Beyond VEGF: Inhibition of the Fibroblast Growth Factor Pathway and Antiangiogenesis

Christopher Lieu1, John Heymach2, Michael Overman1, Hai Tran2, and Scott Kopetz1

Abstract
Fibroblast growth factor (FGF) signaling regulates cell proliferation, differentiation, survival, angiogenesis, and wound healing. Compelling evidence for deregulated FGF signaling in tumorigenesis continues to emerge, and a growing body of research suggests that FGF may also play an integral role in the resistance to anti-VEGF therapy. Although agents targeting FGF signaling are early in development, the potential to target both the VEGF and FGF pathways may translate into improvements in the clinical care of cancer patients. Clin Cancer Res; 17(19); 6130–9. ©2011 AACR.

Introduction
Fibroblast growth factors (FGF) belong to a structurally related family of 22 molecules that interact with high-affinity tyrosine kinase FGF receptors (FGFR) to regulate multiple fundamental pathways and cellular behaviors (1). FGF signaling regulates events in embryonal development, including mesenchymal–epithelial signaling and the development of multiple organ systems (2, 3). FGF signaling also regulates cell proliferation, differentiation, and survival, as well as angiogenesis and wound healing (4). In some situations, FGFs can act as a negative regulator of proliferation and positive regulator of differentiation (5). Given the role of FGF in multiple cellular processes, compelling evidence for deregulated FGF signaling in tumorigenesis continues to emerge (6). Studies with animal models have suggested that aberrant FGF signaling can promote tumor development through increased cell proliferation and survival, as well as increased tumor angiogenesis (7, 8). This body of research indicates that FGF signaling is an important pathway in tumorigenesis and tumor angiogenesis and that appropriate targeting of the FGFR tyrosine kinases may be an effective therapeutic intervention for cancer.

This review describes the FGF family of growth factors and their associated receptors, as well as their association with tumor development, growth, and metastasis. We also describe the effect of FGFs on tumor angiogenesis, including key preclinical and clinical evidence about the role of FGFs in the development of resistance to anti-VEGF therapy. Finally, FGF as a potential therapeutic target is reviewed, including the current state of drug development in this field.

Fibroblast Growth Factor Family

FGFs were first isolated as mitogens from pituitary extracts and bovine brain tissue in the 1970s (9, 10). Since initial discovery, 22 members of the FGF family have been identified, all of which are structurally related signaling molecules ranging from 17 to 34 kDa in size (11). Some FGFs seem to be expressed exclusively during embryonic development (FGF-3, 4, 8, 15, 17, and 19), and others are expressed in both embryonic and adult tissues (FGF-1, 2, 5–7, 9–14, 16, 18, and 20–23; ref. 11).

FGFs are structurally similar to one another, with 28 highly conserved and 6 identical amino acid residues (12). Most FGFs are secreted glycoproteins (FGF-3–8, 10, 15, 17–19, and 21–23), but FGF-1 and FGF-2 are exported from cells by mechanisms that remain unclear. FGF-1 and FGF-2 may be released from damaged cells or by exocytosis that is independent of the endoplasmic reticulum–Golgi pathway (13). FGFs have strong affinities for the glycosaminoglycan side chains of cell surface proteoglycans, which help to sequester FGFs on the surface of the secreting cell or on nearby cells, and in the binding of FGF to the FGFR.

FGFRs are transmembrane tyrosine kinases that contain 2 or 3 extracellular immunoglobulin-like domains and an extracellular heparin-binding sequence (14–16). The 2 proximal immunoglobulin-like extracellular domains bind the FGF ligand, whereas the heparin-binding sequence binds a glycosaminoglycan moiety, resulting in the formation of a complex containing 2 FGFs, 2 FGFRs, and the glycosaminoglycan moiety (17). Only 4 FGFRs are known to exist, designated FGFR-1 through FGFR-4 (Table 1). Their specificity for various ligands is altered by processes that create multiple isoforms. Alternative mRNA splicing of
Translational Relevance

Angiogenic inhibitors have shown promise in the treatment of multiple tumor types and have improved outcomes in patients with metastatic disease. However, many patients will not respond to antiangiogenic therapy, and for those that do, resistance develops quickly. Fibroblast growth factor (FGF) seems to play an integral role in the resistance to antiangiogenic therapy, and agents that specifically target the FGF pathway are being developed and tested in clinical trials. It is critical that investigators review the existing literature on FGF and tumor angiogenesis to understand the importance of this target in various malignancies, as well as to design rational clinical trials that can expedite a potentially meaningful therapy in patients previously treated with antiangiogenic agents.

the FGFR gene significantly alters the ligand specificity by changing the sequence of the carboxy-terminal half of immunoglobulin-domain III. This sequence change results in 2 isoforms termed IIb and IIc (18, 19). In general, IIb isoforms are expressed on epithelial cells, and IIc isoforms are expressed on mesenchymal cells, where they mediate tissue interactions in normal development and wound healing (20–22).

FGF signaling can also be modulated by several membrane proteins, including cell adhesion molecules of the cadherin and immunoglobulin superfamilies (23). The best characterized of these is neural cell adhesion molecule (NCAM). NCAM has been shown to be a major regulator of FGF-FGFR interaction in several cell types, including non-neural tissues (24). NCAM has been shown to act as a nonconventional ligand that can induce a specific FGFR1-mediated cellular migration that is different from the response elicited by FGF-2 (25). Furthermore, NCAM expression has been shown to reduce FGF-stimulated extracellular signal regulated kinase (ERK)1/2 activation, cell proliferation, and cell-matrix adhesion in fibroblast cell lines, suggesting that NCAM acts as a novel control mechanism for FGF signaling (26).

Table 1. Receptors for the FGFR family

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Specific For</th>
</tr>
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<tbody>
<tr>
<td>FGFR-1b</td>
<td>FGF-1, 2, 3, and 10</td>
</tr>
<tr>
<td>FGFR-1c</td>
<td>FGF-1, 2, 4, 5, and 6</td>
</tr>
<tr>
<td>FGFR-2b</td>
<td>FGF-1, 3, 7, and 10</td>
</tr>
<tr>
<td>FGFR-2c</td>
<td>FGF-1, 2, 4, 6, and 9</td>
</tr>
<tr>
<td>FGFR-3b</td>
<td>FGF-1 and 9</td>
</tr>
<tr>
<td>FGFR-3c</td>
<td>FGF-1, 2, 4, 8, and 9</td>
</tr>
<tr>
<td>FGFR-4</td>
<td>FGF-1, 2, 4, 6, 8, and 9</td>
</tr>
</tbody>
</table>

Adapted from Itoh and Ornitz (1).

Fibroblast Growth Factor and Tumor Growth

Aberrant FGF and/or FGFR signaling has a wide range of effects and can involve both tumor cells and the surrounding stroma. These effects include cellular proliferation; resistance to cell death; increased motility and invasiveness; increased angiogenesis; enhanced metastasis; and resistance to chemotherapy (27). Deregulation of FGF signaling in tumorigenesis can result from activating mutations, FGFR gene amplifications, and chromosomal translocations, which lead to increased autocrine and paracrine signaling (28–30). Because aberrant signaling can promote tumorigenesis by affecting major downstream biologic processes, FGFs have been implicated in multiple tumor types, including prostate, astrocytoma, breast, lung, bladder, hepatocellular, and colon cancers (31–41).

Alternative splicing of the FGFR gene has also been implicated in carcinogenesis. Carcinomas have been observed to switch expression of FGF to the mesenchymal isoforms, enabling cells to receive signals usually restricted to the connective tissue, such as ectopic expression of typically stroma-localized FGFR1-IIc (42, 43). The IIc splice variant has been detected in colon carcinoma but not in adenoma-derived cell lines, suggesting that it is upregulated during tumor progression (44). During prostate cancer progression, alternative splicing of FGFR2 can occur in epithelial cells, leading to isoform changes from FGFR2-IIb into the more ligand-promiscuous FGFR2-IIc (Fig. 1; refs. 8, 43). Thus, this aberrant alternative splicing of FGFR potentially destroys the balanced interdependence between stroma and epithelium (8, 43, 45).

Clinical studies of FGF have suggested a critical role of FGF signaling in clinical tumor progression. In 1 study of advanced serous ovarian adenocarcinomas, FGF-1 mRNA copy number was found to be significantly correlated with DNA copy number and protein expression levels (46). Both FGF-1 mRNA and protein levels were associated with worse overall survival, possibly secondary to an increase in tumor angiogenesis and autocrine stimulation of cancer cells. In another study of 100 resected colorectal cancer surgical specimens, high FGF-2 expression was associated with increased grade, stage, lymphovascular invasion, and intratumoral microvessel density (47). Significantly elevated levels of FGF-2 in circulation were found in a small cohort of patients with metastatic colorectal cancer, relative to median levels in control subjects (48). In other studies, although increased levels of FGF-2 were found in plasma from patients with different types of cancer, it was unclear whether the higher levels resulted from tumor invasion and degradation of the extracellular matrix (ECM), liberating FGF to function as a paracrine growth factor, or whether tumor cells induced FGF2 release from stromal inflammatory infiltrate (49, 50).

Loss of expression of NCAM has also been implicated in the progression of tumor metastasis. NCAM has been shown to modulate neurite outgrowth and matrix adhesion of β cells from the Rip1-Tag2 transgenic mouse model of pancreatic neuroendocrine tumors by assembling a FGFR-4
signaling complex that leads to the modulation of β1-integrin–mediated cell-matrix adhesion (51). Ablation of the expression of NCAM in this mouse model resulted in the disruption of the tumor tissue architecture, tumor-associated lymphangiogenesis, and lymph node metastasis (51, 52).

Though a full review of FGF signaling and tumor growth is beyond the scope of this article, please see the comprehensive review from Turner and Grose for additional information (41).

Fibroblast Growth Factors and Angiogenesis

Angiogenesis, the formation of new blood vessels from the endothelium of the existing vasculature, plays a pivotal role in tumor growth, progression, and metastasis (53, 54). Along with embryogenesis, angiogenesis was one of the first areas where FGF signaling was shown to be important (55, 56). In particular, FGF-1 and FGF-2 were found to be important for new blood vessel growth at the site of an excision wound and have been shown to stimulate angiogenesis in various assays (57–59). FGF-2 is a very potent inducer of angiogenesis. In a preclinical model of microvascular endothelial cells grown on a 3-dimensional collage gel, VEGF and FGF-2 were able to induce cells to invade the underlying matrix to form capillary-like tubules (60). Interestingly, FGF-2 was found to be twice as potent as VEGF in this model. The critical role of FGF in tumor angiogenesis was shown through the interference of FGF function with a recombinant adenovirus expressing soluble FGFR (AdsFGFR). AdsFGFR seemed to impair the maintenance of tumor angiogenesis, in contrast to inhibition of the VEGF pathway that predominantly affected the initiation of tumor angiogenesis (61). Injection of AdsFGFR in the Rip1-Tag2 murine model of pancreatic neuroendocrine tumor resulted in repression of tumor growth, with a significant decrease in tumor vessel density. FGFs exert their effects by modulating proliferation and migration of endothelial cells, production of proteases, and promotion of integrin and cadherin receptor expression (62). In particular, FGF-1 and FGF-2 directly affect tumor angiogenesis by promoting the cellular proliferation of endothelial cells. FGF-2 has been shown to induce revascularization in various experimental models in several species, including rabbit, chicken, and mouse (63–65). In a murine model, FGF-1 knockout mice and FGF-1/FGF-2 double-knockout mice had poor wound healing compared with normal control mice (58). FGF-1 is most

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Figure 1. Changes in FGF and FGFR in the microenvironment and epithelium in normal tissue and cancer. Compared with normal tissue, alternative splicing of the FGFR gene can switch expression of FGFR from the IIIb isoform to the ligand promiscuous IIIc isoforms. Furthermore, release of FGF from the tumor and stroma may initiate tumor angiogenesis. FGF-BP–mediated reduction of the affinity of FGF-2 to heparin can induce its release from the ECM. FGF-BP, FGF binding protein; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor.
commonly expressed on endothelial cells, although FGFR-2 has been shown to be present under certain circumstances (50, 66). The presence of FGFR-3 and FGFR-4 has not been reported in the endothelium.

FGFs can exert their angiogenic mechanism of action via paracrine signaling through their release by tumor and stromal cells, or through their mobilization from the ECM (50). FGF-1, in particular, may stimulate endothelial cell growth and the motility of endothelial cells through paracrine signaling, which results in increased proliferation, survival, and motility of endothelial cells (46). FGF-2 has been studied in xenograft models in which liposome-mediated gene transfer was used to deliver episomal vectors containing antisense FGF-2 or FGFR-1 cDNAs into human melanomas grown in nude mice. In contrast to the stimulation seen during deregulated FGF signaling, tumors injected with these antisense constructs showed arrested tumor growth or reduced tumor density because of blocked intratumoral angiogenesis (67). There is also evidence that FGF-2 increases the expression of angiopoietin-2, a potent regulator of vascular branching and angiogenesis, as well as VEGF in cultured human and endothelial cells (68).

FGFs may also exert their effects through autocrine signaling in endothelial cells, stimulating the proliferation of new capillary endothelial cells (66). This induces a proangiogenic state that creates an environment favorable for vascular growth. Evidence for this growth is seen in a particular subtype of Kaposi sarcoma (KS) in which FGF-2, produced by the KS cells, has been found to synergize with human immunodeficiency virus type 1 Tat protein to produce intratumoral angiogenesis (67). There is also evidence of cross-talk between FGF-2 and platelet-derived growth factor (PDGF)–BB. FGF-2 and PDGF-BB together have been shown to synergistically promote tumor angiogenesis and pulmonary metastasis, as well as formation of high-density primitive vascular plexuses coated with pericytes and vascular smooth muscle cells (79). Pericyte recruitment to coat nascent vessels during angiogenesis is essential for the stabilization and further establishment of a tumor’s vascular network. FGF-2 seems to upregulate PDGF receptor (PDGFR) expression, which causes increased responsiveness to PDGF-BB, and PDGF-BB–treated vascular smooth muscle cells become responsive to FGF-2 signaling through upregulation of FGFR-1. Interestingly, overexpression of PDGF-BB alone in tumor cells was shown to result in decreased recruitment of pericytes and dissociation of vascular smooth muscle cells. In tumor cells subjected to prior upregulation of FGF-2 caused by VEGF receptor 2 (VEGFR2) inhibition, PDGFR-β inhibition also attenuated the expression of FGF-2 (80). In a mouse model of cervical carcinogenesis, pharmacologic blockade of PDGFR signaling with imatinib slowed progression of premalignant cervical lesions and impaired the growth of preexisting invasive carcinomas through suppression of the expression of FGF-2 and FGF-7, which resulted in decreased proliferation and angiogenesis within the lesions (81). Treatment with an IGF trap also impaired the angiogenic phenotype similar to the blockade of the PDGFR with imatinib.

Fibroblast Growth Factor–2 Cross-Talk with Angiogenic Factors

VEGF plays an integral role in the development of new blood vessels in tumor formation, and angiogenesis inhibitors targeting the VEGF pathway have proved to be efficacious in preclinical cancer models and in clinical trials (74, 75). A significant amount of cross-talk is thought to exist between members of the VEGF family and FGF-2 during angiogenesis, with VEGF appearing earlier during angiogenesis than does FGF (50). In 1 study, the angiogenic response occurred more quickly when VEGF and FGF-2 were added simultaneously to microvascular endothelial cells on 3-dimensional collagen gels than the response to either cytokine alone, suggesting synergy between the 2 cytokines (60). It has also been shown that induction of FGF-2–induced angiogenesis is partly dependent on the activation of VEGF and the presence of endogenous VEGF and VEGF-C (76). Evidence for synergy between VEGF and FGF-2 has also been shown in xenograft models expressing FGF-2 and VEGF in tumor cell transfectants. Simultaneous expression of FGF-2 and VEGF resulted in fast-growing lesions with high blood vessel density and permeability (77). Interestingly, inhibition of FGF-2 production caused a significant decrease in tumor burden with a concomitant decrease in blood vessel density and size. This differed from the effects of VEGF inhibition, which caused a decrease in pericyte organization, vessel patency, and permeability. This finding suggests that FGF-2 and VEGF stimulate angiogenesis synergistically but with different effects on vessel size and function.

FGF-2 may also have indirect effects on VEGF pathways. In a breast cancer cell line (T47D), FGF-2 was found to activate hypoxia-induced VEGF release through augmentation of the phosphoinositide 3-kinase pathway, as well as hypoxia-inducible factor-1α expression (78). FGF-2 has also been shown to indirectly enhance the effect of VEGF through upregulation of neurolipin-1 (NRP-1), a coreceptor for VEGF. FGF-2 increased NRP-1 levels and enhanced the migration of human vascular smooth muscle cells in response to VEGF.

There is also evidence of cross-talk between FGF-2 and platelet-derived growth factor (PDGF)–BB. FGF-2 and PDGF-BB together have been shown to synergistically promote tumor angiogenesis and pulmonary metastasis, as well as formation of high-density primitive vascular plexuses coated with pericytes and vascular smooth muscle cells (79). Pericyte recruitment to coat nascent vessels during angiogenesis is essential for the stabilization and further establishment of a tumor’s vascular network. FGF-2 seems to upregulate PDGF receptor (PDGFR) expression, which causes increased responsiveness to PDGF-BB, and PDGF-BB–treated vascular smooth muscle cells become responsive to FGF-2 signaling through upregulation of FGFR-1. Interestingly, overexpression of PDGF-BB alone in tumor cells was shown to result in decreased recruitment of pericytes and dissociation of vascular smooth muscle cells. In tumor cells subjected to prior upregulation of FGF-2 caused by VEGF receptor 2 (VEGFR2) inhibition, PDGFR-β inhibition also attenuated the expression of FGF-2 (80). In a mouse model of cervical carcinogenesis, pharmacologic blockade of PDGFR signaling with imatinib slowed progression of premalignant cervical lesions and impaired the growth of preexisting invasive carcinomas through suppression of the expression of FGF-2 and FGF-7, which resulted in decreased proliferation and angiogenesis within the lesions (81). Treatment with an IGF trap also impaired the angiogenic phenotype similar to the blockade of the PDGFR with imatinib.
Fibroblast Growth Factor Signaling and Resistance to Anti-VEGF Therapy

Emerging evidence has suggested that upregulation of FGF and FGFR may serve as a mechanism of resistance to anti-VEGF therapy. Preclinical trials of anti-VEGF therapy in a murine pancreatic neuroendocrine tumor model (PNET), Rip1-Tag2, showed that tumors with an initial response to VEGFR2 blockade expressed higher levels of FGF-2 at the time of progression compared with stable tumors (82). When the tumors were first treated with a VEGFR inhibitor alone and subsequently treated at the peak of response with an FGF trap, the combination attenuated revascularization and slowed tumor growth (Fig. 2). The dual tyrosine kinase inhibitor (TKI) of VEGFR and FGFR, brivanib, has also been studied in this murine model and has proved to be efficacious following the failure of 2 VEGFR inhibitors (83). It was even more effective when used in the frontline setting, suggesting that dual inhibition of VEGFR and FGFR was able to delay induction of evasive resistance. Further evidence for the role of alternative angiogenic factors in tumor escape from angiogenesis inhibitors has been shown in tumors in which growth was impaired by ectopic expression of the endogenous angiogenesis inhibitors thrombospondin-1, tumstatin, and endostatin (84). In that study, renal carcinoma cells transfected with thrombospondin-1 resisted angiogenesis inhibition by upregulating the proangiogenic factors FGF-2, angiopoietin 2, and PDGF-A, despite high baseline levels of VEGF. In 1 xenograft model of renal cell carcinoma, tumors unresponsive to sunitinib treatment were sensitive to a dual inhibitor of the VEGF and FGFRs (85). This inhibitor seemed to reduce blood vessel density through inhibition of FGF-2–induced angiogenesis.

Clinical evidence in colon cancer also supports the role of FGF-2 in resistance to bevacizumab-containing regimens. To determine the dynamic changes in circulating factors during the emergence of therapeutic resistance, profiles of cytokines and angiogenic factors were assessed in 40 patients receiving a regimen of 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) plus bevacizumab. Levels were assessed after a single dose of bevacizumab and FOLFIRI plus bevacizumab, at the time of progression, and at the nadir of radiographic response (86, 87). The investigators showed that FGF-2 levels were elevated immediately prior to progression compared with baseline levels. Strikingly, 30% of patients had an increase in FGF-2 to 10-fold the upper limit of normal, suggesting significant heterogeneity in the FGF-2 response. In 1 study of neoadjuvant bevacizumab with 5-FU and radiation in rectal cancer, the administration of a short regimen of bevacizumab in combination with chemotherapy had no significant effect on plasma FGF-2 levels, suggesting that elevations in FGF-2 are instead a later event temporally associated with the development of resistance to the bevacizumab combination regimen (88).

Elevated FGF-2 levels have also been shown in glioblastoma patients treated with a VEGFR small molecule
inhibitor (89). In patients who experienced tumor progression while receiving treatment, increased tumor enhancement volume was associated with significant increases in plasma levels of FGF-2 and stromal cell–derived factor-1. A statistically significant positive correlation was observed between FGF-2 levels and tumor vessel size measured by MRI. This work provided further clinical evidence that FGF-2 may play a role in tumor relapse in patients treated with anti-VEGF agents (89).

Unlike preclinical models, clinical studies investigating levels of FGF can only show an association of elevated FGF and/or FGFR with the resistance to anti-VEGF therapy; they cannot show causation or an actual resistance mechanism. Furthermore, because most studies are conducted in combination with cytotoxic chemotherapy, it is difficult to discern whether the patient and tumor have become resistant to the chemotherapy, the antiangiogenic therapy, or both. Therefore, high-quality preclinical models will be essential for further investigation to provide a sound preclinical rationale for future clinical studies.

Targeting Fibroblast Growth Factor

Because FGFs have a clearly defined role in tumor angiogenesis, as well as a possible role in resistance to current VEGF inhibitors, several FGF pathway inhibitors are currently under development. The inhibitors entering the clinic are either TKIs or soluble antibody fragments that block ligand binding and receptor dimerization (Table 2). Most of the TKIs have dual specificity for FGF and VEGFR, both as a matter of design and because of the structural similarities in their kinase domains. However, the inhibitors vary in their relative potency for VEGFR and FGFR, with many inhibitors having higher potency for VEGFR than FGFR (90, 91). Targeting both kinases may also increase the toxicity associated with these compounds, although biologically active doses have been shown with most of the compounds (41). The other class of compound in development, FGF ligand trap, has the potential to block the interaction of multiple FGF ligands with the soluble FGFR fragments. In 1 study, such an FGFR-1 antagonist was shown to prevent FGFR-1 ligands from binding, and it had in vitro activity against lung and renal cell carcinoma (92).

The safety of FGFR inhibitors currently under development seems acceptable. Preclinical toxicity studies with these agents have not shown a reproducible class effect, aside from hypertension, which is difficult to attribute to the VEGFR or FGFR inhibitory effects of many of the agents (93, 94). Monoclonal antibodies directed against FGFRI-IIIc resulted in anorexia in mice and monkeys, which was caused by an FGF signaling blockade in the hypothalamus, and a similar toxicity was seen in 1 phase I study (95, 96). Encouragingly, the concerns based on preclinical studies about phosphate and vitamin D metabolism have not been reflected in the reported toxicities in the early-phase studies (97).

Although a separate development strategy is being pursued based on somatic mutation or amplification of FGFR (reviewed in ref. 98), antiangiogenesis strategies targeting the tumor microenvironment pose additional drug development strategies. Prior studies of anti-VEGF antibodies have shown clinical utility when the agents are used in combination with cytotoxic therapy and minimal activity as single agents with rare exceptions (75, 99). Similarly, FGF inhibition alone is unlikely to show a significant benefit in various tumor types. Combination strategies of FGF/FGFR inhibition with traditional cytotoxic therapy in tumor types in which proliferation and angiogenesis is FGF/FGFR-dependent will have the highest likelihood of achieving a clinical benefit.

The timing of FGF/FGFR–directed therapy is also an area of emerging interest given the evolving evidence that the FGF axis may serve as an adaptive resistance mechanism to anti-VEGF therapy. Histopathologic evidence from a murine PNET model suggests that the switch to an FGFR inhibitor during treatment with a VEGFR inhibitor may be more effective at the time of early revascularization prior to detectable tumor growth (83). Future clinical trials will help determine whether dual inhibition of VEGFR and FGFR will be more effective in the front-line setting or whether FGFR inhibition will be better instituted at the time prior to or at progression after treatment with VEGF/VEGFR inhibitors. However, determination of biologic

![Table 2. Current FGF and FGFR-targeting agents](#)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Target(s)</th>
<th>Clinical development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TKI258 (dovitinib; ref. 96)</td>
<td>Novartis</td>
<td>FGF, PDGF, VEGFR</td>
<td>Phase II</td>
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<td>BIBF 1120 (Vargatef; ref. 104)</td>
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<td>FGF, PDGF, VEGFR</td>
<td>Phase III</td>
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<td>Bristol-Myers Squibb</td>
<td>FGF and VEGFR</td>
<td>Phase II and III</td>
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<td>E7080 (106)</td>
<td>Eisai</td>
<td>FGF, PDGF, VEGFR</td>
<td>Phase I</td>
</tr>
<tr>
<td>TSU-68 (SU6668; ref. 107)</td>
<td>Taiho Pharmaceutical</td>
<td>FGF, PDGF, VEGFR</td>
<td>Phase I and II</td>
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<tr>
<td>AZD4547 (108)</td>
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<td>FP-1039 (109)</td>
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<td>Phase I</td>
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<tr>
<td>BJQ398 (110)</td>
<td>Novartis</td>
<td>FGF ligand trap (multiple FGFs)</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Astex FGFR inhibitor (111)</td>
<td>Janssen Oncology</td>
<td>FGF, PDGF, VEGFR</td>
<td>Preclinical</td>
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Published OnlineFirst September 27, 2011; DOI: 10.1158/1078-0432.CCR-11-0659

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resistance to VEGF/VEGFR inhibitors is difficult in the clinic, as resistance to the cytotoxic component of the treatment may be sufficient to induce tumor growth in the absence of single-agent anti-VEGF activity. Determining resistance to these inhibitors is a high hurdle for development of such alternative antiangiogenic therapies, and several strategies are being considered in the early clinical development, including randomized discontinuation studies and enrichment designs.

Biomarkers under consideration for FGF inhibitors include plasma levels of FGF family members and increased FGF-axis expression in the stroma; however, their use as surrogates for FGF/FGFR–dependent tumors remains unclear. Integration of imaging or biomarkers of antiangiogenesis therapy likewise has hurdles of cost reproducibility and lack of correlation with clinical efficacy, and these approaches are not routinely integrated into most clinical development strategies of these agents (100, 101). Based on the VEGF inhibitor experiences, radiographic endpoints with antiangiogenesis strategies will be difficult, and ultimately, the benefits of these agents will be measured by their ability to improve overall survival (102, 103).

Summary

FGFs are a family of growth factors that are involved in many pathways that can contribute to carcinogenesis and affect cellular proliferation, migration, and survival. They also play a large role in angiogenesis, which is a fundamental step in the transition from a dormant to a malignant state, and FGF acts synergistically with VEGF to increase tumor blood vessel growth and maturation. Evidence is also increasing that FGF may be part of the mechanism of resistance to anti-VEGF agents.

Although agents targeting FGF signaling are still early in development, the potential to target both the VEGF and FGF pathways is near, and the combination or sequential inhibition of these 2 critical angiogenic pathways may translate into improvements in the clinical care of cancer patients. Successful strategies will depend on appropriate selection of tumors and patients in whom FGF inhibition is mostly likely to inhibit angiogenesis and proliferation.

Disclosure of Potential Conflicts of Interest

S. Kopetz: commercial research grant, AstraZeneca. The other authors disclosed no potential conflicts of interest.

Grant Support

NIH T32 CA-008566 (C. Lieu); National Research Service Award (NRSA) Research Training Grant; Conquer Cancer Foundation Young Investigators Award (C. Lieu); NIH CA-136980 (S. Kopetz); NIH/National Cancer Institute (NCI) Cancer Center Support Grant (CCSG) Core Grant CA-106672.

Received March 18, 2011; revised July 20, 2011; accepted July 25, 2011; published OnlineFirst September 27, 2011.
Inhibition of the FGF Pathway and Antiangiogenic Therapy


Lieu et al.


cisco, CA; 2009.


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Clin Cancer Res 2011;17:6130-6139. Published OnlineFirst September 27, 2011.

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