View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Biochimica et Biophysica Acta 1823 (2012) 850–860

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Mechanisms of FGFR-mediated carcinogenesis

Imran Ahmad [a,b], Tomoko Iwata [b], Hing Y. Leung [a,b,*]

[a] Beatson Institute for Cancer Research, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1BD, UK
[b] Institute of Cancer Sciences, University of Glasgow, Glasgow, G31 2ER, UK

ARTICLE INFO

Article history:
Received 23 September 2011
Received in revised form 9 January 2012
Accepted 10 January 2012
Available online 18 January 2012

Keywords:
FGF
FGFR
Receptor tyrosine kinase
Signalling
Cancer
Cancer therapy

ABSTRACT

In this review, the evidence for a role of fibroblast growth factor receptor (FGFR) mediated signalling in carcinogenesis are considered and relevant underlying mechanisms highlighted. FGF signalling mediated by FGFR follows a classic receptor tyrosine kinase signalling pathway and its deregulation at various points of its cascade could result in malignancy. Here we review the accumulating reports that revealed the association of FGF/FGFRs to various types of cancer at a genetic level, along with *in vitro* and *in vivo* evidences available so far, which indicates the functional involvement of FGF signalling in tumour formation and progression. An increasing number of drugs against the FGF pathways is currently in clinical testing. We will discuss the strategies for future FGF research in cancer and translational approaches.

© 2012 Elsevier B.V. All rights reserved.

1. Introduction

Carcinogenesis follows the stepwise progression of normal benign cells to cancer cells that have acquired abilities in independent growth, to evade anti-apoptotic signals, to promote angiogenesis, and to invade and metastasise to distant organs [1]. This progression can be characterised by multiple gene mutations, often happening in a specific temporal fashion. Such mutations may include activating mutations, gene amplifications and overexpression of oncogenes, or inactivating mutations and epigenetic silencing of tumour suppressors. However, simple association of the mutations is not sufficient in providing the mechanism underlying cancer progression. The mutations may be 'passenger' mutations, and may not always be the critical 'driver' events that provide the malignant cells survival advantage and the ability for clonal expansion.

Receptor tyrosine kinases (RTKs) consist of 20 subfamilies in humans, all of which share a common structure consisting of extracellular ligand-binding region, a single-pass transmembrane domain and an intracellular tyrosine kinase domain [2]. Binding of a growth factor to the ligand-binding domain results in RTK activation and initiation of intracellular signalling cascades, which lead to cellular effects.

Fibroblast growth factor (FGF) signalling mediated by its high-affinity tyrosine kinase receptors, FGF receptors (FGFRs) is known to instigate a range of responses in different cell types, and is regulated by its complex expression patterns and binding specificity of the FGF ligands and receptors as well as their isoforms [3,4].

FGF signalling is probably most well-known for its regulatory function in multiple developmental processes including mesodermal patterning in the embryo [5] and subsequent formation of numerous organ systems [6]. In adult, it contributes to tissue homeostasis, as well as tissue repair, angiogenesis and inflammation [3,4,7]. Given such a plethora of biological effects that FGF signalling lead to, it may not be surprising that its deregulation can have significant consequences in carcinogenesis.

2. FGF signalling via high-affinity receptor FGFR

2.1. FGF

The prototype members of the FGF family, namely FGF1 (acidic FGF) and FGF2 (basic FGF), were isolated as mitogens from the bovine brain tissue in the 1970s [8]. Since then a plethora of other cellular functions have been identified in a variety of cell types and organs, which include cell survival, differentiation, and migration, as well as angiogenesis [9]. Twenty-two FGFs have been identified in mammals. Most of the FGFs are secreted glycoproteins, however, four members (FGF11–14) do not function as FGF ligands. There is no human equivalent of mouse FGF15; there is no human FGF19 in mice. Most FGF ligands function in a classic autocrine and/or paracrine fashion, with an exception of FGF19, 21 and 23, which were identified as hormones capable of diffusing into the circulation (FGF19 subfamily) [10–15].

FGFs are subjected to many splicing events that affect their function. Intriguingly, some FGFs have been identified as having a nuclear function [9,16], instigating a different downstream effect to the classic RTK pathways. Apart from FGF1 and FGF2, which are exported from cells via undefined mechanism(s), the remaining FGFs utilise a

* Corresponding author at: Beatson Institute for Cancer Research, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1BD, UK. Tel.: +44 1413308695; fax: +44 1419426521.
E-mail address: h.leung@beatson.gla.ac.uk (H.Y. Leung).

0167-4889/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2012.01.004

Table 1
Summary of FGF receptor specificity
FGFRs can either express the IIIb or IIIc exon, which influences FGF ligand specificity.

FGFR IIIb subtype	FGFR IIIc subtype
FGF7 subfamily (3,7,10,22)	
FGF1 subfamily (1,2)	FGF1 subfamily (1,2)
	FGF8 subfamily (8,17,18)
	FGF4 subfamily (4,5.6)
	FGF9 subfamily (9,16,20)
	FGF19 subfamily (19,21,23)

constitutive secretory pathway. FGFs have a strong affinity for the glycosaminoglycan side-chains of cell surface proteoglycans, thus they are normally trapped on the surface of the secretory cell or nearby cells, augmenting their action as short-range signalling molecules and providing a biologic reservoir for FGFs [17].

FGFs also bind to low-affinity receptors present on most cells, the HSPGs (heparin sulphate proteoglycans) [18–20]. HSPGs consist of a proteoglycan core that binds 2 or 3 linear polysaccharides (heparin sulphate chains). The FGFs bind to the negatively charged polysaccharides through electrostatic interactions. HSPGs may protect ligands from degradations, as well as stabilising the FGF ligand–receptor complex by forming a ternary complex with FGFR.

Members of the FGF family are divided into subfamilies according to receptor specificity (Table 1) [21–23]. FGF-7, 10, and 22 are more closely related to each other by sequence homology than to the other FGFs, and, along with FGF3, form the FGF7 subfamily. Similarly, FGF-8, 17, and 18 represent a second subfamily sharing similar activities to each other, and is referred to as the FGF8 subfamily. Finally, the FGF9 subfamily (FGF-9, 16, and 20) shares a similar structure profile to that of FGF9.

2.2. FGFR

FGFRs are transmembrane tyrosine kinase receptors that belong to the immunoglobulin (Ig) superfamily [24] (Fig. 1). Activation by their respective high-affinity FGF ligands results in kinase activation that leads to activation of an intracellular signalling network. In humans, the FGFR family consists of 4 receptor genes encoding closely related transmembrane RTKs [24], namely FGFR1 to FGFR4. Each FGFR monomer consists of an extracellular domain that includes the ligand-binding site, two or three Ig loops that arise by alternative splicing, an acidic box, a transmembrane domain, and a split tyrosine kinase domain (Fig. 1). The first Ig-like domain is postulated to play a role in receptor auto-inhibition [25]. Alternative splicing of the third Ig-like domain occurs in FGFR1–3 and influence the selection of the second half of the third Ig like domain, generating the IIIb or IIIc isoform of the receptor. The second and third Ig-like domains of the receptors are sufficient for FGF ligand binding and contribute to the diversity of preferences in the ligand binging by each FGFR subtypes and isoforms (Table 1)[21,26].

The expression of distinct (different) FGFR splice forms can be observed in a tissue (or cell lineage) specific pattern. The IIIc isoform is usually expressed in mesenchymal tissue while the IIIb isoform is mostly detected in epithelial cells, particularly during development stages. Interestingly, the ligands for epithelial receptors are often expressed mesenchymal tissue and vice versa. This provides the basis for a paracrine signalling mechanism, providing a means for delicate homeostasis between epithelial and mesenchymal tissues. Abnormality of this paracrine signalling interaction between the epithelium and the mesenchyme may significantly contribute to carcinogenesis [17].

2.3. Downstream signalling

Binding of FGFs to FGFRs induces receptor dimerization, leading to conformational changes within the FGFR structure, thus enabling trans-phosphorylation of tyrosines in the intracellular part of the receptor, including the kinase domain and the C-terminus [9,27]. There are 7 autophosphorylation sites in FGFR1, Y463 (juxtamembrane), Y583/Y585 (kinase insert), Y653/Y654 (the activation loop), Y730 (kinase domain) and Y766 (C-terminal tail) [28,29]. Recent studies using crystallography and cultured cells provided a renewed insight into the activation process of FGFR kinase that occurs in three sequential steps [30–32]. Firstly, transphosphorylation of the tyrosine in the activation loop, Y653 in FGFR1, potently activates the kinase by 50–100 fold. Secondly, the tyrosines in the juxtamembrane region Y463, kinase insert Y583/Y585, and in the C-terminal tail,

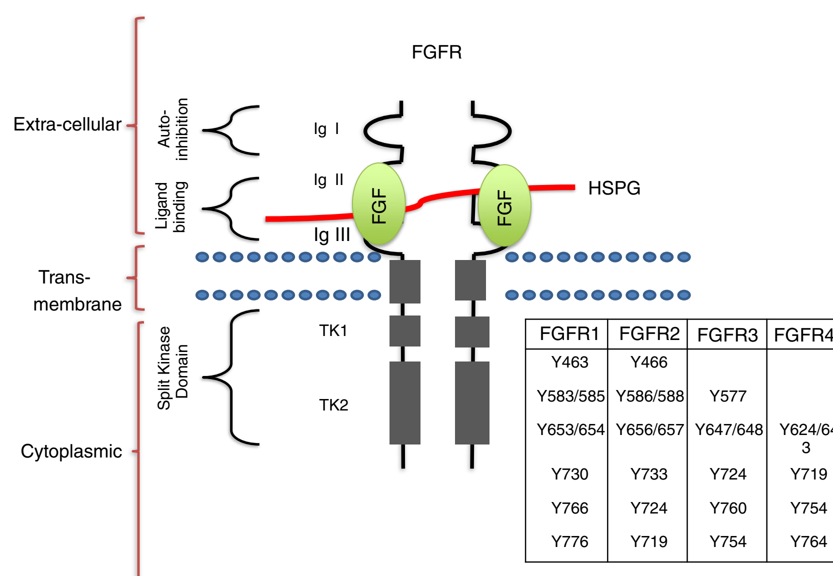

Fig. 1. Fibroblast growth factor receptor (FGFR) structureFGFR possesses three extracellular (EC) immunoglobulin-like domains (IgI–III), a single transmembrane domain (TM), and a split, cytoplasmic (CP) tyrosine kinase domain (TK1 and TK2). The basic structure of the fibroblast growth factor (FGF)–FGFR complex consists of two receptor molecules, two FGFs and one heparin sulphate proteoglycan (HSPG) chain. The second and third Ig domains form the ligand-binding pocket and have distinct domains that bind both FGFs abs HSPGs. The major tyrosine sites of phosphorylation of FGFR1–4 are shown in the table.

Y766, are also phosphorylated and becomes available as docking sites for various downstream proteins (see below for the examples). Finally, the phosphorylation of Y654 in the activation loop activates the kinase activity further by 10-fold.

Kinase domains of the four FGFRs are relatively well-conserved (75–92% homology) with the closest homology between FGFR1 and FGFR2 and the biggest difference between FGFR1 and FGFR4 [33]. Most of the 7 autophosphorylation sites, as well as the additional C-terminal Y776 tyrosine, are conserved among the four FGFRs. However, FGFR3 lacks tyrosine residue equivalent of juxtamembrane Y463 and kinase insert Y585 in FGFR1, and FGFR4 lacks Y463, Y583/Y585 [29,34]. These differences in tyrosine phosphorylation profile among FGFRs may underlie a difference in the overall kinase activity and/or downstream signalling pathways, and all together, may define specific effects mediated by each FGFR (Fig. 2).

Phosphorylated tyrosine residues function as docking sites for various adaptor proteins [27]. Some of the adaptor proteins are phosphorylated directly by FGFR [27]. For example, upon phosphorylation the C-terminal Y766 binds PLCγ [28] and Shb [35], which leads to recruitment of FRS2 (see below). The binding of the docking proteins to FGFRs leads to activation of multiple signal transduction pathways, including the four main downstream pathways, Ras–Raf–MapK, PI3K–Akt, Stats, and PLCγ [3,27].

Some of the main adaptor proteins include:

- FGFR substrate 2 (FRS2) — an adaptor/scaffold protein. FRS2 is particularly specific to FGFRs, although it can bind to other RTKs such as neurotrophic tyrosine kinase receptor type 1 (NTRK1), RET and anaplastic lymphoma kinase (ALK) [36]. It is constitutively associated with the juxtamembrane domain of the FGFR through its phospho-tyrosine binding (PTB) domains. Several tyrosine residues of FRS2 phosphorylated by the activated FGFR kinase serve as docking sites for proteins such as SOS, GRB2 and GAB1, allowing assembly of signalling complexes that promote activation of Ras/Raf/MAPK and PI3K signalling pathways.
- Phospholipase Cγ (PLCγ) — the Src homology 2 (SH2) domain of PLCγ binds to FGFR at its auto-phosphorylated tyrosine in the COOH-terminal tail (Y766 in FGFR1), resulting in phosphorylation and activation of PLCγ [37]. This triggers the release of intracellular calcium to activate calcium-dependent members of the protein kinase C (PKC) family. This could also induce MAPK signalling via phosphorylation of Raf.

Other pathways are also activated by FGFR signalling in a context dependent manner. These include Shb (src homology 2 domain-containing transforming protein B), Src kinase, p38 MAPK, Jun-N-terminal kinase pathways, STATs (signal transducers and activators of transcription), Crk and RSK (ribosomal S6 protein kinase). In particular, STATs and RSK have demonstrated oncogenic properties *in vitro* [3,38,39].

FGFR signalling is also negatively regulated, mediated by several regulator proteins such as MAPK phosphatase 2 (MKP3) [40], the Sprouty (SPRY) proteins [41,42] and "similar expression to FGF" (Sef) family members [43,44]. They act to modulate receptor signalling at several points in the signal transduction cascade. MKP3 acts to dephosphorylate ERK1 and ERK2 to attenuate MAPK signalling [40]. In contrast, SPRY proteins either compete with GRB2 in a dominant negative fashion, preventing SOS-mediated RAS activation, or directly bind to RAF, leading to a block of MAPK signalling [41,42]. The transmembrane form of Sef is capable of directly inhibiting FGFRs whilst both the transmembrane form and a cytoplasmic specific splice variant of Sef can prevent phosphorylation of ERK [44,45]. FGF signalling is also negatively regulated by the endocytosis of FGFR proteins, followed by their degradation in lysosomes [27]. This is thought to be partially under the control of Cbl [46,47].

3. FGFR in cancer

A large amount of evidence now indicates that alteration of FGF function, deregulated at one point within the FGF signalling cascade,

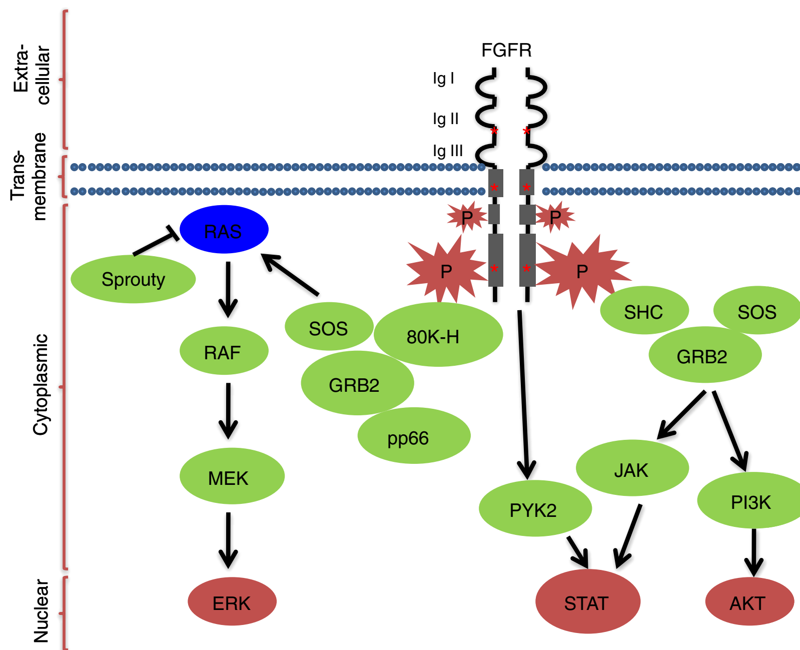

Fig. 2. Intracellular signalling cascades downstream of FGFRs.FGFR phosphorylation triggers several signalling cascades, the most predominant of which is the RAS–RAF–mitogen activated protein kinase kinase (MEK)–extracellular regulated kinase (ERK) pathway. *In vitro* evidence indicates that two signalling complexes mediate this activation pathway: those that involve the SRC-homology-2-domain-containing (SHC), growth factor receptor-bound protein 2 (GRB2) and son of sevenless (SOS) adaptor proteins and those involving 80K-H (a protein kinase C substrate), GRB2, pp66 and SOS adaptor proteins. Alternatively, phosphorylated FGFR can activate the phosphatidylinositol 3-kinase (PI3K) and AKT pathway. Lastly, the activated FGFR can directly or indirectly (through Janus-family kinases (JAKs)) trigger the signal transducer and activator of transcription (STAT) pathway. The activated FGFR can also interact directly with proline-rich tyrosine kinase 2 (PYK2), leading to STAT pathway activation. Notably, mutational activation of HRAS, a central target of receptor tyrosine kinases, triggers similar signalling pathways.Colours refer to cellular localisation (blue = membranous, green = cytoplasmic and red = nuclear).

could lead to cancer, based on *in vitro* and *in vivo* studies using both model and clinical materials. Below, we discuss the originating mutational events at the gene level and the corresponding consequence in tumour formation and progressions reported so far (Table 2).

3.1. Chromosomal translocations

Chromosomal translocations can lead to an expression of fusion proteins with potent oncogenic function. The strongest evidence of the involvement of FGF signalling in cancer has come from haematological malignancies, where FGFR chromosomal translocations result in a fusion protein, whereby the N terminus of a transcription factor is fused to an FGFR kinase domain, resulting in activation of FGFR kinase domain [48–50]. At least 11 fusion partners of FGFR1 have been identified including ZNF198 and BCR [49,50]. Most of the FGFR1 fusion proteins are identified in patients with the myeloproliferative disorder stem cell leukaemia/lymphoma syndrome (SCLL/8p11 myeloproliferative syndrome) [51]. These fusion proteins have been shown to transform cells and induce SCLL in mice [49,52–55]. Recent murine work has demonstrated that FGFR-targeted therapy using tyrosine kinase inhibitors may be beneficial for patients with SCLL [54].

Multiple myelomas (MM) harbour the t(4;14) translocation in 15–20% of the cases. This translocation brings FGFR3 under the control of a strong IgH enhancer region, leading to FGFR3 overexpression [56–58]. This translocation is associated with a poor prognosis in MM and FGFR3 serves as an attractive therapeutic target. Several studies using cell line and xenograft mouse models have provided a proof of principle in the anti-tumour effects of small molecule FGFR3 inhibitors and of FGFR3 targeting antibodies [59–62].

3.2. FGFR overexpression and amplification

Elevated levels of FGFR have been found in a number of cancers, including prostate, breast, lung, brain, gastric, sarcoma, head and neck and MM [57,63–70]. Elevated levels could be due to either deregulated transcription or chromosomal amplification. Despite evidence of upregulated FGFR expression in different tumour types, it remains unclear whether such abnormal receptor expression represents the underlying molecular cause as a driver of cancer, or simply exists as a bystander, or “passenger”, event within the overall mutational profile of cancer.

Recent studies have demonstrated frequent focal amplifications of *FGFR1* in non-small cell lung carcinoma cell lines: 3% of lung adenocarcinomas and 21% of squamous cell carcinomas [71]. These cell lines are dependent on FGFR1 activity for cell growth, since inhibition (with shRNAs or small molecule inhibitors) of FGFR function leads to suppressed cell growth. Interestingly, not all cell lines with FGFR1 amplification were sensitive to FGFR1 inhibition, which may reflect varying phosphorylation status of FRS2, a required downstream effector for FGFR [71]. Overall, in a panel of lung cancer cell lines ($n=83$), the FGFR inhibitor PD1703074 potently influenced tumour growth and survival.

FGFR1 is frequently upregulated in cancer of the prostate [71]. The mechanism of this upregulation remains currently uncertain. The current dogma suggests that FGFR1 upregulation acts to destroy the subtle homeostatic interplay between epithelial and mesenchymal cells [72]. Using a prostate-specific mouse model, Acevedo and colleagues targeted an inducible FGFR1 (iFGFR1) to the prostatic epithelium [72]. Upon epithelial-specific activation of FGFR1, epithelial to mesenchymal transition (EMT) and adenocarcinoma penetrant in all cases were observed. Interestingly, deactivation of FGFR1 in the early cancers leads to complete tumour regression, suggesting a role of FGFR1 in both initiation and progression of prostate cancer. When FGFR1 function was inactivated in late tumours in this model, proliferation and progression of the tumours were impeded, but complete tumour regression was not observed. This demonstrates differences in sensitivity to FGFR1 inhibition at different stages of progression, indicating “susceptibility windows” [72]. This window may be controlled by different signalling molecules, that may require varying therapeutic targets [72].

Amplification of FGFR1 and FGFR2 has been often described so far. Approximately 10% of gastric cancers show FGFR2 upregulation, which is associated with diffuse type cancer, often associated with a poor prognosis [73,74]. *In vitro* studies using gastric cancer cells with evidence of FGFR2 amplification pointed to ligand-independent signalling mechanisms, while paracrine effects of FGF7 further supplemented cellular proliferation [67]. In a proportion of gastric cancer cell lines, amplification of FGFR2 can be accompanied by deletion of the C-terminal exon that modulates receptor internalisation. The deletion results in expression of a truncated receptor variant. The consequence of impaired receptor internalisation results in sustained activation of the receptor [75].

Interestingly, a study by Kunii et al. identified a role for amplified FGFR2 in gastric cancer cell proliferation and pro-survival effects in a panel of cell lines [74]. Indeed FGFR2 kinase inhibition by a specific small-molecule inhibitor (PD173074) resulted in selective and potent growth arrest as well as prominent induction of apoptosis. Cell lines harbouring FGFR2-amplification also exhibited elevated phosphotyrosine levels in EGFR, Her2, and Erbb3. Intriguingly, this elevated phosphorylation in EGFR was not inhibited by gefitinib or erlotinib [74]. Instead, phosphotyrosine activation of EGFR, Her2, and ErbB3 depends on FGFR2 function, thus suggesting that EGFR family kinases function as downstream targets of amplified FGFR2 in this model.

In 10% of human breast cancers, which is predominantly oestrogen receptor (ER) positive, there is an amplification of the gene-rich chromosomal region in 8p11-12, within which the FGFR1 gene is located [76–78]. FGFR1 is not always overexpressed when this region is amplified or it is not always contained in the amplification [79,80]. Nonetheless, it is evidenced *in vitro* that upregulation of FGFR1 can drive mammary carcinogenesis, resulting in cellular transformation of non-transformed murine/human mammary cells [81–83]. Moreover, downregulation of FGFR1 in these mammary cancer cell lines results in cell death, indicating the oncogenic addition to the FGFR1 upregulation [84]. Breast cancer cell lines harbouring FGFR2 amplification (SUM52PE and MFM-223) are well published and sensitive to FGF inhibition [85]. This phenomenon occurs in approximately 2% of breast cancers. It has been found that breast and gastric cancer cell lines harbouring *FGFR2* amplifications predominantly express the IIIb isoform of the receptor. Thus FGFR2-IIIb-specific antibodies (GP369) can suppress ligand-induced phosphorylation of FGFR2-IIIb and downstream signalling, as well as FGFR2-driven proliferation both *in vitro* and *in vivo* [85].

FGFR1 amplification is additionally reported in oral squamous carcinoma, ovarian cancer, bladder cancer and rhabdomyosarcoma [64,86–88].

Table 2
Summary of genetic alterations in FGFRs and FGFs related to cancer.

Cancer Type	Receptor and alteration	References
Bladder	FGFR3 mutation	[70,104]
Breast	FGFR1 and 2 amplification FGFR2 and FGFR4 SNP	[65,66,76–80,84,80,90]
Endometrium	FGFR2 mutation	[97,101]
Gastric	FGFR2 amplification	[73–75]
Multiple myeloma	FGFR3 translocation	[56–58]
Sarcoma	FGFR4 mutation	[127]

3.3. Point mutations and single-nucleotide polymorphisms

A recent screen of 210 different cancers found the FGF signalling pathway was the most commonly mutated system amongst the 1000 somatic mutations found [92]. They found that the FGF

signalling pathway was highly enriched, in particular for the FGFRs, suggesting that these are true "driver" mutations, driving tumour growth and progression. A number of germ-line activating point mutations of FGFR1, FGFR2, and FGFR3 found in human skeletal dysplasias are also found in human cancers [93–95]. Mutated forms are found in cancer of the prostate, bladder, breast, brain, lung, uterus, stomach, head and neck, colon and malignant melanoma [34,70,73,92,96–101].

Based on studies performed in FGFR3 mutant proteins, different functional consequences of each point mutation in FGFRs can be summarised as below [4]:

- Mutations in the extracellular domain of the receptor may facilitate enhanced ligand binding or lead to an alteration of the ligand specificity.
- Mutations in the ligand-binding and transmembrane domains can induce dimerization of the receptor and thus increased or constitutive activation.
- Mutations in the kinase domain may give rise to FGFRs with an increased or constitutive activation.
- Mutations in the intracellular domain may result in impaired degradation of the receptor, leading to continued signalling [102].
- Loss-of-function mutations have been also identified in cancer (see Section 3.7) [103].

FGFR3 is one of the most commonly mutated genes in human urothelial cell carcinoma (UCC) next to alterations in Chromosome 9 [104,105]. They are most prevalent in the low-grade non-muscle invasive phenotype (50–60%), being less common in the high-grade muscle-invasive subtype (10–15%). The somatic mutations found in UCC match that of the germline activating mutations that cause achondroplasia-type of skeletal dysplasia [70]. In UCC, more than half of the mutations in FGFR3 occur in the ligand-binding domain (S249C). The additional cysteine residue generated by the substitution is known to lead to the formation of an intra-molecular disulphide bridge, resulting in a constitutive dimerization and receptor activation [106,107]. Mutations are also found in the transmembrane domain (Y373C), which leads to an enhanced activation of the receptor [107].

Mutations of the amino acid residue K652 in the kinase domain of the FGFR3 are also found in UCC [108]. Crystal structures of FGFR2 kinase domain indicated that the kinase domain mutation is likely to allow the activation loop of the kinase domain to be in an active conformation and to indirectly disengage the auto-inhibition in the kinase hinge region [109]. In cell line and xenograft studies of UCC, the anti-FGFR3 antibodies and small molecule inhibitors showed anti-tumour properties, suggesting that FGFR3 can be a potential therapeutic target [59,110–114]. In contrast, the role of FGFR3 mutations as a driver of UCC is still under debate. Mice with activating Fgfr3 mutations displayed skin papilloma in two independent models, indicating the role of FGFR3 in tumourigenesis [115,116]. However, our recent study introducing the Fgfr3 K644E mutation heterozygously (corresponding to human K652E mutation) in the urothelium did not cause UCC [116]. However, a detailed analysis of this model indicated an activation of negative feedback loops in both Erk/MAPK and PI3K/Akt signalling cascade in a tissue-specific fashion, suggesting a possibility that tumourigenesis in the bladder requires additional mutations.

FGFR3 mutation has also been identified in cancer types such as cervical cancer, MM, prostate cancer and spermatocytic seminomas [96,117–120], as well as benign skin disorders epidermal naevi and seborrhoeic kertosis [115,121,122].

Activating mutations of FGFR2 are found in approximately 10% of endometrial/uterine cancers [97,101,125,126]. The mutations are identical to those found in skeletal disorders such as Apert syndrome (S252W and P253R which alter the ligand binding specificity) and Crouzon syndrome (N549K and N659N which lead to ligand independent receptor activation). In cell line and xenograft experiments, inhibition/knockdown of FGFR2 resulted in anti-tumour effects, suggesting the oncogenic role of FGFR2 [97,124], raising the potential of FGFR2 as a target of therapy in FGFR2 driven cancers.

Interestingly, in endometrial cancer, FGFR2 and K-Ras mutations are mutually exclusive, suggesting redundancy and that only a single 'hit' is required to activate the MAPK signalling pathway [123,124].

Several mutations in FGFR4 have been identified in 7–8% of rhabdomyosarcomas (RMS), associating with advanced stage and poor survival [127,128]. The mutations occur in the auto-phosphorylation sites of the receptor (N535K and V550E) and increase the ability to invade and metastasise in both *in vitro* and *in vivo* studies [127].

SNPs of FGFR have also been identified in human cancers. Similarly, the germline SNP in FGFR4 at nucleotide 388 correlates with a higher resistance to chemotherapy in patients with breast cancer [129]. In a mammary carcinoma model the FGFR4 G388R mutation was found to promote cancer progression and metastasis [130]. This may be because of impaired degradation compared to the wild type receptor, resulting in sustained signalling. A SNP within intron 2 of FGFR2 is associated with an increased risk of ER + ve breast cancer [89,90]. It is speculated that the alteration of binding affinity of two transcription factors (Oct-1/Runx2 and C/EBPβ) causes an increase in FGFR2 expression [66,91]. This increase in FGFR2 signalling due to FGFR2 overexpression has demonstrated an anti-apoptotic effect.

3.4. Alternative splicing

The switch between alternatively spliced isoforms has been shown to result in changes in FGFR signalling which promotes tumourigenesis by the more oncogenic isoforms [75,131–133]. In combination with altered ligand-binding specificity, this can result further deregulation of FGFR-mediated signalling. Alternative splicing of the third Ig-like domain confers the ligand binding specificity on the receptor, with IIIb and IIIc being commonly associated with either epithelial or mesenchymal cells. Interestingly the ligands for IIIb are commonly expressed by the mesenchyme, whilst the IIIc ligands are expressed by the epithelium. Thus this arrangement allows paracrine signalling, but the switch of isoforms results in an autocrine-signalling pattern. In rodent models of prostate and bladder cancer this switch from FGFR2 IIIb to FGFR2 IIIc by alternative splicing results in autocrine activation of FGFR2 and EMT [134–136]. However, it remains unclear whether alternative splicing of the third Ig domain results in tumour promotion in humans. The Ittmann group reported that alternative splicing of the third Ig domain of FGFR2 was rare in human prostate cancer, and only occurred in a subgroup of patients [63].

3.5. Impaired termination of signalling

Impaired termination of FGF signalling can contribute to tumourigenesis. A MAPK-dependent negative feedback loop via FRS2 is capable of regulating FGFR signalling [36]. It is believed that ERK1/2 may phosphorylate FRS2 on multiple serine and/or threonine residues, inhibiting the recruitment of Grb2 [36] to FRS2 can also be attenuated by activation of the MAPK phosphatases, or by Sprouty and Sef proteins [41–44].

In addition endocytosis and degradation of the receptor in lysosomes can terminate signalling in the physiologic context [47,137]. Disruptions of these pathways could lead to impaired signal termination and cellular transformation [138]. Mutation of the receptor can render it insensitive to endocytosis, maintaining it at the cell surface. Indeed, several mutations of the endocytic components have been identified in cancer [139,140]. Mutations in Cbl, the ubiquitin ligase that downregulates many RTKs are found to be mutated in acute myeloid leukaemia (AML), resulting in the accumulation of the RTK FLT3 [138]. Thus it would be interesting to investigate whether similar

mutations affect FGFRs in a subset of cancers. FGFR K650E and G380R, which are found in bladder, prostate and testicular cancer, have been shown to be inefficiently degraded, resulting in active receptors with twice the half-life of the wild type receptor [4].

Sef protein expression is decreased in breast, ovary, thyroid and prostate tumours [141]. Sef has been shown to down-regulate FGF signalling, and it is lost in high-grade and metastatic prostate cancer, correlating with increased FGF2, FGF8, and FGFR4 [71,142,143]. Similarly, the oncogenic splice variants of FGFR2 IIIb with deletion in its COOH-terminal tail resulted in the loss of an endocytic signal sequence [75,131,132], leading to impaired receptor internalisation and subsequently enhanced receptor signalling.

3.6. Increased autocrine or paracrine ligand stimulation of cancer growth

Most of the reported cases of genomic changes outlined so far affect FGFR directly. Ligand-dependent signalling can also have an important role in pathogenesis of cancer, either via autocrine (production of ligand by cancer cell) or paracrine pathways (produced by surrounding stroma, either at physiological levels or in response to the abnormal cancer cell).

Elevated levels of FGF have been found in numerous cancers, followed by validation of its oncogenic potentials in murine models. Increased levels of FGF2 have been identified in melanoma [144]. FGF2 is a potent angiogenic factor, and inhibition of FGF2 in human melanoma xenografts led to tumour regression and a reduction of tumour angiogenesis [144]. Amplification of FGF1 has been reported frequently in ovarian cancer, and is associated with poor survival [145]. FGF1 levels correlate with microvessel density, suggesting that aberrantly expressed FGF1 functions in a paracrine manner, promoting angiogenesis [145]. Elevated levels of FGF3, 4, and 8 have been identified as mammary proto-oncogenes in MMTV-infected mice, whilst FGF8 has been found to be upregulated in human breast cancer [146–150]. Similarly, FGF8 is also upregulated in human prostate cancer, and transgenic mice overexpressing FGF8 in prostatic epithelial cells develop PIN [151]. In a metastasis model, intra-tibial injection of PC cells overexpressing FGF8 increased the tumour incidence and size [152].

Hormonal FGFs, such as FGF19 are increased in the bloodstream of some patients with cancer [153]. Transgenic mice overexpressing FGF19 in the skeletal muscle developed hepatocellular carcinoma (HCC), reflecting its endocrine action [154]. FGF19 is also overexpressed in a proportion of liver, colonic and lung squamous carcinomas. A monoclonal antibody that blocks FGF19 function has shown anti-tumour effects on colonic cancer cells cultured *in vitro* and *in vivo* as xenografts [153].

Murine studies have demonstrated the complex interplay between the epithelium and the mesenchyme in prostate cancer. They have shown that mesenchymal overexpression of FGF10 was sufficient to induce epithelial transformation, resulting in the formation of well differentiated prostatic adenocarcinomas [155].

Genetically, only a few mutations of FGF have been described in humans. Six different somatic FGF9 mutations have been described in colorectal and endometrial cancer [156]. Surprisingly these mutations are predicted to have loss of FGF9 function, and it is still unclear what role these may play in tumourigenesis.

An increase in the release of FGFs stored in ECM could also lead to an increase in FGF signalling. FGFs have a high affinity for heparan sulphate proteoglycans (HSPGs), with most of the ligands stored in the location nearby where they are produced to act as autocrine/paracrine agents. FGFs can then be released by enzymatic cleavage of extracellular matrix [157]. Since cancer cells secrete proteases and heparanases, which can directly lead to the release of sequestered FGFs and increased FGF signalling [158].

Work by the Heasley lab (University of Colorado) has demonstrated the role of FGF2, FGF9 and their respective high-affinity FGFRs compromise a growth factor autocrine loop that is active in a subset of gefitinib-insensitive non-small cell lung cancer (NSCLC) cell lines [69]. Similar results were demonstrated in head and neck squamous cell carcinoma (HNSCC) cell lines. There was frequent co-expression of FGF2 and FGFRs in HNSCC cell lines, instigating an autocrine loop that either in isolation in collaboration with EGFR, drives cell growth [159].

3.7. FGFR as a tumour suppressor gene

FGFRs have also been suggested to have tumour suppressor properties, since downregulated expression of FGFR2 in particular has been found in many cancer subtypes.

Tumour-suppressive function of FGFRs has been suggested by the example of FGFR2, where reduced FGFR2 expression has been reported in several human cancer types including bladder, liver, salivary gland and prostate [160–162]. In addition, loss-of-function mutations in FGFR2 have been identified in melanoma [103,160–163]. Mice that specifically lack FGFR2-IIIb in keratinocytes are sensitised to carcinogenic insults to their skin, developing an increased number of papillomas and carcinomas compared to wild-type mice [164]. Additionally, in a rat model of prostate cancer, when normal epithelial cells expressing FGFR2-IIIb were mixed with stromal cells, benign tumours were observed [135]. However, in the absence of stromal cells, these epithelial cells expressing FGFR2-IIIb began expressing the IIIc isoform. This elegant study demonstrated the crucial role for epithelial–stromal interaction in the paracrine regulation of prostatic epithelial cell proliferation [135]. Finally, the expression of FGFR2-IIIb was shown to block proliferation in bladder cancer cell lines, [165], while in bladder cancers (as well as prostate and salivary) this isoform is downregulated [163,166], indicating the tumour-suppressive effect of FGFR2.

However it is far from clear that FGFR2 serves as a *bona fide* tumour suppressor, since it is also found to be upregulated in gastric, pancreatic and breast cancer, as well as actively mutated in endometrial and lung cancer [97,100,101,167–169] (see Sections 3.2 and 3.3). It is not well understood why it functions differently in different tumour types. Although much interest has surrounded FGFR2-IIIb as being tumour suppressive, with the IIIb isoform being potentially oncogenic, there is currently no evidence to suggest differential splicing of the FGFR2 extracellular domain affects intracellular signalling. Context-dependent variations in FGFR signalling may explain these varying roles of FGFRs in human cancers.

4. FGFR as a target of therapy

Several FGFR tyrosine kinase inhibitors (TKIS) are currently in phase I/II clinical trials [170–176]. All these inhibitors also inhibit VEGFR, due to the high structural similarity of the kinase domains. Although at first it may beneficial to inhibit both angiogenesis and proliferation, many of these multiple targeting TKIs may be relatively less potent as inhibitors against FGFRs. This also increases the side effect profile, limiting the deliverability of the drug at doses necessary for inhibition of FGF signalling. AstraZeneca compound AZD4547 in a dual FGFR1 and 2 inhibitor currently in phase 1 trials against advance solid malignancies [177]. Similarly Novartis have 2 compounds in their development pipeline. Dovitinib is an inhibitor of both VEGFR and FGFRs in phase III development against renal cell carcinoma and phase II development in advanced breast cancer, relapsed MM and bladder cancer. Their other compound BGJ398 is a selective inhibitor of FGFRs, with the phase I study currently on-going [178]. GP369, an FGFR2-IIb-specific antibody has been used *in vitro* and *in vivo* to suppress the IIIb isoform in FGFR2 amplified human breast and gastric cancer cell lines [86].

Thus, the field is currently developing TKIs highly specific to FGFR. As a proof-of-principle, pan-FGFR inhibitors have been demonstrated

to be effective in PTEN null FGFR2 mutant cell lines [124]. Treatment with the compound PD173074 resulted in cell death and cell cycle arrest of endometrial cancer cell lines [124]. The effects correlate with the inhibition of both FGFR1 and FGFR2 transphosphorylation. In a small cell lung cancer model, PD173074 acts to impair cell proliferation both in cell lines and in xenograft tumours [179].

An alternative approach to TKIs is the FGF ligand traps which act as FGF 'sponges', binding multiple FGFs, leading to both anti-proliferative and anti-angiogenic effects such as the Five Prime drug FP-1039 [180]. This has demonstrated efficacy in a variety of preclinical *in vivo* and *in vitro* models. Another approach involves the use of FGFR blocking antibodies. Since antibodies are supposed to be specific to particular FGFRs, they limit pan-FGFR inhibition toxicity. One of the examples is the R3Mab antibody, which targets FGFR3, demonstrating anti-proliferative effects on xenografts of bladder cancer and t(4;14) myeloma cells [59]. A final approach utilises FGF ligands to super stimulate FGFRs. A recombinant FGF7 ligand has been developed for use in mucostitis, induced by myelotoxic therapy [181].

5. Future perspectives

A plethora of reports from *in vivo* and *in vitro* human and animal studies have demonstrated the potential role of FGFR signalling in human carcinogenesis, whether it be in an oncogenic or tumour suppressive capacity. It is still not well understood how FGFRs can act as tumour suppressors, and this mechanism must be further elucidated before we start to target FGFR as a therapeutic target in human diseases. Indeed, up-regulating these tumour suppressor isoforms of FGFR2 may provide an alternative strategy for pharmaceutical developments. It is also crucial that the tumours that are 'driven' by activation of FGF signalling are distinguished from those that merely have FGF signalling as a 'passenger'. In summary, it can be considered that some tumours rely on deregulated FGF signalling on their development and progression, and as such FGF signalling molecules provides an attractive target for treatment. This is promising since multiple agents are now in the pipelines for preclinical and clinical evaluation.

Acknowledgements

IA is funded by a MRC clinical research training fellowship. HYL's research programme is funded by Cancer Research U.K.

References

[1] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[2] J. Schlessinger, Cell signaling by receptor tyrosine kinases, Cell 103 (2000) 211–225.
[3] N. Turner, R. Grose, Fibroblast growth factor signalling: from development to cancer, Nat. Rev. Cancer 10 (2010) 116–129.
[4] E.M. Haugsten, A. Wiedlocha, S. Olsnes, J.r. Wesche, Roles of fibroblast growth factor receptors in carcinogenesis, Mol. Cancer Res. 8 (2010) 1439–1452.
[5] D. Kimelman, M. Kirschner, Synergistic induction of mesoderm by FGF and TGF-[beta] and the identification of an mRNA coding for FGF in the early *Xenopus* embryo, Cell 51 (1987) 869–877.
[6] L. De Moerlooze, B. Spencer-Dene, J. Revest, M. Hajihosseini, I. Rosewell, C. Dickson, An important role for the IIIb isoform of fibroblast growth factor receptor 2 (FGFR2) in mesenchymal–epithelial signalling during mouse organogenesis, Development 127 (2000) 483–492.
[7] C. Dillon, B. Spencer-Dene, C. Dickson, A crucial role for fibroblast growth factor signaling in embryonic mammary gland development, J. Mammary Gland Biol. Neoplasia 9 (2004) 207–215.
[8] D. Gospodarowicz, H. Bialecki, G. Greenburg, Purification of the fibroblast growth factor activity from bovine brain, J. Biol. Chem. 253 (1978) 3736–3743.
[9] A. Beenken, M. Mohammadi, The FGF family: biology, pathophysiology and therapy, Nat. Rev. Drug Discov. 8 (2009) 235–253.
[10] T. Inagaki, M. Choi, A. Moschetta, L. Peng, C.L. Cummins, J.G. McDonald, G. Luo, S.A. Jones, B. Goodwin, J.A. Richardson, R.D. Gerard, J.J. Repa, D.J. Mangelsdorf, S.A. Kliewer, Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis, Cell Metab. 2 (2005) 217–225.
[11] A. Kharitonenkov, T.L. Shiyanova, A. Koester, A.M. Ford, R. Micanovic, E.J. Galbreath, G.E. Sandusky, L.J. Hammond, J.S. Moyers, R.A. Owens, J. Gromada, J.T. Brozinick, E.D. Hawkins, V.J. Wroblewski, D.S. Li, F. Mehrbod, S.R. Jaskunas, A.B. Shanafelt, FGF-21 as a novel metabolic regulator, J. Clin. Invest. 115 (2005) 1627–1635.
[12] M. Riminucci, M.T. Collins, N.S. Fedarko, N. Cherman, A. Corsi, K.E. White, S. Waguespack, A. Gupta, T. Hannon, M.J. Econs, P. Bianco, P. Gehron Robey, FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting, J. Clin. Invest. 112 (2003) 683–692.
[13] K.E. White, G. Carn, B. Lorenz-Depiereux, A. Benet-Pages, T.M. Strom, M.J. Econs, Autosomal-dominant hypophosphatemic rickets (ADHR) mutations stabilize FGF-23, Kidney Int. 60 (2001) 2079–2086.
[14] X. Yu, K.E. White, FGF23 and disorders of phosphate homeostasis, Cytokine Growth Factor Rev. 16 (2005) 221–232.
[15] S. Ezzat, S.L. Asa, FGF receptor signaling at the crossroads of endocrine homeostasis and tumorigenesis, Horm. Metab. Res. 37 (2005) 355–360.
[16] D.M. Bryant, J.L. Stow, Nuclear translocation of cell-surface receptors: lessons from fibroblast growth factor, Traffic 6 (2005) 947–954.
[17] R. Grose, C. Dickson, Fibroblast growth factor signaling in tumorigenesis, Cytokine Growth Factor Rev. 16 (2005) 179–186.
[18] A. Ori, M.C. Wilkinson, D.G. Fernig, The heparanome and regulation of cell function: structures, functions and challenges, Front. Biosci. 13 (2008) 4309–4338.
[19] N.J. Harmer, L.L. Ilag, B. Mulloy, L. Pellegrini, C.V. Robinson, T.L. Blundell, Towards a resolution of the stoichiometry of the fibroblast growth factor (FGF)-FGF receptor–heparin complex, J. Mol. Biol. 339 (2004) 821–834.
[20] M. Mohammadi, S.K. Olsen, O.A. Ibrahimi, Structural basis for fibroblast growth factor receptor activation, Cytokine Growth Factor Rev. 16 (2005) 107–137.
[21] D.M. Ornitz, J. Xu, J.S. Colvin, D.G. McEwen, C.A. MacArthur, F. Coulier, G. Gao, M. Goldfarb, Receptor specificity of the fibroblast growth-factor family, J. Biol. Chem. 271 (1996) 15292–15297.
[22] D.M. Ornitz, N. Itoh, Fibroblast growth factors, Genome Biol. 2 (2001) (3005-3005.3012).
[23] X. Zhang, O.A. Ibrahimi, S.K. Olsen, H. Umemori, M. Mohammadi, D.M. Ornitz, Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family, J. Biol. Chem. 281 (2006) 15694–15700.
[24] D.E. Johnson, L.T. Williams, Structural and functional diversity in the FGF receptor multigene family, Adv. Cancer Res. 60 (1993) 1–41.
[25] S.K. Olsen, O.A. Ibrahimi, A. Raucci, F. Zhang, A.V. Eliseenkova, A. Yayon, C. Basilico, R.J. Linhardt, J. Schlessinger, M. Mohammadi, Insights into the molecular basis for fibroblast growth factor receptor autoinhibition and ligand-binding promiscuity, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 935–940.
[26] X. Zhang, Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family, J. Biol. Chem. 281 (2006) 15694–15700.
[27] V. Knights, S.J. Cook, De-regulated FGF receptors as therapeutic targets in cancer, Pharmacol. Ther. 125 (2010) 105–117.
[28] M. Mohammadi, A.M. Honegger, D. Rotin, R. Fischer, F. Bellot, W. Li, C.A. Dionne, M. Jaye, M. Rubinstein, J. Schlessinger, A tyrosine-phosphorylated carboxy-terminal peptide of the fibroblast growth factor receptor (Flg) is a binding site for the SH2 domain of phospholipase C-gamma 1, Mol. Cell. Biol. 11 (1991) 5068–5078.
[29] M. Mohammadi, I. Dikic, A. Sorokin, W.H. Burgess, M. Jaye, J. Schlessinger, Identification of six novel autophosphorylation sites on fibroblast growth factor receptor 1 and elucidation of their importance in receptor activation and signal transduction, Mol. Cell. Biol. 16 (1996) 977–989.
[30] C.M. Furdui, E.D. Lew, J. Schlessinger, K.S. Anderson, Autophosphorylation of FGFR1 kinase is mediated by a sequential and precisely ordered reaction, Mol. Cell 21 (2006) 711–717.
[31] E.D. Lew, C.M. Furdui, K.S. Anderson, J. Schlessinger, The precise sequence of FGF receptor autophosphorylation is kinetically driven and is disrupted by oncogenic mutations, Sci. Signal. 2 (2009) ra6.
[32] H. Chen, C.F. Xu, J. Ma, A.V. Eliseenkova, W. Li, P.M. Pollock, N. Pitteloud, W.T. Miller, T.A. Neubert, M. Mohammadi, A crystallographic snapshot of tyrosine trans-phosphorylation in action, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 19660–19665.
[33] C.J. Powers, S.W. McLeskey, A. Wellstein, Fibroblast growth factors, their receptors and signaling, Endocr. Relat. Cancer 7 (2000) 165–197.
[34] V. Rand, J. Huang, T. Stockwell, S. Ferriera, O. Buzko, S. Levy, D. Busam, K. Li, J.B. Edwards, C. Eberhart, K.M. Murphy, A. Tsiamouri, K. Beeson, A.J. Simpson, J.C. Venter, G.J. Riggins, R.L. Strausberg, Sequence survey of receptor tyrosine kinases reveals mutations in glioblastomas, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 14344–14349.
[35] N.C. Cross, A. Reiter, Tyrosine kinase fusion genes in chronic myeloproliferative diseases, Leukemia 16 (2002) 1207–1212.
[36] N. Gotoh, Regulation of growth factor signaling by FRS2 family docking/scaffold adaptor proteins, Cancer Sci. 99 (2008) 1319–1325.
[37] V.P. Eswarakumar, I. Lax, J. Schlessinger, Cellular signaling by fibroblast growth factor receptors, Cytokine Growth Factor Rev. 16 (2005) 139–149.
[38] K.C. Hart, S.C. Robertson, M.Y. Kanemitsu, A.N. Meyer, J.A. Tynan, D.J. Donoghue, Transformation and Stat activation by derivatives of FGFR1, FGFR3, and FGFR4, Oncogene 19 (2000) 3309–3320.
[39] S. Kang, S. Elf, S. Dong, T. Hitosugi, K. Lythgoe, A. Guo, H. Ruan, S. Lonial, H.J. Khoury, I.R. Williams, B.H. Lee, J.L. Roesel, G. Karsenty, A. Hanauer, J. Taunton, T.J. Boggon, T.L. Gu, J. Chen, Fibroblast growth factor receptor 3 associates with and tyrosine phosphorylates p90 RSK2, leading to RSK2 activation that mediates hematopoietic transformation, Mol. Cell. Biol. 29 (2009) 2105–2117.
[40] Y. Zhao, Z.Y. Zhang, The mechanism of dephosphorylation of extracellular signal-regulated kinase 2 by mitogen-activated protein kinase phosphatase 3, J. Biol. Chem. 276 (2001) 32382–32391.

[41] T. Casci, J. Vinos, M. Freeman, Sprouty, an intracellular inhibitor of Ras signaling, Cell 96 (1999) 655–665.
[42] N. Hacohen, S. Kramer, D. Sutherland, Y. Hiromi, M.A. Krasnow, Sprouty encodes a novel antagonist of FGF signaling that patterns apical branching of the *Drosophila* airways, Cell 92 (1998) 253–263.
[43] M. Furthauer, W. Lin, S.L. Ang, B. Thisse, C. Thisse, Sef is a feedback-induced antagonist of Ras/MAPK-mediated FGF signalling, Nat. Cell Biol. 4 (2002) 170–174.
[44] M. Tsang, R. Friesel, T. Kudoh, I.B. Dawid, Identification of Sef, a novel modulator of FGF signalling, Nat. Cell Biol. 4 (2002) 165–169.
[45] M. Tsang, I.B. Dawid, Promotion and attenuation of FGF signaling through the Ras–MAPK pathway, Sci. STKE 228 (2004) 7.
[46] C.B. Thien, W.Y. Langdon, Cbl: many adaptations to regulate protein tyrosine kinases, Nat. Rev. Mol. Cell Biol. 2 (2001) 294–307.
[47] E.M. Haugsten, J. Malecki, S.M. Bjorklund, S. Olsnes, J. Wesche, Ubiquitination of fibroblast growth factor receptor 1 is required for its intracellular sorting but not for its endocytosis, Mol. Biol. Cell 19 (2008) 3390–3403.
[48] F. Yagasaki, D. Wakao, Y. Yokoyama, Y. Uchida, I. Murohashi, H. Kayano, M. Taniwaki, A. Matsuda, M. Bessho, Fusion of ETV6 to fibroblast growth factor receptor 3 in peripheral T-cell lymphoma with a t(4;12)(p16;p13) chromosomal translocation, Cancer Res. 61 (2001) 8371–8374.
[49] S. Roumiantsev, D.S. Krause, C.A. Neumann, C.A. Dimitri, F. Asiedu, N.C. Cross, R.A. Van Etten, Distinct stem cell myeloproliferative/T lymphoma syndromes induced by ZNF198–FGFR1 and BCR–FGFR1 fusion genes from 8p11 translocations, Cancer Cell 5 (2004) 287–298.
[50] S. Xiao, S.R. Nalabolu, J.C. Aster, J. Ma, L. Abruzzo, E.S. Jaffe, R. Stone, S.M. Weissman, T.J. Hudson, J.A. Fletcher, FGFR1 is fused with a novel zinc-finger gene, ZNF198, in the t(8;13) leukaemia/lymphoma syndrome, Nat. Genet. 18 (1998) 84–87.
[51] C.C. Jackson, L.J. Medeiros, R.N. Miranda, 8p11 myeloproliferative syndrome: a review, Hum. Pathol. 41 (2010) 461–476.
[52] A. Demiroglu, E.J. Steer, C. Heath, K. Taylor, M. Bentley, S.L. Allen, P. Koduru, J.P. Brody, G. Hawson, R. Rodwell, M.L. Doody, F. Carnicero, A. Reiter, J.M. Goldman, J.V. Melo, N.C. Cross, The t(8;22) in chronic myeloid leukemia fuses BCR to FGFR1: transforming activity and specific inhibition of FGFR1 fusion proteins, Blood 98 (2001) 3778–3783.
[53] M. Ren, X. Li, J.K. Cowell, Genetic fingerprinting of the development and progression of T-cell lymphoma in a murine model of atypical myeloproliferative disorder initiated by the ZNF198-fibroblast growth factor receptor-1 chimeric tyrosine kinase, Blood 114 (2009) 1576–1584.
[54] J. Chen, D.J. Deangelo, J.L. Kutok, I.R. Williams, B.H. Lee, M. Wadleigh, N. Duclos, S. Cohen, J. Adelsperger, R. Okabe, A. Coburn, I. Galinsky, B. Huntly, P.S. Cohen, T. Meyer, D. Fabbro, J. Roesel, L. Banerji, J.D. Griffin, S. Xiao, J.A. Fletcher, R.M. Stone, D.G. Gilliland, PKC412 inhibits the zinc finger 198-fibroblast growth factor receptor 1 fusion tyrosine kinase and is active in treatment of stem cell myeloproliferative disorder, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 14479–14484.
[55] G. Guasch, B. Delaval, C. Arnoulet, M.J. Xie, L. Xerri, D. Sainty, D. Birnbaum, M.J. Pebusque, FOP–FGFR1 tyrosine kinase, the product of a t(6;8) translocation, induces a fatal myeloproliferative disease in mice, Blood 103 (2004) 309–312.
[56] H. Chang, A.K. Stewart, X.Y. Qi, Z.H. Li, Q.L. Yi, S. Trudel, Immunohistochemistry accurately predicts FGFR3 aberrant expression and t(4;14) in multiple myeloma, Blood 106 (2005) 353–355.
[57] M. Chesi, E. Nardini, L.A. Brents, E. Schröck, T. Ried, W.M. Kuehl, P.L. Bergsagel, Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3, Nat. Genet. 16 (1997) 260–264.
[58] J.J. Keats, T. Reiman, A.R. Belch, L.M. Pilarski, Ten years and counting: so what do we know about t(4;14)(p16;q32) multiple myeloma, Leuk. Lymphoma 47 (2006) 2289–2300.
[59] J. Qing, X. Du, Y. Chen, P. Chan, H. Li, P. Wu, S. Marsters, S. Stawicki, J. Tien, K. Totpal, S. Ross, S. Stinson, D. Dornan, D. French, Q.R. Wang, J.P. Stephan, Y. Wu, C. Wiesmann, A. Ashkenazi, Antibody-based targeting of FGFR3 in bladder carcinoma and t(4;14)-positive multiple myeloma in mice, J. Clin. Invest. 119 (2009) 1216–1229.
[60] S. Trudel, A.K. Stewart, E. Rom, E. Wei, Z.H. Li, S. Kotzer, I. Chumakov, Y. Singer, H. Chang, S.B. Liang, A. Yayon, The inhibitory anti-FGFR3 antibody, PRO-001, is cytotoxic to t(4;14) multiple myeloma cells, Blood 107 (2006) 4039–4046.
[61] E.K. Grand, A.J. Chase, C. Heath, A. Rahemtulla, N.C. Cross, Targeting FGFR3 in multiple myeloma: inhibition of t(4;14)-positive cells by SU5402 and PD173074, Leukemia 18 (2004) 962–966.
[62] S. Trudel, S. Ely, Y. Farooqi, M. Affer, D.F. Robbiani, M. Chesi, P.L. Bergsagel, Inhibition of fibroblast growth factor receptor 3 induces differentiation and apoptosis in t(4;14) myeloma, Blood 103 (2004) 3521–3528.
[63] B. Kwabi-Addo, M. Ozen, M. Ittmann, The role of fibroblast growth factors and their receptors in prostate cancer, Endocr. Relat. Cancer 11 (2004) 709–724.
[64] K. Freier, C. Schwaenen, C. Sticht, C. Flechtenmacher, J. Mühling, C. Hofele, B. Radlwimmer, P. Lichter, S. Joos, Recurrent FGFR1 amplification and high FGFR1 protein expression in oral squamous cell carcinoma (OSCC), Oral Oncol. 43 (2007) 60–66.
[65] J. Jacquemier, J. Adelaide, P. Parc, F. Penault-Llorca, J. Planche, O. deLapeyriere, D. Birnbaum, Expression of the FGFR1 gene in human breast-carcinoma cells, Int. J. Cancer 59 (1994) 373–378.
[66] K.B. Meyer, A.T. Maia, M. O'Reilly, A.E. Teschendorff, S.F. Chin, C. Caldas, B.A. Ponder, Allele-specific up-regulation of FGFR2 increases susceptibility to breast cancer, PLoS Biol. 6 (2008) 108.
[67] K. Nakazawa, M. Yashiro, K. Hirakawa, Keratinocyte growth factor produced by gastric fibroblasts specifically stimulates proliferation of cancer cells from scirrhous gastric carcinoma, Cancer Res. 63 (2003) 8848–8852.
[68] J.C. Clark, J.W. Tichelaar, S.E. Wert, N. Itoh, A.K. Perl, M.T. Stahlman, J.A. Whitsett, FGF-10 disrupts lung morphogenesis and causes pulmonary adenomas in vivo, Am. J. Physiol. Lung Cell. Mol. Physiol. 280 (2001) L705–L715.
[69] L. Marek, K.E. Ware, A. Fritzsche, P. Hercule, W.R. Helton, J.E. Smith, L.A. McDermott, C.D. Coldren, R.A. Nemenoff, D.T. Merrick, B.A. Helfrich, P.A. Bunn Jr., L.E. Heasley, Fibroblast growth factor (FGF) and FGF receptor-mediated autocrine signaling in non-small-cell lung cancer cells, Mol. Pharmacol. 75 (2009) 196–207.
[70] B.W. van Rhijn, A.A. van Tilborg, I. Lurkin, J. Bonaventure, A. de Vries, J.P. Thiery, T.H. van der Kwast, E.C. Zwarthoff, F. Radvanyi, Novel fibroblast growth factor receptor 3 (FGFR3) mutations in bladder cancer previously identified in non-lethal skeletal disorders, Eur. J. Hum. Genet. 10 (2002) 819–824.
[71] T. Murphy, S. Darby, M.E. Mathers, V.J. Gnanapragasam, Evidence for distinct alterations in the FGF axis in prostate cancer progression to an aggressive clinical phenotype, J. Pathol. 220 (2010) 452–460.
[72] V.D. Acevedo, R.D. Gangula, K.W. Freeman, R. Li, Y. Zhang, F. Wang, G.E. Ayala, L.E. Peterson, M. Ittmann, D.M. Spencer, Inducible FGFR-1 activation leads to irreversible prostate adenocarcinoma and an epithelial-to-mesenchymal transition, Cancer Cell 12 (2007) 559–571.
[73] J.H. Jang, K.H. Shin, J.G. Park, Mutations in fibroblast growth factor receptor 2 and fibroblast growth factor receptor 3 genes associated with human gastric and colorectal cancers, Cancer Res. 61 (2001) 3541–3543.
[74] K. Kunii, L. Davis, J. Gorenstein, H. Hatch, M. Yashiro, A. Di Bacco, C. Elbi, B. Lutterbach, FGFR2-amplified gastric cancer cell lines require FGFR2 and Erbb3 signaling for growth and survival, Cancer Res. 68 (2008) 2340–2348.
[75] J.Y. Cha, S. Maddileti, N. Mitin, T.K. Harden, C.J. Der, Aberrant receptor internalization and enhanced FRS2-dependent signaling contribute to the transforming activity of the fibroblast growth factor receptor 2 IIIb C3 isoform, J. Biol. Chem. 284 (2009) 6227–6240.
[76] K. Chin, S. DeVries, J. Fridlyand, P.T. Spellman, R. Roydasgupta, W.L. Kuo, A. Lapuk, R.M. Neve, Z. Qian, T. Ryder, F. Chen, H. Feiler, T. Tokuyasu, C. Kingsley, S. Dairkee, Z. Meng, K. Chew, D. Pinkel, A. Jain, B.M. Ljung, L. Esserman, D.G. Albertson, F.M. Waldman, J.W. Gray, Genomic and transcriptional aberrations linked to breast cancer pathophysiologies, Cancer Cell 10 (2006) 529–541.
[77] V. Gelsi-Boyer, B. Orsetti, N. Cervera, P. Finetti, F. Sircoulomb, C. Rouge, L. Lasorsa, A. Letessier, C. Ginestier, F. Monville, S. Esteyries, J. Adelaide, B. Esterni, C. Henry, S.P. Ethier, F. Bibeau, M.J. Mozziconacci, E. Charafe-Jauffret, J. Jacquemier, F. Bertucci, D. Birnbaum, C. Theillet, M. Chaffanet, Comprehensive profiling of 8p11-12 amplification in breast cancer, Mol. Cancer Res. 3 (2005) 655–667.
[78] A. Letessier, F. Sircoulomb, C. Ginestier, N. Cervera, F. Monville, V. Gelsi-Boyer, B. Esterni, J. Geneix, P. Finetti, C. Zemmour, P. Viens, E. Charafe-Jauffret, J. Jacquemier, D. Birnbaum, M. Chaffanet, Frequency, prognostic impact, and subtype association of 8p12, 8q24, 11q13, 12p13, 17q12, and 20q13 amplifications in breast cancers, BMC Cancer 6 (2006) 245.
[79] I. Bernard-Pierrot, N. Gruel, N. Stransky, A. Vincent-Salomon, F. Reyal, V. Raynal, C. Vallot, G. Pierron, F. Radvanyi, O. Delattre, Characterization of the recurrent 8p11-12 amplicon identifies PPAPDC1B, a phosphatase protein, as a new therapeutic target in breast cancer, Cancer Res. 68 (2008) 7165–7175.
[80] M.J. Garcia, J.C. Pole, S.F. Chin, A. Teschendorff, A. Naderi, H. Ozdag, M. Vias, T. Kranjac, T. Subkhankulova, C. Paish, I. Ellis, J.D. Brenton, P.A. Edwards, C. Caldas, A 1 Mb minimal amplicon at 8p11-12 in breast cancer identifies new candidate oncogenes, Oncogene 24 (2005) 5235–5245.
[81] F. Behbod, W. Xian, C.A. Shaw, S.G. Hilsenbeck, A. Tsimelzon, J.M. Rosen, Transcriptional profiling of mammary gland side population cells, Stem Cells 24 (2006) 1065–1074.
[82] W. Xian, L. Pappas, D. Pandya, L.M. Selfors, P.W. Derksen, M. de Bruin, N.S. Gray, J. Jonkers, J.M. Rosen, J.S. Brugge, Fibroblast growth factor receptor 1-transformed mammary epithelial cells are dependent on RSK activity for growth and survival, Cancer Res. 69 (2009) 2244–2251.
[83] W. Xian, K.L. Schwertfeger, T. Vargo-Gogola, J.M. Rosen, Pleiotropic effects of FGFR1 on cell proliferation, survival, and migration in a 3D mammary epithelial cell model, J. Cell Biol. 171 (2005) 663–673.
[84] J.S. Reis-Filho, P.T. Simpson, N.C. Turner, M.B. Lambros, C. Jones, A. Mackay, A. Grigoriadis, D. Sarrio, K. Savage, T. Dexter, M. Iravani, K. Fenwick, B. Weber, D. Hardisson, F.C. Schmitt, J. Palacios, S.R. Lakhani, A. Ashworth, FGFR1 emerges as a potential therapeutic target for lobular breast carcinomas, Clin. Cancer Res. 12 (2006) 6652–6662.
[85] A. Bai, K. Meetze, N.Y. Vo, S. Kollipara, E.K. Mazsa, W.M. Winston, S. Weiler, L.L. Poling, T. Chen, N.S. Ismail, J. Jiang, L. Lerner, J. Gyuris, Z. Weng, GP369, an FGFR2-IIIb-specific antibody, exhibits potent antitumor activity against human cancers driven by activated FGFR2 signaling, Cancer Res. 70 (2010) 7630–7639.
[86] H. Nord, U. Segersten, J. Sandgren, K. Wester, C. Busch, U. Menzel, J. Komorowski, J.P. Dumanski, P.U. Malmström, T. Díaz de Ståhl, Focal amplifications are associated with high-grade and recurrences in stage Ta bladder carcinoma, Int. J. Cancer 126 (2009) 1390–1402.
[87] K.L. Gorringe, S. Jacobs, E.R. Thompson, A. Sridhar, W. Qiu, D.Y. Choong, I.G. Campbell, High-resolution single nucleotide polymorphism array analysis of epithelial ovarian cancer reveals numerous microdeletions and amplifications, Clin. Cancer Res. 13 (2007) 4731–4739.
[88] E. Missiaglia, J. Selfe, M. Hamdi, D. Williamson, G. Schaaf, C. Fang, J. Koster, B. Summersgill, B. Messahel, R. Versteeg, K. Pritchard-Jones, M. Kool, J. Shipley, Genomic imbalances in rhabdomyosarcoma cell lines affect expression of genes frequently altered in primary tumors: an approach to identify candidate genes involved in tumor development, Genes Chromosomes Cancer 48 (2009) 455–467.
[89] D.F. Easton, K.A. Pooley, A.M. Dunning, P.D. Pharoah, D. Thompson, D.G. Ballinger, J.P. Struewing, J. Morrison, H. Field, R. Luben, N. Wareham, S. Ahmed, C.S.

Healey, R. Bowman, K.B. Meyer, C.A. Haiman, L.K. Kolonel, B.E. Henderson, L. Le Marchand, P. Brennan, S. Sangrajrang, V. Gaborieau, F. Odefrey, C.Y. Shen, P.E. Wu, H.C. Wang, D. Eccles, D.G. Evans, J. Peto, O. Fletcher, N. Johnson, S. Seal, M.R. Stratton, N. Rahman, G. Chenevix-Trench, S.E. Bojesen, B.G. Nordestgaard, C.K. Axelsson, M. Garcia-Closas, L. Brinton, S. Chanock, J. Lissowska, B. Peplonska, H. Nevanlinna, R. Fagerholm, H. Eerola, D. Kang, K.Y. Yoo, D.Y. Noh, S.H. Ahn, D.J. Hunter, S.E. Hankinson, D.G. Cox, P. Hall, S. Wedren, J. Liu, Y.L. Low, N. Bogdanova, P. Schurmann, T. Dork, R.A. Tollenaar, C.E. Jacobi, P. Devilee, J.G. Klijn, A.J. Sigurdson, M.M. Doody, B.H. Alexander, J. Zhang, A. Cox, I.W. Brock, G. MacPherson, M.W. Reed, F.J. Couch, E.L. Goode, J.E. Olson, H. Meijers-Heijboer, A. van den Ouweland, A. Uitterlinden, F. Rivadeneira, R.L. Milne, G. Ribas, A. Gonzalez-Neira, J. Benitez, J.L. Hopper, M. McCredie, M. Southey, G.G. Giles, C. Schroen, C. Justenhoven, H. Brauch, U. Hamann, Y.D. Ko, A.B. Spurdle, J. Beesley, X. Chen, A. Mannermaa, V.M. Kosma, V. Kataja, J. Hartikainen, N.E. Day, D.R. Cox, B.A. Ponder, Genome-wide association study identifies novel breast cancer susceptibility loci, Nature 447 (2007) 1087–1093.

[90] D.J. Hunter, P. Kraft, K.B. Jacobs, D.G. Cox, M. Yeager, S.E. Hankinson, S. Wacholder, Z. Wang, R. Welch, A. Hutchinson, J. Wang, K. Yu, N. Chatterjee, N. Orr, W.C. Willett, G.A. Colditz, R.G. Ziegler, C.D. Berg, S.S. Buys, C.A. McCarty, H.S. Feigelson, E.E. Calle, M.J. Thun, R.B. Hayes, M. Tucker, D.S. Gerhard, J.F. Fraumeni Jr., R.N. Hoover, G. Thomas, S.J. Chanock, A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer, Nat. Genet. 39 (2007) 870–874.

[91] J.S. Carroll, C.A. Meyer, J. Song, W. Li, T.R. Geistlinger, J. Eeckhoute, A.S. Brodsky, E.K. Keeton, K.C. Fertuck, G.F. Hall, Q. Wang, S. Bekiranov, V. Sementchenko, E.A. Fox, P.A. Silver, T.R. Gingeras, X.S. Liu, M. Brown, Genome-wide analysis of estrogen receptor binding sites, Nat. Genet. 38 (2006) 1289–1297.

[92] C. Greenman, P. Stephens, R. Smith, G.L. Dalgliesh, C. Hunter, G. Bignell, H. Davies, J. Teague, A. Butler, C. Stevens, S. Edkins, S. O'Meara, I. Vastrik, E.E. Schmidt, T. Avis, S. Barthorpe, G. Bhamra, G. Buck, B. Choudhury, J. Clements, J. Cole, E. Dicks, S. Forbes, K. Gray, K. Halliday, R. Harrison, K. Hills, J. Hinton, A. Jenkinson, D. Jones, A. Menzies, T. Mironenko, J. Perry, K. Raine, D. Richardson, R. Shepherd, A. Small, C. Tofts, J. Varian, T. Webb, S. West, S. Widaa, A. Yates, D.P. Cahill, D.N. Louis, P. Goldstraw, A.G. Nicholson, F. Brasseur, L. Looijenga, B.L. Weber, Y.E. Chiew, A. DeFazio, M.F. Greaves, A.R. Green, P. Campbell, E. Birney, D.F. Easton, G. Chenevix-Trench, M.H. Tan, S.K. Khoo, B.T. Teh, S.T. Yuen, S.Y. Leung, R. Wooster, P.A. Futreal, M.R. Stratton, Patterns of somatic mutation in human cancer genomes, Nature 446 (2007) 153–158.

[93] M.C. Naski, Q. Wang, J. Xu, D.M. Ornitz, Graded activation of fibroblast growth factor receptor 3 by mutations causing achondroplasia and thanatophoric dysplasia, Nat. Genet. 13 (1996) 233–237.

[94] K. Yu, J. Xu, Z. Liu, D. Sosic, J. Shao, E.N. Olson, D.A. Towler, D.M. Ornitz, Conditional inactivation of FGF receptor 2 reveals an essential role for FGF signaling in the regulation of osteoblast function and bone growth, Development 130 (2003) 3063–3074.

[95] A.O. Wilkie, Bad bones, absent smell, selfish testes: the pleiotropic consequences of human FGF receptor mutations, Cytokine Growth Factor Rev. 16 (2005) 187–203.

[96] S. Hernandez, S. de Muga, L. Agell, N. Juanpere, R. Esgueva, J.A. Lorente, S. Mojal, S. Serrano, J. Lloreta, FGFR3 mutations in prostate cancer: association with low-grade tumors, Mod. Pathol. 22 (2009) 848–856.

[97] A. Dutt, H.B. Salvesen, T.H. Chen, A.H. Ramos, R.C. Onofrio, C. Hatton, R. Nicoletti, W. Winckler, R. Grewal, M. Hanna, N. Wyhs, L. Ziaugra, D.J. Richter, J. Trovik, I.B. Engelsen, I.M. Stefansson, T. Fennell, K. Cibulskis, M.C. Zody, L.A. Akslen, S. Gabriel, K.K. Wong, W.R. Sellers, M. Meyerson, H. Greulich, Drug-sensitive FGFR2 mutations in endometrial carcinoma, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 8713–8717.

[98] M. Chesi, L.A. Brents, S.A. Ely, C. Bais, D.F. Robbiani, E.A. Mesri, W.M. Kuehl, P.L. Bergsagel, Activated fibroblast growth factor receptor 3 is an oncogene that contributes to tumor progression in multiple myeloma, Blood 97 (2001) 729–736.

[99] A. Chou, N. Dekker, R.C. Jordan, Identification of novel fibroblast growth factor receptor 3 gene mutations in actinic cheilitis and squamous cell carcinoma of the lip, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 107 (2009) 535–541.

[100] H. Davies, C. Hunter, R. Smith, P. Stephens, C. Greenman, G. Bignell, J. Teague, A. Butler, S. Edkins, C. Stevens, A. Parker, S. O'Meara, T. Avis, S. Barthorpe, L. Brackenbury, G. Buck, J. Clements, J. Cole, E. Dicks, K. Edwards, S. Forbes, M. Gorton, K. Gray, K. Halliday, R. Harrison, K. Hills, J. Hinton, D. Jones, V. Kosmidou, R. Laman, R. Lugg, A. Menzies, J. Perry, R. Petty, K. Raine, R. Shepherd, A. Small, H. Solomon, Y. Stephens, C. Tofts, J. Varian, A. Webb, S. West, S. Widaa, A. Yates, F. Brasseur, C.S. Cooper, A.M. Flanagan, A. Green, M. Knowles, S.Y. Leung, L.H. Looijenga, B. Malkowicz, M.A. Pierotti, B.T. Teh, S.T. Yuen, S.R. Lakhani, D.F. Easton, B.L. Weber, P. Goldstraw, A.G. Nicholson, R. Wooster, M.R. Stratton, P.A. Futreal, Somatic mutations of the protein kinase gene family in human lung cancer, Cancer Res. 65 (2005) 7591–7595.

[101] P.M. Pollock, M.G. Gartside, L.C. Dejeza, M.A. Powell, M.A. Mallon, H. Davies, M. Mohammadi, P.A. Futreal, M.R. Stratton, J.M. Trent, P.J. Goodfellow, Frequent activating FGFR2 mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes, Oncogene 26 (2007) 7158–7162.

[102] J.Y. Cho, C. Guo, M. Torello, G.P. Lunstrum, T. Iwata, C. Deng, W.A. Horton, Defective lysosomal targeting of activated fibroblast growth factor receptor 3 in achondroplasia, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 609–614.

[103] M.G. Gartside, H. Chen, O.A. Ibrahimi, S.A. Byron, A.V. Curtis, C.L. Wellens, A. Bengston, L.M. Yudt, A.V. Eliseenkova, J. Ma, J.A. Curtin, P. Hyder, U.L. Harper, E. Riedesel, G.J. Mann, J.M. Trent, B.C. Bastian, P.S. Meltzer, M. Mohammadi, P.M. Pollock, Loss-of-function fibroblast growth factor receptor-2 mutations in melanoma, Mol. Cancer Res. 7 (2009) 41–54.

[104] D. Cappellen, C. De Oliveira, D. Ricol, S. de Medina, J. Bourdin, X. Sastre-Garau, D. Chopin, J.P. Thiery, F. Radvanyi, Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas, Nat. Genet. 23 (1999) 18–20.

[105] L. Cheng, S. Zhang, D.D. Davidson, G.T. MacLennan, M.O. Koch, R. Montironi, A. Lopez-Beltran, Molecular determinants of tumor recurrence in the urinary bladder, Future Oncol. 5 (2009) 843–857.

[106] E. di Martino, C. L'Hote, W. Kennedy, D.C. Tomlinson, M.A. Knowles, Mutant fibroblast growth factor receptor 3 induces intracellular signaling and cellular transformation in a cell type- and mutation-specific manner, Oncogene 28 (2009) 4306–4316.

[107] N.P. Munro, M.A. Knowles, Fibroblast growth factors and their receptors in transitional cell carcinoma, J. Urol. 169 (2003) 675–682.

[108] M.A. Knowles, Molecular pathogenesis of bladder cancer, Int. J. Clin. Oncol. 13 (2008) 287–297.

[109] H. Chen, J. Ma, W. Li, A.V. Eliseenkova, C. Xu, T.A. Neubert, W.T. Miller, M. Mohammadi, A molecular brake in the kinase hinge region regulates the activity of receptor tyrosine kinases, Mol. Cell 27 (2007) 717–730.

[110] D.C. Tomlinson, C.D. Hurst, M.A. Knowles, Knockdown by shRNA identifies S249C mutant FGFR3 as a potential therapeutic target in bladder cancer, Oncogene 26 (2007) 5889–5899.

[111] J. Martinez-Torrecuadrada, Targeting the extracellular domain of fibroblast growth factor receptor 3 with human single-chain Fv antibodies inhibits bladder carcinoma cell line proliferation, Clin. Cancer Res. 11 (2005) 6280–6290.

[112] M. Miyake, M. Ishii, N. Koyama, K. Kawashima, T. Kodama, S. Anai, K. Fujimoto, Y. Hirao, K. Sugano, 1-Tert-butyl-3-[6-(3,5-dimethoxy-phenyl)-2-(4-diethylamino-butylamino)-pyr ido[2,3-d]pyrimidin-7-yl]-urea (PD173074), a selective tyrosine kinase inhibitor of fibroblast growth factor receptor-3 (FGFR3), inhibits cell proliferation of bladder cancer carrying the FGFR3 gene mutation along with up-regulation of p27/Kip1 and G1/G0 arrest, J. Pharmacol. Exp. Ther. 332 (2010) 795–802.

[113] I. Bernard-Pierrot, A. Brams, C. Dunois-Larde, A. Caillault, S.G. Diez de Medina, D. Cappellen, G. Graff, J.P. Thiery, D. Chopin, D. Ricol, F. Radvanyi, Oncogenic properties of the mutated forms of fibroblast growth factor receptor 3b, Carcinogenesis 27 (2006) 740–747.

[114] J.L. Martinez-Torrecuadrada, L.H. Cheung, P. Lopez-Serra, R. Barderas, M. Canamero, S. Ferreiro, M.G. Rosenblum, J.I. Casal, Antitumor activity of fibroblast growth factor receptor 3-specific immunotoxins in a xenograft mouse model of bladder carcinoma is mediated by apoptosis, Mol. Cancer Ther. 7 (2008) 862–873.

[115] A. Logie, C. Dunois-Larde, C. Rosty, O. Levrel, M. Blanche, A. Ribeiro, J.M. Gasc, J. Jorcano, S. Werner, X. Sastre-Garau, J.P. Thiery, F. Radvanyi, Activating mutations of the tyrosine kinase receptor FGFR3 are associated with benign skin tumors in mice and humans, Hum. Mol. Genet. 14 (2005) 1153–1160.

[116] I. Ahmad, L.B. Singh, M. Foth, C.A. Morris, M.M. Taketo, X.R. Wu, H.Y. Leung, O.J. Sansom, T. Iwata, K-Ras and beta-catenin mutations cooperate with Fgfr3 mutations in mice to promote tumorigenesis in the skin and lung, but not in the bladder, Dis. Model. Mech. 4 (2011) 548–555.

[117] C. Rosty, Clinical and biological characteristics of cervical neoplasias with FGFR3 mutation, Mol. Cancer 4 (2005) 15.

[118] A. Goriely, Activating mutations in FGFR3 and HRAS reveal a shared genetic origin for congenital disorders and testicular tumors, Nat. Genet. 41 (2009) 1247–1252.

[119] Y. Zhang, Y. Hiraishi, H. Wang, K.S. Sumi, Y. Hayashido, S. Toratani, M. Kan, J.D. Sato, T. Okamoto, Constitutive activating mutation of the FGFR3b in oral squamous cell carcinomas, Int. J. Cancer 117 (2005) 166–168.

[120] J. Aubertin, S. Tourpin, F. Janot, J.C. Ahomadegbe, F. Radvanyi, Analysis of fibroblast growth factor receptor 3 G697C mutation in oral squamous cell carcinomas, Int. J. Cancer 120 (2007) 2058–2059.

[121] C. Hafner, J.M. van Oers, T. Vogt, M. Landthaler, R. Stoehr, H. Blaszyk, F. Hofstaedter, E.C. Zwarthoff, A. Hartmann, Mosaicism of activating FGFR3 mutations in human skin causes epidermal nevi, J. Clin. Invest. 116 (2006) 2201–2207.

[122] A. Mandinova, V. Kolev, V. Neel, B. Hu, W. Stonely, J. Lieb, X. Wu, C. Colli, R. Han, M.J. Pazin, P. Ostano, R. Dummer, J.L. Brissette, G.P. Dotto, A positive FGFR3/FOXN1 feedback loop underlies benign skin keratosis versus squamous cell carcinoma formation in humans, J. Clin. Invest. 119 (2009) 3127–3137.

[123] A.H. Jebar, C.D. Hurst, D.C. Tomlinson, C. Johnston, C.F. Taylor, M.A. Knowles, FGFR3 and Ras gene mutations are mutually exclusive genetic events in urothelial cell carcinoma, Oncogene 24 (2005) 5218–5225.

[124] S.A. Byron, M.G. Gartside, C.L. Wellens, M.A. Mallon, J.B. Keenan, M.A. Powell, P.J. Goodfellow, P.M. Pollock, Inhibition of activated fibroblast growth factor receptor 2 in endometrial cancer cells induces cell death despite PTEN abrogation, Cancer Res. 68 (2008) 6902–6907.

[125] K. Yu, A.B. Herr, G. Waksman, D.M. Ornitz, Loss of fibroblast growth factor receptor 2 ligand-binding specificity in Apert syndrome, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 14536–14541.

[126] D.M. Ornitz, P.J. Marie, FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease, Genes Dev. 16 (2002) 1446–1465.

[127] J.G. Taylor, A.T. Cheuk, P.S. Tsang, J.Y. Chung, Y.K. Song, K. Desai, Y. Yu, Q.R. Chen, K. Shah, V. Youngblood, J. Fang, S.Y. Kim, C. Yeung, L.J. Helman, A. Mendoza, V. Ngo, L.M. Staudt, J.S. Wei, C. Khanna, D. Catchpoole, S.J. Qualman, S.M. Hewitt, G. Merlino, S.J. Chanock, J. Khan, Identification of FGFR4-activating mutations in human rhabdomyosarcomas that promote metastasis in xenotransplanted models, J. Clin. Invest. 119 (2009) 3395–3407.

[128] J. Khan, J.S. Wei, M. Ringner, L.H. Saal, M. Ladanyi, F. Westermann, F. Berthold, M. Schwab, C.R. Antonescu, C. Peterson, P.S. Meltzer, Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural networks, Nat. Med. 7 (2001) 673–679.
[129] C. Thussbas, J. Nahrig, S. Streit, J. Bange, M. Kriner, R. Kates, K. Ulm, M. Kiechle, H. Hoefler, A. Ullrich, N. Harbeck, FGFR4 Arg388 allele is associated with resistance to adjuvant therapy in primary breast cancer, J. Clin. Oncol. 24 (2006) 3747–3755.
[130] J. Bange, D. Prechtl, Y. Cheburkin, K. Specht, N. Harbeck, M. Schmitt, T. Knyazeva, S. Muller, S. Gartner, I. Sures, H. Wang, E. Imyanitov, H.U. Haring, P. Knayzev, S. Iacobelli, H. Hofler, A. Ullrich, Cancer progression and tumor cell motility are associated with the FGFR4 Arg(388) allele, Cancer Res. 62 (2002) 840–847.
[131] J.Y. Cha, Q.T. Lambert, G.W. Reuther, C.J. Der, Involvement of fibroblast growth factor receptor 2 isoform switching in mammary oncogenesis, Mol. Cancer Res. 6 (2008) 435–445.
[132] H. Itoh, Y. Hattori, H. Sakamoto, H. Ishii, T. Kishi, H. Sasaki, T. Yoshida, M. Koono, T. Sugimura, M. Terada, Preferential alternative splicing in cancer generates a K-sam messenger RNA with higher transforming activity, Cancer Res. 54 (1994) 3237–3241.
[133] S. Ezzat, L. Zheng, X.F. Zhu, G.E. Wu, S.L. Asa, Targeted expression of a human pituitary tumor-derived isoform of FGF receptor-4 recapitulates pituitary tumorigenesis, J. Clin. Invest. 109 (2002) 69–78.
[134] P. Savagner, A.M. Valles, J. Jouanneau, K.M. Yamada, J.P. Thiery, Alternative splicing in fibroblast growth factor receptor 2 is associated with induced epithelial–mesenchymal transition in rat bladder carcinoma cells, Mol. Biol. Cell 5 (1994) 851–862.
[135] G. Yan, Y. Fukabori, G. McBride, S. Nikolaropolous, W.L. McKeehan, Exon switching and activation of stromal and embryonic fibroblast growth factor (FGF)–FGF receptor genes in prostate epithelial cells accompany stromal independence and malignancy, Mol. Cell. Biol. 13 (1993) 4513–4522.
[136] S. Oltean, B.S. Sorg, T. Albrecht, V.I. Bonano, R.M. Brazas, M.W. Dewhirst, M.A. Garcia-Blanco, Alternative inclusion of fibroblast growth factor receptor 2 exon IIIc in Dunning prostate tumors reveals unexpected epithelial mesenchymal plasticity, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 14116–14121.
[137] E.M. Haugsten, V. Sorensen, A. Brech, S. Olsnes, J. Wesche, Different intracellular trafficking of FGF1 endocytosed by the four homologous FGF receptors, J. Cell Sci. 118 (2005) 3869–3881.
[138] Y. Mosesson, G.B. Mills, Y. Yarden, Derailed endocytosis: an emerging feature of cancer, Nat. Rev. Cancer 8 (2008) 835–850.
[139] K. Haglund, T.E. Rusten, H. Stenmark, Aberrant receptor signaling and trafficking as mechanisms in oncogenesis, Crit. Rev. Oncog. 13 (2007) 39–74.
[140] J.V. Abella, M. Park, Breakdown of endocytosis in the oncogenic activation of receptor tyrosine kinases, Am. J. Physiol. Endocrinol. Metab. 296 (2009) E973–E984.
[141] S. Zisman-Rozen, D. Fink, O. Ben-Izhak, Y. Fuchs, A. Brodski, M.H. Kraus, J. Bejar, D. Ron, Downregulation of Sef, an inhibitor of receptor tyrosine kinase signaling, is common to a variety of human carcinomas, Oncogene 26 (2007) 6093–6098.
[142] S. Darby, T. Murphy, H. Thomas, C.N. Robson, H.Y. Leung, M.E. Mathers, V.J. Gnanapragasam, Similar expression to FGF (Sef) inhibits fibroblast growth factor-induced tumourigenic behaviour in prostate cancer cells and is downregulated in aggressive clinical disease, Br. J. Cancer 101 (2009) 1891–1899.
[143] S. Darby, K. Sahadevan, M.M. Khan, C.N. Robson, H.Y. Leung, V.J. Gnanapragasam, Loss of Sef (similar expression to FGF) expression is associated with high grade and metastatic prostate cancer, Oncogene 25 (2006) 4122–4127.
[144] Y. Wang, D. Becker, Antisense targeting of basic fibroblast growth factor and fibroblast growth factor receptor-1 in human melanomas blocks intratumoral angiogenesis and tumor growth, Nat. Med. 3 (1997) 887–893.
[145] M.J. Birrer, M.E. Johnson, K. Hao, K.K. Wong, D.C. Park, A. Bell, W.R. Welch, R.S. Berkowitz, S.C. Mok, Whole genome oligonucleotide-based array comparative genomic hybridization analysis identified fibroblast growth factor 1 as a prognostic marker for advanced-stage serous ovarian adenocarcinomas, J. Clin. Oncol. 25 (2007) 2281–2287.
[146] M.M. Mattila, P.L. Harkonen, Role of fibroblast growth factor 8 in growth and progression of hormonal cancer, Cytokine Growth Factor Rev. 18 (2007) 257–266.
[147] S.K. Marsh, G.S. Bansal, C. Zammit, R. Barnard, R. Coope, D. Roberts-Clarke, J.J. Gomm, R.C. Coombes, C.L. Johnston, Increased expression of fibroblast growth factor 8 in human breast cancer, Oncogene 18 (1999) 1053–1060.
[148] V. Theodorou, M.A. Kimm, M. Boer, L. Wessels, W. Theelen, J. Jonkers, J. Hilkens, MMTV insertional mutagenesis identifies genes, gene families and pathways involved in mammary cancer, Nat. Genet. 39 (2007) 759–769.
[149] D. Daphna-Iken, D.B. Shankar, A. Lawshe, D.M. Ornitz, G.M. Shackleford, C.A. MacArthur, MMTV-Fgf8 transgenic mice develop mammary and salivary gland neoplasia and ovarian stromal hyperplasia, Oncogene 17 (1998) 2711–2717.
[150] C.A. MacArthur, D.B. Shankar, G.M. Shackleford, Fgf-8, activated by proviral insertion, cooperates with the Wnt-1 transgene in murine mammary tumorigenesis, J. Virol. 69 (1995) 2501–2507.
[151] Z. Song, X. Wu, W.C. Powell, R.D. Cardiff, M.B. Cohen, R.T. Tin, R.J. Matusik, G.J. Miller, P. Roy-Burman, Fibroblast growth factor 8 isoform B overexpression in prostate epithelium: a new mouse model for prostatic intraepithelial neoplasia, Cancer Res. 62 (2002) 5096–5105.
[152] M.P. Valta, J. Tuomela, A. Bjartell, E. Valve, H.K. Vaananen, P. Harkonen, FGF-8 is involved in bone metastasis of prostate cancer, Int. J. Cancer 123 (2008) 22–31.
[153] L.R. Desnoyers, R. Pai, R.E. Ferrando, K. Hotzel, T. Le, J. Ross, R. Carano, A. D'Souza, J. Qing, I. Mohtashemi, A. Ashkenazi, D.M. French, Targeting FGF19 inhibits tumor growth in colon cancer xenograft and FGF19 transgenic hepatocellular carcinoma models, Oncogene 27 (2008) 85–97.
[154] K. Nicholes, S. Guillet, E. Tomlinson, K. Hillan, B. Wright, G.D. Frantz, T.A. Pham, L. Dillard-Telm, S.P. Tsai, J.P. Stephan, J. Stinson, T. Stewart, D.M. French, A mouse model of hepatocellular carcinoma: ectopic expression of fibroblast growth factor 19 in skeletal muscle of transgenic mice, Am. J. Pathol. 160 (2002) 2295–2307.
[155] S. Memarzadeh, L. Xin, D.J. Mulholland, A. Mansukhani, H. Wu, M.A. Teitell, O.N. Witte, Enhanced paracrine FGF10 expression promotes formation of multifocal prostate adenocarcinoma and an increase in epithelial androgen receptor, Cancer Cell 12 (2007) 572–585.
[156] W.M. Abdel-Rahman, J. Kalinina, S. Shoman, S. Eissa, M. Ollikainen, O. Elomaa, A.V. Eliseenkova, R. Butzow, M. Mohammadi, P. Peltomaki, Somatic FGF9 mutations in colorectal and endometrial carcinomas associated with membranous beta-catenin, Hum. Mutat. 29 (2008) 390–397.
[157] J.M. Whitelock, A.D. Murdoch, R.V. Iozzo, P.A. Underwood, The degradation of human endothelial cell-derived perlecan and release of bound basic fibroblast growth factor by stromelysin, collagenase, plasmin, and heparanases, J. Biol. Chem. 271 (1996) 10079–10086.
[158] I. Vlodavsky, M. Elkin, G. Abboud-Jarrous, F. Levi-Adam, L. Fuks, I. Shafat, N. Ilan, Heparanase: one molecule with multiple functions in cancer progression, Connect. Tissue Res. 49 (2008) 207–210.
[159] M.E. Marshall, T.K. Hinz, S.A. Kono, K.R. Singleton, B. Bichon, K.E. Ware, L. Marek, B.A. Frederick, D. Raben, L.E. Heasley, Fibroblast growth factor receptors are components of autocrine signaling networks in head and neck squamous cell carcinoma cells, Clin. Cancer Res. 17 (2011) 5016–5025.
[160] T. Amann, F. Bataille, T. Spruss, K. Dettmer, P. Wild, C. Liedtke, M. Muhlbauer, P. Kiefer, P.J. Oefner, C. Trautwein, A.K. Bosserhoff, C. Hellerbrand, Reduced expression of fibroblast growth factor receptor 2IIIb in hepatocellular carcinoma induces a more aggressive growth, Am. J. Pathol. 176 (2010) 1433–1442.
[161] S.G. Diez de Medina, D. Chopin, A. El Marjou, A. Delouvee, W.J. LaRochelle, A. Hoznek, C. Abbou, S.A. Aaronson, J.P. Thiery, F. Radvanyi, Decreased expression of keratinocyte growth factor receptor in a subset of human transitional cell bladder carcinomas, Oncogene 14 (1997) 323–330.
[162] B. Naimi, A. Latil, G. Fournier, P. Mangin, O. Cussenot, P. Berthon, Down-regulation of (IIIb) and (IIIc) isoforms of fibroblast growth factor receptor 2 (FGFR2) is associated with malignant progression in human prostate, Prostate 52 (2002) 245–252.
[163] Y. Zhang, H. Wang, S. Toratani, J.D. Sato, M. Kan, W.L. McKeehan, T. Okamoto, Growth inhibition by keratinocyte growth factor receptor of human salivary adenocarcinoma cells through induction of differentiation and apoptosis, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 11336–11340.
[164] R. Grose, V. Fantl, S. Werner, A.M. Chioni, M. Jarosz, R. Rudling, B. Cross, I.R. Hart, C. Dickson, The role of fibroblast growth factor receptor 2b in skin homeostasis and cancer development, EMBO J. 26 (2007) 1268–1278.
[165] D. Ricol, D. Cappellen, A. El Marjou, S. Gil-Diez-de-Medina, J.M. Girault, T. Yoshida, G. Ferry, G. Tucker, M.F. Poupon, D. Chopin, J.P. Thiery, F. Radvanyi, Tumour suppressive properties of fibroblast growth factor receptor 2-IIIb in human bladder cancer, Oncogene 18 (1999) 7234–7243.
[166] D. Giri, F. Ropiquet, M. Ittmann, Alterations in expression of basic fibroblast growth factor (FGF) 2 and its receptor FGFR-1 in human prostate cancer, Clin. Cancer Res. 5 (1999) 1063–1071.
[167] S. Nomura, H. Yoshitomi, S. Takano, T. Shida, S. Kobayashi, M. Ohtsuka, F. Kimura, H. Shimizu, H. Yoshidome, A. Kato, M. Miyazaki, FGF10/FGFR2 signal induces cell migration and invasion in pancreatic cancer, Br. J. Cancer 99 (2008) 305–313.
[168] T. Toyokawa, M. Yashiro, K. Hirakawa, Co-expression of keratinocyte growth factor and K-sam is an independent prognostic factor in gastric carcinoma, Oncol. Rep. 21 (2009) 875–880.
[169] K. Cho, T. Ishiwata, E. Uchida, N. Nakazawa, M. Korc, Z. Naito, T. Tajiri, Enhanced expression of keratinocyte growth factor and its receptor correlates with venous invasion in pancreatic cancer, Am. J. Pathol. 170 (2007) 1964–1974.
[170] M. Koziczak, T. Holbro, N.E. Hynes, Blocking of FGFR signaling inhibits breast cancer cell proliferation through downregulation of D-type cyclins, Oncogene 23 (2004) 3501–3508.
[171] M. Mohammadi, Crystal structure of an angiogenesis inhibitor bound to the FGF receptor tyrosine kinase domain, EMBO J. 17 (1998) 5896–5904.
[172] D. Sarker, R. Molife, T.R. Evans, M. Hardie, C. Marriott, P. Butzberger-Zimmerli, R. Morrison, J.A. Fox, C. Heise, S. Louie, N. Aziz, F. Garzon, G. Michelson, I.R. Judson, D. Jadayel, E. Braendle, J.S. de Bono, A phase I pharmacokinetic and pharmacodynamic study of TKI258, an oral, multitargeted receptor tyrosine kinase inhibitor in patients with advanced solid tumors, Clin. Cancer Res. 14 (2008) 2075–2081.
[173] S. Machida, Y. Saga, Y. Takei, I. Mizuno, T. Takayama, T. Kohno, R. Konno, M. Ohwada, M. Suzuki, Inhibition of peritoneal dissemination of ovarian cancer by tyrosine kinase receptor inhibitor SU6668 (TSU-68), Int. J. Cancer 114 (2005) 224–229.
[174] J. Chen, B.H. Lee, I.R. Williams, J.L. Kutok, C.S. Mitsiades, N. Duclos, S. Cohen, J. Adelsperger, R. Okabe, A. Coburn, S. Moore, B.J. Huntly, D. Fabbro, K.C. Anderson, J.D. Griffin, D.G. Gilliland, FGFR3 as a therapeutic target of the small molecule inhibitor PKC412 in hematopoietic malignancies, Oncogene 24 (2005) 8259–8267.
[175] J. Matsui, Y. Yamamoto, Y. Funahashi, A. Tsuruoka, T. Watanabe, T. Wakabayashi, T. Uenaka, M. Asada, E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition, Int. J. Cancer 122 (2008) 664–671.
[176] F. Hilberg, G.J. Roth, M. Krssak, S. Kautschitsch, W. Sommergruber, U. Tontsch-Grunt, P. Garin-Chesa, G. Bader, A. Zoephel, J. Quant, A. Heckel, W.J. Rettig, BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy, Cancer Res. 68 (2008) 4774–4782.

[177] AstraZeneca, http://www.astrazeneca-annualreports.com/2009/additional_information/index.html.
[178] Novartis, http://www.novartisoncology.com/research-innovation/pipeline/bgj398.jsp?usertrack.filter_applied=true&NovaId=2935376892995015019.
[179] O.E. Pardo, J. Latigo, R.E. Jeffery, E. Nye, R. Poulsom, B. Spencer-Dene, N.R. Lemoine, G.W. Stamp, E.O. Aboagye, M.J. Seckl, The fibroblast growth factor receptor inhibitor PD173074 blocks small cell lung cancer growth in vitro and in vivo, Cancer Res. 69 (2009) 8645–8651.
[180] Five-Prime, http://fiveprime.com/index.php?option=com_content&view=article&id=222&Itemid=153.
[181] R. Spielberger, Palifermin for oral mucositis after intensive therapy for hematologic cancers, N. Engl. J. Med. 351 (2004) 2590–2598.