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Fibroblast growth factors, old kids on the new block

Xiaokun Li¹, Cong Wang¹, Jian Xiao¹, Wallace L. McKeehan², and Fen Wang²

¹College of Pharmacy, Wenzhou Medical University, Wenzhou, Zhejiang, China

²Institute of Biosciences and Technology, Texas A&M University Health Science Center, Houston, TX 77030

Abstract

The fibroblast growth factors (FGFs) are a family of cell intrinsic regulatory peptides that control a broad spectrum of cellular activities. The family includes canonic FGFs that elicit their activities by activating the FGF receptor (FGFR) tyrosine kinase and non-canonic members that elicit their activities intracellularly and via FGFR-independent mechanisms. The FGF signaling axis is highly complex due to the existence of multiple isoforms of both ligands and receptors, as well as cofactors that include the chemically heterogeneous heparan sulfate (HS) cofactors, and in the case of endocrine FGFs, the Klotho coreceptors. Resident FGF signaling controls embryonic development, maintains tissue homeostasis, promotes wound healing and tissue regeneration, and regulates functions of multiple organs. However, ectopic or aberrant FGF signaling is a culprit for various diseases, including congenital birth defects, metabolic disorder, and cancer. The molecular mechanisms by which the specificity of FGF signaling is achieved remain incompletely understood. Since its application as a druggable target has been gradually recognized by pharmaceutical companies and translational researchers, understanding the determinants of FGF signaling specificity has become even more important in order to get into the position to selectively suppress a particular pathway without affecting others to minimize side effects.

It has been gratifying for early basic researchers on fibroblast growth factors (FGF) that their Cinderella in the growth factor arena is now drawing so much attention as a druggable target by pharmaceutical companies and translational researchers. The first two prototype FGFs, FGF1 and FGF2, discovered in the early seventies, were designated acidic and basic FGF (aFGF and bFGF) based on their activity to stimulate fibroblast proliferation and their isoelectric point (1, 2). Subsequently 20 more FGF homologues have been identified as the family members in mammals (3–20). Genes coding for a large number of FGFs were cloned based on homology in the amino acid sequence. It was soon found that the name “fibroblast growth factor” was not the best name to describe the diverse functions of the family members and their receptors since many FGFs do not even have receptors expressed in

Corresponding authors: Cong Wang, College of Pharmacy, Wenzhou Medical University, Wenzhou, Zhejiang, China. ; Email: wangcong0814@163.com or Fen Wang, Institute of Biosciences and Technology, Texas A&M University Health Science Center, Houston, TX 77030-3303. ; Email: fwang@ibt.tamhsc.edu.

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fibroblasts and elicit no activity in fibroblasts. In addition, many FGFs induce diverse cellular responses beyond growth promoting signals in different target cells. Despite being misleading to some degrees, the name “fibroblast growth factor” followed by a number (FGF1, 2, 3, 4, etc.) has been preserved and replaced numerous other names used to describe either tissue origin, target, function, or properties of the FGF molecule. FGF signaling has long not been a favorite of pharmaceutical companies largely because of the diversity of both ligands and receptors in the family, its wide range of target cell types, diverse functions, and complexity of FGF signals that intersect either directly or indirectly with multiple pathways. The complexity of the multi-subunit transmembrane FGF signaling complex in both the extracellular and the intracellular portions has also been a major factor. Several cofactors are integral regulatory components of the FGF signaling complex. These include the chemically heterogeneous heparan sulfate (HS) cofactors, and in the case of endocrine FGFs, the Klotho coreceptors. These cofactors and coreceptors not only participate in FGF receptor-binding specificity and affinity, but also in specifying signaling activities. Therefore, a full understanding of the molecular mechanisms underlying the specificity of FGF signaling is important for therapeutic usage of FGFs.

1. FGF signaling axis

FGFs

The FGFs are single chain polypeptides that are tissue regulatory molecules controlling a broad spectrum of cellular processes in both embryonic and adult tissues. The polypeptides have one conserved domain flanked by non-conserved extensions (Fig. 1A). Most FGFs have an N-terminal signal peptide that facilitates secretion through classical mechanisms. However, several FGFs, including FGF1 and FGF2, do not have a cleavable signal peptide and are secreted in a non-conventional manner. Seven FGF subfamilies have been defined based on their sequence homology and function (Fig. 1B). These FGF subfamilies can also be divided into two general groups, the canonical FGFs comprising paracrine or autocrine-acting FGF1–10, FGF16–18, FGF20, and FGF22 and the endocrine-acting FGFs, FGF15 (mouse)/FGF19 (human), FGF21, and FGF23; and the non-canonical FGFs comprising FGF11–14. The canonical FGFs elicit regulatory functions through high affinity binding to and activating FGF receptors (FGFR). An autocrine canonical FGF acts on the cells of origin as a self-stimulator, and a paracrine FGF is secreted by one cell and acts on another locally within tissues. In contrast, the endocrine FGF originates at a distal organ site and reaches the target through the blood circulation in a classical endocrine mode of action. The non-canonical FGFs do not bind to the FGFR but elicit their activities intracellularly, such as through interaction with voltage-gated sodium channels and calcium channels (21–23).

FGFRs

The FGFR is a single chain transmembrane tyrosine kinase that consists of a ligand binding extracellular domain, a single transmembrane domain, and an intracellular tyrosine kinase domain that is separated into two parts by an insertion domain (Fig. 2). The mammalian FGFR is encoded by four highly homologous genes (24–27). Except for the *Fgfr4* gene for which only one splice isoform occurs naturally (28), other three *Fgfrs* have been found to encode multiple splice variants. These splice variants generate diversity of sequence and

function in the ligand-binding extracellular domain and the intracellular substrate-binding and kinase domains (29). It has been speculated that the combination of FGFR1 splice variation sequences can potentially encode up to 256 splice isoforms (29). FGFR3 and FGFR4 have 3 immunoglobulin (Ig)-like domains in the extracellular domains. As a consequence of alternative splicing, the extracellular domain of both FGFR1 and FGFR2 can contain either 2 or 3 Ig-like loops. The presence of the first Ig-loop modulates the affinity for both FGF and FGFR-binding heparin/heparan sulfate (30–32). Two major isoforms generated by alternative splicing in the second half of Ig-loop III, namely IIIb and IIIc in FGFR1, FGFR2, and FGFR3 have been reported. This variation defines ligand-binding affinity and specificity of FGFR1–3 (33, 34). Several other splice variations at the extracellular domain have been found in FGFR2, although the functional significance of these variants remains unknown (35). The role of the alternatively spliced dipeptide VT (valine-threonine) in the intracellular juxtamembrane domain of FGFR is controversial. It has been shown that the presence of VT is required for FGFR to bind FRS2 α and FRS2 β and therefore contributes to signaling specificity (36, 37). However, other reports show that the dipeptide is dispensable for the binding of FRS2 α and FRS2 β to FGFR1 even though it enhances the binding affinity between substrate and the receptor kinase (38). The variations in the kinase domain and C-terminal tail following the kinase domain of FGFRs have only been found in cancer cells (29, 39). Although the kinase domains of the four FGFR isotypes are highly homologous (>80%) in the primary amino acid sequence and share common tyrosine phosphorylation sites (Fig.2), the four FGFRs elicit receptor-, cofactor-, coreceptor-, and cell type-specific activities in cells (40–43). Seven major tyrosine autophosphorylation sites have been identified in the FGFR1 kinase domain (44–47). Y (tyrosine) 653 is predominant in activation (derepression) of the receptor kinase activity (44–47) while Y654 contributes to maximal activation (48). Phosphorylation of Y766 is required for recruiting phospholipase C γ (PLC γ) via its SH2 domains to the FGFR1 kinase (49–51). Y463 is a binding site for the adapter proteins CRK and CRK-like (52–54) and phosphorylated Y730 is a binding site for the 85 kDa regulatory subunit alpha of phosphatidylinositol 3-kinase (PI3K) (45, 49, 55). The function of other phosphorylation sites, including Y583, and Y585 has not been clearly established, despite some evidence that they contribute to the intensity and extent of FGFR signaling (48). An FGFR2 splice variant that lacks exon 16 has been reported in prostate epithelial cells, which does not have the PLC γ -binding site (56). The significance of this splice variant remains to be elucidated.

Heparan sulfate (HS) cofactors

HS is the glycan component of proteoglycans in the pericellular matrix and on the cell surface. It is a highly heterogeneous glycosaminoglycan (46, 57–59). Variations in degrees and patterns of sulfation on HS motifs affect their interaction with FGFs and FGFRs and have been shown to play a role in determination of ligand-binding and downstream signaling specificity of FGFR complexes (60–65). Although HS motifs with high affinity for FGFs and FGFRs are normally sulfated, emerging evidence shows that the affinity is not simply proportional to total charge density and degree of sulfation. Instead, these high-affinity motifs are often less than fully sulfated and have unique sulfation patterns (66, 67). Because of affinity for both FGF and FGFR, HS in the tissue environment largely plays two general roles that impact overall FGFR signaling. Tissue matrix HS acts as an FGFR-independent

depot and stabilizes influence for canonical paracrine/autocrine FGFs (68, 69). It limits access of FGF that are generally long-lived and at considerable concentrations in the matrix to cell membrane FGFR except when needed (46). The second role is as an integral part of the FGF signaling complex through a distinct HS-binding domain in the extracellular domain of FGFR. Motifs within this class of HS are thought to be less abundant and potentially more specific than matrix HS (66, 67). FGFR-bound HS interacts concurrently with both FGFR and FGF within the FGF-FGFR-HS signaling complex.

Both our early models based on protein mutagenesis and *in silico* modeling (70, 71) and the crystal structure (72) of the FGF2-FGFR1c-HS complex show a 2-2-2 complex of FGF-FGFR-HS, in which one single heparan sulfate chain may contact Ig-loop II of one FGFR, the inter-Ig-loop connector sequence and Ig-loop III of the same FGFR, and extend to Ig-loop III of the adjacent FGFR in the FGFR dimer. Ig loops II and III cooperate both within monomers and across dimers with cellular HS to confer cell type-dependent specificity of the FGFR complex for FGF ligands (73). It is unclear whether FGF stabilizes proximity of random interactions of monomeric units or activates a pre-existing inactive oligomeric complex of HS-FGFR via conformation changes (46, 61, 66, 67). However, emerging data pose that together with HS, the FGFR forms a dimer constitutively in the absence of FGF (70, 71, 74). Interaction with HS restrains FGFR dimers in an inactive conformation and FGF binding converts the HS-FGFR complex from the inactive repressed conformation to an active arrangement that allows an initial trans-phosphorylation between the kinase domains of FGFR dimers. Structural studies indicate that trans-phosphorylation of tyrosine 653 and then 654 (in FGFR1) changes conformation of an autoinhibitory loop within the kinase domain that normally restricts access of substrates to the active site of the FGFR kinases (48, 75).

Klothos

Unlike paracrine/autocrine FGFs, the endocrine FGFs, FGF15/FGF19, FGF21, and FGF23 have little or no affinity for HS (76). This property permits their endocrine circulation and movement through tissue matrices without being trapped and stored prior to reaching distal target cells. The specificity of endocrine FGF signaling at the cellular level is directed by a family of membrane-anchored proteins that include α Klotho (α KL) and β Klotho (KLB). Although endocrine FGFs signal through the same FGFR as canonical FGFs, they have little affinity for FGFR in the absence of Klothos. KLB interacts with FGFR independent of FGF and with FGF independent of FGFR (77–79). Although α KL binds the extracellular domain of FGFR1, it poorly interacts with FGF23. Instead, binding of α KL with FGFR1 forms a *de novo* site generated at the composite FGFR1c- α KL interface, which binds the C-terminal domain of FGF23 (80). Thus, the major role of α KL and KLB is to facilitate high affinity binding and subsequent activation of FGFRs by endocrine FGFs. α KL specifically facilitates binding of FGF23 to its receptor and controls mineral metabolism via a vitamin D controlled bone to kidney axis where α KL is expressed (81). Inactivation of α KL induces hyperphosphatemia in mice that highly express FGF23 (82). The cofactor KLB facilitates high affinity binding and signaling of FGF19 (mouse FGF15) and FGF21 and controls cholesterol/bile acid, lipid, and glucose metabolism in the liver and adipocytes (83).

Expression of neither KLB nor FGFR4 alone affects cell population dynamics in KLB- and FGFR4-deficient cells. However, co-expression of KLB and FGFR4 restricts cell population growth via apoptosis in an endocrine FGF19 or FGF1 dependent manner (84). This indicates that the KLB interaction with the FGFR4 tyrosine kinase complex not only serves to confer high affinity for endocrine FGF19, but also plays a role in directing signaling of the FGFR4 complex independent of the activating FGF (84, 85).

The FGF signaling pathways

The signaling cascade downstream of the transmembrane receptor, including PLC- γ , MAP kinase, and PI3K pathways have been implicated in all four FGFR kinases (Fig. 3). Among them, PLC- γ binds to a specific phosphorylated tyrosine residue at the C-terminal tail of the FGFR kinases (50, 51). However, the MAP kinase and PI3K pathways need to be recruited to the FGFR by a membrane-anchored adaptor protein, FRS2 α (FGF receptor substrate 2 α), which undergoes an extensive pattern of tyrosine and serine/ threonine phosphorylation upon FGFR activation (86–93). In addition, CRK has also been proposed to serve as a functional adaptor that binds to the FGFR (52), which has been reported to further link the ERK pathway to FGFR1. The activation of the ERK pathway by the FGFR tyrosine kinase is tightly regulated by both positive and negative feedback loops at both transcriptional and post translational levels (Fig. 3). Sprouty (SPRY) proteins, which comprise four conserved members, SPRY1–4, present a feedback regulator of the FGF pathway at the posttranslational level (94). Tyrosine phosphorylation of SPRY creates a decoy site that binds the docking molecule GRB2 and prevents translocation of SOS to the plasma membrane to activate RAS. SEF (similar expression of FGF) inhibits binding of FRS2 α to the FGFR and prevents activation of ERK, and, therefore, negatively regulates the RAS-MAPK pathway (95, 96). Activation of the ERK and PI3K/AKT pathways has been implicated in most FGFR regulatory functions. Deletion of the PLC γ binding site on FGFR1 does not affect FGFR1-elicited cellular responses, which include mitogenesis, neuronal differentiation, mesoderm induction, induction of urokinase-type plasminogen activator, and chemotaxis. However, the PLC- γ binding site is required for FGFR1 to induce benign prostate cancer cells to acquire the proliferative response to FGFR1, although it appears not to be required for the mitogenic response (97). This suggests that pathways linked to FGFR1 Y766 contribute to prostate cancer progression rather than playing a direct role in cell cycle and mitogenesis. Experiments with purified recombinant FGFRs *in vitro* or when overexpressed at high levels in cell lines, such as Sf9 insect cells or COS7 mammalian cells, indicate that the four FGFR isotypes exhibit similar if not identical substrate phosphorylation patterns (Wang, unpublished results). However, in the experiments with moderate expression levels in cells, the results are not consistent. In some experimental systems, the four FGFR isotypes elicit similar and redundant effects on cell phenotypes, and in others, exert different effects (40). Overexpression of the FGFR kinase at levels far beyond the minute normal cellular levels likely homogenizes and masks receptor and cell type specific effects of the different FGFR kinases. More sensitive analytical approaches *in situ* as well as robust and controlled experimental systems that hold promise of revealing and dissecting such differences are needed for developing FGFR isotype- and cell type-specific inhibitors or activators.

The FRS2 family is composed of two highly homologous members, FRS2 α and FRS2 β , which belong to a category of adaptor proteins that have binding sites for molecules both upstream and downstream of it in signaling networks. It physically presents downstream molecules to the upstream molecules. Depletion of FRS2 α abrogates the ability of FGFR kinases to activate the MAP kinase and PI3K/AKT pathways (Wang, unpublished data). Ablation of *Frs2a* in mice causes severe defects in embryonic development and results in early embryonic lethality at E7.0–7.5 (98). Although it is not clear whether the two FRS2 members are functionally redundant, expression of FRS2 β in FRS2 α -deficient cells restores the ability of FGFR1 to activate both the MAPK and PI3K/AKT pathways (99). In addition, FRS2 α is also engaged in the feedback regulation of the FGF signaling pathway (100, 101). As illustrated in Fig. 3, FRS2 appears to be the key adaptor protein in the FGFR signaling cascade that mediates multiple downstream pathways of the FGFR, as well as control of the amplitude of the signaling intensity. However, whether FRS2 is also involved in the receptor and cell type specificity of signaling elicited by the FGFR kinases remains to be elucidated.

2. Translational application of the FGFs and their signaling pathways

Aberrant FGF signaling in diseases

In embryos, the FGF, FGFR kinase, and heparan sulfate components of the FGF signaling complex are expressed in a spatiotemporally- and cell-specific pattern that changes constantly as development proceeds. In adult organs, components of the FGF signaling axis are expressed in a cell type-specific mode and are important in the mediation of external signals and communication within compartments that maintain tissue homeostasis and function. Abnormal expression of FGF and FGFR and aberrant activation of the FGF signaling axis are frequently found associated with various adult tissue-specific pathologies and cause developmental disorders (40, 46, 53, 102–110). The subversion of the homeostasis-promoting activity of resident epithelial FGFR2 in a variety of tissues (40, 41, 46, 111) and concurrent ectopic expression of normally mesenchymal FGFR1IIIc in epithelial cells (40, 112–115) is often found associated with tumor progression. Changes in core protein expression of HS proteoglycans as well as sulfation patterns have been reported to contribute to progression of premalignant tumor cells to malignancy (46). Currently, extensive efforts have been taken to explore the translational application of manipulation of the FGF signaling activities, both using the FGF directly and chemical agonists or antagonists as in the areas summarized hereafter. As a heparin-binding protein, delivery of heparin-binding FGF through the circulation and the tissue matrix remains a challenging issue. Treating large traumatic tympanic membrane perforation with FGF2 improved closure rates compared with the control group (116). Recently, new technologies, including multi-walled carbon nanotubes, have been used to deliver FGF2, which improves bone regeneration in animal models (117, 118).

Wound healing

As potent mitogenic factors, both FGF1 and FGF2 have been extensively explored for their potential in wound healing. FGF1 induces cell proliferation in the wounded area and promotes the cells to produce cytokines and other growth factors that induce migration of macrophages and monocytes towards the wounded area to remove damaged or dead cells

(119, 120). FGF1 also induces epithelial cells and vessel endothelial cells to migrate toward the healing tissues. True to its original name, FGF promotes growth and differentiation of fibroblasts, and induces cells to release collagenase and plasminogen activators to promote angiogenesis in the wounded tissues (121, 122). In addition, FGF1 also down regulates α I procollagen expression and suppresses collagen production and deposit in fibroblasts and therefore prevents scar formation (123, 124).

Recombinant FGF1 and 2 (rFGF1 and rFGF2) have been developed for clinical trials in several countries. Since 1992, recombinant FGF2 has been used in several hospitals in China, and the results show that recombinant FGF2 improves healing in burn trauma, skin flap grafts, intractable cerebrospinal fluid rhinorrhea, intractable skin ulcer, postoperative mastoid cavity problems, pressure ulcers, chronically ischaemic tissue and traumatic ulcers, bone fracture, periodontitis-induced damage of human periodontal tissue, diabetic gangrene, diabetes-related chronic ulcers, peripheral artery disease, and gastric ulcers (124–149). The outcomes of the clinical trials demonstrate that FGF2 can be used as an agent to accelerate the healing of fresh and chronic wounds and improve the quality of healing of wounds of diverse types. In addition, FGF1 has been shown to elicit modest nerve regeneration after spinal cord injury (150). FGF7 acts exclusively through a subset of FGF receptor isoforms (FGFR2b) and has been developed by Amgen (palifermin) to prevent and speed up the healing of severe sores in the mouth and throat caused by chemotherapy and radiation therapy, which are used to treat cancers of the blood or bone marrow (151–156).

Cardiac protection

Heart failure also called congestive heart failure or congestive cardiac failure occurs when the heart fails to pump sufficient blood to meet the needs of the body. It remains a major cause of morbidity and mortality and causes critical health problems especially in Western societies. Reduction in the efficiency of the myocardium through overloading or damage leads to cardiac hypertrophy and fibrosis, which subsequently progresses to heart failure. Several members of the FGF family, including FGF1, FGF2, FGF5, FGF16, FGF21, and FGF23 have been shown to play roles in the heart. FGF signaling is essential for cardiomyocyte homeostasis through phosphorylating connexin 43 (Cx43), which is required for the maintenance of gap junctions (157). FGF1 is released from the myocardial tissue into pericardial fluid during severe myocardial ischemia (158).

Treatment with biodegradable hydrogel microspheres containing FGF2 improved left ventricle function and inhibited left ventricle remodeling by angiogenesis in pigs with chronic myocardial infarction (159). Intramyocardial injection of FGF-2 plus heparin suppresses the progression of cardiac failure in rat models (160). Similarly, treating pigs with adenovirus carrying FGF5 cDNA improves wall-thickening and cardiac function (161). In humans, FGF treatment has likewise shown cardioprotective effects: a single intracoronary infusion of rFGF2 shows trends toward symptomatic improvement of angina and myocardial function in patients with advanced coronary artery disease (162). Treatment of patients with a bicistronic VEGF/FGF2 plasmid improves cardiac function with respect to exercise tolerance and clinical symptoms (163). Intracoronary administration FGF-2 in patients with severe ischemic heart disease increases regional wall thickening and reduces

the extent of the ischemic area (164). Treatment with Ad5-FGF4 results in favorable anti-ischemic effects (165). All these initial small and unblinded studies with FGF proteins or encoding cDNAs were encouraging and demonstrated both clinical improvement and evidence of angiogenesis. However, subsequent double-blind placebo-controlled trials did not confirm the initial high efficacy observed in the small trials (166). Future larger trials are needed to confirm whether FGF treatment is efficacious, safe, and practical for the heart failure patients.

Metabolic disorders

The FGFs are best known for their diverse roles in mediating cellular homeostasis through short-range cell-to-cell communication within tissues (167). However, FGF19 (or mouse FGF15), FGF21, and FGF23, have been identified as endocrine hormones since they originate in tissues distal to the metabolic organs they target and are transported through the circulation (17, 168–171). A diurnal physiologic role of the ileal FGF19-hepatocyte FGFR4 axis in bile acid metabolism during normal feeding has been established (169, 172). FGF21 regulates energy homeostasis mainly through activating the FGFR1/KLB complex in adipocytes (173), and represents a novel target for the development of therapies for the treatment of obesity, diabetes, and cardiovascular diseases.

Expression of FGF21 is controlled by a complex network of transcriptional regulators, which modulate FGF21 expression in response to a wide array of physiological stimuli or pharmacologic agents (174). The function of FGF21, if any, in normally fed mice is not clear. Generally, the liver FGF21-adipocyte FGFR1 signaling axis appears to come into effect only after prolonged starvation, when it uncouples lipid metabolism between the adipocytes and hepatocytes, prolonging the supply of lipid fuels to maintain lifesaving glucose levels as long as possible until a feeding opportunity arises (175). When administered, both FGF19 and FGF21 dramatically reverse obesity and its associated symptoms, including type 2 diabetes (176–178). Studies with tissue-specific *Fgfr1*-knockout animals have revealed that the adipocyte, via FGFR1, is the specific target of FGF19 and FGF21 that alleviates obesity and allied symptoms (173, 175, 179). Although several reports show that FGF21 controls ketogenic and triglyceride clearance in the liver (180–183), unlike FGF19, FGF21 is unable to bind FGFR4-KLB complex with affinity comparable to FGFR1-KLB (83, 170, 184, 185). Therefore, at physiological concentrations, FGF21 is unlikely to signal in the liver where FGFR4-KLB predominantly resides. It has been shown that the metabolic effects of FGF21 on glucose homeostasis and insulin sensitivity are mediated in part by controlling adiponectin production and release in adipocytes (186, 187). More recently, it has been shown that FGF21 is produced by a variety of tissues other than liver under other than extreme metabolic conditions as starvation or obesity (188). The common features of the conditions that elicit FGF21 in organisms cause diverse tissue and cellular stress. Thus it has been proposed that FGF21 is largely a stress hormone that calls on adipocytes and its metabolic and hormonal secretory products (adipokines) to alleviate diverse tissue stresses (188). Although numerous reports (189) suggest FGF21, which requires FGFR1-KLB, may directly target other tissues than adipocytes that are very low in KLB, the significance relative to adipocytes on overall FGF21 action remains to be determined.

Endocrine FGF19 and FGF21 act on the same FGFR1 that also mediates the effects of paracrine/autocrine FGFs on cellular homeostasis in developing and mature organs as well as driving numerous proliferative pathologies, such as cancer. However, the canonical cellular activities of FGF19 and FGF21, most prominently their mitogenicity, are prevented by the transmembrane co-factor KLB, which participates directly in the FGFR signaling complex and redirects its output to metabolic signaling (79, 84, 176). Co-expression of KLB directs FGFR4 signaling from growth-controlling to apoptosis-promoting, which may explain why FGFR4 elicits specific cellular context control of cell population expansion and tumor suppression rather than tumor promotion (84). Breast tumor progression in *Fgfr4* null mice is delayed rather than accelerated (190). This correlates with a fortuitous chronic compensatory elevation of ileal FGF19 and an unexpected chronic elevation of circulating FGF21 in the FGFR4-knockout model (191), indicating that persistently elevated FGF19 and FGF21 has a tumor suppressive effect. The persistent elevation of FGF21 in cancer is consistent with its overall role as a stress hormone since cancer is a major source of stress on the organism affecting many tissues.

Obesity and its associated aspects of metabolic syndrome are strong promoters for several cancers, which include breast and prostate cancer. Normally, FGF19/FGF21 serves to maintain normal metabolic homeostasis between adipocytes and other tissues, primarily hepatocytes. Antitumorigenic effects of FGF21 may occur systemically through fat tissues and locally distributed adipocytes, via regulating release of their metabolites and adipokines, which affect tumor cells directly or indirectly by changing the tumor microenvironment (Fig. 4). Although FGF19 directly regulates specific aspects of hepatic contribution to metabolic homeostasis, FGF21 has exquisite specificity for adipocytes via FGFR1/KLB without direct effects on hepatic FGFR signaling. This very narrow physiologic role of FGF21 and adipocyte target specificity makes it especially attractive as a pharmacologic antiobesity, antidiabetic, and now antitumor agent for which few side effects are predicted.

Aberrant FGF signaling in cancer

Ectopic expression of FGF ligand or receptor, as well as mutations in the FGFR that cause activation of the FGF/FGFR signaling axis is common in many epithelial cancers including hepatocellular carcinoma, melanoma, lung, breast, bladder, endometrial, head and neck, and prostate cancers (192). Point mutations causing constitutive activation of FGFR3 have been detected in more than 60% of non-muscle invasive urothelial carcinomas (193), and a point mutation in the transmembrane domain of *Fgfr4* has been reported in human prostate carcinoma (194). Gene amplification and mutations in the intronic sequence leading to overexpression of FGFR tyrosine kinases is also a mechanism underlying excessive FGF signaling in cancer. For example, amplification of chromosomal region 8p11–12, which encompasses *Fgfr1*, is frequently found in human prostate carcinoma (195) and approximately 10% of breast carcinomas (192), a point mutation in intron 2 of the *Fgfr2* alleles has been found associated with breast cancer (196). Alternative splicing of FGFR resulting in variants with altered ligand specificities constitutes the third mechanism leading to aberrant FGF signaling in cancer (192). In addition, downregulation of feed-back controllers of FGF signaling, such as Spry or SEF can also contribute to oncogenic activity of FGF signaling (197).

Aberrant FGF signaling has been implicated in prostate carcinoma development and progression (40, 112, 198, 199). Elevated production of FGF ligands by prostatic secretory epithelial cells creates an autocrine signaling loop stimulating aberrant epithelial growth and cellular dysplasia and promoting independence from stromal regulation. Upregulation of FGF family members in primary prostate cancer correlates with higher grades of cancer and clinical stage (197, 200). FGF8 is expressed at low levels in normal prostate. However, FGF8 and its cognate receptors are overexpressed in human samples of prostatic intraepithelial neoplasia (PIN) and prostate carcinoma (201–204). Furthermore, overexpression of FGF8 is associated with decreased patient survival (205). Exogenous FGF1 induces expression of matrix metalloproteinases and promotes tumor metastasis in prostate carcinoma cells (206). Overexpression of FGF9 augments reactive stroma formation and promotes cancer progression in mouse models of prostate carcinoma (207). Attenuating FGF2 activity inhibits cell proliferation, migration, and invasion in cell culture (208, 209). Consistent with this, ablation of FGF2 inhibits prostate tumor progression in the TRAMP transgenic mouse model of prostate cancer (210). In addition, hyperactivation of the FRS2 α -mediated pathway increases tumor angiogenesis and predicts poor outcomes of prostate carcinoma patients (211).

FGFs also have a role in the development of bone metastases, which occur in approximately 80% of patients with advanced prostate cancer (212). These metastases often abnormally express FGF8 and/or FGF9, which promote osteoblast proliferation/differentiation in culture (213, 214). Forced expression of FGF8 promotes bone growth of prostate carcinoma in a mouse model (215). Advanced prostate cancer is frequently resistant to castration. Multiple FGFs have been reported to be aberrantly expressed in castration-resistant (205, 216, 217) or chemotherapy resistant prostate cancer (218, 219). Inhibition of FGF8 and FGF9 signaling has an antitumor effect in mouse models of castrate-resistant prostate cancer (213, 220).

Dysregulated expression of FGFRs has also been associated with prostate cancer. Overexpression of FGFR1 has been found in human prostate cancer and accelerates tumor progression of rat premalignant prostate epithelial cells (40, 115). Exposure to aberrant FGFR1 signaling leads to dosage- and time-dependent lesions of prostate, ranging from low-grade PIN to carcinoma *in situ* of the prostate, invasive carcinoma, and metastasis. Forced expression of constitutively active mutants of FGFR1 leads to development of high-grade PIN lesions (221, 222). JOCK-1 is a transgenic mouse model overexpressing an FGFR1 kinase construct, iFGFR1, which contains the membrane anchored FGFR1 intracellular kinase domain in frame fused with a 12 kDa FK506 binding protein (FKBP12) at the C-terminus. Treating the mice with FK506, a dimer inducer to activate the FGFR1 kinase, causes the mice to develop invasive prostate carcinoma and metastasis (223). On the other hand, deletion of *Frs2 α* or *Fgfr1* in prostate epithelial cells inhibits the initiation and progression of prostate cancer in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model (224, 225). Tissue recombination experiments *in vitro* also show that ectopic FGFR1 is required for prostate cancer initiation and progression (226). Epithelial-mesenchymal transition (EMT) is a process whereby polarized epithelial cells lose epithelial characteristics and acquire mesenchymal features, including enhanced migratory capacity, invasiveness, and elevated resistance to apoptosis (227). Shifts in alternative splicing of FGFR1 and FGFR2 from IIIb (epithelial) to IIIc (mesenchymal) isoforms are associated

with EMT in prostate and other types of cancer (228). In contrast, downregulation of epithelial cell resident FGFR2 is associated with prostate cancer progression (40, 114). Together, these data suggest that aberrant activation of FGFR1 signaling is sufficient to disrupt prostate tissue homeostasis leading to over-proliferation of prostate cells, and contribute to initiation and progression of the lesion to malignancy in mouse models of prostate cancer.

In contrast to ectopic FGFR isoforms, however, resident FGFR signaling in prostate cells maintains tissue homeostasis, communication with stromal cells, and mediates androgen signaling. The stromal FGF7/FGF10 to epithelial FGFR2 signaling axis maintains prostate tissue homeostasis and mediates androgen signaling in the epithelial cells. Therefore, both FGF7 and FGF10 have been called andromedins (112, 199). Although ablation of *Fgfr2* was insufficient to cause full progression to carcinoma, it leads to development of low-grade PIN (Wang and McKeehan, unpublished data). The epithelial FGF9 to stromal FGFR3 signaling axis is engaged in communication between epithelial and stromal cells in the prostate and is lost in advanced prostate cancer. Reinstatement of this signaling axis in advanced rat prostate cancer cells restores the interactions between cancer cells and stromal cells and induces prostate cancer cell differentiation in the Dunning R3327 rat prostate cancer model (216).

FGF pathway inhibitions in cancer treatment

A number of targeted agents that inhibit FGF/FGFR signaling have been developed, which include tyrosine kinase inhibitors (TKIs), monoclonal antibodies, and FGF ligand traps. The TKIs include both ATP binding site and non ATP binding site molecules. With the exception of AZD4547 that is relatively FGFR specific (229, 230), most ATP binding site inhibitors, including dovitinib (TKI258), nintedanib (BIBF 1120), lenvatinib, brivanib, orantinib, and PD173074, cross-inhibit multiple receptor tyrosine kinases (231–237). Non-ATP binding site inhibitors of FGFR kinase may exhibit a better specificity than the ATP-binding site inhibitors. Several non-ATP binding site inhibitors have been developed, which include L6123, Aea4, Aea25, A114, and A117 (238–240). All these non-ATP binding site inhibitors exhibit highly FGFR kinase specific inhibitory activities and suppress cancer cell proliferation, migration, and induce cell apoptosis. It remains to be determined, however, whether these non-ATP binding site inhibitors are safe and efficacious for use on cancer patients.

In addition to kinase inhibitors, several strategies have also been developed to block ligand-receptor binding, which includes antibodies against FGF or FGFR, ligand traps, and small peptides that compete with FGF for binding to the receptors. MFGR1877S is a monoclonal antibody against FGFR3 that is currently undergoing phase 1 testing for patients with advanced solid tumors (241). Both the GP369 antibody that specifically blocks FGFR2 IIIb isoform and the 1A6 antibody that neutralizes FGF19 activities are currently in preclinical development (242, 243). The fusion protein HGS1036 (FP-1039) comprises the extracellular domain of FGFR1c fused with the Fc portion of IgG1, is expected to trap FGF ligands for the FGFR1IIIc isoform and functions as a decoy receptor. It inhibits tumor cell proliferation and blocks angiogenesis and suppresses growth of patient-derived xenograft tumor models

of various tissue origins (244). It has been shown to cause shrinkage of prostate cancer in a phase 1 clinical trial (245). Two short peptides, P8 (PLLQATAGGGS) that binds to FGF2 and P7 (LSPPRYYP) that binds to FGFR1 were identified by screening a phage display library using FGF2 and FGFR1 as the bait, respectively (246, 247). Both peptides exhibit activities to suppress FGF2–FGFR1 binding and block FGF2-induced cell proliferation activity without cytotoxic effect in multiple cell lines. The clinical application of these two peptides in cancer treatment is currently being explored.

3. Perspective

Soon after its discovery in the early seventies, the FGF family was recognized to elicit a broad spectrum of regulatory activities. There are few tissues where no members of this large family are expressed or have an impact on some tissue response marker. Often multiple members of the family, both ligands and receptor isoforms, are co-expressed although they are most commonly cell-specific and compartmented when examined more closely. Cell culture analyses in the absence of physiological restrictions often indicate a considerable redundancy among the family members. However, as FGF family member expression and associated activities have been more closely dissected under physiological conditions, results have indicated an increasing degree of receptor isoform- tissue and cell type contextual specificity. Aberrant and ectopic expression of FGF signaling has been reported as a causal factor for multiple diseases, including cancer. Yet, the determinants of FGF isotype and cell type signaling specificity are poorly understood. It is particularly challenging to understand how the same FGFR isotype can have diverse and often opposing biological endpoints. Sometimes the endpoints are temporally dependent on the point at which activation begins and how long it is sustained. Little is known with respect to kinase-substrate specificity of the FGFR tyrosine kinases, although emerging evidence shows that FGFR elicits isoform-specific activities. The role of co-factors and co-receptors, such as heparan sulfate proteoglycans and Klothos, in FGF signaling specificity should not be ignored. In fact, it has been reported that with or without co-expression of KLB, FGFR4 elicits different activities in 293 cells (84). In addition, heparan sulfates affect ligand binding specificity of the FGFR, and it remains to be investigated whether heparan sulfates also contribute to signaling specificity at the substrate level. Understanding the signaling specificity of the FGF signaling axis will provide new strategies for developing drugs that will selectively suppress a particular pathway to minimize side effects. As new technologies emerge, unraveling the “gaitou” of FGF signaling specificity is no longer a dream. Therefore, future applications of FGF, the new focus in the pharmaceutical arena, for improving wound healing, alleviating damages of cardiovascular diseases, controlling obesity and diabetes, and suppressing cancer progression and metastasis are visible on the horizon.

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A**B**

Autocrine/Paracrine FGF

- **FGF1 subgroup: FGF1, FGF2,**
- **FGF3 subgroup: FGF3, FGF7, FGF10, FGF22**
- **FGF4 subgroup: FGF4, FGF5, FGF6**
- **FGF8 subgroup: FGF8, FGF17, FGF18**
- **FGF9 subgroup: FGF9, FGF16, FGF20**

Endocrine FGF

- **FGF15/FGF19, FGF21, FGF23**

Non canonical FGF

- **FGF11, FGF12, FGF13, FGF14**

Fig. 1. The FGF family

A. Schematic of the FGF. Red box, signal peptide; open boxes, non-conserved, N- and C-terminal domains; solid box, conserved core domain. **B.** FGF sub-families. The 22 FGFs are grouped into 7 subfamilies based on sequence homology and function.

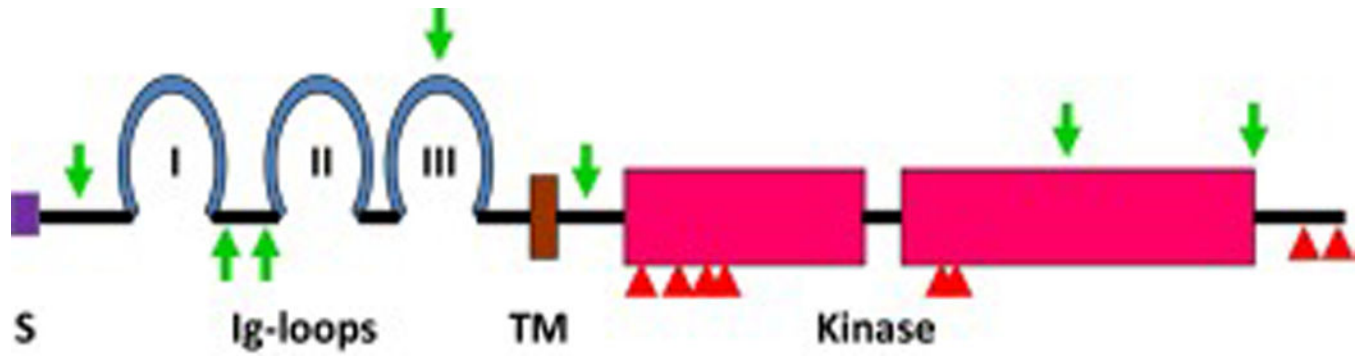


Fig. 2. Topology of a prototypical FGF receptor tyrosine kinase

S, signal peptide; I, II, III, immunoglobulin-like domain 1, 2, and 3; TM, transmembrane domain. Red box, tyrosine kinase domain that is separated by a kinase insertion sequence; green arrows, alternative splice sites; triangles, tyrosine phosphorylation sites.

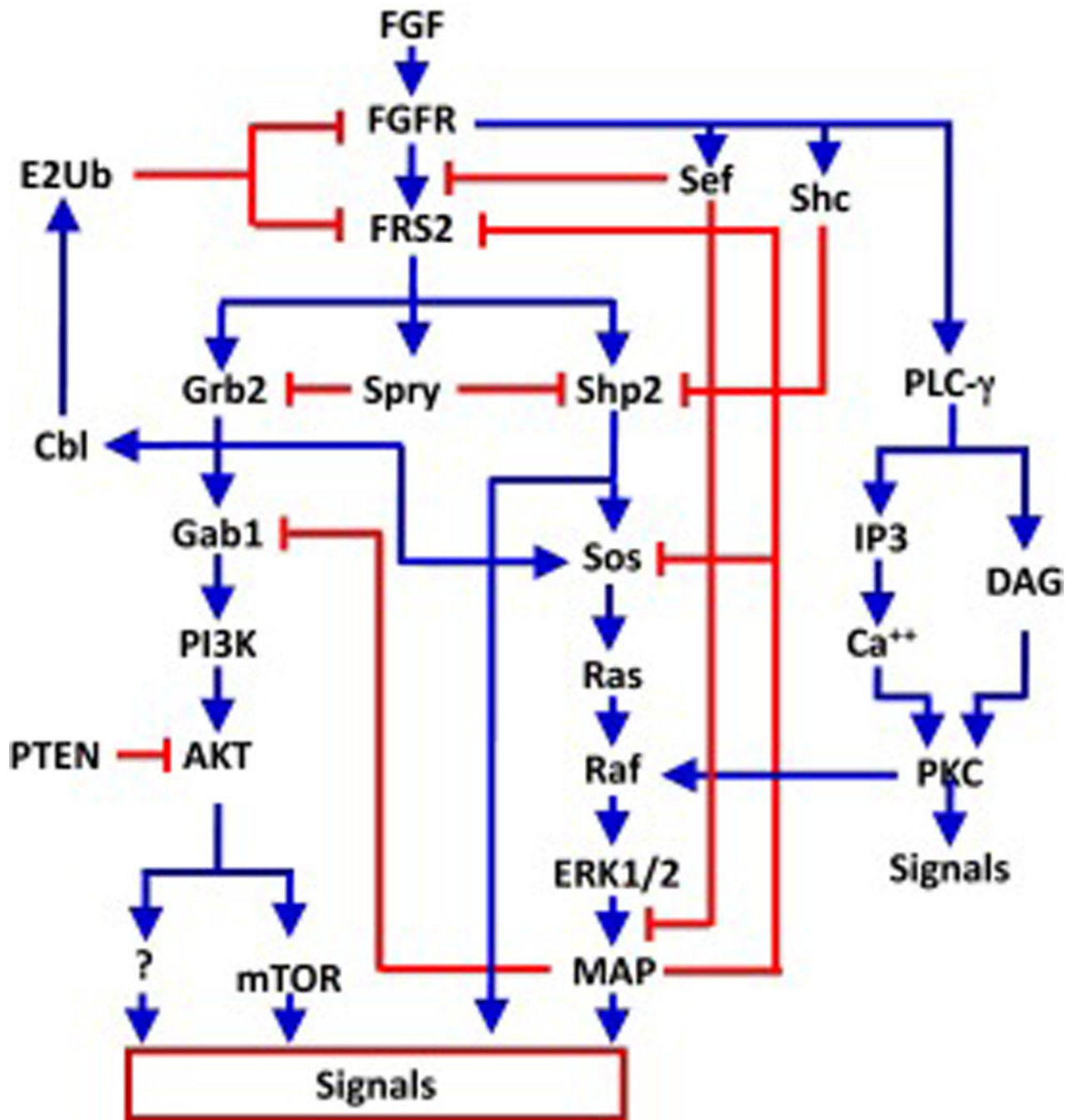


Fig. 3. Signaling pathways downstream of FGFR tyrosine kinase

Shown is a wiring diagram with blue lines indicating positive effects, and red lines indicating negative effects.

Endocrine FGFs suppress prostate tumor progression and metastasis by regulating adipokine secretion

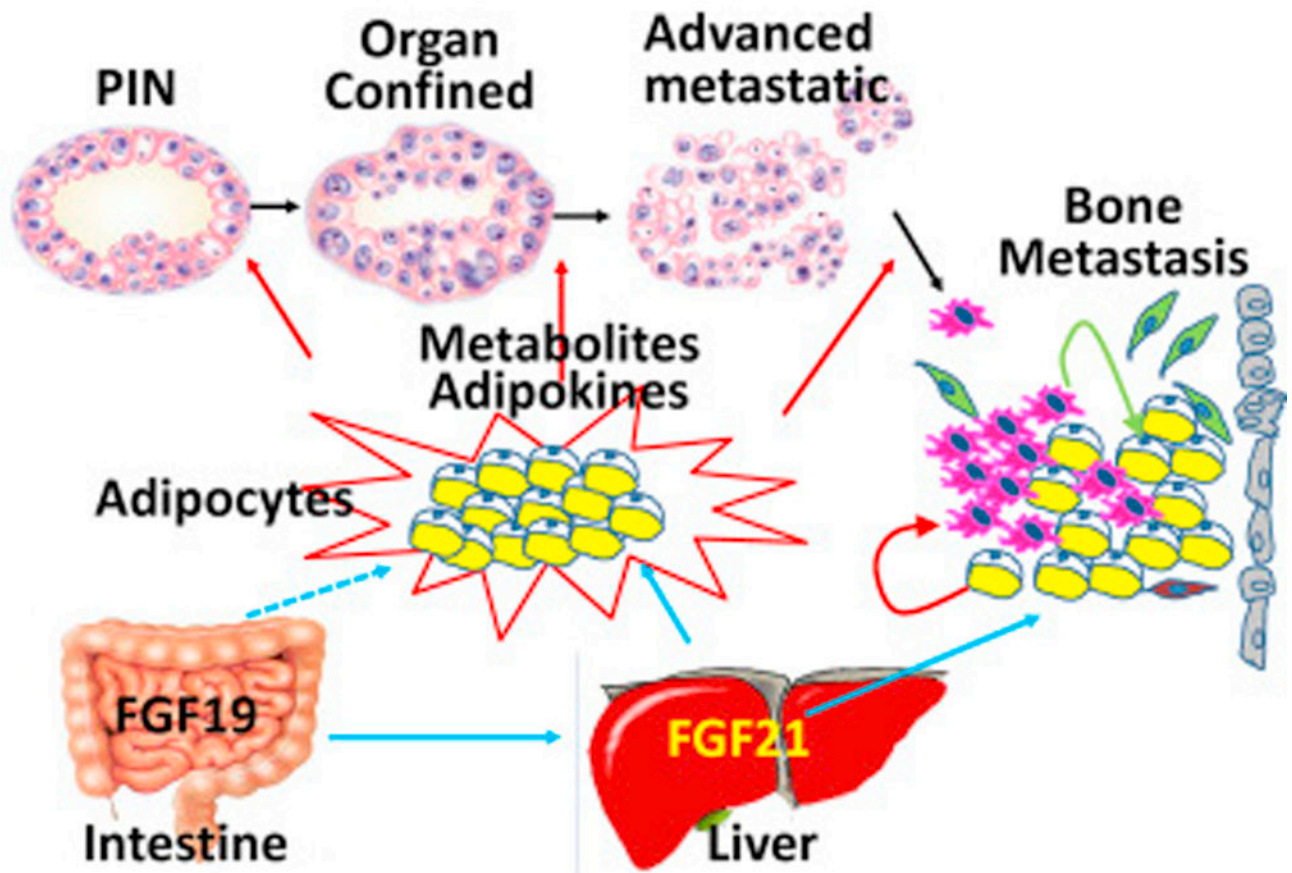


Fig. 4. Endocrine FGFs suppress prostate tumor progression and metastasis by regulating adipokine secretion

FGF21 produced by hepatocyte affects prostate cancer progression via controlling adipokine productions in both adipose tissues and local adipocytes in the tumor microenvironment.