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REVIEW ARTICLE

Fibroblast growth factors and their receptors in cancer

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FGFs (fibroblast growth factors) and their receptors (FGFRs) play essential roles in tightly regulating cell proliferation, survival, migration and differentiation during development and adult life. Deregulation of FGFR signalling, on the other hand, has been associated with many developmental syndromes, and with human cancer. In cancer, FGFRs have been found to become overactivated by several mechanisms, including gene amplification, chromosomal translocation and mutations. FGFR alterations are detected in a variety of human cancers, such as breast, bladder, prostate, endometrial and lung cancers, as well as haematological malignancies. Accumulating evidence indicates that FGFs and FGFRs may act in an oncogenic fashion to promote multiple steps of cancer progression by inducing mitogenic and survival signals, as well as promoting epithelial–mesenchymal transition, invasion and tumour angiogenesis. Therapeutic strategies targeting FGFs and FGFRs in human cancer are therefore currently being explored. In the present review we will give an overview of FGF signalling, the main FGFR alterations found in human cancer to date, how they may contribute to specific cancer types and strategies for therapeutic intervention.

Key words: cancer, fibroblast growth factor (FGF), fibroblast growth factor receptor (FGFR), receptor tyrosine kinase, signalling, therapy.

INTRODUCTION

Cancer

Human cancers usually develop through a multi-stage process that may extend over decades. During cancer development, normal cells are progressively transformed into highly malignant cells by accumulating a number of genetic changes and acquiring a set of specific properties that have been summarized as the hallmarks of cancer [1–5]. Four of these hallmarks, self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis and limitless replicative potential, contribute to uncontrolled cancer cell proliferation [1]. Malignant cancer cells also acquire the capabilities of invading the adjacent normal tissue and metastasizing to distant organs, as well as of sustained angiogenesis to access nutrients and oxygen to promote the growth of the tumour [1]. In addition to these six classical hallmarks, further hallmarks of cancer cells have been proposed, including evasion of immune surveillance [6], enhanced anabolic metabolism [5], various stress phenotypes (i.e. DNA damage, and mitotic, metabolic, proteotoxic and oxidative stresses) [4] and genomic instability [3]. Given the complexity of carcinogenesis, the mechanisms and the temporal sequence by which these features are acquired will probably vary between cancer types and subtypes [1].

Cancers may be hereditary or sporadic depending on whether the tumour-causing mutations occur in the germline or in somatic cells respectively [3]. Tumours display a tremendous complexity and heterogeneity in the pattern of mutations, and often display mutations in multiple genes, chromosomal abnormalities and changes in gene expression [4]. The accumulation of genetic alterations leading to overactivation of growth-promoting oncogenes and/or inactivation of growth-inhibitory tumour suppressor genes is strongly linked to tumour progression [7]. It is thought that some mutations, so-called driver mutations, give cancer cells a considerable growth advantage and promote cancer cell expansion, whereas others, termed passenger mutations, do not contribute to cancer progression [8]. Increasing evidence suggests that the continued activity of one or a few driving oncogenes promote the malignant phenotype of tumours that become dependent on these oncogenes for the maintenance of the tumour hallmarks, a phenomenon called ‘oncogene addition’ [9]. RTKs (receptor tyrosine kinases) represent an important family of genes that is commonly affected by mutations and alterations in human cancers.

RTKs in cancer

RTKs constitute a large family of cell-surface receptors with 58 members divided into 20 subfamilies in humans, all of which share a common overall composition with an extracellular ligand-binding region, a single-pass transmembrane domain and an intracellular tyrosine kinase domain [10]. Growth factor binding to the ligand-binding domain induces RTK activation and the initiation of intracellular signalling cascades that control vital

Abbreviations used: BCR, breakpoint cluster region; EGF, epidermal growth factor; EGFR, EGF receptor; EMS, 8p11 myeloproliferative syndrome; EMT, epithelial–mesenchymal transition; ESCRT, endosomal sorting complex required for transport; FGF, fibroblast growth factor; FGFR, FGF receptor; FKHR, forkhead in Rhabdomyosarcoma; FLRT, fibronectin-leucine-rich transmembrane protein; FRS2, FGFR substrate 2; GRB2, growth-factor-receptor-bound protein 2; HGF, hepatocyte growth factor; HSPG, heparan sulfate proteoglycan; MAPK, mitogen-activated protein kinase; MM, multiple myeloma; MMSET, MM SET domain; MT1-MMP, membrane-type 1 matrix metalloproteinase; NCAM, neural cell-adhesion molecule; NSCLC, non-small cell lung carcinoma; PAX3, paired box 3; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PI3K, phosphoinositide 3-kinase; PIN, prostatic intraepithelial neoplasia; PKC, protein kinase C; PLCγ, phospholipase Cγ; RMS, Rhabdomyosarcoma; RTK, receptor tyrosine kinase; SCLC, small cell lung carcinoma; SCLL, stem cell leukaemia lymphoma syndrome; SEF, similar expression to FGF; SNP, single-nucleotide polymorphism; SPRED2, Sprouty-related enabled/vasodilator-stimulated phosphoprotein homology 1 domain-containing protein; UCC, urothelial cell carcinoma; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

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cellular processes, such as cell proliferation, differentiation, migration and survival [10]. RTKs thereby play key roles in maintaining tissue homoeostasis during the development and adult life of multicellular organisms [11,12]. Accumulating evidence indicates that deregulation of RTK signalling, on the other hand, is linked to the development of various human diseases, including cancer [11,13]. Mechanisms that have been implicated to contribute to aberrant RTK activation in carcinogenesis include gene amplification, chromosomal translocation, point mutation, autocrine activation and impaired receptor down-regulation [11,14–17]. Most often altered RTKs act as oncoproteins, but in certain cases RTKs may also have tumour suppressor functions (see below) [13]. Prominent examples of RTKs that have been found altered in human cancer include members of the ErbB/EGFR [EGF (epidermal growth factor) receptor], PDGFR [PDGF (platelet-derived growth factor) receptor], VEGFR [VEGF (vascular endothelial growth factor) receptor), HGFR [HGF (hepatocyte growth factor) receptor]/MET and FGFR [FGF (fibroblast growth factor) receptor] families [11,16].

Aberrant RTK activation following the above alterations may promote several steps of cancer progression. Most cancers originate from epithelial tissues and the consensus view is that the majority of human sporadic cancers originate from a single progenitor cell containing somatic driver mutations that give survival and growth advantages to the cell [13]. Growth factors and their receptors have been implicated in a number of the subsequent steps of progression to a malignant cancer phenotype [13]. First, growth factors, such as EGF and IGF-1 (insulin-like growth factor-1), may participate in promoting the clonal cancer cell expansion that leads to the formation of benign lesions [13]. These cells may further undergo EMT (epithelial–mesenchymal transition), a process that involves loss of epithelial cell polarity, enhanced migratory capacity, the acquirement of a mesenchymal phenotype and secretion of proteases [18]. This is followed by degradation of the basement membrane and migration and invasion of the cells into the normal adjacent tissue, giving rise to malignant lesions [18]. A large number of oncogenes and tumour suppressors, as well as growth factors, including TGFβ (transforming growth factor β), HGF, FGF and EGF, have been implicated in these processes [13,19]. Having invaded neighbouring tissues, cancer cells can gain access to and enter blood and lymphatic vessels (intravasation), followed by their transport through the circulation, lodging in capillaries in distant tissues and exit from vessels (extravasation) to penetrate into the surrounding tissues to form micrometastases, some of which may eventually grow to macroscopic metastases [20]. The growth and survival of primary and secondary tumours larger than a few millimetres in size require access to the circulation and the generation of new vessels by tumour angiogenesis [21]. VEGF, PDGF and FGF all play roles in stimulating angiogenesis [13,22]. Taken together, RTKs may thus participate in promoting several steps of carcinogenesis, including clonal cancer cell expansion, EMT, invasion and angiogenesis.

In the present review we will focus on FGFs and FGFRs, deregulation of which have been identified in a variety of human cancers. We will start by giving an overview of signalling pathways and biological processes induced by FGFs and their receptors. We will then discuss the main mechanisms by which FGFs and FGFRs have been found to be altered in human cancer, and highlight the cancer types in which FGF/FGFR alterations have been commonly found to date and how they may contribute to a malignant phenotype. We will finally discuss possibilities for therapeutic interventions of FGFs and FGFRs in treatment of human cancer.

THE FGF SIGNALLING SYSTEM

FGFs and FGFRs

The FGF family consists of 18 ligands that bind to four homologous high-affinity FGFRs (FGFR1–FGFR4) [12,22,23]. The FGFs are secreted polypeptidic growth factors that bind to receptors expressed at the cell surface of target cells. Most FGFs have signal sequences for secretion, except FGF1 and FGF2 that utilize a non-classical secretion pathway circumventing the ER (endoplasmic reticulum). In addition to the 18 secreted ligands that bind to cell-surface receptors, four members of the FGF family, the FHFs (FGF homologous factors), are not secreted and act intracellularly [12].

The FGFRs have an overall structure similar to most RTKs [23]. They are single-pass transmembrane proteins that consist of an extracellular part that binds FGF ligands, a transmembrane domain and an intracellular tyrosine kinase domain that transmits the signal to the interior of the cell (Figure 1). The intracellular kinase domain is similar to the VEGFR and PDGFR kinases in that it has an insert, resulting in a split kinase domain. The extracellular part is composed of three Ig-like domains (I–III) with an acidic, serine-rich region between domains I and II (termed the acid box). The first Ig-like domain is, together with the acid box, thought to play a role in receptor autoinhibition [24]. Domains II and III constitute the FGF ligand-binding site. In FGFR1–3, alternative splicing in Ig-like domain III creates isoforms with different ligand-binding specificities (FGFR1 IIIb–FGFR3 IIIb and FGFR1 IIIc–FGFR3 IIIc) [12,23]. The FGFR IIIb isoforms are predominantly epithelial and the IIIc isoforms are predominantly mesenchymal, with their corresponding ligands only activating either the epithelial or mesenchymal isoforms, except FGF1 which binds all receptor isoforms [25]. Thus paracrine signalling is achieved by, for instance, epithelial cells producing ligands that only activate the corresponding mesenchymal FGFR IIIc isoforms, and vice versa.

FGFs also bind to low-affinity receptors present on most cells, the HSPGs (heparan sulfate proteoglycans) [12]. HSPGs consist of a proteoglycan core that binds two or three linear polysaccharides (heparan sulfate chains). The FGFs bind to the negatively charged polysaccharides through electrostatic interactions. HSPGs both protect the ligands from degradation and are also involved in the complex formation between the FGFs and the FGFRs. Binding of FGFs to the receptors forces the dimerization of a ternary complex consisting of FGF, FGFR and heparan sulfate (Figures 1 and 2).

FGF signalling

The dimerization event triggers the activation of the FGFRs by bringing the intracellular kinases into close proximity, enabling them to transphosphorylate each other. Seven phosphorylation sites have been identified in FGFR1 (Tyr^{463}, Tyr^{583}, Tyr^{585}, Tyr^{653}, Tyr^{654}, Tyr^{730} and Tyr^{766}) [26,27]. Some of these phosphotyrosine groups acts as docking sites for downstream signalling molecules containing SH2 (Src homology 2) domains.

One prominent example is PLCγ (phospholipase Cγ), which binds to a phosphotyrosine in the C-terminal tail of the activated receptors (Tyr^{766} in FGFR1, Figure 2) [27]. PLCγ hydrolyses PIP_2 (phosphatidylinositol 4,5-bisphosphate) to produce DAG (diacylglycerol) and IP_3 (inositol 1,4,5-triphosphate) which triggers the release of calcium and subsequent activation of PKC (protein kinase C).

The adaptor protein FRS2 (FGFR substrate 2) acts as a hub linking several signalling pathways to the activated FGFRs

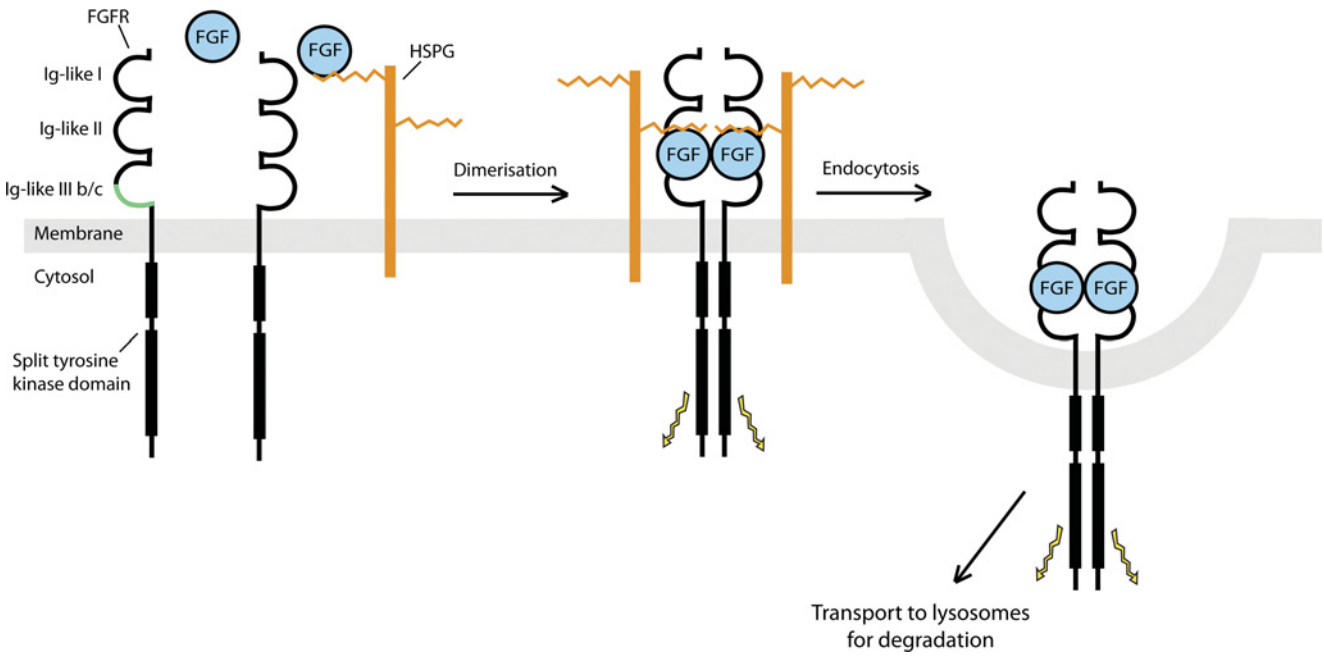

Figure 1 Complex formation between FGF, FGFR and HSPG initiates signalling

The basic structure of an FGFR is shown on the left-hand side. FGFRs are single-pass transmembrane RTKs with an extracellular part composed of three Ig-like domains (I–III), and an intracellular part containing a split tyrosine kinase domain. The complex formed by two FGFs, two heparan sulfate chains and two FGFRs causes dimerization and transphosphorylation by the kinases on several tyrosine residues in the intracellular part of the FGFRs, causing activation of downstream signalling cascades. After activation, the complex is internalized by endocytosis and transported to lysosomes for degradation. See the text for more details. An animated version of the Figure is available at http://www.BiochemJ.org/bj/437/0199/bj4370199add.htm.

[28]. FRS2 binds to the juxtamembrane region of the FGFR, and upon activation of the receptor it becomes phosphorylated on several tyrosine residues, creating docking sites for additional adaptor proteins. By binding to phosphorylated FRS2, the adaptor GRB2 (growth-factor-receptor-bound protein 2) recruits the Ras/MAPK (mitogen-activated protein kinase) pathway through the Ras guanine-nucleotide-exchange factor SOS (Son of sevenless) and the PI3K (phosphoinositide 3-kinase)/Akt pathway through GAB1 (GRB2-associated-binding protein 1) (Figure 2).

Many other signalling molecules have been reported to be activated by FGFRs, including RSK2 (p90 ribosomal protein S6 kinase 2), STATs (signal transducers and activators of transcription) and the non-RTK Src [12,22].

Modulation of FGF signalling

A number of regulators are implicated in modulating the signalling output from activated FGFRs. The Sprouty proteins, for example, are important negative regulators that are induced by FGF signalling [29–31]. Sprouty proteins seem to inhibit signalling by several mechanisms. They inhibit signalling by binding to GRB2 and thereby decouple downstream signalling (Figure 2) [32].

Other proteins induced by FGF signalling, such as MKP3 (MAPK phosphatase 3), and SEF (similar expression to FGF), also act to attenuate the MAPK signalling pathway (Figure 2) [22,33–35]. In addition, the MAPKs themselves phosphorylate FRS2 on serine and threonine residues, thereby inhibiting the recruitment of GRB2 and creating a negative-feedback loop [36].

Positive regulators of FGF signalling also exist. The transmembrane protein FLRT3 (fibronectin-leucine-rich transmembrane protein 3) was first identified in *Xenopus laevis* to accentuate MAPK signalling initiated by FGFRs [37]. Further studies in mammals have also implicated other members of the family (FLRT1 and FLRT2) to be positive regulators of FGF signalling [38].

The signal from the activated FGF–FGFR complex is efficiently terminated by internalization and degradation in lysosomes (Figure 1). The ubiquitin ligase Cbl can bind to activated FRS2 and mediate FGFR ubiquitination that acts as a signal for receptor degradation [39]. In the case of FGFRs, ubiquitination does not seem to be required for endocytosis [40]. Instead, the endocytic adaptor protein extended-synaptotagmin binds directly to FGFRs and recruits them to undergo clathrin-mediated endocytosis via adaptin-2 [41].

After endocytosis, the ubiquitinated receptors are sorted into multivesicular bodies by the ESCRT (endosomal sorting complex required for transport) machinery and are then further transported to lysosomes where they are degraded [42,43]. The four FGFRs are ubiquitinated to different extents and this seems to dictate whether they are efficiently degraded or transported back to the plasma membrane via recycling endosomes. FGFR1 is heavily ubiquitinated and is transported to lysosomes, whereas FGFR4 is only lightly ubiquitinated, inefficiently degraded and rather recycled to the cell surface, resulting in prolonged signalling from FGFR4 compared with FGFR1 [40,42]. In addition to the ESCRT proteins, a Sprouty-related protein, SPRED2 (Sprouty-related enabled/vasodilator-stimulated phosphoprotein homology 1 domain-containing protein), was also shown to direct FGFRs to lysosomes by interacting with the late endosomal protein NBR1 [neighbour of BRCA1 (breast cancer early-onset 1)]. SPRED2 thereby attenuates FGF signalling by causing degradation of the receptors in lysosomes [44].

Differential ligand binding can also dictate the routing of FGFRs as shown for FGFR2b [KGFR (keratinocyte growth

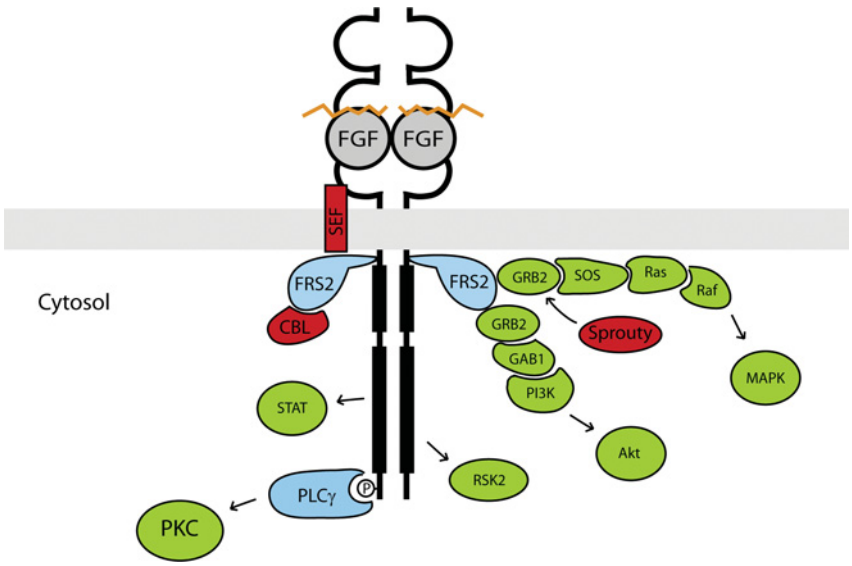

Figure 2 Intracellular signalling pathways downstream of FGFRs

After ligand-induced FGFR activation, several downstream signalling cascades are initiated. Two central players, FRS2 and PLCγ (in blue) bind directly to the receptors. FRS2 is constitutively associated with the receptor, and upon activation of the receptor kinase, it is phosphorylated on several tyrosine residues which, in turn, recruit two important signalling pathways, the Ras/MAPK and PI3K/Akt pathways. PLCγ binds to a phosphotyrosine in the C-terminal tail of FGFRs. PLCγ recruitment culminates in the activation of PKC. Several negative regulators are also associated with FGF signalling (in red). Soluble heparin (in orange), a highly sulfated polysaccharide, can take the place of HSPG in the FGF complex and is often used experimentally to increase FGF signalling. See the text for more details.

factor receptor)]. The binding of FGF7 to FGFR2b causes efficient ubiquitination, resulting in degradation of the complex in lysosomes. Another FGFR2b ligand, FGF10, however, does not induce receptor ubiquitination, and the complex is transported to recycling endosomes causing prolonged signalling [45].

Yet another interesting example of differential trafficking of FGFRs is the re-routing of FGFR1 after binding to NCAM (neural cell-adhesion molecule). The interaction of FGFR1 with NCAM causes recycling and sustained signalling, which is important for the stimulation of cell migration [46].

Biological responses

FGF signalling pathways are implicated in a multitude of biological processes. They stimulate proliferation, act as pro-survival/anti-apoptotic signals and stimulate cell migration in many cell types [12]. Proliferation signals are mainly transmitted through the MAPK signalling cascade and anti-apoptotic signals are through the PI3K/Akt pathway. However, there is considerable cross-talk between the signalling pathways, for example, during FGF-induced cell migration, both MAPK and PI3K seem to be required.

FGFs are crucial during development where they have been shown to be key molecules in organogenesis [22,47]. FGF signalling is implicated in the formation of the heart, the lungs, the limbs and the nervous system, and also plays an important role in mammary and prostate gland development. During early development, induction of the mesoderm is orchestrated through FGF-dependent epithelial–mesenchymal communication.

In addition, FGF signalling plays a role in the formation of new blood vessels, the process of angiogenesis, by influencing other key signalling molecules such as HGF and VEGF [48]. Interestingly, FGFs, and in particular FGF2, have been shown to support the undifferentiated self-renewal of human embryonic stem cells and are routinely used to cultivate such cells in the laboratory [49].

It is evident that FGFs and FGFRs constitute a robust signalling system orchestrating many important signalling pathways and biological responses, and efficient negative regulation is crucial. We will in the next sections see how out of control FGF signalling can cause disease.

MECHANISMS FOR DEREGULATION OF FGF SIGNALLING IN CANCER

As discussed above, FGFs and FGFRs constitute a highly complex signalling system, and since signals from these receptors regulate many key processes, they must be kept tightly regulated. However, FGF signalling is often subverted to cause constitutive signalling without proper regulation in cancer [14,50–56]. There are several ways by which the FGF signalling network can be deregulated in human cancers, and we will in the following sections discuss common ways that lead to aberrant signalling from FGFs and FGFRs (Figure 3).

Mutations

FGF signalling is crucial during development, and mutated FGFRs have been found to be the cause of several developmental syndromes [28,57]. Prominent examples include the germline gain-of-function mutations often found in human skeletal dysplasia. For instance, in achondroplasia, a mutation in the transmembrane helix of FGFR3 (G380R) promotes dimerization and subsequent activation of the tyrosine kinase domain [58]. In the lethal skeletal disorder thanatophoric dysplasia, single mutations generating a new cysteine residue (S249C or Y373C) in the extracellular part of the receptors cause the formation of a disulfide bond, linking two individual receptors [59]. Thus an

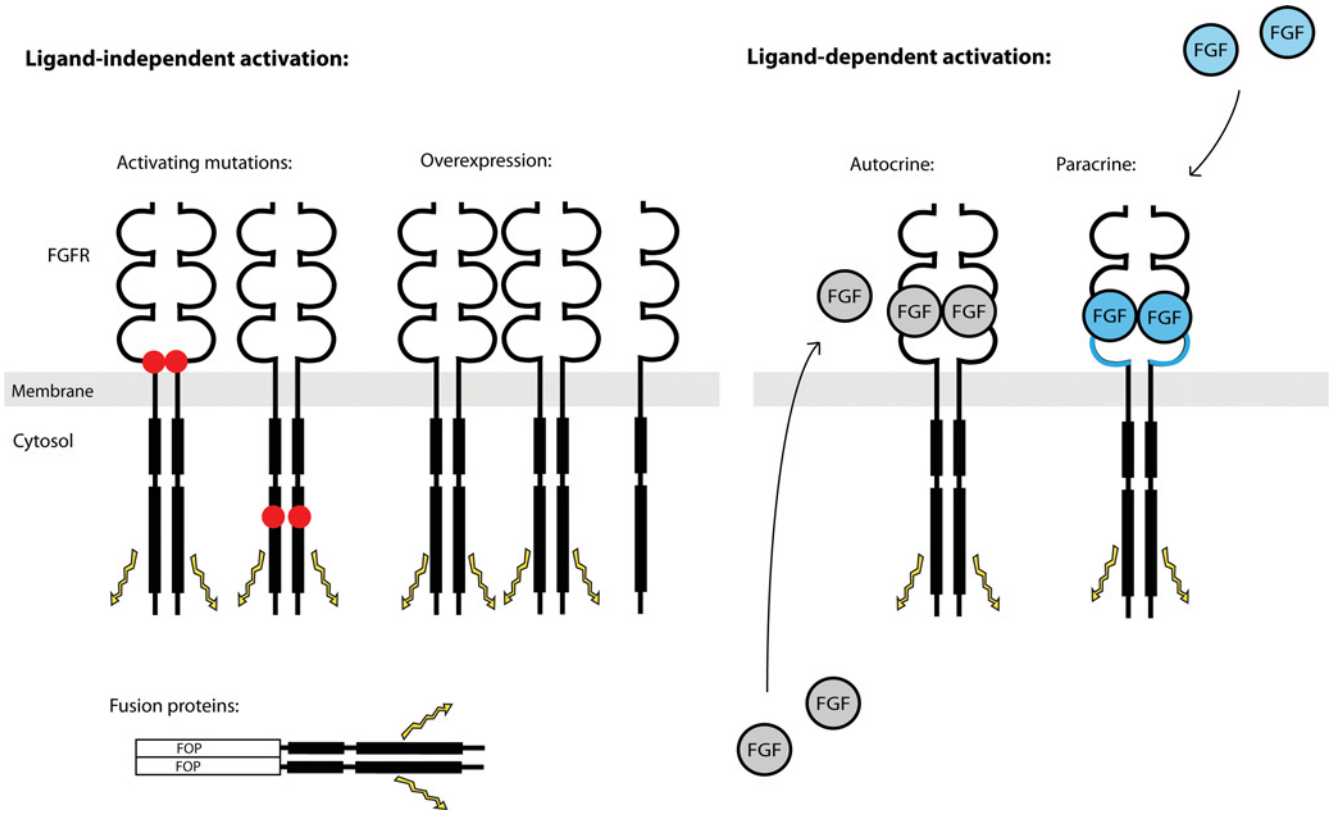

Figure 3 Possible mechanisms for deregulated FGF signalling

The FGFR can be activated independently of ligand stimulation by several mechanisms. Some point mutations (in red) can lead to increased receptor dimerization, whereas other mutations in the kinase domain can result in constitutively active kinases. FGFR overexpression leading to excessive signalling may be caused by gene amplification or aberrant transcriptional regulation. Chromosomal translocation can result in fusion of the kinase domain of an FGFR to a dimerization domain from another protein leading to constitutive kinase activation. In other cases, aberrant signalling can be caused by autocrine loops when the same cell produces both a ligand and a corresponding FGFR, or paracrine loops if the cell produces FGFRs with altered ligand specificity towards FGFs (in blue) secreted by surrounding cells. See the text for more details.

intermolecular bond forces dimerization in the absence of ligand, resulting in ligand-independent constitutive signalling.

Interestingly, the same mutations discovered to be the cause of many developmental disorders are also found mutated in tumour cells (Table 1). The mutations found in achondroplasia and thanatophoric dysplasia, which cause dimerization and thereby constitutive activation of FGFR3, are also frequently found in bladder cancer [60]. Yet other mutations in FGFR2 that cause dimer formation are implicated in craniosynostosis syndromes and have also been found in endometrial cancers [55,61].

A mutation that promotes dimerization is just one mechanism that can increase ligand-independent signalling from FGFRs. Other mutations located to the kinase domain of FGFRs can change the conformation of the domain to cause permanently active kinases. Mutations in the kinase domain of FGFR4 have been found in the childhood sarcoma RMS (Rhabdomyosarcoma), and these mutations were shown to cause autophosphorylation and constitutive signalling [50].

Some mutations in FGFRs identified in human cancer have also been shown to cause loss-of-function suggesting that, in certain circumstances, FGFRs can act as tumour suppressors [62].

The majority of FGF ligand mutations described in human disease are germline loss-of-function mutations. Examples include the FGF3 mutation that causes deafness, mutations in FGF8 that result in Kallmann syndrome and FGF10 mutations that have been described in LADD (Lacrimo-Auriculo-Dento-Digital) syndrome. In cancer, however, the prevalence of mutations in FGF ligands is rare and the consequences of such mutations are not clear. The only mutations described in cancer are, to our knowledge, the somatic mutations in FGF9 found in colorectal and endometrial cancers [63]. The mutations were predicted to result in loss-of-function and it is not known whether these mutations participate in tumour formation.

SNPs (single-nucleotide polymorphisms)

Certain germline SNPs have been identified in FGFRs and are believed to modulate the malignant phenotype in some cancer types. The FGFR4 G388R SNP has been shown to confer a more aggressive behaviour and increased metastatic potential in several forms of cancer (e.g. breast, lung, skin, colon and prostate cancers) [64–68]. The molecular mechanism by which FGFR4 G388R promotes tumour progression and metastasis is not fully understood, but it has been reported that FGFR4 G388R exhibits sustained signalling compared with wild-type FGFR4 due to impaired lysosomal degradation [69]. Recently, it was also shown that FGFR4 G388R forms a complex with MT1-MMP (membrane-type 1 matrix metalloproteinase) and thereby decreases MT1-MMP lysosomal degradation leading to increased invasion [70].

Several SNPs within intron 2 in FGFR2 have been shown to be associated with an increased risk of breast cancer. It has been proposed that these SNPs alter binding affinity for

Table 1 FGFR aberrations identified in human cancer

The Table lists FGFR mutations, amplifications and translocations that have been associated with altered kinase activity. Included in the Table are only the aberrations identified in human tumour samples. For references and a more complete list, see Supplementary Tables S1–S3 (at http://www.BiochemJ.org/bj/437/bj4370199add.htm). The FGFR3 IIIb isoform is two amino acids longer than FGFR3 IIIc, and in order to avoid confusion, numberings according to both the FGFR3 IIIb and IIIc isoforms are indicated. FGFR1 IIIc (GenBank® accession number NM_023110), FGFR2 IIIc (GenBank® accession number NP_000132), FGFR3 IIIc (GenBank® accession number NP_000133), FGFR4 (GenBank® accession number X57205). ACH, achondroplasia; amp, amplification; AN, acanthosis nigricans; AS, Apert syndrome; CR, craniosynostosis; CS, Crouzon syndrome; HCH, hypochondroplasia; PS, Pfeiffer syndrome; SADDAN, severe achondroplasia with developmental delay and acanthosis nigricans; TDI/II, Thanatophoric Dysplasia I/II; trans, translocation.

Cancer	Receptor	Abberation	Association with other syndromes	Molecular consequence
Breast	FGFR1	8p11-12 amp	Not known	Amplification of FGFR1
Bladder	FGFR3	R248C	TDI	Enhanced kinase activity
	FGFR3	S249C	TDI	Enhanced kinase activity
	FGFR3	G370/372C	TDI	Enhanced kinase activity
	FGFR3	S371/373C	TDI	Enhanced kinase activity
	FGFR3	Y373/375C	TDI	Enhanced kinase activity
	FGFR3	G380/382R	ACH	Enhanced kinase activity
	FGFR3	A391/393E	CS	Enhanced kinase activity
	FGFR3	K650/652E/Q/M/T	TDI, TDII, HCH, SADDAN, AN	Enhanced kinase activity
Prostate	FGFR3	S249C	TDI	Enhanced kinase activity
	FGFR3	A391E	CS	Enhanced kinase activity
Endometrial	FGFR2	S252W	AS	Alter ligand specificity
	FGFR2	P253R	AS	Alter ligand specificity
	FGFR2	N549K	Not known	Enhanced kinase activity
	FGFR2	K659N	CR	Enhanced kinase activity
Lung	FGFR1	8p12 amp	Not known	Amplification of FGFR1
	FGFR2	W290C	PS	Not known*
RMS	FGFR4	N535K	Not known	Enhanced kinase activity
	FGFR4	V550E	Not known	Enhanced kinase activity
MM	FGFR3	t(4:14) trans	Not known	Overexpression of FGFR3
	FGFR3	R248C	TDI	Enhanced kinase activity
	FGFR3	K650/652M	TDI, SADDAN	Enhanced kinase activity
Brain	FGFR1	N546K	Not known	Enhanced kinase activity
	FGFR1	K656E	Not known	Enhanced kinase activity
Head and neck	FGFR3	R248C	TDI	Enhanced kinase activity
	FGFR3	S249C	TDI	Enhanced kinase activity
	FGFR3	G697C	Not known	Enhanced kinase activity
Melanoma	FGFR2	I642V	Not known	Reduced kinase activity
EMS	FGFR1	8p11-12 trans	Not known	Constitutively active FGFR1-fusion proteins

*FGFR2 W290G forms ligand-independent dimers

transcription factors causing an increase in FGFR2 expression [71,72].

Fusion proteins

Potent aberrant FGF signalling can be the result of chromosomal translocations in which protein domains causing dimerization are fused to the kinase domain of an FGFR (Figure 3). These intracellularly localized fusion proteins are permanently dimerized in the absence of ligand, resulting in continuous signalling. As these fusion proteins are not expressed at the cell surface, but rather reside in the cytosol, they escape the normal down-regulation routes operating for wild-type receptors. They are neither degraded in lysosomes nor inhibited by some of the feedback inhibitors, giving rise to constitutively active receptor kinases with little negative regulation. They are therefore particularly potent oncogenes that can drive proliferation of cancer cells. Most FGFR-fusion proteins have been found in EMS (8p11 myeloproliferative syndrome), also called SCLL (stem cell leukaemia lymphoma syndrome), where the kinase domain of FGFR1 is fused to one of several different N-terminal dimerization domains [e.g. ZNF198, BCR (breakpoint cluster region), FOP2] (Supplementary Table S3 at http://www.BiochemJ.org/bj/437/bj4370199add.htm) [73].

Differential expression

Ligand-independent signalling can also occur from overexpressed FGFRs. When overexpressed, individual FGFRs can interact and phosphorylate each other, probably because of the local crowding of receptors at the cell surface (Figure 3). Overexpression is often caused by amplification of distinct pieces of the chromosome resulting in multiple copies of the gene. In human breast cancer, ~10 % of the patients harbour the 8p11-12 amplicon that contains *FGFR1* and, in most cases, results in overexpression of FGFR1 [74–76]. Aberrant transcriptional regulation can also lead to increased levels of the receptors.

It should also be noted that, in some tumours, FGFR expression has been found to be down-regulated, indicating that in certain cases they may act as tumour suppressors [22]. Expression of FGFs or FGFRs out-of-context can lead to autocrine or paracrine signalling loops (Figure 3). For instance, if an FGFR-expressing cell also overexpresses its matching ligand, an autocrine loop can be established and the cancer cell becomes self-sufficient in growth signals [22].

If the cancer cells overexpress an FGFR with altered ligand-binding specificity, FGFs secreted from neighbouring cells can stimulate the cancer cells, creating a paracrine loop. For instance, alternative splicing of the third Ig-like domain in FGFR1–3 can switch the binding affinity of the receptor towards FGFs found in

the surrounding milieu, creating an aberrant paracrine signalling loop (Figure 3).

Impaired down-regulation of FGF signalling

Increased levels of FGFRs on the cell surface can also be the result of impaired down-regulation. After binding, the ligand–receptor complex is normally endocytosed and transported to lysosomes for degradation (Figure 1). Defective internalization will result in higher levels of receptor on the cell surface and prolonged signalling. Mutations in any protein involved in the internalization of FGFRs could thus potentially increase FGF signalling. Alterations in proteins involved in the endocytic machinery have been found in many cancers [15]. For example, Cbl, the ubiquitin ligase responsible for the proper down-regulation of many RTKs, has been found mutated in AML (acute myeloid leukaemia), causing an accumulation of the RTK FLT3 (FMS-like tyrosine kinase 3). It would be interesting to investigate whether similar mechanisms operate for FGFRs in certain cancers.

There is also the possibility that alterations in the FGFRs themselves can prevent efficient internalization and degradation of the receptors. For instance, the FGFR3 G380R mutation found in achondroplasia and bladder cancer promotes dimerization, but in addition also increases recycling of the receptor, thereby avoiding efficient receptor degradation and resulting in prolonged signalling [77].

A splice variant of FGFR2 found in several cancer cell lines results in a shortened C-terminus [78]. The deleted C-terminal tail contains an endocytic motif, and it was shown that the transforming capacity of the FGFR2 variant was partly due to inefficient down-regulation, causing increased receptor levels at the cell surface and thus enhanced signalling capacity [78].

Deregulation of negative regulators of FGF signalling has also been suggested to be involved in oncogenicity [22]. For instance, the expression of SEF and Sprouty is decreased in prostate cancer and could cause excessive signalling by relieving an inhibitory brake [79,80].

We will now give an overview of the most common types of human cancer in which FGF and FGFR alterations have been found and how they may contribute to cancer progression.

THE ROLES OF FGFS AND FGFRS IN CANCER

Breast cancer

FGFRs and several of the FGFs play a critical role in regulating normal mammary gland development and tissue homoeostasis. In particular, FGFR2 IIIb and FGF10 are required for embryonic mammary gland development, and for survival and proliferation of epithelial cells during postnatal development [81–83]. Ectopic expression of a number of FGF/FGFR family members has been reported in human breast cancer. The most common alteration involves amplification of FGFR1. As mentioned previously, amplification of the chromosomal region 8p11-12, where FGFR1 is located, appears in approximately 10 % of human breast cancers and is associated with poor prognosis (Table 1) [74–76]. Studies from breast cancer cell lines and mouse models support a role for FGFR1 signalling in mammary carcinogenesis. Activation of FGFR1 in mouse or human mammary cell lines resulted in increased cell proliferation, survival and invasion [84,85], confirming the potential oncogenic nature of FGFR1 signalling. Moreover, expression and constitutive activation of FGFR1 in the mouse mammary epithelium induced proliferation and invasive lesions [86]. Recently it was also reported that FGFR1 amplification drives resistance to endocrine therapy [53]. Taken together, there is strong evidence that FGFR1 amplification plays a role in breast carcinogenesis. It is, however, worth mentioning that FGFR1 is not always overexpressed when the 8p11-12 region is amplified, and genes other than FGFR1 in the 8p11-12 amplicon are also likely to contribute to carcinogenesis [87–89].

FGFR2 has also been implicated in some cases of breast cancer. Amplification of FGFR2 has been described in a subgroup of triple-negative breast tumours, which are aggressive breast tumours negative for the oestrogen receptor, progesterone receptor and HER2 (human EGFR 2)/ErbB2 [90]. Cell lines derived from these tumours showed constitutive activation of FGFR2, and were sensitive to FGFR2 inhibition using a specific FGFR inhibitor (PD173074) and to RNAi silencing. Triple-negative breast cancers are not efficiently treated with current targeted therapies [91], and FGFR2 might therefore be a novel therapeutic target in the subset of triple-negative breast tumours harbouring *FGFR2* gene amplification.

Ectopic expression of FGFR4 has also been reported in human breast cancer [92] and has been associated with resistance to chemotherapy in breast cancer cell lines [93]. In an experimental approach to identify signalling pathways that define chemoresistance in cancer, a breast cancer cell line was treated with doxorubicin and gene expression levels of surviving cells were analysed. Isolated clones of surviving cells showed up-regulated expression of FGFR4, and interfering with FGFR4 (using an antagonistic FGFR4 antibody) enhanced chemosensitivity in FGFR4-expressing breast cancer cells [93]. These findings implicate FGFR4 as an important factor in breast-cancer-cell resistance during chemotherapy, and FGFR4 may be a potential therapeutic target in these cells.

High expression of FGFs has been reported in human breast cancer. Amplification of FGF3 occurs in approximately 15–20 % of human breast cancers [94–96] and was shown to correlate with increased invasiveness in node-negative breast carcinoma. FGF8 is highly expressed in human breast cancer as opposed to normal breast tissue [97], and overexpression of FGF8b in breast cancer cells increased cell growth in culture and led to tumour formation and neovascularisation when injected into nude mice [98]. Moreover, a neutralizing antibody against FGF8 displays potent anti-tumour activity against mammary mouse tumours [99]. Also, FGF10 is highly expressed in a subset of human breast carcinomas [100]. It has been shown that subcutaneous injection of FGF10-expressing breast cancer cells into mice resulted in malignant tumours, indicating a role for FGF10 in mammary tumourigenesis [100].

Taken together, there is good evidence supporting a role for several FGF/FGFR family members in human breast cancer.

Bladder cancer

The most common form of bladder cancer, UCC (urothelial cell carcinoma), begins in the urothelial lining of the bladder wall [101] and arises and progresses along two distinct pathways [102]. One pathway, accounting for 70–80 % of UCC, is characterized by low-grade and non-invasive tumours. These tumours harbour frequent mutations in FGFR3 (approximately 70 %), indicating a crucial role of FGFR3 in this tumorigenic pathway [60]. The other pathway, accounting for 20–30 % of UCC, is characterized by high-grade invasive tumours and has frequent defects in the *p53* gene. Approximately 70 % of the low-grade non-invasive

tumours will recur, but only approximately 15 % will proceed into invasive tumours [101].

Many of the FGFR3 mutations that have been identified in human UCC result in an amino acid substitution in the extracellular, transmembrane and/or cytoplasmic domain, and are identical with activating mutations associated with human skeletal disorders [60,103,104]. The most common FGFR3 mutations in UCC (R248C, S249C, G370/372C and Y373/375C) lead to ligand-independent dimerization (Table 1). Several mutations in the kinase domain of FGFR3, leading to enhanced kinase activity, are also found in bladder cancer [103,105,106].

The presence of FGFR3 mutations in a substantial group of UCC suggests FGFR3 as a potential therapeutic target in low-grade non-invasive tumours. Several studies indicate an oncogenic role for mutationally activated FGFR3 in UCC. Knockdown of mutated FGFR3 or inhibition of FGFR3 using antibody-based targeting or specific FGFR inhibitors, such as SU5402 or PD173074 in UCC cell lines reduced their tumour properties [107–110]. Moreover, inhibition of mutated FGFR3 (using a specific FGFR inhibitor, PD173074, or a monoclonal antibody targeting FGFR3, R3Mab) in mouse xenografts decreased tumour growth [108,109,111]. These studies indicate that FGFR3 plays an important role in bladder cancer growth and thus could be considered an attractive candidate for targeted therapy.

The high recurrence rate (60–80 %) of low-grade non-invasive UCC requires long-term expensive patient monitoring [112]. New urinary tumour markers may increase the accuracy of predicting tumour recurrence and lower the cost of long-term patient monitoring. Recent data suggest that detection of FGFR3 mutations in voided urine from patients with a low-grade FGFR3 mutant primary tumour indicates recurrence [113,114]. Thus identification of FGFR3 mutations is not only a potential biomarker for bladder cancer diagnosis and prognosis, but could also indicate tumour recurrence.

Elevated levels of FGF/FGFR family members in bladder cancer have been reported for FGFR3, as well as for FGFR1, FGFR2 and FGF2 [106,115,116]. Decreased levels of FGFR2 have also been reported in a subset of human UCC [117], and a role for FGFR2 in human bladder cancer is unclear. An experimental study in urothelial cell lines has suggested a role for FGFR1 in human bladder cancer [116]. Tomlinson et al. [116] reported that expression of FGFR1 in normal urothelial cells induced increased cell proliferation and survival, and that subcutaneous injection of FGFR1-knockdown cells into nude mice led to reduced tumour growth compared with control cells. These data indicate that FGFR1 displays tumourigenic properties when overexpressed in urothelial cells and may represent a potential therapeutic target in some cases of urothelial carcinoma.

Prostate cancer

The interplay between mesenchymal/stromal cells and epithelial cells in the prostate gland play important roles during prostate gland development, but also help to maintain tissue homoeostasis in the adult. Stromal–epithelial cross-talk is also integral to prostate cancer progression and metastasis [118]. Normal prostate stromal cells produce several FGFs, including FGF2, FGF7 and FGF9, whereas epithelial cells express corresponding FGFRs, and FGF/FGFR family members act as mediators of communication between the epithelium and the stroma [119].

In prostate cancer several FGFs, including FGF1, FGF2, FGF6, FGF7, FGF8 and FGF9, are up-regulated [119,120]. Stromal up-regulation and release of FGF2 has a tumour-promoting effect on neighbouring epithelial cells [121]. Overexpression of FGF10 in the stromal compartment of the murine prostate resulted in epithelial transformation and the formation of well-differentiated prostate carcinomas [122]. These data indicate an important role for FGFs produced in the tumour microenvironment in cancer progression.

Ectopic expression of FGFs in epithelial cells might also disturb the stromal–epithelial cross-talk by initiating autocrine signalling in the epithelium which can eventually lead to tumorigenesis. High expression of FGF8 in malignant prostate epithelium has been associated with decreased patient survival [123], and transgenic mice overexpressing FGF8 in prostate epithelial cells developed PINs (prostatic intraepithelial neoplasias) [124,125]. In a murine model for bone metastasis, intratibial inoculations of prostate cells expressing FGF8 increased tumour growth [126]. This indicates a role for FGF8 in prostate cancer metastasis. Interestingly, a neutralizing antibody against FGF8 displays potent anti-tumour activity against prostate tumours in mouse models [127] and might be considered as a candidate for therapeutic treatment of cancers that are dependent on FGF8 signalling for growth and survival. Previously it was also suggested that FGF9 is involved in bone metastasis in prostate cancer [128].

Overexpression of FGFRs in the prostate epithelium can also lead to autocrine signalling and disturb the stromal–epithelial communication. FGFR1 is frequently overexpressed in prostate cancer [129,130], and conditional activation of FGFR1 in prostate epithelial cells in a mouse model led to EMT and induction of adenocarcinomas [131]. Moreover, deactivation of FGFR1 during early stages of cancer progression led to regression, indicating that FGFR1 is necessary for both maintenance and progression of PINs. On the other hand, inhibition of FGFR1 later in cancer progression, reduced proliferation and progression of adenocarcinoma, but did not lead to regression. The differences in responsiveness to FGFR1 inhibition seem to depend on tumour stage and indicate a ‘susceptibility window’ for targeting FGFR1 in prostate cancer.

Although not entirely clear, taken together, the data indicate a potential role for FGF signalling in prostate cancer development.

Endometrial cancer

Previously, mutations in FGFR2 have been identified in approximately 10 % of human endometrial carcinomas (Table 1) [55,61,132]. Many of the mutations identified were identical with the germline-activating mutations in FGFR2 and FGFR3 that cause skeletal disorders and can result in enhanced activation through both ligand-dependent and ligand-independent mechanisms.

The importance of the mutations of FGFR2 identified in endometrial cancer has been investigated in endometrial cancer cell lines. In endometrial cell lines bearing N549K or K659N mutations, treatment with an FGFR inhibitor (PD173074) or knockdown of FGFR2 blocked cell proliferation and survival [55,133]. These data suggest that activation of FGFR2 plays a role in endometrial carcinogenesis and implicate FGFR2 as a potential therapeutic molecular target in the treatment of endometrial cancer.

Lung cancer

The two main types of lung cancer are SCLC (small cell lung carcinoma) and NSCLC (non-small cell lung carcinoma). A role for FGF/FGFR family members has been indicated in both types of lung cancer.

Paracrine signalling between epithelial cells expressing FGFR2 IIIb and mesenchymal cells expressing its ligands, FGF7 and FGF10, is critical to normal lung development and tissue homoeostasis [134,135]. Gene expression array data obtained from a panel of NSCLC cell lines demonstrated frequent co-expression of distinct FGFs and FGFRs, suggesting that an FGFR-dependent autocrine signalling pathway may operate in a significant fraction of NSCLCs [136]. Moreover, studies employing silencing of FGF2 and a pharmacological tyrosine kinase inhibitor (RO4383596) which also targets FGFR, indicated a functional role for an FGFR autocrine signalling pathway in NSCLC cell lines [136].

Recently, frequent amplification of FGFR1 was identified in human squamous cell lung cancer, the most common type of NSCLC [56]. Treatment of FGFR1-amplified lung cancer cell lines with the specific inhibitor (PD173074) resulted in growth inhibition and apoptosis. The PD173074-mediated cytotoxic effect could be rescued by ectopic expression of a PD173074-resistant FGFR1 mutant. Moreover, treatment with PD173074 resulted in tumour shrinkage in mice engrafted with FGFR1-amplified cells. These data suggest that FGFR1 may be a potential therapeutic option in this group of patients [137].

High copy number gain of the *FGFR1* gene has also been identified in SCLC [138]. Also, FGF2 has been suggested to play an important role in SCLC, in which high levels of serum FGF2 are associated with a poor prognosis [139]. Moreover, FGF2 induces proliferation and chemoresistance in SCLC cells [140,141]. Both of these effects could be blocked by using a specific FGFR inhibitor (PD173074) [142]. It has been shown that FGF2 up-regulates expression of anti-apoptotic proteins and thereby mediates a cytoprotective effect in SCLC [141,143,144]. Oral administration of the FGFR inhibitor in SCLC xenograft mouse models impaired tumour growth, reduced intra-tumour proliferation and increased apoptosis [142]. The data imply FGF/FGFR family members as potential therapeutic targets in SCLC.

In addition, somatic mutations in FGFR1, FGFR2 and FGFR4 have been identified in lung carcinomas [14,52,145]. One of the mutations identified in FGFR2 (W290C) may confer gain-of-function and is also associated with Pfeiffer syndrome, a skeletal disorder resulting in premature fusion of the sutures of the skull and deformity of the skull [146]. A similar mutation (FGFR2 W290G) has been demonstrated to result in ligand-independent receptor dimerization and constitutive kinase activity (Table 1) [147]. In a large screen aimed to identify somatic mutations in lung adenocarcinoma, FGFR4 was identified as one of the genes that is mutated at significantly high frequency and might be involved in carcinogenesis [52]. Taken together, the above data suggest that deregulated FGF/FGFR signalling may contribute to lung carcinogenesis.

RMS

RMS is a cancer originating from skeletal muscle and is the most frequent soft tissue sarcoma in children [148]. Recently, several mutations in FGFR4 were identified in 7–8 % of RMS tumours [50]. Many of these are clustered in the kinase domain of the receptor and at least two of them, N535K and V550E, increased autophosphorylation of the receptor (Table 1) [50]. The mutants promoted proliferation and metastatic potential when expressed in an RMS cell line [50].

High expression of FGFR4 has also been associated with advanced stage and poor survival in RMS [50,149,150]. Chromosomal translocation is common in alveolar RMS, a subtype of RMS. One of the most common translocations leads to expression of the fusion protein PAX3 (paired box 3)–FKHR (forkhead in RMS). Recently it was reported that PAX3–FKHR acts as a strong FGFR4 expression enhancer [151]. Knockdown of FGFR4 in RMS cell lines overexpressing FGFR4 reduced cell proliferation [50]. Moreover, FGFR4 knockdown in a human RMS cell line transplanted into mice gave rise to reduced tumour growth and metastasis [50]. Taken together, these data indicate a role for FGFR4 in RMS tumorigenesis. Also, FGFR1 and FGFR2 have been reported to be overexpressed in RMS [152–154], and it has also been reported that FGFR3-positive RMS cells are more tumorigenic than FGFR3-negative cells [155].

MM (multiple myeloma)

MM is a plasma cell malignancy that is characterized by accumulation of clonal plasma cells in bones and bone marrow where they cause bone lesions and interfere with the production of normal blood cells. Approximately 15–20 % of patients suffering from MM overexpress FGFR3 as a consequence of the t(4;14)(p16.3;q32) translocation (Table 1) [156–158]. The chromosomal translocation brings FGFR3 under the influence of a strong IgH enhancer region leading to FGFR3 overexpression. It should be noted that the t(4;14) translocon in MM also results in ectopic expression of MMSET (MM SET domain) and, although ectopic expression of MMSET is found in all (t4;14) MM patients, approximately 75 % of the t(4;14)-positive patients overexpress FGFR3 [158]. Moreover, carrying the t(4;14) translocation has been associated with poor prognosis irrespective of FGFR3 expression [159]. Therefore the role for FGFR3 in MM is not entirely clear.

However, experiments in MM cell lines and MM mouse models have demonstrated an oncogenic potential of FGFR3. Overexpression of FGFR3 enhanced MM cell proliferation and survival [160]. Also, inhibition of FGFR3, using highly specific antibody-targeting of FGFR3, reduced tumour growth in t(4;14)-positive MM mouse models [108,161]. A fraction of MM patients also harbour activating mutations in FGFR3, identical with those found in skeletal disorders and bladder cancer [162–164]. The activating mutations include R248C, Y373/375C, G380/G382R, G382/384D and K650/652E (Table 1 and Supplementary Table S2 at http://www.BiochemJ.org/bj/437/bj4370199add.htm).

Since FGFR3 is frequently overexpressed and/or mutated in MM and has been recognized as a potent oncogene, it is an attractive target for novel drug development. Several new FGFR3-targeting inhibitors/antibodies have been developed [108,161,165,166] and might prove useful for FGFR3 inhibition alone or in combination with other inhibitors in the subset of MM patients with t(4;14) FGFR3 overexpression.

EMS

EMS/SCLL is a rare but aggressive neoplasm with a high rate of progression into acute leukaemia [73]. At the molecular level, the disorder is associated with chromosomal translocations involving the FGFR1 gene on chromosome 8p11-12, resulting in constitutively active FGFR kinase-fusion proteins (Figure 3 and Table 1, and Supplementary Table S3). The first translocation identified, and the most common, is a disruption and recombination of the *ZNF198* gene with the *FGFR1* gene. This translocation creates a chimaeric protein composed of the proline-rich zinc-finger motif of ZNF198 and the tyrosine kinase domain of FGFR1, resulting in constitutive dimerization and activation of the FGFR1 tyrosine kinase [167]. Other FGFR1-fusion partners

include FOP (FGFR1OP1), CEP110 (centriolin), BCR, TRIM24 (Tripartite motif-containing 24), FGFR1OP2, LRRFIP1 (leucine-rich repeat flightless-interacting protein 1), MYO18A (myosin-XVIIIa), CPSF6 (cleavage and polyadenylation specificity factor subunit 6), HERV-K (human endogenous retrovirus K) and CUX1 (cut-like homoeobox 1) [73,168].

Some of the FGFR1 kinase-fusion proteins can transform cell lines and induce SCLL or chronic myelogenous leukaemia-like diseases in mice [169–173]. Moreover, in a murine model of ZNF198–FGFR1-induced myeloproliferative disorder, treatment with a multi-tyrosine kinase inhibitor (PKC412) resulted in prolonged survival [171], and administration of the tyrosine kinase inhibitor to a patient with SCLL was beneficial, although not sufficient [171]. It has also been reported that growth of ZNF198–FGFR1-, FGFR1OP2–FGFR1- or BCR–FGFR1-expressing cell lines is blocked by FGFR inhibition, and treatment of FGFR1OP2–FGFR1-positive cells with multi-targeted tyrosine kinase inhibitors or siRNA (small interfering RNA) against FGFR1 resulted in apoptosis [171,173–176]. Although activation of FGFR1 appears to be the critical event in oncogenesis of EMS, it has also been suggested that the fusion partners of FGFR1 might play a role [177].

Other types of cancer

Several additional examples of aberrant FGFR signalling in human cancers are described in the literature. Elevated levels of FGF/FGFR family members have been described in many human cancers, such as brain cancer, head and neck cancer, gastric cancer and ovarian cancer, as well as in osteosarcoma [150,178–181]. Mutated forms of FGFRs have been identified in malignancies such as brain cancer, head and neck cancer, stomach cancer and colon cancer [182–184]. Interestingly, loss-of-function mutations have been identified in FGFR2 in melanoma (Table 1) [62]. In an attempt to collect a complete up-to-date list of the reported alterations in FGFR expression in human cancers, an extensive literature search was performed and is provided with references in Supplementary Tables S1–S3 (at http://www.BiochemJ.org/bj/437/bj4370199add.htm). Some of the alterations found to date are frequently reported, whereas others are more rarely reported. Moreover, some reports are based on large comprehensive studies with a large number of patient samples and/or cell lines analysed, whereas others are more restricted. Alterations that are frequently reported and/or described in large studies are often regarded as the most significant. However, less frequently reported and less studied alterations might still be of significance. Note that the studies included in the Supplementary Tables are not filtered for quality or validity, and are meant as a work of reference.

STRATEGIES FOR THERAPY

On the basis of the involvement of FGF/FGFR family members in multiple steps of cancer development and their deregulation in a variety of human cancers as described above, several therapeutic strategies aiming at interfering with FGFs or FGFR activity are being developed, including (i) small-molecule tyrosine kinase inhibitors, (ii) monoclonal antibodies and (iii) FGF ligand traps.

Small-molecule tyrosine kinase inhibitors targeting FGFRs

Small-molecule tyrosine kinase inhibitors inhibit the receptor kinase activity by targeting the ATP-binding site of the intracellular tyrosine kinase domain [185]. Such inhibitors have been successfully used for therapy to target a number of different RTKs in cancer [11,13]. In the case of FGFRs, tyrosine kinase inhibitors would be relevant therapeutics for the treatment of subsets of cancers overexpressing FGFRs (e.g. breast cancer and MM), displaying activating FGFR mutations (e.g. bladder or endometrial cancers), or expressing chimaeric fusion proteins of dimerization domains fused to FGFR kinase domains (e.g. EMS) (see discussion above). Small-molecule tyrosine kinase inhibitors targeting FGFRs are currently in early phases of clinical trials (e.g. TKI258, E3810, E7080, BIBF1120, Masitinib) (http://ClinicalTrials.gov) [12,22,186]. Most of these inhibitors show broad specificity and target not only FGFRs, but also PDGFRs and/or VEGFRs due to high structural similarity of their kinase domains [12,22,186]. Although inhibition of several RTKs may increase the effectiveness of the treatment by interference with redundant pathways for particular cancer types, simultaneous targeting of several kinases may be associated with increased side effects. Efforts to develop more specific FGFR inhibitors are underway.

FGFR-specific tyrosine kinase inhibitors have shown promising results in interfering with FGFRs in cancer cells and mouse models. Widely used in the laboratory are the two specific FGFR kinase inhibitors SU5402 and PD173074. It should be noted that although PD173074 is widely accepted as a specific FGFR inhibitor, the use of slightly higher concentrations will also lead to VEGFR kinase inhibition [187,188]. Both inhibitors show potent anti-tumour activity in cancer cell lines and mouse models with FGFR alterations (see above), thus suggesting a potential use of small-molecule tyrosine kinase inhibitors to target FGFRs in cancer therapy. Despite their specificity against FGFRs and promising results in the laboratory, neither of these compounds has a high probability to be successfully used in the clinic owing to toxicity issues [186]. Other new specific FGFR kinase inhibitors are under development. One example is AZD4547 that is going to be tested in Phase II clinical trials for the treatment of breast cancer with FGFR1 overexpression (http://ClinicalTrials.gov). BGJ398, another example, is going to be tested in Phase I clinical trials in patients with advanced solid malignancies with FGFR amplifications or mutations (http://ClinicalTrials.gov).

The broad expression of FGFRs throughout the body and the importance of the FGFRs in various physiological processes, as well as the high degree of homology between the kinase domains of FGFRs, have to be considered in the development and application of FGFR tyrosine kinase inhibitors for cancer treatment. Certain toxicity issues and side effects, such as, for example, tissue calcification upon blockade of FGF23 signalling [22], could possibly be circumvented using inhibitors targeting particular FGFR subtypes.

Monoclonal antibodies against FGFs and FGFRs

Monoclonal antibodies targeting RTKs or their ligands can block ligand binding and receptor dimerization, and may act to promote tumour cell removal by the immune system [13,186,189]. This strategy has been successfully used for treatment of various types of cancer with deregulated RTKs [11,13,189]. Importantly, monoclonal antibodies can be produced that very specifically bind their targets due to high specificity in antibody–antigen interactions [189]. This holds promise for the generation of highly specific antibodies that target particular FGF or FGFR isoforms [186]. Since monoclonal antibodies act extracellularly, they may be relevant to use in cancers that overexpress FGFs or FGFRs, or display activating FGFR mutations, but probably not in cancers

with cytoplasmic chimaeric proteins consisting of dimerization domains fused to FGFR kinase domains.

Currently there are several ongoing efforts to generate monoclonal antibodies against FGFs or FGFRs [12,22,186]. Monoclonal antibodies against FGFs have shown anti-tumour activity in mouse models of, for example, breast and prostate cancer (FGF8), as well as colon and hepatocellular cancer (FGF19) and melanoma (FGF2) [99,127,190,191]. Also, monoclonal antibodies against the FGFRs have shown anti-tumour effects in mouse models and cancer cell lines. For example, R3Mab and PRO-001 that inhibit ligand binding to and dimerization of FGFRs, exhibited potent anti-tumour activity in mouse models of MM and bladder cancer overexpressing FGFR3 [108,161]. Furthermore, a monoclonal antibody (GP369) targeting the FGFR2 IIIb isoform has been shown to inhibit growth of human breast and gastric cancer xenografts with activated FGFR2 signalling in mice [192]. These studies indicate that monoclonal antibodies targeting specific FGF or FGFR isoforms can be generated and provide proof-of-principle that therapeutic antibodies against FGFs/FGFRs may have the potential to be used in cancer therapy. It remains to be determined whether monoclonal antibodies targeting FGFs/FGFRs will show promising results in clinical trials.

FGF ligand traps

Another strategy to interfere with FGFR signalling is represented by so-called FGF ligand traps that sequester FGF ligands to prevent their binding to FGFRs. FGF traps may be most useful in cancers displaying FGF overexpression. The FGF trap FP-1039 (Five Prime Therapeutics) is a soluble fusion protein consisting of the extracellular FGFR1 IIIc domain fused to the Fc portion of IgG1. It prevents FGF1, FGF2 and FGF4 from binding to their respective receptors, thereby inhibiting FGFR kinase activation and therefore potentially blocking FGFR-induced proliferation and angiogenesis. This FGF trap is going to be used in Phase II clinical trials to test its activity and safety in advanced or recurrent endometrial cancers with specific FGFR2 mutations (http://ClinicalTrials.gov).

CONCLUDING REMARKS

In summary, deregulation of FGFs and FGFRs is detected in a number of solid human tumours and haematological malignancies, and may sustain several of the cancer hallmarks. In particular, FGFs and FGFRs seem to act oncogenically to stimulate several steps of cancer progression, including cancer cell proliferation and survival, as well as EMT, invasion/metastasis and angiogenesis. Targeting FGFs/FGFRs in cancer is relatively new and it remains to be seen whether ongoing clinical trials and future developments will appear promising in the treatment of human cancer. Despite promising examples of the use of molecular-targeted therapies against RTKs, a number of challenges still exist, as shown in the case of the FGFR. Moreover, an obstacle experienced with both small-molecule tyrosine kinase inhibitors and monoclonal antibody therapies is the development of resistance in patients owing to the emergence of mutations that give rise to drug-resistant RTK variants or compensatory signalling networks to overcome the need for the inhibited RTK [11,13]. Moreover, since the responses to small-molecule tyrosine kinase inhibitors and monoclonal antibodies are often low or moderate, they usually need to be used in combination with chemo- or radio-therapy to achieve enhanced responses [193]. Future challenges in targeting FGFs/FGFRs in cancer therapy include increasing the knowledge about the effect of FGFRs in progression of specific cancer types, the development of FGFR therapeutics with few side effects, and the development of diagnostic and prognostic biomarkers to enable appropriate patient selection for cancer treatment.

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SUPPLEMENTARY ONLINE DATA

Fibroblast growth factors and their receptors in cancer

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Supplementary Tables S1–S3 are on the following pages.

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Table S1 Altered expression of FGFRs reported in human cancers

MPD, myeloproliferative disorders

Cancer type	Receptor	Up-regulated (references)	Down-regulated (references)	Other
Brain	FGFR1	[1–5]		
	FGFR2	[6]	[7,8]	
	FGFR4	[9]		
Head and neck	FGFR1	[10–17]		
	FGFR2	[16–21]	[22]	
	FGFR3	[19,20,23,24]		
	FGFR4	[25]		
Sarcoma	FGFR1	[26,27]		Chondrosarcoma
		[28]		Osteosarcoma
	FGFR2	[28]		Osteosarcoma
	FGFR3	[28]		Osteosarcoma
Soft tissue sarcoma	FGFR1	[29,30]		Rhabdomyosarcoma
		[31]		Cystosarcoma
	FGFR2	[32]		Kaposi's sarcoma
		[33]		Rhabdomyosarcoma
	FGFR3	[34]		Rhabdomyosarcoma
	FGFR4	[28,33,35–39]		Rhabdomyosarcoma
Thyroid	FGFR1	[40,41]		
	FGFR2		[42]	
	FGFR3	[40]		
	FGFR4	[40]		
Lung	FGFR1	[43–53]		
	FGFR2	[45–48,54–56]		
	FGFR3	[45,46,57,58]		
	FGFR4	[45]	[59]	
Breast	FGFR1	[60–76]		
	FGFR2	[60,64,73,74,76–79]		
	FGFR3	[80]		
	FGFR4	[74,81,82]		
Liver	FGFR1	[83]		
	FGFR2	[84]	[85]	
	FGFR3	[84,86]		
	FGFR4	[84,87,88]		
Pancreas	FGFR1	[89–93]		
	FGFR2	[94–96]		
	FGFR3	[92]		
	FGFR4	[92,97]		
Stomach	FGFR1	[98,99]		
	FGFR2	[98,100–110]		
	FGFR4	[98]		
Bladder	FGFR1	[111–115]		
	FGFR2	[111,112]	[116]	
	FGFR3	[117–121]		
Prostate	FGFR1	[122–130]		
	FGFR2	[127–129]	[131]	
	FGFR4	[122,123,132,133]		
Testis	FGFR1	[134]		
Colon	FGFR1	[135]	[136]	
	FGFR3		[137]	
Uterus	FGFR1	[138,139]		
	FGFR2	[140–142]		
Ovary	FGFR1	[67,143,144]		
	FGFR2	[145]		
	FGFR4	[82]		
Cervix	FGFR2	[146–148]		
Skin	FGFR1	[149,150]		
	FGFR3	[151,152]		
	FGFR4	[153]		
Multiple myeloma	FGFR3	[154–171]		
Leukaemia/MPD/lymphoma	FGFR1	[172–177]		
	FGFR3	[178–181]		

Table S2 FGFR point mutations identified in human cancers

Mutated FGFRs for which functional experiments demonstrated loss-of-function mutations are underlined and gain-of-function mutations are indicated in bold. Normal lettering indicates mutations for which the function has not been determined experimentally. MM, multiple myeloma, RMS, rhabdomyosarcoma, X, stop codon, PS, Pfeiffer syndrome, AS, Apert syndrome, CS, Crouzon syndrome, BSS, Beare–Stevenson syndrome, LADD, Lacrimo-Auriculo-Dento-Digital syndrome, CR, nonsyndromic craniosynostosis, TD, Thanatophoric dysplasia, ACH, Achondroplasia, HCH, Hypochondroplasia, SADDAN, Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans, AN, Acanthosis Nigricans. Note that in the literature some of the mutations are numbered relative to the alternative IgIIIc or IIIb isoform whereas we here only number the mutations relative to the FGFR1 IIIc (GenBank® accession number NM_023110), FGFR2 IIIc (GenBank® accession number NP_000132), FGFR3 IIIc (GenBank® accession number NP_000133) and FGFR4 (GenBank® accession number X57205).

Receptor	Mutation	Cancer type	Consequence	Syndrome
FGFR1	G70R [44,182] (SNP)	Lung		
	R78H [183]	Prostate		
	S125L [184,185] S125L [186]	Breast, skin		
	T141R [182] (SNP)	Lung		
	P252T [184,187]	Lung	P252R is associated with PS and results in altered ligand specificity [188]	
	P252S [183]	Skin		
	A268S [183]	Stomach, Colon		
	A429S [189]	Colon		
	N546K [190]	Brain	Enhanced kinase activity [191]	
	R576W [190]	Brain	Predicted to result in enhanced activity [190]	
	P576H	Lung		
	K656E [6]	Brain	Enhanced kinase activity [192]	
	V664L [184]	Lung		
FGFR2	S24F [193]	Skin		
	M71T [183]	Bladder, lymphoma		
	V77M [193]	Skin		
	A97T [194]	Cervix		
	D101Y [194]	Endometrial		
	E160A [193]	Skin	Predicted to negatively affect interaction with HSPG [193]	
	R203C [184,185,195]	Breast		
	N211I [194]	Lung		
	Q212K [6]	Brain		
	H213Y [193]	Skin	Predicted to negatively affect interaction with HSPG [193]	
	E219K [193]	Skin	Predicted to reduce receptor dimerization [193]	
	G227E [193]	Skin	Predicted to destabilize the IgII domain [193]	
	V248D [193]	Skin	Predicted to destabilize the IgII domain [193]	
	R251Q [193]	Skin	Loss of ligand binding [193]	
	S252W [194,196–198]	Endometrial	Alter ligand specificity [200]	AS [201]
	S252W [199]	Ovary		
	P253R [194]	Endometrial	Alter ligand specificity [200]	AS [201]
	S267P [202]	Stomach	Ligand-independent dimerization [203]	CS [201]
	G271E [193]	Skin	Predicted to destabilize the IgIII domain [193]	
	G272V [184]	Ovary		
	D283N [184,187]	Lung		
	W290C [184,187,194]	Lung	W290G forms ligand-independent dimers [204]	PS [205]
	G305R [193]	Skin		
	K310R [194,197,198]	Endometrial		
	A314D [194]	Endometrial		PS [194]
	A315T [197]	Endometrial		
	Q361R* [206]	Colon		
	T370R [193]	Skin		
	S372C [198]	Endometrial		BSS [204]
	Y375C [197,198]	Endometrial		BSS [204]
	Y375C [199]	Ovary		
	I380V	Lung		
	C382R [194,197,198]	Endometrial		
	A389T [194]	Endometrial		
	M391R [197]	Endometrial		
	G462E [206]	Brain		
	W474X [193]	Skin		
	E475K [193]	Skin	Enhanced kinase activity but less stable [193]	
	D530N [193]	Skin	Reduced kinase activity [193]	
	H544Q [182] (SNP)	Lung		
	I547V [197,198]	Endometrial		
	N549K [194,197,198]	Endometrial	Enhanced kinase activity [194]	
	E574K [193]	Skin		
	P582L [206]	Colon		
	R612T† [184,187]	Lung		
	E636K [193]	Skin		
	M640I [193]	Skin	Predicted to decrease kinase activity [193]	
	I642V [193]	Skin	Reduced kinase activity [193]	
	A648T [193]	Skin	Reduced kinase activity [193]	LADD[207]

Table S2 Continued

Receptor	Mutation	Cancer type	Consequence	Syndrome
	K659M [194]	Endometrial		
	K659N [194]	Endometrial	Enhanced kinase activity [208]	CR [209]
	K659E [197,198]	Endometrial		
	S688F [193]	Skin		
	G701S [193]	Skin	Predicted to decrease kinase activity [193]	
	P708S [193]	Skin		
	R759X/Q [193]	Skin		
	L770V [193]	Skin	Predicted to impair phosphorylation of Tyr^{769} [193]	
FGFR3	T79S [184]	Lung		
	G197S [171] (SNP)	MM		
	C228R [184]	Colon	Mutation of analogous cysteine residue in FGFR2 causes PS [210]	
	Y241C [159]	MM		
	R248C [121,211–227]	Bladder	Ligand-independent dimerization [229]	TDI [229]
	R248C [228]	Head and neck		
	R248C [161,165]	MM		
	S249C [226,230,231]	Cervix	Ligand-independent dimerization [229]	TDI [229]
	S249C [121,211–227,232–234]	Bladder		
	S249C [235]	Head and neck		
	S249C [236]	Prostate		
	P250R [171] (SNP)	MM		
	E322K [202]	Colon		
	G370C [121,211–215,217–219,221–227,234]	Bladder	Ligand-independent dimerization [229,237]	TDI [229,237]
	S371C [121,211,213,214,217,220,227]	Bladder	Ligand-independent dimerization [229,237]	TDI [229,237]
	Y373C [121,211-224,227,232–234,238,239]	Bladder	Ligand-independent dimerization [229,237]	TDI [229,237]
	Y373C [169,170,240,241]	MM		
	I376C [214]	Bladder		
	G380R [121,211,213,214,242]	Bladder	Enhanced kinase activity [244]	ACH [245]
	G380R [243]	MM		
	G382D [240]	MM	Enhanced kinase activity [240]	
	F384L [211,213,220] (SNP)	Bladder		
	F384L [236]	Prostate		
	F384L/C [171,241,246]	MM		
	A391E [121,212,214,218,221,225]	Bladder	Stabilization of dimer [247]	CS [248]
	A391E [236]	Prostate		
	S433C [171]	MM		
	A441T [171] (SNP)	MM		
	A452S [171] (SNP)	MM		
	E466K [249]	Brain		
	D617G [228]	Head and neck		
	V630M [228]	Head and neck		
	D646Y [250]	Bladder		
	K650E [121,184,218–221,223,224,226,227,234,239]	Bladder	Enhanced kinase activity [252,253]	TDII [253]
	K650E [251]	Testis		
	K650E [170,240,241]	MM		
	K650Q [121,217,234]	Bladder	Enhanced kinase activity [253]	HCH [253]
	K650M [212,215,218,219,221–223,227,242]	Bladder	Enhanced kinase activity [253]	TDI, SADDAN [253]
	K650M [251]	Testis		
	K650M [170,171,241]	MM		
	K650N [251]	Testis	Enhanced kinase activity [253]	HCH [253]
	K650T [218,221,222,242]	Bladder	Enhanced kinase activity [253]	AN [254]
	K650T [251]	Testis		
	E686K [228]	Head and neck		
	G697C [255]	Head and neck	Enhanced kinase activity [255]	
	A717T [171] (SNP)	MM		
	I726F [171] (SNP)	MM		
FGFR4	C56S [35]	RMS		
	R72L [35]	RMS		
	T122A [35]	RMS		
	A175T [35]	RMS		
	R183S [182] (SNP)	Lung		
	S232I [182] (SNP)	Lung		
	R234H [35]	RMS		
	Y367C [183]	Breast	Constitutive activation [256]	
	G388R [257–259] (SNP)	Lung	A common SNP that occurs in approximately 50 % of the population [268]	
	G388R [87]	Liver		
	G388R [25,183,260,261]	Head and neck		
	G388R [35]	RMS		
	G388R [262]	Soft tissue sarcoma		
	G388R [183,263–267]	Prostate		

Table S2 Continued

Receptor	Mutation	Cancer type	Consequence	Syndrome
	G388R [268]	Colon		
	G388R [183,265,268]	Breast		
	G388R [183]	Brain		
	G388R [153,183]	Skin		
	G388R [269]	Stomach		
	N535D	RMS		
	N535K [35]	RMS	Enhanced kinase activity [35]	
	V550E [35]	RMS	Enhanced kinase activity [35]	
	V550L [35]	RMS		
	V550M‡ [184,185]	Breast		
	A554V [35]	RMS		
	G576D [35]	RMS		
	R616G [182] (SNP)	Lung		
	E681K [182,270] (SNP)	Lung		
	P712T‡ [184,187]	Lung		
	P716R [193]	Skin		
	A729G [182] (SNP)	Lung		
	S772N‡ [184]	Lung		

*Glu^{361} is only present in FGFR2 IIIb

†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.

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

Table S3 FGFR fusion proteins identified in human cancer

Fusion proteins reported to display oncogenic properties in cell lines and mouse models are indicated in bold. L/EMS/L, Leukaemia/8p11 myeloproliferative disorder/Lymphoma; TKD, tyrosine kinase domain; RRM, RNA recognition motif; HLH, helix-loop-helix; LRR, leucine-rich repeat; CC, coiled coil; PDZ, PSD-95/Dlg/ZO-1.

Receptor	Fusion partner	Cancer/Disease	Oligomerization domain	Oncogenic potential
FGFR1	**ZNF198/RAMP/FIM/ZMYM2** [271–277]	L/EMS/L	Zinc finger	Yes [278–282]
	FOP/FGFR1OP1 [283–286]	L/EMS/L, lung	LRR	Yes [287,288]
	CEP110/CEP1 [286,289–292]	L/EMS/L	Leucine zipper	Yes[290]
	BCR [278,293–296]	L/EMS/L	CC	Yes [278,281]
	LRRFIP1 [297]	L/EMS/L	CC	ND
	FGFR1OP2 [298,299]	L/EMS/L	CC	Yes [298]
	TRIM24/TIF1 [300]	L/EMS/L	CC	ND
	MYO18A [301]	L/EMS/L	PDZ? CC?	ND
	CPSF6 [302]	L/EMS/L	RRM?	ND
	HERV-K [303]	L/EMS/L		ND
	PLAG1 [304]	Head and neck		ND (fusion does not include TKD of FGFR)
	CUX1 [305]	L/EMS/L		Yes [305]
FGFR3	**TEL/ETV6** [306]	L/EMS/L	HLH	Yes [307]

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