Fibroblast growth factor receptors in breast cancer: expression, downstream effects, and possible drug targets

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Abstract

Cancer treatments are increasingly focusing on the molecular mechanisms underlying the oncogenic processes present in tumors of individual patients. Fibroblast growth factor receptors (FGFRs) are among the many molecules that are involved in oncogenesis and are currently under investigation for their potential as drug targets in breast cancer patients. These receptor tyrosine kinases play a role in several processes including proliferation, angiogenesis, and migration. Alterations in these basal processes can contribute to the development and progression of tumors. Among breast cancer patients, several subgroups have been shown to harbor genetic aberrations in FGFRs, including amplifications of FGFR1, FGFR2, and FGFR4 and mutations in FGFR2 and FGFR4. Here, we review in vitro and in vivo models that have partly elucidated the molecular implications of these different genetic aberrations, the resulting tumor characteristics, and the potential of FGFRs as therapeutic targets for breast cancer treatment.

Endocrine-Related Cancer (2012) 19 R115–R129

Introduction

Breast cancer is the most commonly occurring cancer in women with 1.4 million new cases diagnosed worldwide annually (Jemal et al. 2010). Currently, breast surgery and irradiation are the local therapies of choice, and chemohormonal and antihuman epidermal growth factor receptor 2 (HER2 (ERBB2)) therapies are commonly used as a systemic treatment to prevent outgrowth of distant metastases (Prosnitz et al. 2001). Progress in local and systemic treatment has clearly improved the prognosis of breast cancer patients, but still 458 503 women died from the disease in 2008 (Ferlay et al. 2008).

Therefore, the development of new therapies is focused on the specific genetic abnormalities in individual cancers, resulting in more personalized treatment (Bild et al. 2006, Alvarez et al. 2010). In order to develop these personalized therapies, it is important to fully understand the molecular basis of the oncogenic pathways that can be targeted in breast cancer.

Receptor tyrosine kinases (RTKs) regulate cell proliferation, differentiation, and apoptosis: processes that are often deregulated in cancer. Several RTKs, including epidermal growth factor receptor (EGFR), HER2, and platelet-derived growth factor receptor (PDGFR (PDGFRB)), have been extensively studied leading to the development of targeted inhibitors, such as trastuzumab and imatinib, that have been successfully used to treat cancer patients overexpressing HER2 and PDGFR respectively (Arteaga 2003, Mukai 2010, Peterson 2011).

This review focuses on the fibroblast growth factor receptor (FGFR) family of RTKs. FGFR signaling cascades, the genetic aberrations in FGFRs, and their correlations with other genotypic and phenotypic features found in breast cancer will be summarized. Finally, therapies currently under development as well as new possibilities to target the FGFR pathway will be discussed. Articles were retrieved through PubMed using the search items ‘breast’ or ‘mammary’ and ‘FGFR’. In addition, the references of the retrieved papers were screened for additional papers. Only papers in English were further considered.
The FGFR family comprises four members, *FGFR1*, -2, -3, and -4 (Turner & Grose 2010), located on chromosomes 8p12, 10q26, 4p16.3, and 5q35.1-qter respectively. All FGFRs contain an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase (TK) domain (Eswarakumar *et al.*, 2005). The extracellular domain has three immunoglobulin (Ig)-like domains (IgI–III, Fig. 1). The second and third Ig domains are responsible for binding the FGF ligand (Beenken & Mohammadi 2009). The FGF family of secreted glycoproteins consists of 18 members. The different FGFs and their corresponding receptors are expressed in a tissue-specific way. This tissue-specific expression pattern and the differences in binding affinity contribute to the specificity of the ligand–receptor interaction (Eswarakumar *et al.*, 2005, Turner & Grose 2010). Furthermore, this specificity is also regulated by splicing. *FGFR1*, -2, and -3 have two splice variants of the IgIII domain, resulting in IIIb and IIIc isoforms. The IIIb isoform is present on the epithelial cells and IIIc is expressed by mesenchymal cells (Beenken & Mohammadi 2009).

FGFs are released from the extracellular matrix (ECM) by heparins, proteases, or specific FGF-binding proteins. FGFs bind FGFRs and form a stable structure together with heparin sulfate proteoglycans on the cell surface (Harmer *et al.*, 2004, Mohammadi *et al.*, 2005, Turner & Grose 2010). Klotho family proteins also facilitate the FGF–FGFR interaction (Wu *et al.*, 1991, Kurosu *et al.*, 2006) by binding to FGFRs and increasing the affinity of FGF for its receptor, thus

**Figure 1** FGF–FGFR structure and downstream signaling. The extracellular domain of FGFRs consists of three ligand-binding Ig domains. Binding of the ligand is stabilized by HSPG and Klotho. Intracellular tyrosine kinase domains (TK) are present. Upon ligand binding, the receptors dimerize, resulting in cross-phosphorylation of the tyrosine kinase domains. This leads to binding of several docking proteins, which can also be phosphorylated. Downstream signaling occurs through four main pathways: PLCγ, STATs, AKT, and MAPK. FGF, fibroblast growth factor; HSPG, heparin sulfate proteoglycans; TK, tyrosine kinase domain; STAT, signal transducer and activator of transcription; FRS2α, fibroblast growth factor receptor substrate 2α; GRB2, growth factor receptor-bound protein 2; GAB1, GRB2-associated binding protein 1; PI3K, phosphoinositide-3 kinase; AKT, v-akt murine thymoma viral oncogene; SOS, son of sevenless; RAS, rat sarcoma; MAPK, mitogen-activated protein kinase; PLCγ, phospholipase Cγ; PI2, phosphatidylinositol 4,5-biphosphate; IP3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PKC, protein kinase C.
resulting in increased receptor activation (Kurosu et al. 2006). Each FGFR isoform can bind multiple FGF ligands and some ligands are common to several receptors (Eswarakumar et al. 2005).

Ligand binding results in FGFR dimerization and subsequent activation of the intracellular kinase domain, leading to cross-phosphorylation of tyrosine residues present on the intracellular tail of the receptor (Turner & Grose 2010). Several docking proteins are able to bind to these phosphorylated residues, resulting in their phosphorylation and subsequent activation. Major pathways downstream of activated FGFRs include the rat sarcoma mitogen-activated protein kinase (RAS–MAPK) pathway and the phosphoinositide-3 kinase v-akt murine thymoma viral oncogene (PI3K (PIK3CA)–AKT (AKT1)) pathway whose kinase activity is mediated via FGFR substrate 2 (FRS2) and several other adaptor molecules. Furthermore, protein kinase C is activated via phospholipase Cγ (PLCγ (PLCG)), and finally activation of signal transducer and activator of transcription (STAT) signaling can take place (Acevedo et al. 2009, Turner & Grose 2010; Fig. 1).

All these pathways play an important role in cell proliferation, differentiation, inhibition of apoptosis, and migration. In addition, FGFR signaling is involved in angiogenesis and wound repair (Eswarakumar et al. 2005, Turner & Grose 2010). Downstream effector activation is cell type specific and may be dependent on cross talk with other signaling pathways (Dailey et al. 2005). Although different FGFRs signal via similar pathways, differences in downstream effector activation have been described. Activation of downstream targets by FGFR4 is less strong than FGFR1 (Vainikka et al. 1994), and FGFR1 signaling sustains longer than FGFR2 because of faster degradation of FGFR2 after activation (Xian et al. 2007). Finally, even though FGFR isoforms have some specificity for different FGF ligands (Eswarakumar et al. 2005), no conclusive evidence has been found that specific FGFs activate specific downstream pathways (Dailey et al. 2005).

**Aberrations in FGFRs found in breast cancer**

Deregulation of FGFR activity could contribute to cancer development by increasing cell proliferation, angiogenesis, and inhibiting apoptosis. Genetic aberrations in FGFRs have indeed been found to be associated with breast cancer and are described below.

**FGFR1**

No germ-line mutations in *FGFR1* have been identified to date. However, a somatic mutation (*K566R*) was found in a sample from a patient with basal-like, triple-negative breast cancer (Kan et al. 2010). Whether this mutation is present in other breast cancer patients remains to be investigated. Furthermore, a *S125L* mutation was described in a ductal breast carcinoma cell line (HCC1395; Stephens et al. 2005, Greenman et al. 2007). However, whether these mutations have consequences for FGFR1 function and its role is in breast cancer development and/or progression have not been investigated.

Several studies have identified amplifications of *FGFR1* in breast cancer (Chin et al. 2006, Letessier et al. 2006, Reis-Filho et al. 2006, Elbauomy Elsheikh et al. 2007, Marchio et al. 2008, Andre et al. 2009, Kadota et al. 2009, Moelans et al. 2010; Table 1). The percentage of *FGFR1* amplifications found using different techniques ranges from 7.5 to 17%. This variability could be caused by differences between tumor samples, which were not selected for histopathological type or clinical parameters. Furthermore, each study used a different technique to assess the copy number alterations, which can also account for the

<table>
<thead>
<tr>
<th>Breast cancer cases (n)</th>
<th>Technique, whole genome/gene specific</th>
<th>Results: <em>FGFR1</em> amplification/loss</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
<td>aCGH: 70 kb interval, whole genome</td>
<td>Highly amplified in 10%</td>
<td>Andre et al. (2009)</td>
</tr>
<tr>
<td>161</td>
<td>SNP DNA microarray, whole genome</td>
<td>Amplified in 7.5%</td>
<td>Kadota et al. (2009)</td>
</tr>
<tr>
<td>1319</td>
<td>FISH, gene specific</td>
<td>Amplified in 9.4%</td>
<td>Letessier et al. (2006)</td>
</tr>
<tr>
<td>496</td>
<td>CISH, gene specific</td>
<td>Amplified in 8.7%</td>
<td>Elbauomy Elsheikh et al. (2007)</td>
</tr>
<tr>
<td>104</td>
<td>MLPA, gene specific</td>
<td>Amplified in 17% (7%; highly amplified)</td>
<td>Moelans et al. (2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lost in 10%</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>CISH, gene specific</td>
<td>Amplified in 16.6%</td>
<td>Marchio et al. (2008)</td>
</tr>
</tbody>
</table>

aCGH, array comparative genome hybridization; FISH, fluorescent *in situ* hybridization; CISH, chromogenic *in situ* hybridization; MLPA, multiplex ligation-dependent probe amplification.
discrepancies in the results. Microarray expression analyses showed that FGFR1 amplifications were associated with increased FGFR1 RNA expression (Chin et al. 2006, Andre et al. 2009).

Several studies have described that FGFR1 amplifications were not associated with some pathological characteristics (Table 2). Associations with proliferation and HER2 status are inconsistent between studies, possibly due to differences in techniques. Proliferation was estimated by assessing the percentage of Ki-67-positive cells (Letessier et al. 2006) or the mitotic activity index (Moelans et al. 2010), and HER2 expression was also evaluated in different ways (Letessier et al. 2006, Elbauomy Elsheikh et al. 2007, Kadota et al. 2009, Moelans et al. 2010). Even though estrogen receptor (ER) and progesterone receptor (PR) statuses were assessed in the same way in the different studies, the correlations with FGFR1 amplification were inconsistent. Confounder effects by clinical or pathological parameters could provide an explanation for the differences in association between expression of these hormone receptors and FGFR1 amplification.

In addition to pathological features, association analysis of FGFR1 amplification with clinical outcome has also been performed (Table 2). Patients with an FGFR1 amplification were more likely to develop distant metastases (Elbauomy Elsheikh et al. 2007). In addition, a trend for FGFR1 amplification and a shorter disease-free survival (DFS) was observed. Finally, amplification of FGFR1 was significantly

Table 2 Association of FGFR1 amplification in unselected cohorts with clinical and pathological parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Association: yes/no</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of distant metastasis</td>
<td>Yes: positive association</td>
<td>Elbauomy Elsheikh et al. (2007)</td>
</tr>
<tr>
<td>Grade</td>
<td>No</td>
<td>Letessier et al. (2006), Elbauomy Elsheikh et al. (2007), and Moelans et al. (2010)</td>
</tr>
<tr>
<td>Tumor size</td>
<td>No</td>
<td>Letessier et al. (2006), Elbauomy Elsheikh et al. (2007), and Moelans et al. (2010)</td>
</tr>
<tr>
<td>Histopathological type</td>
<td>No</td>
<td>Letessier et al. (2006), Kadota et al. (2009), and Moelans et al. (2010)</td>
</tr>
<tr>
<td>Lymph node invasion</td>
<td>No</td>
<td>Letessier et al. (2006), Elbauomy Elsheikh et al. (2007), and Kadota et al. (2009)</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>No</td>
<td>Letessier et al. (2006) and Moelans et al. (2010)</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>No</td>
<td>Elbauomy Elsheikh et al. (2007) and Kadota et al. (2009)</td>
</tr>
<tr>
<td>Molecular subtypes (basal-like, luminal A/B, ERBB2-positive, normal-like)</td>
<td>No</td>
<td>Letessier et al. (2006) and Moelans et al. (2010)</td>
</tr>
<tr>
<td>PS3 status</td>
<td>No</td>
<td>Letessier et al. (2006)</td>
</tr>
<tr>
<td>EGFR status</td>
<td>No</td>
<td>Elbauomy Elsheikh et al. (2007)</td>
</tr>
<tr>
<td>Expression of low- and high-molecular weight cytokeratins</td>
<td>No</td>
<td>Elbauomy Elsheikh et al. (2007)</td>
</tr>
<tr>
<td>Androgen receptor status</td>
<td>No</td>
<td>Elbauomy Elsheikh et al. (2007)</td>
</tr>
<tr>
<td>Proliferation</td>
<td>No</td>
<td>Elbauomy Elsheikh et al. (2007)</td>
</tr>
<tr>
<td>ER status: positive or negative</td>
<td>Yes: positive association</td>
<td>Letessier et al. (2006)</td>
</tr>
<tr>
<td>PR status: positive or negative</td>
<td>Yes: associated with a positive status</td>
<td>Letessier et al. (2006), Elbauomy Elsheikh et al. (2007), and Kadota et al. (2009)</td>
</tr>
<tr>
<td>Age (&lt;50/≥50)</td>
<td>Yes: trend with a negative status</td>
<td>Letessier et al. (2006) and Moelans et al. (2010)</td>
</tr>
<tr>
<td>HER2 status</td>
<td>Yes: inverse correlation with Her2 overexpression</td>
<td>Elbauomy Elsheikh et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Yes: amplification was positively associated with Her2+ status</td>
<td>Kadota et al. (2009)</td>
</tr>
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</table>

EGFR, epidermal growth factor receptor; ER, estrogen receptor; PR, progesterone receptor.
associated with a shorter overall survival (OS), independent of other prognosticators such as grade, tumor size, lymph node invasion, and ER status. Interestingly, FGFR1 amplification remained a significant independent risk factor for poor DFS and OS in ER-positive but not in ER-negative cases (Elbouamy Elsheikh et al. 2007). This suggests that there may be an interaction between FGFR1 and ER signaling resulting in a poor prognosis. The observation that FGFR1 amplification is associated with a poor prognosis in ER-positive breast cancer was confirmed in a group of ER-positive tumor samples from patients treated with adjuvant endocrine therapy (tamoxifen). In this group, FGFR1 amplification was significantly associated with decreased metastasis-free survival compared with samples with normal FGFR1 levels (Turner et al. 2010b). Finally, two studies showed an association between amplification of 8p11–12 where FGFR1 is located and poor disease outcome. Although these analyses do not specifically show FGFR1 amplification in the breast cancer samples, they support the findings in previous studies (Chin et al. 2006, Letessier et al. 2006).

The function of FGFR1 as an oncogene has been disputed due to the results of functional studies in cell lines carrying 8p11–12 amplifications, which showed that FGFR inhibition did not affect the proliferation (Ray et al. 2004). Several studies have identified other potential oncogenes located on 8p11–12, including PPAPDC1B, RAB11FIP1, LSM1, BAG4, C8ORF4, and WHSC1L1 (Garcia et al. 2005, Gelsi-Boyer et al. 2005, Yang et al. 2006, Bernard-Pierrot et al. 2008). These results do not exclude the possibility of multiple genes in the 8p11–12 region acting as oncogenes, which might even cooperate. In addition to its suggested role as an oncogene, there is some evidence that FGFR1 may have a tumor suppressor function in breast cancer. Loss of FGFR1 was found in 10% of invasive breast cancer samples (Moelans et al. 2010). Another study identified a deletion of 8p11–12 in breast carcinomas, which was shown to be associated with a poor outcome (Chin et al. 2006). However, as this region contains many genes, it is not certain whether poor prognosis can be attributed to the specific loss of FGFR1.

**FGFR2**

So far, only one somatic mutation (R203C) in FGFR2 has been identified in the breast cancer cell line HCC1143 (Stephens et al. 2005, Sjöblom et al. 2006, Greenman et al. 2007). However, several single nucleotide polymorphisms (SNPs) in FGFR2 were found to be highly associated with breast cancer risk and identified FGFR2 as a breast cancer susceptibility gene (Hunter et al. 2007). Four of these SNPs are located in intron 2 of FGFR2. An independent study, using a different panel of SNPs, found an association of another SNP in intron 2 of FGFR2 with breast cancer (Easton et al. 2007). The risk allele of this SNP was significantly associated with a positive ER and PR status and a lower grade (Garcia-Closas et al. 2008). Further analysis of the SNPs located in the second intron of FGFR2 identified a haplotype block of eight SNPs as the minor disease-predisposing allele (Easton et al. 2007, Meyer et al. 2008). This haplotype block is not in linkage disequilibrium with any coding region of FGFR2, excluding a change in protein sequence. Also, when comparing the expression levels of the two most common splicing variations (including or excluding exon 3), no significant difference was observed between the minor and common homozygotes (Meyer et al. 2008). These results indicate that the change in the protein sequence due to the SNPs does not result in a functional difference.

However, when correlating the expression levels of FGFR2 in invasive breast cancer samples with the haplotype of the eight SNPs, mRNA levels of FGFR2 were significantly increased in tumor samples that were homozygous for the minor alleles when compared with samples homozygous for the common alleles (Meyer et al. 2008). This indicates that the risk genotype results in increased expression of FGFR2, which could contribute to the development of breast cancer.

In a genome-wide screen identifying copy number alterations, FGFR2 was found to be amplified in only two (1.2%) out of 161 primary breast cancer samples (Kadota et al. 2009). Other genome-wide screens analyzing large groups of unselected breast cancer samples also showed that FGFR2 is rarely amplified (Adelaide et al. 2007), and others did not find any amplifications or losses of FGFR2 (Andre et al. 2009). However, FGFR2 was amplified in 4% of triple-negative breast cancer samples, whereas no amplification was found in other molecular subtypes. In addition, the mRNA expression levels of FGFR2 were significantly increased in amplified vs nonamplified tumor samples (Turner et al. 2010a), suggesting a potential role for FGFR2 in triple-negative breast cancer. FGFR2 is also suggested to play a role in a subgroup of familial breast cancer patients. When comparing the RNA expression profiles of breast cancer samples of patients with a germ-line mutation in breast cancer 1 and 2 (BRCA1 and -2), FGFR2...
expression was significantly higher in breast cancers of BRCA2 mutation carriers (Bane et al. 2009). Finally, increased FGFR2 protein levels in samples from invasive ductal carcinoma (IDC) patients were found to be associated with lower (disease-free) survival rates (Sun et al. 2011). How FGFR2 is regulated in these and BRCA2-mutated patients and whether it is involved in the development or progression of breast cancer are not clear.

**FGFR3**

Even though activating mutations in FGFR3 have been identified in several cancer types (Cappellen et al. 1999, Sibley et al. 2001, Zhang et al. 2005, Hafner et al. 2006), no FGFR3 mutations have been found in breast cancer (Sibley et al. 2001, Koziczak et al. 2004, Greenman et al. 2007). FGFR3 mutations cause Saethre–Chotzen syndrome, consisting of premature fusion of one or more skull sutures often accompanied by facial asymmetry and fusion of digits (Sahlin et al. 2009). There is one documented case of a Saethre–Chotzen patient with a heterozygous missense mutation in exon 7 of FGFR3 (P250R) who also developed breast cancer. This mutation is located in the ligand-binding domain of FGFR3, which leads to activation of the kinase domain (Sahlin et al. 2009). Moreover, this mutation is located near mutational hot spots found in the bladder and cervical carcinomas (R248C and S249C; Sibley et al. 2001). It is unclear whether the mutation found to cause Saethre–Chotzen syndrome also increases the risk of developing breast cancer; therefore, more studies are required to further elucidate this.

A possible role for FGFR3 in therapy resistance was identified in a group of 429 ER-positive breast cancer patients who received tamoxifen as primary therapy. FGFR3 protein levels were significantly increased in patients who did not respond to the treatment (Tomlinson et al. 2012).

**FGFR4**

A Gly388Arg (Arg^{388}) missense mutation, now known as SNP rs351855, was identified in the transmembrane domain of FGFR4 (Bange et al. 2002). Immunohistochemical analysis of breast cancer samples did not show any correlation of the Arg^{388} SNP genotype with FGFR4 expression levels (Thussbas et al. 2006). Sequence analysis of breast cancer samples revealed that the Arg^{388} genotype, either heterozygous or homozygous, was present in 37–43% and 8–11% respectively (Table 3; Bange et al. 2002, Jezequel et al. 2004, Thussbas et al. 2006, Marme et al. 2010). No significant difference could be identified when comparing the distribution of the Arg^{388} allele in healthy controls and breast cancer patients. This indicates that this SNP is not associated with the initiation of breast cancer (Bange et al. 2002).

Arg^{388} did not correlate with age, HER2, ER and PR status, and grade (Bange et al. 2002, Jezequel et al. 2004, Thussbas et al. 2006, Marme et al. 2010). Correlations were found for tumor stage (Thussbas et al. 2006, Marme et al. 2010), tumor size (Thussbas et al. 2006), and axillary lymph node involvement (Bange et al. 2002, Jezequel et al. 2004, Thussbas et al. 2006, Marme et al. 2010), but not all of these associations were confirmed by other studies (Bange et al. 2002, Jezequel et al. 2004, Thussbas et al. 2006). Finally, when analyzing the DFS period, no correlation was found with the Arg^{388} allele (Bange et al. 2002). However, in primary lymph node-positive patients (N+), DFS was significantly shorter in Arg^{388} than Gly^{388} carriers (Bange et al. 2002, Thussbas et al. 2006). This suggests that Arg^{388} could be a marker for increased tumor aggressiveness in advanced breast cancer. However, another study did not find a significant association of Arg^{388} with DFS in unselected N+ breast cancer cases (Jezequel et al. 2004). Arg^{388} was not associated with DFS in patients who did not receive adjuvant systemic therapy.

**Table 3 FGFR4 Arg^{388} allele distribution in breast cancer patients and healthy controls and associations with clinical or pathological parameters**

<table>
<thead>
<tr>
<th>Cases (n)</th>
<th>Gly/Gly (%)</th>
<th>Gly/Arg (%)</th>
<th>Arg/Arg (%)</th>
<th>Correlations with Arg allele</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls (n=123)</td>
<td>45</td>
<td>49</td>
<td>6</td>
<td>Axillary lymph node involvement</td>
<td>Bange et al. (2002)</td>
</tr>
<tr>
<td>145</td>
<td>46</td>
<td>43</td>
<td>11</td>
<td>Axillary lymph node involvement</td>
<td>Bange et al. (2002)</td>
</tr>
<tr>
<td>234</td>
<td>52</td>
<td>37</td>
<td>11</td>
<td>Axillary lymph node involvement</td>
<td>Jezequel et al. (2004)</td>
</tr>
<tr>
<td>372</td>
<td>49</td>
<td>43</td>
<td>8</td>
<td>Tumor stage, tumor size, axillary lymph node involvement</td>
<td>Thussbas et al. (2006)</td>
</tr>
<tr>
<td>352</td>
<td>46</td>
<td>43</td>
<td>11</td>
<td>Tumor stage, axillary lymph node involvement</td>
<td>Marme et al. (2010)</td>
</tr>
</tbody>
</table>
When adjuvant systemic therapy was used, DFS and OS were shorter in patients carrying one or two Arg^{388} alleles, making it a possible marker for therapy resistance in this patient group (Thussbas et al. 2006).

Interestingly, in patients who received neoadjuvant chemotherapy, the Arg^{388} allele was significantly and independently associated with a better clinical and pathological response (Marme et al. 2010).

In addition to the Arg^{388} germ-line mutation, a somatic mutation (V510M) in FGFR4 was identified in a tumor sample from a lobular carcinoma patient (Stephens et al. 2005, Greenman et al. 2007). This mutation has not been found in other (breast) cancer patients to date, making its significance unclear.

Amplification of FGFR4 has been reported in breast cancer samples. In a small study, 10% of breast tumors had FGFR4 amplifications, which were associated with ER and PR positivity and lymph node metastases (Jaakkola et al. 1993). Furthermore, FGFR4 mRNA levels were elevated in 32% of breast cancer samples (Penault-Llorca et al. 1995). In a retrospective study analyzing ER-positive breast cancers from patients treated with neoadjuvant tamoxifen, high levels of FGFR4 were independently associated with tumor response and survival after treatment (Meijer et al. 2008).

Molecular implications of genetic aberrations in FGFRs on tumor characteristics

As described earlier, genetic aberrations in FGFRs have been shown to contribute to breast cancer risk, tumor progression, and response to therapy. These different outcomes can be due to the fact that FGFRs signal through downstream signaling pathways whose activation depends on several factors. The *in vitro* and *in vivo* studies described below give more insight into the functional effects of abnormal FGFR signaling.

**FGFR1**

Inducible activation of *Fgfr1* (*iFgfr1*) in transgenic mice resulted in increased cell proliferation in the lateral buds and ductal branching of the mammary epithelium (Welm et al. 2002). Furthermore, there was recruitment of macrophages, which are required for lateral bud formation and also play a role in the formation of small blood vessels (Schwertfeger et al. 2006) through the production of interleukin 1β (Reed et al. 2009). After sustained induction of FGFR1, epithelial cells further proliferated, forming multicellular lesions that eventually became invasive. These invasive lesions were characterized by loss of cell polarity, cell detachment from the basement membrane, and anoikis resistance. Finally, the invasive lesions in *iFgfr1* transgenic mice were surrounded by an increased number of highly branched small blood vessels (Welm et al. 2002).

The observed changes in the breast epithelium of *iFgfr1* mice were recapitulated in 3D cultures of HC11 and MCF10A cells transfected with inducible FGFR1 (Welm et al. 2002, Xian et al. 2005, 2009). These models have shown that the induction of *Fgfr1* expression results in epithelial to mesenchymal transition.

The molecular downstream targets that are activated upon induction of iFGFR1 include ribosomal protein S6 kinase (RSK (RPS6KA1)), the PI3K–Akt pathway, and the MAPK–ERK pathway (Welm et al. 2002, Xian et al. 2005, 2009). Target genes activated by FGFR1 include several clusters that are linked to tumor formation through angiogenesis, cell cycle regulation, chemotaxis, and the response to inflammation (Schwertfeger et al. 2006).

Activation of FGFR1 does not only affect the characteristics of epithelial cells but also influences the myoepithelium and microenvironment. Long-term activation of FGFR1 in transgenic mice resulted in a disruption of the myoepithelial cell barrier and ECM disorganization (Welm et al. 2002).

Activation of FGFR1 signaling using a small amount of FGFR2 in the MDA-MB-134, CAL120, JIMT-1, MFM223, S68, SUM44 (Turner et al. 2010b), CMA, MDA-MB-361, and HCC38 (Shiang et al. 2010) cell lines, which have endogenous *FGFR1* amplifications, resulted in downstream activation of multiple pathways, including FRS2, ERK1/2 (MAPK3/1), and RSK phosphorylation. A different study showed that these pathways were already basally activated without ligand (Turner et al. 2010b). Also, cells harboring *FGFR1* amplifications seem to have an oncogenic addiction to FGFR1 signaling as they are highly sensitive to inhibition of FGFR1 by siRNA or SU5402, an FGFR1 TK inhibitor (TKI; Reis-Filho et al. 2006). Furthermore, *FGFR1*-amplified cell lines were resistant to treatment with 4-hydroxytamoxifen (4-OHT), suggesting that *FGFR1* amplification is involved in resistance to endocrine therapy (Turner et al. 2010b). This notion supports the observation that amplification of *FGFR1* is associated with a poor prognosis in ER-positive patients that were treated with tamoxifen as an adjuvant endocrine therapy. Interestingly, inhibition of *FGFR1* by siRNA increased the sensitivity of *FGFR1*-amplified cell lines to 4-OHT, making this a possible drug therapy (Turner et al. 2010b).
Another indication for interacting pathways comes from the mouse mammary tumor virus–wingless type 1 (MMTV–Wnt1) mouse model. Crossing these mice with Ifgfr1 transgenic mice and subsequent activation of FGFR1 dramatically accelerated tumor formation, suggesting an interaction between FGFR1 and WNT (WNT) signaling (Pond et al. 2010). Further experiments are needed to explore whether genetic aberrations in FGFRs affect tumor formation in other mouse mammary tumor models harboring mutations in oncogenes that frequently occur in breast cancer patients.

**FGFR2**

The FGFR2-amplified SUM52PE and MFM223 cell lines depend on FGFR2 signaling for survival. This addiction to FGFR2 is due to activation of the PI3K–AKT signaling pathway that results in inhibition of apoptosis. Furthermore, downstream targets of FGFR signaling like FRS2, AKT, and ERK were phosphorylated in the absence of serum and inactivated by an FGFR inhibitor. This indicates that the phosphorylation of these targets is independent of ligand binding and is dependent on FGFR kinase activity. In contrast, the HCC1143 cell line, in which a mutation in FGFR2 is due to activation of the PI3K–AKT signaling pathway that results in inhibition of apoptosis. Furthermore, downstream targets of FGFR signaling like FRS2, AKT, and ERK were phosphorylated in the absence of serum and inactivated by an FGFR inhibitor. This indicates that the phosphorylation of these targets is independent of ligand binding and is dependent on FGFR kinase activity. In contrast, the HCC1143 cell line, in which a mutation in FGFR2 has been described, showed no evidence of FGFR-dependent signaling and is not dependent on FGFR for proliferation (Turner et al. 2010a).

As described earlier, SNPs in intron 2 of FGFR2 correlate with higher FGFR2 mRNA expression levels (Meyer et al. 2008). As the sequence of intron 2 includes a regulatory region, SNPs could alter one or more transcription factor binding sites, thereby regulating the expression levels of FGFR2 (Easton et al. 2007). The SNPs rs35054928 and rs2981578 are located next to an organic cation transporter (OCT)-binding site. The risk allele of rs2981578 also creates a putative binding site for runt-related transcription factor (RUNX) and the risk allele of rs10736303 one for ER (Katoh & Katoh 2009). The risk allele of rs7895676 has reduced binding capacity to CCAAT/enhancer binding protein β (C/EBPβ (CEBPB)). Whereas the rs2981578 variants have equal affinity for OCT1 (POU2F1), the high-risk allele has much higher affinity for RUNX2 (Meyer et al. 2008), thought to be due to differences in H3/H4 acetylation of the SNP sites (Zhu et al. 2009). Overall, the differences in binding affinity result in a higher expression of FGFR2 in cell lines carrying the high-risk alleles. This is in accordance with the increased expression levels of FGFR2 in breast cancer samples that were homozygous for the high-risk alleles (Meyer et al. 2008). Remarkably, ER binding was not altered for any of the SNPs, whereas the increased risk for breast cancer due to the high-risk alleles of FGFR2 are highly associated with ER-positive tumors (Garcia-Closas et al. 2008). A possible explanation for this association is that ER and OCT1/RUNX may cooperate to increase the expression of FGFR2 (Meyer et al. 2008), which is supported by the finding that OCT and ER sites often cluster together (Carroll et al. 2006). The exact role of ER in the FGFR2 allele resulting in increased breast cancer risk remains to be investigated.

**FGFR3**

MCF7 cells were used to study the molecular mechanisms behind the involvement of FGFR3 in tamoxifen resistance in ER-positive breast cancer. Inducible activation of FGFR3 decreased the sensitivity of MCF7 cells to 4-OHT treatment independent of ER activity. Activation of PLCγ1 (PLCG1) was essential for this resistance phenotype and downstream activation of PI3K signaling was an important component of this reduced sensitivity to endocrine therapy (Tomlinson et al. 2012).

**FGFR4**

The poor response to chemotherapy associated with overexpression of FGFR4 (Meijer et al. 2008) has been recapitulated in several FGFR4 overexpressing breast cancer cell lines, which are resistant to doxorubicin and cyclophosphamide (Roidl et al. 2009). FGFR4 contributes to this resistance by activating antiapoptotic signaling via activation of MAPK and subsequent increase in the B-cell lymphoma-extra large (BCL-XL) levels. In accordance with this, inhibition of FGFR4 reduced ERK phosphorylation and decreased levels of BCL-XL, ultimately leading to increased chemosensitivity to drugs (Roidl et al. 2009).

The Arg388 SNP in FGFR4 affects its structure, but TK activity was not increased in breast cancer cells expressing this FGFR variant (Bange et al. 2002). This suggests that FGFR4-mediated resistance to chemotherapy may not be due to increased kinase activity of the receptor. Interestingly, Gly388-expressing cells are less invasive compared with Arg388-expressing cells or cells that have no endogenous FGFR4 expression (Stadler et al. 2006). This indicates that the Gly388 allele protects patients from tumor invasion, which is consistent with a better prognosis (Bange et al. 2002). The kinase domain was proven to be essential for this protective effect (Stadler et al. 2006), suggesting that downstream signaling plays an important role. Gene expression analysis revealed...
upregulation of the lysophosphatidic acid (LPA) receptor gene (EDG2 (LPARI)), matrix metalloproteinase 1 (MMP1), and downregulation of plasminogen activator inhibitor (PAI1 (SERPINE1)) in Arg388 compared with Gly388-expressing cells, possibly contributing to increased cell motility and invasion. EDG2 induces cell migration by activation of PI3 and AKT upon binding of the LPA ligand, which is consistent with increased cell motility in cells expressing Arg388. The observed upregulation of MMP1 in Arg388-expressing cells may contribute to increased invasion due to increased degradation of the ECM (Stadler et al. 2006). PAI1 has been shown to inhibit urokinase plasminogen activator (uPA) resulting in a decrease in migration and invasion. In addition, upregulation of uPA sensitizes the Arg388-expressing cells to chemotherapy-induced apoptosis (Whitley et al. 2004). All these (indirect) downstream targets of the Arg388FGFR4 variant seem to increase tumor invasion and decrease sensitivity to chemotherapy, explaining the worse clinical prognosis of Arg388 carriers (Bange et al. 2002, Thussbas et al. 2006).

Decreased invasion and no change in proliferative capacity of Gly388-expressing breast cancer cells was also observed in the whey acidic protein—transforming growth factor α (WAP–TGFα) breast cancer mouse model in which either the Arg385 or Gly385 allele (the mouse equivalents of the human 388 alleles) was knocked in. The tumors of the mice carrying the Arg385 allele were more invasive than in their Gly385 littermates due to increased migration (Seitzer et al. 2010).

In addition to increased invasion, WAP–TGFα mice carrying the Arg385 allele also developed highly proliferative lung metastases. Genes suggested to contribute to this effect are cyclin-dependent kinase (CDK) inhibitor 1A (p21), which is downregulated in Arg385 tumor samples and CDK1, FLK1 (KDR; fetal liver kinase-1), CD44, MMP13, and MMP14, which are upregulated in the Arg385 tumors and are involved in cell invasion (Seitzer et al. 2010). Interestingly, the involvement of MMPs in Arg388-mediated tumor progression has also been suggested in breast cancer patients (Sugiyama et al. 2010a,b).

**Therapeutic targets and drugs in development**

Based on the genetic aberrations in FGFRs identified in breast cancer patients and their consequences on a molecular level, several approaches can be used to target FGFR signaling.

**Upstream intervention**

As described earlier, cell lines with FGFR1 amplifications and overexpression have low levels of downstream signaling in the absence of ligand. However, ligand binding strongly induces downstream activation, making inhibition of ligand–receptor interaction a useful approach to inhibit FGFR1 signaling. In FGFR2-amplified cell lines, downstream signaling is ligand independent. Whether the presence of a ligand increases signaling, making ligand interference a useful target, is yet unclear. For patients overexpressing FGFR4, the dependence on ligand binding has yet to be investigated in more detail to determine whether it is useful to target ligand binding.

A possible method to inhibit ligand binding is by designing FGF ligand traps such as FP-1039 (Turner & Grose 2010); a fusion protein comprising the extracellular domain of FGFR1 and the Fc region of IgG. FP-1039 has been shown to have antiangiogenic effects in vivo. Moreover, FP-1039 was able to block tumor formation of breast cancer cell line xenografts, depending on their expression of FGFs and FGFRs (Zhang et al. 2007). FP-1039 is currently being tested in a phase I clinical trial (Keer 2010). Furthermore, as the FGFRs have several ligands in common, not only FGFR1 activation but also activation of FGFR3 and FGFR4 is blocked by binding of FP-1039 to FGFs (Zhang et al. 2007), making FP-1039 a rather universal blocker of FGFR signaling.

A second method to interfere with ligand binding is the use of antagonistic peptide mimics. These could be effective drugs for patients harboring FGFR amplifications that depend on the presence of a ligand to induce signaling. However, at present, only agonistic peptide mimics have been designed for FGFR1-IIIc and FGFR2-IIIb. These were proven to be functional FGFR agonists with apparent therapeutic potential (Li et al. 2008).

**Intervention on the FGFR level**

Several methods can be used to target the FGFRs at the receptor level. First of all, numerous TKIs targeting FGFRs have been developed. These small molecules compete with ATP to bind to the receptor resulting in reduced activity of the kinase domain (Katoh & Katoh 2009, Turner & Grose 2010). However, as the kinase domains of RTKs are very similar, most TKIs are not specific for one FGFR and also inhibit the activity of VEGFRs and/or PDGFRs (Turner & Grose 2010). This may in fact increase their activity in cancer patients but perhaps cause more side effects. Brivanib alinate is an example of a TKI targeting both FGFRs and VEGFRs. Its effect in breast cancer has so far only been
tested *in vitro*: cell lines with FGFR1 amplification/overexpression are more sensitive than nonamplified ones (Marme *et al.* 2010). The effect of this drug on other FGFRs and in patients remains to be investigated.

Another multitarget drug is dovitinib, an inhibitor of FGFRs, PDGFRs, and VEGFRs. This TKI was tested in a phase II clinical trial (NCT00958971) including HER2-negative breast cancer patients and only showed antitumor activity in patients with an FGFR1 amplification and an ER- and/or PR-positive status, whereas other subgroups only showed stabilization of tumor growth (Andre *et al.* 2011). Another phase II trial (NCT01262027) with dovitinib has been started to control inflammatory breast cancer and also evaluate the safety of this drug. E-3810 is a multitarget small-molecule inhibitor targeting VEGFRs and FGFR1, which is currently being tested in a phase I clinical trial. After initial testing in patients with solid tumors, breast cancer patients with *FGFR1* amplifications are included in the dose expansion phase to obtain preliminary data on the antitumor activity of this drug (clinical trial: NCT01283945). Finally, BIBF1120 was developed as a kinase inhibitor targeting FGFRs, PDGFRs, and VEGFRs. Testing of this drug in multiple cancer mouse models and clinical trials including different cancer types has already been shown to be successful (Hilberg *et al.* 2008, Antoniu & Kolb 2010). A phase I/II clinical trial (NCT01484080) is currently investigating its efficacy in combination with paclitaxel (a mitotic inhibitor used to treat several types of cancer) in patients with early HER2-negative breast cancer.

PD173074 and SU5402 are the first compounds that have been designed as FGFR-specific TKIs. PD173074 was effective in ER-, PR-, and HER2-negative cell lines with *FGFR2* amplification/overexpression (Turner *et al.* 2010a). SU5402 decreased proliferation exclusively in cell lines with *FGFR1* amplification and overexpression (Reis-Filho *et al.* 2006). It must be noted, however, that not every cell line with *FGFR1* amplifications is sensitive to FGFR1 inhibition, which was found to depend on the oncogenic background (Reis-Filho *et al.* 2006). In this regard, further *in vitro* and *in vivo* studies will have to be performed in order to identify the right subgroup among patients with *FGFR1* amplification and overexpression who will respond to FGFR-specific drugs.

The efficacy and safety of AZD4547, a TKI that targets FGFRs, are currently being tested in a phase IIa clinical trial (NCT01202591). The patients included are ER positive and have *FGFR1* polysomy or gene amplification and are also treated with exemestane, an aromatase inhibitor used to treat ER-positive breast cancer (Lintermans *et al.* 2011). Another pan-FGFR inhibitor (BGJ398) is also currently being tested in a phase 1 clinical trial to determine the maximum tolerated dose (clinical trial NCT01004224). This trial includes patients with solid tumors with *FGFR1* or -2 amplifications or *FGFR3* mutations.

Monoclonal antibodies may be a good solution to circumvent the side effects of unspecific TKIs. There are FGFR1-IIIc- and FGFR3-specific antibodies that have not yet been tested in any breast cancer model (Turner & Grose 2010). An anti-FGFR4 antibody (10F10) strongly increased sensitivity to doxorubicin in cell lines naturally overexpressing *FGFR4* (Roidl *et al.* 2009).

Another potentially highly specific way to target FGFRs is by RNA aptamers. These short RNA oligonucleotides are selected for their high affinity and specificity for their target protein, thereby acting as synthetic antibodies (Ireson & Kelland 2006). Currently, RNA aptamers that target the *FGFR2* kinase domain, the *FRS2* interacting domain, and the extracellular domain of *FGFR2* are being developed, but their effectiveness remains to be tested (Katoh & Katoh 2009). Therapeutic strategies using siRNA or miRNA are still in a very early stage of development focusing on off-target effects and delivery (Katoh & Katoh 2009).

**Downstream intervention**

Many of the proteins involved in FGFR signaling also play a role in other signaling pathways and in healthy cells. This makes it very difficult to target these proteins without side effects. No extensive research has been performed on targeting the downstream effectors of FGFR signaling. The targets suggested below are therefore mostly hypothetical, whereas for some, preliminary data are present.

In FGFR1-transfected MCF10A cells, treatment with chloromethylketone (CMK), an irreversible small molecule inhibitor specific for RSK (Cohen *et al.* 2005), reduced proliferation and restored sensitivity to anoikis (Xian *et al.* 2009). Interestingly, the inhibitory effect of CMK was only observed in breast cancer cell lines overexpressing *FGFR1* (Xian *et al.* 2009). The effect of CMK in *vivo* remains to be investigated.

MMPs could also be possible drug targets downstream of FGFR1. Inhibition of MMPs in HC11 cells overexpressing *FGFR1* with a pan-MMP inhibitor (GM6001) resulted in decreased invasion and epithelial mesenchymal transition (EMT), although proliferation, apoptosis, and cell polarity were not changed (Xian *et al.* 2005). This indicates that inhibition of MMP activity may not suffice as mono...
treatment but could be useful when used in combination with other drugs.

PI3 kinase is a possible drug target for patients with FGFR2 amplifications, as FGFR2-amplified cell lines are dependent on PI3K-mediated inhibition apoptosis for their survival. This idea is supported by a study in FGFR2-amplified cell lines, which found that dual targeting of FGFR2 and PI3 kinase by PD173074 and BEZ235 (a PI3 kinase/mTOR inhibitor), respectively, was very effective (Adelaide et al. 2007). As PI3K signaling is also suggested to be important in FGFR3-mediated resistance to tamoxifen, the inhibition of this pathway could also be a potential treatment for this group of patients.

In patients with FGFR4 overexpression, targeting the antiapoptotic pathway that activates BCL-XL via MAPK might be a possibility. As these proteins have been shown to mediate chemotherapy resistance in this group of patients, drugs targeting them could increase the response rate. No clinical studies in this field have been performed so far, but administration of UO126 (a specific MEK inhibitor) to FGFR4-expressing breast cancer cells has been shown to decrease BCL-XL expression (Roidl et al. 2009). In addition to a broad panel of MEK inhibitors that have been developed to treat different types of cancer (Fremin & Meloche 2010), BCL-XL inhibitors are also available for clinical research (Kang & Reynolds 2009).

As the FGFR4-Arg388 polymorphism does not result in increased TK activity (Bange et al. 2002), drugs interfering with ligand binding or the TK activity of the receptor are unsuitable for treating FGFR4-Arg388 breast cancer patients. However, as described earlier, numerous downstream effectors of FGFR4 play a role in the increased migration capacity of Arg388-expressing cells. Interference with any of these molecules could be a potential therapeutic strategy for breast cancer patients harboring the Arg388 allele. This is supported by the observation that siRNA targeting EDG2 significantly reduces the migration of cells carrying the Arg388FGFR4 allele (Stadler et al. 2006).

In general, when targeting FGFR signaling, its role in proliferation, differentiation, migration, and angiogenesis should be kept in mind. Interfering in these important basic processes could have many side effects. Further investigation of the context-dependent activation of downstream pathways is necessary to anticipate these side effects.

**Conclusion**

In the past decade, our understanding of the important role of FGFRs in breast cancer has been growing. Genetic aberrationsTcharrsid10362901 in different FGFRs have been identified in subgroups of breast cancer patients, and their (molecular) implications on tumor characteristics have been partly elucidated. Overall, it is very clear that FGFRs are promising drug targets. FGFR2 amplifications could be a very interesting drug target in triple-negative breast cancer patients, as other targeted therapies are not effective. Although several mutations in FGFR3 have been found in other types of cancer and its overexpression has been associated with endocrine resistance, genetic aberrations affecting FGFR3 have not been identified in breast cancer patients (Sibley et al. 2001). Future experiments should be focused on the molecular mechanism behind the increased breast cancer risk associated with the SNPs in intron 2 of FGFR2, especially addressing the role of ER. Some contradicting results regarding the involvement of the Arg388FGFR4 allele in the prognosis and therapy resistance of breast cancer patients should be clarified by large-scale studies in which the clinical and pathological parameters are monitored closely. Furthermore, the FGFR1 gene amplification observed that several different types of breast cancer make it a very relevant drug target. As the inducible FGFR1 models have greatly increased the understanding about its molecular mechanism, the next step should be to screen for possible drugs. Interestingly, in contrast to FGFR1, expression of FGFR2 did not induce neoplasia in the prostate (Freeman et al. 2003), suggesting that FGFR1 is more oncogenic than FGFR2. However, whether this is also the case in mammary tissue or this oncogenic potency is an issue of context remains to be investigated.

Several FGFR-targeting strategies are in different phases of development. In addition to the drugs described earlier, several other compounds targeting FGFRs are being tested on other types of cancer, including urothelial carcinoma, non-small-cell lung cancer, and ovarian cancer (Katoh & Katoh 2009, Antoniu & Kolb 2010, Turner & Grose 2010, Bello et al. 2011, Lamont et al. 2011). Even though most of these drugs are not specific for FGFRs, but also target PDGFRs and VEGFRs, this might actually be an advantage as these RTKs are known for their roles in tumor angiogenesis and proliferation (Petrelli & Giordano 2008). Likely, further refinements in FGFR-targeting drugs will be necessary to increase effectiveness and limit side effects. At the same time, translational studies need to identify the subgroup of breast cancer patients that will best respond to the various FGFR-targeted therapies.
Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

Funding
Supported by unrestricted educational grants from Aegon, Inc. and Pink Ribbon, The Netherlands.

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