

Subject Review

Roles of Fibroblast Growth Factor Receptors
in Carcinogenesis

Ellen Margrethe Haugsten, Antoni Wiedlocha, Sjur Olsnes, and Jørgen Wesche

Abstract

The fibroblast growth factor receptors (FGFR) play essential roles both during development and in the adult. Upon ligand binding, FGFRs induce intracellular signaling networks that tightly regulate key biological processes, such as cell proliferation, survival, migration, and differentiation. Deregulation of FGFR signaling can thus alter tissue homeostasis and has been associated with several developmental syndromes as well as with many types of cancer. In human cancer, FGFRs have been found to be deregulated by multiple mechanisms, including aberrant expression, mutations, chromosomal rearrangements, and amplifications. In this review, we will give an overview of the main FGFR alterations described in human cancer to date and discuss their contribution to cancer progression. *Mol Cancer Res*; 8(11); 1439–52. ©2010 AACR.

Introduction

Carcinogenesis and the hallmarks of cancer

Carcinogenesis is a multistep process during which normal cells are transformed into cancer cells by accumulating several genetic changes and acquiring several common features that promote the malignant phenotype, often referred to as the hallmarks of cancer. The six classic hallmarks of cancer include self-sufficiency in growth signals, insensitivity to antigrowth signals, limitless replication, evasion of apoptosis, sustained angiogenesis, and the ability to invade tissue and form metastasis (1). Other common features of malignant cells are enhanced anabolic metabolism, avoidance of immunoresponse, and several stress phenotypes (2–4). Many of these features are caused by genetic alterations that involve the gain-of-function mutation, amplification, and/or overexpression of key oncogenes together with the loss-of-function mutation, deletion, and/or epigenetic silencing of tumor suppressors (3). Notably, however, not all of the genetic alterations found in malignant cells contribute to cancer progression and are referred to as passenger mutations. Driver mutations, in contrast, give cancer cells a considerable growth advantage and are implicated in cancer cell expansion (5). Functional experiments are therefore required to establish whether a certain alter-

ation is relevant for cancer progression. Within the family of fibroblast growth factor receptors (FGFR), several alterations and mutations have been identified in a variety of human cancers.

Receptor tyrosine kinases and cancer

FGFRs belong to the family of receptor tyrosine kinases (RTK), all of which are single-pass transmembrane receptors with extracellular ligand-binding domains and an intracellular tyrosine kinase domain (6). Activation of RTKs by their respective ligands induces kinase activation that in turn initiates intracellular signaling networks that ultimately orchestrate key cellular processes, such as cell proliferation, growth, differentiation, migration, and survival (6, 7). In this way, RTKs play pivotal biological roles during the development and adult life of multicellular organisms. Therefore, it is not surprising that deregulation of a large number of RTKs has been linked to the development of numerous human diseases, including cancer (7, 8). In this review, we will focus on the alterations and mutations of members of the FGFR subfamily of RTKs in human cancers. First, we will give an overview of the members of the FGFR family, their ligands, downstream signaling pathways, as well as their biological functions. We will then present the main FGFR alterations described in human cancers and highlight how these abnormalities may contribute to carcinogenesis and the development of a malignant phenotype.

Fibroblast Growth Factor Receptors

The FGFR family consists of four genes encoding closely related transmembrane, tyrosine kinase receptors (termed FGFR1 to FGFR4; ref. 9). A typical FGFR consists of a signal peptide that is cleaved off, three immunoglobulin (Ig)-like domains, an acidic box, a transmembrane domain, and a split tyrosine kinase domain (Fig. 1A). Additionally, alternative splicing of the transcribed receptor

Authors' Affiliation: Centre for Cancer Biomedicine, Faculty of Medicine, University of Oslo, and Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital, Montebello, Oslo, Norway

Corresponding Authors: Ellen Margrethe Haugsten, Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway. Phone: 47-22-78-19-13; E-mail: Ellen.M.Haugsten@rr-research.no or Jørgen Wesche, Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway. Phone: 47-22-78-19-31; Fax: 47-22-78-18-45. E-mail: Jorgen.Wesche@rr-research.no

doi: 10.1158/1541-7786.MCR-10-0168

©2010 American Association for Cancer Research.

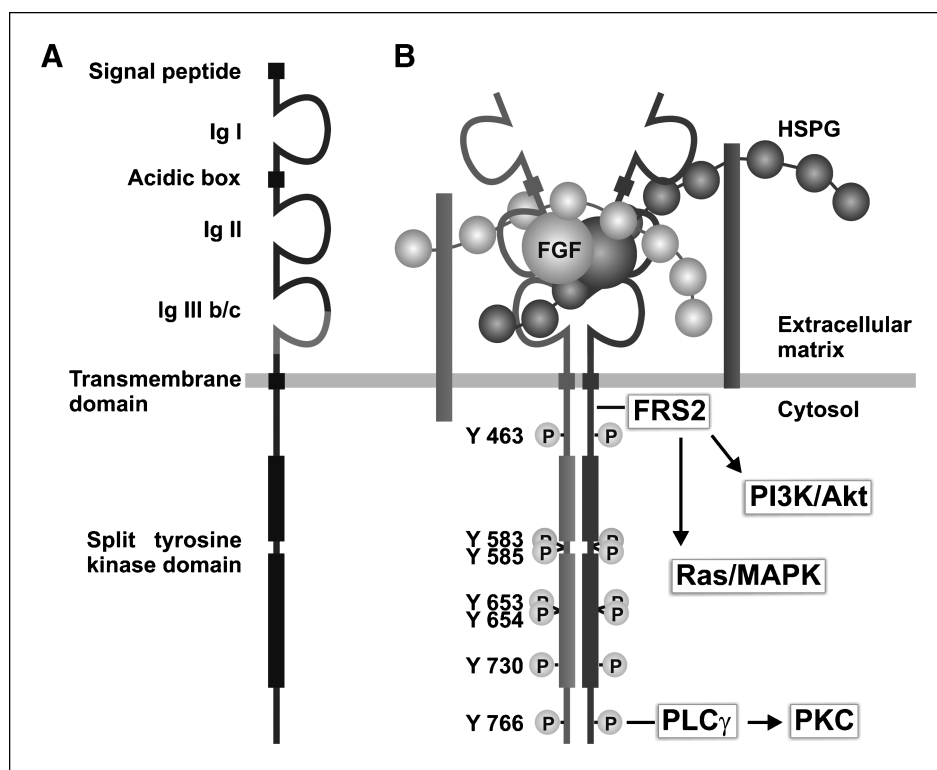


FIGURE 1. A, schematic overview of the prototypical FGFR structure. The Ig-like domains are referred to by their roman numerals. Alternative splicing of the second half of the third Ig-like domain gives rise to alternative IIIb or IIIc isoforms of FGFR1 to FGFR3. B, an illustration of binding of FGF to FGFRs. In a model of the activation of FGFRs by FGF and HSPGs, a 2:2:2 complex of FGFR-FGF-HSPG is formed. This leads to receptor autophosphorylation. The major autophosphorylation sites in FGFR1 are indicated, as well as the major downstream signaling pathways.

genes results in a variety of receptor isoforms. The different isoforms include soluble, secreted FGFRs, FGFRs with truncated COOH-terminal domain, FGFRs with either two or three Ig-like domains, as well as FGFR isoforms arising via alternative splicing of the third Ig-like domain of the receptor. Alternative splicing of the third Ig-like domain occurs only for FGFR1, FGFR2, and FGFR3 and specifies the second half of the third Ig-like domain, resulting in either the IIIb or the IIIc isoform of the receptor. The second and the third Ig-like domains of the receptors are necessary and sufficient for ligand binding, whereas the first Ig-like domain is thought to play a role in receptor autoinhibition (10). Thus, the different receptors and their isoforms display different ligand-binding specificities (9, 11, 12).

Together, 18 ligands, FGFs, can bind to the distinct FGFRs and their splice variants. The FGFs also bind to heparan sulfate proteoglycans (HSPG), and thereby, a dimeric 2:2:2 FGF-FGFR-HSPG ternary complex forms on the cell surface (Fig. 1B; ref. 13). The ternary complex is stabilized by multiple interactions between the different components in the complex. Two FGF-binding sites, a heparin-binding site, and a receptor-receptor interaction site have been identified within the Ig-like domains II and III of the receptor.

Binding of FGFs to FGFRs induces receptor dimerization, which enables transphosphorylation of a tyrosine in the activation loop of the kinase domain. Subsequently, a network of hydrogen bonds, which acts as a molecular brake by keeping the kinase in an autoinhibited state, dissociates. This leads to a 50- to 100-fold stimulation of the

intrinsic kinase activity of the receptor followed by phosphorylation of tyrosines in the COOH-terminal tail of the receptor, the kinase domain, and the juxtamembrane regions (14, 15). In FGFR1, seven tyrosine residues have been identified (Y463, Y583, Y585, Y653, Y654, Y730, and Y766) as the major autophosphorylation sites (Fig. 1B; refs. 16, 17).

The active FGFRs have been shown to phosphorylate multiple intracellular proteins such as FRS2 (FGFR substrate 2) and PLC γ (phospholipase C γ ; ref. 18). PLC γ binds directly to an autophosphorylated tyrosine in the COOH-terminal receptor tail (Y766 in FGFR1), resulting in PLC γ phosphorylation and activation. Activated PLC γ produces two second messengers: diacylglycerol and inositol 1,4,5-trisphosphate. This, in turn, releases intracellular calcium storages and activates calcium-dependent members of the PKC (protein kinase C) family of serine-threonine kinases (Fig. 1B). FRS2, on the other hand, is constitutively associated with the juxtamembrane domain of the FGFR and becomes phosphorylated on tyrosine residues by the activated FGFR kinase. The phosphorylated tyrosine residues in FRS2 then serve as docking sites for the assembly of signaling complexes that promote activation of the Ras/MAPK (mitogen-activated protein kinase) and PI3K (phosphoinositide 3-kinase)/Akt signaling pathways (Fig. 1B). Numerous additional factors such as Shb (src homology 2 domain-containing transforming protein B), Src kinase, RSK (ribosomal S6 protein kinase), STATs (signal transducers and activators of transcription), and Crk have also been implicated in promoting FGF-mediated signaling

(19). Negative regulation of FGFR signaling, on the other hand, is mediated by several proteins such as the MAPK phosphatase 3 (MKP3), the Sprouty proteins, and Sef (similar expression to FGF) family members (20). Another process leading to attenuation of FGFR signaling is FGFR endocytosis followed by receptor degradation in lysosomes (21).

FGFR signaling produces distinct biological responses in different cell types, ranging from stimulation of cell proliferation and survival to growth arrest, migration, and differentiation. FGF signaling is regulated by the spatial and temporal expression patterns of the ligands and receptors as well as the ligand-receptor binding specificity (20, 22). The different FGFRs play important roles both during development and in the adult organism. During embryonic development, FGFR signaling orchestrates a multitude of processes. FGFs/FGFRs are key regulators of mesenchymal-epithelial communication, and FGFRs are thus well-known inducers of mesoderm. They have also been shown to be relevant in organogenesis, particularly for the formation of the nervous system, the limbs, the midbrain, and the lungs (23). FGF/FGFRs also play a key role in the induction and development of the embryonic mammary gland (24-27). In the adult, FGFR signaling continues to regulate tissue homeostasis and is also involved in processes such as tissue repair, angiogenesis, and inflammation (23). In angiogenesis and neovascularization, FGFR signaling is thought to mainly play an indirect role by influencing other growth factors such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF; ref. 28). Imbalances in FGFR signaling are implicated in several diverse human pathologic conditions such as skeletal disorders, Kallman syndrome, and cancer (29). Here, we will focus on the imbalances of FGFR signaling found in human cancers.

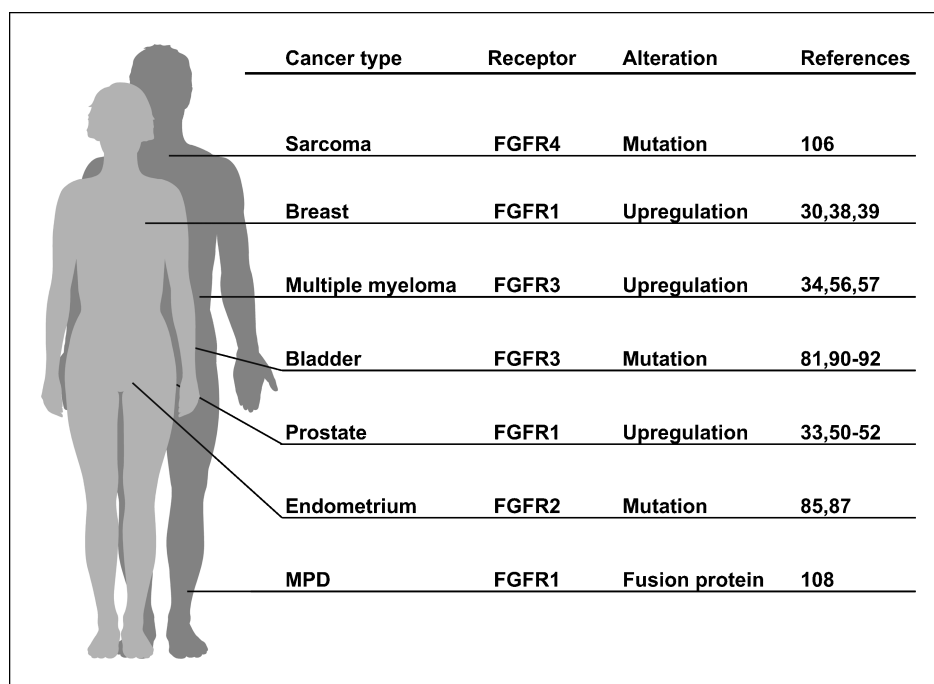
Mechanisms That Can Lead to Imbalanced FGFR Signaling

Deregulated FGFR activity is most often recognized as oncogenic. However, in some cases, FGFRs have also been identified as tumor suppressors (see text below). Several mechanisms may cause excessive FGFR signaling. First, upregulated FGFR expression might lead to increased FGFR signaling. Second, mutations or chromosomal rearrangements in the genes encoding FGFRs can give rise to receptors with altered signaling activities. Third, the availability of ligand influences FGFR signaling. Furthermore, impaired termination of FGFR signaling such as deregulation of inhibitory proteins or defective degradation can also result in increased FGFR signaling. In the following paragraphs, we will discuss these mechanisms and their involvement in various types of human cancer.

Upregulated FGFR expression

Overexpression of a gene can be caused by its amplification or aberrant transcriptional regulation. Elevated levels of FGFRs have been found in numerous human cancers such as cancer of the brain, head and neck, lung, breast, stomach, and prostate and in sarcomas and multiple myeloma (MM; Fig. 2; refs. 30-37). However, an elevated level of a protein in cancer cells does not necessarily mean that this protein plays a role in carcinogenesis and it is not always clear if the FGFR alterations found in human cancers are “drivers” or “passengers.” For example, amplification of the chromosomal region 8p11-12, where *FGFR1* is located, is one of the most common amplifications, appearing in ~10% of human breast cancers, and it is associated with poor prognosis (30, 38, 39). The 8p11-12 region is gene rich, and because

FIGURE 2. Summary of central aberrations of FGFRs in human cancer discussed in the text. The figure was produced using Servier Medical Art. MPD, myeloproliferative disorders.



Cancer type	Receptor	Alteration	References
Sarcoma	FGFR4	Mutation	106
Breast	FGFR1	Upregulation	30,38,39
Multiple myeloma	FGFR3	Upregulation	34,56,57
Bladder	FGFR3	Mutation	81,90-92
Prostate	FGFR1	Upregulation	33,50-52
Endometrium	FGFR2	Mutation	85,87
MPD	FGFR1	Fusion protein	108

FGFR1 is not always overexpressed when it is amplified or it is not always contained in the amplification, its role in the amplicon is debated (40-42). However, activation of FGFR1 in nontransformed mouse or human mammary cells resulted in cellular transformation (43, 44), and inhibition of FGFR1 kinase activity in a breast cancer–derived cell line that overexpresses FGFR1 resulted in cell death, indicating that this cell line was addicted to continued FGFR1 signaling for viability (45). Although a search for an absolute driver of the 8p11-12 amplification might be elusive, imbalanced FGFR1 signaling can contribute to carcinogenesis in mammary cells and may therefore be a potential therapeutic target in patients with 8p11-12 amplification.

Interestingly, single-nucleotide polymorphisms (SNP) identified within intron 2 of *FGFR2* are associated with an increased risk of breast cancer (46, 47). Because this intron contains several putative transcription factor–binding sites that lie in close proximity to the reported SNPs, it was speculated that the association with breast cancer risk was mediated through regulation of FGFR2 expression (46). At least two of the reported SNPs in intron 2 of *FGFR2* have been suggested to alter the binding affinity for two transcription factors (Oct-1/Runx2 and C/EBP β) and (at least in the case of Oct-1/Runx2) cause an increase in FGFR2 expression (48). Recently, overexpression of FGFR2 in breast cancer cell lines was reported to lead to constitutive FGFR2 activation. Interestingly, inhibition of FGFR2 signaling in these cells induced apoptosis (49). Thus, constitutive FGFR2 signaling due to FGFR2 overexpression can lead to protection from apoptosis, which is one of the hallmarks of cancer cells.

FGFR1 is also frequently overexpressed in human prostate cancer and is believed to disrupt the interplay between mesenchymal and epithelial cells of the prostate (33, 50-52). To monitor the consequences of FGFR1 activation on prostate cancer progression *in vivo*, a mouse model in which the mice express a prostate-specific, inducible chimeric version of FGFR1 has been developed (53). In this model, conditional activation of FGFR1 in prostate epithelial cells led to epithelial to mesenchymal transition (EMT) and induction of adenocarcinomas in 100% of the treated mice (54). Moreover, deactivation of FGFR1 early during cancer progression led to regression, indicating that FGFR1 is necessary for both maintenance and progression of prostatic intraepithelial neoplasias (PIN). Inhibition of FGFR1 relatively late in cancer progression, on the other hand, significantly reduced proliferation and progression of adenocarcinoma, but did not lead to regression. The temporal differences in responsiveness to FGFR1 inhibition indicate a “susceptibility window” for targeting FGFR1 in prostate cancer. Using the same mouse model, Winter et al. (55) showed that activation of FGFR1 led to increased angiogenesis.

Another example of overexpression of FGFRs in cancer comes from the study of MM. MM is a cancer of white blood cells (WBC) that is characterized by multiple genetic abnormalities. About 15% to 20% of MM patients harbor a chromosomal translocation, t(4;14), which brings *FGFR3* under the influence of a strong IgH enhancer region, leading to FGFR3 overexpression (34, 56, 57). The

t(4;14) translocation is associated with poor prognosis, and FGFR3 has been recognized as a potent oncogene in MM and an attractive target for novel drug development. Several studies have reported antitumor activity of small-molecule FGFR3 inhibitors as well as inhibitory anti-FGFR3 antibodies in MM cell lines carrying the t(4;14) translocation and in MM xenograft mouse models (58-61). It should be noted that the t(4;14) translocation in MM also results in ectopic expression of MMSET (multiple myeloma SET domain). Ectopic expression of MMSET is found in all t(4;14) MM patients, whereas ~25% of the t(4;14)-positive patients do not express FGFR3 (57). Moreover, carrying the t(4;14) translocation has been associated with poor prognosis irrespective of FGFR3 expression (62). The role of FGFR3 in MM is therefore not clear. However, recent results obtained from a MM mouse model indicate that FGFR3 expression is likely to be essential at least for the early stage of t(4;14) MM tumors (63).

Switching between alternatively spliced isoforms

Switching between alternatively spliced isoforms may also lead to imbalanced FGFR signaling. Several reports have indicated different oncogenic potential of the various isoforms of the FGFRs (64-68). A shift in splicing generating the more oncogenic isoforms during carcinogenesis could thus promote tumor growth. Moreover, a shift in splicing that generates isoforms with altered FGF-binding capacity can also lead to imbalanced FGFR signaling. Alternative splicing of the third Ig-like domain determines the ligand-binding specificity of the receptor and generates the IIIb or the IIIc isoform of the FGFRs. The IIIb isoforms are usually expressed in epithelial cells, whereas the IIIc isoforms are normally expressed in mesenchymal cells. In contrast, the ligands for the IIIb isoforms are usually expressed in mesenchymal cells and the ligands for the mesenchymal-restricted IIIc isoforms in epithelial cells. In this way, FGFR signaling functions in a paracrine manner between the epithelial and mesenchymal cells. A switch from one isoform to another can thus lead to autocrine signaling. Exon switching in epithelial cells from the epithelial FGFR2 IIIb isoform to the mesenchymal FGFR2 IIIc isoform by alternative splicing has been described in rat models of prostate and bladder cancer (69-71). This switch resulted in autocrine activation of FGFR2, disturbed the signaling balance between the epithelial and mesenchymal cells, and led to EMT. It is not clear whether the alternative splicing of the third Ig-like domain contributes to carcinogenesis in humans (33). In a study of human prostate cancer, alternative splicing of the third Ig-like domain was rare and, in the case of FGFR2, occurred only in a subgroup of cases (72). It is worth to note that downregulation of FGFR2 IIIb as well as FGFR2 IIIc has been reported in several human cancers, suggesting that FGFR2 in some cases might function as a tumor suppressor (see text below).

FGFR mutations

A variety of human skeletal dysplasias have been shown to be driven by germline gain-of-function mutations in FGFR1

to FGFR3, and many of the same mutations are found in human cancers (Fig. 1; Table 1; ref. 73). Mutated forms of FGFRs have been identified in cancer of the brain, head and neck, lung, breast, stomach, prostate, colon, uterus, and bladder as well as in MM (74-88). Many of the identified mutations give rise to more active forms of the receptors. Point mutations found in the extracellular domain of the receptor can enhance ligand binding and/or alter ligand specificity. Some mutations have also been shown to induce dimerization of the receptor and thereby constitutive activation of the receptor kinase domain. Mutations identified in the kinase domain of the receptor might give rise to FGFRs with a constitutively active kinase. Moreover, impaired termination of FGFR signaling can also be a consequence of mutations in the intracellular domain of the receptors. It should be noted that loss-of-function mutations in FGFRs have also been identified in human cancers (89).

FGFR3 seems to be one of the most commonly mutated oncogenes in human bladder cancer (90). Somatic activating mutations in FGFR3 have been identified in approximately 60% to 70% of nonmuscle-invasive and in 16% to 20% of muscle-invasive bladder cancer, with S249C and Y373C mutations being the most frequent (Table 1; refs. 81, 91, 92). These mutants represent highly activated forms of the receptor and are also found in the lethal skeletal disorder thanatophoric dysplasia. The mutations in the extracellular domain generating an additional cysteine residue lead to the formation of an intermolecular cysteine disulfide bridge, which results in constitutive receptor dimerization and activation (93). Several mutations of amino acid residue K650 in the kinase domain of FGFR3 are also found in bladder cancer (80, 81, 92). The mutations K650Q/M/N/E are thought to drive the activation loop of the kinase to an active conformation as well as to disengage the autoinhibitory molecular brake in the kinase domain (15). This results in constitutive FGFR3 activation (94). In bladder cell culture experiments and mouse models, RNA interference, small-molecule inhibitors, and anti-FGFR3 antibodies have been reported to decrease cell proliferation and have antitumor activities (59, 79, 95-98). These studies indicate that FGFR3 plays an important role in bladder cancer growth and thus could be considered an attractive candidate for targeted therapy.

In human bladder cancer, the FGFR3 mutations are strongly associated with noninvasive, low tumor grade and stage (99). A two-pathway model of bladder carcinogenesis, which separates a favorable pathway characterized by mutations in FGFR3 and a clinically unfavorable pathway characterized by genetic instability and mutations in p53, has been suggested (90, 100). Moreover, in noninvasive bladder carcinomas, FGFR3 mutations confer increased risk of tumor recurrence (99). The high recurrence rate (60-80%) of noninvasive tumors requires long-term, expensive patient monitoring. Recent data suggest that detection of FGFR3 mutations in urine from patients with FGFR3 mutations in the primary tumor indicates recurrence (101, 102). Thus, identification of FGFR3 mutations is not only a potential biomarker for bladder cancer diagnosis and prognosis but could also indicate tumor recurrence.

Activating mutations in FGFR2 are present in ~10% of human endometrial/uterine carcinomas (85, 87). The majority of mutations identified are identical to mutations that cause skeletal disorders and include S252W and P253R, which are associated with Apert syndrome, and N549K and K659N, which are associated with Crouzon syndrome. S252W and P253R are located within the region between the second and the third Ig-like domain of the receptor and alter FGFR ligand-binding specificity (103). N549K and K659N are thought to lead to ligand-independent receptor activation by loosening the autoinhibitory molecular brake in the kinase domain of the receptor (15). In endometrial cell lines bearing such FGFR2 mutations, treatment with an FGFR inhibitor or knockdown of FGFR2 blocked cell proliferation and survival (85, 104). Moreover, inhibition of FGFR signaling in an endometrial cell line expressing FGFR2 N549K led to cell cycle arrest, indicating that imbalanced FGFR2 signaling can render cells insensitive to antigrowth signals.

Rhabdomyosarcoma (RMS) is a cancer originating from skeletal muscle and is the most common soft tissue sarcoma in children (105). Recently, several mutations in FGFR4 were identified in approximately 7% to 8% of RMS tumors (106). In addition, FGFR4 is often highly expressed in RMS and FGFR4 expression correlates with advanced stage and poor survival (37, 106, 107). Several of the mutations identified in RMS were clustered in the kinase domain, and at least two of them, N535K and V550E, promoted autophosphorylation of the receptor. The oncogenic potential of the mutations was examined in murine RMS models as well as in several cell lines, and the mutations were reported to increase invasiveness, metastasis, and poor survival (106). The ability to invade tissue and form metastasis is the cause of 90% of human cancer deaths (1). Thus, FGFR4 is a strong candidate for targeted therapy in patients with RMS.

FGFR fusion proteins

Chromosomal rearrangements can lead to intragenic, reciprocal translocations, which result in fusion proteins. The fusion protein can exhibit functional properties derived from each of the original proteins, and the result can be a potent oncogene. At least 11 fusion partners have been identified for FGFR1 to date. These include ZNF198, FOP, and BCR (Fig. 2; Table 2; ref. 108). For FGFR3, one partner has been identified (Table 2; ref. 109). In these fusion proteins, the tyrosine kinase domain of the FGFR is typically juxtaposed to a dimerization domain from the partner gene, inducing constitutive dimerization and activation of the tyrosine kinase (108). Most of the FGFR fusion proteins are identified in patients with the myeloproliferative disorder stem cell leukemia/lymphoma syndrome (SCLL; also known as the 8p11 myeloproliferative syndrome; ref. 110). SCLL is a rare condition that rapidly progresses into acute leukemia, and treatment with conventional chemotherapy is often not effective. Some of the FGFR fusion proteins have been shown to transform cell lines and

Table 1. Point mutations of FGFRs identified in human tumors

	FGFR1			FGFR2		
	Mut	Cancer	Refs.	Mut	Cancer	Refs.
Extracellular part						
N-term				S24F	Skin	89
				V77M	Skin	89
IgI	G70R (SNP)	Lung	86	A97T	Cervix	85
				D101Y	Endometrial	85
	S125L	Breast	76			
	T141R (SNP)	Lung	86			
IgII				R203C	Breast	76
				N211I	Lung	85
				Q212K	Brain	175
				H213Y	Skin	89
				G227E	Skin	89
				V248D	Skin	89
				S252W	Endometrial,	85
	P252T	Lung	76,77		Ovary	176
				P253R	Endometrial	85
				S267P	Stomach	83
IgIII				G272V	Ovary	76
				D283N	Lung	76,77
				W290C	Lung	76,77,85
				A314D	Endometrial	85
				S372C	Endometrial	104
				Y375C	Endometrial	87,104
					ovary	176
Trans-Membr. Domain				I380V (SNP)	Lung	86
				C382R	Endometrial	85,87
				A389T	Endometrial	85
				M391R	Endometrial	87
Intracellular part						
Tyrosine Kinase Domain						
				W474X	Skin	89
				H544Q (SNP)	Lung	86
				I547V	Endometrial	87
	N546K	Brain	74	N549K	Endometrial	87
	R576W	Brain	74	E574K	Skin	89
	K656E	Brain	175	R612T [†]	Lung	76
	V664L	Lung	76	I642V	Skin	89
				K659M/N/E	Endometrial	85,87
				S688F	Skin	89
				P708S	Skin	89
C-term						

(Continued on the following page)

induce SCLL or chronic myelogenous leukemia-like diseases in mice (111-115). Growth of ZNF198-FGFR1- or BCR-FGFR1-expressing cell lines is blocked by FGFR inhibition, and treatment of FGFR1OP2-FGFR1-positive cells with a multitargeted tyrosine kinase inhibitor or small interfering RNA against FGFR1 resulted in apoptosis (113, 115-117). Furthermore, treatment with a multityrosine kinase inhibitor resulted in prolonged survival in a murine model of ZNF198-FGFR1-induced myeloproliferative disorder, and administration of the tyrosine kinase inhibitor to

a patient with SCLL was beneficial, although not sufficient (113). Taken together, the data indicate that FGFR-targeted therapy may be beneficial for patients with SCLL.

Availability of ligand

Increased ligand availability might lead to increased FGFR signaling. Both inappropriate expression of FGFs, such as upregulation of FGF expression in malignant cells or in the environment surrounding the malignant cells, and release of FGFs from local reservoirs in the

Table 1. Point mutations of FGFRs identified in human tumors (Cont'd)

FGFR3			FGFR4		
Mut	Cancer	Refs.	Mut	Cancer	Refs.
T79S	Lung	76	C56S	RMS	106
			R72L	RMS	106
			T122A	RMS	106
G197S	MM	177	A175T	RMS	106
C228R	Colon	76	R183S (SNP)	Lung	86
Y241C	MM	178	S232I (SNP)	Lung	86
			R234H	RMS	106
R248C	Bladder, MM, Head and neck	81,92,99,179,182 75			
S249C	Cervix, bladder, Head and neck prostate	180,81,99,182 181 84			
E322K	Colon	83			
G370C	Bladder	81,92,99,182			
S371C	Bladder	92,99,182			
Y373C	Bladder	81,92,99,182			
1376C	Bladder	99	G388R (SNP)*	Lung, RMS, liver, Soft tissue sarcoma	155,190,106 189
G380R	Bladder	92,99,182		Breast, skin	151,153
F384L	Bladder	182		Colon, prostate, Head and neck	151,152 154
A391E	MM. prostate Bladder, prostate	183,84 92,99,84			
E466K	Brain	184			
D617G	Head and Neck	75	N535D/K	RMS	106
V630M	Head and Neck	75	V550E/L/M [†]	RMS, breast	106,76
D646Y	Bladder	185	A554V	RMS	106
K650E/Q/M/N/T	Bladder, testis	76,81,92,186,187	G576D	RMS	106
E686K	Head and neck	75	R616G (SNP)	Lung	86
G697C	Head and neck	188	E681K (SNP)	Lung	86
			P712T [†]	Lung	76,77
			A729G (SNP)	Lung	86
			S772N [†]	Lung	76

NOTE: The different domains of the receptors are indicated to the left. Mutated FGFRs where functional experiments showed loss-of-function mutations are indicated in blue and gain-of-function mutations are indicated in red. The black labeling indicates mutations where the function has not been determined experimentally. Mutations only identified in cell lines are not included in the table. Note that, in the literature, some of the mutations are numbered relative to the alternative Ig IIIc or IIIb isoforms, whereas we here only number the mutations relative to FGFR1 IIIc (NM_023110), FGFR2 IIIc (NP_000132), FGFR3 IIIc (NP_000133), and FGFR4 (X57205).

Abbreviation: X, stop codon.

*FGFR4 G388R allele is common and occurs in ~50% of the population (151).

[†]FGFR4 V550M, P712T, and S772N are referred to as V510M, P672T, and S732N (respectively) in the literature and in the COSMIC database, due to a numbering relative to FGFR4 transcript variant 2, which lacks 40 amino acids (including the transmembrane domain), compared with X57205.

[‡]FGFR2 R612T is referred to as R496T in the literature due to a numbering relative to FGFR2 isoform 7 precursor, which lacks two exons compared with transcript variant 1.

Table 2. FGFR fusion proteins identified in human cancer

Receptor	Fusion partner	Cancer	References
FGFR1	ZNF198/RAMP/ FIM/ZMYM2	SCLL	191
	FOP/FGFR1OP1	SCLL, lung	192, 193
	CEP110/CEP1	SCLL	193
	BCR	SCLL	115
	LRRFIP1	SCLL	194
	FGFR1OP2	SCLL, acute myeloid leukemia	116, 195
	TRIM24/TIF1	SCLL	196
	MYO18A	SCLL	197
	CPSF6	SCLL	198
	HERV-K	SCLL	199
	PLAG1*	Head and neck	200
FGFR3	TEL/ETV6	T-cell lymphoma	201

NOTE: Fusion proteins reported to display oncogenic properties in cell lines and mouse models are indicated in red. The black labeling indicates fusion proteins, where the function has not been determined experimentally.

*The fusion protein does not include the tyrosine kinase domain of FGFR.

extracellular matrix might lead to increased ligand availability. Increased levels of FGFs have been found in several human cancers, and studies done in mouse models or cancer cell lines have revealed their oncogenic potentials.

For example, elevated levels of FGF8 have been reported in human breast and prostate cancer (33, 118-120). FGF8 as well as FGF3 and FGF4 have been identified as mammary proto-oncogenes in MMTV (mouse mammary tumor virus)-infected mice (121-123), and transgenic mice overexpressing FGF8 in prostate epithelial cells developed PINs (124). In an *in vivo* mouse model of prostate cancer bone metastasis, intratibial inoculations of prostate cancer cells expressing FGF8 increased the tumor occurrence and growth compared with nonexpressing cells (125). This indicates a role of FGF8 in metastasis. Interestingly, a neutralizing antibody against FGF8 displays potent antitumor activity against mammary and prostate tumors in mouse models (126, 127) and might be considered as a candidate for therapeutic treatment of cancers that are dependent on FGF8 signaling for growth and survival.

Elevated levels of FGF2 might also play an important role in cancer progression. FGF2 is a potent angiogenic factor, and antisense-mediated inhibition of FGF2 in human melanoma xenografts led to tumor regression and block of intratumoral angiogenesis (128). Although FGF2 levels are elevated in several human cancers, the FGF2 levels do not generally correlate with microvessel density (129). Thus, FGF2 may contribute to cancer pro-

gression not only by playing a role in angiogenesis but also by acting directly on tumor cells. Moreover, there is substantial cross talk between FGF and VEGF signaling in angiogenesis, and in some cases, FGF-induced signaling may mediate resistance to VEGF receptor targeting (130). Recent studies have identified FGF2 inhibitors such as an FGF2-binding peptide and a neutralizing antibody to FGF2 with antitumor activities (131-133).

Abnormal expression of FGFs in the environment surrounding malignant cells has been reported in head and neck squamous carcinoma (134). Moreover, studies from a mouse model, which allows for genetic manipulation of the prostate epithelium and mesenchyme, independently showed that enhanced expression of mesenchymal FGF10 was sufficient to induce epithelial transformation and the formation of well-differentiated prostate carcinoma (135). These data indicate an important role of FGFs produced in the tumor microenvironment for cancer progression.

An increase in the release of FGFs sequestered in the extracellular matrix could also lead to excessive FGF signaling. FGFs have a high affinity to HSPG, and most secreted FGFs are retained by the pericellular heparan sulfates in the location where they are produced. Thus, most FGFs function in an autocrine or paracrine manner. FGFs can be released from local reservoirs in the extracellular matrix by enzymatic cleavage of extracellular matrix components (136). Tumor cells and cells in the tumor microenvironment readily secrete proteases and heparanases, which degrade the extracellular matrix and enable the tumor cells to migrate into adjacent tissues (137, 138). Secretion of proteases and heparanases could also lead to release of the sequestered FGFs and in that way increase FGF signaling.

Mutations in the genes encoding FGFs can give rise to FGFs with altered properties, which may cause deregulated FGFR signaling. However, only a few mutations in the genes encoding FGFs have been described in human cancer. Six different somatic mutations in FGF9 have been identified in colorectal and endometrial cancer (139). All of these mutations were predicted to result in loss of FGF9 function, and it is not clear how, or if, these mutations play a role in malignant growth.

Impaired termination of FGFR signaling

Impaired downregulation of FGFR activity can lead to imbalanced FGFR signaling. Termination of FGFR signaling occurs through dephosphorylation/phosphorylation events and by endocytosis and degradation of the receptor in lysosomes. For example, activated MAPKs can phosphorylate FRS2 on threonine and serine residues, which, in contrast to phosphorylated tyrosine residues, inhibit MAPK activation (140). Thus, there is a MAPK-mediated negative feedback mechanism for the control of FGFR signaling pathways that are dependent on FRS2. FGFR signaling can also be attenuated through the activation of phosphatases, such as the MAPK phosphatases, or by Sprouty and Sef proteins (20). It is worth to note that most of these factors are common regulators of signaling cascades induced by multiple growth factors.

In the case of Sef, its protein expression is decreased in intermediate or high-grade tumors originating from the breast, ovary, thyroid, and prostate (141). Recent studies showed that Sef attenuates FGF-mediated mitogenic stimulation in prostate cancer cells and that loss of Sef is associated with high-grade and metastatic prostate cancer (142, 143). Furthermore, loss of Sef correlated with increased FGF2, FGF8, and FGFR4 expression in metastatic prostate tumors (144). Thus, loss of regulatory factors that control the activity of FGFRs can play a role in carcinogenesis and the development of a malignant phenotype.

Endocytosis followed by degradation of FGFRs in lysosomes leads to termination of signaling (21, 145). Disruptions in any of the endocytic components required for this pathway may delay signal termination and lead to oncogenesis (146). Several endocytic components have been found mutated in different types of cancers (147, 148). Moreover, changes/mutations in the receptors could uncouple the receptor from the endocytic pathway, trapping the receptor at the cell surface or in endosomes, and result in sustained signaling (148). Interestingly, some of the oncogenic FGFR mutants have been shown to be inefficiently degraded. For example, the constitutively active mutants of FGFR3, K650E and G380R, which are found in bladder, prostate, and testicle cancer, and MM, as well as in skeletal disorders (Table 1), were shown to escape into a recycling pathway, where they accumulated as active receptors with a half-life of about twice that of wild-type FGFR3 (149). Thus, defective endocytosis contributes to the gain of function of these FGFR3 mutants.

Splicing variants of FGFR2 IIIb with deletions in the COOH-terminal tail of the receptor show upregulated expression in some cancer cell lines and enhanced transforming properties compared with full-length FGFR2 IIIb (64, 66, 68, 150). A recent report suggests that the potent transforming potential of these splicing variants could be mediated, at least in part, by a mechanism involving loss of an endocytic signal sequence in the COOH-terminal tail of the receptor (67). Loss of the endocytic signal sequence led to impaired receptor internalization and thus enhanced receptor signaling.

Another example concerns the germline SNP in FGFR4, which results in the expression of either glycine or arginine at codon 388. Some reports show that FGFR4 G388R is associated with poor prognosis in several malignancies such as lung, skin, head and neck, colon, breast, and prostate cancer (151-155). Others, however, find no correlation between FGFR4 G388R and poor prognosis (156-159). The FGFR4 G388R allele is common and occurs with at least one copy in ~50% of the population (151). Breast cancer studies correlate FGFR4 G388R with higher resistance to chemotherapy, and expression of FGFR4 G388R in breast cancer cell lines has been shown to increase cell motility and invasion (151, 160). Moreover, FGFR4 G388R promoted breast cancer progression and metastasis in a mouse mammary carcinoma model (161). Recently, it was reported that degradation of FGFR4 G388R was markedly decreased compared with wild-type FGFR4, resulting in

sustained signaling, and thereby probably contributing to its oncogenic potential (162).

FGFR signaling and tumor suppression

As mentioned above, the role of deregulated RTKs in cancer is most often attributed to increased receptor activity, leading to oncogenic transformation. FGFRs have, however, also been suggested to have tumor suppressor activity. The fact that downregulated expression of FGFRs has been observed in several cancer types suggests a tumor suppressor role of FGFR signaling in these cases. This is best illustrated by studies of FGFR2. Reduced expression of FGFR2 has been reported in several human cancers, such as bladder, liver, salivary gland, and prostate cancer (163-166). In addition, several loss-of-function mutations in FGFR2 have been identified in melanoma (89). Interestingly, studies in mice have shown that mutant mice with a FGFR2 IIIb deletion in keratinocytes were highly sensitive to carcinogenic insult and developed an increased number of papillomas and carcinomas compared with wild-type mice. This suggests a tumor-protective role of FGFR2 in keratinocytes (167). Furthermore, a switch from the FGFR2 IIIb to the FGFR2 IIIc splice variant during carcinogenesis in prostate and bladder rat models resulted in a more malignant phenotype. This was probably due to the altered ligand-receptor specificity, creating an FGF autocrine signaling loop (see text above). However, reexpression of the FGFR2 IIIb isoform in prostate and bladder cancer cell lines resulted in growth suppression *in vitro* and in reduced tumor formation *in vivo* (168-170).

Taken together, these data indicate a tumor-suppressive role of FGFR2 in carcinogenesis. On the other hand, FGFR2 is often found to be overexpressed in human cancers such as cancer of the stomach, pancreas, and breast (31, 49, 171, 172), and activating mutations have been identified in several human cancers including endometrial and lung cancer (77, 85, 87). It is currently not well understood how FGFR2 signaling in some cells seems to exhibit tumor-suppressive effects, whereas FGFR2 signaling displays oncogenic effects in others. It is clear, however, that signaling is dependent on the context. For instance, in a mouse model of the childhood brain tumor medulloblastoma, FGF2 halted proliferation of medulloblastoma cells by inhibition of Sonic hedgehog signaling and thereby suppressed the growth of the tumor cells (173). Context-dependent variations in FGFR signaling could thus explain the different roles of FGFRs in human cancers.

Perspectives

In summary, several alterations, most often leading to increased FGFR signaling, have been associated with human carcinogenesis. Moreover, numerous *in vitro* and *in vivo* studies connect increased FGFR signaling, due to either increased receptor expression, activating mutations, increased ligand availability, or impaired termination of signaling, with carcinogenesis and the development of a

malignant phenotype. Aberrant FGFR signaling can alter cell physiology, and many of the acquired traits that the cells gain or lose on impaired FGFR signaling are similar to those described by Hanahan and Weinberg (1) as the hallmarks of cancer cells. Clearly, imbalanced FGFR signaling can contribute to carcinogenesis and could thus be a potent therapeutic target in several human cancers. Several promising FGFR tyrosine kinase inhibitors and FGFR-blocking antibodies have been developed, and some of them are in early phases of clinical trials (20, 174).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

- Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100:57–70.
- Kroemer G, Pouyssegur J. Tumor cell metabolism: cancer's Achilles' heel. *Cancer Cell* 2008;13:472–82.
- Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. *Cell* 2009;136:823–37.
- Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009;30:1073–81.
- Stratton MR, Campbell PJ, Futreal PA. The cancer genome. *Nature* 2009;458:719–24.
- Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell* 2000;103:211–25.
- Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell* 2010;141:1117–34.
- Witsch E, Sela M, Yarden Y. Roles for growth factors in cancer progression. *Physiology (Bethesda)* 2010;25:85–101.
- Johnson DE, Williams LT. Structural and functional diversity in the FGF receptor multigene family. *Adv Cancer Res* 1993;60:1–41.
- Olsen SK, Ibrahim OA, Raucci A, et al. Insights into the molecular basis for fibroblast growth factor receptor autoinhibition and ligand-binding promiscuity. *Proc Natl Acad Sci U S A* 2004;101:935–40.
- Zhang X, Ibrahim OA, Olsen SK, Umemori H, Mohammadi M, Ornitz DM. Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. *J Biol Chem* 2006;281:15694–700.
- Ornitz DM, Xu J, Colvin JS, et al. Receptor specificity of the fibroblast growth factor family. *J Biol Chem* 1996;271:15292–7.
- Schlessinger J, Plotnikov AN, Ibrahim OA, et al. Crystal structure of a ternary FGF-FGFR-heparin complex reveals a dual role for heparin in FGFR binding and dimerization. *Mol Cell* 2000;6:743–50.
- Lew ED, Furdul CM, Anderson KS, Schlessinger J. The precise sequence of FGF receptor autophosphorylation is kinetically driven and is disrupted by oncogenic mutations. *Sci Signal* 2009;2:ra6.
- Chen H, Ma J, Li W, et al. A molecular brake in the kinase hinge region regulates the activity of receptor tyrosine kinases. *Mol Cell* 2007;27:717–30.
- Mohammadi M, Dikic I, Sorokin A, Burgess WH, Jaye M, Schlessinger J. Identification of six novel autophosphorylation sites on fibroblast growth factor receptor 1 and elucidation of their importance in receptor activation and signal transduction. *Mol Cell Biol* 1996;16:977–89.
- Mohammadi M, Honegger AM, Rotin D, et al. A tyrosine-phosphorylated carboxy-terminal peptide of the fibroblast growth factor receptor (Fig) is a binding site for the SH2 domain of phospholipase C- γ 1. *Mol Cell Biol* 1991;11:5068–78.
- Eswarakumar VP, Lax I, Schlessinger J. Cellular signaling by fibroblast growth factor receptors. *Cytokine Growth Factor Rev* 2005;16:139–49.
- Klint P, Claesson-Welsh L. Signal transduction by fibroblast growth factor receptors. *Front Biosci* 1999;4:D165–177.
- Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer* 2010;10:116–29.
- Haugsten EM, Malecki J, Bjorklund SM, Olsnes S, Wesche J. Ubiquitination of fibroblast growth factor receptor 1 is required for its intracellular sorting but not for its endocytosis. *Mol Biol Cell* 2008;19:3390–403.
- Dailey L, Ambrosetti D, Mansukhani A, Basilico C. Mechanisms underlying differential responses to FGF signaling. *Cytokine Growth Factor Rev* 2005;16:233–47.
- Powers CJ, McLeskey SW, Wellstein A. Fibroblast growth factors, their receptors and signaling. *Endocr Relat Cancer* 2000;7:165–97.
- Dillon C, Spencer-Dene B, Dickson C. A crucial role for fibroblast growth factor signaling in embryonic mammary gland development. *J Mammary Gland Biol Neoplasia* 2004;9:207–15.
- Mailleux AA, Spencer-Dene B, Dillon C, et al. Role of FGF10/FGFR2b signaling during mammary gland development in the mouse embryo. *Development* 2002;129:53–60.
- Lu P, Ewald AJ, Martin GR, Werb Z. Genetic mosaic analysis reveals FGF receptor 2 function in terminal end buds during mammary gland branching morphogenesis. *Dev Biol* 2008;321:77–87.
- Parsa S, Ramasamy SK, De LS, et al. Terminal end bud maintenance in mammary gland is dependent upon FGFR2b signaling. *Dev Biol* 2008;317:121–31.
- Murakami M, Simons M. Fibroblast growth factor regulation of neovascularization. *Curr Opin Hematol* 2008;15:215–20.
- Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov* 2009;8:235–53.
- Chin K, DeVries S, Fridlyand J, et al. Genomic and transcriptional aberrations linked to breast cancer pathophysiologies. *Cancer Cell* 2006;10:529–41.
- Toyokawa T, Yashiro M, Hirakawa K. Co-expression of keratinocyte growth factor and K-sam is an independent prognostic factor in gastric carcinoma. *Oncol Rep* 2009;21:875–80.
- Behrens C, Lin HY, Lee JJ, et al. Immunohistochemical expression of basic fibroblast growth factor and fibroblast growth factor receptors 1 and 2 in the pathogenesis of lung cancer. *Clin Cancer Res* 2008;14:6014–22.
- Kwabi-Addo B, Ozen M, Iltmann M. The role of fibroblast growth factors and their receptors in prostate cancer. *Endocr Relat Cancer* 2004;11:709–24.
- Chang H, Stewart AK, Qi XY, Li ZH, Yi QL, Trudel S. Immunohistochemistry accurately predicts FGFR3 aberrant expression and t(4;14) in multiple myeloma. *Blood* 2005;106:353–5.
- Allerstorfer S, Sonvilla G, Fischer H, et al. FGF5 as an oncogenic factor in human glioblastoma multiforme: autocrine and paracrine activities. *Oncogene* 2008;27:4180–90.
- Freier K, Schwaenen C, Sticht C, et al. Recurrent FGFR1

Acknowledgments

We thank Drs. Kaisa Haglund and Vigdis Sørensen for critical reading of the manuscript. We apologize for the many studies that could not be cited due to space restrictions.

Grant Support

E.M. Haugsten is a postdoctoral fellow of the Norwegian Cancer Society and J. Wesche has a research fellowship from the Norwegian Cancer Society.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 04/19/2010; revised 09/17/2010; accepted 10/01/2010; published OnlineFirst 10/13/2010.

- amplification and high FGFR1 protein expression in oral squamous cell carcinoma (OSCC). *Oral Oncol* 2007;43:60–6.
37. Baird K, Davis S, Antonescu CR, et al. Gene expression profiling of human sarcomas: insights into sarcoma biology. *Cancer Res* 2005;65:9226–35.
 38. Gelsi-Boyer V, Orsetti B, Cervera N, et al. Comprehensive profiling of 8p11-12 amplification in breast cancer. *Mol Cancer Res* 2005;3:655–67.
 39. Letessier A, Sircoulomb F, Ginestier C, et al. Frequency, prognostic impact, and subtype association of 8p12, 8q24, 11q13, 12p13, 17q12, and 20q13 amplifications in breast cancers. *BMC Cancer* 2006;6:245.
 40. Ray ME, Yang ZQ, Albertson D, et al. Genomic and expression analysis of the 8p11-12 amplicon in human breast cancer cell lines. *Cancer Res* 2004;64:40–7.
 41. Bernard-Pierrot I, Gruel N, Stransky N, et al. Characterization of the recurrent 8p11-12 amplicon identifies PPAPDC1B, a phosphatase protein, as a new therapeutic target in breast cancer. *Cancer Res* 2008;68:7165–75.
 42. Garcia MJ, Pole JC, Chin SF, et al. A 1 Mb minimal amplicon at 8p11-12 in breast cancer identifies new candidate oncogenes. *Oncogene* 2005;24:5235–45.
 43. Xian W, Pappas L, Pandya D, et al. Fibroblast growth factor receptor 1-transformed mammary epithelial cells are dependent on RSK activity for growth and survival. *Cancer Res* 2009;69:2244–51.
 44. Xian W, Schwertfeger KL, Vargo-Gogola T, Rosen JM. Pleiotropic effects of FGFR1 on cell proliferation, survival, and migration in a 3D mammary epithelial cell model. *J Cell Biol* 2005;171:663–73.
 45. Reis-Filho JS, Simpson PT, Turner NC, et al. FGFR1 emerges as a potential therapeutic target for lobular breast carcinomas. *Clin Cancer Res* 2006;12:6652–62.
 46. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature* 2007;447:1087–93.
 47. Hunter DJ, Kraft P, Jacobs KB, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet* 2007;39:870–4.
 48. Meyer KB, Maia AT, O'Reilly M, et al. Allele-specific up-regulation of FGFR2 increases susceptibility to breast cancer. *PLoS Biol* 2008;6:e108.
 49. Turner N, Lambros MB, Horlings HM, et al. Integrative molecular profiling of triple negative breast cancers identifies amplicon drivers and potential therapeutic targets. *Oncogene* 2010;10:116–29.
 50. Sahadevan K, Darby S, Leung HY, Mathers ME, Robson CN, Gnanapragasam VJ. Selective over-expression of fibroblast growth factor receptors 1 and 4 in clinical prostate cancer. *J Pathol* 2007;213:82–90.
 51. Giri D, Ropiquet F, Ittmann M. Alterations in expression of basic fibroblast growth factor (FGF) 2 and its receptor FGFR-1 in human prostate cancer. *Clin Cancer Res* 1999;5:1063–71.
 52. Hamaguchi A, Tooyama I, Yoshiki T, Kimura H. Demonstration of fibroblast growth factor receptor-1 in human prostate by polymerase chain reaction and immunohistochemistry. *Prostate* 1995;27:141–7.
 53. Freeman KW, Welm BE, Gangula RD, et al. Inducible prostate intraepithelial neoplasia with reversible hyperplasia in conditional FGFR1-expressing mice. *Cancer Res* 2003;63:8256–63.
 54. Acevedo VD, Gangula RD, Freeman KW, et al. Inducible FGFR-1 activation leads to irreversible prostate adenocarcinoma and an epithelial-to-mesenchymal transition. *Cancer Cell* 2007;12:559–71.
 55. Winter SF, Acevedo VD, Gangula RD, Freeman KW, Spencer DM, Greenberg NM. Conditional activation of FGFR1 in the prostate epithelium induces angiogenesis with concomitant differential regulation of Ang-1 and Ang-2. *Oncogene* 2007;26:4897–907.
 56. Chesi M, Nardini E, Brents LA, et al. Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3. *Nat Genet* 1997;16:260–4.
 57. Keats JJ, Reiman T, Belch AR, Pilarski LM. Ten years and counting: so what do we know about t(4;14)(p16;q32) multiple myeloma. *Leuk Lymphoma* 2006;47:2289–300.
 58. Trudel S, Ely S, Farooqi Y, et al. Inhibition of fibroblast growth factor receptor 3 induces differentiation and apoptosis in t(4;14) myeloma. *Blood* 2004;103:3521–8.
 59. Qing J, Du X, Chen Y, et al. Antibody-based targeting of FGFR3 in bladder carcinoma and t(4;14)-positive multiple myeloma in mice. *J Clin Invest* 2009;119:1216–29.
 60. Grand EK, Chase AJ, Heath C, Rahemtulla A, Cross NC. Targeting FGFR3 in multiple myeloma: inhibition of t(4;14)-positive cells by SU5402 and PD173074. *Leukemia* 2004;18:962–6.
 61. Trudel S, Stewart AK, Rom E, et al. The inhibitory anti-FGFR3 antibody, PRO-001, is cytotoxic to t(4;14) multiple myeloma cells. *Blood* 2006;107:4039–46.
 62. Keats JJ, Reiman T, Maxwell CA, et al. In multiple myeloma, t(4;14)(p16;q32) is an adverse prognostic factor irrespective of FGFR3 expression. *Blood* 2003;101:1520–9.
 63. Zingone A, Cultraro CM, Shin DM, et al. Ectopic expression of wild-type FGFR3 cooperates with MYC to accelerate development of B-cell lineage neoplasms. *Leukemia* 2010;24:1171–8.
 64. Cha JY, Lambert QT, Reuther GW, Der CJ. Involvement of fibroblast growth factor receptor 2 isoform switching in mammary oncogenesis. *Mol Cancer Res* 2008;6:435–45.
 65. Ezzat S, Zheng L, Zhu XF, Wu GE, Asa SL. Targeted expression of a human pituitary tumor-derived isoform of FGF receptor-4 recapitulates pituitary tumorigenesis. *J Clin Invest* 2002;109:69–78.
 66. Itoh H, Hattori Y, Sakamoto H, et al. Preferential alternative splicing in cancer generates a K-sam messenger RNA with higher transforming activity. *Cancer Res* 1994;54:3237–41.
 67. Cha JY, Maddileti S, Mitin N, Harden TK, Der CJ. Aberrant receptor internalization and enhanced FRS2-dependent signaling contribute to the transforming activity of the fibroblast growth factor receptor 2 IIIb C3 isoform. *J Biol Chem* 2009;284:6227–40.
 68. Takeda M, Arai T, Yokote H, et al. AZD2171 shows potent antitumor activity against gastric cancer over-expressing fibroblast growth factor receptor 2/keratinocyte growth factor receptor. *Clin Cancer Res* 2007;13:3051–7.
 69. Savagner P, Valles AM, Jouanneau J, Yamada KM, Thiery JP. Alternative splicing in fibroblast growth factor receptor 2 is associated with induced epithelial-mesenchymal transition in rat bladder carcinoma cells. *Mol Biol Cell* 1994;5:851–62.
 70. Yan G, Fukabori Y, McBride G, Nikolaropolous S, McKeenan WL. Exon switching and activation of stromal and embryonic fibroblast growth factor (FGF)-FGF receptor genes in prostate epithelial cells accompany stromal independence and malignancy. *Mol Cell Biol* 1993;13:4513–22.
 71. Oltean S, Sorg BS, Albrecht T, et al. Alternative inclusion of fibroblast growth factor receptor 2 exon IIIc in Dunning prostate tumors reveals unexpected epithelial mesenchymal plasticity. *Proc Natl Acad Sci U S A* 2006;103:14116–21.
 72. Kwabi-Addo B, Ropiquet F, Giri D, Ittmann M. Alternative splicing of fibroblast growth factor receptors in human prostate cancer. *Prostate* 2001;46:163–72.
 73. Wilkie AO. Bad bones, absent smell, selfish testes: the pleiotropic consequences of human FGF receptor mutations. *Cytokine Growth Factor Rev* 2005;16:187–203.
 74. Rand V, Huang J, Stockwell T, et al. Sequence survey of receptor tyrosine kinases reveals mutations in glioblastomas. *Proc Natl Acad Sci U S A* 2005;102:14344–9.
 75. Chou A, Dekker N, Jordan RC. Identification of novel fibroblast growth factor receptor 3 gene mutations in actinic cheilitis and squamous cell carcinoma of the lip. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:535–41.
 76. Greenman C, Stephens P, Smith R, et al. Patterns of somatic mutation in human cancer genomes. *Nature* 2007;446:153–8.
 77. Davies H, Hunter C, Smith R, et al. Somatic mutations of the protein kinase gene family in human lung cancer. *Cancer Res* 2005;65:7591–5.
 78. Ruhe JE, Streit S, Hart S, et al. Genetic alterations in the tyrosine

- kinase transcriptome of human cancer cell lines. *Cancer Res* 2007; 67:11368–76.
79. Tomlinson DC, Hurst CD, Knowles MA. Knockdown by shRNA identifies S249C mutant FGFR3 as a potential therapeutic target in bladder cancer. *Oncogene* 2007;26:5889–99.
 80. van Rhijn BW, van Tilborg AA, Lurkin I, et al. Novel fibroblast growth factor receptor 3 (FGFR3) mutations in bladder cancer previously identified in non-lethal skeletal disorders. *Eur J Hum Genet* 2002; 10:819–24.
 81. van Rhijn BW, Montironi R, Zwarthoff EC, Jobsis AC, Van der Kwast TH. Frequent FGFR3 mutations in urothelial papilloma. *J Pathol* 2002;198:245–51.
 82. Stephens P, Edkins S, Davies H, et al. A screen of the complete protein kinase gene family identifies diverse patterns of somatic mutations in human breast cancer. *Nat Genet* 2005;37:590–2.
 83. Jang JH, Shin KH, Park JG. Mutations in fibroblast growth factor receptor 2 and fibroblast growth factor receptor 3 genes associated with human gastric and colorectal cancers. *Cancer Res* 2001;61: 3541–3.
 84. Hernandez S, de MS, Agell L, et al. FGFR3 mutations in prostate cancer: association with low-grade tumors. *Mod Pathol* 2009;22: 848–56.
 85. Dutt A, Salvesen HB, Chen TH, et al. Drug-sensitive FGFR2 mutations in endometrial carcinoma. *Proc Natl Acad Sci U S A* 2008;105: 8713–7.
 86. Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* 2008;455:1069–75.
 87. Pollock PM, Gartside MG, Dejeza LC, et al. Frequent activating FGFR2 mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes. *Oncogene* 2007;26:7158–62.
 88. Chesi M, Brents LA, Ely SA, et al. Activated fibroblast growth factor receptor 3 is an oncogene that contributes to tumor progression in multiple myeloma. *Blood* 2001;97:729–36.
 89. Gartside MG, Chen H, Ibrahim OA, et al. Loss-of-function fibroblast growth factor receptor-2 mutations in melanoma. *Mol Cancer Res* 2009;7:41–54.
 90. Cheng L, Zhang S, Davidson DD, et al. Molecular determinants of tumor recurrence in the urinary bladder. *Future Oncol* 2009;5:843–57.
 91. Knowles MA. Novel therapeutic targets in bladder cancer: mutation and expression of FGF receptors. *Future Oncol* 2008;4:71–83.
 92. Tomlinson DC, Baldo O, Harnden P, Knowles MA. FGFR3 protein expression and its relationship to mutation status and prognostic variables in bladder cancer. *J Pathol* 2007;213:91–8.
 93. d'Avis PY, Robertson SC, Meyer AN, Bardwell WM, Webster MK, Donoghue DJ. Constitutive activation of fibroblast growth factor receptor 3 by mutations responsible for the lethal skeletal dysplasia thanatophoric dysplasia type I. *Cell Growth Differ* 1998;9:71–8.
 94. Webster MK, d'Avis PY, Robertson SC, Donoghue DJ. Profound ligand-independent kinase activation of fibroblast growth factor receptor 3 by the activation loop mutation responsible for a lethal skeletal dysplasia, thanatophoric dysplasia type II. *Mol Cell Biol* 1996;16:4081–7.
 95. Miyake M, Ishii M, Koyama N, et al. PD173074, a selective tyrosine kinase inhibitor of FGFR3, inhibits cell proliferation of bladder cancer carrying the FGFR3 gene mutation along with up-regulation of p27/Kip1 and G₁/G₀ arrest. *J Pharmacol Exp Ther* 2009;332: 795–802.
 96. Bernard-Pierrot I, Brams A, Dunois-Larde C, et al. Oncogenic properties of the mutated forms of fibroblast growth factor receptor 3b. *Carcinogenesis* 2006;27:740–7.
 97. Martinez-Torrecuadrada J, Cifuentes G, Lopez-Serra P, Saenz P, Martinez A, Casal JL. Targeting the extracellular domain of fibroblast growth factor receptor 3 with human single-chain Fv antibodies inhibits bladder carcinoma cell line proliferation. *Clin Cancer Res* 2005;11:6280–90.
 98. Martinez-Torrecuadrada JL, Cheung LH, Lopez-Serra P, et al. Anti-tumor activity of fibroblast growth factor receptor 3-specific immunotoxins in a xenograft mouse model of bladder carcinoma is mediated by apoptosis. *Mol Cancer Ther* 2008;7:862–73.
 99. Hernandez S, Lopez-Knowles E, Lloreta J, et al. Prospective study of FGFR3 mutations as a prognostic factor in nonmuscle invasive urothelial bladder carcinomas. *J Clin Oncol* 2006;24:3664–71.
 100. Castillo-Martin M, Domingo-Domenech J, Karni-Schmidt O, Matos T, Cordon-Cardo C. Molecular pathways of urothelial development and bladder tumorigenesis. *Urol Oncol* 2010;28:401–8.
 101. Miyake M, Sugano K, Sugino H, et al. Fibroblast growth factor receptor 3 mutation in voided urine is a useful diagnostic marker and significant indicator of tumor recurrence in non-muscle invasive bladder cancer. *Cancer Sci* 2010;101:250–8.
 102. Zuiverloon TC, van der Aa MN, Van der Kwast TH, et al. Fibroblast growth factor receptor 3 mutation analysis on voided urine for surveillance of patients with low-grade non-muscle-invasive bladder cancer. *Clin Cancer Res* 2010;16:3011–8.
 103. Yu K, Herr AB, Waksman G, Ornitz DM. Loss of fibroblast growth factor receptor 2 ligand-binding specificity in Apert syndrome. *Proc Natl Acad Sci U S A* 2000;97:14536–41.
 104. Byron SA, Gartside MG, Wellens CL, et al. Inhibition of activated fibroblast growth factor receptor 2 in endometrial cancer cells induces cell death despite PTEN abrogation. *Cancer Res* 2008;68: 6902–7.
 105. De Giovanni C, Landuzzi L, Nicoletti G, Lollini PL, Nanni P. Molecular and cellular biology of rhabdomyosarcoma. *Future Oncol* 2009; 5:1449–75.
 106. Taylor JG, Cheuk AT, Tsang PS, et al. Identification of FGFR4-activating mutations in human rhabdomyosarcomas that promote metastasis in xenotransplanted models. *J Clin Invest* 2009;119: 3395–407.
 107. Khan J, Wei JS, Ringner M, et al. Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural networks. *Nat Med* 2001;7:673–9.
 108. Jackson CC, Medeiros LJ, Miranda RN. 8p11 myeloproliferative syndrome: a review. *Hum Pathol* 2010;41:461–76.
 109. Maeda T, Yagasaki F, Ishikawa M, Takahashi N, Bessho M. Transforming property of TEL-FGFR3 mediated through PI3-K in a T-cell lymphoma that subsequently progressed to AML. *Blood* 2005;105: 2115–23.
 110. Patnaik MM, Tefferi A. Molecular diagnosis of myeloproliferative neoplasms. *Expert Rev Mol Diagn* 2009;9:481–92.
 111. Roumiantsev S, Krause DS, Neumann CA, et al. Distinct stem cell myeloproliferative/T lymphoma syndromes induced by ZNF198-FGFR1 and BCR-FGFR1 fusion genes from 8p11 translocations. *Cancer Cell* 2004;5:287–98.
 112. Guasch G, Delaval B, Arnoulet C, et al. FOP-FGFR1 tyrosine kinase, the product of a t(6;8) translocation, induces a fatal myeloproliferative disease in mice. *Blood* 2004;103:309–12.
 113. Chen J, Deangelo DJ, Kutok JL, et al. PKC412 inhibits the zinc finger 198-fibroblast growth factor receptor 1 fusion tyrosine kinase and is active in treatment of stem cell myeloproliferative disorder. *Proc Natl Acad Sci U S A* 2004;101:14479–84.
 114. Ren M, Li X, Cowell JK. Genetic fingerprinting of the development and progression of T-cell lymphoma in a murine model of atypical myeloproliferative disorder initiated by the ZNF198-fibroblast growth factor receptor-1 chimeric tyrosine kinase. *Blood* 2009; 114:1576–84.
 115. Demiroglu A, Steer EJ, Heath C, et al. The t(8;22) in chronic myeloid leukemia fuses BCR to FGFR1: transforming activity and specific inhibition of FGFR1 fusion proteins. *Blood* 2001;98:3778–83.
 116. Gu TL, Goss VL, Reeves C, et al. Phosphotyrosine profiling identifies the KG-1 cell line as a model for the study of FGFR1 fusions in acute myeloid leukemia. *Blood* 2006;108:4202–4.
 117. Chase A, Grand FH, Cross NC. Activity of TKI258 against primary cells and cell lines with FGFR1 fusion genes associated with the 8p11 myeloproliferative syndrome. *Blood* 2007;110:3729–34.
 118. Marsh SK, Bansal GS, Zammit C, et al. Increased expression of fibroblast growth factor 8 in human breast cancer. *Oncogene* 1999;18:1053–60.
 119. Mattila MM, Harkonen PL. Role of fibroblast growth factor 8 in growth and progression of hormonal cancer. *Cytokine Growth Factor Rev* 2007;18:257–66.

120. Murphy T, Darby S, Mathers ME, Gnanapragasam VJ. Evidence for distinct alterations in the FGF axis in prostate cancer progression to an aggressive clinical phenotype. *J Pathol* 2009;220:452–60.
121. Theodorou V, Kimm MA, Boer M, et al. MMTV insertional mutagenesis identifies genes, gene families and pathways involved in mammary cancer. *Nat Genet* 2007;39:759–69.
122. Dphna-Iken D, Shankar DB, Lawshe A, Ornitz DM, Shackelford GM, MacArthur CA. MMTV-Fgf8 transgenic mice develop mammary and salivary gland neoplasia and ovarian stromal hyperplasia. *Oncogene* 1998;17:2711–7.
123. MacArthur CA, Shankar DB, Shackelford GM. Fgf-8, activated by proviral insertion, cooperates with the Wnt-1 transgene in murine mammary tumorigenesis. *J Virol* 1995;69:2501–7.
124. Song Z, Wu X, Powell WC, et al. Fibroblast growth factor 8 isoform B overexpression in prostate epithelium: a new mouse model for prostatic intraepithelial neoplasia. *Cancer Res* 2002;62:5096–105.
125. Valta MP, Tuomela J, Bjartell A, Valve E, Vaananen HK, Harkonen P. FGF-8 is involved in bone metastasis of prostate cancer. *Int J Cancer* 2008;123:22–31.
126. Maruyama-Takahashi K, Shimada N, Imada T, et al. A neutralizing anti-fibroblast growth factor (FGF) 8 monoclonal antibody shows anti-tumor activity against FGF8b-expressing LNCaP xenografts in androgen-dependent and -independent conditions. *Prostate* 2008;68:640–50.
127. Shimada N, Ishii T, Imada T, et al. A neutralizing anti-fibroblast growth factor 8 monoclonal antibody shows potent antitumor activity against androgen-dependent mouse mammary tumors *in vivo*. *Clin Cancer Res* 2005;11:3897–904.
128. Wang Y, Becker D. Antisense targeting of basic fibroblast growth factor and fibroblast growth factor receptor-1 in human melanomas blocks intratumoral angiogenesis and tumor growth. *Nat Med* 1997;3:887–93.
129. Presta M, Dell'Era P, Mitola S, Moroni E, Ronca R, Rusnati M. Fibroblast growth factor/fibroblast growth factor receptor system in angiogenesis. *Cytokine Growth Factor Rev* 2005;16:159–78.
130. Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 2005;8:299–309.
131. Tao J, Xiang JJ, Li D, Deng N, Wang H, Gong YP. Selection and characterization of a human neutralizing antibody to human fibroblast growth factor-2. *Biochem Biophys Res Commun* 2010;394:767–73.
132. Li D, Wang H, Xiang JJ, et al. Monoclonal antibodies targeting basic fibroblast growth factor inhibit the growth of B16 melanoma *in vivo* and *in vitro*. *Oncol Rep* 2010;24:457–63.
133. Wang C, Lin S, Nie Y, et al. Mechanism of antitumor effect of a novel bFGF binding peptide on human colon cancer cells. *Cancer Sci* 2010;101:1212–8.
134. Dellacono FR, Spiro J, Eisma R, Kreutzer D. Expression of basic fibroblast growth factor and its receptors by head and neck squamous carcinoma tumor and vascular endothelial cells. *Am J Surg* 1997;174:540–4.
135. Memarzadeh S, Xin L, Mulholland DJ, et al. Enhanced paracrine FGF10 expression promotes formation of multifocal prostate adenocarcinoma and an increase in epithelial androgen receptor. *Cancer Cell* 2007;12:572–85.
136. Whitelock JM, Murdoch AD, Iozzo RV, Underwood PA. The degradation of human endothelial cell-derived perlecan and release of bound basic fibroblast growth factor by stromelysin, collagenase, plasmin, and heparanases. *J Biol Chem* 1996;271:10079–86.
137. Vlodaysky I, Elkin M, Abboud-Jarrous G, et al. Heparanase: one molecule with multiple functions in cancer progression. *Connect Tissue Res* 2008;49:207–10.
138. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. *Nat Rev Cancer* 2009;9:239–52.
139. Abdel-Rahman WM, Kalinina J, Shoman S, et al. Somatic FGF9 mutations in colorectal and endometrial carcinomas associated with membranous β -catenin. *Hum Mutat* 2008;29:390–7.
140. Gotoh N. Regulation of growth factor signaling by FRS2 family docking/scaffold adaptor proteins. *Cancer Sci* 2008;99:1319–25.
141. Zisman-Frozen S, Fink D, Ben-Izhak O, et al. Downregulation of Sef, an inhibitor of receptor tyrosine kinase signaling, is common to a variety of human carcinomas. *Oncogene* 2007;26:6093–8.
142. Darby S, Murphy T, Thomas H, et al. Similar expression to FGF (Sef) inhibits fibroblast growth factor-induced tumorigenic behaviour in prostate cancer cells and is downregulated in aggressive clinical disease. *Br J Cancer* 2009;101:1891–9.
143. Darby S, Sahadevan K, Khan MM, Robson CN, Leung HY, Gnanapragasam VJ. Loss of Sef (similar expression to FGF) expression is associated with high grade and metastatic prostate cancer. *Oncogene* 2006;25:4122–7.
144. Murphy T, Darby S, Mathers ME, Gnanapragasam VJ. Evidence for distinct alterations in the FGF axis in prostate cancer progression to an aggressive clinical phenotype. *J Pathol* 2010;220:452–60.
145. Haugsten EM, Sorensen V, Brech A, Olsnes S, Wesche J. Different intracellular trafficking of FGF1 endocytosed by the four homologous FGF receptors. *J Cell Sci* 2005;118:3869–81.
146. Mosesson Y, Mills GB, Yarden Y. Derailed endocytosis: an emerging feature of cancer. *Nat Rev Cancer* 2008;8:835–50.
147. Haglund K, Rusten TE, Stenmark H. Aberrant receptor signaling and trafficking as mechanisms in oncogenesis. *Crit Rev Oncog* 2007;13:39–74.
148. Abella JV, Park M. Breakdown of endocytosis in the oncogenic activation of receptor tyrosine kinases. *Am J Physiol Endocrinol Metab* 2009;296:E973–984.
149. Cho JY, Guo C, Torello M, et al. Defective lysosomal targeting of activated fibroblast growth factor receptor 3 in achondroplasia. *Proc Natl Acad Sci U S A* 2004;101:609–14.
150. Tannheimer SL, Rehemtulla A, Ethier SP. Characterization of fibroblast growth factor receptor 2 overexpression in the human breast cancer cell line SUM-52PE. *Breast Cancer Res* 2000;2:311–20.
151. Bange J, Prechtel D, Cheburkin Y, et al. Cancer progression and tumor cell motility are associated with the FGFR4 Arg(388) allele. *Cancer Res* 2002;62:840–7.
152. Wang J, Stockton DW, Ittmann M. The fibroblast growth factor receptor-4 Arg388 allele is associated with prostate cancer initiation and progression. *Clin Cancer Res* 2004;10:6169–78.
153. Streit S, Mestel DS, Schmidt M, Ullrich A, Berking C. FGFR4 Arg388 allele correlates with tumour thickness and FGFR4 protein expression with survival of melanoma patients. *Br J Cancer* 2006;94:1879–86.
154. Streit S, Bange J, Fichtner A, Ihrlir S, Issing W, Ullrich A. Involvement of the FGFR4 Arg388 allele in head and neck squamous cell carcinoma. *Int J Cancer* 2004;111:213–7.
155. Spinola M, Leoni V, Pignatiello C, et al. Functional FGFR4 Gly388Arg polymorphism predicts prognosis in lung adenocarcinoma patients. *J Clin Oncol* 2005;23:7307–11.
156. Spinola M, Leoni VP, Tanuma J, et al. FGFR4 Gly388Arg polymorphism and prognosis of breast and colorectal cancer. *Oncol Rep* 2005;14:415–9.
157. Matakidou A, el Galta R, Rudd MF, et al. Further observations on the relationship between the FGFR4 Gly388Arg polymorphism and lung cancer prognosis. *Br J Cancer* 2007;96:1904–7.
158. Jezequel P, Campion L, Joalland MP, et al. G388R mutation of the FGFR4 gene is not relevant to breast cancer prognosis. *Br J Cancer* 2004;90:189–93.
159. Naidu R, Har YC, Taib NA. Polymorphism of FGFR4 Gly388Arg does not confer an increased risk to breast cancer development. *Oncol Res* 2009;18:65–71.
160. Thussbs C, Nahrigh J, Streit S, et al. FGFR4 Arg388 allele is associated with resistance to adjuvant therapy in primary breast cancer. *J Clin Oncol* 2006;24:3747–55.
161. Seitzer N, Mayr T, Streit S, Ullrich A. A single nucleotide change in the mouse genome accelerates breast cancer progression. *Cancer Res* 2010;70:802–12.
162. Wang J, Yu W, Cai Y, Ren C, Ittmann MM. Altered fibroblast growth factor receptor 4 stability promotes prostate cancer progression. *Neoplasia* 2008;10:847–56.

163. Diez de Medina SG, Chopin D, El MA, et al. Decreased expression of keratinocyte growth factor receptor in a subset of human transitional cell bladder carcinomas. *Oncogene* 1997;14:323–30.
164. Naimi B, Latil A, Fournier G, Mangin P, Cussenot O, Berthon P. Down-regulation of (IIb) and (IIIc) isoforms of fibroblast growth factor receptor 2 (FGFR2) is associated with malignant progression in human prostate. *Prostate* 2002;52:245–52.
165. Amann T, Bataille F, Spruss T, et al. Reduced expression of fibroblast growth factor receptor 2IIIb in hepatocellular carcinoma induces a more aggressive growth. *Am J Pathol* 2010;176:1433–42.
166. Zhang Y, Wang H, Toratani S, et al. Growth inhibition by keratinocyte growth factor receptor of human salivary adenocarcinoma cells through induction of differentiation and apoptosis. *Proc Natl Acad Sci U S A* 2001;98:11336–40.
167. Grose R, Fantl V, Werner S, et al. The role of fibroblast growth factor receptor 2b in skin homeostasis and cancer development. *EMBO J* 2007;26:1268–78.
168. Matsubara A, Kan M, Feng S, McKeenan WL. Inhibition of growth of malignant rat prostate tumor cells by restoration of fibroblast growth factor receptor 2. *Cancer Res* 1998;58:1509–14.
169. Ricol D, Cappellen D, El MA, et al. Tumour suppressive properties of fibroblast growth factor receptor 2-IIIb in human bladder cancer. *Oncogene* 1999;18:7234–43.
170. Yasumoto H, Matsubara A, Mutaguchi K, Usui T, McKeenan WL. Restoration of fibroblast growth factor receptor2 suppresses growth and tumorigenicity of malignant human prostate carcinoma PC-3 cells. *Prostate* 2004;61:236–42.
171. Nomura S, Yoshitomi H, Takano S, et al. FGF10/FGFR2 signal induces cell migration and invasion in pancreatic cancer. *Br J Cancer* 2008;99:305–13.
172. Cho K, Ishiwata T, Uchida E, et al. Enhanced expression of keratinocyte growth factor and its receptor correlates with venous invasion in pancreatic cancer. *Am J Pathol* 2007;170:1964–74.
173. Fogarty MP, Emmenegger BA, Gräsfeder LL, Oliver TG, Wechsler-Reya RJ. Fibroblast growth factor blocks Sonic hedgehog signaling in neuronal precursors and tumor cells. *Proc Natl Acad Sci U S A* 2007;104:2973–8.
174. Knights V, Cook SJ. De-regulated FGF receptors as therapeutic targets in cancer. *Pharmacol Ther* 2010;125:105–17.
175. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* 2008;455:1061–8.
176. Byron SA, Gartside MG, Wellens CL, et al. FGFR2 mutations are rare across histologic subtypes of ovarian cancer. *Gynecol Oncol* 2010;117:125–9.
177. Claudio JO, Zhan F, Zhuang L, et al. Expression and mutation status of candidate kinases in multiple myeloma. *Leukemia* 2007;21:1124–7.
178. Onwuazor ON, Wen XY, Wang DY, et al. Mutation, SNP, and isoform analysis of fibroblast growth factor receptor 3 (FGFR3) in 150 newly diagnosed multiple myeloma patients. *Blood* 2003;102:772–3.
179. Intini D, Baldini L, Fabris S, et al. Analysis of FGFR3 gene mutations in multiple myeloma patients with t(4;14). *Br J Haematol* 2001;114:362–4.
180. Cappellen D, De Oliveira C, Ricol D, et al. Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas. *Nat Genet* 1999;23:18–20.
181. Shotelersuk V, Ittiwut C, Shotelersuk K, Triratanachai S, Poovorawan Y, Mutirangura A. Fibroblast growth factor receptor 3 S249C mutation in virus associated squamous cell carcinomas. *Oncol Rep* 2001;8:1301–4.
182. Zieger K, Dyrskjot L, Wiuf C, et al. Role of activating fibroblast growth factor receptor 3 mutations in the development of bladder tumors. *Clin Cancer Res* 2005;11:7709–19.
183. Fracchiolla NS, Luminari S, Baldini L, Lombardi L, Maiolo AT, Neri A. FGFR3 gene mutations associated with human skeletal disorders occur rarely in multiple myeloma. *Blood* 1998;92:2987–9.
184. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science* 2008;321:1807–12.
185. Sung MT, Zhang S, Lopez-Beltran A, et al. Urothelial carcinoma following augmentation cystoplasty: an aggressive variant with distinct clinicopathological characteristics and molecular genetic alterations. *Histopathology* 2009;55:161–73.
186. van Oers JM, Lurkin I, van Exsel AJ, et al. A simple and fast method for the simultaneous detection of nine fibroblast growth factor receptor 3 mutations in bladder cancer and voided urine. *Clin Cancer Res* 2005;11:7743–8.
187. Goriely A, Hansen RM, Taylor IB, et al. Activating mutations in FGFR3 and HRAS reveal a shared genetic origin for congenital disorders and testicular tumors. *Nat Genet* 2009;41:1247–52.
188. Zhang Y, Hiraishi Y, Wang H, et al. Constitutive activating mutation of the FGFR3b in oral squamous cell carcinomas. *Int J Cancer* 2005;117:166–8.
189. Morimoto Y, Ozaki T, Ouchida M, et al. Single nucleotide polymorphism in fibroblast growth factor receptor 4 at codon 388 is associated with prognosis in high-grade soft tissue sarcoma. *Cancer* 2003;98:2245–50.
190. Ho HK, Pok S, Streit S, et al. Fibroblast growth factor receptor 4 regulates proliferation, anti-apoptosis and α -fetoprotein secretion during hepatocellular carcinoma progression and represents a potential target for therapeutic intervention. *J Hepatol* 2009;50:118–27.
191. Xiao S, Nalabolu SR, Aster JC, et al. FGFR1 is fused with a novel zinc-finger gene, ZNF198, in the t(8;13) leukaemia/lymphoma syndrome. *Nat Genet* 1998;18:84–7.
192. Mano Y, Takahashi K, Ishikawa N, et al. Fibroblast growth factor receptor 1 oncogene partner as a novel prognostic biomarker and therapeutic target for lung cancer. *Cancer Sci* 2007;98:1902–13.
193. Sohal J, Chase A, Mould S, et al. Identification of four new translocations involving FGFR1 in myeloid disorders. *Genes Chromosomes Cancer* 2001;32:155–63.
194. Soler G, Nusbaum S, Varet B, et al. LRRFIP1, a new FGFR1 partner gene associated with 8p11 myeloproliferative syndrome. *Leukemia* 2009;23:1359–61.
195. Grand EK, Grand FH, Chase AJ, et al. Identification of a novel gene, FGFR1OP2, fused to FGFR1 in 8p11 myeloproliferative syndrome. *Genes Chromosomes Cancer* 2004;40:78–83.
196. Belloni E, Trubia M, Gasparini P, et al. 8p11 myeloproliferative syndrome with a novel t(7;8) translocation leading to fusion of the FGFR1 and TIF1 genes. *Genes Chromosomes Cancer* 2005;42:320–5.
197. Walz C, Chase A, Schoch C, et al. The t(8;17)(p11;q23) in the 8p11 myeloproliferative syndrome fuses MYO18A to FGFR1. *Leukemia* 2005;19:1005–9.
198. Hidalgo-Curtis C, Chase A, Drachenberg M, et al. The t(1;9)(p34;q34) and t(8;12)(p11;q15) fuse pre-mRNA processing proteins SFPQ (PSF) and CPSF6 to ABL and FGFR1. *Genes Chromosomes Cancer* 2008;47:379–85.
199. Guasch G, Popovici C, Mugneret F, et al. Endogenous retroviral sequence is fused to FGFR1 kinase in the 8p12 stem-cell myeloproliferative disorder with t(8;19)(p12;q13.3). *Blood* 2003;101:286–8.
200. Persson F, Winnes M, Andren Y, et al. High-resolution array CGH analysis of salivary gland tumors reveals fusion and amplification of the FGFR1 and PLAG1 genes in ring chromosomes. *Oncogene* 2008;27:3072–80.
201. Yagasaki F, Wakao D, Yokoyama Y, et al. Fusion of ETV6 to fibroblast growth factor receptor 3 in peripheral T-cell lymphoma with a t(4;12)(p16;p13) chromosomal translocation. *Cancer Res* 2001;61:8371–4.

Molecular Cancer Research

Roles of Fibroblast Growth Factor Receptors in Carcinogenesis

Ellen Margrethe Haugsten, Antoni Wiedlocha, Sjur Olsnes, et al.

Mol Cancer Res 2010;8:1439-1452. Published OnlineFirst October 13, 2010.

Updated version Access the most recent version of this article at:
doi:[10.1158/1541-7786.MCR-10-0168](https://doi.org/10.1158/1541-7786.MCR-10-0168)

Cited articles This article cites 196 articles, 74 of which you can access for free at:
<http://mcr.aacrjournals.org/content/8/11/1439.full#ref-list-1>

Citing articles This article has been cited by 13 HighWire-hosted articles. Access the articles at:
<http://mcr.aacrjournals.org/content/8/11/1439.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://mcr.aacrjournals.org/content/8/11/1439>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.