Fibroblast growth factor signalling: from development to cancer

Nicholas Turner and Richard Grose‡*

Abstract | Fibroblast growth factors (FGFs) and their receptors control a wide range of biological functions, regulating cellular proliferation, survival, migration and differentiation. Although targeting FGF signalling as a cancer therapeutic target has lagged behind that of other receptor tyrosine kinases, there is now substantial evidence for the importance of FGF signalling in the pathogenesis of diverse tumour types, and clinical reagents that specifically target the FGFs or FGF receptors are being developed. Although FGF signalling can drive tumorigenesis, in different contexts FGF signalling can mediate tumour protective functions; the identification of the mechanisms that underlie these differential effects will be important to understand how FGF signalling can be most appropriately therapeutically targeted.

Fibroblast growth factors (FGFs) that signal through FGF receptors (FGFRs) regulate fundamental developmental pathways, controlling events such as mesoderm patterning in the early embryo[1] through to the development of multiple organ systems[2]. FGF signalling extends to many physiological roles in the adult organism, including the regulation of angiogenesis and wound repair. FGFRs are expressed on many different cell types and regulate key cell behaviours, such as proliferation, differentiation and survival, which makes FGF signalling susceptible to subversion by cancer cells.

There is compelling evidence for deregulated FGF signalling in the pathogenesis of many cancers that originate from different tissue types. Aberrant FGF signalling can promote tumour development by directly driving cancer cell proliferation and survival, and by supporting tumour angiogenesis. Mouse models have confirmed that FGF signalling has oncogenic potential, but have also importantly demonstrated that FGF signalling can have tumour suppressive functions in certain contexts. Coupled with the importance of FGF signalling in tissue development and homeostasis, this underlines the importance of appropriate targeting of any potential therapeutic interventions.

FGF signalling

FGF signalling has evolved to become a highly complex growth factor signalling pathway, reflecting the multitude of physiological functions that are controlled by FGF signalling. The mammalian FGF family comprises 18 ligands (BOX 1), which exert their actions through 4 highly conserved transmembrane tyrosine kinase receptors (FGFR 1, FGFR2, FGFR3 and FGFR4) (FIG. 1). A fifth related receptor, FGFR5 (also known as FGFRL1), can bind FGFs, but has no tyrosine kinase domain, and might negatively regulate signalling[3] (FIG. 2).

FGFs are secreted glycoproteins that are generally readily sequestered to the extracellular matrix, as well as the cell surface, by heparan sulphate proteoglycans (HPSGs). To signal, FGFs are released from the extracellular matrix by heparinases, proteases or specific FGF-binding proteins, and the liberated FGFs subsequently bind to cell surface HPSGs (reviewed in REF. 4). Cell surface HPSGs also stabilize the FGF ligand–receptor interaction, forming a ternary complex with FGFR[5,6] (FIG. 1). The specificity of the FGF–FGFR interaction is established partly by the differing ligand-binding capacities of the receptor paralogues[7,8], but also by alternative splicing of FGFR, which substantially alters ligand specificity (FIG. 1). Further control of FGF–FGFR specificity is mediated by the tissue-specific expression of particular ligands and receptors, coupled with several cell surface or secreted proteins that facilitate the FGF–FGFR interaction[9], such as the Klotho family[10] for hormonal FGFs (BOX 1), which further increases ligand specificity.

Downstream signalling. FGF receptors signal as dimers, and ligand-dependent dimerization leads to a conformational shift in receptor structure that activates the intracellular kinase domain, resulting in intermolecular transphosphorylation of the tyrosine kinase domains and intracellular tail. Phosphorylated tyrosine residues on the receptor function as docking sites for adaptor proteins, which themselves may also

**Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, London SW3 6JB, UK, and Royal Marsden Hospital, London SW3 6JJ, UK.*
‡Queen Mary University of London, Barts & The London School of Medicine and Dentistry, Institute of Cancer, London EC1M 6BQ, UK.
e-mails: Nicholas.turner@icr.ac.uk; r.p.grose@qmul.ac.uk
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At a glance

- Fibroblast growth factors (FGFs) and their receptors (FGFRs) drive crucial developmental signalling pathways, which are responsible for many functions, including cell proliferation, survival and migration. As such, they are susceptible to hijack by cancer cells and have been shown to have oncogenic roles in many cancers.
- Conversely, FGFR signalling can also have tumour suppressive roles, through driving differentiation, regulating other oncogenic pathways, protecting cells from damage or perhaps by mediating immune surveillance.
- The specific cellular context in which FGF signalling occurs is clearly important for determining whether oncogenic or tumour protective outcomes are evoked, and understanding more about context-specific FGF signalling is a key area of research.
- There are several types of genetic evidence that support an oncogenic function for FGFRs: identification of gene amplifications, activating mutations, chromosomal translocations, single nucleotide polymorphisms and aberrant splicing at the post-transcriptional level. Expression of FGFs can also be affected by gene amplification.
- There is now evidence from multiple cancer types to implicate FGF signalling in several oncogenic behaviours, including proliferation, survival, migration, invasion and angiogenesis.
- Therapeutic targeting of FGFs and their receptors is a major area of drug development research. Most agents are small-molecule tyrosine kinase inhibitors, but blocking antibodies and ligand-trap approaches are also being developed.

be directly phosphorylated by FGFR[11], leading to the activation of multiple signal transduction pathways (FIG. 2). FGFR substrate 2 (FRS2) is a key adaptor protein that is largely specific to FGFRs, although it can also bind other tyrosine kinase receptors, such as neurotrophic tyrosine kinase receptor type 1 (NTRK1), RET and anaplastic lymphoma kinase (ALK)[12]. FRS2 binds to the juxtamembrane region of FGFRs through its phosphotyrosine-binding (PTB) domains. The activated FGFR phosphorylates FRS2 on several sites, allowing the recruitment of the adaptor proteins son of sevenless (SOS) and growth factor receptor-bound 2 (GRB2) to activate RAS and the downstream RAF and MAPK pathways[11]. A separate complex involving GRB2-associated binding protein 1 (GAB1) recruits a complex, which includes PI3K, and this activates an AKT-dependent anti-apoptotic pathway[13].

Elsewhere on the intracellular portion of the activated receptor, and independently of FRS2 binding, the Src homology 2 (SH2) domain of phospholipase Cγ (PLCγ) binds to a phosphotyrosine residue towards the carboxyl terminus[14] (FIG. 2). After PLCγ is activated, it hydrolyses phosphatidylinositol-4,5-biphosphate (PIP_2) to phosphatidylinositol-3,4,5-triphosphate (PIP_3) and diacylglycerol (DAG)[15], activating protein kinase C (PKC), which partly reinforces the activation of the MAPK pathway by phosphorylating RAF. Several other pathways are also activated by FGFRs, depending on the cellular context, including the p38 MAPK and Jun N-terminal kinase pathways, signal transducer and activator of transcription (STAT) signalling[16] and ribosomal protein S6 kinase 2 (RSK2)[17].

Negative regulation of signalling. The mechanisms of attenuation and negative feedback control of FGFR signalling are only partly understood. Following activation receptors are internalized, resulting in receptor degradation or recycling, in a process that is partly controlled by CBL-mediated monoubiquitylation[18] (FIG. 2). MAPK signalling, particularly ERK1 and ERK2 signalling, has been shown to phosphorylate FRS2 on many serine and/or threonine residues, inhibiting the recruitment of GRB2 (REF. 12). Downstream signalling can be attenuated through the induction of MAPK phosphatases such as MAPK phosphatase 3 (MKP3)[19], Sprouty (SPRY) proteins[20,21] and SEF[22,23] family members that modulate receptor signalling at several points in the signal transduction cascade[24] (FIG. 2). MKP3 dephosphorylates ERK1 and ERK2 to attenuate MAPK signalling[19], and SPRY proteins are thought to function in either a dominant-negative fashion, by competing for GRB2 binding and so preventing SOS-mediated RAS activation, or by directly binding to RAF and blocking subsequent MAPK signalling[20,21]. Similarly, SEF may function at multiple levels and has a transmembrane form that can directly interact with FGFRs; both the transmembrane form and a splice variant that is confined to the cytoplasm seem to be capable of inhibiting ERK phosphorylation[25].

Context-dependent signalling. Studies of FGF signalling during development reinforce the crucial importance of cellular context in determining the functional outcome of FGFR activation (BOX 2). Although in most cellular contexts FGFs induce proliferation and migration[2], in certain cell types physiological FGF signalling induces differentiation and/or cell cycle arrest. This has been most clearly demonstrated in the development of endochondral and membranous bone, in which mouse models have shown that FGFR3 and FGFR2 can negatively regulate proliferation and positively drive differentiation[26,27]. In humans, several gain-of-function germline mutations in the FGFR genes result in skeletal dysplasias, with *FGFR2* mutations a common cause of craniosynostosis syndromes and *FGFR3* mutations common in chondrodysplasia syndromes[28]. Similarly, activating germline mutations in *FGFR1* are a cause of Pfeiffer syndrome, a rare craniosynostosis syndrome[29]. Through several different mechanisms, these germline mutations result in ligand-independent activation of the receptor, which induces the premature fusion of cranial sutures[28] and the differentiation of chondrocytes in the endplates of long bones[28]. There is a lack of evidence regarding whether germline FGFR mutations predispose to cancer.

The predominant signalling pathway activated downstream of FGFRs in development seems to be MAPK signalling[30], and although it is incompletely understood current evidence points to the importance of differential effects of MAPK signalling in determining the cellular response of FGFR activation. The downstream effect of MAPK signalling is mostly cell proliferation; for example, through the induction of cyclin D1 expression, thereby promoting entry into the S phase of the cell cycle[31,32]. However, MAPK signalling induces cell cycle arrest and differentiation in other contexts, such as the p21-dependent cell cycle arrest in chondrocytes[33] and the differentiation of neuronal PC-12 cells[34]. Similarly, divergent responses can occur in cancer development (discussed below).

Craniosynostosis syndromes
Characterized by premature fusion of the skull sutures, which often results in cranial deformities and associated pathologies.

Chondrodysplasia syndromes
Characterized by abnormal shortening of long bones owing to premature growth arrest of chondrocytes in the epiphyseal plates.

Seborrhoeic keratosis
A benign wart-like growth of skin keratinocytes.

There are many factors that underlie context-dependent signalling, including the cell type-specific expression of different adaptor molecules, signal transduction enhancers, transcription factors and co-activators[32]. Other factors that are important in context specificity include crosstalk with other signalling networks, such as Wnt signalling[35], and importantly the kinetics of signalling, with sustained strong signalling inducing differentiation, senescence and apoptosis, and less pronounced signalling inducing proliferation and survival[36].

A further factor that affects the context specificity of FGF signalling might be differences in signalling between the FGFRs. Although all four FGFRs signal through a similar network of pathways in general, the kinase domain of FGFR1 drives stronger downstream pathway activation than FGFR4 (REF. 37). There is also some evidence that differential responses to signalling are initiated by the FGFR1 and FGFR2 kinase domains, with more rapid attenuation of FGFR2 signalling mediated by receptor internalization and degradation[38–40]. Although splicing of the extracellular domain controls ligand specificity, there is no evidence to suggest that this affects intracellular signalling *per se*.

Deregulation of FGF signalling in cancer

In this section we discuss the substantial evidence that supports the existence of aberrant FGF signalling in the pathogenesis of multiple types of cancer. The underlying mechanism driving FGF signalling is largely tumour specific, and can be split into genomic FGFR alterations that drive ligand-independent receptor signalling compared with alterations that support ligand-dependent activation (FIG. 3; TABLE 1).

Activating mutations. The importance of FGF signalling in tumour pathogenesis was highlighted by a screen of more than 1,000 somatic mutations found in the coding exons of 518 protein kinase genes from 210 different human cancers[41]. Of the non-synonymous mutations, components of the FGF signalling pathways were the most commonly mutated[41].

Bladder cancer has the most established link to FGFR mutations. Overall ~50% of bladder cancers have somatic mutations in the *FGFR3*-coding sequence[42], and most of the mutations precisely match the activating germline mutations of thanatophoric dysplasia, a lethal form of dwarfism[43]. Mutations in bladder cancer are strongly associated with non-muscle invasive disease, with 50–60% of non-muscle invasive cancers possessing *FGFR3* mutations, and mutations occurring less commonly in muscle-invasive bladder cancers (10–15% of these cancers only). In contrast to the epidermal growth factor receptor (*EGFR*) gene, in which activating mutations occur almost exclusively in the kinase domain, more than half of the mutations in *FGFR3* occur at a single position in the extracellular domain (S249C). This mutation leads to the formation of an aberrant intermolecular cysteine disulphide bridge, which results in constitutive dimerization and activation of the receptor[44,45]. Mutations are also commonly found in the transmembrane domain (such as Y373C), as well as less common kinase domain mutations (such as K652E)[46], with Y373C and to a lesser extent K652E constitutively activating the receptor[44,45].

FGFR3 mutations have also been identified in many other cancer types, including cervical cancers[47], multiple myeloma, prostate cancer[48] and spermatocytic seminomas[49] (TABLE 1). A single report identified *FGFR3* mutations in oral squamous carcinomas[50], but this was not confirmed by a follow-up study[51]. *FGFR3*-activating mutations are also found at a high frequency in the benign skin conditions epidermal nevi[52] and seborrhoeic keratosis[53], which do not progress to malignancy[54].

Mutations of *FGFR2*, which are also frequently extracellular and identical to the activating germline mutations found in craniosynostosis syndromes[28], have been described in 12% of endometrial carcinomas[55]. *FGFR2*-mutant endometrial cancer cell lines are highly sensitive to FGFR tyrosine kinase inhibitors[28], which reflects oncogenic addiction to the mutant-activated FGFR.

Interestingly, *FGFR3* and *HRAS* mutations are mutually exclusive in bladder cancer[56], but *PIK3CA* mutations are more commonly found in bladder cancers with *FGFR3* mutations[57,58]. Similarly, *FGFR2* and *KRAS* mutations are mutually exclusive in endometrial cancer[59]. This suggests that in these cancers only a single mechanism of activation is required to fully activate MAPK signalling, although oncogenic PI3K signalling can be enhanced by multiple 'hits'.

FGFR gene amplifications. In contrast to the activation of *FGFR3* by mutation, amplifications of *FGFR3* have been described only rarely in cancers[60]. Conversely, amplifications of both *FGFR1* and *FGFR2* have more commonly been described. Approximately 10% of gastric cancers show *FGFR2* amplification, which is associated with poor prognosis diffuse-type cancers[61,62]. Gastric cancer cell lines with *FGFR2* amplifications show evidence of ligand-independent signalling and are highly sensitive to FGFR inhibitors[61,62], although

Box 1 | **The FGF family**

The fibroblast growth factor (FGF) family nomenclature describes 23 members, although there are only 18 FGF receptor (FGFR) ligands. Four family members do not function as FGF ligands (FGF11, FGF12, FGF13 and FGF14) and are more correctly referred to as FGF homologous factors, and there is no human *FGF15* gene; the gene orthologous to mouse *Fgf15* is *FGF19*. Most FGF ligands function in a classic autocrine or paracrine fashion. A surprising recent development is the identification of a family of FGFs (FGF19, FGF21 and FGF23) that function as hormones (reviewed in REF. 158). The hormonal FGFs bind poorly to heparan sulphate proteoglycans and can diffuse from the source of production into the circulation.

FGFs are subject to multiple splicing events that affect function, and although FGFs are normally thought of as secreted glycoproteins some have also been shown to have nuclear functions (reviewed in REF. 158). Furthermore, there is strong evidence emerging that FGFRs also traffic to the nucleus (reviewed in REF. 159), where they may evoke an entirely different downstream effect to that of the classic receptor tyrosine kinase signalling pathways.

Several germline FGF mutations have been identified in human disease, including loss-of-function mutations of *FGF3* in deafness[160], *FGF8* in Kallmann syndrome[161] and *FGF10* in Lacrimo-auditory-dento-digital syndrome[162]. Gain-of-function mutations in *FGF23* have been identified in hypophosphataemic rickets[163].

paracrine secretion of FGF7 by fibroblasts may also contribute to cellular proliferation *in vivo*[63]. Interestingly, in some gastric cancer cell lines amplification of *FGFR2* is accompanied by deletion of the most C-terminal coding exon[64]. This results in the expression of a C-terminally truncated receptor, which can also be generated by aberrant splicing in cell lines that lack the C-terminal deletion. This C-terminal FGFR2 truncation interferes with receptor internalization[65], therefore preventing a potential mechanism of signalling attenuation and contributing to constitutive activation of the receptor.

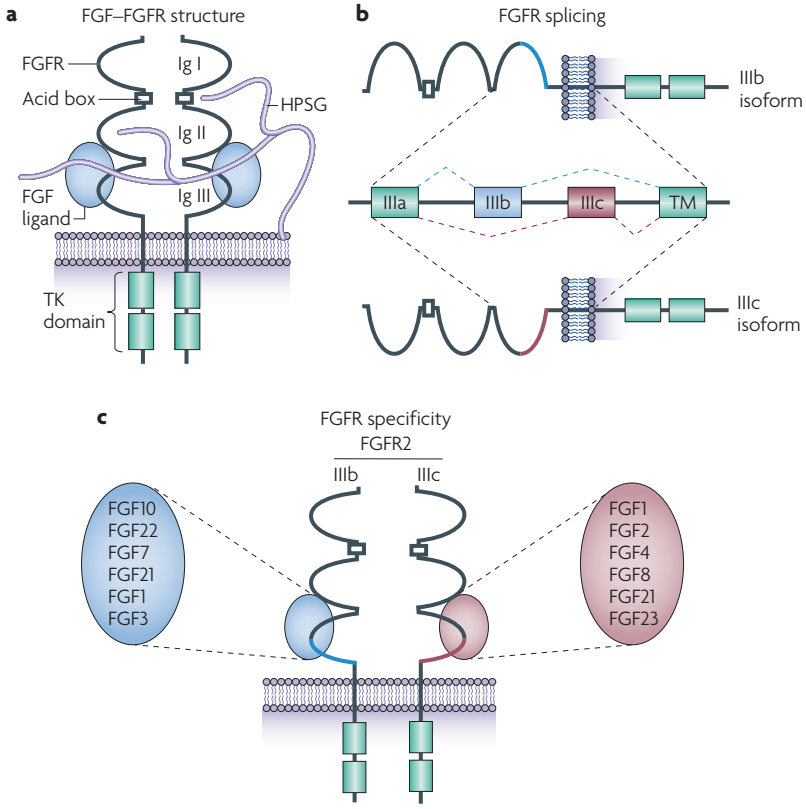

Figure 1 | **FGFR structure and control of ligand specificity. a** | The basic structure of the fibroblast growth factor (FGF) –FGF receptor (FGFR) complex comprises two receptor molecules, two FGFs and one heparan sulphate proteoglycan (HSPG) chain. The FGF signalling pathway comprises 4 highly conserved transmembrane receptors and 18 FGF ligands (BOX 1). FGFs bind with low affinity to cell surface HSPGs (purple) and with high affinity to specific FGFRs. The FGFRs, which are phylogenetically closely related to the vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs), consist of three extracellular immunoglobulin (Ig) domains, a single transmembrane helix and an intracellular split tyrosine kinase (TK) domain. The second and third Ig domains form the ligand-binding pocket and have distinct domains that bind both FGFs and HSPGs. **b** | Ligand-binding specificity is generated by alternative splicing of the Ig III domain. The first half of Ig III is encoded by an invariant exon (IIIa), which is spliced to either exon IIIb or IIIc, both of which splice to the exon that encodes the transmembrane (TM) region. Epithelial tissues predominantly express the IIIb isoform and mesenchymal tissues express IIIc. FGFR4 is expressed as a single isoform that is paralogous to FGFR-IIIc. **c** | Examples of the extent to which ligand specificity can differ between FGFR-IIIb and FGFR-IIIc isoforms, illustrated with the differing ligand specificty of FGFR2 isoforms. The FGFR2-IIIb ligands are shown in blue and the FGFR2-IIIc ligands are shown in brown. For example, FGF7 and FGF10 bind specifically to FGFR2-IIIb and have essentially no binding to FGFR2-IIIc[7]. The mechanisms controlling splice isoform choice are becoming clearer and defined control elements have been identified in the introns surrounding alternatively spliced exons[177–179].

Amplification of the chromosomal region 8p11–12, the genomic location of *FGFR1*, is one of the most common focal amplifications in breast cancer[66–68], and occurs in approximately 10% of breast cancers, predominantly in oestrogen receptor (ER)-positive cancers[66]. *FGFR1* amplifications have also been reported in oral squamous carcinoma[69] and are found at a low incidence in ovarian cancer[70], bladder cancer[71] and rhabdomyosarcoma[72] (TABLE 1). In contrast to *FGFR2* amplifications, overexpression of wild-type FGFR1 occurs in cancer; it is unclear whether the higher levels of FGFR1 lead to tumours that aberrantly respond to paracrine FGF ligands, such as FGF2, or whether at higher levels of FGFR1 expression ligand-independent signalling occurs. It is also important to note that the 8p11–12 region is gene dense and it is not universally accepted that *FGFR1* is the causative oncogene in this amplified region in breast cancer[73,74]. FGFR1 might also be important in breast cancers that lack *FGFR1* amplifications, and one study suggested that an FGFR inhibitor blocked the proliferation of non-amplified cancer cell lines by downregulating D-type cyclins[75].

Chromosomal translocations in haematological malignancies. Some of the strongest evidence linking FGF signalling to oncogenesis has come from the study of haematological malignancies, in which translocations involving the FGFRs have been identified. Several FGFR intragenic translocations have been identified, which typically result in a fusion protein comprising the N terminus of a transcription factor fused to an FGFR kinase domain. This leads to constitutive FGFR dimerization and activation[76–78] (TABLE 1). A different translocation is found in multiple myeloma: 15% of multiple myelomas harbour a t(4;14) translocation that links *FGFR3* at 4p16.3 to the immunoglobulin heavy chain *IGH* locus at 14q32 (REFS 79,80). These translocations are intergenic, with the breakpoints occurring ~70 kb upstream of *FGFR3*, and bring *FGFR3* under the control of the highly active *IGH* promoter. It is important to note that the translocations involving *FGFR3* in multiple myeloma also involve the adjacent multiple myeloma SET domain-containing (*MMSET*) gene, and the relative contributions of *FGFR3* and *MMSET* to oncogenesis are subject to ongoing debate[81]. However, the importance of FGFR3 overexpression and mutation in haematological malignancy has been modelled using transgenic mice[82] (BOX 3), and t(4;14) myeloma cell lines are highly sensitive to FGFR3 targeting[83,84].

FGFR3 translocation in multiple myeloma is associated with a poor prognosis and is rarely found in monoclonal gammopathy of uncertain significance, a precursor condition of multiple myeloma, which suggests that *FGFR3* translocations promote a rapid conversion to full multiple myeloma[85]. The ultimate effect of the translocation is to overexpress FGFR3 out of context, which might result in aberrant ligand-dependent signalling[86] (with hypersensitivity to ligands by swamping negative feedback and receptor internalization and degradation pathways) or ligand-independent signalling. In a small proportion of t(4;14) multiple myeloma, *FGFR3* is also mutated (~5% translocated cases)[87], presumably further

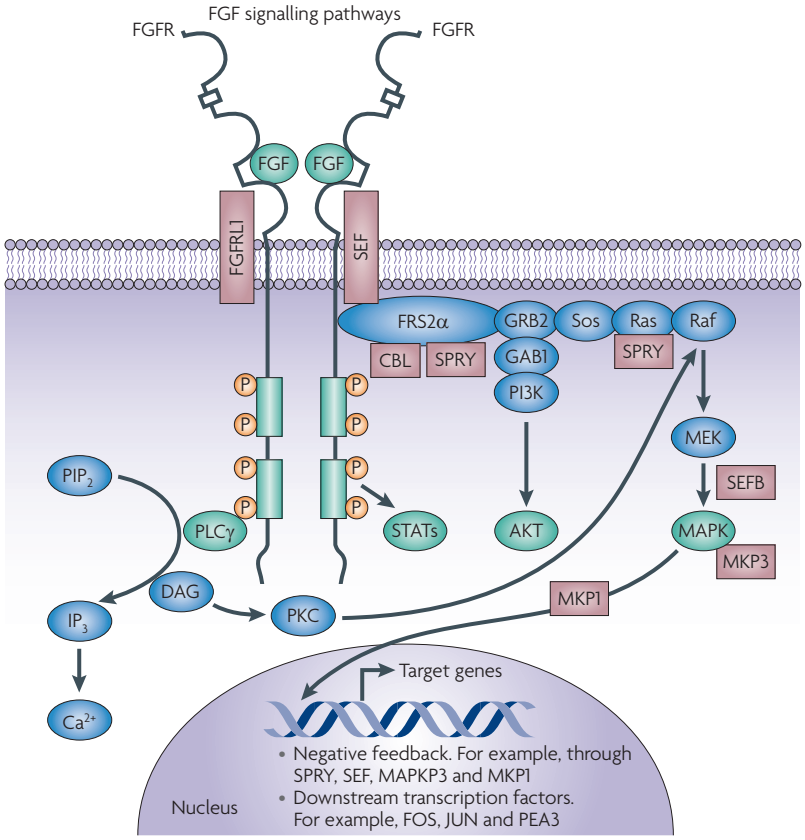

Figure 2 | **FGFR signalling network.** The signal transduction network downstream of fibroblast growth factor (FGF) receptors (FGFRs), along with negative regulators. Following ligand binding and receptor dimerization, the kinase domains transphosphorylate each other, leading to the docking of adaptor proteins and the activation of four key downstream pathways: RAS–RAF–MAPK, PI3K–AKT, signal transducer and activator of transcription (STAT) and phospholipase Cγ (PLCγ) (green). FGFRs have also been shown to bind and directly phosphorylate ribosomal S6 kinase[17] (not shown). Signalling can be negatively regulated at several levels by receptor internalization or the induction of negative regulators, including FGFR-like 1 (FGFRL1), SEF, Sprouty (SPRY), CBL, MAPK phosphatase 1 (MKP1) and MKP3 (brown). These regulators may modulate ligand binding (FGFRL1 and SEF) or interfere with intracellular signalling, principally through modulation of the MAPK pathway. DAG, diacylglycerol; FRS2α, FGFR substrate 2α; GRB2, growth factor receptor-bound 2; IP_3, inositol triphosphate; P, phosphorylation; PIP_2, phosphatidylinositol-4,5-biphosphate; PKC, protein kinase C; Sos, son of sevenless.

reinforcing FGFR3 signalling[82]. Interestingly, *FGFR3* translocations also occur mutually exclusively of *NRAS* and *KRAS* mutations[88].

Autocrine and paracrine signalling. Most of the genomic aberrations discussed above lead to constitutive receptor activation and ligand-independent signalling. Ligand-dependent signalling is likely to have a similarly important role in the pathogenesis of cancer, through either autocrine production of ligand in cancer cells or paracrine production of ligand from stromal cells that may be expressed physiologically or in response to cancer cells in a 'paracrine loop'. Several mouse models have shown that ectopic expression of FGF can promote cancer. This has been achieved by expressing FGF in either epithelial cells or stromal fibroblasts, which results in the autocrine and paracrine stimulation of cancer cells, respectively (BOX 3).

Monoclonal gammopathy of uncertain significance
A clonal proliferation of plasma cells that manifests as excess monoclonal immunoglobulin in the blood. A common condition of old age that progresses to multiple myeloma at a rate of ~2% per year.

The first strong evidence for autocrine FGF signalling driving human tumorigenesis comes from studies of melanoma, which expresses high levels of FGFR1 and FGF2. The growth of human melanoma xenografts regressed after antisense-mediated inhibition of FGFR1 or FGF2 (REF. 89), suggesting that an FGF2–FGFR1 autocrine loop promotes the development of some melanomas. Frequent amplification of *FGF1*, resulting in increased FGF1 expression, has also been reported in ovarian cancer and is associated with poor survival[90]. The FGF1 expression levels correlated with microvessel density, suggesting that aberrantly expressed FGF1 functions in a paracrine fashion to promote angiogenesis[90]. Whether FGF1 also functions in an autocrine manner in ovarian cancer to promote tumour cell proliferation or survival is unclear. An autocrine FGF2–FGFR1-IIIc feedback loop has also been reported in non-small-cell lung cancer cell lines that show resistance to the EGFR antagonist gefitinib[91].

Unequivocal evidence that paracrine FGF released from the stroma functions on human cancer cells to promote tumorigenesis is lacking, principally because it is difficult to model such an interaction *in vitro*. Increased plasma levels of FGF2 and other FGFs are found in multiple cancer types[92]. This partly reflects the increased release of FGFs: as tumours invade and degrade the extracellular matrix FGF is liberated[4], freeing it to function as a paracrine growth factor. Tumour cells may also induce FGF2 release from stromal inflammatory infiltrate (reviewed in REF. 93), which may promote tumour survival in a classic paracrine loop or promote angiogenesis. The angiogenic response can be further augmented by the establishment of an autocrine FGF2 signal in endothelial cells[93].

In prostate cancer, several FGFs, including FGF2 (REF. 94) and FGF6 (REF. 95), are upregulated. Similarly, FGFR1-IIIc is upregulated in poorly differentiated prostate cancers[94], which suggests the potential existence of a paracrine loop, and FGFR2-IIIb is downregulated. In astrocytomas, a similar increase in FGFR1 expression has been reported in high-grade tumours[96]. However, it is unclear to what extent the expression of FGFR1-IIIc in prostate cancer drives tumour progression, and to what extent the expression of this splice form is a consequence of tumour progression, particularly the epithelial–mesenchymal transition (EMT), which could lead to secondary changes in FGFR splicing and expression[97]. Loss of the expression of negative regulators, including SPRY1 and SPRY2 (REF. 98) and SEF[99], can also increase FGF signalling in prostate cancer. It has been proposed that these changes in prostate cancer may result in androgen independence[100]. As in prostate cancer, the expression of FGF1, FGF2 and FGF7 is higher in breast cancer stroma than in normal breast stroma[101,102].

As mentioned above, increased levels of several FGFs are detected in the serum of cancer patients, but some hormonal FGFs, such as FGF19, signal physiologically through the bloodstream. Transgenic mice expressing FGF19 in skeletal muscle developed hepatocellular carcinomas[103], which presumably reflects an endocrine action of the increased levels of circulating FGF19 (BOX 3). FGF19 was overexpressed in a subgroup of liver, colonic and lung squamous carcinomas[103].

A monoclonal antibody that sequesters FGF19 blocked the growth of colonic cancer cell lines and xenografts that overexpress FGF19 (REF. 104), suggesting that the growth of these cells may be driven by an autocrine loop functioning through FGFR4 (REF. 105). FGF19 requires β-klotho expression to interact with FGFR4, at least in physiological signalling, however, the expression of β-klotho is still to be established in these tumour types.

Germline single nucleotide polymorphisms. A further link between FGFR signalling and breast cancer has been provided by recent genome-wide association studies that identified *FGFR2* as a breast cancer susceptibility gene[106,107]. In pioneering studies, single nucleotide polymorphisms (SNPs) located in the second intron of *FGFR2* were found to correlate with an increased risk of developing breast cancer. The 'at risk' minor allele is prevalent, with 40% of the population carrying at least one copy, but the increase in risk is relatively small, increasing risk by 1.26-fold in a heterozygote and 1.63-fold in a homozygote[106]. Interestingly, the SNP seems to appreciably increase the risk of developing ER-positive breast cancer[108] only, with little or no effect on ER-negative breast cancer.

There remains substantial uncertainty regarding how the minor *FGFR2* allele increases breast cancer risk and exactly which of the multiple SNPs in the second intron — which are in strong linkage disequilibrium — are mechanistically important. One study suggested that the SNPs result in modest increases in *FGFR2* mRNA expression through the modification of a binding site for the transcription factors OCT1 and runt-related transcription factor 2 (RUNX2)[109]. Binding sites for ER and OCT1 often cluster together[110], suggesting a model in which ER and OCT1 cooperate in regulating *FGFR2* expression and potentially also cooperate with C/EBPβ to drive transcription[109]. The potential role of ER in determining the functional effects of this SNP may explain the apparent restriction of the risk attributed for this SNP to ER-positive breast cancer[108].

A second SNP, *FGFR4* G388R, does not seem to increase the incidence of cancer, but has been reported to associate with poor prognosis in multiple cancer types, including breast cancer[111], colon cancer[111] and lung adenocarcinoma[112]. The *FGFR4* G388R allele is common, with at least one copy present in approximately half the population. How this SNP influences cancer prognosis is less clear, and it potentially promotes cancer cell motility and invasion[111] or resistance to chemotherapy[113].

Oncogenic mechanisms of FGF signalling

FGF signalling can promote cancer development by affecting a range of major downstream biological processes. The following sections highlight examples for which particular aspects of FGF signalling affect various cancer cell behaviours in different tumour types.

FGF and proliferation. Excessive cell proliferation is one of the hallmarks of cancer, and many cell-based studies and mouse models have demonstrated that FGF signalling promotes tumour cell proliferation (BOX 3). Studies of the FGFR translocations of human haematological malignancies (TABLE 1) have shown that the mechanism driving a proliferative response to FGF signalling differs depending on context. The zinc finger 198 (ZNF198; also known as ZMYM2)–FGFR1 fusion proteins identified in 8p11 myeloproliferative syndrome delete the FRS2-binding site of FGFR1, and require PLCγ binding at Y766 along with STAT5 activation for proliferation[76,77]. By contrast, the breakpoint cluster region (BCR)–FGFR1 fusion proteins of chronic myelogenous leukaemia (CML) activate GRB2 through FGFR1-mediated phosphorylation of a BCR tyrosine residue[76,77], and the ETV6–FGFR3 fusion proteins found in peripheral T cell lymphoma are oncogenic, at least partly though PI3K signalling[114]. These data demonstrate an important principle, in which the signal transduction pathways initiating FGFR-dependent oncogenesis differ depending on cellular context.

Mouse studies have further added to our understanding of how FGFs can influence proliferation (BOX 3). FGF10 overexpression in the stromal compartment of the murine prostate resulted in epithelial hyperproliferation, which was concomitant with the upregulation of the androgen receptor[115]. FGF10 signalling was potentially dependent on FGFR1 as a dominant-negative FGFR1-IIIc construct attenuated cancer development[116], although this construct might also inhibit FGFR2 signalling through receptor heterodimerization. Expression of activated AKT in prostate epithelium combined with the high FGF10 expression in the stroma to further promote tumorigenesis[116]. Similarly, in an independent study, *Pten* deficiency in prostate epithelium (which results in increased phospho-AKT levels) synergized with autocrine overexpression of FGF8, leading to prostate adenocarcinoma[117]. Finally, ablation of *Frs2* inhibited prostate cancer development in the mouse[118]. These data emphasize the potential importance of FGF signalling for prostate cancer development, but also suggest

Box 2 | **FGF signalling in development**

A substantial body of knowledge has been compiled on the importance of fibroblast growth factor (FGF) signalling in development, and some of the principles are relevant to our understanding of how FGF signalling may affect tumorigenesis.

Gene targeting studies in mice have identified crucial functions for many FGF ligands and receptor isoforms in development, with knockout phenotypes often resulting in death *in utero* or at birth from a failure to execute fundamental developmental programmes, including gastrulation[164,165] and organogenesis[2,166–168]. For example, FGF10 plays a key part in lung development signalling through FGFR2-IIIb, as well as being required for the normal branching ductal development in the mammary gland[169,170] and prostate[171,172].

In development, FGFs have been shown to operate through reinforcing paracrine loops, in which active FGF signalling drives cell proliferation, migration and survival. For example, in the developing limb, paracrine networks involving FGF4, FGF8, FGF10, FGFR2-IIIb and FGFR2-IIIc initiate and maintain limb development and underpin epithelial–mesenchymal interactions[173].

that a second hit in the PI3K–AKT pathway might be required to enhance the oncogenic potential of FGF signalling.

FGF and survival. The mitogenic effects of FGF signalling may also be enhanced by pro-survival signalling. FGF signalling has the potential, depending on the cell type, to activate anti-apoptotic pathways through either the activation of PI3K–AKT or STAT signalling. This prosurvival effect has also been linked to resistance to chemotherapy. FGF2 has been suggested to play an important part in small-cell lung cancer, in which high levels of serum FGF2 are associated with a poor prognosis[119]. Studies have suggested that FGF2 mediates a cytoprotective effect by upregulating the expression of the anti-apoptotic proteins BCL-2, BCL-X_L, X-linked inhibitor of apoptosis (XIAP) and inhibitor of apoptosis 1 (IAP1; also known as BIRC3) through an S6 kinase (S6K2 and RSK2)-mediated pathway, therefore promoting resistance to chemotherapy[120–122].

Additional evidence supporting the importance of the S6K2 pathway in FGFR-driven cancer came from a breast carcinoma model, in which non-transformed MCF-10A breast cancer cells expressing conditionally activated FGFR1 became transformed in an S6K2-dependent manner. Inhibition of S6K2 by small interfering RNA or small molecule inhibitors caused the death of FGFR1-transformed cells, whereas non-transformed parental cells were unaffected[123].

The RSK2 and PI3K pathways are not the only ones to mediate FGF-dependent survival signalling. Evidence from studies of FGFR1, which is expressed in addition to FGFR3 in bladder cancer, suggested that the increased expression of FGFR1 in normal and cancerous urothelial cell lines promotes FGF2-induced proliferation and decreased apoptosis[124]. These effects were transduced by MAPK signalling through FRS2 and PLCγ, and mediated by cyclin D1 (which promotes proliferation), MCL1 and phospho-BAD (which promotes survival). Some urothelial cancer cell lines also showed FGFR1-dependent growth in soft agar[124]. Together, these data confirm that cell survival is a major readout of FGF signalling, and multiple pathways can result in similar outcomes.

FGF and migration and invasion. In addition to effects on proliferation and survival, FGF signalling can promote cell migration in several ways. Simple *in vitro* models,

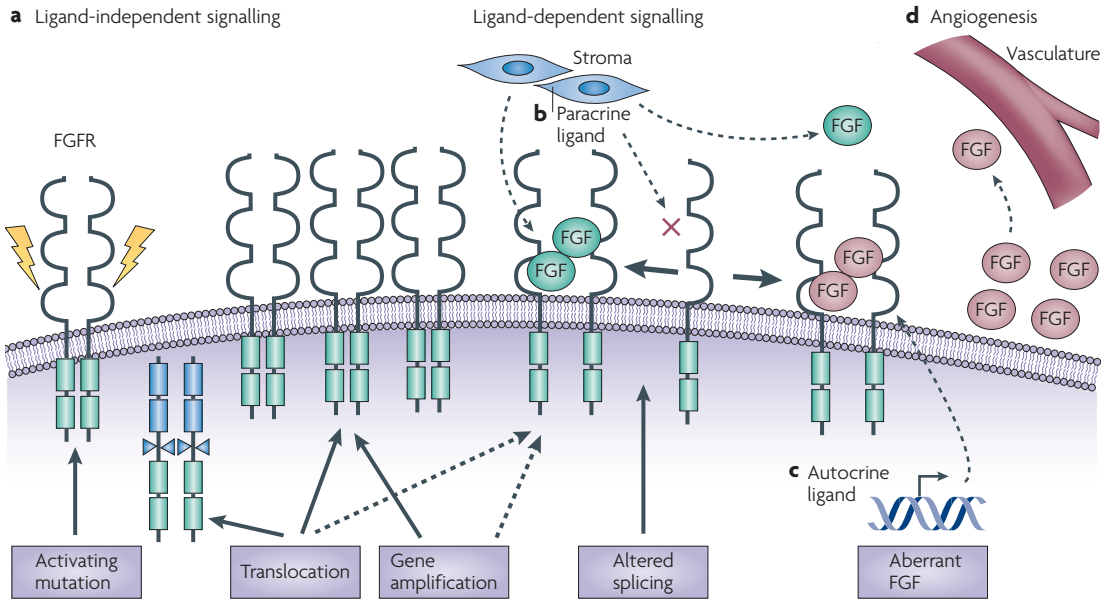

Figure 3 | **Mechanisms of pathogenic cancer cell FGF signalling.** The ways in which fibroblast growth factors (FGFs) and FGF receptors (FGFRs) can be altered in cancer fall into four main groups. **a** | Genomic alteration of FGFR can occur through three mechanisms, leading to ligand-independent signalling. First, activating mutations can result in ligand-independent dimerization or constitutive activation of the kinase (shown by yellow lightning). Second, chromosomal translocations can also lead to ligand-independent signalling. Intragenic translocations generate fusion proteins, usually with the amino terminus of a transcription factor fused to the carboxy-terminal FGFR kinase domain, resulting in dimerization of the fusion protein and constitutive signalling; for example, FGFR3 is brought under the control of an unrelated promoter, resulting in FGFR3 overexpression. Third, receptor gene amplification, which results in supraphysiological receptor overexpression. FGFR2 overexpression can also be accompanied by altered C-terminal splicing that might contribute to receptor accumulation. **b** | Establishment of a paracrine loop. Altered FGFR expression on a cancer cell can potentially occur by splicing, which alters FGFR specificity, or by amplification of an FGFR gene to express FGFR out of context, which is activated by FGF (green) expressed by a stromal component. Tumour cells can stimulate stromal cells to release FGF ligands and increase the release of ligands from the extracellular matrix. **c** | Establishment of an autocrine loop. FGF ligands are produced in an autocrine fashion by a cancer cell (brown). The autocrine loop can be established by FGFR expression out of context or by the increased expression of FGF ligands. **d** | FGF stromal effects, including angiogenesis. FGF released from stromal cells or cancer cells can act on endothelial cells to promote angiogenesis.

Table 1 | **Genetic alterations in FGF receptors and FGFs related to cancer**

Gene	Cancer type (incidence)	Refs
FGFR1		
Amplification	Breast cancer (10%), ovarian cancer (~5%), bladder cancer (3%) and rhabdomyosarcoma (3%)	66,67,70–72
Mutation	Melanoma (rare)	180
Translocation	Stem cell leukaemia and lymphoma syndrome (8p11 myeloproliferative syndrome characterized by *FGFR1* translocations) and chronic myeloid leukaemia (rare)	76,77
FGFR2		
Amplification	Gastric cancer (10%) and breast cancer (~1%)	61,62
Mutation	Endometrial cancer (12%) and gastric cancer (rare)	55,181
Germline SNP	Second intron SNP: increased incidence of breast cancer	106,107
FGFR3		
Amplification	Bladder (NR), salivary adenoid cystic cancers (NR)	60,182
Mutation	Bladder cancer (50–60% non-muscle invasive type, 10–15% invasive type), cervical cancer (5%), myeloma (5% translocated cases), prostate (3%) and spermatocytic seminoma (7%)	42,46–50, 87,183
Translocation	Myeloma (15%) and peripheral T cell lymphoma (rare)	78–80
FGFR4		
Germline SNP	Coding SNP: poor prognosis breast, colon and lung adenocarcinoma	111,112
FGF1		
Amplification	Ovarian (NR)	181

FGF, fibroblast growth factor; NR, not reported; SNP, single nucleotide polymorphism.

such as the invasion of pancreatic cancer cells through Matrigel-coated Transwell filters, have shown FGF10- and FGFR2-IIIb-dependent invasion[125]. In a breast cancer model with a membrane-tethered chemically inducible FGFR1 kinase domain[126], activation of FGFR1 in the mammary epithelium in adult mice induced MAPK- and AKT-dependent proliferation and ultimately led to invasive mammary lesions[126]. *In vitro* studies of the same inducible construct in three-dimensional cultures of HC11 mouse mammary epithelial cells demonstrated that, as well as increasing cell proliferation and survival, constitutive FGFR1 signalling led to the loss of polarity and the gain of a matrix metalloproteinase 3 (MMP3)-dependent invasive phenotype[127]. Interestingly, this effect was specific to the FGFR1 kinase domain, and an identical FGFR2 construct showed no effect on cell survival and invasion[38].

The same inducible FGFR1 construct induced prostatic intraepithelial neoplasia when expressed and chemically activated in the mouse prostate[40]. Interestingly, in this model prostatic intraepithelial neoplasia progressed over the course of 1 year to a transitional sarcomatoid-type carcinoma, suggesting that EMT had occurred. This EMT phenotype was accompanied by upregulation of both *Sox9*, an FGF target gene associated with EMT[128], and the pro-angiogenic factor angiopoietin 2 (ANG2)[129]. EMT is important in cancer cell metastasis, disrupting cell–cell contacts and promoting tumour cell invasion[130], and these data therefore suggest that activation of FGFR1 signalling can both initiate cancer development and promote invasion and metastasis.

SOX9 was also upregulated in a study of androgen-induced prostate carcinogenesis, in which the FGF and Wnt signalling pathways were significantly upregulated. This study potentially uncovered a reactivation of signalling pathways used in the embryo for both proliferation and invasion in prostate cancer progression[131]. In development, Wnt–β-catenin and FGF signalling function in concert to coordinate collective cell migration during morphogenesis through differential regulation of the chemokine receptors CXCR4b and CXCR7b, and a similar molecular mechanism could theoretically regulate the collective cell migration that underpins metastasis[132].

FGF in angiogenesis. Alongside embryogenesis, one of the first areas in which FGF signalling was shown to be important in terms of cell proliferation and migration was during wound healing[133]. Initial studies showed a key role for FGF signalling in epithelial repair but some FGF members, in particular FGF2, are known to be important for new blood vessel growth at the wound site (reviewed in REF. 134). Angiogenesis is key to the repair process, delivering nutrients and oxygen to support the energy-consuming process of tissue remodelling[134]. If a tumour is to grow more than 1 mm^3 and metastasize, it must establish its own blood supply to provide oxygen and nutrients[135], and FGFs have also been implicated in tumour angiogenesis[93,136].

Endothelial cells express high levels of FGFR1-IIIc, as well as FGFR2-IIIc in some circumstances, and both FGF1 and FGF2 (and to a lesser extent FGF4 and FGF8b) are potent pro-angiogenic growth factors[93]. FGFs stimulate new vessel formation and

vessel maturation by driving endothelial cell proliferation, promoting extracellular matrix degradation, altering intercellular adhesion and communication by affecting cadherins and gap junctions, respectively, and modulating integrin expression (reviewed in REF. 93). Although most of these effects are transduced through MAPK activation, PKC activation is also required for FGF-induced endothelial cell proliferation[137] and migration[138]. Furthermore, a model of FGFR1-mediated chemotaxis was dependent on PI3K signalling to drive endothelial cell motility, with wortmannin (a PI3K inhibitor) treatment blocking migration independently of receptor tyrosine kinase activity[139].

Evidence for a role of FGFs in tumour angiogenesis includes the increased mobilization of FGF ligands from the extracellular matrix, as has been shown for FGF-binding protein[140], the paracrine release of FGF2 from tumour cells acting on endothelial cells to initiate angiogenesis[89], FGF1 expression in ovarian cancer[90] and the autocrine release of FGF2 from capillary endothelial cells[141]. Autocrine FGF2 signalling might also be important in the growth of endothelial tumours such as Kaposi's sarcoma[142]. Finally there is substantial crosstalk between FGFR and vascular endothelial growth factor receptor (VEGFR) signalling in angiogenesis, and the FGFR system may mediate resistance to VEGFR targeting in some situations[143,144].

Box 3 | **Mouse models of FGF-driven carcinogenesis**

Autocrine FGF signalling

The earliest evidence linking activation of fibroblast growth factor (FGF) signalling to mammary oncogenesis came from studies of the mouse mammary tumour virus (MMTV), which as a result of vertical transmission was shown to be responsible for a high rate of cancer in certain mice lineages in the 1970s. MMTV exerts oncogenic effects by insertional mutagenesis, and along with members of the Wnt pathway the commonest integration sites included three members of the FGF family (*Fgf3*, *Fgf4* and *Fgf8*)[174]. Multiple studies have demonstrated that overexpression of FGFs in the epithelium induces carcinogenesis through an autocrine signal loop. Examples include the expression of FGF8 from the *MMTV-LTR* promoter, which causes lobular-type mammary adenocarcinoma at 1 year of age[175]; FGF8 in the prostate epithelium, which initiates prostatic intraepithelial neoplasia (PIN); and prostate cancer when expressed in a *Pten* haploinsufficient background[117]. The conditional expression of FGF10 in lung epithelium induced pulmonary tumours[176].

Paracrine FGF signalling

One important study has demonstrated that FGF10 expressed in the stromal compartment can induce prostate carcinoma[116]. Increased levels of FGF10 led to PIN and the subsequent development of cancer with increased androgen receptor expression; FGF10 expression also synergized with activated AKT signalling[116].

Hormonal FGF signalling

One study demonstrated that FGF19 expressed in skeletal muscle induced hepatocellular carcinoma, presumably owing to increased circulating FGF19 levels[103].

FGFR activation

Two studies using the same chemically inducible FGFR1 construct expressed from a tissue-specific promoter have demonstrated that constitutive activation of FGFR1 can induce mammary invasive lesions[126], and in the prostate can induce PIN that subsequently progressed to a sarcomatoid prostate cancer[40,128]. By contrast, ablation of *Frs2* in the prostate epithelium offered partial protection against SV40 T antigen-induced prostate cancer, potentially owing to impaired epithelial proliferation[118]. Retroviral expression of FGFR3 in the murine bone marrow induced lymphoma or leukaemia development, with a latency that was markedly reduced on the expression of FGFR3 with an activating mutation[82].

FGF tumour suppressive effects in cancer

As well as the wealth of evidence that links activation of FGF signalling with oncogenesis, there is unequivocal evidence from mouse models for a tumour suppressive role of FGFR2 in some contexts. Mice that specifically lack FGFR2-IIIb in keratinocytes are sensitive to carcinogenic insults to their skin[145]. In mouse models of medulloblastoma, FGF signalling inhibits Sonic Hedgehog signalling, which blocks the proliferation of cancer cells[146]. In addition, studies in a rat model of prostate cancer showed that when non-malignant epithelial cells expressing FGFR2-IIIb were mixed with stromal cells they formed non-malignant tumours. However, when the stromal cells were absent, epithelial cells underwent a splicing switch from the FGFR2-IIIb to the FGFR2-IIIc isoform, and expression of FGF2 was upregulated, potentially initiating an autocrine loop. These studies established the importance of epithelial–stromal interactions in the paracrine regulation of prostate epithelial cell proliferation[147].

Several studies of human tumours and cancer cell lines potentially support a tumour protective effect of FGFR2 signalling. In bladder cell lines, expression of FGFR2-IIIb expression blocks proliferation[148]. FGFR2-IIIb, which is physiologically expressed in many epithelial structures, is downregulated on progression in bladder cancers[148], prostate cancer[94] and salivary adenocarcinomas[149]. In prostate cancer cell lines, the expression of a conditionally active FGFR1 kinase domain promotes proliferation, but a conditionally active form of FGFR2 does not[39]. Finally, inactivating mutations of *FGFR2* have been described in melanoma[150].

In some circumstances FGFR2 signalling is clearly oncogenic, so what explains the potential tumour suppressive effects? In general, it is important to draw a distinction between genuine tumour suppressive effects and oncogene-induced senescence. It is well recognized that context-dependent differences in signalling can lead to either tumour promotion or senescence in response to activated FGF signalling. Similarly, the genuine tumour suppressive effects of FGFR2-IIIb are also likely to reflect context-dependent differences in signalling. Although there has been much focus on FGFR2-IIIb, as opposed to FGFR2-IIIc, being tumour protective, there is no evidence that splicing of the extracellular domain affects intracellular signalling. Therefore, it seems likely that differences in extracellular splicing reflect changes in cellular phenotype.

Other mechanisms have been proposed for the tumour suppressive function of FGFR2. FGF signalling may induce cytoprotective pathways in epithelial cells, helping to maintain genomic stability following challenge with carcinogens, reactive oxygen species or other cytotoxic stresses, as shown in mice that lack the NRF2 transcription factor — which is known to be regulated by FGF7 (REF. 151). Another speculative mechanism is a potential role for FGFR2-IIIb in immune surveillance. γδ-T cells release both FGF7 (REF. 152)

Table 2 | **Current status of FGF and FGFR-targeting therapies***

Drug name	Company	Range of activity or target	Clinical development	Refs
Small molecular tyrosine kinase inhibitors				
SU5402	*In vitro* reagent	Selective FGFR inhibitor (now superseded by availability of PD173074)	NA	75
PD173074	*In vitro* reagent	Selective FGFR inhibitor	NA	184
TKI258	Novartis	FGFR, PDGFR and VEGFR inhibitor	Phase II	185
BIBF 1120	Boehringer Ingelheim	FGFR, PDGFR and VEGFR inhibitor	Phase III	186
BMS-582,664 (Brivanib)	Bristol-Myers Squibb	FGFR and VEGFR inhibitor	Phase II	187
E7080	Eisai	FGFR, PDGFR and VEGFR inhibitor	Phase I	188
TSU-68	Taiho Pharmaceutical	FGFR, PDGFR and VEGFR inhibitor	Phase I/II	189
FGFR antibodies and FGF ligand traps				
IMC-A1	ImClone	FGFR1-IIIc-specific antibody	NA	156
PRO-001	ProChon Biotech	FGFR3-specific blocking antibody	NA	84
R3Mab	Genentech	FGFR3-specific antibody	NA	155
1A6	Genentech	FGF19-specific antibody	NA	104
FP-1039	Five Prime Therapeutics	FGF ligand trap (multiple FGFs)	Phase I	157
FGF ligand for mucosal chemoprotection				
Palifermin (Kepivance)	Biovitrum AB	Recombinant FGF7 (activates FGFR2-IIIb)	Licensed	190

FGF, fibroblast growth factor; FGFR, FGF receptor; NA, not applicable; PDGFR, platelet-derived growth factor receptor; VEGFR vascular endothelial growth factor receptor.*Several pharmaceutical companies have highly potent and selective FGFR inhibitors in preclinical development.

and FGF10, which may signal through FGFR2-IIIb in epithelia to promote immune surveillance, and loss of epithelial FGFR2 could therefore interfere with tumour surveillance.

Therapeutic approaches

Several pharmaceutical companies have developed FGFR tyrosine kinase inhibitors (TKIs) (TABLE 2) that are in the early phases of clinical trials. So far, all of the TKIs are ATP-competitive VEGFR2 inhibitors. The VEGFR and FGFR kinase domains have high structural similarity, and several VEGFR TKIs also inhibit the FGFRs. Dual inhibition with VEGFRs has the obvious potential benefit of targeting two pro-angiogenic growth factors, or of simultaneously targeting angiogenesis and tumour cell proliferation. However, many of these TKIs with multiple targets are less potent against the FGFRs and it is uncertain if this will be a disadvantage in clinical development. Targeting multiple kinases may also increase the side effects of these compounds, limiting the ability to deliver drugs at doses required for FGFR inhibition. Consequently, several pharmaceutical companies are developing highly potent FGFR TKIs, which are selective over VEGFRs. Preclinical development of potent FGFR TKIs has been complicated by tissue calcification. FGF23 is involved in phosphate homeostasis[153], and in preclinical models highly potent (but not less potent) FGFR tyrosine kinase inhibitors have caused hyperphosphataemia-mediated tissue calcification owing to blockade of FGF23 signalling. It is unknown whether this will be an issue in humans.

To minimise the side effects of targeting FGFRs, therapeutic antibodies may have substantial benefits, as they can be used to treat cancer cells that are reliant on a particular FGFR and therefore reduce the potential toxicity of pan-FGFR inhibition. Antibodies targeting FGFR3 have been shown to have an anti-proliferative effect on bladder cancer cells[154,155] and t(4;14) myeloma[155]. A single chain Fv antibody that targeted FGFR1-IIIc could not be pursued further after it was found to potentially block FGF signalling in the hypothalamus, resulting in severe anorexia in rodents and monkey models[156]. It remains to be ascertained whether this would be a class effect for all FGFR1-IIIc antibodies.

A third approach is to develop FGF ligand traps; for example, FP-1039 (Five Prime Therapeutics), a soluble fusion protein that consists of extracellular FGFR1-IIIc fused to the Fc domain of IgG1. These traps could potentially block the activity of multiple FGF ligands and receptors, and exert both anti-angiogenic and anti-proliferative effects[157].

Finally, a different approach is the use of FGF ligands to stimulate FGFRs. A recombinant FGF7 ligand, also known as keratinocyte growth factor, has been licensed for the treatment of mucositis induced by myelotoxic therapy requiring haematopoietic stem cell support (TABLE 2). This compound should not be used outside the licensed indications, as safety has not been established in any tumour types known to express FGFR2-IIIb, the receptor for FGF7.

Future prospects

The past decade has seen a dramatic increase in our understanding of the relevance of FGFs and their receptors to cancer biology. Depending on the tumour type, aberrant FGF signalling can function in a cell-autonomous fashion, or through modulating tumour–stroma

interactions, and activate different downstream pathways depending on cellular context. The emerging data on FGF signalling has sparked several pharmaceutical companies to develop drugs that target FGFRs. These are now entering the clinic, and many more are in preclinical development.

It is currently not well understood how FGFR2 signalling can be tumour promoting in some contexts, but tumour suppressive in others. Until the underlying mechanisms of the context specificty of FGF signalling are better understood, the non-selective targeting of FGFRs should be used cautiously in an adjuvant or curative setting. An assessment of the safety of long-term FGFR inhibition in preclinical models would be reassuring. The mechanisms underlying tumour suppressive effects could, however, also present an opportunity in cancer treatment. The potentiation or reinstatement of these FGF-mediated tumour suppressive signals may represent a new avenue in tumour therapy.

The presence of many different genomic aberrations, each one largely specific to the tumour type and often occurring at a low frequency, presents practical problems for clinical development. Successful strategies will depend on the selection of tumours in which FGF signalling is driving proliferation and survival, and it is likely that a set of tumour-specific companion diagnostics will be required to select patients. This becomes a more difficult problem when identifying tumours in which paracrine and autocrine signalling is driving tumour cell proliferation. Although the activation of signalling loops will be highly prevalent in some tumour types, for other types it will be a challenge to differentiate tumours in which changes in FGFR receptor expression and splicing are driving proliferation from those in which these changes occur merely as consequence of tumour progression. The identification of tumours in which FGF2 is driving angiogenesis presents a similar problem. Much translational research is required to help address these questions. It is also likely that additional tumour types that are driven by FGF signalling, with different mechanisms of FGF pathway activation, will emerge in the next few years to further strengthen the role of FGF signalling in cancer biology.

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Competing interests statement
The authors declare no competing financial interests.

DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/gene
EGFR | *FGF1* | *HRAS* | *IGH* | *KRAS* | *MMSET* | *NRAS* | *PIK3CA* | *Pten* | *Sox9*
National Cancer Institute Drug Dictionary:
http://www.cancer.gov/drugdictionary
gefitinib
OMIM: http://www.ncbi.nlm.nih.gov/omim
CML | Kaposi's sarcoma | multiple myeloma | Pfeiffer syndrome
UniProtKB: http://www.uniprot.org
ALK | ANG2 | β-catenin | β-klotho | BAD | BCL-2 | BCL-X_L | BCR | CBL | cyclin D1 | ERK1 | ERK2 | ETV6 | FGF2 | FGF6 | FGF7 | FGF8 | FGF10 | FGF19 | FGF23 | FGFR1 | FGFR2 | FGFR3 | FGFR4 | FRS2 | GAB1 | GRB2 | IAP1 | MCL1 | MKP3 | MMP3 | NRF2 | NTRK1 | OCT1 | p21 | RSK2 | RUNX2 | S6K2 | SPRY1 | SPRY2 | VEGFR2 | XIAP | ZNF198

FURTHER INFORMATION
Richard Grose's homepage:
http://www.cancer.qmul.ac.uk/staff/grose.html

ALL LINKS ARE ACTIVE IN THE ONLINE PDF