergh J, Brennan DJ, Jirström K and Ostman A. Prognostic significance of stromal platelet-derived growth factor beta-receptor expression in human breast cancer. Am J Pathol 2009; 175: 334-341.
[136] Wu CP, Lusvarghi S, Wang JC, Hsiao SH, Huang YH, Hung TH and Ambudkar SV. Avapritinib: a selective inhibitor of KIT and PDGFRα that reverses ABCB1 and ABCG2-mediated multidrug resistance in cancer cell lines. Mol Pharm 2019; 16: 3040-3052.
[137] Jansson S, Aaltonen K, Bendahl PO, Falck AK, Karlsson M, Pietras K and Rydén L. The PDGF pathway in breast cancer is linked to tumour aggressiveness, triple-negative subtype and early recurrence. Breast Cancer Res Treat 2018; 169: 231-241.
[138] Jitariu AA, Raica M, Cîmpean AM and Suciu SC. The role of PDGF-B/PDGFR-BETA axis in the normal development and carcinogenesis of the breast. Crit Rev Oncol Hematol 2018; 131: 46-52.
[139] Pinto MP, Dye WW, Jacobsen BM and Horwitz KB. Malignant stroma increases luminal breast cancer cell proliferation and angiogenesis through platelet-derived growth factor signaling. BMC Cancer 2014; 14: 735.
[140] D'Ippolito E, Plantamura I, Bongiovanni L, Casalini P, Baroni S, Piovan C, Orlandi R, Gualeni AV, Gloghini A, Rossini A, Cresta S, Tessari A, De Braud F, Di Leva G, Tripodo C and Iorio MV. miR-9 and miR-200 regulate PDGFRβ-mediated endothelial differentiation of tumor cells in triple-negative breast cancer. Cancer Res 2016; 76: 5562-5572.
[141] Akhand SS, Chen H, Purdy SC, Liu Z, Anderson JC, Willey CD and Wendt MK. Fibroblast growth factor receptor facilitates recurrence of minimal residual disease following trastuzumab emtansine therapy. NPJ Breast Cancer 2021; 7: 5.
[142] Plotnikov AN, Schlessinger J, Hubbard SR and Mohammadi M. Structural basis for FGF receptor dimerization and activation. Cell 1999; 98: 641-650.
[143] Cheng Q, Ma Z, Shi Y, Parris AB, Kong L and Yang X. FGFR1 overexpression induces cancer cell stemness and enhanced Akt/Erk-ER signaling to promote palbociclib resistance in luminal A breast cancer cells. Cells 2021; 10: 3008.
[144] Tenhagen M, van Diest PJ, Ivanova IA, van der Wall E and van der Groep P. Fibroblast growth factor receptors in breast cancer: expression, downstream effects, and possible drug targets. Endocr Relat Cancer 2012; 19: R115-129.
[145] Babina IS and Turner NC. Advances and challenges in targeting FGFR signalling in cancer. Nat Rev Cancer 2017; 17: 318-332.
[146] Courjal F, Cuny M, Simony-Lafontaine J, Louason G, Speiser P, Zeillinger R, Rodriguez C and Theillet C. Mapping of DNA amplifications at 15 chromosomal localizations in 1875 breast tumors: definition of phenotypic groups. Cancer Res 1997; 57: 4360-4367.
[147] Brunello E, Brunelli M, Bogina G, Caliò A, Manfrin E, Nottegar A, Vergine M, Molino A, Bria E, Massari F, Tortora G, Cingarlini S, Pedron S, Chilosi M, Zamboni G, Miller K, Martignoni G and Bonetti F. FGFR-1 amplification in metastatic lymph-nodal and haematogenous lobular breast carcinoma. J Exp Clin Cancer Res 2012; 31: 103.
[148] Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, Wacholder S, Wang Z, Welch R, Hutchinson A, Wang J, Yu K, Chatterjee N, Orr N, Willett WC, Colditz GA, Ziegler RG, Berg

CD, Buys SS, McCarty CA, Feigelson HS, Calle EE, Thun MJ, Hayes RB, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover RN, Thomas G and Chanock SJ. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 2007; 39: 870-874.

[149] Formisano L, Stauffer KM, Young CD, Bhola NE, Guerrero-Zotano AL, Jansen VM, Estrada MM, Hutchinson KE, Giltnane JM, Schwarz LJ, Lu Y, Balko JM, Deas O, Cairo S, Judde JG, Mayer IA, Sanders M, Dugger TC, Bianco R, Stricker T and Arteaga CL. Correction: association of FGFR1 with ERα maintains ligand-independent ER transcription and mediates resistance to estrogen deprivation in ER(+) breast cancer. Clin Cancer Res 2019; 25: 1433.

[150] Marian C, Ochs-Balcom HM, Nie J, Kallakury BV, Ambrosone CB, Trevisan M, Edge S, Shields PG and Freudenheim JL. FGFR2 intronic SNPs and breast cancer risk: associations with tumor characteristics and interactions with exogenous exposures and other known breast cancer risk factors. Int J Cancer 2011; 129: 702-712.

[151] Cerliani JP, Guillardoy T, Giulianelli S, Vaque JP, Gutkind JS, Vanzulli SI, Martins R, Zeitlin E, Lamb CA and Lanari C. Interaction between FGFR-2, STAT5, and progesterone receptors in breast cancer. Cancer Res 2011; 71: 3720-3731.

[152] Cerliani JP, Vanzulli SI, Piñero CP, Bottino MC, Sahores A, Nuñez M, Varchetta R, Martins R, Zeitlin E, Hewitt SM, Molinolo AA, Lanari C and Lamb CA. Associated expressions of FGFR-2 and FGFR-3: from mouse mammary gland physiology to human breast cancer. Breast Cancer Res Treat 2012; 133: 997-1008.

[153] Johnston CL, Cox HC, Gomm JJ and Coombes RC. Fibroblast growth factor receptors (FGFRs) localize in different cellular compartments. A splice variant of FGFR-3 localizes to the nucleus. J Biol Chem 1995; 270: 30643-30650.

[154] Koziczak M and Hynes NE. Cooperation between fibroblast growth factor receptor-4 and ErbB2 in regulation of cyclin D1 translation. J Biol Chem 2004; 279: 50004-50011.

[155] Brown WS, Akhand SS and Wendt MK. FGFR signaling maintains a drug persistent cell population following epithelial-mesenchymal transition. Oncotarget 2016; 7: 83424-83436.

[156] Kim SY, Toretsky JA, Scher D and Helman LJ. The role of IGF-1R in pediatric malignancies. Oncologist 2009; 14: 83-91.

[157] Chitnis MM, Yuen JS, Protheroe AS, Pollak M and Macaulay VM. The type 1 insulin-like growth factor receptor pathway. Clin Cancer Res 2008; 14: 6364-6370.

[158] Surmacz E. Growth factor receptors as therapeutic targets: strategies to inhibit the insulin-like growth factor I receptor. Oncogene 2003; 22: 6589-6597.

[159] Krassas GE, Pontikides N, Kaltsas T, Dumas A, Frystyk J, Chen JW and Flyvbjerg A. Free and total insulin-like growth factor (IGF)-I, -II, and IGF binding protein-1, -2, and -3 serum levels in patients with active thyroid eye disease. J Clin Endocrinol Metab 2003; 88: 132-135.

[160] Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM and Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004; 363: 1346-1353.

[161] Duggan C, Wang CY, Neuhouser ML, Xiao L, Smith AW, Reding KW, Baumgartner RN, Baumgartner KB, Bernstein L, Ballard-Barbash R and McTiernan A. Associations of insulin-like growth factor and insulin-like growth factor binding protein-3 with mortality in women with breast cancer. Int J Cancer 2013; 132: 1191-1200.

[162] Wang Y, Min J, Deng X, Feng T, Hu H, Guo X, Cheng Y, Xie B, Yang Y, Chen CC, Guo RT, Dong C and Zhou HB. Discovery of novel covalent selective estrogen receptor degraders against endocrine-resistant breast cancer. Acta Pharm Sin B 2023; 13: 4963-4982.

[163] Liang Y, Liu J, Ge J, Shi Q, Zhang G, Wan A, Luo T, Tian H, Fan L, Wang S, Chen L, Tang P, Zhu K, Jiang J, Bian X, Zhang Y and Qi X. Safety and efficacy of anlotinib combined with taxane and lobaplatin in neoadjuvant treatment of clinical stage II/III triple-negative breast cancer in China (the neoALTAL trial): a single-arm, phase 2 trial. EClinicalMedicine 2024; 71: 102585.

[164] Krzyscik MA, Porębska N, Opaliński Ł and Otlewski J. Targeting HER2 and FGFR-positive cancer cells with a bispecific cytotoxic conjugate combining anti-HER2 Affibody and FGF2. Int J Biol Macromol 2024; 254: 127657.

[165] Wang K, Yu Y, Wang W, Jiang Y, Li Y, Jiang X, Qiao Y, Chen L, Zhao X, Liu J, Yang A, Li J and Zhang R. Targeting the E3 ligase NEDD4 as a novel therapeutic strategy for IGF1 signal pathway-driven gastric cancer. Oncogene 2023; 42: 1072-1087.

[166] Saridogan T, Akcakanat A, Zhao M, Evans KW, Yuca E, Scott S, Kirby BP, Zheng X, Ha MJ, Chen H, Ng PKS, DiPeri TP, Mills GB, Rodon Ahnert J, Damodaran S and Meric-Bernstam F. Efficacy of futibatinib, an irreversible fibroblast growth factor receptor inhibitor, in FGFR-altered breast cancer. Sci Rep 2023; 13: 20223.

[167] Rajoria B, Zhang X and Yee D. IGF-1 stimulates glycolytic ATP production in MCF-7L cells. Int J Mol Sci 2023; 24: 10209.

[168] He Q, Kong L, Shi W, Ma D, Liu K, Yang S, Xin Q, Jiang C and Wu J. Ezetimibe inhibits triple-negative breast cancer proliferation and promotes cell cycle arrest by targeting the PDGFR/AKT pathway. Heliyon 2023; 9: e21343.
[169] Duan Z, Li Z, Wang Z, Chen C and Luo Y. Chimeric antigen receptor macrophages activated through TLR4 or IFN-γ receptors suppress breast cancer growth by targeting VEGFR2. Cancer Immunol Immunother 2023; 72: 3243-3257.
[170] Baammi S, El Allali A and Daoud R. Potent VEGFR-2 inhibitors for resistant breast cancer: a comprehensive 3D-QSAR, ADMET, molecular docking and MMPBSA calculation on triazolopyrazine derivatives. Front Mol Biosci 2023; 10: 1288652.
[171] Wu X, Seraia E, Hatch SB, Wan X, Ebner DV, Aroldi F, Jiang Y, Ryan AJ, Bogenrieder T, Weyer-Czernilofsky U, Rieunier G and Macaulay VM. CHK1 inhibition exacerbates replication stress induced by IGF blockade. Oncogene 2022; 41: 476-488.
[172] Wester L, Venneker S, Hazenoot M, Pont C, Koedoot E, Timmermans AM, Martens JWM, Jansen MPHM, Kockx CEM, van IJcken WFJ, Meerman JHN, Zhang Y and van de Water B. A kinase inhibitor screen reveals MEK1/2 as a novel therapeutic target to antagonize IGF1R-mediated antiestrogen resistance in ERα-positive luminal breast cancer. Biochem Pharmacol 2022; 204: 115233.
[173] Chen L, Jiang YZ, Wu SY, Wu J, Di GH, Liu GY, Yu KD, Fan L, Li JJ, Hou YF, Hu Z, Chen CM, Huang XY, Cao AY, Hu X, Zhao S, Ma XY, Xu Y, Sun XJ, Chai WJ, Guo X, Chen X, Xu Y, Zhu XY, Zou JJ, Yang WT, Wang ZH and Shao ZM. Famitinib with camrelizumab and nab-paclitaxel for advanced immunomodulatory triple-negative breast cancer (FUTURE-C-Plus): an open-label, single-arm, phase II trial. Clin Cancer Res 2022; 28: 2807-2817.
[174] Abdelmalek CM, Hu Z, Kronenberger T, Küblbeck J, Kinnen FJM, Hesse SS, Malik A, Kudolo M, Niess R, Gehringer M, Zender L, Witt-Enderby PA, Zlotos DP and Laufer SA. Gefitinib-tamoxifen hybrid ligands as potent agents against triple-negative breast cancer. J Med Chem 2022; 65: 4616-4632.
[175] Tian M, Chen K, Huang J, Chu D, Li J, Huang K and Ma C. Asiatic acid inhibits angiogenesis and vascular permeability through the VEGF/VEGFR2 signaling pathway to inhibit the growth and metastasis of breast cancer in mice. Phytother Res 2021; 35: 6389-6400.
[176] Shin SU, Cho HM, Das R, Gil-Henn H, Ramakrishnan S, Al Bayati A, Carroll SF, Zhang Y, Sankar AP, Elledge C, Pimentel A, Blonska M and Rosenblatt JD. Inhibition of vasculogenic mimicry and angiogenesis by an anti-EGFR IgG1-human endostatin-P125A fusion protein reduces triple negative breast cancer metastases. Cells 2021; 10: 2904.
[177] Ni H, Guo M, Zhang X, Jiang L, Tan S, Yuan J, Cui H, Min Y, Zhang J, Schlisio S, Ma C, Liao W, Nister M, Chen C, Li S and Li N. VEGFR2 inhibition hampers breast cancer cell proliferation via enhanced mitochondrial biogenesis. Cancer Biol Med 2021; 18: 139-154.
[178] Grünewald S, Politz O, Bender S, Héroult M, Lustig K, Thuss U, Kneip C, Kopitz C, Zopf D, Collin MP, Boemer U, Ince S, Ellinghaus P, Mumberg D, Hess-Stumpp H and Ziegelbauer K. Rogaratinib: a potent and selective pan-FGFR inhibitor with broad antitumor activity in FGFR-overexpressing preclinical cancer models. Int J Cancer 2019; 145: 1346-1357.
[179] Gerber DE. Targeted therapies: a new generation of cancer treatments. Am Fam Physician 2008; 77: 311-319.
[180] Joo WD, Visintin I and Mor G. Targeted cancer therapy--are the days of systemic chemotherapy numbered? Maturitas 2013; 76: 308-314.
[181] Sooro MA, Zhang N and Zhang P. Targeting EGFR-mediated autophagy as a potential strategy for cancer therapy. Int J Cancer 2018; 143: 2116-2125.
[182] Yamaoka T, Ohba M and Ohmori T. Molecular-targeted therapies for epidermal growth factor receptor and its resistance mechanisms. Int J Mol Sci 2017; 18: 2420.
[183] Seshacharyulu P, Ponnusamy MP, Haridas D, Jain M, Ganti AK and Batra SK. Targeting the EGFR signaling pathway in cancer therapy. Expert Opin Ther Targets 2012; 16: 15-31.
[184] Gan HK, Burgess AW, Clayton AH and Scott AM. Targeting of a conformationally exposed, tumor-specific epitope of EGFR as a strategy for cancer therapy. Cancer Res 2012; 72: 2924-2930.
[185] Metro G, Finocchiaro G and Cappuzzo F. Anticancer therapy with EGFR inhibitors: factors of prognostic and predictive significance. Ann Oncol 2006; 17 Suppl 2: ii42-45.
[186] Johnston JB, Navaratnam S, Pitz MW, Maniate JM, Wiechec E, Baust H, Gingerich J, Skliris GP, Murphy LC and Los M. Targeting the EGFR pathway for cancer therapy. Curr Med Chem 2006; 13: 3483-3492.
[187] Giaccone G, González-Larriba JL, van Oosterom AT, Alfonso R, Smit EF, Martens M, Peters GJ, van der Vijgh WJ, Smith R, Averbuch S and Fandi A. Combination therapy with gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, gemcitabine and cisplatin in patients with advanced solid tumors. Ann Oncol 2004; 15: 831-838.

[188] Petrelli F, Borgonovo K, Cabiddu M, Ghilardi M and Barni S. Cetuximab and panitumumab in KRAS wild-type colorectal cancer: a meta-analysis. Int J Colorectal Dis 2011; 26: 823-833.
[189] Rocha-Lima CM, Soares HP, Raez LE and Singal R. EGFR targeting of solid tumors. Cancer Control 2007; 14: 295-304.
[190] Tomasello C, Baldessari C, Napolitano M, Orsi G, Grizzi G, Bertolini F, Barbieri F and Cascinu S. Resistance to EGFR inhibitors in non-small cell lung cancer: clinical management and future perspectives. Crit Rev Oncol Hematol 2018; 123: 149-161.
[191] Ciardiello F and Tortora G. EGFR antagonists in cancer treatment. N Engl J Med 2008; 358: 1160-1174.
[192] Díaz-Serrano A, Gella P, Jiménez E, Zugazagoitia J and Paz-Ares Rodríguez L. Targeting EGFR in lung cancer: current standards and developments. Drugs 2018; 78: 893-911.
[193] Zhao Y and Adjei AA. Targeting angiogenesis in cancer therapy: moving beyond vascular endothelial growth factor. Oncologist 2015; 20: 660-673.
[194] Ilic I, Jankovic S and Ilic M. Bevacizumab combined with chemotherapy improves survival for patients with metastatic colorectal cancer: evidence from meta analysis. PLoS One 2016; 11: e0161912.
[195] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R and Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355: 2542-2550.
[196] Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag D and Ray-Coquard I. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014; 32: 1302-1308.
[197] Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD and Ohtsu A. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15: 1224-1235.
[198] Tabernero J, Takayuki Y and Cohn AL. Correction to Lancet Oncol 2015; 16: 499-508. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 2015; 16: e262.
[199] Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, Gorbunova V, Kowalyszyn RD, Pikiel J, Czyzewicz G, Orlov SV, Lewanski CR, Thomas M, Bidoli P, Dakhil S, Gans S, Kim JH, Grigorescu A, Karaseva N, Reck M, Cappuzzo F, Alexandris E, Sashegyi A, Yurasov S and Pérol M. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014; 384: 665-673.
[200] Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R and Allegra C. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012; 30: 3499-3506.
[201] Al-Sanea MM, Hamdi A, Mohamed AAB, El-Shafey HW, Moustafa M, Elgazar AA, Eldehna WM, Ur Rahman H, Parambi DGT, Elbargisy RM, Selim S, Bukhari SNA, Magdy Hendawy O and Tawfik SS. New benzothiazole hybrids as potential VEGFR-2 inhibitors: design, synthesis, anticancer evaluation, and in silico study. J Enzyme Inhib Med Chem 2023; 38: 2166036.
[202] Li Y, Liu Y, Zhang D, Chen J, Yang G, Tang P, Yang C, Liu J, Zhang J and Ouyang L. Discovery, synthesis, and evaluation of novel dual inhibitors of a vascular endothelial growth factor receptor and Poly(ADP-Ribose) polymerase for BRCA wild-type breast cancer therapy. J Med Chem 2023; 66: 12069-12100.
[203] Levêque D, Becker G, Bilger K and Natarajan-Amé S. Clinical pharmacokinetics and pharmacodynamics of dasatinib. Clin Pharmacokinet 2020; 59: 849-856.
[204] Weiss J, Glode A, Messersmith WA and Diamond J. Sacituzumab govitecan: breakthrough targeted therapy for triple-negative breast cancer. Expert Rev Anticancer Ther 2019; 19: 673-679.
[205] Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Henschel V, Molinero L, Chui SY, Maiya V, Husain A, Winer EP, Loi S and Emens LA. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020; 21: 44-59.

[206] Ferrara N, Gerber HP and LeCouter J. The biology of VEGF and its receptors. Nat Med 2003; 9: 669-676.
[207] Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. Oncology 2005; 69 Suppl 3: 4-10.
[208] Sahni J, Patel SS, Dugel PU, Khanani AM, Jhaveri CD, Wykoff CC, Hershberger VS, Pauly-Evers M, Sadikhov S, Szczesny P, Schwab D, Nogoceke E, Osborne A, Weikert R and Fauser S. Simultaneous inhibition of angiopoietin-2 and vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD phase 2 randomized trial. Ophthalmology 2019; 126: 1155-1170.
[209] Wu Y, Yi Z, Li J, Wei Y, Feng R, Liu J, Huang J, Chen Y, Wang X, Sun J, Yin X, Li Y, Wan J, Zhang L, Huang J, Du H, Wang X, Li Q, Ren G and Li H. FGFR blockade boosts T cell infiltration into triple-negative breast cancer by regulating cancer-associated fibroblasts. Theranostics 2022; 12: 4564-4580.
[210] Dey N, Williams C, Leyland-Jones B and De P. Mutation matters in precision medicine: a future to believe in. Cancer Treat Rev 2017; 55: 136-149.
[211] Shao F, Sun H and Deng CX. Potential therapeutic targets of triple-negative breast cancer based on its intrinsic subtype. Oncotarget 2017; 8: 73329-73344.
[212] García-Becerra R, Santos N, Díaz L and Camacho J. Mechanisms of resistance to endocrine therapy in breast cancer: focus on signaling pathways, miRNAs and genetically based resistance. Int J Mol Sci 2012; 14: 108-145.
[213] Rugo HS, Vidula N and Ma C. Improving response to hormone therapy in breast cancer: new targets, new therapeutic options. Am Soc Clin Oncol Educ Book 2016; 35: e40-54.
[214] Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Feyereislova A, Révil C and Jones A. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 2009; 27: 5529-5537.
[215] Johnston S, Pippen J Jr, Pivot X, Lichinitser M, Sadeghi S, Dieras V, Gomez HL, Romieu G, Manikhas A, Kennedy MJ, Press MF, Maltzman J, Florance A, O'Rourke L, Oliva C, Stein S and Pegram M. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 2009; 27: 5538-5546.
[216] Guarneri V, Generali DG, Frassoldati A, Artioli F, Boni C, Cavanna L, Tagliafico E, Maiorana A, Bottini A, Cagossi K, Bisagni G, Piacentini F, Ficarra G, Bettelli S, Roncaglia E, Nuzzo S, Swaby R, Ellis C, Holford C and Conte P. Double-blind, placebo-controlled, multicenter, randomized, phase IIb neoadjuvant study of letrozole-lapatinib in postmenopausal hormone receptor-positive, human epidermal growth factor receptor 2-negative, operable breast cancer. J Clin Oncol 2014; 32: 1050-1057.
[217] Kalinsky K, Accordino MK, Chiuzan C, Mundi PS, Sakach E, Sathe C, Ahn H, Trivedi MS, Novik Y, Tiersten A, Raptis G, Baer LN, Oh SY, Zelnak AB, Wisinski KB, Andreopoulou E, Gradishar WJ, Stringer-Reasor E, Reid SA, O'Dea A, O'Regan R, Crew KD and Hershman DL. Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: MAINTAIN trial. J Clin Oncol 2023; 41: 4004-4013.
[218] Zhang X, Zhang B, Liu J, Liu J, Li C, Dong W, Fang S, Li M, Song B, Tang B, Wang Z and Zhang Y. Mechanisms of Gefitinib-mediated reversal of tamoxifen resistance in MCF-7 breast cancer cells by inducing ERα re-expression. Sci Rep 2015; 5: 7835.
[219] Morrison G, Fu X, Shea M, Nanda S, Giuliano M, Wang T, Klinowska T, Osborne CK, Rimawi MF and Schiff R. Therapeutic potential of the dual EGFR/HER2 inhibitor AZD8931 in circumventing endocrine resistance. Breast Cancer Res Treat 2014; 144: 263-272.
[220] Johnston S, Basik M, Hegg R, Lausoontornsiri W, Grzeda L, Clemons M, Dreosti L, Mann H, Stuart M and Cristofanilli M. Inhibition of EGFR, HER2, and HER3 signaling with AZD8931 in combination with anastrozole as an anticancer approach: phase II randomized study in women with endocrine-therapy-naïve advanced breast cancer. Breast Cancer Res Treat 2016; 160: 91-99.
[221] Formisano L, Stauffer KM, Young CD, Bhola NE, Guerrero-Zotano AL, Jansen VM, Estrada MM, Hutchinson KE, Giltnane JM, Schwarz LJ, Lu Y, Balko JM, Deas O, Cairo S, Judde JG, Mayer IA, Sanders M, Dugger TC, Bianco R, Stricker T and Arteaga CL. Association of FGFR1 with ERα maintains ligand-independent ER transcription and mediates resistance to estrogen deprivation in ER(+) breast cancer. Clin Cancer Res 2017; 23: 6138-6150.
[222] Servetto A, Formisano L and Arteaga CL. FGFR signaling and endocrine resistance in breast cancer: challenges for the clinical development of FGFR inhibitors. Biochim Biophys Acta Rev Cancer 2021; 1876: 188595.