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# The role of HER2, EGFR, and other receptor tyrosine kinases in breast cancer

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## Abstract

Breast cancer affects approximately 1 in 8 women, and it is estimated that over 246,660 women in the United States will be diagnosed with breast cancer in 2016. Breast cancer mortality has decline over the last two decades due to early detection and improved treatment. Over the last few years, there is mounting evidence to demonstrate the prominent role of receptor tyrosine kinases (RTKs) in tumor initiation and progression, and targeted therapies against the RTKs have been developed, evaluated in clinical trials, and approved for many cancer types, including breast cancer. However, not all breast cancers are the same as evidenced by the multiple subtypes of the disease, with some more aggressive than others, showing differential treatment response to different types of drugs. Moreover, in addition to canonical signaling from the cell surface, many RTKs can be trafficked to various subcellular compartments, such as the multivesicular body and nucleus, where they carry out critical cellular functions, such as cell proliferation, DNA replication and repair, and therapeutic resistance. In this review, we provide a brief summary on the role of a selected number of RTKs in breast cancer and describe some mechanisms of resistance.

## 1.1. Introduction

Breast cancer is the most common cancer type and the second leading cause of cancer-related deaths among women in the United States with an estimated 40,450 deaths for 2016 (1). The metastatic form of the disease remains the leading cause of death in the majority of breast cancer patients. Breast cancers are categorized into five different subtypes, luminal A/B, HER2-positive ($HER^+$), basal-like, claudin-low, and normal breast-like, based on the expression levels of estrogen and progesterone receptors (ER and PR), HER2, cytokeratins 5/6, and claudins 3/4/7 (2–4). The triple-negative breast cancer (TNBC) subtype, which shares striking similarities with basal-like breast cancer and accounts for 15–20% of breast

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cancers, lacks the expression of estrogen receptor (ER), progesterone receptor (PR), and HER2, and has high metastatic potential (5, 6).

As a result of early detection and advances in therapeutic development, survival rates for breast cancer have vastly improved. For breast cancer that is detected in the breast only, the 5-year survival rate is 99% whereas when distant metastasis (metastatic breast cancer) has occurred, the rate drops significantly to 26% (7). Treatment options for early-stage breast cancer, including chemotherapy, radiation therapy, surgery, hormone therapy, and targeted therapy, have demonstrated efficacy, but for patients with the metastatic form of the disease, response rates are low (8). Therefore, increasing our understanding of the mechanisms underlying breast cancer may lead to more effective therapeutic approaches and improve the low response rate faced by breast cancer patients.

Receptor tyrosine kinases (RTKs) regulate important biological processes, including cell proliferation, differentiation, metabolism, and survival (9, 10) by activating an array of downstream signaling pathways. In humans, there are a total of 58 members of the RTK family that are further divided into 20 subfamilies (11). Activation of RTK begins with the binding of growth factors and hormones followed by cross-linking with adjacent RTKs (oligomerization) and *trans* autophosphorylation, subsequently initiating downstream signaling pathways through complex substrate protein phosphorylation (10–15). Following ligand activation, cell surface RTKs are sent to the lysosome for degradation, recycled to the cell surface, or translocated into subcellular compartments, such as the nucleus (16–19).

Aberrant expression and mutations within the genes encoding the RTKs are well known to lead to the development of many diseases, including breast cancer (20, 21). Targeted therapies against RTKs, such as small molecule inhibitors and monoclonal antibodies, have demonstrated efficacy in treating cancers (22, 23). In this chapter, we discuss the roles of RTKs in breast cancer, with a particular emphasis on the ERBB family members and their implications in therapeutic resistance.

## 1.2. HER/ERBB Family

The ERBB family of RTKs consists of four members, EGFR (epidermal growth factor receptor, also known as ERBB1/HER1), ERBB2 (HER2), ERBB3 (HER3), and ERBB4 (HER4), cytoplasmic membrane-anchored proteins that share structural and sequence similarities, containing an extracellular ligand-binding domain, a transmembrane domain, and intracellular tyrosine kinase domain (24, 25). A total of 11 extracellular ligands with a conserved EGF motif can bind to the ERBB receptors, with the exception of ERBB2, which does not directly bind any ligands (26, 27). Following ligand binding, homo- and heterodimeric interactions between the ERBB receptors in various combinations induce autophosphorylation on the intracellular tyrosine kinase domain (24). ERBB3 *trans* phosphorylation relies on another member of the ERBB family, as it is generally known to lack kinase tyrosine activity (see later section on ERBB3). These phosphorylated residues serve as docking sites for a number of adapter and scaffolding proteins, triggering a myriad of downstream signaling pathways, such as PI3K/AKT, Ras/MEK/ERK, PLC$\gamma$/PKC, and JAK/STAT, that regulate cell survival, proliferation, differentiation, motility, apoptosis,

survival, invasion, migration, adhesion, and angiogenesis (24); these pathways also upregulate expression of genes that activate epithelial mesenchymal transition, a key process of caner cell migration and invasion, leading to initiation of metastasis (28). The potency and outcome of activated signaling cascades are determined by the specific ligands, ERBB dimeric complexes, and proteins that are associated with the tyrosine phosphorylated residues in the C-terminal tail of the ERBB receptors (29).

Although ERBB receptors are critical regulators for normal cellular processes, it has become evident that their dysregulation, as a consequence of gene amplification, protein overexpression, and/or activating mutations, leads to the development of cancers (21, 30). Of the ERBB family members, HER2 and EGFR are frequently overexpressed in various cancers, including breast cancer, and are currently targets of many US FDA-approved drugs (31), for example, tyrosine kinase inhibitors (TKIs) and ectodomain targeting monoclonal antibodies (mAbs).

### 1.2.2. EGFR

As briefly mentioned above, activation of EGFR through the binding of one of seven ligands, EGF, transforming growth factor-α, heparin-binding EGF-like growth factor (HB-EGF), amphiregulin, epiregulin, betacellulin, and epigen, induces EGFR homodimerization or heterodimerization with ERBB2, ERBB3, or ERBB4, and transphosphorylation, triggering activation of downstream molecules, e.g., phosphatidylinositol 3-kinase (PI3K), Ras, phospholipase Cγ (PLCγ), and Janus-activated kinase (JAK) (21, 27). EGFR-dependent PI3K activation is primarily a result of EGFR/ERBB3 dimerization via the six docking sites for the p85 subunit on ERBB3. For EGFR-mediated Ras signaling, binding of the adapter proteins Grb2 and guanine exchange factor, Sos, directly or through Shc adaptor to the docking sites on the receptor, recruits Ras GTP-binding protein and results in Ras activation, which triggers the kinase cascade that activates Raf, MEK, and ERK, and subsequent phosphorylation of transcriptional factors that are involved in cell proliferation in the nucleus. PI3K is comprised of a regulatory subunit p85 that binds to specific docking sites on the receptor, and a catalytic domain p110 that converts lipid phosphatidylinositol-4,5-bisphosphate [$PI(4,5)P_2$] to phosphatidyl-inositol-3,4,5-trisphosphate [$PI(3,4,5)P_3$], which activates serine/threonine protein kinase AKT, leading to cell survival and inhibition of apoptosis. Tumor suppressor phosphatase and tensin homolog (PTEN) reverses this process by dephosphorylating $PIP_3$ (32, 33). PLCγ interacts with activated EGFR and hydrolyzes $PIP_2$ to yield second messengers, inositol 1,4,5-triphosphate, which induces transient increase in intracellular calcium, and 1,2-diacylglycerol, which functions as a co-activator of protein kinase C (33). EGFR and JAK can bind to and directly activate signal transducer and activator of transcription (STAT) proteins via the Src homology 2 domain, and upon activation, STATs homo- and hetero-dimerize and translocate into the nucleus to drive expression of specific target genes involved in proliferation, differentiation, and survival. Increased EGFR activity has been demonstrated to promote persistent activation of STAT3, which leads to tumor progression (34).

Dysregulation of the EGFR signaling cascade due to overexpression or constitutively activating mutations is well established in many cancer types, including breast cancer (35). In addition, ligand-independent activation of EGFR attributed to kinase domain mutations and extracellular domain deletion is well documented in lung cancer and glioblastoma (GBM). Moreover, both overexpression of urokinase-type plasminogen activator receptor, which induces the association between EGFR and α5β1 integrin, leading to activation of ERK signaling, and cellular stresses, which can elevate EGFR phosphorylation by inhibiting phosphatases, can occur independently of EGFR ligand (36, 37).

Overexpression of EGFR is observed in 15–30% of breast carcinoma, and is associated with large tumor size and poor clinical outcomes (38–40). Most notably, EGFR is frequently overexpressed and associated with poor prognosis in TNBC (41–43), a breast cancer subtype for which many therapeutics targeting EGFR have been considered. Overexpression of EGFR is partly attributed to *EGFR* gene amplification and observed in many cancer types, including breast, lung, colorectal, and esophageal cancers, and GBM (44–48). For example, in a cohort of 47 metaplastic breast carcinomas, which harbor basal-like phenotype, examination of the EGFR protein and gene expression revealed that about 23% of the cases had *EGFR* amplification (49). Other mechanisms have also been reported to upregulate EGFR expression. For instance, downregulation of BRCA1, a tumor suppressor critical for DNA damage repair, upregulates both EGFR mRNA and protein levels (50). In addition, tissue transglutaminase (tTG), a GTP-binding protein/acyltransferase associated with development of drug resistance and metastasis whose expression is upregulated in glioblastoma, was reported to upregulate EGFR levels by blocking ubiquitination-mediated degradation of EGFR in GBM (51). tTG protein is also amplified in other cancer types, including breast cancer (52, 53). Whether the tTG-EGFR pathway also exists in breast cancer remains to be investigated.

EGFR-activating mutations (10–35% frequency) in lung cancer have been well demonstrated to have greater sensitivity to EGFR TKI (erlotinib and gefitinib) treatment (54–56). For example, exon 19 deletion and L858R point mutation, located in the kinase domain, are the most common in non-small cell lung cancer (NSCLC) with a 48% and 43% frequency of mutation, respectively, in *EGFR*-mutated NSCLC (57). In addition, about 50% of *EGFR*-mutated tumors with acquired resistance to erlotinib/gefitinib harbor the second site T790M mutation in the kinase domain.

In contrast to lung cancer, mutation of EGFR in breast cancer is rare (46). Mutational analysis of 70 TNBC tumor issues showed that 11.4% (8/70) harbored EGFR mutations (58). Among the mutations identified were those that have been previously reported in lung cancer, including exon 19 deletions and exon 21 mutations in the EGFR kinase domain (58). However, other studies have reported zero or varying percentages of TNBC harboring EGFR mutations (59). Several clinical trials testing EGFR TKIs and mAbs in TNBC have been evaluated or are ongoing, but none has been approved due to limited positive results (31, 43, 59). Thus, understanding the activation of EGFR in TNBC and identification of biomarkers to stratify patients who will respond to EGFR TKIs and mAbs will be required to allow these drugs to effectively target this disease.

Another well-known EGFR mutation is EGFRvIII, which contains an in-frame deletion of 281 amino acids in its extracellular domain and occurs at a frequency of 25–64% high-grade gliomas with wild-type EGFR amplification (60, 61). The truncated EGFRvIII, localized on the cell surface, cannot bind ligands but is constitutively active. In breast cancer, the frequency of EGFRvIII varied substantially, depending on the methods used for detection (61). In a study in which the presence of EGFRvIII was confirmed in primary breast carcinomas by multiple detection methods, Del Vecchio et al. reported that EGFRvIII-positive cells also had increased expression of stem cell associated markers and genes (62). The authors further demonstrated that EGFRvIII modulates cancer stem cell (CSC) phenotype in primary breast carcinoma via the Wnt/β-catenin signaling pathway, which is known for its role in CSC activity, such as self-renewal and migration (63).

Activated EGFR can also be internalized in endosomes to be degraded via lysosome-mediated degradation pathway, recycled to the cell surface via receptor recycling pathway, or translocated to other subcellular compartments, e.g., the nucleus and mitochondria (7, 24, 64). Nuclear EGFR was first detected more than two decades ago in regenerating hepatocytes (65) and later described in cells and tissues of many cancer types, including breast cancer (66). Moreover, increased nuclear EGFR expression is associated with poor clinical outcome in breast cancer as well as several other cancer types (67–72). Among the members of the ERBB family, nuclear EGFR has been the most extensively studied and well demonstrated to play a role in cell proliferation, DNA damage and repair, DNA replication, transcriptional regulation, and drug resistance in response to growth factors stimulation, $H_2O_2$, UV, irradiation, and chemotherapy (73–80). As a transcriptional co-activator, nuclear EGFR has been reported to bind to the promoters of genes, such as *CCND1* (cyclin D1), *AURKA* (Aurora-A kinase), *iNOS* (inducible nitric oxide synthase), and *BCRP* (breast cancer-resistant protein), which are involved in tumorigenesis, chromosome instability, and therapeutic resistance, through association with STAT and E2F1 transcriptional factors and RNA helicase A (74, 77, 81–83). Nuclear EGFR also associates with ataxia telangiectasia mutated (ATM), a DNA damage response mediator, proliferative cell nuclear antigen (PCNA), a component of the DNA replication machinery, and DNA-dependent protein kinase (DNA-PK), a molecular sensor of DNA damage (84, 85).

### 1.2.1. HER2/ERBB2

Contrary to other ERBB family members, HER2 does not directly bind to any known ligands. Instead, activation of HER2-mediated signaling pathways occurs by heterodimerization with ligand-activated EGFR or ERBB3, or by homodimerization when it is present in high concentrations, such as in cancer (26, 86). Activated ERBB2, via interaction with one of the ligand-bound partners, initiates downstream signaling cascades similar to EGFR. Among all ERBB pairs, the HER2/ERBB3 heterodimer is the most potent activator of the PI3K/AKT signaling cascade via binding of the p85 subunit of PI3K to ERBB3 (30). In addition, ERBB3 but not EGFR is consistently phosphorylated in *HER2*-amplified human breast cancer tissues (88). Knocking down HER3 but not EGFR inhibits viability of *HER2*-overexpressing breast cancer cells, and sh*ERBB3*-expressing *HER2*-amplified xenografts demonstrated rapid regression (88). Likewise, an ERBB3-neutralizing antibody also efficiently reduced growth of *HER2*-amplified human breast cancer xenografts

(89). These findings all point to the essential role of ERBB3 in HER2-mediated oncogenic signaling.

Overexpression of HER2 is primarily attributed to *HER2* gene amplification and results in constitutive activation of the HER2 signaling network (24). HER2 overexpression/amplification is observed in about 20–30% of breast cancers and is associated with poor clinical outcome and disease progression (90, 91). Somatic mutations in *HER2* have been reported in breast, gastric, lung, bladder and endometrial cancers, and these mutations are almost always identified in the absence of *HER2* gene amplification (6, 92). Bose et al. functionally characterized 13 HER2 mutations in *HER2* gene amplification negative breast cancer and found that some were sensitive to HER2-targeted therapies; their findings provided critical preclinical results to suggest that breast cancer patients with *HER2* mutations may benefit from existing HER2-targeted drugs (93).

Several HER2-targeted therapies that have been approved by the U.S. Food and Drug Administration (FDA) or are in clinical trials for breast cancer include mAbs, e.g., trastuzumab (Herceptin®), pertuzumab (Perjeta®), and trastuzumab emtansine (Kadcyla®), and TKIs, e.g., lapatinib (Tykerb®) and neratinib (in clinical trials) (94). The recombinant humanized monoclonal antibody, trastuzumab (Herceptin), which targets the juxtamembrane region of the extracellular domain of HER2, was the first targeted therapy approved by the FDA in 1998 for breast cancer (95). Pertuzumab prevents dimerization of HER2 with other ERBB/HER receptors, particularly, the most potent signaling heterodimer HER2/HER3 (96). Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that combines trastuzumab and cytotoxic agent emtansine, which inhibits microtubules (97). Lapatinb is a reversible ATP-competitive TKI against EGFR and HER2 whereas neratinib is an irreversible ATP-competitive TKI of ERBB receptors, EGFR, HER2, and ERBB4 (98, 99).

Trastuzumab is considered as standard of care for patients with early and metastatic breast cancer harboring HER2 overexpression. Trastuzumab inhibits HER2 ectodomain cleavage, blocks ligand-independent HER2-containing dimers, activates antibody-dependent cellular cytotoxicity, and induces HER2 internalization and degradation (100, 101). Although trastuzumab has significantly improved the outcome in breast cancer patients, resistance to trastuzumab have also been observed. Several mechanisms have been shown to contribute to trastuzumab resistance, including constitutive activation of the downstream PI3K pathway due inactivation or loss of tumor suppressor phosphatase and tensin homolog (PTEN) or *PI3KCA* gene mutations (102, 103); Src kinase activation conferred by PTEN deficiency (104); overexpression of other RTKs, e.g., EGFR family receptors, insulin-like growth factor receptor 1, hepatocyte growth factor receptor (Met), and Eph receptor A2 (105–108); intrinsic *HER2* alterations, e.g., alternative translation initiation, splice variants, and mutations; and proteolytic shedding of full-length HER2 which generates a truncated form of HER (p95HER2) lacking the trastuzumab binding domain (109). Another potential mechanism of trastuzumab resistance is the binding of mucin-4 to the extracellular domain of HER2, which masks the trastuzumab-binding site on HER2 (110). We recently reported that phosphorylation of SIR6 by AKT leads to MDM2-mediated degradation of SIRT6, which promotes trastuzumab resistance in breast cancer cells (111). Other mechanisms contributing to trastuzumab resistance include defects in the apoptotic machinery, increased

levels of inhibitor of apoptosis protein, survivin, alterations in cell cycle control (94). To combat resistance, various combination therapies have been evaluated in clinical trials, including combinations of mABs and TKIs (94).

In addition to cell surface signaling, HER2/ERBB2 also translocates into the nucleus and harbors transcriptional activity (80, 112). p185neu, which is the rat homolog of human HER2/ERBB2 was the first-membrane associated RTK demonstrated to associate with transcriptional activation (113). For instance, nuclear ERBB2 binds to and transactivates the *COX2* promoter in ERBB2-overexpressing breast cancer cell lines as well as in ERBB2-positive human primary breast tumors (112). Moreover, nuclear ERBB2 also serves as a STAT3 transcriptional co-activator and promotes breast cancer cell growth (114). Taxol resistance has been attributed to co-localization of ERBB2 and cyclin-dependent kinase p34CDC2 in the nucleus as well as the cytoplasm in breast cancer cells (115). Nuclear p95, which represents the truncated form of ERBB2, also contributes to TKI resistance (109). Interestingly, nuclear ERBB2 was reported to be an independent prognostic predictor of worse overall survival in patients with ERBB2-overexpressing breast tumors (116).

### 1.2.3. ERBB3

Although ERBB3 lacks innate kinase activity, it interacts with other receptor tyrosine kinases, most notably, ERBB2, upon ligand binding (neuregulins, NRG1 and NRG2), and relies on their kinase activity to phosphorylate the tyrosine residues in its C-terminal domain, which serve as docking sites for downstream molecules, leading to potent activation of PI3K-induced AKT and Ras/MEK/ERK signaling cascades (117, 118). Interestingly, even though ERBB3 has been generally considered kinase inactive, more recent studies by Shi et al. indicated that the kinase domain of ERBB3 does indeed bind to ATP with similar affinity compared to other known active kinases and harbors kinase activity albeit much weaker than that observed for EGFR (119).

ERBB3 plays a crucial role in HER2 signaling, and co-expression of ERBB3 and HER2 is frequently observed in breast cancer cell lines and primary tumors (120, 121). ERBB3 is also implicated in HER2-mediated therapeutic resistance (30). Overexpression of ERBB3 in breast cancer has been reported to be between 17.5–43%, depending on the antibody used and has been implicated in shorter disease-free survival of breast cancer patients (122–124). Morrison et al. reported *ERBB3* copy number gains in 12.3%, 21.1%, and 27.6% of luminal A, luminal B, $HER2^+$ breast tumors, respectively, and that *ERBB3* mRNA expression correlated positively with luminal A/B subtypes but not basal-like or claudin-low in primary breast cancers (125).

Compared to EGFR and HER2 for which mutations are well known and serve as targets of cancer therapeutics, *ERRB3* mutations have been reported for some cancers, but the occurrence is rare and sporadic (6, 126–128). Sequencing of all coding exons of *ERBB3* identified specific somatic mutations in ERBB3, and expression of the ERBB3 mutants in breast epithelial cells led to oncogenic transformation in the presence of HER2 (129). Several investigational drugs at various stages of development have been described for ERBB3 (130), and whether the more recently identified ERBB3 mutations are sensitive to ERBB3 and/or HER2 targeted therapies remain to be addressed.

Like EGFR and ERBB2/HER2, ERBB3 can also translocate into the nucleus. Full-length ERBB3 in nucleus was first reported in nonmalignant and malignant human mammary epithelial cells (131). Studies by Andrique et al. indicated that $ERBB3_{80\ kDa}$, a nuclear variant of ERBB3 in lung cancer cells, binds to the *CCND1* promoter to activate its transcription, which increases cyclin D 1 protein expression, leading to increased cell proliferation (132). Brand et al. later demonstrated that full-length nuclear ERBB3 can associate with a 122 bp region of the *CCND1* promoter in breast and lung cancer cell lines (133). In malignant prostate cancer tissues, nuclear localized ERBB3 is associated with the risk of disease progression (134). Moreover, increased nuclear translocation of ERBB3 was observed in prostate cancer cells that metastasized to the lymph nodes or bone (135). More studies will be required to better characterize the role of nuclear ERBB3 in breast cancer progression.

### 1.2.4. ERBB4

ERBB4 binds to neuregulins (NRG1–4) as well HB-EGF, epiregulin, and β-cellulin, which also bind to EGFR (136). Ligand-stimulated ERBB4 can form homodimers or heterodimerize with another ERBB receptor, which results in *trans* autophosphorylation and subsequent activation of downstream signaling cascades. The role of ERBB4 in breast cancer seems controversial. Some studies have point to the role of ERBB4 as a tumor suppressor while others indicated ERBB4 possesses oncogenic activities (137). For example, in breast cancer ERBB4 expression correlates with sensitivity to endocrine therapies and more favorable prognosis (138, 139). In contrast, downregulation of ERBB4 inhibits breast cancer cell proliferation (140). More recently, Canfield et al. provided evidence to suggest that ERBB4 mediates acquired resistance to ERBB2/HER2 inhibitors in breast cancer (141). Gene expression profile analysis of TNBC tissue specimens indicated increased *ERBB4* expression associated with poor prognosis and suggested that *ERBB4* expression may be a useful prognostic marker in TNBC patients (142). *ERBB4* mutations have been reported in melanoma, lung cancer, and medulloblastoma, and a recent study identified four *ERBB4* activating mutations in NSCLC that increased both basal and ligand-induced ERBB4 phosphorylation (143–146). More studies are warranted to establish the significance of ERBB4 expression and mutations in breast cancer.

Similar to other ERBB family members, ERBB4 has been identified in the nucleus of normal and cancer cells (147–149). Most notably, the intracellular domain (ICD) generated by γ-secretase-mediated cleavage of ERBB4, can translocate to the nucleus (150). Nuclear-localized ERBB4 ICD and STAT5A were reported to bind to the promoter of β-casein to induce its gene expression in breast cancer cells (151). ERBB4 ICD also co-localizes with and bind Eto-2, a transcriptional corepressor involved in cell differentiation, in the nucleus to block Eto-2-mediated transcriptional repression (152). On the other hand, ERBB4 ICD promotes ubiquitination and degradation of Hdm2 oncogene, which in turn increases the levels of tumor suppressor p53 (153). Other studies have reported that nuclear ERBB4 ICD is associated with worse clinical outcome than cell surface full-length ERBB4 whereas nuclear ERBB4 ICD functions as a co-activator of ERα and improves response to hormone therapy (154, 155). The role of ERBB4 ICD also remains controversial and requires further investigation.

## 1.3. Other RTKs

### 1.3.1. HGFR

Several RTKs in addition to the ERBB family members are also implicated in breast cancer. The hepatocyte growth factor receptor (HGFR; also known as c-MET) is encoded by the proto-oncogene *MET*. Binding of c-Met to its ligand HGF triggers receptor dimerization and *trans* autophosphorylation of tyrosine residues, which serve as docking sites for adaptor and scaffolding proteins, subsequently activating major downstream signaling pathways, PI3K/AKT, Ras/MEK/ERK, and STAT, to regulate various biological processes, such as morphogenesis, cell proliferation, survival, differentiation, and protection from apoptosis (156). c-Met is known to drive many oncogenic processes and implicated in progression and metastasis in many human cancers.

Mechanisms attributed to aberrant c-Met signaling include gene amplification, activating gene mutations, protein overexpression, ligand-dependent paracrine or autocrine loops, and interaction with other cell surface receptors (157, 158). In lung cancer, *MET* amplification (~5–20%) is responsible for acquired resistance to EGFR TKIs in patients with EGFR-mutated lung cancer by driving ERBB3-dependent activation of the PI3K pathway (159). Although *MET* amplification and mutations are rare in breast cancer, overexpression of c-Met and HGF are frequently observed in breast cancers (158). c-Met is overexpressed in 20–30% of breast cancers, and has been also shown to be an independent prognostic of poor prognosis for breast cancer patients (160–162). Shattuck et al. showed that co-expression of c-Met and HER2 contributes to trastuzumab resistance of HER2-overexpressing breast cancer cells (107). Minuti et al. later showed that high *MET* and *HGF* gene copy numbers were associated with higher risk of failure of trastuzumab treatment in breast cancer patients (163). Kim et al. recently reported high levels of c-Met expression in TNBC cell lines, and we also showed that *MET* mRNA expression was significantly higher in TNBC than in non-TNBC tumors (164–166).

Nuclear translocation of c-Met has also been detected. First reported in 1996 in mouse, nuclear c-Met was detected during hepatocarcinogenesis induced by phenobarbitone and later found in the nucleus of normal and malignant tissues as well as cancer cell lines (167, 168). In an aggressive MDA-MB-231 breast cancer cell line, c-Met was observed in the nucleus in an HGF-independent manner (169). Nuclear c-Met has been shown to induce $Ca^{2+}$ signaling and play a role as a transcriptional factor (169, 170). It was recently reported that in response to ROS activation, c-Met is able to translocate to nucleus to interact with and phosphorylate poly (ADP-ribose) polymerase (PARP), rendering breast cancer cells resistant to PARP inhibitors, which are promising therapeutics for many diseases including cancer (166). One PAPR inhibitor, olaparib, has been approved by the FDA to treat ovarian cancer harboring mutations in genes encoding BRCA1 and BRCA2, which are essential in repairing DNA double strand breaks, but discrepant clinical observations for this inhibitor have been reported in TNBC patients. The findings that c-Met contributes to PARP resistance suggested that combined inhibition of c-Met and PARP may benefit patients whose tumors exhibit high c-Met expression and who do not respond to PARP inhibition alone (166).

### 1.3.2. IGFIR

The type I insulin-like growth factor receptor (IGFIR) belongs to the insulin receptor (IR) family and is activated upon binding to its ligands, IGF1 and IGF2, triggering two main downstream pathways, PI3K/Akt and Ras/MEK/ERK, to control apoptosis, cell growth, and differentiation. A large body of evidence points to the role of IGFIR in many cancer types, including high levels of expression in breast and colorectal cancer (171). IGFIR is reported to be an important mediator of brain metastasis in an experimental model of brain metastasis of breast cancer (172).

Analysis of TCGA database indicated that IGFIR is amplified, overexpressed, or somatically mutated in 9% of breast tumors (173). The authors further indicated that IGFIR mRNA extend to be more highly expressed in Luminal A and B subtypes compared with the basal-like and HER2-positive subtypes (173). Many IGFIR inhibitors (mAbs and TKIs) and IGF1/IGF2 neutralizing mABs have been developed and evaluated in clinical trials with some success in early trials but have failed to show benefits in larger phase III trials (174). Exploring predictive biomarkers may identify subpopulation of patients who may benefit from IGFIR inhibitors.

Nuclear IGFIR has been detected in numerous human tumors, including ductal carcinoma of the breast, ductal carcinoma *in situ*, NSCLC, pancreatic adenocarcinoma, colorectal cancer; lymphoma, uterine malignant mixed mesodermal tumor, and ovarian serous adenocarcinoma, and is associated with poor prognosis in renal cell carcinoma (RCC) (175). SUMOylation of IGFIR mediates its translocation to the nucleus, where it associates with the transcription factor LEF1 to increase the promoter activity of LEF1 downstream targets, *CCND1* and *AXIN2*, both of which have been implicated in human tumorigenesis (176). Nuclear IGFIR can also bind to and phosphorylate histone H3, which stabilizes the binding of chromatin remodeling protein, Brg1, to histone H3, subsequently increasing the gene expression of *SNAI2* oncoprotein (177). In hepatocellular carcinoma, targeting EGFR by TKI induces nuclear translocation of IGFIR, suggesting that nuclear IGFIR may also contribute to drug resistance (178).

### 1.3.5. ALK, ROS1, and RYK

RTKs, anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), and receptor-like tyrosine kinase (RYK), are known as orphan receptors because there are no established growth factor, cytokine, or hormone ligands for these three RTKs. Interestingly, heparin was recently identified as an activating ALK ligand, and antibodies against the extracellular domain of ALK blocked heparin binding and heparin-mediated activation, suggesting their potential therapeutic application as cancer treatment (179).

ALK activates many signaling pathways, including PI3K/AKT, Ras/MEK/ERK, JAK/STAT, PLC$\gamma$, and sonic hedgehog, which are critical for cell growth, differentiation, transformation, and anti-apoptosis. ALK was first discovered in anaplastic large-cell non-Hodgkin's lymphoma (ALCL) as the nucleophosmin (NPM)-ALK fusion protein from a 2;5 chromosomal translocation. The NPM-ALK fusion protein comprises the kinase domain of ALK fused to N-terminal portion of NPM and is constitutively activated (180). In addition to

the NPM-ALK fusion in ALCL, a variety of genes that translocate with *ALK* have been described in many cancers, such as diffuse large B cell lymphoma, renal medulla carcinoma, RCC, NSCLC, inflammatory myofibroblastic tumour (IMT), breast cancer, and colorectal cancer (57, 180). The echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) gene rearrangement has been reported in breast cancer (181). *ALK* gene amplification and mutations, and ALK protein overexpression are also present in many human cancer cell lines and tumor tissues (180, 182). Studies have indicated increased ALK copy number, gene amplification and translocation in inflammatory breast cancer and TNBC (183, 184).

Crizotinib (Xalkori®), a dual c-Met/ALK TKI, was approved in 2011 by the FDA for the treatment of patients with locally advanced or metastatic ALK-positive NSCLC as detected by a companion FDA-approved test kit. Although initial findings indicated promising therapeutic potential for crizotinib as treatment for ALK-positive NSCLC patients, similar to EGFR TKIs, several crizotinib-induced secondary mutations in ALK were identified (185). Second- and third-generation TKIs, e.g., ceritinib (Zykadia™) and lorlatinib, respectively, were developed against ALK kinase domain mutations with acquired resistance to crizotinib. Paradoxically, a metastatic non-small-cell lung cancer patient who had initially responded to third-generation TKI, lorlatinib, after developing resistance to crizotinib and without showing response to second-generation TKI, later became resensitized to crizotinib (186). Molecular assessment of the lorlatinib-resistant tumor led to the identification of a novel mutation in the ALK ATP-binding pocket contributing to this resistance. These findings highlight the invaluable insight into the mechanisms underlying resistance in each individual patient from repeated tumor biopsies, which can lead to more effective treatment options.

Although ROS1 shares similar structural organization with EGFR, there is currently no known ligand that binds to this receptor. Studies using chimera proteins consisting of ROS1 kinase domain and extracellular domain of other ligand-binding receptors found that the chimeric receptors can activate various signaling molecules, such as PI3K/AKT, PLCγ, and STAT3, upon corresponding ligand stimulation (187). *ROS1* gene rearrangement, comprised of the C-terminal kinase domain of ROS1 and N-terminal region of fusion partner, was first described in a human glioblastoma cell line and subsequently identified in various cancers (188). Various ROS1 gene fusions have been found in NSCLC, gastric adenocarcinoma, colorectal cancer, IMT, angiosarcoma (188). ROS gene fusions harbor constitutive kinase activity and their transforming potentials are well established (188). The c-Met/ALK inhibitor, crizotinib, also potently inhibits the ROS1 kinase and has demonstrated activity in *ROS1*-rearranged NSCLC preclinical models (189). The FDA approved the expanded use of crizotinib for patients with *ROS1*-positive metastatic NSCLC in 2016 following results from a multicenter study showing marked anti-tumor activity of crizotinib in patients with metastatic *ROS1* rearrangement–positive NSCLC with an objective response rate of 66% (190). Retrospective analysis of a European study of 32 *ROS*-positive NSCLC patients treated with crizotinib indicated an overall response rate of 80% and a progression-free survival of 9.1 months (191). *ROS1* mutations associated with acquired resistance to ROS1 TKI have been reported, and several next-generation ROS1 TKIs were shown to overcome crizotinib resistance (57). Although there is currently no report of *ROS1* gene rearrangement in breast cancer, a study that examined gene and protein expression of ROS1 in invasive

ductal carcinoma (IDC) of the breast indicated that ROS1 expression is related to cell proliferation and reported a potential association between higher ROS1 expression and better prognosis (192, 193). More studies are needed to determine whether current ROS1 inhibitors may be useful as treatment for IDC in the future.

The related-to-receptor tyrosine kinase (Ryk) receptor is an atypical member of the RTK family because it does not harbor detectable kinase activity in its C-terminal domain (194). The extracellular region of Ryk contains a Wnt inhibitory factor-1 domain and has been reported to function as a receptor (or co-receptor) of Wnts, a large family of secreted glycoproteins that are involved in pattern formation, cell fate, axon guidance, neurite outgrowth, and tumor formation (195). In response to Wnt stimulation, Ryk is cleaved at its C-terminus, which generates an intracellular C-terminal fragment that can translocate to the nucleus (196). Lyu et al. reported that the Cdc37 subunit of the molecular chaperone Hsp90 binds to and stabilizes Ryk ICD (197). Nuclear localized Ryk ICD has been reported to regulate the expression of target genes essential for neuronal differentiation (198). Overexpression of Ryk has been observed in malignant ovarian tumors and is associated with shorter overall survival of patients (199). Ryk is also highly expressed in leukemia cells, but not in normal cells (200). The significance of the Ryk receptor has not been established in breast cancer, and more studies will be required.

## 1.4. Conclusion

The discovery of binding receptors for EGF on human fibroblast cells by Carpenter and co-workers over 40 years ago and later work by various groups that identified EGFR as an RTK have substantially contributed to our understanding of the functions of RTK signaling as well as the downstream pathways governing fundamental biological processes such as cell proliferation, differentiation, migration, metabolism, and survival (12, 201–203). However, when RTKs are mutated or altered, they can potently activate downstream signaling, leading to cell transformation, and consequently the development and progression of many human cancers. These findings have led to the development of RTK-based cancer therapies by targeting their ligand-binding extracellular domains using mAbs or kinase domains by small molecule inhibitors. Although RTK-based therapies have demonstrated clinical success, there also exist many challenges due to the rise of resistance illustrated by the development of acquired resistance to each successive generation of drugs in lung cancer (see above). Effective therapeutic approaches will require blocking multiple targets via various drug combinations.

We recently reported that that extracellular domain of EGFR can be methylated by protein arginine methyltransferase 1 (PRMT1), and that methylated EGFR may contribute to EGFR mAb resistance in colorectal cancer (204). Overexpression of EGFR is frequently observed in TNBC, but EGFR-targeted therapies have demonstrated disappointing results in clinical trials for TNBC. It would be of interest to determine whether stratifying patients by the status of EGFR methylation may maximize response to EGFR mAb. PRMT1 inhibitors are currently under development (205), and it may be worthwhile to evaluate the combination of PRMT1 inhibitors and EGFR mAbs for TNBC showing increased levels of methylated EGFR.

Finally, antibodies against immune checkpoints, e.g., PD-1 and CTLA-4, which put brakes on T cell activation, have gained significant traction in cancer therapy by unleashing T-cell mediate anti-tumor activity (206). In addition, combining immune checkpoint therapy with targeted therapies may boost efficacy and provide lasting effects against tumor cells (207, 208). For instance, Yang et al. reported that T-cell-mediated immune response is associated with EGFR mAb efficacy (209), further supporting the potential therapeutic effects of EGFR-targeted therapy combined with immune checkpoint blockade.

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