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Subject Review

Molecular Cancer Research

Roles of Fibroblast Growth Factor Receptors in Carcinogenesis

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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 alteration 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.

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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

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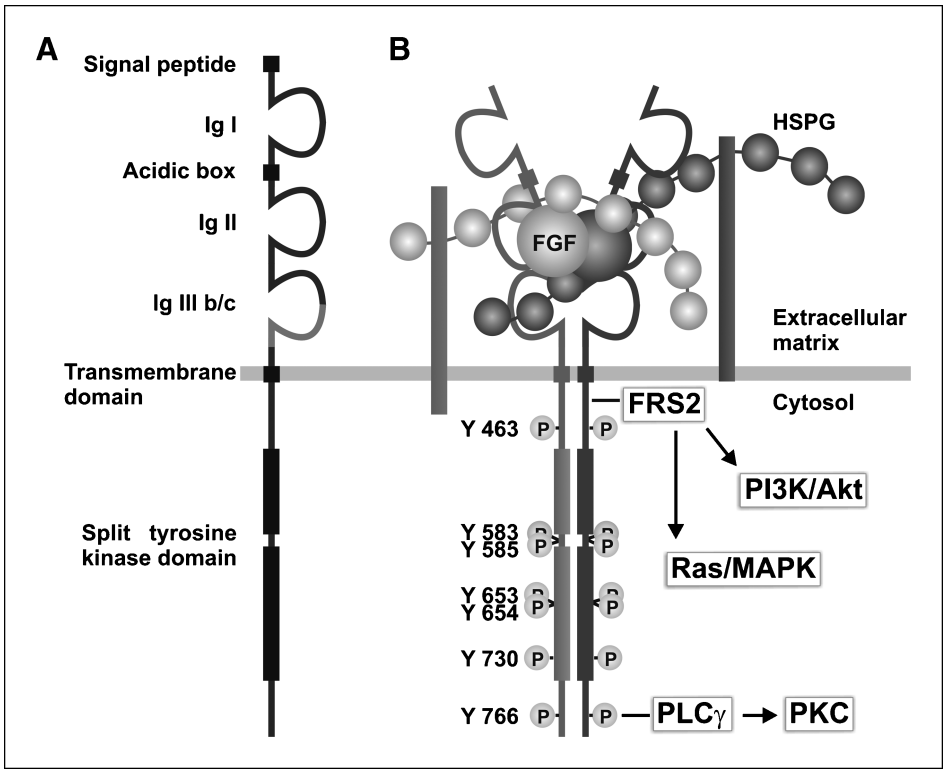

FIGURE 1. A, schematic overview of the prototypical FGFR structure. The Ig-like domains are referred to by their roman numerals. Alternative splicing of the second half of the third Ig-like domain gives rise to alternative IIIb or IIIc isoforms of FGFR1 to FGFR3. B, an illustration of binding of FGF 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).

Altogether, 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 PLCγ (phospholipase Cγ; ref. 18). PLCγ binds directly to an autophosphorylated tyrosine in the COOH-terminal receptor tail (Y766 in FGFR1), resulting in PLCγ phosphorylation and activation. Activated PLCγ 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

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(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

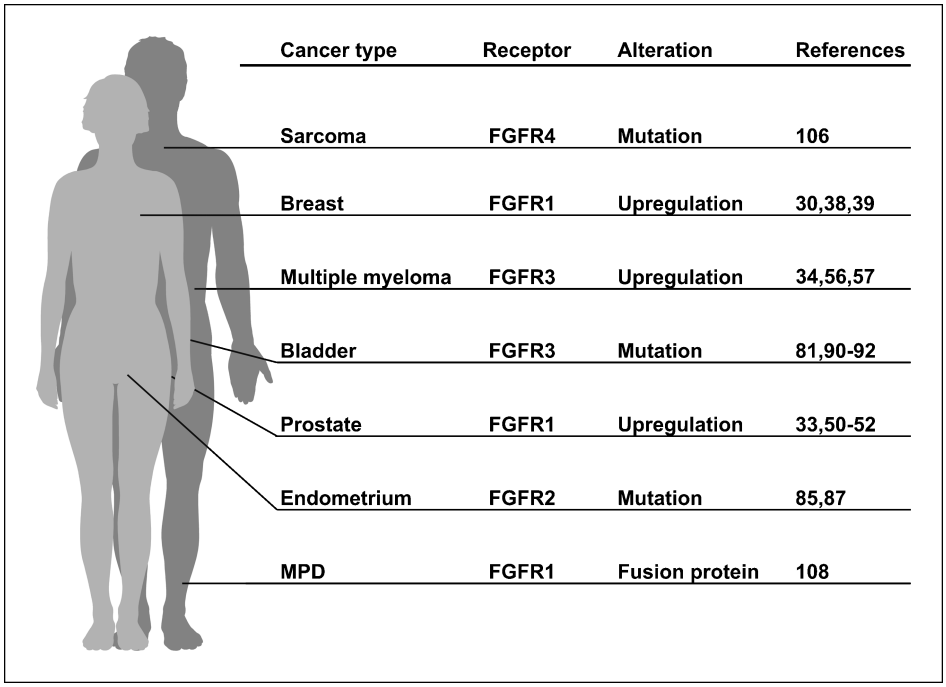

FIGURE 2. Summary of central aberrations of FGFRs in human cancer discussed in the text. The figure was produced using Servier Medical Art. MPD, myeloproliferative disorders.

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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/EBPβ) 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

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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

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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						
				W474X	Skin	89
Tyrosine Kinase Domain				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

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

FGFR3			FGFR4		
Mut	**Cancer**	**Refs.**	**Mut**	**Cancer**	**Refs.**
			C56S	RMS	106
T79S	Lung	76	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,	81,92,99,179,182			
	Head and neck	75			
S249C	Cervix, bladder,	180,81,99,182			
	Head and neck	181			
	prostate	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,	155,190,106
G380R	Bladder	92,99,182		Soft tissue sarcoma	189
F384L	Bladder	182		Breast, skin	151,153
	MM. prostate	183,84		Colon, prostate,	151,152
A391E	Bladder, prostate	92,99,84		Head and neck	154
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			G576D	RMS	106
	Bladder, testis	76,81,92,186,187	R616G (SNP)	Lung	86
E686K	Head and neck	75	E681K (SNP)	Lung	86
G697C	Head and neck	188	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.

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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 progression 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.

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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

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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.

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