Potential for Targeting the Fibroblast Growth Factor Receptors in Breast Cancer

Nancy E. Hynes and Julien H. Dey

Abstract
Breast cancer is the most common cancer of women, accounting yearly for approximately 30% of newly diagnosed cases and ranking second as a cause of death. Despite improvements in breast cancer detection and development of new therapeutic approaches, there are still tumors for which no targeted therapies are available. This review summarizes recent findings on the fibroblast growth factor receptors (FGFR) and the data supporting their role in breast cancer. We will describe the approaches being made to develop therapeutics targeting these receptors. Finally, to improve the chances for success with FGFR signal transduction inhibitors, strategies to choose appropriate breast cancer patients for treatment will be discussed. Cancer Res; 70(13); 5199–202. ©2010 AACR.

Breast cancer is a heterogeneous disease, from the cellular morphology to the array of expressed genes in individual tumors. Despite this heterogeneity, there are specific genetic alterations that are found in a relatively high percentage of breast cancers, such as the ERBB2 amplicon on chromosome 17q21 present in approximately 25% of primary tumors. As a transmembrane receptor with kinase activity, ErbB2 has proved to be an excellent target for cancer therapy. Various types of signal transduction inhibitors, including monoclonal antibodies and tyrosine kinase inhibitors (TKI), are used to treat patients whose tumors possess the ERBB2 amplicon and overexpress the receptor (reviewed in ref. 1). Currently much effort is going into targeting additional genetic alterations driving breast cancer. Here, we will discuss the fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) network, whose members have multiple, essential developmental roles and have also been implicated in different types of human tumors, including breast cancer.

In mammals, there are four FGFRs that encode transmembrane receptors with tyrosine kinase activity. Furthermore, alternative splicing of FGFR 1, 2, and 3 in the third Ig-like loop domain gives rise to the IIIb and IIIc isoforms, which are expressed in epithelial or mesenchymal compartments, respectively. There are 22 FGF ligands, 18 of which bind specific FGFR isoforms, inducing receptor dimerization, kinase activation, and autophosphorylation of intracellular tyrosine residues (reviewed in ref. 2). In addition to phosphorylation of tyrosine residues on the receptors and on PLCγ, the adaptor protein FRS2 that links FGFRs to the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways, is heavily phosphorylated in response to receptor activation. Other effector proteins including STAT transcription factors and Src are also activated by FGFRs (Fig. 1, center panel; reviewed in ref. 3).

Different types of FGF/FGFR alterations, including abnormal expression levels, single nucleotide polymorphisms (SNP), mutations, and amplifications, have been described in cancer (reviewed in ref. 4). The association between aberrant FGF/FGFR expression and mammary cancer was established more than 20 years ago in mouse mammary tumor virus (MMTV)–induced tumors, in which proviral insertion mutagenesis induced FGF3 transcriptional activation. Indeed, in >65% of mammary tumors, MMTV proviruses transcriptionally activate different members of the FGF/FGFR network (e.g., Fgf4, Fg6, Fg8, Fg10, and Fg62; refs. 5–7). In this review we will concentrate on breast cancer, presenting the evidence for FGF/FGFR involvement in human disease and discussing current approaches that might be used for targeting oncogenic FGFRs in breast cancer.

Large-scale analyses of human cancer genomes have revealed that FGFRs are often amplified or mutated (8). In breast cancer, different types of genetic alterations in FGF/FGFR have been described, with amplification the most common and activating mutations being rarer. The 8p11-12 am-plicon harboring FGFR1 has been detected in 8 to 10% of breast cancers (9). This is a complex amplicon with at least two cores, which had led to variation in reports of FGFR1 overexpression (10). In two large studies, 8p11-12 amplification was shown to correlate with poor outcome (9, 10), and, in a recent study, high FGFR1 levels in the estrogen receptor (ER)–positive, highly proliferative luminal B subtype, correlated with tamoxifen resistance (11). FGFR2 amplification (10q26) and overexpression have also been described in a small subgroup (6 of 165 = 4%) of triple-negative breast tumors [negative for ER, for progesterone receptor (PR), and for high ErbB2]. Interestingly, no case of FGFR2 amplification was found in >200 tumors that were not triple negative (12).
Activating mutations in FGFR3 have been found in many types of human tumors; however, in breast cancer these seem to be very rare. There is one report on a Saethre-Chotzen syndrome patient with breast cancer whose tumor carries a gain-of-function FGFR3 mutation (P250R; ref. 10). Whether additional breast cancer patients with activating mutations in FGFR3 will be uncovered, or if this mutation had a causal role in the disease, remains to be studied.

Regarding FGFR4, an activating mutation (Y367C) that causes constitutive receptor dimerization was discovered in the MDA-MB453 breast tumor cell line (13). The mutation is in a homologous region to mutations in FGFR2 and FGFR3, which are associated with human diseases. Currently, activating FGFR4 mutations do not seem to be common in primary breast tumors.

SNPs associated with breast cancer risk and with breast cancer severity have also been described. Genome-wide screens aimed at uncovering breast cancer-associated genes identified SNPs in intron 2 of FGFR2 (14, 15). These SNPs were shown to predispose selectively for ER-positive cancer (15) and, in vitro, to alter Oct-1/Runx2 binding, leading to an increase in FGFR2 transcription (16). FGFR2 was also shown to be transcriptionally activated in some MMTV-induced mammary tumors (7), and in human tumors there is evidence that FGFR2 is involved in breast cancer progression.
that FGFR2 ligands are abnormally expressed. Indeed, amplification of FGFR3 (11q13) occurs in 15% of breast tumors and was shown to correlate with increased aggressiveness in node-negative breast carcinoma (17). Taken together, these data suggest that inappropriate expression or activation of FGFR2, which has an important role in normal development of the gland (18), might predispose to breast cancer.

A SNP in FGFR4, which converts Gly to Arg at codon 388 in the transmembrane region of the receptor, has been implicated in poor prognosis of various types of human tumors (mentioned in ref. 19). In some breast cancer cohorts, the FGFR4Arg388 allele has been correlated with poor response to chemotherapy (20) and endocrine therapy (21). Interestingly, MDA-MB-453 breast tumor cell clones resistant to the DNA-damaging agents doxorubicin or cyclophosphamide showed upregulation of FGFR4 (22). The significance of this SNP has been tested by introducing the FGFR4Arg388 allele into a transgenic mammary tumor model in which it was shown to cause a more rapid tumor development and tumor progression compared with the FGFR4Gly388 allele (19). Although the molecular changes underlying the ability of the FGFR4Arg388 allele to promote tumor progression have not been molecularly clarified, evidence for enhanced receptor kinase activity as well as increased FGFR4 protein stability have been presented (19). The latter activation mechanism has also been reported for other FGFRs. Using a mammary epithelial 3-D cell-culture model, it was shown that active FGFR1 is more stable and promotes prolonged signaling in comparison to FGFR2 (23).

From this brief discussion it should be clear that there is good evidence supporting distinct roles for specific FGF/FGFR family members in breast cancer. The next step will be to use in vitro and in vivo preclinical tumor models to examine the potential of blocking FGF/FGFR activity. The most advanced approaches for targeting the network are the small molecule TKIs and blocking antibodies for specific receptors or ligands (Fig. 1, left and right panels; reviewed in 4). Because of space constraints, we will concentrate on TKIs that have been tested in breast cancer models. The important points to be considered are: FGFR inhibitor activity, how to choose appropriate breast cancer patients for treatment, and potential side-effects of blocking FGFRs.

There are a number of small molecule TKIs that block FGFR activity and are either used for in vitro experimental work or are in various stages of clinical development (for a complete list see ref. 4). Most of the published data on FGFR inhibitors have been done with inhibitors referred to as multitargeted because they block not only the FGFRs (class V family), but also class III [platelet-derived growth factor receptor (PDGFR) family] and IV [vascular endothelial growth factor receptor (VEGFR) family] receptor tyrosine kinases (RTK) at similar low nmol/L concentrations (Fig. 1, right panel; ref. 24), e.g., PD173074, TKI168, or BMS-582664 (Brivanib; ref. 25). For TKI168, a phase I, first-in-human study in patients with advanced solid cancers, including breast, showed that 2 of 35 treated patients had a partial response (26). There was some dose-limiting toxicity reported, although overall the inhibitor was well tolerated (26). The activity as well as the side effects of the multitargeted inhibitors might reflect blockade of FGFR as well as the inhibition of the other classes of RTKs that they affect. Newer, more selective FGFR inhibitors are being developed; however, no data on efficacy or toxicity are available. Although it is only possible to speculate on possible side-effects, the importance of the metabolic FGFRs (FGFR1, 21, and 23) in many physiological functions (reviewed in ref. 27) must be considered when blocking FGFR activity.

What is known on the activity of the FGFR TKIs in preclinical models? Data generated with breast tumor cell lines displaying FGFR1 (11) or FGFR2 (12, 28) amplification showed that they were very sensitive to treatment with the multitargeted inhibitor PD173074. MDA-MB-453 breast tumor cells with the activating FGFR4 Y367C mutation (13) are also very sensitive to PD173074, showing a strong proliferative block following treatment with the inhibitor (28). Moreover, a breast cancer model showing autocrine ligand-mediated FGFR activity was very responsive to TKI168 both in vitro and in vivo (29). Despite these good responses, it has become increasingly clear that clinical management of breast cancer will require rational combinations of signal transduction inhibitors (30). Regarding this, it was shown that FGFR1-driven breast cancer models were very sensitive to a small-molecule ribosomal S6 kinase (RSK) inhibitor (31), suggesting that this kinase could be targeted together with FGFR. Overexpression and activation of FGFR and ErbB2 has also been observed in a breast cancer model and combined inhibition of both RTKs had stronger antitumor activity than individual treatments (32). With increasing knowledge of essential effectors downstream of FGFRs, it is likely that other appropriate combinations will emerge and potentially prolong the appearance of FGFR inhibitor resistance.

In considering choice of patients to be treated with FGFR inhibitors, tumor-specific gene amplification and protein overexpression are generally good indicators for sensitivity to a targeted inhibitor. ErbB2 is a good example because patients whose tumors do not show the 17q21 amplicon generally do not respond to an ErbB2-targeted therapy. Thus, screening for amplification of FGFR1 and FGFR2, which is rarer at 0.5 to 1%, should help in choosing patients for FGFR inhibitor treatment. The FGFR amplicons can be screened for via standard FISH procedures; however, it would be very important to develop diagnostic antibodies that can be used to choose those patients that do overexpress these receptors, in particular because the FGFR1 amplicon is so complex (10). It has recently been shown that ER-positive tumors with the FGFR1 amplicon tend to be PR negative, which reflects FGFR-mediated transcriptional repression of PR expression (11). Thus, high FGFR1 levels and ER positivity accompanied by PR negativity could be a characteristic of breast tumors with active FGFR1 signaling and might be useful in choosing patients for treatment. In breast cancer cell lines, it has been reported that increased levels of FGFR4 are found in cells resistant to chemotherapeutics (22). When treated with doxorubicin plus an FGFR4-blocking antibody, the cells responded showing increased cell death when the receptor was blocked (22). Whether elevated FGFR4 levels can be used to predict...
response to TKIs in combination with chemotherapeutics remains to be tested in the clinical setting. Finally, FRS2 tyrosine phosphorylation is another biomarker that might also be considered as a reporter for activity of any of the FGFRs. It might be useful to test for an association between FGFR amplification or activation together with FRS2 phosphorylation. In conclusion, although there are still some hurdles to be overcome, there is enough good evidence suggesting that targeting FGFRs in certain subtypes of breast cancer would be a valuable approach in the future.

References


Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Correction: Potential for Targeting the Fibroblast Growth Factor Receptors in Breast Cancer

In this article (Cancer Res 2010;70:5199–202), which was published in the July 1, 2010 issue of Cancer Research, the TKI numerology provided on page 5201 is incorrect. The correct numerology is TKI258.

Reference

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