INTRODUCTION OF THE FGF/FGFR SIGNALING

Fibroblast growth factors (FGFs) are broad-spectrum mitogens and regulate a wide range of cellular functions, including migration, proliferation, differentiation, and survival. It is well documented that FGF signaling plays essential roles in development, metabolism, and tissue homeostasis. The malfunction of FGF/FGFR signaling, such as congenital craniosynostosis and dwarfism syndromes, as well as chronic kidney disease (CKD), obesity, insulin resistance, and various tumors (Fig. 1).

FGF family is one of the most diverse growth factor groups in vertebrates. In mice and humans, 22 FGF ligands have been identified. Based on sequence homology and phylogeny, the 18 canonical mammalian FGFs are divided into six subfamilies, including five paracrine subfamilies and one endocrine subfamily. Five paracrine subfamilies contain the FGF1 subfamily (FGF1 and FGF2), the FGF4 subfamily (FGF4, FGF5, and FGF6), the FGF7 subfamily (FGF3, FGF7, FGF10, and FGF22), the FGF8 subfamily (FGF8, FGF17, and FGF18), and the FGF9 subfamily (FGF9, FGF16, and FGF20). The FGF19 subfamily (FGF19, FGF21, and FGF23) signals in an endocrine manner. 1

FGFs exert their pleiotropic effects by binding and activating high-affinity tyrosine kinase receptors that are coded by four genes (FGFR1, FGFR2, FGFR3, and FGFR4) and FGFR1, a truncated FGF without intracellular domain, in mammals. FGFRs are single-pass transmembrane proteins containing an extracellular domain, a transmembrane domain (TMD), and an intracellular tyrosine kinase domain. Among them, the extracellular domain is composed of three immunoglobulin (Ig)-like domains (D1–D3), an acidic region, a heparin-binding motif for FGFs, heparan cofactors, and partner proteins. The TMD anchors the receptors in the cell membrane and facilitates its dimerization. In the cytosol, the juxtamembrane region of FGFRs is involved in receptor dimerization, while the split kinase domains are required for the transmitting of FGF-related signaling. 3

The binding of FGFs to the inactive monomeric FGFRs will trigger the conformational changes of FGFRs, resulting in dimerization and activation of the cytosolic tyrosine kinases by phosphorylating the tyrosine residues within the cytosolic tail of FGFRs. Then, the phosphorylated tyrosine residues serve as the docking sites for downstream signaling molecules, such as FGF substrate 2a, which is localized on the plasma membrane. FGFRs also recruit and phosphorylate SH2 domain-containing substrate phospholipase Cγ (PLCγ) by formatting an allosteric 2:1 FGF-PLCγ complex, indicating that FGF dimerization plays an obligatory role in substrate phosphorylation. Depending on the cellular content in distinct cells and tissues, the classical FGF/FGFR downstream signaling pathways include Ras/Raf-MEK-MAPKs (mitogen-activated protein kinases), phosphatidylinositol-3 kinase/protein kinase B (PI3K/AKT), PLCγ, and signal transducer and activator of transcription (STAT). Additionally, several proteins belonging to FGF synexpression group have been identified, such as Sprouty (Spry), XLFRT3, SEF, MKP3, and so forth. These proteins are themselves regulated by FGF signaling and are tightly co-expressed with FGFs. Most of them inhibit FGF/FGFR signaling by establishing negative feedback loops (Fig. 2).

The diversified functions of FGF/FGFR signaling indicate the complexity regulation of the signaling cascades. FGF/FGFR signaling can be modified at several levels, including ligand–receptor binding specificity, expressions and alternative splicing, and the cross talk between FGFs/FGFRs and other signaling cascades, such as BMP (bone morphogenetic protein) and Wnt signalings.

Diversified tissue distribution and different expression levels of signaling components, which influence the function
of FGF/FGFR signaling, eventually affect the tissue development, maintenance, and disease pathogenesis. Alternative splicing and translational initiation generate multiple isoforms of FGFs/FGFRs and regulate their expression levels. For example, the tissue-specific alternative splicing in D3 of FGFR1, FGFR2, and FGFR3 can generate b and c isoforms, and thus determines the binding specificity/promiscuity for individual FGFs at diverse cells and tissues. Furthermore, it is well documented that epigenetic mechanisms, the posttranslational modifications, such as phosphorylation, glycosylation, ubiquitination, and cellular trafficking of FGFs/FGFRs are also involved in the regulation of the expressions of FGF/FGFR signaling components and the signal specificity, intensity, and timing.

During the past decades, repaid progresses have been made about the modulation of FGF/FGFR signaling cascades; these studies not only deepen our understanding of the unique properties of FGF/FGFR signaling, but also raise the opportunity for developing new therapies targeting causative FGF/FGFR signaling.

Coreceptors of FGFs/FGFRs

Usually, specific ligands require assembly of the ternary complexes composed of ligand, receptor, and coreceptor at the cell surface to initiate signal transduction. The coreceptors of FGF/FGFR cascade include heparan sulfate proteoglycans (HSPGs) (for paracrine FGFs) and Klotho (for endocrine FGFs).

HSPGs. HSPGs are glycoproteins, containing one or more covalently attached heparan sulfate (HS) chains. According to their location, the HSPGs are grouped into three groups: membrane HSPGs, such as syndecans and glycosylphosphatidylinositol-anchored proteoglycans (glypicans), the secreted extracellular matrix HSPGs (agrin, perlecan, type XVIII collagen), and the secretory vesicle proteoglycan, serglycin. HSPGs is a mandatory cofactor in paracrine FGF signaling. Paracrine FGFs have moderate to high affinity for HSPGs, which shortens FGF diffusion distance away from their secretion cells. The interaction also provides a depot of regulatory factors that can be released by selective degradation of the HS chains facilitating the formation of FGF gradients essential for cell specification during development and regeneration.

Structural studies have revealed that the HSPG binding site of FGFs contains the B1–B2 loop and the extended B10–B12 region, and each FGF ligand has discrete affinity for HSPGs. HSPG-mediated FGF-specific morphogenetic gradients contribute to the distinct function of FGFs. Importantly, endocrine FGFs such as...
FGF19 and FGF23 lack the paracrine-conserved glycine box and the truncated β10–β12 region in the potential HS binding region, reducing the binding affinity between HSPGs and the endocrine FGFs (FGF19 subfamily), which allows these FGF ligands to permeate through the HSPG-rich extracellular matrix (ECM) and subsequently enter the blood circulation.

Detailed crystal studies reveal that HSPGs promote the formation of a 2:2:2 dimer between FGF, FGFR, and HSPGs. By engaging ligand and receptors in the dimer, HSPGs promote the kinetics and thermodynamics of FGF-FGFR binding and dimerization, which is required for the transmission of a sustained and robust intracellular signals.

Klotho. Klotho are coreceptors for endocrine FGF signaling. As single-pass transmembrane proteins, Klotho consists of tandem KL domains, and are homologous to β-glucosidases. Modeling studies showed that the endocrine FGFs (FGF19, FGF21, and FGF23) exhibit a negligible HSPGs binding affinity and poor affinity for their cognate FGFRs, resulting in ineffective endocrine FGF/FGFR binding and dimerization. It is well established that α/β Klotho coreceptors are required for these ligands to initiate respective signaling activity. The Klotho coreceptors associate constitutively with the c-splice isoforms of FGFR1-3 and FGFR4 to promote their binding of FGFs and dimerization, reinforcing FGF/FGFR signaling specificity. For example, FGF23 can bind and activate FGFR1c–α-Klotho, FGFR3c–α-Klotho, and FGFR4–α-Klotho. A recent atomic structure study showed that α-Klotho simultaneously binds FGFR1c and FGF23, and dimerization of the stabilized ternary complexes and receptor activation depend on the binding of HS. FGF19 activates FGFR1c–β-Klotho (KLB) and FGFR4–KLB, whereas FGFR21 mainly activates the FGFR1c–KLB complex.

Endocrine FGF/FGFR signaling rely on the interaction between FGFs and Klothos. Biochemical studies revealed that α-Klotho combines with FGFR1c to create a de novo site for the FGF23 carboxy tail, whereas KLβ uses two distinct sites to independently bind FGF and the carboxy tail of FGF19 or FGF21. The proteolytically cleaved FGF23 carboxy tail can competitively inhibit the binding of native FGF23 to the FGFR1c–α-Klotho complex and thus downregulate FGF23 signaling. In patients with autosomal-dominant hypophosphatemic rickets (ADHR), the mutations in the RXXR motif located in the carboxy tail abrogate the proteolytic cleavage of FGF23 and thus elevate the serum levels of full-length bioactive FGF23, which accelerates the excretion of phosphate from the kidney. Mutations in D3 hydrophobic groove of FGFRC isoforms and FGFR4 residues abolishes Klotho binding, indicating the overlapping between FGFs and Klotho binding sites on FGFRs. The association of FGFRs with the Klotho coreceptor decreases the ability of these receptors to respond to paracrine FGFs, such as FGF8, supporting the notion that endocrine and paracrine FGF signaling affect each other.

Modulators of FGF/FGFR signaling

Cell adhesion molecules (CAMs). CAMs are typically single-pass transmembrane receptors and include four major groups: cadherins, integrins, the Ig superfamily of CAMs (IgCAMs), and the superfamily of C-type of lectin-like domains proteins. A growing body of data reveals that various CAMs can act as FGFR binding partners, participating in the modulating of FGF/FGFR signaling and are strongly implicated in cell fate determination of different cell lineages.

Cadherins play an essential role in the formation and adaptive reinforcement of adherens junctions, and modulation of the dynamics of actin cytoskeleton. Different members of the cadherin family are expressed in a cell type-specific manner, and most of the cell types express multiple cadherins, including VE-, N-, and T-cadherin. N-cadherin is associated with FGFRs through their acidic box-mediated activation of FGFRs and their downstream signaling in numerous cells.

In breast cancer cells,
formation of N-cadherin complexes with FGFR1 can decrease the internalization and lysosomal degradation of FGFR1, and thus sustain the receptor signaling via MAPKs, whereas silencing of N-cadherin results in the accelerated FGFR1 degradation. Thus, N-cadherin stabilizes FGFR1 and simultaneously enhances FGF2-induced proliferation and differentiation of epiblast stem cells.46 In addition, cadherin-11–FGFR1 interaction occurs through their extracellular domains. Cadherin-11 initiates intracellular signaling pathways via FGFR1 and recruits FGFR1 into the cell–cell contact area. The cadherin-11-induced FGFR1 signaling stimulates neurite outgrowth.57

The FGFR/neural CAM (NCAM) complexes have been observed in multiple cell types.48 The FN3 domains of NCAMs mediate its interaction with the Ig2–Ig3 region of FGFRs.49 NCAMs bind to FGFR1–FGFR3 to activate the receptor and initiation of signaling cascades and inhibit FGFR K27- and K29-linked polyubiquitination and lysosomal degradation.50 Interestingly, NCAMs can affect the cellular trafficking of FGFRs.51 In contrast to FGFR-induced activation and lysosomal degradation of endocytic FGFR1, NCAM can promote the stabilization of FGFR1, which is recycled from endosomes to the cell surface through a Rab11 and Src-dependent manner.51

Integrins act as the receptors for extracellular matrix molecules, playing a key role in regulating intercellular contact and intracellular signaling. Eighteen α-subunits and eight β-subunits assemble into 24 functional integrins that vary in terms of ligand specificity and cellular function.52 Each α–β combination can bind to unique matrix components. Increasing evidences showed that integrins modify FGF/FGFR signaling.53 For example, the fibronectin-binding α5β1-integrin dimer upregulates FGF2 expression, while secreted FGF2 directly binds to αvβ3 integrin.45,54 FGFI, FGFR1 and integrin αvβ3 can be assembled into a ternary complex, in which FGFI acts as a bridging molecule, to maintain sustained activation of FGFR1-dependent kinases ERK1/2.56

NCAM is a member of IgCAMs containing Ig-like and fibronectin type III (FNIII) domains. NCAM plays a critical role in neurite outgrowth as binding partners affecting the signaling process. A peptide derived from the NCAM FNIII region binds to FGFR1 directly to stimulate FGFR1 phosphorylation in primary rat neurons.51 In PC12 cells, NCAM requires FGFRs to promote neurite growth.57 Specifically, the NCAM-FGFR interaction activates PLCγ and diacylglycerol lipase to generate arachidonic acid, elevating intracellular calcium levels and activating Ca2+/calmodulin-dependent kinases.52 Each α–β combination can bind to unique matrix components. Increasing evidences showed that integrins modify FGF/FGFR signaling.53 For example, the fibronectin-binding α5β1-integrin dimer upregulates FGF2 expression, while secreted FGF2 directly binds to αvβ3 integrin.45,54 FGFI, FGFR1 and integrin αvβ3 can be assembled into a ternary complex, in which FGFI acts as a bridging molecule, to maintain sustained activation of FGFR1-dependent kinases ERK1/2.56

G protein-coupled receptors. G protein-coupled receptors (GPCRs) constitute the largest groups of receptors that mainly transmit various signals across cell membranes through binding and activating heterotrimeric G proteins. Structurally, GPCRs are composed of an N-terminal extracellular domain, seven-transmembrane helices, and a C-terminal region.49 A growing number of studies have revealed that various members of GPCRs and receptor tyrosine kinase (RTKs) can form heterocomplexes together and trigger different intracellular signaling and cellular responses.49,62 The GPCRs can transactivate multiple RTKs,63 including epidermal growth factor receptor,47 platelet-derived growth factor receptors (PDGFRs),65 and insulin-like growth factor receptors,56 and so on.

In the central nervous system, both GPCR and FGFR signaling are involved in the control of proliferation, migration, survival, and differentiation of neurons. More and more studies have showed that GPCRs form heterocomplexes with FGFRs and regulate the cell fate of neurons.55 Multiple methods have confirmed the interaction between FGFR1 and adenosine receptor A2AR. The function study revealed that this interaction is required for the enhanced activation of ERK1/2, which is important for the regulation of the synaptic plasticity.56 Another study showed that cannabinoid receptor 1 (CB1R)-FGFR1 complexes occur in the lipid rafts of the plasma membrane, leading to activation of ERK1/2, and play important roles in neuronal differentiation.69 CB1R activates Fyn and Src via PKC signaling, inducing the transactivation of FGFR1 by phosphorylating its kinase domain.69 The interactions between FGFR1 and muscarinic acetylcholine receptor (mACRH) subtype M1R and 5-hydroxytryptamine receptor 1A (5-HT1A) have been visualized.70 Stimulation of hippocampal neurons with M1R agonist oxotremorine-M activated FGFR1, and the crosstalk between mACRH and FGFR1 enhanced the neurite growth.71 Treatment of FGF2 and 5-HT1A agonist 7-(dipropylamino)-5,6,7,8-tetrahydro-naphthalen-1-ol (8-OH-DPAT) can increase the FGFR1–5-HT1A complexes; activation of 5-HT1A by 8-OH-DPAT causes subsequent FGFR1 phosphorylation mediated by Src.70 Interestingly, the FGFR1–5-HT1A heterocomplexes display anti-depressive effects and thus may be the novel targets for the treatment of mood disorders.72

Other RTKs. FGF/FGFR signaling can also be modified by their interplay with other members of RTK family. The crosstalk among RTKs can occur at different levels, such as the ligand, receptor, and downstream cascades. Among them, different RTKs can form receptor heterocomplexes and subsequently cause tyrosine phosphorylation of one receptor by tyrosine kinase of the other one. Binding with other RTKs gives another way to modify FGF/FGFR activities more elegantly.

Eph receptors constitute the largest family of RTKs, including EphA (EphA1-EphA10) and EphB (EphB1-EphB8) receptors, and are activated by ephrin ligands.73 The Eph receptors contain structural features characteristic for RTKs. The Eph receptor-ephrin complexes regulate cell adhesion, organization of cytoskeleton, angiogenesis, neuronal development, and plasticity.74 EphA4 receptor interacts with FGFs through the tyrosine kinase domain of Eph4 and the JM domain of FGFR1–4.75 More detailed analysis revealed that phosphorylation of the tyrosine residues within JM domain of Eph4 is required for the formation of EphA4–FGFR complexes. Kinase domains of EphA4 and FGFRs can transphosphorylate each other.75 Importantly, the ternary complex, involving FGFR1, EphA4, and FRS2α, was detected. FRS2α may act as a tethering molecule that integrates signals from both receptors and regulates the self-renewal, proliferation, and differentiation of neural stem/progenitor cells.76 Studies also showed that FGFR1 phosphorylate ephexin1, a targeting molecule of EphA receptors.77 Scaffolding protein Dlg1, which directly interacts with EphA receptors, can also modulate FGF signaling.78 PDGFRα and PDGFRβ are activated by multiple PDGFs: PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC, and PDGF-DD.79 PDGFR-mediated signaling can regulate cell motility, proliferation, angiogenesis, and are involved in a range of diseases.80 In vitro and in vivo experiments revealed that both PDGFRα and PDGFRβ interact with high affinity with FGFR1.81 The formation of PDGFRα–FGFR1 complexes is facilitated by the presence of ligands for both receptors. In receptor heterocomplex, PDGFRβ can directly phosphorylate FGFR1 on tyrosine residues.82 Interestingly, FRS2α functions as a bridging molecule between PDGFRβ and FGFR1, further supporting the speculation that FRS2α may act as a tethering molecule integrating signals from different RTKs.81

Nuclear FGFs and FGFRs

In addition to the FGF/FGFR complexes at plasma membrane, it has been recognized that canonical FGF ligands and FGFRs can enter the nucleus of multiple types of cells and tissues.82 Nuclear localization of FGFs/FGFRs lends an additional layer of regulatory complexity.83,84 Nuclear FGFs/FGFRs can exert their effects on proliferation, lineage commitment, and gene expressions. Dysregulation of nuclear FGFs/FGFRs has been found in congenital skeletal disorders and neoplastic transformation.85
Nuclear localization of FGFs and FGFRs has been demonstrated in different pathophysiological conditions. During gonadal development, FGFR2 is mainly localized to the plasma membrane of proliferating sex cord cells, but in the early stage of specification and differentiation, FGFR2 is colocalized with SRα and SOX9 in the nucleus of sex cord cells. In the development of salivary gland, nuclear FGFR2 is specifically located in proliferating epithelial cells at the branch tips in response to FGF10. In human pancreatic cancer cells, FGFR1 and FGFR2 are localized to the nucleus where they facilitate the proliferation and invasion. In breast mucinous carcinoma, nuclear FGFR2 is commonly found colocalized with STAT5 and Runx2. The nuclear FGFR3 levels in breast, bladder, and pancreatic cancer cells are higher than those in corresponding non-tumor tissues.

Several FGF ligands contain a nuclear localization signal to facilitate their nuclear import, and different mechanisms are involved in the receptor nuclear localization. In some cases, nuclear localization of full-length FGFs occurs through a ligand-dependent mechanism. For example, FGF2, FGF1, and FGF10 localize to the nucleus with FGFR1 and FGFR3. Structurally, all ligand-dependent mechanisms for nuclear FGFR translocation, activation of down-stream pathways, and target genes, as well as its functions in different pathophysiological conditions in the future study.

Once in the nucleus, FGFs and FGFRs can promote gene expressions through multiple approaches, such as epigenetic mechanisms. In embryonic stem cells and neuronal cells, FGFR1 binds the proximal promoters and activates the transcription of pluripotency-related genes, Wnt/β-catenin signaling components, and P53. In preosteoblasts, FGFR2 and FGFR2 localize to the nucleus to recruit histone remodeling factors, such as the CBP homolog p300, to ribosomal DNA (rDNA) and activate RNA polymerase I-mediated transcription, increasing ribosome biogenesis and subsequently protein synthesis. Nuclear FGF/FGFR-mediated regulation of transcription suggests an alternative way through which FGFs/FGFRs can directly induce specific and rapid changes of gene expressions. In osteoprogenitor cells, nuclear FGFR2-mediated regulation of rDNA transcription promotes self-renewal over terminal osteoblast differentiation. In invading breast cancer cells, FGFR1 undergoes nuclear translocation and activates the transcription of genes critical for cell migration. The activating mutant FGFR2 Y376C in endometrial cancer has increased perinuclear localization and appears to be involved in disrupting cell polarity in metastatic cells. In pancreatic cancer, nuclear FGFR3 correlates with metastatic disease and poor overall prognosis.

Compared with the well-established mechanisms in transmembrane signaling, the mechanisms for FGF/FGFR cascades in the nucleus are less studied. Nuclear localization of RTKs is not unique to the FGFs/FGFRs. It is very important to clarify the precise mechanisms for nuclear FGFR translocation, activation of downstream pathways, and target genes, as well as its functions in different pathophysiological conditions in the future study.

### FGF SIGNALING IN SKELETON DEVELOPMENT AND REPAIR/REGENERATION

Expressions of FGFs and FGFRs during skeleton development and repair have characteristic spatiotemporal expression patterns throughout all stages of skeletal development (Table 1).

During limb bud development, the active epithelial–mesenchymal interactions between ectoderm-expressed FGF (FGF8) and FGF2b, and the mesenchyme-expressed FGF (FGF10) and FGFR1c, are indispensable for the outgrowth and patterning of limbs.

| Table 1. FGF and FGFR expression in long bone development |
|-----------------------------------------------------------|
| Developmental Events/Location                              | FGFRs/FGFs                                                                 |
| Mesenchymal cells                                          | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| Mesenchymal condensation                                   | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| Perichondrium                                              | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| Resting zone                                               | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| Proliferative zone                                         | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| Hypertrophic zone                                          | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| Periosteum                                                 | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| Growth plate                                               | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| FGF1, FGF2, FGF3, FGF5                                      | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| FGF7, FGF8, FGF16-19                                       | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
| FGF21, FGF23                                               | FGF1, FGF2, FGF3, FGF4, FGF5                                               |
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9, and 17 are specifically expressed in the mouse apical ectodermal ridge (AER), a major signaling center at the distal edge to ensure proper development of limb buds. FGFR9 is located in regions corresponding to mesenchymal condensations in AER, and is only expressed in the mesenchyme surrounding the cartilaginous condensations at the later stage. FGFR9 is then expressed in the perichondrium/periosteum and primary spongiosa. In rat, Lazarus et al. found that FGFRs 1, 2, 6, 7, 9, 18, 21, and 22 are expressed in the perichondrium, while FGFRs 2, 7, 18, and 22 are expressed in the growth plate. FGFRs 1, 2, 17, and 19 are the predominant FGF ligands expressed in human fetal growth plate cartilage. FGFR18 is expressed in the periosteum, the articular surface, synovial tissue, and in cells within the perichondrial groove of Ranvier. During intramembranous bone formation, FGF3 is expressed in developing calvarial osteoblasts, FGFR9 is expressed in calvarial mesenchyme, and FGFR18 is expressed in mesenchymal cells and differentiating osteoblasts, whereas FGF23 is mainly produced by differentiated osteoblasts and osteocytes.

FGFR1 and FGFR2 are existed in mesenchymal cells prior to morphological indication of mesenchymal condensation, FGFR1 is evenly expressed in limb bud mesenchyme, while the expression of FGFR2 is increased in chondrogenic condensation area, as the first marker of chondrogenic condensation. Both FGFR1 and FGFR2 are expressed in the periphery of the condensation, where is the location of the origin cells of perichondrium and periosteum. In the established growth plates, FGFR3 is expressed mainly in the resting, proliferating, and prehypertrophic zone. As chondrocytes begin to hypertrophy, FGFR3 expression is shut down, while the expression of FGFR1 is elevated. It has also been found that FGFR2 is expressed in the resting zone, while FGFR4 is expressed in the resting and proliferative zones. FGFR3 is expressed more intensely in latent chondroprogenitor cells located in the groove of Ranvier and ring of Lacroix. The expressions of FGFR1 and FGFR2 in osteoblasts have been well characterized. FGFR3 is also found expressed in osteoblasts in cranial sutures, FGFRs are expressed in a spatially-dependent manner. FGFR2 is predominantly expressed in osteoprogenitor cells, while FGFR1 is located in more differentiated osteoblasts. FGFR3 has lower expression in the periosseum and suture osteogenic fronts at the late stage of suture development.

FGF/FGFR-related genetic diseases with abnormal skeleton development in humans:

The characteristic expression patterns of FGFs/FGFRs imply the critical roles of FGFs/FGFRs in skeletal development, and both gain-of-function (GOF) and loss-of-function (LOF) mutations in individual FGFs or FGFRs have been found to cause a variety of genetic skeletal diseases in humans.

Mutations and single-nucleotide polymorphisms (SNPs) of FGFs have been linked to multiple skeletal disorders. Constitutionally increased dosage of FGFR3 and FGFR4 genes is a risk factor of craniosynostosis. Heterozygous mutation in FGFR3 gene causes deafness, congenital inner ear agenesis, microtia, and microdactyli. Heterozygous mutation of FGFR8 can lead to autosomal-dominant hypogonadotropic hypogonadism-6 with or without anosmia characterized by short stature, hyperlaxity of the digits, camptodactyly, and mild scoliosis. FGFR8 mutation also accounts for a small percentage of Kallmann syndrome (KS). FGFR9 heterozygous missense mutations S99N and R62G have been identified to be responsible for multiple synostoses syndrome 3, and some individuals showed sagittal suture synostosis and homoruderal synostoses in humans. LOF mutations in FGFR10 cause an autosomal-dominant multiple congenital disorder characterized by lachrymal duct aplasia, malformed ears and deafness, and disturbed distal limb segments, named lacrimo-auculo-dento-digital syndrome. FGFR10 is identified as a genetic risk factor for nonsyndromic cleft lip with or without cleft palate. Truncated mutations of FGFR16 are associated with X-linked recessive hand malformations with metacarpal 4/S fusion. Congenital hypogonadotropic hypogonadism individuals caused by missense mutations of FGFR17 displayed low bone mass. Missense mutations such as R176Q, R179W, and R179Q in FGFR2 cause ADHR, frequently present with rickets, bone pain, and tooth abscesses. LOF mutations in FGFR2 cause a rare autosomal recessive metabolic disorder, hyperphosphatemic familial tumoral calcinosis, characterized by the progressive ectopic calcifications and elevated serum phosphate levels.

A GOF missense mutation in FGFR1 (P252A) leads to Pfeiffer syndrome (PS), a craniosynostosis syndrome with characteristic abnormalities, including broad thumbs and toes, brachydactyly or variable syndactyly, and elbow ankylosis. Several FGFR1 mutations, such as N330I and C379R, result in osteoglycogen dysplasia (OGD), characterized by craniofacial abnormalities, including craniosynostosis and depressed nasal bridge, rhizomelic dwarfism, and non-ossifying bone lesions. LOF mutations such as C277Y, R622X, and A167S in FGFR1 are responsible for autosomal-dominant KS, characterized by hypogonadotropic hypogonadism and anosmia. Some KS cases present skeletal abnormalities, such as scoliosis, limb anomalies, and loss of nasal cartilage. GOF mutations of FGFR2, mainly in the third Ig-like domain and adjacent linker regions (exons IIIa and IIIc), lead to multiple types of autosomal-dominant craniosynostoses, such as Apert syndrome (AS), Crouzon syndrome, and PS, as well as Beare-Stevenson cutis gyrata syndrome. Several de novo missense mutations of FGFR2 have been identified responsible for a perinatal lethal skeletal dysplasia entitled as BBDS-FGFR2 type characterized by deformities in multiple bone, including mineralization disorder of the calvarium, craniosynostosis, and dysmorphic facial features, as well as bent long bones and osteopenia. GOF mutations in FGFR3 affect predominantly bones developed through endochondral ossification causing hypochondroplasia, achondroplasia (ACH), and thanatophoric dysplasia (TD, type I/II). GOF mutations in FGFR3 have also been found to cause craniosynostoses. The A334T mutation of FGFR3 causes mild craniosynostosis, while A391T mutation in FGFR3 TMD is responsible for Crouzon syndrome with acanthosis nigricans. FGFR3 P250R and P252R mutations cause Muenke syndrome, an autosomal-dominant disorder characterized by uni- or bi-coronal synostosis, macrocephaly, midfacial hypoplasia, and developmental delay. Some TD patients exhibit joint fusion and craniosynostoses. FGFR3 with R621H substitution in the tyrosine kinase domain and a homozygous missense mutation T546K, leading to partial loss of FGFR3 function, cause camptodactyly, tall stature, and hearing loss syndrome. To date, no mutation of FGFR4 has been found responsible for genetic skeletal disorders in humans.

FGF/FGFR signaling in skeleton development and homeostasis:

Accumulating studies dissecting the roles of FGFs/FGFRs in the development and homeostasis of skeleton have been carried out by using animal models and cell/tissue culture systems.

FGFs in skeleton development and homeostasis. FGF1 has been shown to play an important role in regulating the fate of bone marrow stromal cells (BMSCs) by inhibiting osteogenesis and promoting adipogenesis. FGF2 is expressed in osteoblasts and the stall cells in the bone. Stored in the extracellular matrix, FGF2 promotes both osteoblastic and chondrogenic differentiation of cranial neural crest cells. Mice with non-targeted overexpression of FGF2 show shortened long bones caused by premature closure of the epiphyseal plate. Sobue et al. found that overexpression of FGF2 in mice leads to osteopenia and defective mineralization, proposing that FGF2 functions as a negative regulator of bone formation. The roles of the nuclear
FGFRs in skeletal development and homeostasis. The roles of FGFRs in skeletal development and especially in genetic skeletal diseases have been further dissected by employing genetically modified animal models. Zhou et al. found that mice carrying a P252R mutation in FGFR1 can mimic human PS with premature fusions of multiple sutures, accelerated osteoblast proliferation, and increased expressions of osteogenic genes, and further uncovered that CBFA1 may be a downstream target of FGFR1-FGFR1 signals in vitro. Trokovic et al. concluded that FGFR1 is expressed in pharyngeal region and create a permissive environment for neural crest cell migration in mice homozygous for a hypomorphic allele of FGFR1 with craniofacial defects. The hush puppy FGFR1 W691R mutation is unresponsive to FGF1 in calcium mobilization and downstream signaling through MAPK or PLCγ and can lead to ear defects and skull abnormalities in mice. By deletion of FGFR1 in osteochondro-progenitor cells and differentiated osteoblasts in mice, it is proposed that FGFR1 promotes the differentiation of mesenchymal progenitors into osteoblasts, but inhibits the maturation and mineralization of osteoblasts. Mice lacking FGFR1 in chondrocytes showed shortened stature and tiatal length with expanded hypertrophic zone in growth plate, indicating the important role of FGFR1 during chondrocyte maturation. FGFR1 signaling in mature osteoblasts/osteocytes is required for the survival of osteocytes and bone mass maintaining in mice. In addition, our group revealed that FGFR1 can positively regulate the differentiation and resorption activity of osteoclasts.

GOF mutation in FGFR2 (S252W) resulted in increased apoposis of osteogenic cells, disturbed osteoblastic proliferation and differentiation, and the presence of ectopic cartilage at the midline sagittal suture. We observed that FGFR2-P253R mutation can directly affect both intramembranous and endochondral ossification in mice. Cells isolated from limbs of mice with FGFR2 S252W mutation can differentiate into chondrocytes in the osteogenic medium, suggesting that FGFR2 may affect the fate of mesenchymal cells. Further studies on BDOS resulting from FGFR2 mutations revealed that nuclear FGFR2 regulates the developing limb, musculoskeletal integration, and cell fate determination. Targeted disruption of FGFR2illic in mice leads to narrowed proliferative and hypertrophic zones in growth plate, and disturbed ossification with downregulation of IHH, PTHRP, and RUNX2. Yu et al. found that conditional deletion of FGFR2 in mesenchyme can lead to skeletal dwarfism and increased bone mineral density with dramatically disturbed proliferation of osteoprogenitors and anabolic function of mature osteoblasts in mice. In zebrafish, FGFR2 is essential for the mesenchyme condensation, later chondrogenic differentiation, and survival of chondrocytes in late cranial cartilage development. Mice with FGFR3 mutation mimicking human ACH and TD II exhibit dome-shaped skulls and chondrodysplasia, while FGFR3 deficiency in mice causes increased bone length, indicating that FGFR3 is a negative regulator of endochondral bone formation. The expression levels of P16, P19, and P21 are upregulated in growth plates of ACH mice and FGFR2 treatment can stimulate the expressions of P21 and P27 in RCS cells, suggesting that the upregulation of cell-cycle inhibitors may be involved in activated FGFR3-induced growth arrest of chondrocytes. FGFR3 downregulates PTH/PTHrP (PTH-related peptide) signaling partially through the Janus kinase/STAT pathway. Reduced telomerase activity may participate in the inhibitory effect of FGFR3 on the proliferation of chondrocytes. There are contradicitories about the role of FGFR3 in the differentiation of chondrocytes. FGFR3 deficiency in mice causes enhanced chondrocyte hypertrophy; activated FGFR3 inhibits the hypertrophic differentiation of chondrocytes in cultured metatarsals. However, Minina et al. revealed that FGFR3 signaling can accelerate the hypertrophic differentiation of chondrocytes in

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cultured limbs. It has also been reported that FGFR3 promotes the terminal hypertrophic differentiation of chondrocytes partially through MAPK. Activation of endogenous FGFR3 by FGF2 stimulation leads to reversible premature senescence of RCS cells. FGFR3 inhibits the synthesis of chondrocyte ECM such as aggrecan and collagen 2, and promotes the degradation of ECM via stimulation of several MMPs, including MMPs 3, 9, 10, and 13 in chondrocytes, as a negative regulator of ECM. FGFR3 signaling is involved in macroautophagy of growth plate chondrocytes, which is important for the postnatal skeleton development. Recently, it was found that activated mutations of FGFR3 result in long bone defects potentially due to the dysfunction of primary cilia, including shortened length, reduced IFT20 trafficking, and aberrant HH signaling, suggesting that FGFS/FGFR3 may be involved in the function of primary cilia. Furthermore, FGFR3 directly and indirectly regulates the osteogenesis process. Mice carrying FGFR3 P244R mutation display FGFR3 deficiency and constitutively activation leads to osteopetrosis and perturbed bone mineralization accompanied with changed osteoclastic activity, while FGFR3 has a direct positive effect on osteoclastic bone resorption.

In general, FGFR1-3 all play critical roles in both chondrogenesis and osteogenesis, but FGFR3 is relatively more important in chondrogenesis.

The role of FGF signaling in skeletal repair

Accumulating evidences have supported the crucial roles of FGFs/FGFRs in the injury repair of skeleton, including both cartilage and bone.

Endogenous FGF signaling in skeletal injury repair

Injury and degeneration of cartilage: Cartilage is an essential part of the skeleton. Growth plate is critical for the growth of long bone, while the articular cartilage provides smooth and low-friction interaction between the bones of joints.

Growth plate is fragile in growing skeleton. Given the role of FGF signaling in growth plate, it may play potential role in growth plate injuries. However, the roles of FGF signaling in growth plate injuries and healing is largely unknown. In young rat growth plate injury model, FGF2 is expressed in fibrogenic response phase and osteogenic stage coinciding with mesenchymal cell infiltration and bony bridge formation, suggesting the possible involvement of FGF2 in the repair of injured growth plates. In addition, FGF2 is involved in the regulatory role of tumor necrosis factor-α (TNF-α) in injured growth plates and contributes to the pathogenesis of osteonecrosis, osteopenia, and growth arrest. OA is a degenerative disease affecting mainly the articular cartilage. Human adult articular chondrocytes express FGFR1-4 with evident higher levels of FGFR1 and FGFR3, while the expression levels of FGFs/FGFRs were altered in the articular cartilage of OA patients. In human osteoarthritic chondrocytes, FGFR1 expression is increased with a concomitant suppression of FGFR3 expression. In murine models, disruption of FGFR1 in adult articular cartilage can delay the cartilage degeneration progression with downregulation of MMP13. ACH individuals resulting from FGFR3 GOF mutation exhibit a lower incidence of OA. Consistent with this, we revealed that FGFR3 delays OA progression in the knee joints and temporomandibular joints partially through downregulation of IHH in both spontaneous and surgically induced OA models in mice. Recently, we found that FGFR3 deficiency enhances the chemotaxis of macrophages via upregulating CXCR7, exacerbating the destruction of synovial joints. Both FGFs 1 and 2 are associated with radiographic phenotypes of knee OA at early phase. FGF1 is considered as a catabolic factor through down-regulating of CCN2 by interaction and enhancing the degradation of cartilaginous ECM by MMP13. FGF2 has both beneficial and deleterious effects on articular cartilage. In human articular chondrocytes, FGF2 can accelerate matrix degradation via a neuro-endocrine pathway and stimulation of ADAMTS5 expression through upregulating the transcription of c-FOS/AP1 and CBP1. On the contrary, FGF2 can promote the expression of TIMP1 (tissue inhibitor of metalloproteinases 1) and suppress interleukin-1 (IL-1)-induced aggrecanase activity. Ablation of full-length FGF2 in mice accelerates the development of spontaneous and surgically induced OA. Deletion of LMW FGF2 isoform can accelerate murine OA, while loss of HMW FGF2 isoforms plays a protective role. Elevated FGF2 is involved in the role of HMW FGF2 in OA development by modulating Wnt/β-catenin signaling. FGF8 promotes the degradation of cartilage, leading to exacerbation of OA through enhancing the production of protease MMP3 and prostaglandin E2 produced by the injured synovium. We revealed that the expression of FGF9 is decreased with aging. Elsworth et al. showed that FGF18 can act as an anabolic factor in cultured articular chondrocytes through stimulating collagen 2, proteoglycan accumulation, and chondrocyte proliferation.

Bone regeneration: Multiple studies have demonstrated that FGFs and FGFRs recapitulate their expression pattern in skeleton development during fracture healing process. In rat closed femoral fracture model, FGFR1 and FGFR2 have similar expression pattern; they are expressed in inflammatory cells, periosteal cells, chondrocytes, osteoblasts, and osteoclasts in fracture callus during both endochondral and intramembranous bone formation processes. The expression of FGF3 is existed in mesenchymal cells, prehypertrophic, and hypertrophic chondrocytes in the fracture callus at a relative later stage. In mouse long bone fracture model, FGFs 1, 2, 5, 6, 9, and 16-18 are expressed throughout the healing process. FGFs 1, 2, and 5 are mainly expressed in inflammatory stage; FGFs 16 and 18 peak at endochondral bone formation phase; FGF2, 9, 16, and 18 are highly expressed, while FGF1 and 17 show peak expression at the bony callus formation and remodeling stage. FGF1 expression is increased during the formation of a cartilaginous callus in fracture, especially in fibroblast-like mesenchymal cells. In rat femoral distraction osteogenesis model, the expression of FGF2 was detected in fibrous mesenchymal cells, immature osteoblastic-like cells, and the periostem adjacent to the areas of chondroid tissues.

Skeletal phenotypes in mice with genetically modifying FGFs/FGFRs and the expression patterns of FGFs/FGFRs during fracture healing indicate the dispensable function of FGF signaling in bone regeneration. The SNPs of FGFR1 are associated with fracture nonunion. We found that mice with FGFR2 GOF mutation (P253R) have enhanced bone formation induced by mechanical ablation of long bone marrow via upregulation of Wnt/β-catenin signaling. Our group using murine tibia fracture model reveal that FGFR3 plays a negative role in bone repairing through its regulation of both chondrogenesis and osteogenesis. In addition, FGFR3 inhibits the remodeling of injured tissue after cortical injury through downregulation of osteoclastic resorption. FGF1 may promote bone repair by inhibiting adipogenic differentiation and increasing the number of osteoblasts in the inflammatory environment. Using transgenic mice, Hurley's...
group proved that LMW FGF2 accelerates the tibia fracture healing process through promoting chondrocyte and osteoblast differentiation and vascular invasion, and enhances the calvaria defect healing through canonical Wnt signaling. There is a strong positive association between plasma FGF2 levels and BMD in healthy women, although FGF2 promotes bone loss in mice. The serum FGF23 level may be a predictor of reduction of trabecular parameter and an indicator of nonunion.

Application of FGF signaling modulator in skeleton repairment

Degeneration and injury of cartilage: FGF18 promotes, while FGF3 suppresses OA pathogenesis, suggesting that antagonists or neutralizing antibodies of FGF18, and agonists or FGF ligands with high binding affinity for FGF3, could be valuable therapeutics for OA. We revealed that pharmacologically antagonizing FGF18 can alleviate OA progression in surgically induced mouse OA model and the osteoarthritic phenotype of cultured cartilage explants. As a high-affinity FGF ligand for FGF3, exogenous FGF9 can attenuate cartilage degradation while aggravate osteophyte formation in murine post-traumatic OA model. In animal experiments, FGF18 has been repeatedly shown to have beneficial effects on OA and improve the healing of cartilage. To date, recombinant human FGF18 (rhFGF18) (trade name surprifermin) is the only FGF-based drug in clinical trials for OA. Clinical trial data show that intraarticular application of FGF18 can increase cartilage thickness and reduce cartilage loss without discernible local or systemic safety concerns. Exogenous FGF2 can enhance the repair of articular cartilage defect in vivo. FGF2 has also been used in combination with mesenchymal stem/progenitor cells to improve epiphyses turning, lung budding, branching morphogenesis, and protein delivery systems, need to be further explored to effectively promote bone regeneration and achieve better clinical applications.

Fibroblast growth factor (FGF) signaling in lung development and diseases

The mammalian lung is derived through a series of epithelial branching events, leading to a complex branched airways and blood vessels, which eventually form a fully functioning air exchange organ. Lung development can be morphologically divided into several stages that correspond to key developmental transitions: the embryonic, pseudoglandular, canalicular, saccular, and alveolar stages. In chronological order, these stages involve endoderm induction, anterior-posterior and dorsal-ventral patterning, lung specification, lung budding, branching morphogenesis, and finally maturation.

Expressions of FGF ligands and receptors in the lung

The expressions of FGF ligands and receptors have been found during lung development. Using in situ hybridization and RNA-sequencing, Danopoulos et al. assessed the expressions and distribution of FGF ligands in the cultured human fetal lung. It is demonstrated that the expression of FGF7 is in both the epithelium and mesenchyme; FGF9 is mainly expressed in the distal epithelial, while FGF10 is diffusely expressed throughout the parenchyma, and some expression of FGF10 is found in the smooth muscle cells (SMCs). FGF2 is highly expressed in proximal, distal epithelial cells, and SMCs. FGF3 is mostly expressed in the epithelial cells, and expressed lower in the mesenchyme, while FGF4 is highly expressed in the mesenchyme and distal epithelium. The expressions of FGF ligands and FGF receptors (FGFR1-4) have also been reported in the developing rodent lung.

Roles of FGF/FGFR signaling during lung development

FGF/FGFR signaling is essential for lung development. FGF1 stimulates lung epithelial cell proliferation and airway bud formation, and FGF7 causes cell proliferation in vitro inducing the formation of cysts from epithelia. Transgenic mice overexpressing FGF7 exhibit lung malformation. During the early phase of lung development, FGF9 controls epithelial branching and mesenchymal proliferation. Deletion or overexpression of FGF9 results in branching defects in mice with disturbance of the HH and Wnt/β-catenin pathway and the expressions of FGF10 and BMP4. FGF10 expression is drastically decreased in FGF9-deficient lungs from E14.5 onwards, and in FGF9-overexpressing lung, BMP4 expression is increasingly expressed in the proximal and distal airway epithelium, whereas FGF10 expression is upregulated locally in the distal mesenchyme. Deletion of FGF10 results in complete distal lung agenesis. In cultured human fetal lung both FGF7 and FGF10 can induce liquid secretion and enlargement in distal tips. Using in vitro organoid cultures from the distal tip epithelium of human embryonic lung at pseudoglandular stage, Nikolic et al. have revealed that FGF10 is not required for the initial establishment of
SOX2+/SOX9+ progenitors and for human lung branching. A recent study shows that foregut spheroids treated with high levels of FGF10 and 1% fetal bovine serum can form human lung organoids containing airway-like structures, mesenchymal cells, and alveolar epithelial cell type I and type II markers. FGF18 plays a role in lung alveolar development during late embryonic lung development. FGF18 knockout mice show narrow alveolar space, thick interstitial mesenchymal compartments, and more embedded capillaries. Blocking the function of FGF2 by a dominant-negative mutation results in blocked airway branching and epithelial differentiation. Mice deficient in both FGF3 and FGF4 show failure of alveogenesis, but deletion of either receptor alone does not disrupt lung development. A recent in vivo study demonstrated that FGF3 and FGF4 in mesenchymal cells have a function to control the organization of postnatal alveolar elastin, thereby driving the formation of alveolar septa for increasing the gas-exchange surface.

Roles of FGF/FGFR signaling in lung diseases

SNPs and mutations of FGFS/FGFRs in human lung diseases

Genetic analysis has found that SNPs in FGFs are associated with various types of lung diseases. SNPs in FGF10 may be associated with susceptibility to chronic obstructive pulmonary disease (COPD). FGF10 SNPs are also associated with airway branch variants. SNPs in FGF3, FGF7, and FGF4 are associated with respiratory distress syndrome (RDS). FGF4 (rs1966265) is also associated with bronchopulmonary dysplasia (BPD), the common chronic lung disease of premature birth. Besides, mutations in FGFS and FGFRs also have been found in human lung diseases. Mutations in FGF10, FGF2, or FGFR3 have been identified in LADD (lacrimo-auriculo-dento-digital) patients. Rare FGF10 mutations have been identified in lethal pulmonary hypoplasia. Defects in the formation of tracheal cartilaginous ring resulting in mortality, resulting from respiratory distress, have been reported in Crouzon, AS, and PS caused by activating mutations of FGFR2. Homozygous loss-of-function mutation (R255Q) of FGFR2 contributes to ectrodactyly and pulmonary acinar dysplasia. All these findings suggest the crucial roles of FGF signaling in lung diseases.

Abnormal expressions of FGFS/FGFRs in lung diseases

In human fetal congenital cystic adenomatoid malformation, the epithelial FGF9 expression is 4-fold higher than that of normal fetal lung, whereas FGF10 and FGF2 gene expressions have no change in the lung mesenchyme. Reduced FGF10 expression has been shown in BPD. FGF18 expression is decreased in hypoplastic lungs from patients harboring congenital diaphragmatic hernia (CDH). Plasma FGF23 levels is significantly elevated in COPD patients. FGF1/FGF signaling is aberrantly increased in idiopathic pulmonary fibrosis (IPF) and may lead to the pathogenesis of lung fibrosis by promoting fibroblast migration via increased MAPK signaling.

Regulation of FGF/FGFR signaling in lung diseases using in vivo and in vitro models

Studies in rodent models and in vitro lung cells have further implicated the roles of FGF signaling pathway in lung diseases. In lung of CDH rat, FGF7 and FGF10 gene expressions have been decreased significantly compared with controls. Studies using rat doxorubicin-induced EA-TEF (esophageal atresia-tracheoesophageal fistula) model have found that disturbed FGF10/CTSH signaling is associated with impaired airway branching and consequent impairment of epithelial cells in the lung. BPD model established by exposing newborn mice to sublethal hyperoxia shows decreased expressions of FGFR3 and FGFR4. Klotho knockout mice show COPD and airway inflammation with elevated FGF4 in the lung, whereas airway inflammation was attenuated in mice with overexpression of klotho. FGF9 and FGF18 promote survival and migration of human lung fibroblasts from patients with IPF, and inhibit myofibroblast differentiation of human lung fibroblasts from patients with IPF. Recent studies have demonstrated that alveolar type 2 stem cells are maintained by FGF10-FGFR2B signaling. Loss of FGF10-FGFR2B signaling in bronchial epithelial cells leads to impaired generation of both basal and type II epithelial cells after bleomycin injury, which can cause IPF. Deletion of FGFRs (FGFR1, 2, and 3) in lung mesenchyme decreases pulmonary fibrosis development in response to bleomycin. FGF7 and FGF10 can improve the lung repair and increase the epithelial survival after injury through FGFR2b signaling in rodents. FGF10 can also increase lung-resident mesenchymal stem cells and reduce the inflammatory response after acute lung injury (ALI). FGF10 has preventive roles in alveolar repair and resolution in ALI or acute RDS.

FGF/FGFR signaling as a target for the therapies of lung diseases

FGF/FGFR signaling represents a privileged target for the therapeutic approach. Therapeutics targeting FGF signaling pathways are largely classified into “pro-FGF signaling” and “anti-FGF signaling” therapeutics. Recombinant FGFs or FGF analogs have been developed as pro-FGF signaling therapeutics to improve the beneficial effects of FGF signaling. On the other hand, tyrosine kinase inhibitors (TKIs), anti-FGF antibodies or peptides, and FGF traps have been found as approaches aimed to block FGF signaling. A TKI, Nintedanib, which targets FGFRs 1-3, PDGFR receptors α/β, and VEGF receptors 1-3, has been approved in the USA and the EU to treat IPF. Recent studies found that FGF1 may have preventative and therapeutic effects on transforming growth factor-β1 (TGF-β1)-induced pulmonary fibrosis through inducing AEC proliferation, inhibiting myofibroblast differentiation, regulating TGF-β1 signaling, and FGFR1 expression. Thus, modulating FGF1 signaling may be a potential therapeutic strategy for the treatment of pulmonary fibrosis. Considering that FGF2 acts as an angiogenic mediator involved in various lung disorders such as COPD, pulmonary fibrosis, pulmonary hypertension, asthma, and lung cancer, FGF2 could also be an crucial target for the treatment of these lung disorders. FGF7 stimulates proliferation of lung epithelial cells and has been considered as a potential therapy for lung injury. FGF9 is a strong candidate contributing to the progression of IPF, which makes it a potential target for the therapies of IPF. Because of its important roles in lung development and diseases, FGF10 becomes an intriguing target for preventing and treating lung diseases.

However, FGF family is comprised of various ligands and receptors with multiple effects on different cell types in the lung, limiting the potential therapeutic efficacy. For instance, in contrast to its anti-fibrotic effect in TGF-β1-induced lung fibrosis, FGF1 and FGF14 are also expressed increasingly in IPF lungs, and FGF1 treatment led to decreased collagen production and increased apoptosis of IPF-derived lung fibroblasts, suggesting that FGF1 may lead to the pathogenesis of lung fibrosis.

Recent studies reported that FGF9 and FGF18 decreased normal fibroblast apoptosis, but had no effect on fibroblasts from IPF patients. FGF9, but not FGF18, decreased basal and TGF-β1-mediated expression of collagen and myofibroblast differentiation of fibroblasts. All these studies suggest that individual members of FGF family may exert variable effects, depending on the responding cells and the involvement of other signalings. Thus, investigation of specific roles of distinct FGF ligands and receptors in different types of lung cells will help to target differential pathways with precision and optimize the efficacy of future therapies for patients with lung diseases.

FGF SIGNALING IN URINARY SYSTEM DEVELOPMENT AND DISEASES

Expression pattern of FGFS/FGFRs in kidney development

The metanephric kidney develops from nephrogenic cord and Wolffian (nephric) duct, which then generate ureteric bud (UB)
and the metanephric mesenchyme (MM), respectively. \textsuperscript{333} FGFR1-4 and FGFs are highly expressed in mammalian embryonic kidney and lower urinary tract and play critical roles in the development of kidney. Although all FGFRs were detected in embryonic kidneys, FGFR3 or FGFR4 global knockout mice does not show significant structural defects of the kidney or bladder. \textsuperscript{350,351} which indicates that FGFR1, FGFR2, and FGFRL1 play more necessary roles in kidney development. FGFR1 is mainly expressed in MM lineages (early MM, developing into nephrons starting with vesicles and cap mesenchyme), the ureteric lineage, and renal cortical stroma. \textsuperscript{334,335} FGFR2 is mainly present in the Wolfian duct, the tips and trunks of UB, and differentiating nephrons, but has fewer expressions in early MM and stromal mesenchymal adjacent to the Wolfian duct. \textsuperscript{353} FGFR1 is located in renal vesicles. \textsuperscript{336} The expressions of FGF 1, 2, 7, 8, 9, 10, 12, and 20 during kidney development have been reported. \textsuperscript{338} FGF2 can be secreted by ureteric tips. FGF1, 7, and 10 are expressed in renal stroma. FGFR8 is mainly observed in the renal vesicle. FGF9 mostly locates in the UB as well as in the cap mesenchyme. FGF12 only presents in the UB. FGF20 is detected in nephron progenitors.

FGFs/FGFRs in urinary system development

FGFs/FGFRs in nephron development. Early researches in rodents and Xenopus laevis explants have found that exogenous FGF2 can maintain the sustained mesenchymal tissue growth and in some conditions induce formation of epithelial nephrons. \textsuperscript{340-342} More definitive evidences indicate the essential roles of FGF signaling in nephron formation. Deletion of FGF8 with either Pax3Cre \textsuperscript{344} (in the MM) or brachyury (T) Cre (in mesodermal) lineage results in small kidneys with a complete block in nephron formation after the epithelial vesicle stage. Like the conditional FGFR8 knockouts, global deletion of FGFR1 \textsuperscript{336} also leads to blockade of nephron differentiation. \textsuperscript{339} These data indicate that FGFR1 might be the candidate FGFR that binds to and mediates the effects of FGF8 in the nephron lineages.

FGF signaling also has positive effects on the maintenance of nephron progenitors. Among the growth factors known to have expression in embryonic kidney, FGF1, 2, 9, and 20 were found to promote proliferation of nephron progenitors in vitro. \textsuperscript{343} Global knockout of FGF9 and FGFR20 alone or together led to nephron progenitor apoptosis and subsequent renal agenesis. \textsuperscript{345} Exogenous FGF9 or FGFR20 is sufficient to maintain the stemness of MM or sorted nephron progenitors in vitro. \textsuperscript{347} However, FGF1 knockout mice, alone and in combination with FGFR1 knockout, have no nephron progenitor defects, \textsuperscript{348} and FGF1-null mice \textsuperscript{349} have no renal defects. Mice with double knockout of FGFR1 and FGFR2 in Pax3-positive cells display severe defect of MM, while mice with either FGFR1 or FGFR2 deficiency have well-developed kidneys. \textsuperscript{335} These results indicate that FGFR1 and FGFR2 may have a redundant role in establishing and sustaining early MM. Conditional deletion of FGFR1 and FGFR2 with Six2Cre (in nephron progenitors) reduces Six2-positive nephron progenitors leading to severe renal cystic dysplasia. \textsuperscript{349} FRS2a is the main driver of FGF signaling through ectopically activating notch signaling in nephron progenitors. \textsuperscript{349} Double mutant mice, carrying the point mutation in the FRS2a binding site of FGFR2 and conditional deletion of FGFR1 with Pax3Cre, show nephron progenitor depletion at later stages of development. \textsuperscript{350} Considering the similarity of the phenotypes in knockout mice, FGF9 and FGFR2 are the likely ligands for FGF/FRS2a in nephron development.

FGFs/FGFRs in ureteric branching and induction. FGF7 and FGFR10 bind to FGFR2 and regulate the growth and branching morphogenesis of the collecting duct system. FGF7-null mice show marked reduction in developing ureteric bud and mature collecting system with secondary loss of nephrons. \textsuperscript{351} Meanwhile, FGF7 administration could augment ureteric bud growth and increase the number of nephrons in vitro. \textsuperscript{351} FGFR10-null mice also have smaller kidneys with fewer collecting ducts. \textsuperscript{352} FGF7 and FGFR10 activate the b isoform of FGFR2. Consistently, mice deficient for FGFR2-IIb have dysgenesis of the kidney similar to that observed in FGFR7- and FGFR10-null mice. \textsuperscript{353} Recent studies further investigated the role of FGFR1 and FGFR2 in renal development using conditional knockout mice, since global deficiency of FGFR1 or FGFR2 leads to embryonic lethality prior to kidney development. Conditional loss of FGFR2 in the Wolfian duct and its derivatives, including the ureteric bud using Hoxb7Cre, leads to renal hypoplasia, such as small ampullary, few ureteric branches, and thin trunks. \textsuperscript{356,354} Furthermore, neither knockout FGFR1 alone nor double knockout of FGFR1 and FGFR2 with Hoxb7Cre led to additional abnormalities beyond single knockout of FGFR2. \textsuperscript{336} Global deletion of FGFR3 or FGFR4 in mice results in no obvious gross phenotype of kidney. \textsuperscript{359,106} These data together suggest that among four FGFRs, FGFR2 seems to be the most important one regulating ureteric bud branching morphogenesis and stromal mesenchyme patterning.

FGF signaling in kidney diseases

FGF and human genetic kidney diseases. Some mutations in FGFs or FGFRs in humans are associated with structural kidney and lower urinary tract diseases. Activating mutations of FGFR1, FGFR2, and FGFR3 lead to PS, AS, or TD. Some of these patients also have unilateral renal aplasia, hydrourereter, vesicoureteral reflux, renal hypoplasia, and/or cystic dysplasia. \textsuperscript{350} Patients with Kallman syndrome due to LOF mutations in FGFR1 have unilateral renal aplasia. Inactivating mutations of FGFR20 was found to cause bilateral renal aplasia. \textsuperscript{356} FGF signaling in CKD: Some endocrine FGFs (FGF21, FGF23) play important roles in CKD.

FGF21: FGF21 binds to a complex of KLB and FGFR1c to induce catabolic metabolism. Increased serum FGF21 levels are detected in CKD patients as early as stage 2. \textsuperscript{350} Since FGF21 was reported to have anti-aging effects, increasing the levels of FGF21 might be useful for the longevity of CKD patients. \textsuperscript{350} However, increased FGF21 also has many side effects. High FGF21 level can induce growth retardation, which might be related to the growth hormone resistance in children with CKD. \textsuperscript{357} Overexpression of FGF21 leads to osteopenia and increased adipogenesis in bone marrow that may contribute to the progress of CKD-mineral and bone disorder (CKD-MBD). \textsuperscript{356} High FGF21 may also be involved in the neuropsychiatric symptoms in CKD patients. Overexpression of FGF21 in mice causes disturbed circadian rhythm that can be rescued by specific ablation of KLB in the suprachiasmatic nucleus. \textsuperscript{359} Some researchers speculate that the circadian rhythm disorder related with high FGF21 level may contribute to the blood pressure fluctuation in CKD patients. \textsuperscript{350} FGF21 also increases serum corticosterone concentration that has been found to cause depression. \textsuperscript{359,360} Both depression and high FGF21 are associated with high mortality in dialysis patients. \textsuperscript{361,362} In brief, FGF21-KLB axis could be a potential treatment target in CKD.

FGF23: FGF23 is secreted from bone tissue and binds to a complex of α-Klotho and FGFFR1c, FGFFR3c, or FGFR4 in kidney as a hormone to regulate systemic phosphate homeostasis and vitamin D metabolism. \textsuperscript{363} A secondary elevation of serum FGF23 levels is commonly detected in CKD patients that are partly due to decreased renal clearance. \textsuperscript{364} The increased FGF23 is beneficial for lowering serum phosphate level and reducing 1,25(OH)\textsubscript{2}D\textsubscript{3}, which further increases the PTH level. These disturbed hormones would lead to CKD-MBD, which causes abnormalities of bone turnover, mineralization, bone volume, extraskeletal calcification, and increased mortality. \textsuperscript{365} Clinical studies indicate that elevated serum FGF23 concentrations can be used to predict kidney disease progression, especially in the early stages of diabetic
FGF/FGFR signaling in kidney disease and health
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FGF signaling in kidney injury and repair. Elevated FGF23 levels in the circulation and urine were reported in acute kidney injury (AKI) patients by numerous studies.377–381 FGF23 has been found to be an early marker of incident AKI. In three independent cardiac surgery cohorts, patients with AKI have higher levels of C-terminal FGF23 (cFGF23) than those who did not develop AKI as early as cardiopulmonary bypass ending.377,378,382 The predictive performance of cFGF23 was higher than other urinary injury biomarkers, including NAG (n-acetyl-b-D-glucosaminidase), KIM-1 (kidney injury molecule-1), and NGAL (neutrophil gelatinase-associated lipocalin) at the end of cardiopulmonary bypass.377 FGF23 is also thought to be a candidate prognostic marker for the adverse outcomes in AKI patients. Patients with the highest quartiles of cFGF23 and intact, biologically active protein (iFGF23) had a significantly increased risk of 60-day mortality than those having the lowest quartiles in two cohorts of critical illness involved AKI patients.383 Further study is required to clarify whether aberrant FGF23 contributes to the poor outcomes of AKI.

The mechanisms underlying the increased plasma FGF23 in AKI are not clear. Increased production of FGF23 in osteoblasts may be one of the major causes. Increased mRNA expressions of FGF23 in the bone, bone marrow, and renal tissues are found in several AKI mouse models.384–386 This could be reversed by pretreatment with PD173074, an FGFR inhibitor, or blocking the erythropoietin receptor.384,386 These results indicate that the increased circulating erythropoietin and erythropoietin receptor activation are involved in the mechanisms leading to increased plasma FGF23 in AKI. Resection of the obstructed kidney had no effect on the increased circulating iFGF23 levels,387 excluding the possibility that production of FGF23 by the kidneys contributes to plasma FGF23.

Considering the relevance of FGF signaling in kidney development and diseases, there may be potential therapeutic strategies to regulate the process of renal development and diseases by manipulating FGF signaling. For example, recombinant FGF10 may be useful in alleviating ureteric branching defects in Fraser syndrome (FRAS1 mutations).388 The requirement for FGF2 signaling in lower urinary tract mesenchyme389 suggests that FGF-related therapies could be used to repair the smooth muscle defects in the ureter or bladder. FGF7 expression levels are increased after chemically induced kidney injury in rats.390 Intravenous administration of recombinant truncated human FGF7 largely prevented cyclophosphamide-induced urothelial injury in rats,391 indicating that FGF7 could be a potential therapy for patients with bladder urothelial injury.

FGF SIGNALING IN MUSCLE AND HEART DEVELOPMENT AND DISEASE

FGF signaling in the skeletal muscle. FGFs are essential for the self-renewal of SCs and are needed for skeletal muscle maintenance and regeneration. FGF1, FGF2, FGF4, and FGF6 can be detected in SCs.393,394 FGF1 and FGF4 can be found in isolated myofiber cultures and in vivo injured adult skeletal muscle tissue.394,395

FGF2: FGF2 is present in the extracellular matrix and basal lamina of skeletal muscles,396 and is produced by fibroblasts,397 myofibers,398 and SCs,399 while the relative contribution of FGF2 to these cells is difficult to distinguish. FGF2 has been used as a routine medium supplement in SC primary culture.392 Although SCs from young mice (3–6 months) do not need supplementation of FGF2 in the culture medium, SCs from geriatric mice (29–33 months) cannot proliferate without the addition of FGF2.402 FGF2 is considered as a mitogen for SCs; it triggers SC proliferation by repressing myogenesis.303,404 However, FGF2 is not able to stimulate cell division without serum.405,406 Recently, it is reported that excessive FGF2 removes age-associated proliferative inhibition of SCs.407 The upregulated expression of FGF2 in aged muscle fibers and downregulated expression of SPRY1 in aged SCs increase the FGF signaling under homeostatic conditions and break the quiescence of SCs, resulting in SC depletion and losing self-renewing capacity.408 SPRY1, an inhibitor of FGF signaling, is highly expressed in quiescent adult SCs in uninjured muscle,409 while muscle stem cell niche, the muscle fiber, expresses FGF2 under homeostatic conditions. Spry1 is needed for the maintenance of the endogenous adult Pax7-positive SCs in their native environment, but it is downregulated in proliferating myogenic progenitors in injured muscles.410 Overexpression of SPRY1 in SCs or inhibition of FGF1 signaling can prevent SC depletion. Thus, blockade of FGFR2/FGF1 signaling might be a new therapeutic method to recover the regeneration capacity of skeletal muscles during aging.408 The expression of FGF2 is found to be increased during the muscle regeneration,398 and exogenous FGF2 could promote muscle regeneration in dystrophic muscle.411
mice. However, this effect is wiped out in FGF2-null mice, and injection of FGF-blocking antibodies also inhibits the regeneration process.412

FGF6: FGF6 can be detected in both embryonic and adult skeletal muscle tissues,13,414 and isolated myofibers.394 In adult mice, FGF6 is secreted by fast-twitch fibers, and its expression is increased after skeletal muscle injury.13 FGF6 mainly performs its function through binding to FGFRI.416 Presently, the role of FGF6 in the skeletal muscle is controversial. Interbreeding of FGF6-deficient mutants with dystrophic mdx mice (a model for Duchenne muscular dystrophy) results in tremendous dystrophic changes in skeletal muscles, including degeneration of myotube, emergence of many mononuclear cells, and collagen deposition. MyoD mRNA is normally upregulated in mdx; however, it is not observed in double mutant mice.415 It is also reported that FGF6-deficient mice show regeneration defects with myotube degeneration and severe fibrosis.13 The numbers of MyoD+ Myogenin+ activated SCs are severely reduced in mutant mice after injury, and which is not caused by the decreased quiescent SCs, probably by the lack of activated SCs.415 However, another team declared that no skeletal muscle phenotype is found in FGF6-deficient mice, and FGF6 might not play an essential role in muscle regeneration or its function is compensated by other FGFs.417 Using FGF6 global knockout mice and rescue experiments, Armand et al.415 found that FGF6 is participated in soleus regeneration of adult mice in a specific dose-dependent manner: FGF6 promotes the proliferation of the myogenic cells at high doses, while it regulates the differentiation of myogenic cells and muscle phenotype via a calcineurin signaling pathway at lower doses. Genetic deletion of FGF2 and FGF6 in mdx mice leads to much more severe dystrophic phenotypes in FGF2/FGF6/MDX triple-mutant mice than in mdx mice, which further supports that FGF6 plays an important role in muscle regeneration.

FGF15/19: Recently, FGF19 has been reported to have novel function in enlarging muscle fiber size, and in protecting the skeletal muscle from atrophy.420 Pharmacological dosage of FGF19 significantly increases human myotube size in vitro.420 Treatment of mice with FGF19 causes skeletal muscle hypertrophy, while genetic deletion of KLB eliminates the hypertrophic effect of FGF19 in mice.420 Both in vitro and in vivo, FGF19 stimulates the phosphorylation of ERK1/2 and the ribosomal protein S6 kinase (S6K1), which is an mTOR-dependent key regulator of muscle cell growth.420 Studies also found that FGF19 relieves the skeletal muscle wasting induced by glucocorticoid, obesity, or sarcopenia in mice. Therefore, FGF19 have the therapeutic potential for promotion of the skeletal muscle mass and treatment of muscle wasting.420

FGFRs in the skeletal muscle. Among the four FGFs, SCs express high levels of FGFRI and FGFRII, low levels of FGFRIII, and little or no detectable FGFRIII.404,421 However, studying the relative contributions of the FGFRs to SCs is rather difficult, because they usually activate multiple intracellular signaling pathways and their functions are often compensated by each other when inhibited by one of the FGFRs.

FGFRI: FGFRI is highly expressed in freshly isolated SCs and myogenic cultures, and it has been considered in the context of adult myogenesis.394,422 FGFRI-null mice cannot gastrulate.423,424 Myogenic-specific (MyoDCre-driven) ablation of FGFRI in mice seems to have no overt effect on the histology characteristics of muscle and the progress of muscle regeneration following cardiotoxin-induced injury.404 In contrast, SCs could not respond to the stimulation of FGF2 in isolated myofibers from FGFRI-ablated mice,404 which suggests that other FGFRs may compensate the function of FGFRI during SC differentiation. FGFRI downstream signals include both ERK regulating SC proliferation425 and p38α and p38β (p38α/β) MAPK pathways that is involved in the exit of SCs from quiescence,426,427 asymmetric division of SCs,427 and differentiation of SCs in vivo.427 Recently, it is reported that SCs from aged mice autonomously lose their self-renewal ability due to alterations in FGFRI, p38α, and p38β MAPK signaling.428 Ectopic activation of phospho-FGFRI partially rescues their age-associated self-renew ability with asymmetric localization of phospho-p38α/β MAPK in dividing SCs.428 These results highlight an age-associated deregulation of homeostatic network of SCs and hints a therapeutic potential for the treatment of muscle wasting.

FGFRII: FGFRII is expressed in intact myofibers, muscle connective tissue, isolated proliferating and differentiating SCs in culture.394 FGFRII plays a role in cell fate determination during embryonic muscle development.429 However, FGFRII-null mice are healthy and fertile with no evident muscle defects, which hints that FGFRII is dispensable during embryonic development.306

FGF signaling in the heart
Unlike other tissues and organs such as muscle, blood, and liver, the mammalian heart possesses very limited regenerative capacity. Mammalian cardiomyocytes could robustly proliferate in the second heart field during early organogenesis.430 However, recent lineage tracing studies dubbed c-Kit-positive cardiac stem cells (CSCs), which had no cardiogenic activity and could not support heart repair in adulthood.431,432 Instead, the injured myocardium develops scar and fibrosis.435 Thus, researchers have been tempted to uncover the mechanisms of the cardiogenesis and regeneration, which may make it possible to stimulate and manipulate the regenerative potential of heart. FGF signaling pathways, especially FGFs, have been shown to be highly involved in the cardiac development, diseases, and repair.

FGF1. FGF1 together with TNF-related weak inducer of apoptosis (TWEAK), by binding to FGFRI, could induce cardiomyocyte cycle re-entry.436 This effect can be blocked by inhibiting the TNF receptor superfamily member FGF-inducible molecule 14. TWEAK induces the activation of cardiomyocyte cycle, which can be inhibited by blocking FGF1 signaling.437 Co-stimulation experiments showed that FGF1 and TWEAK could regulate the cardiomyocyte cycle induction via PI3K/AKT signaling.438 It is also reported that the treatment of FGF1 stimulation and p38 inhibition have protective effect on ischemic heart disease by inhibiting cardiomyocyte apoptosis.437,438 In vitro postnatal mammalian cardiomyocytes can proliferate under the FGF1 stimulation and p38 MAPK (p38) inhibition,439 and the combination treatment also increases cardiomyocyte mitosis after acute myocardial injury in 8–10-week-old rats. Four weeks after injury, the treatment reduces heart scarring, wall thinning, and markedly rescues cardiac function.439 However, cardiac-specific overexpression of FGF1 only delays the formation of myocardial infarct, but has no significant effect on maximal infarct size.440 In contrast, inhibition of p38 fails to rescue heart function despite increased cardiomyocyte mitosis. These results imply that FGF1 might promote the survival of newly generated cardiomyocytes through the enhancement of angiogenesis.439 Even so, the combination of FGF1 stimulation and p38 inhibition may have therapeutic effect by improving human cardiac regeneration.435

FGF2. FGF2 is widely expressed in murine heart. In FGF2 transgenic mice, the hearts exhibit exacerbated cardiac hypertrophy assessed by myocyte cross-sectional area and heart weight-to-body weight ratios, which is eliminated in the presence of ERK inhibitor, but not p38 pathway inhibitor.441 In contrast, the chronic elevation of blood pressure, fibrosis, and hypertrophy induced by two-kidney one-clip can be attenuated in FGF2
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knockout mice.\textsuperscript{542} Isoproterenol-induced and myocardial infarction-induced cardiac fibrosis and hypertrophy can also be attenuated in FGF2 knockout mice.\textsuperscript{441,443} Besides, FGFR2 is a cardio-protector in myocardial infarction models and ischemia/reperfusion (I/R) injury.\textsuperscript{444} The expression of FGF2 is shown to be upregulated after a cardiac injury.\textsuperscript{445} FGF2 inhibits the autophagy and increased the clearance of ubiquitinated protein through PI3K/AKT/mTOR signaling in mouse myocardial I/R injury model.\textsuperscript{446} FGF2 also suppresses endoplasmic stress and mitochondrial dysfunction through PI3K/AKT and RAS/MAPK signaling pathways.\textsuperscript{446} Therefore, FGF2 is being tried for treating ischemic conditions in several clinically relevant trials.\textsuperscript{447–449}

FGF9. FGF9, expressed in the endocardium and epicardium, regulates cardiomyocyte proliferation during embryogenesis,\textsuperscript{555} and newborn FGF9 knockout mice develop a dilated cardiomyopathy due to premature differentiation of cardiomyocytes.\textsuperscript{450} FGF9 is also shown to improve systolic function and heart failure mortality by stimulating the hypertrophy of non-infarcted left ventricular after myocardial infarction with increased microvessel density (MVD), reduced fetal gene expression, and interstitial fibrosis in myocardium-specific transgenic FGF9 mice.\textsuperscript{451} However, FGF9 only stimulates the network formation and the proliferation of endothelial cells (ECs) without induction effects on myocardial hypertrophy in culture.\textsuperscript{452} It is reported that FGF9 can mediate the differentiation of monocytes to M2 macrophages; FGF9 treatment of an infarcted myocardium in diabetic mice increased anti-inflammatory cytokines and M2 macrophage differentiation, which resulted in reduced adverse remodeling and improved cardiac function.\textsuperscript{453} Therefore, FGF9 may have novel therapeutic potential for this type of myocardial infarction.

FGF10. FGF10 is found in the second heart field during early heart development,\textsuperscript{439} and also expressed in progenitors for the right ventricle and outflow tract.\textsuperscript{453} Neonatal mouse hearts possess the regenerative ability, but gradually lose this ability after postnatal day 7.\textsuperscript{454} FGF10 is reported to promote regional fetal cardiomyocyte proliferation and cell-cycle re-entry of adult cardiomyocytes, but has no effect on fibroblasts that is mediated by FOXO3/P27.\textsuperscript{454} In addition, FGF10 deficiency mice display misplacement of the heart in the thoracic cavity with right ventricular hypoplasia due to reduced cardiomyocyte proliferation.\textsuperscript{455} In contrast, overexpression of FGF10 in the myocardium of mice promotes cardiomyocyte proliferation after heart injury without the increase of epithelial-to-mesenchymal transition and fibrosis;\textsuperscript{456} thus, FGF10 may be a potential drug for cardiac repair.

**FGF SIGNALING IN ANGIOGENESIS, LYMPHANGIOGENESIS, AND RELATED DISEASES**

Angiogenesis or lymphangiogenesis is the process of vascular or lymphatic formation during physiological and pathological conditions, such as embryogenesis, trauma, inflammation, and tumor development. Since lymphatics can be derived from the sprouting of veins, lymphangiogenesis is considered to be associated with angiogenesis.\textsuperscript{457} FGF/FGFR signaling has been demonstrated to play important roles in angiogenesis and lymphangiogenesis.

Expressions of FGFs/FGFRs during angiogenesis and lymphangiogenesis

FGFR1 is expressed in vascular ECs and FGRF1 knockdown leads to upregulated FGFRII expression in the endothelium.\textsuperscript{458} FGRF2 was found expressed in murine aortic endothelium.\textsuperscript{459} ECs express the FGFRIIIIC, FGFRIIIC, and FGFRIIIIC isoforms of FGFRs, but not the IIIb isoforms or FGFR4, and vascular SMCs (VSMCs) express the similar isoforms of FGFRs; several FGFs are expressed in ECs (FGFs 1, 2, 5, 7, 8, 16, and 18) and VSMCs (FGF1, 2, 5, 8, 16, and 18). FGRF1 and FGRF3 are expressed in lymphatic ECs (LECs) during lymphangiogenesis as demonstrated by several studies,\textsuperscript{458,460} and they were reported to be critical for the lymphatic formation.

FGF signaling in vascular and lymphatic formation

FGF signaling can influence the whole process of angiogenesis. Activation of FGRF1 or FGRF2 has been demonstrated to have a positive effect on vascular endothelial proliferation.\textsuperscript{461} One important step of angiogenesis is extracellular matrix degradation. Some FGFs, including FGF1, FGF2, and FGF4, promote the expressions of MMPs in ECs.\textsuperscript{462} FGF2 can stimulate shedding of MMP2 and MMP9 in cell surface membrane vesicles from ECs, which is able to stimulate the angiogenesis of ECs seeded in Matrigel.\textsuperscript{463} Another essential step of angiogenesis is endothelium migration. FGF1, FGF2, FGF8, and FGF10 were demonstrated to stimulate endothelium chemotaxis.\textsuperscript{464} The pro-chemotactic effect of FGF2 depends on activation of MAPK.\textsuperscript{465}

The role of FGRF3 in lymphangiogenesis is controversial. It is revealed that FGRF3 is a novel target gene of PROX1, which is essential for lymphatic development. Knockdown FGRF3 by small interfering RNA (siRNA) inhibited LEC proliferation.\textsuperscript{466} Meanwhile, 9-cis retinoic acid (9-cisRA) was reported to activate FGF signaling and enhance lymphatic formation and regeneration by promoting the proliferation, migration, and tube formation of LECs.\textsuperscript{466} FGRF3 expression in LECs was upregulated after 9-cisRA treatment. 9-cisRA-induced LEC proliferation and migration were significantly inhibited by soluble FGRF3 recombinant protein as well as FGRF inhibitor PD173074.\textsuperscript{466} However, Yu et al.\textsuperscript{467} showed that FGRF3 alone is not enough to influence lymphangiogenesis. Vascular and lymphatic vessel defects were observed in FGRF1/FGRF3 double mutant mice, but single knockout of FGRF1 or FGRF3 led to no abnormality in lymphatic front migration in embryonic mouse skin examined by whole-mount staining for VEGF3 (vascular endothelial growth factor receptor 3) and PECAM1 (platelet and endothelial cell adhesion molecule-1). The controversial effects of FGRF3 on lymphatics may be due to its differential influence on LECs during embryonic phase or adulthood.

FGF/FGFR-related diseases with abnormal angiogenesis and lymphangiogenesis

There are few clinical reports about the relationships between FGFs/FGFRs and diseases with abnormal angiogenesis and lymphangiogenesis. Some experimental results demonstrate that FGFs/FGFRs may play an essential role in diseases with abnormal vascular formation. Many tumor cell lines produce FGF2.\textsuperscript{467} Inhibition of FGRF1 by FGF2 antisense complementary DNAs (cDNAs) suppressed vascularization and growth of human melanomas in nude mice.\textsuperscript{468} Furthermore, FGF levels were correlated with intratumoral MVD, an important parameter for tumor progression.\textsuperscript{469} In some tumors like melanoma, FGRF2 level has a strong correlation with MVD and clinical outcome of the patients.\textsuperscript{469} However, whether FGFRs/FGFRs also influence tumor parenchyma needs to be further clarified. Inflammation is an important trigger for angiogenesis. It is revealed that monocytes, mononuclear phagocytes, and mast cells express FGF2.\textsuperscript{470} Inflammatory cytokines including IL-1β can stimulate FGF2 production in ECs.\textsuperscript{471} inflammatory mediators might stimulate angiogenesis through increasing FGF signaling in endothelium. EC death can lead to increased FGF2 release. Hypoxia upregulates VEGF and FGF2 production and increases endothelial responsiveness to FGF2.\textsuperscript{472} The activity of FGF/FGFR signaling may be strongly associated with inflammation and influence angiogenesis at multiple levels.

FGF signaling and EndMT

Endothelial-to-mesenchymal transition (EndMT) is the process through which ECs transform into mesenchymal cells. EndMT plays important roles in the pathogenesis of various human diseases, including cardiac fibrosis, atherosclerosis, and...
heterotopic ossification (HO). EndMT was first confirmed in animal models in which Tie1+ endothelials adopted cardiac fibroblast fate during cardiac fibrosis development. Further investigations found that Tie2+ vascular ECs contributed to HO formation in fibrodsplasia ossificans progressiva and BMP4-induced HO mouse models. Currently, TGF-β1 signaling is regarded as the main inducer of EndMT. FGF signaling has recently been demonstrated to downregulate TGF-β signaling and inhibit EndMT. Basal FGF signaling maintains endothelial homeostasis through inhibiting the expressions of TGF-β, TGF-βR1, and SMAD2 via controlling the let-7 microRNA (miRNA) levels. Meanwhile, in vitro and in vivo experiments showed that inflammatory cytokines, including interferon-γ, TNF-α, and IL-1β, decreased FGFR1 expression, leading to reduced FGF signaling activation in ECs. Another study reported that FGF2 can induce miRNA-20a expression, which represses TGF-β signaling in endothelium and inhibits EndMT. Therefore, it is plausible that FGF signaling downregulation by inflammatory cytokines contributes to vascular neointima formation and fibrosis driven by TGF-β-induced EndMT.

Therapeutic modulation of angiogenesis and lymphangiogenesis

Therapeutic angiogenesis is a promising approach to the recovery of ischemic diseases. It was shown that intracoronary FGF2 administration preserved myocardial function by increasing vascularization. Some clinical trials demonstrated that FGF2 administration can improve the symptoms of patients with coronary artery disease or peripheral artery disease. In addition, inhibition of FGFR2/FGFR1 by antisense cDNAs blocked intratumoral angiogenesis and arrested the growth of human melanomas grown subcutaneously in nude mice. FGF-based angiogenic therapy has been shown to be a potential treatment for patients with ischemic diseases. However, many details including timing, dosage, application alone, or in combinations with other drugs and effective delivery approach need to be further clarified. There are few reports about the therapeutic modulation of lymphangiogenesis based on FGF signaling. c-Src was reported to have a therapeutic effect on lymphatic regeneration and secondary lymphedema in experimental mouse models, which could be dependent on FGF signaling in LECs.

FGF SIGNALING IN INFLAMMATORY RESPONSE

Inflammation is a complex adaptive response that can be induced by endogenous and exogenous substances/stimuli. Besides the recognition of inducers, inflammatory response includes multiple processes such as the production of multiple inflammatory mediators, including inflammatory factors, chemokines, and vasoactive amines, which are released by immune cells like macrophages and mast cells. There are lots of studies reported that FGFs/FGFRs play important roles in the regulation of inflammatory response.

FGFs in inflammation

FGF1 in inflammation. FGF1 can accentuate inflammatory response. Generally, FGF1 is highly expressed in the inflammatory cells and tissues. High levels of FGF1 can be found in multiple tissues of inflammatory arthritic joints, including bone, cartilage, synovium, ligament, and tendon. Besides, most T cells in synovial tissue in rheumatoid arthritis express FGFR1 for FGF1. FGF1 can enhance IL-2 production and activation of NF-κB in T cells. Rossini et al found that both FGF1 and FGFR1 are expressed in filtering lymphocytes and macrophages during the renal inflammation, and FGFR1 is highly expressed in tubules, suggesting that FGF1 might have both autocrine and paracrine functions. Hackshaw and Shi reported that FGF1 affects the calcium mobilization and increases the level of cytosolic calcium in macrophages. FGF1 causes ATP release from spinal astrocytes and opens gap junction channels after spinal cord injury, which may aggravate the inflammation in neurological disease and injury. Recently, Huang et al engineered the FGF1 mutants (termed FGF1ΔHBS) with reduced ability to activate FGFR, and found that FGF1ΔHBS inhibited inflammation and oxidative stress in CKD via activating PI3K/AKT and GSK-3β/NfκB pathways, which inhibited the ASK1/JNK. The results suggest that FGF1 bears the responsibility of anti-inflammation, especially in certain chronic inflammatory diseases. Besides, FGF1 has the ability of anti-inflammation in diabetic nephropathy via inhibition of JNK (c-Jun N-terminal kinase) and NF-κB pathways. Thus, the effects of FGF1 on inflammation may vary from different diseases and conditions.

FGF2 in inflammation. FGF2 is also involved in several inflammation-related diseases such as multiple sclerosis and rheumatoid arthritis. Ectopic expression of FGF2 exacerbates inflammatory response and symptom of colitis and collagen-induced arthritis models. FGF2 contributes to the inflammation in articular cartilage during the process of OA. Besides, the level of FGF2 is increased during the whole blood inflammatory reaction induced by the artificial surface. During the infection of HIV, FGF2 shows a positive correlation with the number of CD4+ T cell. FGF2 induces the expression of RANKL via ERK1/2 activation in human bone marrow mesenchymal stromal cells, which suggests that FGF2 may play the osteoimmunological role during bone regeneration. Pawlowski et al found that FGF2 is highly expressed in fibroblasts and adipocytes, and FGF2 may contribute to perpetuation of inflammation in the orbital tissue of Graves’ orbitopathy. FGF2 has close relationship with inflammatory response during angiogenesis such as activation of pro-inflammatory chemokines in ECs and engagement of monocyte/macrophage. FGF2 increases the concentrations of cellular IL-1β in human VSMC. The above studies indicate that FGF2 has the function of pro-inflammation. However, exogenic FGF2 could attenuate inflammatory response such as the decreased expression of IL-1β in epileptogenesis-associated neuroinflammation. In addition, inhaling recombinant FGF2 decreases lung inflammation in asthma and COPD. Thus, targeting FGF2 is a potential method to alleviate certain inflammatory diseases such as neuroinflammation, asthma, and COPD.

FGF3/FGF21/FGF23 in inflammation. Unlike FGF1 and FGF2, there are few studies that reported the relationship between FGF3 and inflammation. The level of FGF3 in sinonasal tissues is significantly upregulated in acute allergic rhinitis and chronic sinonasal inflammation mouse models. However, FGF3 level in middle ear is significantly downregulated in mouse model for acute otitis media. Combining these results, we speculate that the role of FGF3 in inflammation may be distinct in the different tissues/organisms.

FGF21 can be induced by inflammatory stimuli. FGF21 is associated with the suppression of cardiac, renal, and hepatic inflammation. FGF21 is thought to be one of the potential immunotherapy targets for cardiovascular inflammation and pancreatic fibrogenesis as it can alter the macrophage polarization states. Exogenous FGF21 was found to alleviate soaking of inflammatory cells in the lung potentially via elevation of IL-10. FGF21 inhibits macrophage migration and significantly reduces inflammatory factor expression in oxidized low-density lipoprotein-induced THP-1 macrophages. In addition, FGF21 can also repress inflammatory factors induced by insulin resistance. FGF21 has anti-inflammatory effect on preadipocytes via FRS2/ERK1/2 signaling pathway. Besides, FGF21 can suppress the production of IL-1β mediated by NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome. In general, inflammation increases the expression of FGF21, which is an
anti-inflammatory factor in many diseases.

The relationship between inflammation and FGF23 may be bidirectional. Lang et al. suggested that the increase of FGF23 induced by inflammatory signaling may amplify inflammation by suppressing the synthesis of the anti-inflammatory 1,25(OH)2D3 in inflammatory diseases. Besides, FGF23 can induce multiple inflammatory signaling pathways like TNF-α signaling. In addition, FGF23 activates calcineurin signaling by activating FGFR4 in hepatocytes, which causes the increased level of inflammatory cytokines in CKD. In summary, inflammatory response can induce the expression of FGF23 and FGF23 can act as a pro-inflammatory factor.

FGFRs in inflammation
In addition to the FGFs, the receptors of FGFs also play important roles in inflammatory response. FGFR1 promotes inflammation via activating NF-κB signaling pathway in prostate cancer cells. However, FGF2/FGFR1 pathway has inhibitive effects on astrocyte-mediated neuroinflammation after infrasound exposure. In turn, there is a profound reduction in FGFR1 in human umbilical vein ECs treated by TNF-α and IL-1β, while other inflammatory cytokines such as IL-6 could not inhibit the expression of FGFR1. Besides, our group recently identified that FGFR3 deficiency promoted chemotaxis of macrophages via activation of NF-κB/CXCR7 signaling pathway, which reveals the negative role of FGFR3 in synovial inflammatory response. More studies about the roles of FGFRs in inflammation are needed in the future.

Inflammatory response is regulated by multiple factors in a variety of cellular behaviors. Targeting pro-inflammatory factors such as IL-6 and TNF-α has been shown to be an effective therapy for some inflammatory diseases, and therapeutic antibodies are also promising strategy to treat inflammatory diseases. From the above studies, we can conclude that FGF signaling has close relationships with inflammatory response, and whether it exerts a pro-inflammatory or an anti-inflammatory role mainly depends on the types of FGFs and inflammation of diseases. Application of specific modulatory molecules such as antibodies against pro-inflammatory FGFs/FGFRs like FGF23 will benefit for certain inflammation-related diseases.

FGF SIGNALING IN METABOLISM
Among the 22 members of the FGF family, FGF15/19, FGF21, and FGF23 comprise the FGF19 subfamily that functions as endocrine hormones to regulate bile acid (BA), fatty acid, glucose, and mineral metabolism.

FGF15/FGF19 in energy homeostasis
FGF15 and its human ortholog FGF19 (FGF15/19) are gut-derived circulating hormone that represses hepatic BA synthesis through FGFR4 and the coreceptor KLB complex. Furthermore, FGF15/19 also regulates global body energy and glucose homeostasis (Fig. 3).

FGF15 is highly expressed in the ileum, jejunum, and duodenum of adult mice. FGF19 is expressed in human ileum and gallbladder epithelial cells, and is not detected normally in human liver. The expression and production of FGF15/19 are regulated by many factors, such as BAs, nutrition, and so on.

Effect on liver and gallbladder
BA homeostasis: FGF15/19 negatively regulates BA synthesis. FGF19 treatment inhibits the expression of cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting and major regulatory enzyme of BAs, by an autocrine/paracrine mechanism in hepatocytes. Deletion of FGF15 in mice results in enhanced BA production by upregulating CYP7A1 expression in the liver, while FGF15 administration inhibits BA production by decreasing CYP7A1 mRNA levels.

The alternation of gallbladder filling and emptying regulates the bile flowing into the intestine. FGF15/FGF19 is required for gallbladder filling as evidenced by the absence of bile in the gallbladder of FGF15 knockout mice, and FGF15 or FGF19 treatment leads to significant increase in gallbladder volume, which is partially caused by a cAMP-dependent relaxation of gallbladder smooth muscle.

Hepatic glucose and lipid metabolism: Fed FGF15 knockout mice showed decreased hepatic glycogen stores in the liver, and administration of FGF19 significantly promotes glycogen

![Fig. 3](image-url) The regulation of FGF15/19 on energy metabolism. FGF15/19 regulates energy metabolism both peripherally and centrally. In the liver, FGF15/19 inhibits BA production and promotes gallbladder filling. As for lipid and glucose metabolism, FGF15/19 improves glycogen synthesis, but suppresses lipogenesis and gluconeogenesis. In the adipose tissue, FGF15/19 promotes energy expenditure and fatty acid oxidation. In the brain, FGF15/19 promotes the expression of CRF in the hypothalamus and stimulates sympathetic nerve activity, and then increases energy expenditure in the adipose tissue. Furthermore, FGF15/19 promotes peripheral insulin sensitivity and glucose metabolism by repressing HPA axis and AGRP/NPY neuron activity. AGRP agouti-related protein, BA bile acid, HPA hypothalamic-pituitary-adrenal, NPY neuropeptide Y.
accumulation and protein synthesis in the liver of fasted mice, which is independent of insulin action.\textsuperscript{541} FGF15/19 also suppresses hepatic metabolic, such as the tricarboxylic acid cycle flux and gluconeogenesis, through inhibiting CREB-PGC-1α (cyclic AMP response element binding protein-peroxisome proliferator-activated receptor-γ coactivator-1α) signaling.\textsuperscript{542}

FGF15/19 represses liver fat storage. FGF19 transgenic mice show decreased expression of lipogenic enzymes and liver triglyceride levels.\textsuperscript{530} FGF19 inhibits the expression of lipogenic enzymes and the insulin lipogenic action in rat primary hepatocytes through activating STAT3 signaling and repressing PGC-1β expression,\textsuperscript{543} and also enhances the expression of fatty acid oxidation-related proteins.\textsuperscript{544,545} Long-term treatment by FGF19 reduces liver lipid accumulation in vivo and protects liver from diet-induced steatosis.\textsuperscript{546}

Effect on body energy and glucose homeostasis. FGF15/19 is beneficial for global energy balance. FGF19 transgenic mice have a significantly reduced fat mass resulted from increased metabolic rate that leads to enhanced energy expenditure, and do not become diabetic or obese when fed a high-fat diet (HFD).\textsuperscript{530} In HFD fed mice, FGF19 increases the metabolic rate simultaneously with an increased fatty acid oxidation, and alleviates the obesity in ob/ob mice.\textsuperscript{529} Adeno-associated virus (AAV) delivery of FGF15 and FGF19 reduces fat mass and increases energy expenditure in diet-induced obesity (DIO) mice, and FGF19 can also overt diabetes in db/db mice.\textsuperscript{531}

In addition to the direct effects of FGF15/19 on body energy metabolism, FGF15/19 also regulates the energy and glucose metabolism by affecting brain after binding to FGF14 and KLB in the brain.\textsuperscript{538,546} FGF19 activates ERK signaling in the hypothalamus.\textsuperscript{547} Intracerebroventricular (ICV) injection of FGF19 induces the sympathetic nerve activity to BAT and increases energy expenditure,\textsuperscript{548} and also improves peripheral insulin sensitivity and glucose metabolism by reducing hypothalamic agouti-related protein/neuropeptide Y neuron activity and activating of ERK1/2 signaling in obese and insulin-resistant states.\textsuperscript{549} Furthermore, FGF15/19 signaling in the central nervous system has an insulin-independent glucose-lowering effect. Acute ICV FGF19 injection reduces food intake and body weight, and improves glucose tolerance without changing plasma insulin levels.\textsuperscript{546,549} The suppressed hypothalamic-pituitary-adrenal (HPA) axis and subsequent decreased hepatic acetyl CoA level are responsible for mediating the insulin-independent, glucose-lowering effects of FGF19.\textsuperscript{549}

Metabolic role of FGF21

FGF21 is mainly expressed in the liver, adipose tissue and pancreas,\textsuperscript{550,551} and also expressed in the muscle.\textsuperscript{552} Under physiologic conditions, FGF21 in the blood is mostly derived from the liver.\textsuperscript{551} FGF21 activates FGF signaling by binding to FGFRIc and its coreceptor protein KLB in the liver, adipose tissue, and brain.\textsuperscript{552}

FGF21 is a hormone regulating glucose and lipid homeostasis, and insulin sensitivity. FGF21 can cause weight loss, decrease plasma glucose and triglycerides level, and improve insulin sensitivity in obese and diabetic animal models without affecting total caloric intake.\textsuperscript{553,554} Mice with overexpressed FGF21 resist to DIO. In both ob/ob and db/db mice,\textsuperscript{553,554} treatment of FGF21 decreased serum glucose and triglycerides to near normal levels. FGF21 regulates glucose and lipid metabolism mainly by affecting liver, adipose tissue, and brain (Fig. 4).

The effect on liver. Nutritional stresses, such as starvation, amino acid restriction, ketogenic, and HFD, can strongly induce the expression and release of FGF21 in liver.\textsuperscript{535}

FGF21 decreases insulin resistance, enhances fat oxidation, and suppresses hepatic steatosis in the liver of DIO and ob/ob mice,\textsuperscript{553,554} which is related to the increased level of adiponectin in vivo.\textsuperscript{556} FGF21 participates in high-fat, low-carbohydrate ketogenic diet-induced triglyceride clearance, hepatic lipid oxidation, and ketogenesis. Downregulated hepatic FGF21 in ketogenic diet-fed mice altered the expressions of lipid and ketone metabolism-related genes in the liver, and leads to fatty liver, lipemia, and decreased serum ketone.\textsuperscript{557} FGF21 stimulates hepatic gluconeogenesis and ketogenesis in the liver during fasting and starvation\textsuperscript{558,559} by inducing the expression of PGC-1α.\textsuperscript{557} FGF21 knockout mice fail to induce PGC-1α expression and have impaired gluconeogenesis and ketogenesis in response to a prolonged fast.\textsuperscript{559} However, the mechanisms for the regulation of FGF21 on liver metabolism need to be further explored.

The effect on adipose tissue. In addition to liver, adipose tissue is another source of systemic FGF21. White adipose tissue (WAT) stores energy, and brown adipose tissue (BAT) expends energy to generate heat through a process known as adaptive thermogenesis.\textsuperscript{560} FGF21 in WAT is induced by fasting/refeeding regimens and the thiazolidinedione drugs.\textsuperscript{558} FGF21 in BAT is induced by cold exposure.\textsuperscript{561}

FGF21 stimulates glucose uptake in adipocytes in an insulin-independent manner through induction of GLUT1 expression,\textsuperscript{562} and inhibits lipolysis of adipocytes.\textsuperscript{563,558} However, FGF21 stimulates lipolysis in WAT during starvation.\textsuperscript{558}

The thermogenic activity of BAT and browning of WAT are important components of energy expenditure, which can be induced by FGF21.\textsuperscript{559,564} Cold exposure induces expression of mitochondrial uncoupling protein 1 (UCP1) in BAT. UCP1 uncouples oxidative phosphorylation, releasing chemical energy as heat.\textsuperscript{565} FGF21 improves the expression of UCP1 in WAT by upregulating PGC-1α protein level and promoting browning of WAT in adaptive thermogenesis.\textsuperscript{559,566} FGF21 knockout mice show diminished browning of WAT and a decreased adaption to chronic cold exposure.\textsuperscript{566} In addition, FGF21 also upregulates UCP1 mRNA expression through CREB\textsuperscript{567} signaling, and induces phosphorylation of STAT3 to activate the oxidative metabolism in adipose tissues.\textsuperscript{567}

FGF21 also promotes adipocyte differentiation and insulin sensitivity by stimulating peroxisome proliferator-activated receptor-γ (PPAR-γ) transcriptional activity through inhibiting its SUMOylation in WAT\textsuperscript{568,569} in DIO mice. FGF21 knockout mice show decreased WAT mass with reduced PPAR-γ activity, adipocyte size, and insulin sensitivity in DIO mice.\textsuperscript{569}

The effect on brain. In addition to regulating liver and adipose tissue, FGF21 also involves in energy metabolism through regulating brain. FGF21 is not expressed in the central nervous system,\textsuperscript{532} but can cross the blood–brain barrier to enter into the brain.\textsuperscript{570} ICV injection of FGF21 in obese rats increases hepatic insulin sensitivity and energy expenditure.\textsuperscript{571} FGF21 improves the expression of neuropeptide corticotropin-releasing factor in the hypothalamus and stimulates sympathetic nerve activity, and then promotes energy expenditure in BAT.\textsuperscript{572} Furthermore, FGF21 activates the HPA axis for the release of corticosterone that stimulates hepatic gluconeogenesis.\textsuperscript{555}

The effect of FGF23 on mineral metabolism

FGF23 is mainly secreted by osteoblasts and osteocytes in bone tissue,\textsuperscript{573} and regulates systemic phosphate homeostasis and vitamin D metabolism through binding FGFR and the coreceptor α-Klotho complex in cell membranes of target tissues.\textsuperscript{574} (Fig. 5).

The effect on metabolism of phosphate, sodium, and calcium. Clinical studies identified the important role of FGF23 in regulating phosphate metabolism. Mutations in an RXRα site in FGF23 lead to ADHR characterized by low serum phosphorus level, osteomalacia, and rickets, as well as short stature and bone pain.\textsuperscript{126} FGF23 is also
the cause of tumor-induced osteomalacia and fibrous dysplasia because of its overexpression in tumors and osteogenic cells in fibrous dysplastic lesions. Furthermore, multiple FGF23 gene mutations lead to reduced FGF23 level in patients, which is responsible for hyperphosphatemia in patients with hypophosphatemia and tumor-like soft tissue calcifications. In mouse models, overexpression of FGF23 in the liver, osteoblasts, or ubiquitously in mice lead to decreased serum phosphate concentration and rachitic bone.

Phosphate homeostasis is simultaneously regulated by several organs, including the kidney, intestine, and bone. Type II sodium-phosphate co-transporters (NPT2) are responsible for the absorption of extracellular phosphate. Type Ila sodium-phosphate co-transporter (NPT2a, NaPi-2a) is mainly expressed in the brush-border membrane of proximal tubules of the kidney. FGF23 inhibits renal phosphate reabsorption and leads to phosphate loss by inhibiting the expression of NaPi-2a/2c through binding to a FGFR1-α-Klotho coreceptor complex and activating ERK signaling. NaPi-2b is expressed in the luminal membrane of the ileum and regulates phosphate absorption in the intestine. 1,25(OH)₂D₃ also promotes phosphate absorption in the intestine. FGF23 can reduce NaPi-2b level to inhibit phosphate absorption in the intestine. 1,25(OH)₂D₃ also promotes phosphate absorption in the intestine. FGF23 can reduce 1,25(OH)₂D₃ level by inhibiting the expression of NaPi-2a/2c.

In addition, FGF23 also regulates the metabolism of sodium and calcium. FGF23 promotes sodium reabsorption by increasing the sodium chloride co-transporter expression in the distal renal tubules and then may indirectly suppress 1,25(OH)₂D₃-mediated intestinal phosphate absorption.

The regulation of FGF23, FGF signaling participates in the regulation of FGF23. Several OGD patients caused by activating mutations of FGFR1 present hypophosphatemia and increased serum level of FGF23. Inhibition of FGFR1 decreased FGF23 mRNA expression in the bone. Integrative nuclear FGFR1 promotes FGF23 transcription by activating the transcription factor CREB. HMW isoform of FGF2, (HMWFGF2), the ligand for nuclear FGFR1, stimulates FGF23 expression. Transgenic mice with overexpression of HMW FGF2 in immature and mature
osteoblasts display increased FGF23 level, hypophosphatemia, and rickets.\textsuperscript{592}

Some proteins regulating phosphate homeostasis are also expressed in osteoblasts and osteocytes, such as DMP1 and PHEX,\textsuperscript{593,594} and regulate FGF23 expression. Inactivating mutations in DMP1 and PHEX lead to XLH (X-linked hypophosphatemic rickets) and ARHR (autosomal recessive hypophosphatemic rickets), respectively, accompanying with increased serum FGF23 level.\textsuperscript{594,595} Both DMP1 and PHEX knockout mice exhibit hypophosphatemic rickets and increased FGF23 expression.\textsuperscript{594,596} Although PHEX is a peptidase expressed in the bone, it can inhibit the expression FGF23 without regulating FGF23 degradation.\textsuperscript{597}

Some circulating proteins also regulate FGF23 level. FGF23 is regulated by feedback loops, including the phosphate level, 1,25(OH)\textsubscript{2}D\textsubscript{3} and PTH. Either dietary phosphate or administration of 1,25(OH)\textsubscript{2}D\textsubscript{3} can increase the serum FGF23 level in humans and rodents.\textsuperscript{596,599} which depends on both translational and post-translational regulation of FGF23.\textsuperscript{600} FGF23 inhibits PTH synthesis and secretion,\textsuperscript{601,602} and then contributes to its own negative feedback regulation. Patients with hyperparathyroidism have high FGF23 level,\textsuperscript{603} and some studies including cell culture experiments showed that PTH induces FGF23 expression in human and rodent cells through activating the orphan nuclear receptor Nurr1.\textsuperscript{604,605}

Furthermore, iron can regulate FGF23 expression. Iron deficiency not only increases FGF23 transcription,\textsuperscript{606} but also its cleavage.\textsuperscript{607} However, the detailed mechanism is still unclear.

FGF SIGNALING IN TUMORS

A typical regulation of the FGF/FGFR system occurs in multiple human tumors, leading to the deregulated activation of ligand-dependent or -independent FGFR signaling.

The expressions and mutations of FGFR signaling molecules in tumors

FGF signal is highly related to the initiation and progression of several tumors including urothelial carcinoma, multiple myeloma, prostate cancer, and hepatocellular carcinoma (Table 2).

Expressions of FGFs. FGF5 is overexpressed in breast cancer tissue.\textsuperscript{608} Guo et al.\textsuperscript{609} reported that FGF6 was significantly decreased in non-metastatic liver cancer lesion tissues and increased in metastatic liver carcinoma tissue. FGF7 is expressed in normal mucosal gland epithelium and in stromal fibroblasts, and FGF7 protein levels were elevated in gastric inflammation and gastric adenocarcinoma.\textsuperscript{610} Overexpression of FGF8 in prostate cancer is highly related to the decreased patient survival and persists in androgen-independent disease.\textsuperscript{611} FGF8, as cell growth regulator, can mediate the tumor suppression effect of Annexin-A7 in prostate tumorigenesis.\textsuperscript{612} FGF9 is expressed in many non-small cell lung carcinoma (NSCLC) primary tumors and derived cell lines. The NSCLC patients with high FGF9 expression had shorter overall survival.\textsuperscript{613} Aberrant signaling of FGF10 through FGFR2b, and in some instances FGFR1b, contributes to the progression of a number of human cancers, including breast cancer, prostate cancer, and pancreatic adenocarcinoma, as well as gastric cancer (GC), skin cancers, and lung squamous cell carcinomas.\textsuperscript{614} FGF12 gene was overexpressed in esophageal squamous cells.\textsuperscript{615} FGF13 was highly upregulated in aggressively metastatic breast tumors and pancreatic endocrine tumors.\textsuperscript{616} FGF14 was preferentially methylated in colorectal cancer.\textsuperscript{616} The expression of FGF16 is markedly increased in ovarian tumors.\textsuperscript{617} FGF17 is overexpressed as a potential mediator of FGF8 function in human prostate cancer.\textsuperscript{518} In genomically stable and chromosomal instable subtypes of GC, FGF18 was overexpressed with relevance to poor survival.\textsuperscript{619} FGF18/FGFR3IIc was upregulated and could drive growth of tumor cell in CD44\textsuperscript{+} subpopulation of colon adenoma cells.\textsuperscript{620} Aberrant signaling through FGF19 and its receptor FGFR4 seems to be the oncogenic driver for a subset of human hepatocellular carcinoma (HCCs) and is associated with poor prognosis.\textsuperscript{621} Ectopic expression of FGF20 in NIH 3T3 cells rendered the cells transformed in vitro and tumorigenic in nude mice.\textsuperscript{622} The mRNA level of FGF20 was upregulated in adenomas in mice and FGF20 is found to be a critical element in Wnt signaling-induced oncogenesis.\textsuperscript{623} Huang et al.\textsuperscript{624} found that overexpression of FGF21 delayed the appearance of diethylnitrosamine-induced liver tumors and proposed that FGF21 might delay development of adenomas through activation of resident hepatocyte FGF4 at early time. Liu et al.\textsuperscript{625} demonstrated that FGF22 expression was tightly associated with the poor overall survival. FGF23 is present at an increased level and promotes the progression of prostate cancer.\textsuperscript{626}

Mutations of FGFs and FGFRs in tumors

The risk of relapse in the subgroup of progesterone-receptor-negative patients of breast tumors was five times greater for those with int-2/FGF3 amplification than for those without this alteration.\textsuperscript{627} High-throughput tissue microarray analysis showed that gene amplifications of FGF3 and FGF4 were observed in urinary bladder cancer.\textsuperscript{628} Kim and his colleagues\textsuperscript{629} revealed that three SNPs in the FGF23 gene (rs11063118, rs13312789, and rs7955866) were associated with an increased risk of prostate cancer. Mutations of FGFRs are commonly observed in many tumors, including the breast cancer, lung cancer, liver cancer, GC, uterine cancer, and bladder cancer.\textsuperscript{630} FGFR1 amplification is one of the most common focal amplifications in breast cancer.\textsuperscript{631} FGFR1 amplification was observed in 32% of small cell lung cancer samples.\textsuperscript{632} A single somatic FGFR1 mutation (c.C754A p.P252T) was also detected in a bronchoalveolar cancer.\textsuperscript{633} Constitutional and somatic FGFR1 alterations were frequently observed in dysembryoplastic neuroepithelial tumor (DNET) and played a key role in the pathogenesis of DNET.\textsuperscript{634} FGFR2 amplifications have been observed in nearly 10% of GCs, playing a critical role in the proliferation and survival of GC cell.\textsuperscript{635} GC cell lines with FGFR2 amplifications were highly sensitive to FGFR inhibitors.\textsuperscript{636} Dutt et al.\textsuperscript{637} reported that somatic mutations of FGFR2 were present in 12% of endometrial carcinomas, and inhibition of FGFR2 kinase activity in endometrial carcinoma cell line bearing such FGFR2 mutations could inhibit its transformation and survival, implicating FGFR2 as a novel therapeutic target in endometrial carcinoma. FGFR2 fusions were reported to be present in up to 13% of liver cancers such as intrahepatic cholangiocarcinoma.\textsuperscript{638,639} FGFR2 amplifications occur in triple-negative breast cancer, and are associated with high sensitivity to FGFR inhibitors.\textsuperscript{640} FGFR2 is shown to be associated with a higher risk of sporadic post-menopausal breast cancer.\textsuperscript{641} Amplifications of FGFR3 have been described rarely in cancer, while activation of FGFR3 by mutation was quite common.\textsuperscript{642} FGFR3 alterations (mutations or translocation) are among the most frequent genetic events in bladder carcinoma. Single-nucleotide substitution mutations of FGFR3 were present in 35% of bladder carcinomas.\textsuperscript{643} The mutations of FGFR3 could lead to an aberrant activation of FGFR3 signaling, conferring an oncogenic dependence, while inhibition of FGFR3 signaling decreased cell viability in vitro and tumor growth in vivo.\textsuperscript{644} FGFR3 mutations were also identified in cervical cancers,\textsuperscript{645} multiple myeloma,\textsuperscript{38} prostate cancer,\textsuperscript{646} testicular tumors,\textsuperscript{647} and lung adenocarcinoma.\textsuperscript{648} FGFR1-3 gene fusions have been observed in breast cancer to occur with multiple gene partners (i.e., TACC1-3, BAIAP2L1, AFF3, SLCA45A3, and AHCYL1).\textsuperscript{649} A very low level of amplifications of FGFR3 and FGFR4 were detected in breast cancer.\textsuperscript{649} Mutations in FGFR4 in human rhabdomyosarcoma (RMS) could lead to its activation and contribute to RMS progression as an oncogene.\textsuperscript{650} The mutation of FGFR4 gene transcript in MDA-MB-453 mammary carcinoma cells lead to the substitution of glycine by arginine at position 388, which
increased cell motility. The FGFR4 Arg388 allele was related to the metastasis of colon cancer in patients.651

FGFs and FGFRs in tumorigenesis

FGF/FGFR signaling is involved in the major steps of tumor progression, including cancer cell survival and proliferation, angiogenesis, invasion, and metastatic dissemination and response to therapy.

**FGFs and FGFRs in tumor growth.** The expression of FGF4 was increased in germ cell tumors, especially in non-seminomas, which could promote malignant growth of cultured embryonal carcinoma by targeting all-trans-retinoic acid.652 FGF2 can induce breast cancer growth through ligand-independent activation and stimulate the MYC gene expression through recruitment of ERα and PRB δ4 isoform to MYC regulatory sequences. 653 The results from Betsuyaku, T.'s group showed that the FGF2 aptamer that can block FGF2 activity could inhibit the growth of FGF2-FGFR pathway-dependent lung cancer cells.654

Increased expression of FGF4 in ovarian cancer stem-like cells/cancer-initiating cells is involved in the upregulating tumor initiation capacity of fibroblasts.655 Fang et al.656 demonstrated that miR-188-Sp suppressed the tumor cell proliferation and metastasis by directly targeting FGF5 in HCC. The neutralizing antibody to FGF8b could significantly inhibit cell growth of prostate cancer.511 In mouse Leydig tumor cells, FGFR9/FGFR2 signaling can increase its proliferation by activating ERK1/2, Rb/E2F1, and cell-cycle pathways.657 Downregulation of FGF18 suppressed the tumor formation abilities, induced G1-phase cell-cycle arrest and enhanced anticancer drug sensitivity.519 The antibody of FGFR1 could inhibit the growth of colon tumor xenografts in vivo and effectively prevent HCCs in FGFR1 transgenic mice, suggesting that the inactivation of FGFR1 could be beneficial treatment for cancers and other malignancies involving interaction of FGFR1 and FGFR4.658 Low concentration exogenous FGF19 promoted the growth of prostate cancer cells, while inhibition of FGF19 in prostate cancer cells could decrease proliferation in vitro and tumor growth in vivo.629 FGF9 greatly contributes to Pregnane X receptor-mediated tumor aggressiveness in humans and mice.659 In endoplasmic reticulum stress-induced HCC cells, FGF19 overexpression promoted cell survival and increased resistance to apoptosis, whereas FGF19 silencing counteracted these effects.660 FGF19 gene amplification has been found to be corresponding with an increased dependency upon FGF19/FGFR4 autocrine signaling mediated by ERK/AKT-p70S6K-S6 activation in head and neck squamous cell carcinomas.661 FGF23 enhances the proliferation, invasion, and anchorage-independent growth of prostate cancer cell lines in vitro, while FGF23 KD also decreases tumor growth in vivo.629 Activation of FGFR1 leads to rapid tumor growth as a result of increased proliferation in prostate cancer cells.662 FGFR2 promotes breast cancer tumorigenicity by maintaining tumor-initiating cells.663 FGFR3 is overexpressed in the early stages of bladder cancer, and targeting the extracellular domain of FGFR3 with human single-chain Fv antibodies could suppress the proliferation of bladder carcinoma cell line.664

**FGFs and FGFRs in the invasion and migration tumors.** Henriksson et al.665 reported that colorectal cancer cells activate adjacent fibroblasts, which results in enhanced FGF1/FGFR3 signaling and subsequent increased invasion of tumor cells. Abrogation of the nuclear translocation of FGFR1 and FGFR2 in pancreatic cancer cells

### Table 2. Somatic GOF mutations of FGFRs in cancers

| Gene   | Type       | Site                                      | Cancers                                      |
|--------|------------|-------------------------------------------|----------------------------------------------|
| FGFR1  | Amplification |                                            | Breast cancer (ER+)                           |
|        |            |                                            | Gastric cancer                               |
|        |            |                                            | Lung cancer (SCC, SC)                        |
|        |            |                                            | Ovarian cancer                               |
|        |            |                                            | Urothelial cancer                            |
|        |            |                                            | Glioblastoma                                 |
| Fusion |            | FGF1R-TACC1                                | Breast cancer (TNBC)                         |
|        |            | BCR-FGFR1, CNTRL-FGFR1, ZMYM2-FGFR1, etc. | Gastric cancer                               |
| Mutation |            | N546K                                    | Ewing sarcoma                                |
|         |            | N546K, K656E                              | Glioblastoma                                 |
| FGFR2  | Amplification |                                            | Breast cancer                               |
|        |            |                                            | Cholangiocarcinoma                           |
| Fusion |            | FGF2R-AFF3, FGF2-CASP7                     | Breast cancer                               |
|        |            | FGF2R-BIC1, FGF2-PHHLN1, etc.             | Cholangiocarcinoma                           |
| Mutation |            | R203C, N549K, K659N                       | Breast cancer                               |
|         |            | S252W, P253R, N549K, K659E               | Endometrial cancer                           |
|         |            | S252W, P253R, K659E                       | Lung cancer                                 |
| FGFR3  | Amplification |                                            | Ovarian and urothelial cancers               |
| Fusion |            | FGF3R-TACC3                               | Glioblastoma and lung cancer                |
|        |            | t(4;14) (p16q32)                          | Lymphoma                                    |
|        |            | FGF3R-BAIAP2L1, FGF3R-JAKMIP1, FGF3R-TACC3| Multiple myeloma                            |
| Mutation |            | R248C, S249C, G370C, Y373C, G380R, K650M | Urothelial cancer                            |
|         |            | R248C, S249C, G370C, K650E               | Gallbladder cancer                           |
|         |            | R248C, Y373C, K650E/M                    | Lung cancer                                 |
|         |            | R248C, S249C, G370C, S371C, Y373C, N540S,| Multiple myeloma                            |
|         |            | K650E/M                                  | Urothelial cancer                            |
| FGFR4  | Mutation | N535K, V550E                            | Rhabdomyosarcoma                            |
significantly inhibit cancer cell invasion. FGF7/KGF could trigger cell transformation and invasion of immortalized human prostatic epithelial PNT1A cells. FGF7/FGFR2/THBS1 promotes the invasion and migration in human GC. FGF9 secreted by cancer-associated fibroblasts is considered as a possible mediator by promoting the anti-apoptosis and invasive capability of GC cells. FGF10/FGFR2 signal can significantly promote the cell migration and invasion in pancreatic cancer. FGF16 enhanced the invasion of SKOV-3 ovarian cancer cells through activation of MAPK signaling pathway. The members of FGF8 subfamily including FGF8, FGF17, and FGF18 are involved in autocrine and paracrine signaling in HCC and enhance the survival of tumor cells, tube formation, and neoangiogenesis. FGF18 has been reported to control the migration, invasion, and tumorigenicity of ovarian cancer cells through NF-κB activation, which increased the production of oncogenic cytokines and chemokines. FGF9 greatly contributes to Pregnane X receptor-mediated tumor aggressiveness in humans and mice.

**FGFs and FGFRs in tumor angiogenesis.** The onset of angiogenesis is a discrete step that occurs at any stage of tumor progression. FGF ligands and receptors promote angiogenesis in a variety of tumors. Wang and Becker showed that delivery of an episomal vector containing antisense FGF2 or FGF1 cDNA could completely prevent the growth of tumors partially through the blockage of angiogenesis in the human melanoma grown as a subcutaneous tumor model in nude mice. FGF2 can induce tumor growth and neoangiIALIZATION in vivo. FGF2 and MMP2 may cause increased angiogenesis and invasion of bone marrow plasma cells in several unidentified monoclonal gamma globulin disease and multiple myeloma cases. FGF binding protein can be used as an angiogenesis conversion molecule in human tumors via promoting the release of biologically active FGF2 and leading to tumor growth. The type 1 repeats of thrombospondin-1 (TSP1) can block angiogenesis driven by FGF2 or vascular VEGF and inhibit tumor growth. IL-10 blocks the proliferation of microvascular ECs induced by VEGF and FGF2 in vitro and has a direct effect on preventing angiogenesis in human lymphomas. It has been reported that the average serum FGF2 level was significantly increased (~7 times) in testicular cancer patients, and the expression level of FGF2 was also significantly increased in tumor biopsies. Targeting the mRNA of early growth response (EGRI) an upstream of FGF2, can inhibit the expression of EGRI protein and block tumor angiogenesis. Human melanoma cell survival and growth depend on autocrine action of FGF2. In addition, neutralized FGF2 with antibodies could block the angiogenesis in melanoma cell lines transplanted nude mice models. In addition, FGF2 is shown to be involved in angiogenesis in the formation of pituitary tumors. FGF1 can cause increased angiogenesis that contributes to the poor survival rate of patients with advanced serous ovarian cancer. Two angiogenic factors PDGF-BB and FGF2 in tumors can synergistically promote the neovascularization and metastasis in murine tumor model. Targeted inhibition of PDGF receptors can downregulate the expression of FGF2 and epithelial growth factor FGF7, thereby reducing angiogenesis.

**THERAPEUTICS AND STRATEGIES FOR TARGETING FGF SIGNALING**

FGF signaling plays critical roles in tissue/organ development and homeostasis, and dysregulated FGF signaling has been found in a variety of diseases and injuries (see above). It is a promising therapeutic strategy for these diseases/injuries by modifying or correcting the aberrant FGF signaling. So far, FGF-based therapeutics are largely classified into three classes, including enhancing FGF signaling therapeutics, blocking FGF signaling therapeutics, and gene therapy.

**Enhancing FGF signaling therapeutics**

FGFs are involved in numerous pathophysiological processes; recombinant FGF or FGF analogs have been developed as first-generation strategies to augment the beneficial effects of FGFs/FGFRs (shown in Table 3).Canonical FGFs, encoded by FGF1, FGF4, FGF7, FGF8, and FGF9 subfamily gene, by binding to heparan sulfate proteoglycans largely exert their effects locally. A single injection of mouse recombinant FGF1 causes potent, dose- and insulin-dependent glucose lowering in diabetic mice without hypoglycemia. Recombinant human FGF1 (rhFGF1) is also able to normalize blood glucose in diabetic mice. In addition, trafermin (rhFGF2) has been supported for their use in the patients with skin ulcers, and in phase III clinical trial, trafermin was further approved for its application in patients with periodontal surgery. Palifermin, a truncated form of FGF7, has been approved for the treatment of patients with oral mucositis. In pediatric patients, palifermin may provide advantage to prevent chemotherapy-induced mucositis. Repifermin, a truncated form of FGF10, with the pharmacological effects similar to that of FGF7, promotes the healing of ulcerated oral and intestinal mucosal tissue, and reduces the complications in preclinical tests. However, the clinical trials about the effect of repifermin on mucositis were terminated in 2004 as no effective evidence for reducing the incidence or severity. In addition, rhFGF18 have been approved for treating OA and cartilage injury of the knee in phase II clinical trial.

Endocrine FGFs, encoded by FGF19 subfamily gene, which bind and activate FGFRs with the Klotho family protein, regulate a wide range of metabolic processes. Based on the structure–function principle, separating mitogenic and metabolic activities of FGF19 through mutagenesis of five N-terminal and heparin-binding regions of FGF19 yielded a series of FGF19 variants, which retain the beneficial metabolic effects, while reduce the side effects of FGF19 on tumorigenicity. In addition, a new constructed FGF19 variant (25-194 of FGF19 and 1-20 of FGF21), impaired in activating FGF4 and still had beneficial effects on glucose and lipid metabolism. These studies provide a strategy for engineering FGF19 as a potential therapy for related diseases/injuries. These variants were found to be devoid of BA regulatory activity. However, another FGF19 variant NGM282 (M70) retains the beneficial BA metabolism effects, while is devoid of murine mitogenic activity by inactivating the STAT3 pathway. To date, M70 and another FGF19 variant was studied through phase II clinical trials for their use in patients with primary sclerosing cholangitis and diabetes mellitus. In addition, several FGF19-inhibiting strategies (farnesoid X receptor agonists) such as obeticholic acid and Pxa-104 were tested through phase II clinical trials and provided with further support for their use in the patients with primary/secondary BA malabsorption and nonalcoholic fatty liver disease, respectively.

Several strategies have been used to optimize the “druggability” of FGF21. LY2405319, a novel FGF21 variant, was reconstructed by introducing an additional disulfide bond firstly in the C terminal of FGF21 by mutations (L118C, A134C), and then further optimized by deleting His-Pro-Ile-Pro in the N terminal of FGF21 along with a mutation to replace the major site of O-linked glycosylation (Ser167Ala). Subcutaneous administration of LY2405319 in DIO mice exhibited a potency similar to FGF21, resulting in decreased plasma glucose along with a reduction in body weight. To date, LY2405319 has been tested through phase I clinical trial to reduce body weight and fasting insulin, and is noteworthy in improving dyslipidemia in patients with type 2 diabetes mellitus. Another FGF21 variant is reconstructed through the introduction of p-acetyl phenylalanine into the N-terminal residue of rhFGF21 for the attachment of PEG (PEGylated rhFGF21). PEGylated rhFGF21 has the ability to normalize insulin-mediated glucose utilization in diabetic murine models, but exhibits remarkably
| Class | Drug Targeting | Targets | Diseases | Drug development |
|-------|----------------|---------|----------|------------------|
| Recombinant FGFs or FGF analogs | rmFGF1 | FGF1 receptor | T2DM | Preclinical |
| | rhFGF1 | FGF1 receptor | T2DM | Preclinical |
| | rhFGF2 (trafermin) | FGF2 receptor | Skin ulcers | Approved Japan |
| | FG7 (palifermin) | FGF7 receptor | Oral mucositis | Approved USA |
| | FG7 (palifermin) | FGF7 receptor | Oral mucositis | Clinical trials were terminated in 2004 |
| | rhFGF8 (spipermin) | FGF8 receptor | Osteoarthritis | P2 (NCT01919164) |
| | FGF19-4/4-5/6 | FGF19 receptor | Tumorigenicity | Preclinical |
| | FGF19 variant (FGF19v) | FGF19 receptor | Mitogenic | Preclinical |
| | NGM282 (M70) | FGF10 receptor | T2DM | P2 (NCT01943045) |
| | Obeticholic acid and Px-104 | FGF10 receptor | Primary/secondary bile acid malabsorption | P2 (NCT01585025) |
| | | | Obesity | P2 (NCT01625026) |
| | | | Non-alcoholic fatty liver disease (NAFLD) | P2 (NCT01999101) |
| | LY2405319 | FGF21 receptor | T2DM | P1 (NCT01869959) |
| | FGF21variant (PEG-FGF21G71C, Fc-FGF21(RG)) | FGF21 receptor | T2DM | Preclinical |
| Non-selective TKIs | PF-05231023 (CVX-334) | FGF1 receptor | T2DM | P1 (NCT01285518) |
| | Lucitanib (EJ810) | FGF1/2, VEGFR1/2/3, and PDGFRα/u | Cancer with FGF alteration | P2 (NCT02747797) |
| | Nintedanib (BIBF1120) | FGF1/2/3, VEGFR1/2/3, and PDGFRα/u | Cancer with FGF alteration | Submitted P3 |
| | Dovitinib (CH2R58 or TK258) | VEGFR1/2/3, FGF1/2/3, PDGFRα, c-KIT, RET, TrkA, CSF-1R, and FLT3 | Cancer with FGF alteration | P2 (NCT01719549) |
| | Regorafenib | | | P2 (NCT01929616) |
| | Brivanib | | | P2 (NCT03150712) |
| | Ponatinib | FGF1/2/3 | Cancer with FGF alteration | P2 (NCT03609359) |
| | Lenvatinib | FGF1/2/3 | Cancer with FGF alteration | P2 (NCT01253369) |
| | Pazopanib | | | P3 (NCT01465464) |
| | Orantinib | | | P2 (NCT00768144) |
| | Sunitinib | | | P3 (NCT00399035) |
| | Cediranib | | | P2 (NCT01253369) |
| Selective TKIs | AZD4547 | FGF1/2/3 | Cancer with FGF alteration | P2 (NCT01824901) |
| | BGJ398 (NVP-BGJ398) | FGF1/2/3 | Cancer with FGF alteration | P2 (NCT01791985) |
| | JNJ-42756493 (erdafitinib) | FGF1/2/3/4 | Cancer with FGF alteration | P2 (NCT01713207) |
| | LY287445, Debio-1347, TAS-120, and BAY-1163877 | FGF1/2/3/4 | Cancer with FGF alteration | P2 (NCT02365597) |
| | | | Cancer with FGF alteration | P2 (NCT02699066) |
| Neutralizing monoclonal antibodies (mAbs) | KRN23 | FGF23 | XLH | P3 (NCT02537431) |
| | Bermalizumab (FPA144) | FGF2b | Neoplasms | P1 (NCT02318329) |
| | BAY1179470 | FGF2 | Neoplasms | P1 (NCT01881217) |
| | MFGR1877S | FGF3 | Neoplasms | P1 (NCT01122875) |
| | hlgG1-1A2 | FGF2 | | |
| | GAL-F2 | FGF2 | | |
| | 3F12E7 | FGF2 | | |
| | KM1334 | FGF8b | Neoplasms | Preclinical |
| | FGFl0 mAb | FGF10 | | |
| | FN1 and FC1 | FGF23 | | |
| | RIMAAb | FGF1 | | |
| | FGF traps | FP-1039 (GSK3052230) | FGF1/2/4 | Neoplasms | P1 (NCT01868022) |
| | SM27 | FGF2 | Angiogenesis | Preclinical |
| | NSC12 | FGF2 | Lung tumors | Preclinical |
| | sFGFR2IIic (S252W) | FGF2 | AS | Preclinical |
| | sFGFR3 | FGF2/9/18 | Chondrodyplasia | Preclinical |
| | Peptide P3 | FGF3 | Chondrodyplasia | Preclinical |
| | XRP0038 (NVI-FGF) | FGF1 receptor | Peripheral vascular diseases | P2 (NCT00566657) |
| Gene therapy | Expression of FGF18 cDNA | FGF18 receptor | Murine models | Preclinical |
| | AA9-Fgfr2-shRNA | Fgf2-P25SR allele | AS | Preclinical |
| | CRISPR/Cas9 | Fgf3-G374R | Achoondroplasia | Preclinical |

**Abbreviations:** T2DM type 2 diabetes mellitus, PSC primary sclerosing cholangitis, NAFLD non-alcoholic fatty liver disease, XLH X-linked hypophosphatemia, AS Apert syndrome, P1 phase I clinical trial, P2 phase II clinical trial, P3 phase III clinical trial.
lower bioactivity than FGF21, along with induction of renal vacuole formation. Song et al. further optimized FGF21 by introducing G71C mutation to generate the mimetic PEG-FFG21G71C, which exhibits increased half-life. Subsequently, an alternative strategy was adopted to yield Fc-FFG21 by fusing Fc fragment of human IgG1 to the N-terminal end of FGF21 to improve the pharmacokinetic properties of FGF21, which exhibited a prominently increased half-life compared to the native FGF21. Since, the C-terminal region of Fc-FFG21, especially between Pro171 and Ser172, was rapidly degraded, Pro171Gly mutation was introduced to retain biological activity, while eliminating the proteolytic degradation. Moreover, FGF21 has the additional concern of forming aggregates during protein production. By combining Pro171Gly and Leu99Arg mutations into one molecule, a novel variant named Fc-FFG21 (RG) was generated with resistance to aggregation and proteolysis. Another approach to improve plasma half-life is to fuse FGF21 to a scaffold monoclonal antibody (mAb). Blocking FGFs signaling therapeutics

Given that a variety of human diseases and injuries caused by excessive FGF signaling. So far, the measures blocking FGF signaling can be generally classified to TKIs, neutralizing mAbs, and FGF traps.

TKIs

Nonselective TKIs: Nonselective TKIs have been developed as first-generation strategies to blocking FGFs signaling. These TKIs have the benefit of concurrently targeting tumor proliferation and angiogenesis, while also displaying a remarkable effect against FGFR signaling pathways, together with a multiplicity of adverse effects that limit their use in clinic.

Lucitabin (E3810) is a triple TKI, which targeting FGFRs, VEGFRs, and PDGFRs. E3810 showed a promising efficacy and a manageable side effect in patients with both FGF-aberrant or angiogenesis-sensitive tumor types. Until 2018, E3810 were completed phase II clinical trials, which inhibits the growth of tumor by antiangiogenesis.

Nintedanib (BIBF1120) is another novel triple angiokinase inhibitor, with less activity against SRC, RET, and FLT3. BIBF1120 competitively binds to the ATP-binding pocket of these receptors, and blocks the intracellular signaling critical for the proliferation and survival of angiogenesis-related cells. Up-to-date, BIBF1120 has been approved for the treatment of pulmonary fibrosis and as a second-line therapy for NSCLC in combination with docetaxel. Phase III clinical trials are still ongoing to study the response of patients selected for specific FGF alterations.

Dovitinib (CHIR258 or TK258) is an oral ATC-competitive multikinase inhibitor that targets FGFRs, VEGFRs, and PDGFRs. TK258 has a promising inhibitory activity in cell lines with FGF translocations or amplification. In phase II trials, TK258 can stabilize disease in multiple myeloma bearing t (4; 14) translocation by blocking FGF3 activity.

Beyond that, several other nonselective TKIs are shown in Table 3, which have been developed and are in preclinical and clinical evaluation. However, these nonselective TKIs induce a series of side effects: cardiotoxicity or proteinuria on account of the concurrent VEGFR inhibition, as well as cutaneous reactions, digestive disorders, and gastrointestinal disease, for example.

Selective TKIs: To overcome the off-target effects, second-generation selective FGFR TKIs have been developed. AZD45477 is a potent reversible TKI specific for FGFRs. Of note, AZD4547 is able to sharply diminish cancer stem-like cells by inducing MET via MEK/ERK pathway downstream of FGF signaling. In addition, administered AZD4547 prominently impairs ductal branching and stem cell-like characteristics in mammary epithelial cell and spontaneous tumor cells. In phase I/II trials, AZD4547 further showed promising inhibitory activity in models of cancer with FGFR alteration.

BGJ398 (NVP-BGJ398) is a selective reversible ATP-competitive inhibitor targeting FGFRs, which showed superior potency to ponatinib and dovitinib, and exerted a more potent therapeutic effect against chemotherapy-refractory cholangiocarcinoma containing FGFR2 fusions. Of note, in phase I/II trials, BGJ398 promoted tumor reduction in patients with FGFR-related advanced solid tumors. JNJ42756493 (erdafitinib) with potent TKI activity can target all FGFRs, which suppresses phospho-FGFR and phospho-ERK resulting in dose-dependent antitumor activity. Further in phase I/II trials, the administered erdafitinib has an inhibitory activity in patients with advanced solid tumors characterized by FGFR translocations or FGFR3-TACC3 fusions.

Other selective TKIs are shown in Table 3, and showed promising results in preclinical and clinical evaluation on different oncotypes.

Unfortunately, drug resistance limits the success of TKIs with mutations at the “gatekeeper” residue, leading to tumor progression. Structural analyses showed that the FGFR1 “gatekeeper” mutation (V561M) can induce a potently increased autophosphorylation, in part, by a network of interacting residues forming a hydrophobic spine to stabilize the active conformation. Further kinetic assays established that V561M confers significant resistance to E3810, while it retains affinity for AZD4547 due to a flexible linker that allows multiple inhibitor binding modes. In addition, JNJ42756493 binds to the ATP pocket of the FGFR1 KD with unique structural conformations, and its inhibitory efficacy is reduced by 200-fold in the FGFR3 “gatekeeper” mutation (V555M), while an increase in efficacy for TK258. In contrast, some FGFR2 “gatekeeper” mutations drive acquired resistance to TK258 by causing steric hindrance to the binding of the TKI to the receptor (such as N550K, E566G, and K660E) or by stabilizing the active conformation of the kinase (V561I). Moreover, recurrent patients have point mutations in the FGFR2 KD at progression, and each mutation drives acquired resistance to BGJ398, and was surmountable by structurally distinct FGFR inhibitors. Thus, designing inhibitor with flexibility to overcome drug resistance may be an vital way for exploiting effective inhibitor against mutation.

Neutralizing mAbs: When compared to TKIs, neutralizing mAbs have unique advantages of low toxicity due to the absence of off-target effects.

Burosumab (formerly KRN23) is a fully human IgG1 mAb that binds to and blocks the biologic activity of FGF23. Injection of Burosumab normalized both phosphate and vitamin D concentrations in hypophosphatemia mouse models. In 2019, phase II clinical trials for Burosumab was completed and provided support for its use for XLH.

Bemarituzumab (FPA144) is a rhlgG1 mAb that specifically binds to the IgG III region of the FGFR2b receptor isoform to prevent ligand binding and downstream signaling activation. In phase I clinical trial, a single dose of FPA144 was conducted in gastroesophageal adenocarcinoma (GEA) patients with FGFR2b overexpression, which remarkably inhibited GEA growth.

MGFR1877S is a mAb targeting FGFR3 by hampering its dimerization, which is well tolerated with low toxicities in patients with multiple myeloma and solid tumors in phase I clinical trials.

Beyond that, there are other mAbs awaiting further confirmation in preclinical and clinical testing, such as BAY1179470, hlgG1-1A2, GAL-F2, 3F12E7, KM1334, FGF10 mAb, FN1, FC1, and RIMAb1, as detailed in Table 3.

FGF traps: An alternative strategy to modulate the activity of the FGF/FGFR signaling is to use the molecules able to bind and
neutralize multiple FGF ligands. This strategy represents a novel path for the development of FGF traps.

FP-1039 (GSK3052230) is an FGF ligand trap that binds and neutralizes multiple FGFs and thus inhibits the activation of FGFR1. In preclinical trials, FP-1039 blocked FGF2-stimulated tumor cell proliferation and inhibited tumor growth in xenograft models.767 In phase I clinical trials, associated with paclitaxel and carboplatin, or docetaxel, intraperitoneal injection of FP-1039 was well tolerated in patients with solid malignancies.735 However, FP-1039 does not effectively inhibit endocrine FGFs (FGF19, FGF21, and FGF23).734 Therefore, FP-1039 has the potential to effectively block the neoplasms or advanced cancer-promoting FGFs, with less toxicity compared to small molecules such as FGF kinase inhibitors.

The development of FGF trap agents has also relied on the structural characterization of the interactions of FGFs with their natural “interactor,” including thrombospondin-1 (TSP1), HSPGs, and pentraxin-3 (PTX3).732 Structural analysis of the complex between FGF2 and TSP1 identified a new small-molecule SM27 that inhibits FGF2-induced angiogenesis through binding to FGF2.729 Similar to the integrative TSP1, SM27 perturbs FGF2 dynamics in distant regions, including the FGFR1 binding site, by binding the heparin affinity site of FGF2, thus preventing FGF2 binding to HSPG and FGFR1.729 Therefore, SM27 acts as a dual direct and allosteric inhibitor of the binding between FGF2 and its receptors, which has unique benefits for the development of novel cancer drug. In addition, structural analysis of the complex between FGF2 and the N terminal of PTX3 identified an acetylated pentapeptide ARPCA as the minimal FGF2 binding peptide that inhibits FGF8b-induced angiogenesis.731 Besides, based on pharmacophore modeling of the ARPCA/FGF2 interaction, NSC12 was identified as multi-FGF trap that can participate in the formation of the HSPG/FGF2/FGFR1 ternary complex. In tumor models, administration of NSC12 can block the growth, angiogenesis, and metastasis of FGFR-dependent lung tumors.732

In addition, a soluble FGFR2 mutant with S252W (sFGFR2IIIc (S252W)) was found to partially alleviate the AS in mice by alleviating the premature closure of coronal suture in cultured cartilages and transgenic mice.733,734 Moreover, sFGFR3, a recombinant protein, acts as a FGF trap to prevent FGF ligand binding to FGFR3. In ACH mice, subcutaneous injection of sFGFR3, to compete with endogenous FGFR3 ligands, showed a dose-dependent rescue of chondroproliferative phenotypes.735 Besides, in TD II model, administration of peptide P3 with the FGFR-related binding specificity to downregulate the activity of FGFR3 rescues the lethal phenotype and partially restores the structural distortion of growth plates.736

Gene therapy

At present, gene therapy is inevitable, especially in the era of precision medicine. Expression of FGF18 by AAV-mediated gene transfer in the pinnae of nude mice resulted in a noteworthy increased thickness due to an FGF18-mediated increase in chondrocyte proliferation and ECM production.239 Conditional expression of FGF18 in stromal cells surrounding proximal airway cartilage in normal mouse lung is capable of enhancing proximal programs during lung morphogenesis.277 Up-to-date, only few FGF signaling-related gene therapies have entered clinical trials. NV1FGF is a plasmid-based angiogenic gene delivery system for local expression of FGF1. Intramuscular administration of NV1FGF resulted in a noteworthy reduced risk of major amputation in patients with critical limb ischemia.738 In 2017, phase II clinical trials for NV1FGF was completed and provided further support for its use in patients with severe peripheral artery occlusive disease.

The above-described molecules such as sFGFR2IIIc (S252W)733,734 or MEK inhibitor39 or glycosaminoglycans740 can partially alleviate the AS, but may bring undesired effects as they do not specifically antagonize the mutant FGFR2 itself. In contrast, RNA interference (RNAi) could inhibit the expression of mutant alleles at the transcriptional level. A short hairpin RNA (shRNA) targeting the dominant mutant form of FGFR2 (FGFR2 (S252W)) prevents the phenotypes of AS in mice.739 Safety and efficiency are the two major concerns for the application of RNAi-related therapeutics. AAV has unique advantages of gene transfer for therapeutic treatment of a number of diseases, including congenital blindness, hemophilia, and spinal muscular atrophy.341,742 Our group screened a siRNA specifically targeting the FGFR2-P253R allele, when this siRNA was delivered to the skulls in AS mouse model using AAV9 (AAV9-FGFR2-shRNA), it attenuated the premature closure of coronal suture and the decreased calvaria bone volume.743 Such biological strategy, in combination with other therapies including surgeries, provides experimental clues for the biological therapies of other genetic skeletal diseases.

In recent years, CRISPR/Cas9-based method has been developed for gene therapy. Some studies have verified the advantage of CRISPR/Cas9 technology for the correction of human hereditary genetic diseases, such as liver diseases,744 cataract disorder,745 Duchenne muscular dystrophy,746 tyrosinemia,747 thalassemia,748 and so forth. Miao et al.749 found that Cas9 protein can achieve higher frequency of precise correction of the FGFR3-G374R mutation than Cas9 mRNA. These strategies completely suppressed phenotypes of ACH without off-target effects checked by whole-genome sequencing. CRISPR/Cas9 technology can precisely correct individual mutations with high fidelity and is potentially translatable for clinical therapies of human diseases, especially genetic diseases in the future.

CONCLUSION AND PERSPECTIVE

Knowledge of the role of FGF/FGFR signaling in pathological and physiological conditions has advanced considerably in the past decades. In this review, we summarized the structure and function of FGF signaling molecules and the detailed regulatory mechanisms. FGF/FGFR system contributes to the pathophysiology of multiple disorders in humans, including genetic diseases, dysplastic diseases, various types of cancer, metabolic disorders, and degenerative diseases, as well as injuries and regeneration. Much remains to be learned. The spatiotemporal expression patterns, accurate roles, and underlying mechanisms of individual FGFs/FGFRs in the development and diseases/injuries are largely unknown.

Activation of FGF signaling is tightly controlled with diverse transcription specificity, which mainly depends on the molecular structures of FGFs/FGFRs. With the advance of multiple disciplines including structure biology, we have acquired more information about FGFs/FGFRs, such as their structures, binding partners, key amino acids mediating the specific binding and signaling pathways. We need to know from the viewpoint of structure why individual FGFs have variable binding affinities of respective FGFRs; why the same FGF ligand bind distinct group of FGFRs at different ways. We need to know from the viewpoint of structure why individual FGFs/FGFRs have variable binding affinities of respective FGFRs; why the same FGF ligand bind distinct group of FGFRs at different concentrations and in physiological and pathologic circumstance; can we switch the binding affinity of individual FGFs, based on their structure, to HS and FGFRs to have novel therapeutic effects on aberrant FGF signaling-related disease? With this information, we will have the possibility to fine tune FGF-related signaling to achieve better therapeutic outcome in the future.

There are complex interactions among individual FGFs and FGFRs. Most FGF can bind multiple FGFRs with differential binding affinities. So far, there are few studies about the differential signaling pathways activated by individual FGF through corresponding FGFRs. Considering the differential even opposite effects of each FGF in the homeostasis maintenance and occurrence of diseases, for example, FGFR1 promotes while FGFR3 suppresses OA pathogenesis, the effects of individual FGF on OA and cartilage injuries are the summed effects of all signaling pathways of FGFs.
activated by the applied FGF. More studies are needed to know the individual FGFRs activated by the applied FGFs at specific concentrations.

To obtain these knowledges, we need new strategies such as omics technology, single-cell analysis, and in vivo imaging, as well as utilization of more species of model animals and more spatiotemporally tunable genetic approaches. For example, our commonly used strategy to study the role of individual FGFs or FGFRs in the disease pathogenesis has limitation. We need to use conditional approach to spatiotemporally delete or overexpress individual FGFs or FGFRs in a certain type of cells, for example, chondrocytes, aimed to dissect the role of individual FGFs or FGFRs in the development and maintenance of the targeted cells. In addition, it is appreciated that mutations of individual FGFs or FGFRs can have detrimental effects, but a systematic understanding of intracellular pathway activation and dynamics is still lacking.750

To mimic the effects obtained from omics and conditional knockout study, we need to use targeted therapy approaches, which means to precisely modulate individual FGFs, FGFRs, and downstream signaling in specific types of cells at specific disease stages. The good news is that we are having more and more approach to exert these targeted treatments. For example, aptamer-based cell lineage or tissue targeting approaches are increasingly utilized. Several aptamers have been discovered to specifically target bone-forming site, osteoblasts, osteoclasts, and osteocytes in the skeletal tissue. We can similarly find aptamers specifically targeting for distinct cells at different growth phases, or inflammatory cells, paracancerous, and non-tumorous tissues, and so on.

FGF pathway interacts extensively with other signaling pathways during a variety of development and disease processes. Clarifying the interactions among FGF signaling, and these signaling pathways, such as BMP/FGF-β, PTH, hedgehog, and retinoid pathways, will provide us with the molecular bases for searching for combined therapies.51

Interventions targeting FGFs/FGFRs represent new approaches for the treatment of a wide range of diseases including genetic disorders, cancer, metabolic disease, degenerative disease, and injury repair. Developments in this field will likely be facilitated by structure-based drug design of agonists and antagonists for FGF signaling.

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REFERENCES
1. Omritz, D. M. & Itoh, N. The fibroblast growth factor signaling pathway. Wiley Interdiscip. Rev. Dev. Biol. 4, 215–266 (2015).
2. Wiedemann, M. & Trueb, B. Characterization of a novel protein (FGFRL1) from human cartilage related to FGF receptors. Genomics 69, 275–279 (2000).
3. Goetz, R. & Mohammadi, M. Exploring mechanisms of FGF signaling through the lens of structural biology. Nat. Rev. Mol. Cell. Biol. 14, 166–180 (2013).
4. Farrell, B. & Breeze, A. L. Structure, activation and dysregulation of fibroblast growth factor receptor kinases: perspectives for clinical targeting. Biochem. Soc. Trans. 46, 1753–1770 (2018).
5. Gotoh, N. Regulation of growth factor signaling by FRS2 family docking/scaffold adaptor proteins. Cancer Sci. 99, 1319–1325 (2008).
6. Huang, Z. et al. Two FGF receptor kinase molecules act in concert to recruit and transphosphorylate phospholipase Cgamma. Mol. Cell 61, 98–110 (2016).
7. Turner, N. & Grose, R. Fibroblast growth factor signalling: from development to cancer. Nat. Rev. Cancer 10, 116–129 (2010).
8. Futahauer, M. et al. Sprouty4 acts in vivo as a feedback-induced antagonist of FGF signaling in zebrafish. Development 128, 2175–2186 (2001).
9. Maffeis, A. A. et al. Evidence that SPROUTY2 functions as an inhibitor of mouse embryonic lung growth and morphogenesis. Mech. Dev. 102, 81–94 (2001).
10. Harker, R. T., Pollet, N., Delius, H. & Niehrs, C. The transmembrane protein XFLRT3 forms a complex with FGF receptors and promotes FGF signalling. Nat. Cell Biol. 6, 38–44 (2004).
11. Tsang, M., Friesel, R., Kudoh, T. & Dawid, I. B. Identification of Sef, a novel modulator of FGF signalling. Nat. Cell Biol. 4, 165–169 (2002).
12. Tori, S. et al. Sef is a spatial regulator for Ras/MAP kinase signaling. Dev. Cell 7, 33–44 (2004).
13. Zhao, Y. & Zhang, Y. The mechanism of dephosphorylation of extracellular signal-regulated kinase 2 by mitogen-activated protein kinase phosphatase 3. J. Biol. Chem. 276, 32382–32391 (2001).
14. Kawakami, Y. et al. MKP3 mediates the cellular response to FGF signalling in the vertebrate limb. Nat. Cell Biol. 5, 513–519 (2003).
15. Thiese, B. & Thisse, C. Functions and regulations of fibroblast growth factor signaling during embryonic development. Dev. Biol. 287, 390–402 (2005).
16. Belov, A. A. & Mohammadi, M. Molecular mechanisms of fibroblast growth factor signaling in physiology and pathology. Cold Spring Harb. Perspect. Biol. 5, a015958 (2013).
17. Eswarakumar, V. P. et al. The Ilc alternative of Fgf2 is a positive regulator of bone formation. Development 129, 3783–3793 (2002).
18. Miraou, H. & Marie, P. J. Fibroblast growth factor receptor signaling crosstalk in skeletogenesis. Sci. Signal. 3, re9 (2010).
19. Qi, H. et al. FGRF3 induces degradation of BMP type I receptor to regulate skeletal development. Biochim. Biophys. Acta 1843, 1237–1247 (2014).
20. Minina, E. et al. Interaction of FGF, Ihh/Pthlh, and BMP signaling integrates chondrocyte proliferation and hypertrophic differentiation. Dev. Cell 3, 439–449 (2002).
21. Katoh, M. & Katoh, M. Cross-talk of WNT and FGF signaling pathways at GSKbeta to regulate beta-catenin and SNAIL signaling cascades. Cancer Biol. Ther. 5, 1059–1064 (2006).
22. Lin, X. Functions of heparan sulfate proteoglycans in cell signaling during development. Development 131, 6009–6021 (2004).
23. Gong, S. G. Isoforms of receptors of fibroblast growth factors. J. Cell. Physiol. 229, 1887–1895 (2014).
24. Yeh, B. K. et al. Structural basis by which alternative splicing confers specificity in fibroblast growth factor receptors. Proc. Natl Acad. Sci. USA 100, 2266–2271 (2003).
25. Zhu, X., Lee, K., Asa, S. L. & Ezzat, S. Epigenetic silencing through DNA and histone methylation of fibroblast growth factor receptor 2 in neoplastic pituitary cells. Am. J. Pathol. 170, 1618–1628 (2007).
26. Sarabiour, S. & Hristova, K. Mechanism of FGF receptor dimerization and activation. Nat. Commun. 7, 10262 (2016).
27. Triantis, V. et al. Glycosylation of fibroblast growth factor receptor 4 is a key regulator of fibroblast growth factor 19-mediated down-regulation of cytochrome P450 7A1. Hepatology 52, 656–666 (2010).
28. Wheeler, J. A. & Clinkenbeard, E. L. Regulation of fibroblast growth factor 23 by iron, EPO, and HIF. Curr. Mol. Biol. Rep. 5, 8–17 (2019).
29. Kucinska, M. et al. Differential regulation of fibroblast growth factor receptor 1 trafficking and function by extracellular galectins. Cell Commun. Signal 17, 65 (2019).
30. Porebska, N. et al. Targeting cellular trafficking of fibroblast growth factor receptors as a strategy for selective cancer treatment. J. Clin. Med. 8, 7 (2019).
31. Li, J. P. & Kusche-Gullberg, M. Heparan sulfate: biosynthesis, structure, and function. Int. Rev. Cell. Mol. Biol. 325, 215–273 (2016).
32. Pellegrini, L. Role of heparan sulfate in fibroblast growth factor signalling: a structural view. Curr. Opin. Struct. Biol. 11, 629–634 (2001).
33. Goetz, R. et al. Molecular insights into the klotho-dependent, endocrine mode of action of fibroblast growth factor 19 subfamily members. Mol. Cell. Biol. 27, 3417–3428 (2007).
34. Schlessinger, J. et al. Crystal structure of a ternary FGF–FGFR–heparin complex reveals a dual role for heparin in FGF binding and dimerization. Mol. Cell 6, 743–750 (2000).
35. Chen, G. et al. Alpha-Klotho is a non-enzymatic molecular scaffold for FGF23 hormone signalling. Nature 553, 461–466 (2018).
36. Kuro-o, M. The Klotho proteins in health and disease. Nat. Rev. Nephrol. 15, 27–44 (2019).
37. Wu, X. et al. C-terminal tail of FGF19 determines its specificity toward Klotho co-receptors. J. Biol. Chem. 283, 33304–33309 (2008).
38. Goetz, R. et al. Klotho co-receptors inhibit signaling by paracrine fibroblast growth factor 8 subfamily ligands. Mol. Cell. Biol. 32, 1944–1954 (2012).
39. Goetz, R. et al. Isolated C-terminal tail of FGFR3 alleviates hypophosphatemia by inhibiting FGFR3-FGFR-Klotho complex formation. Proc. Natl Acad. Sci. USA 107, 407–412 (2010).

40. White, K. E. et al. Autosomal-dominant hypophosphatemic rickets (ADHR) mutations stabilize FGFR-23. Kidney Int. 60, 2079–2086 (2001).

41. Shimada, T. et al. Mutant FGFR-23 responsible for autosomal dominant hypophosphatemic rickets is resistant to proteolytic cleavage and causes hypophosphatemia in vivo. Endocrinology 143, 3179–3182 (2002).

42. Cavallaro, U. & Dejana, E. Adhesion molecule signalling: not always a sticky business. Nat. Rev. Mol. Cell. Biol. 12, 189–197 (2011).

43. Latko, M. et al. Cross-talk between fibroblast growth factor receptors and other cell surface proteins. Cells 8, 455 (2019).

44. Leckband, D. E. & de Rooy, J. Cadherin adhesion and mechanotransduction. Annu. Rev. Cell Dev. Biol. 30, 291–315 (2014).

45. Sanchez-Heras, E., Howell, F. V., Williams, G. & Doherty, P. Neurite outgrowth stimulated by integrin-mediated FGFR signalling and angiogenesis. Mol. Biol. Cell 181, 1101–1116 (2009).

46. Bachmann, M., Kukkurainen, S., Hytonen, V. P. & Wehrle-Haller, B. Cell adhesion molecules as regulators of vascular smooth muscle marker gene expression. J. Biol. Chem. 283, 18066–18075 (2008).

47. Rho family GTPases, by Shigekuni, S., Hytonen, V. P. & Wehrle-Haller, B. Cell adhesion molecules as regulators of vascular smooth muscle marker gene expression. J. Biol. Chem. 283, 18066–18075 (2008).

48. Lonn, C. et al. Neurite outgrowth induced by a synthetic peptide ligand of N-cadherin and all of the major isoforms of neural cell adhesion molecule. J. Biol. Chem. 281, 35208–35216 (2006).

49. Qian, X. et al. N-cadherin/FGFR promotes metastasis through epithelial-to-mesenchymal transition and stem/progenitor cell-like properties. Oncogene 33, 3411–3421 (2014).

50. Boscher, C. & Mege, R. M. Cadherin-11 interacts with the FGF receptor and induces neurite outgrowth through associated downstream signalling. Cell Signal. 20, 1061–1072 (2008).

51. Williams, E. J., Furness, J., Walsh, F. S. & Doherty, P. Activation of the FGF receptor underlies neurite outgrowth stimulated by L1, N-CAM and the N-cadherin. Neuron 13, 583–594 (1994).

52. Carafoli, F., Saffell, J. L. & Hohenester, E. Structure of the tandem fibronectin type 3 domains of neural cell adhesion molecule. J. Mol. Biol. 377, 524–534 (2008).

53. Koon, E. et al. N-cadherin-regulated FGFR ubiquitination and degradation control mammalian neocortical projection neuron migration. Elife. 8, e47673 (2019).

54. Francavilla, C. et al. The binding of NCAM to FGFR1 induces a specific cellular response mediated by receptor trafficking. J. Cell Biol. 187, 1101–1116 (2019).

55. Ronn, L. C. et al. Neurite outgrowth induced by a synthetic peptide ligand of N-cadherin and all of the major isoforms of neural cell adhesion molecule. J. Biol. Chem. 281, 35208–35216 (2006).

56. Mori, S. et al. Direct binding of integrin alphavbeta3 to FGFR1 plays a role in FGFR1 signalling. J. Biol. Chem. 283, 18066–18075 (2008).

57. Mori, S. et al. Neurite outgrowth induced by a synthetic peptide ligand of N-cadherin and all of the major isoforms of neural cell adhesion molecule. J. Biol. Chem. 281, 35208–35216 (2006).

58. Mori, S. et al. The integrin-binding defective FGFR2 mutants potently suppress FGFR2 signalling and angiogenesis. Biosci. Rep. 37, BSR20170173 (2017).

59. Rusnati, M. et al. alphavbeta3 integrin mediates the cell-adhesive capacity and biological activity of basic fibroblast growth factor (FGF-2) in cultured endothelial cells. Mol. Biol. Cell 8, 2449–2461 (1997).

60. Mori, S. et al. Direct binding of integrin alphavbeta3 to FGFR1 plays a role in FGFR1 signalling. J. Biol. Chem. 283, 18066–18075 (2008).

61. Rons, L. C. et al. Neurite outgrowth induced by a synthetic peptide ligand of N-cadherin and all of the major isoforms of neural cell adhesion molecule. J. Biol. Chem. 281, 35208–35216 (2006).

62. Mei, K. F., Saffell, J. L., Walsh, F. S. & Doherty, P. Neurite outgrowth stimulated by neural cell adhesion molecules requires growth-associated protein-43 (GAP-43) function and is associated with GAP-43 phosphorylation in growth cones. J. Neurosci. 18, 10429–10437 (1998).

63. Kiriyushko, D., Konshunova, I., Berezin, V. & Bock, E. Neural cell adhesion molecule induces intracellular signaling via multiple mechanisms of Ca2+ homeostasis. Mol. Biol. Cell 17, 2278–2286 (2006).

64. Weis, W. I. & Koblika, B. K. The molecular basis of G protein-coupled receptor activation. Annu. Rev. Biochem. 87, 897–919 (2018).

65. Liebmann, C. & Bohmer, F. D. Signal transduction pathways of G protein-coupled receptors and their cross-talk with receptor tyrosine kinases: lessons from Bradykinin signaling. Curr. Med. Chem. 7, 911–943 (2000).

66. Natarajan, K. & Berk, B. C. Cadherin crosslink mechanism of G protein-coupled receptors and receptor tyrosine kinases. Methods Mol. Biol. 332, 51–77 (2006).

67. Catteano, F. et al. Cell-surface receptors transactivation mediated by G protein-coupled receptors. Int. J. Mol. Sci. 15, 19700–19728 (2014).

68. Wang, Z. Transactivation of epidermal growth factor receptor by G protein-coupled receptors: recent progress, challenges and future perspective. Int. J. Mol. Sci. 17, 95 (2016).

69. Alderton, F. et al. Tethering of the platelet-derived growth factor beta receptor to G-protein-coupled receptors. A novel platform for integrative signaling by these receptor classes in mammalian cells. J. Biol. Chem. 276, 28578–28585 (2001).

70. Rongvent, E., Sinnett-Smith, J. & Kisfalvi, K. Crossstalk between insulin/insulin-like growth factor-1 receptors and G protein-coupled receptor signaling systems: a novel target for the anti-diabetic drug metformin in pancreatic cancer. Clin. Cancer Res. 16, 2505–2511 (2010).

71. Di Liberto, V., Mudo, G. & Belluardo, N. Crossstalk between receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCR) in the brain: Focus on heteroreceptor complexes and related functional neurotrophic effects. Neuropharmacology 152, 67–77 (2019).

72. Flajolet, M. et al. FGFR acts as a co-transmitter through adenosine A2A receptor to regulate synaptic plasticity. Nat. Neurosci. 11, 1402–1409 (2008).

73. Asimaki, O. et al. Cannabinoid 1 receptor-dependent transactivation of fibroblast growth factor receptor 1 emanates from lipid rafts and amplifies extra-cellular signal-regulated kinase 1/2 activation in embryonic cortical neurons. J. Neurochem. 116, 866–873 (2011).

74. Borroto-Escuela, D. O. et al. Fibroblast growth factor receptor 1-5-hydroxytryptamine 1A heteroreceptor complexes and their enhancement of hippocampal plasticity. Biol. Psychiatry 71, 84–91 (2012).

75. Di Liberto, V. et al. Evidence of muscarinic acetylcholine receptor (mAChR) and fibroblast growth factor receptor (FGFR) heteroreceptor complexes and their enhancement of neurite outgrowth in neural hippocampal cultures. Biochim. Biophys. Acta Gen. Subj. 1861, 235–245 (2017).

76. Xie et al. FGF/FGFR signaling in health and disease, Springer Nature Signal Transduction and Targeted Therapy (2020) 5:181.
101. Carpenter, G. Nuclear localization and possible functions of receptor tyrosine
107. Krejci, P., Krakow, D., Mekikian, P. B. & Wilcox, W. R. Fibroblast growth factors 1,
116. Iseki, S., Wilkie, A. O. & Morriss-Kay, G. M. Fgfr1 and Fgfr2 have distinct differ-
119. Tekin, M. et al. Homozygous mutations in
120. Falardeau, J. et al. Decreased FGF8 signaling causes de

Signal Transduction and Targeted Therapy (2020) 5:181
28

152. Coffin, J. D., Homer-Bouthiette, C. & Hurley, M. M. Fibroblast growth factor 2 and its receptors in bone biology and disease. J. Endocr. Soc. 2, 657–671 (2018).

153. Meo Burt, P. et al. FGF2 high molecular weight isoforms contribute to osteoarthritis in male mice. Endocrinology 157, 4602–4616 (2016).

154. Vincent, T. L. et al. FGF-2 is bound to pericellular in the peripheral matrix of articular cartilage, where it acts as a chondrocyte mecanotransducer. Osteoarthr. Cartil. 152, 752–763 (2007).

155. Chia, S. L. et al. Fibroblast growth factor 2 is an intrinsic chondroprotective agent that suppresses ADAMTS-5 and delays cartilage degradation in murine osteoarthritis. Arthritis Rheum. 60, 2019–2027 (2009).

156. Muddasani, P. et al. Basic fibroblast growth factor activates the MAPK and NFkappaB pathways that converge on Elk-1 to control production of matrix metalloproteinase-13 by human articular chondrocytes. J. Biol. Chem. 282, 31409–31421 (2007).

157. Nummenmaa, E. et al. Effects of FGF-2 and FGF receptor antagonists on MMP enzymes, aggrecan, and type II collagen in primary human OA chondrocytes. Scand. J. Rheumatol. 44, 321–330 (2015).

158. Nixon, A. J. et al. Gene therapy in musculoskeletal repair. Ann. NY Acad. Sci. 1117, 310–327 (2007).

159. Im, H. J. et al. Basic fibroblast growth factor accelerates matrix degradation via a neuro-endocrine pathway in human adult articular chondrocytes. J. Cell. Physiol. 215, 452–463 (2008).

160. Anderson, M. J., Schimmang, T. & Lewandoski, M. An FGF4–BMP signaling axis regulates caudal neural tube closure, neural crest specification and anterior–posterior axis extension. PLoS Genet. 12, e1006018 (2016).

161. McCarthy, N., Sidik, A., Bertrand, J. V. & Eberhart, J. K. An Fgf5–Shh signaling hierarchy regulates early specification of the zebrafish skull. Dev. Biol. 415, 261–277 (2016).

162. Murohashi, M. et al. An FGFR–FRS2alpha–Cdx2 axis in trophoblast stem cells induces Bmp4 to regulate proper growth of early mouse embryos. Stem Cells 28, 113–121 (2010).

163. Boulet, A. M. & Capecci, M. R. Signaling by FGF4 and FGF5 is required for axial elongation of the mouse embryo. Dev. Biol. 371, 235–245 (2012).

164. Kratochwil, K. et al. FGF4, a direct target of LEF1 and Wnt signaling, can rescue cleft palate in severe dwarf mice. J. Cell. Biol. 161, 327–338 (2003).

165. Kratochwil, K. et al. FGF4, a direct target of LEF1 and Wnt signaling, can rescue cleft palate in severe dwarf mice. J. Cell. Biol. 161, 327–338 (2003).

166. Schmidt, L. et al. Increased FGF8 signaling promotes chondrogenic rather than osteogenic development in the embryonic skull. Dis. Model. Mech. 11, dmm031526 (2018).

167. Xu, J. et al. FGF8 signaling alters the osteogenic cell fate in the hard palate. J. Dent. Res. 97, 589–596 (2018).

168. Tang, L. et al. A point mutation in FgF9 impedes joint interzone formation leading to multiple synostoses syndrome. Hum. Mol. Genet. 26, 1280–1293 (2017).

169. Hajhosseini, M. K. et al. Evidence that Fgf10 contributes to the skeletal and visceral defects of an Apert syndrome model mouse. Dev. Dyn. 238, 376–385 (2009).

170. Koweek, H. J. Hypoxia-induced fibroblast growth factor 11 stimulates osteoclast-mediated resorption of bone. Calcif. Tissue Int. 100, 382–391 (2017).

171. Ohbayashi, N. et al. FGF18 is required for normal cell proliferation and differentiation during osteogenesis and chondrogenesis. Genes Dev. 16, 870–879 (2002).

172. Liu, Z., Xu, J., Colvin, J. S. & Orntz, D. M. Coordination of chondrogenesis and osteogenesis by fibroblast growth factor 18. Genes Dev. 16, 859–869 (2002).

173. Hu, W. et al. Fibroblast growth factor 21 is associated with bone mineral density, but not with bone turnover markers and fractures in Chinese postmenopausal women. J. Clin. Densitom. 22, 179–184 (2019).

174. Wu, S., Levenson, A., Kharitonenkov, A. & De Luca, F. Fibroblast growth factor 21 (FGF21) inhibits chondrocyte function and growth hormone action directly at the growth plate. J. Biol. Chem. 287, 26600–26607 (2012).

175. Ishida, K. & Haudenschild, D. R. Interactions between FGF21 and BMP-2 in osteogenesis. Biochem. Biophys. Res. Commun. 432, 677–682 (2013).

176. Bornstein, S. et al. FGF21 and skeletal remodeling during and after lactation in C57BL/6j mice. Endocrinology 155, 3516–3526 (2014).

177. Shimada, T. et al. FGF-23 transgenic mice demonstrate hypophosphatemic rickets with reduced expression of sodium phosphate cotransporter type IIa. Biochem. Biophys. Res. Commun. 314, 404–414 (2004).

178. Liu, S. et al. Pathogenic role of FgF23 in Hpy mice. Am. J. Physiol. Endocrinol. Metab. 291, E38–E49 (2006).

179. Shahbouh, V. et al. Fibroblast growth factor 23 (FGF23) and alpha-klotho stimulate osteoblastic MC3T3E1 cell proliferation and inhibit mineralization. Calcif. Tissue Int. 89, 140–150 (2011).
208. Krejci, P. et al. Interaction of fibroblast growth factor and C-natriuretic peptide signaling in regulation of chondrocyte proliferation and extracellular matrix homeostasis. J. Cell Sci. 118, 5089–5100 (2005).
209. Cinque, L. et al. FGF signaling regulates chondrocyte bone growth through autophagy. Nature 528, 272–275 (2015).
210. Wang, X. et al. FGFR3/fibroblast growth factor receptor 3 inhibits autophagy through decreasing the ATG12–ATG5 conjugate, leading to the delay of cartilage development in achondroplasia. Autophagy 11, 1998–2013 (2015).
211. Martin, L. et al. Constitutively-active FGFR3 disrupts primary cilium length and IF20 trafficking in various chondrocyte models of achondroplasia. Hum. Mol. Genet. 27, 1–13 (2018).
212. Kunova Bosakova, M. et al. Regulation of cilary function by fibroblast growth factor signaling identifies FGFR3-related disorders achondroplasia and thalamosphoric dysplasia as ciliopathies. Hum. Mol. Genet. 27, 1093–1105 (2018).
213. Twiggs, S. R. et al. Skeletal analysis of the Fgfr3(2P44R) mouse, a genetic model for the Muenke craniosynostosis syndrome. Dev. Dyn. 238, 331–342 (2009).
214. Mugniery, E. et al. An activating Fgfr3 mutation affects trabecular bone formation via a paracrine mechanism during growth. Hum. Mol. Genet. 21, 2503–2513 (2012).
215. Matsushita, T. et al. FGFR3 promotes synchondrosis closure and fusion of ossification centers through the MAPK pathway. Hum. Mol. Genet. 18, 227–240 (2009).
216. Wen, X. et al. Chondrocyte FGFR3 regulates bone mass by inhibiting osteogenesis. J. Biol. Chem. 291, 24912–24921 (2016).
217. Valverde-Franco, G. et al. Defective bone mineralization and osteopenia in young adult Fgfr3(−/−) mice. Hum. Mol. Genet. 13, 271–284 (2004).
218. Su, N. et al. Deletion of Fgfr3 in osteosteat lineage cells results in increased bone mass in mice by inhibiting osteoblastic bone resorption. J. Bone Miner. Res. 31, 1676–1687 (2016).
219. Zhou, F. H., Foster, B. K., Sander, G. & Xian, C. J. Expression of proinflammatory cytokines and growth factors at the injured growth plate cartilage in young rats. Bone 35, 1307–1315 (2004).
220. Zhou, F. H. et al. TNF-alpha mediates p38 MAP kinase activation and negatively regulates bone formation at the injured growth plate in rats. J. Bone Miner. Res. 21, 1075–1088 (2006).
221. Damron, T. A. et al. Temporal changes in PTHrP, Bcl-2, Bax, caspase, TGF-beta, and FGF-2 expression following growth plate irradiation with or without radioprotectant. J. Histochem. Cytochem. 52, 157–167 (2004).
222. Daoulti, S. et al. Development of comprehensive functional genomic screens to identify novel mediators of osteoarthritis. Osteoarthritis Cartil. 13, 508–515 (2008).
223. Yan, D. et al. Fibroblast growth factor receptor 1 is principally responsible for fibroblast growth factor 2-induced catabolic activities in human articular chondrocytes. Arthritis Res. Ther. 13, R130 (2011).
224. Weng, T. et al. Genetic inhibition of fibroblast growth factor receptor 1 in knee cartilage attenuates the degeneration of articular cartilage in adult mice. Arthritis Rheum. 64, 3982–3992 (2012).
225. Klag, K. A. & Horton, W. A. Advances in treatment of achondroplasia and osteoarthritis. Hum. Mol. Genet. 25, R2–R8 (2016).
226. Tang, J. et al. Fibroblast growth factor receptor 3 inhibits osteoarthritis progression in the knee joints of adult mice. Arthritis Rheumatol. 68, 2432–2443 (2016).
227. Zhou, S. et al. Conditional deletion of Fgfr3 in chondrocytes leads to osteoarthritis-like defects in temporomandibular joint of adult mice. Sci. Rep. 6, 24039 (2016).
228. Kuang, L. et al. FGFR3 deficiency enhances CXCL12-dependent chemotaxis of macrophages via upregulating CXCR7 and aggravates joint destruction in mice. Ann. Rheum. Dis. 79, 112–122 (2020).
229. Kisand, K., Tamm, A. E., Lintrop, M. & Tamm, A. O. New insights into the natural tophoric dysplasia as ciliopathies. Autophagy 12, 1673–1687 (2016).
230. Mugniery, E. et al. An activating Fgfr3 mutation affects trabecular bone formation via a paracrine mechanism during growth. Hum. Mol. Genet. 21, 2503–2513 (2012).
231. Im, H. J. et al. Basic bone marrow stromal cells in 3D collagen gels. Exp. Cell Res. 338, 136–148 (2015).
232. Wang, J., Liu, S., Li, J. & Yi, Z. The role of the fibroblast growth factor receptor 1 inhibitor protects against cartilage degradation in a murine model of osteoarthritis. Arthritis Res. Ther. 26, 1733–1743 (2018).
233. Xu, W. et al. Inducible activation of FGFR2 in adult mice promotes bone formation after bone marrow ablation. J. Bone Miner. Res. 32, 2194–2206 (2017).
234. Xu, W. et al. FGFR3 deficient mice have accelerated fracture repair. Int. J. Biol. Sci. 13, 1029–1037 (2017).
235. Chen, H. et al. PTH 1–34 ameliorates the osteopenia and delayed healing of stabilized tibia fracture in mice with achondroplasia resulting from gain-of-function mutation of Fgfr3. Int. J. Biol. Sci. 13, 1254–1265 (2017).
236. Le Blanc, S. et al. Fibroblast growth factors 1 and 2 inhibit adipogenesis of human bone marrow stromal cells in 3D collagen gels. Exp. Cell Res. 338, 136–148 (2015).
237. Wang, J., Liu, S., Li, J. & Yi, Z. The role of the fibroblast growth factor family in bone-related diseases. Clin. Biochem. Drug Commun. 37, 1470–1479 (2019).
238. marker, J. et al. Accelerated fracture healing in transgenic mice over-expressing an anabolic isoform of fibroblast growth factor 2. J. Cell. Biochem. 117, 599–611 (2016).
239. Xiao, L. et al. Fibroblast growth factor-2 isoform (low molecular weight/18 kDa) overexpression in preosteoblast cells promotes bone regeneration in critical size defects in male mice. Endocrinology 155, 965–974 (2014).
240. Lee, P. et al. Fibroblast growth factor 21 (FGF21) and bone: is there a relationship in humans? Osteopores Int. 24, 3053–3057 (2013).
241. Wei, W. et al. Fibroblast growth factor 21 promotes bone loss by potentiating the effects of peroxisome proliferator-activated receptor gamma. Proc. Natl Acad. Sci. USA 109, 3143–3148 (2012).
242. Rupp, T. et al. High FGF23 levels are associated with impaired trabecular bone microarchitecture in patients with osteoporosis. Osteoporos. Int. 30, 1655–1662 (2019).
243. Goebel, S. et al. FGF23 is a putative marker for bone healing and regeneration. J. Orthop. Res. 27, 1141–1146 (2009).
244. Clinkenbeard, E. L. & White, K. E. Systemic control of bone homeostasis by FGF23 signaling. Curr. Mol. Biol. Rep. 2, 62–71 (2016).
245. Xu, W. et al. A novel fibroblast growth factor receptor 1 inhibitor protects against cartilage degradation in a murine model of osteoarthritis. Sci. Rep. 6, 24042 (2016).
246. Tan, Q. et al. A novel FGF1-binding peptide attenuates the degeneration of articular cartilage in adult mice. Osteoarthritis Cartil. 26, 1733–1743 (2018).
247. Yao, X. et al. Fibroblast growth factor 18 exerts anti-osteoarthritis effects through PI3K-AKT signaling and mitochondrial fusion and fission. Pharam. Res. 139, 314–324 (2019).
248. Howard, D., Wardale, J., Gueruing, H. & Henson, F. Delivering rhFGF-18 via a bilayer collagen membrane to enhance microfracture treatment of chondral defects in a large animal model. J. Orthop. Res. 33, 1120–1127 (2015).
264. Power, J. et al. Intra-articular injection of rhFGF-18 improves the healing in microfracture treated chondral defects in an ovine model. J. Orthop. Res. 32, 669–676 (2014).

265. Eckstein, F. et al. Brief report: intraarticular sprifermin not only increases cartilage thickness, but also reduces cartilage loss: location-independent post hoc analysis using magnetic resonance imaging. Arthritis Rheumatol. 67, 2916–2922 (2015).

266. deMello, D. E. et al. Intra-articular sprifermin (recombinant human fibroblast growth factor 18) in knee osteoarthritis: a randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 66, 1820–1831 (2014).

267. Onoara, S. Osteoarthrosis: Sprifermin shows cartilage-protective effects in knee OA. Nat. Rev. Rheumatol. 10, 322 (2014).

268. Hochberg, M. C. et al. Effect of intra-articular sprifermin vs placebo on femoro-ethical joint cartilage thickness in patients with osteoarthritis: The FORWARD Randomized Clinical Trial. JAMA 322, 1360–1370 (2019).

269. Tang, Z. F. & Li, H. Y. Effects of fibroblast growth factors 2 and low intensity pulsed ultrasound on the repair of knee articular cartilage in rabbits. Eur. Rev. Med. Pharm. Sci. 22, 2447–2453 (2018).

270. Cuevas, P., Burgos, J. & Baird, A. Basic fibroblast growth factor (FGF) promotes cartilage repair in vivo. Biochem. Biophys. Res. Commun. 156, 611–618 (1988).

271. Panetta, N. J., Longaker, M. T. & Quarto, N. Different endogenous growth factors and angiogenic cytokines in teratomas. Am. J. Pathol. 177, 680–685 (2010).

272. Poudel, S. B. et al. Local delivery of recombinant human FGF7 enhances bone healing in models of fronto-parietal and vertebral bone. Bone 67, 618–625 (2016).

273./highlight=green
274. Behr, B. et al. Fgf-18 is required for osteogenesis but not angiogenesis during cartilage repair in vivo. Bone 67, 2916–2922 (2016).

275. Lohmander, L. S. et al. Intraarticular sprifermin (recombinant human keratinocyte growth factor) vs placebo for tibial shaft fractures: a randomized, placebo-controlled trial. J. Bone Miner. Res. 22, 2069–2075 (2011). discussion 207

276. MacKenzie, B. et al. Increased FGF1-FGFRc expression in idiopathic pulmonary fibrosis. Proc. Natl Acad. Sci. USA 104, 1360–1365 (2007).

277. Sekine, K. et al. Fgf10 is essential for limb and lung formation. Nat. Genet. 21, 138–144 (1999).

278. de Moerlooze, L. et al. An important role for the Ibb isoform of fibroblast growth factor receptor 2 (FGFR2) in mesenchymal–epithelial signalling during mouse organogenesis. Development 127, 483–492 (2000).

279. Graeff, R. W., Wang, G. & McClay, P. B. Jr KGF and FGF-10 stimulate liquid secretion in human fetal lung. Pediatr. Res. 62, 523–529 (1999).

280. Danopoulos, S. et al. Human lung branching morphogenesis is orchestrated by the spatiotemporal distribution of ACTA2, SOX2, and SOX9. Am. J. Physiol. Lung Cell. Mol. Physiol. 314, L144–L149 (2018).

281. Nikolic, M. Z. et al. Human embryonic lung epithelial tips are multipotent progenitors that can be expanded in vitro as long-term self-renewing organoids. Elife 6, e26275 (2017).

282. Miller, A. J. et al. Generation of lung organoids from human pluripotent stem cells in vitro. Nat. Protoc. 14, 518–540 (2019).

283. Usui, H. et al. Fgf18 is required for embryonic lung alveolar development. Biochem. Biophys. Res. Commun. 322, 887–892 (2004).

284. Peters, K. et al. Targeted expression of a dominant negative FGF receptor blocks branching morphogenesis and epithelial differentiation of the mouse lung. EMBO J. 13, 3296–3301 (1994).

285. Srisuma, S. et al. Fibroblast growth factor receptors control epithelial-mesenchymal interactions necessary for alveolar elongation. Am. J. Respir. Crit. Care Med. 181, 838–850 (2010).

286. Weinstein, M., Xu, X., Ohyama, K. & Deng, C. X. FGF-3 and FGF-4 function cooperatively to direct alveogenesis in the murine lung. Development 125, 3615–3623 (1998).

287. Ren, J. T. et al. Relationship between the gene polymorphism in fibroblast growth factor-10 and susceptibility to chronic obstructive pulmonary disease 220 cases. Zhonghua Yi Xue Za Zhi 36, 935–939 (2013).

288. Smith, B. M. et al. Human airway branch variation and chronic obstructive pulmonary disease. Proc. Natl Acad. Sci. USA 115, 1516–1521 (2018).

289. Rezvani, M. et al. Association of a FGF-4 gene polymorphism with broncho-pulmonary dysplasia and neonatal respiratory distress. Dis. Markers 35, 633–640 (2013).
320. Teramoto, H., Yoneda, A. & Puri, P. Gene expression of fibroblast growth factors 10 and 7 is downregulated in the lung of nitrogen-induced diaphragmatic hernia in rats. J. Pediatr. Surg. 38, 1021–1024 (2003).
321. Wang, J., Liu, H., Gao, L. & Liu, X. Impaired FGFR10 signaling and epithelial development in experimental lung hypoplasia with esophageal atresia. Front. Pediatr. 6, 109 (2018).
322. Park, M. S. et al. Altered expressions of fibroblast growth factor receptors and alveolarization in neonatal mice exposed to 85% oxygen. Pediatr. Res. 62, 652–657 (2007).
323. Joannes, A. et al. FGFR9 and FGFR18 in idiopathic pulmonary fibrosis promote survival and migration and inhibit myofibroblast differentiation of human lung fibroblasts in vitro. Am. J. Physiol. Lung Cell. Mol. Physiol. 310, L615–L629 (2016).
324. Tunc, T. et al. FGFR signaling in skeletal development and homeostasis: learning from mouse models. Bone Res. 2, 1403 (2014).
325. Guzy, R. D. et al. Pulmonary fibrosis requires cell-autonomous mesenchymal fibroblast growth factor (FGF) signaling. J. Biol. Chem. 292, 10364–10378 (2017).
326. Brown, A. C. et al. FGF/EGF signaling regulates the renewal of early nephron progenitors during embryonic development.
327, 643–649 (2000).
327. Revest, J. M. et al. Fibroblast growth factor receptor 2 ligand enhances survival of Shh and Fgf4 and is required for limb bud maintenance but not for the induction of Fgf8, Fgf10, Mx1, or Bmp4. Dev. Biol. 231, 47–62 (2001).
328. Barak, H. et al. FGFR and FGFR2 cooperate to induce nephrogenesis. Dev. Biol. 301, 424–434 (2007).
329. Gerber, S. D. et al. The mouse Fgfrl1 receptor is essential for the development of the pronephric glomus in vivo. J. Clin. Invest. 124, 2534–2535 (2011).
330. El-Saeed, A. M. & El-Mohasseb, G. F. Circulating fibroblast growth factors 21 and 23 as biomarkers of progression in diabetic nephropathy in type 2 diabetes with normal or near-normal blood pressure. J. Clin. Endocrinol. Metab. 100, 1368–1375 (2015).
331. Dalrymple, L. S. & Go, A. S. Epidemiology of acute infections among patients with severe acute kidney injury and death following cardiac surgery. J. Clin. Invest. 124, 2534–2535 (2011).
332. Bates, C. M. Role of FGF and BMP signaling pathways regulates development of metanephric mesenchyme. Genes Dev. 13, 1601–1613 (1999).
333. Lee, C. H. et al. Role of fibroblast growth factor receptors 1 and 2 in the metanephric mesenchyme. Dev. Biol. 291, 325–339 (2006).
334. Polad, D. P. et al. Role of fibroblast growth factor receptors 1 and 2 in the metanephric mesenchyme. Dev. Biol. 291, 325–339 (2006).
335. Xiao, H. et al. Role of fibroblast growth factor receptors 1 and 2 in the metanephric bud. Dev. Biol. 276, 403–415 (2004).
336. Walker, K. A., Sims-Lucas, S. & Bates, C. M. Fibroblast growth factor receptor signaling in the developing kidney. J. Pediatr. Nephrol. 31, 885–895 (2016).
337. Gerber, S. D. et al. The murine Fgf11 receptor is essential for the development of the metanephric kidney. Dev. Biol. 335, 106–119 (2009).
338. Barash, J. et al. Ureteric bud cells secrete multiple factors, including bFGF, which rescue renal progenitors from apoptosis. Am. J. Physiol. 273, F577–F5767 (1997).
339. Brennan, H. C., Nijjar, S. & Jones, E. A. The specification and growth factor inducibility of the pronephric glomus Xenopus laevis. Development 126, 5847–5856 (1999).
340. Pliszow, S. Y. et al. TGF beta 2, LIF and FGF2 cooperate to induce nephrogenesis. Development 128, 1045–1057 (2001).
341. Grieshammer, U. et al. FGFR is required for cell survival at distinct stages of nephrogenesis and for regulation of gene expression in nascent nephrons. Development 132, 3487–3487 (2005).
342. Perantoni, A. O. et al. Inactivation of FGFR4 in early mesoderm reveals an essential role in kidney development. Development 132, 3859–3871 (2005).
343. Brown, A. C. et al. FGFR signaling regulates the renewal of early nephron progenitors during embryonic development. Development 138, 5099–5112 (2011).
344. Barak, H. et al. FGFR9 and FGFR20 maintain the stemness of nephron progenitors in mice and man. Dev. Cell 22, 1191–1207 (2012).
345. Miller, D. L. et al. Compensation by fibroblast growth factor 1 (FGF1) does not account for the mild phenotypic defects observed in FGFR2 null mice. Mol. Cell. Biol. 20, 2260–2260 (2000).
346. Zhou, M. et al. Fibroblast growth factor 2 control of vascular tone. Nat. Med. 4, 201–207 (1998).
347. Di Giovanni, V. et al. Fibroblast growth factor receptor-Frs2alpha signaling is critical for nephron progenitors. Dev. Biol. 400, 82–93 (2015).
380. Brown, J. R. et al. Fibroblast growth factor-23 and the long-term risk of hospital-associated AKI among community-dwelling older individuals. Clin. J. Am. Soc. Nephrol. 9, 239–246 (2014).

381. Ali, F. N., Hassinger, A., Price, H. & Langman, C. B. Preoperative plasma FGF23 levels predict acute kidney injury in children: results of a pilot study. Pediatr. Nephrol. 28, 959–962 (2013).

382. Volokolovsky, O. et al. Early postoperative measurement of fibroblast growth factor 23 predicts severe acute kidney injury in infants after cardiac surgery. Clin. Nephrol. 90, 165–171 (2018).

383. Leaf, D. E. et al. Fibroblast growth factor 23 associates with death in critically ill patients. Clin. J. Am. Soc. Nephrol. 13, 531–541 (2018).

384. Hassan, A. et al. The fibroblast growth factor receptor mediates the increased FGF23 expression in acute and chronic uremia. Am. J. Physiol. Ren. Physiol. 310, F217–F221 (2016).

385. Christov, M. et al. Plasma FGF23 levels increase rapidly after acute kidney injury. Kidney Int. 84, 776–785 (2013).

386. Smith, E. R., Tan, S. J., Holt, S. G. & Hewitson, T. D. FGF23 is synthesised locally by renal tubules and activates injury-prime fibroblasts. Sci. Rep. 7, 3345 (2017).

387. Mace, M. L. et al. Kidney fibroblast growth factor 23 does not contribute to elevation of its circulating levels in uremia. Kidney Int. 92, 165–178 (2017).

388. Michos, O. et al. Kidney development in the absence of Gdnf and Spry1 requires a Wnt/Fzd/Beta-catenin pathway. Kidney Int. 92, 165–178 (2017).

389. Yaman, J., L., K. H. & Kuremoto, K. I. FGF-10/FGFR2B signaling during acute cyclophosphamide-induced bladder urothelial injury in mice. J. Urol. 185, e547–e548 (2011).

390. Motaohashi, N. & Asakura, A. Muscle satellite cell heterogeneity and self-renewal. Front. Cell Dev. Biol. 2, 1 (2014).

391. Sheehan, S. M. & Allen, R. E. Skeletal muscle satellite cell proliferation in response to members of the fibroblast growth factor family and hepatocyte growth factor. J. Cell Physiol. 181, 499–506 (1999).

392. Kastner, S., Elias, M. C., Rivera, A. J. & Yablonka-Reuveni, Z. Gene expression and transplantation for cell-mediated gene therapy. Genes Dev. 15, 549–554 (1993).

393. DeLapeyriere, O. et al. Expression of the Fgf6 gene is restricted to developing skeletal muscle in the mouse embryo. Development 118, 601–611 (1993).

394. Floss, T., Arnold, H. H. & Braun, T. A. Role for Fgf-6 in skeletal muscle regeneration. Genes Dev. 11, 2040–2051 (1997).

395. Cool, S. M. et al. Temporal and spatial expression of fibroblast growth factor receptor 4 isoforms in murine tissues. Histochem. J. 34, 291–297 (2002).

396. Engel, F. B., Hsieh, P. C., Lee, R. T. & Keating, M. T. FGF1/p38 MAP kinase inhibitor therapy induces cardiomyocyte mitosis, reduces scarring, and rescues function after myocardial infarction. Proc. Natl Acad. Sci. USA 103, 15546–15551 (2006).

397. Novofatseva, T. et al. FGF1-mediated cardiomyocyte cycle reentry depends on the interaction of FGF1-1 and Fn14. FASEB J. 28, 2492–2503 (2014).
Cuevas, P. et al. Fibroblast growth factor-1 prevents myocardial apoptosis triggered by ischemia reperfusion injury. Eur. J. Med. Res. 2, 465–468 (1997).

Baines, C. P. & Molkentin, J. D. STRESS signaling pathways that modulate cardiac myocyte apoptosis. J. Mol. Cell Cardiol. 38, 47–62 (2005).

Engel, F. B. et al. p38 MAP kinase inhibition enables proliferation of adult mammalian cardiomyocytes. Genes Dev. 19, 1175–1187 (2005).

Buehler, A. et al. Angiogenesis-independent cardioprotection in FGF-1 transgenic mice. Cardiovasc. Res. 55, 768–777 (2002).

House, L. S. et al. Fibroblast growth factor 2 mediates isoproterenol-induced cardiac hypertrophy through activation of the extracellular regulated kinase. Mol. Cell Pharmacol. 2, 143–154 (2010).

Pelleix, C. et al. Dilated cardiomyopathy and impaired cardiac hypertrophic response to angiotensin II in mice lacking FGF-2. J. Clin. Invest. 108, 1843–1851 (2001).

Virag, J. A. et al. Fibroblast growth factor-2 regulates myocardial infarct repair: effects on cell proliferation, scar contraction, and ventricular function. Am. J. Pathol. 171, 1431–1440 (2007).

House, L. S. et al. Fibroblast growth factor 2 is an essential cardioprotective factor in a closed-chest model of cardiac ischemia-reperfusion injury. Physiol. Rep. 3, e12278 (2015).

Dettileux, K. A. Sheikh, F., Kardami, E. & Cattini, P. A. Biological activities of fibroblast growth factor-2 in the adult myocardium. Cardiovasc. Res. 57, 8–19 (2003).

Wang, Z. G. et al. bFGF regulates autophagy and ubiquitin-protein accumulation induced by myocardial ischemia/reperfusion via the activation of the PI3K/Akt/mTOR pathway. Sci. Rep. 5, 9237 (2015).

Ruel, M. et al. Long-term effects of surgical angiogenic therapy with fibroblast growth factor 2 protein. J. Thorac. Cardiovasc. Surg. 124, 28–34 (2002).

Simons, M. et al. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2: double-blind, randomized, controlled clinical trial. Circulation 105, 788–793 (2002).

Simons, M. & Ware, J. A. Therapeutic angiogenesis in cardiovascular disease. Nat. Rev. Drug Discov. 2, 863–871 (2003).

Lavine, K. J. et al. Endocardial and epicardial derived FGF signals regulate myocardial proliferation and differentiation in vivo. Dev. Cell 8, 85–95 (2005).

Korf-Klingebiel, M. et al. Conditional transgenic expression of fibroblast growth factor 9 in the adult mouse heart reduces heart failure mortality after myocardial infarction. Circulation 123, 504–511 (2011).

Singla, D. K., Singla, R. D., Abdelli, L. S. & Glass, C. Fibroblast growth factor-9 enhances M2 macrophage differentiation and attenuates adverse cardiac remodeling in the infarcted diabetic heart. PLoS ONE 10, e0120739 (2015).

Kelly, R. G., Brown, N. A. & Buckingham, M. E. The arterial pole of the mouse heart forms from Flt10-expressing cells in pharyngeal mesoderm. Dev. Cell 1, 435–440 (2001).

Roehais, F. et al. FGFR10 promotes regional foetal cardiomyocyte proliferation and adult cardiomyocyte cycle-re entry. Cardiovasc. Res. 104, 432–442 (2014).

Marguerie, A. et al. Congenital heart defects in Flgfr2-IIIb and Fgf10 mutant mice. Cardiovasc. Res. 71, 50–60 (2006).

Rubin, N. et al. FGFR10 signaling enhances epicardial cell expansion during neonatal mouse heart repair. J. Cardiovasc. Dis. Diagn. 1, 101 (2013).

Nicenboim, J. et al. Lymphatic vessels arise from specialized angioblasts within a venous niche. Nature 522, 56–61 (2015).

Yu, P. et al. FGF-dependent metabolic control of vascular development. Nature 455, 234–228 (2017).

DelfEra, P. et al. Paracrine and autocrine effects of fibroblast growth factor-4 in endothelial cells. Oncogene 20, 2655–2663 (2001).

Shin, J. W. et al. Prox1 promotes lineage-specific expression of fibroblast growth factor (FGF) receptor-3 in lymphatic endothelium: a role for FGF signaling in lymphangiogenesis. Mol. Biol. Cell 17, 576–584 (2006).

Cross, M. J. & Claesson-Welsh, L. FGF and VEGF function in angiogenesis: signalling pathways, biological responses and therapeutic inhibition. Trends Pharm. Sci. 22, 201–207 (2001).

Mignatti, P. & Rifkin, D. B. Nonenzymatic interactions between proteinases and M17–MMP as membrane vesicle-associated components by endothelial cells. Am. J. Pathol. 160, 673–680 (2002).

Gillis, P. et al. Keratinocyte growth factor induces angiogenesis and protects endothelial barrier function. J. Cell Sci. 112(Par. 12), 2049–2057 (1999).

Choi, I. et al. 9-Cis retinoic acid promotes lymphangiogenesis and enhances lymphatic vessel regeneration: therapeutic implications of 9-cis retinoic acid for secondary lymphedema. Circulation 125, 872–882 (2012).

Moscadelli, D., Presta, M., Joseph-Silverstein, J. & Rifkin, D. B. Both normal and tumor cells produce basic fibroblast growth factor. J. Cell. Physiol. 129, 273–276 (1986).

Wang, T. & Becker, D. Antisense targeting of basic fibroblast growth factor and bFGF growth factor-receptor-1 in human melanoma blocks intratumoral angiogenesis and tumor growth. Nat. Med. 3, 887–893 (1997).

Presta, M. et al. Fibroblast growth factor/bFGF growth factor receptor system in angiogenesis. Cytokine Growth Factor Rev. 16, 159–178 (2005).

Domenico, R. et al. Angiogenic activity of rat mast cells in the chick embryo choioallantoic membrane is down-regulated by treatment with recombiant human alpha-2 antiplasmin and partly mediated by fibroblast growth factor-2. Haematologica 87, 465–471 (2002).

Hyung Taek, L., Jeong Goo, L., Moonseok, N. & Kay, E. D. P. FGF-2 induced by interleukin-1 beta through the action of phosphatidylinositol 3-kinase mediates endothelial mesenchymal transformation in comeal endothelial cells. J. Biol. Chem. 279, 32325 (2004).

Lavine, K. J. et al. A PPARgamma-FGF1 axis is required for adaptive adipose remodelling and metabolic homeostasis. Nature 483, 391–394 (2012).

Jonker, J. W. et al. A PPAlgamma-FGF1 axis is required for adaptive adipose remodelling and metabolic homeostasis. Nature 485, 391–394 (2012).

Sano, H. et al. Detection of high levels of heparin binding growth factor-1 (acidal fibroblast growth factor) in inflammatory arthritic joints. J. Cell Biol. 110, 1417–1426 (1990).

Byrd, V. M., Ballard, D. W., Miller, G. G. & Thomas, J. W. Fibroblast growth factor-1 (FGF-1) enhances IL-2 production and nuclear translocation of NF-kappaB in FGF receptor-bearing Jurkat T cells. J. Immunol. 162, 5853–5859 (1999).

Rossini, M. et al. Immunolocalization of fibroblast growth factor-1 (FGF-1), its receptor (FGFR-1), and fibroblast-specific protein-1 (FSP-1) in inflammatory renal disease. Kidney Int. 68, 2621–2628 (2005).

Hacksch, K. V. & Shi, Y. Fibroblast growth factor mobilize peritoneal macrophage intracellular calcium. Life Sci. 54, 661–670 (1994).

Garre, J. M. et al. FGF-1 induces ATP release from spinal astrocytes in culture and opens pannein and connexin hemichannels. Proc. Natl Acad. Sci. USA 107, 22659–22664 (2010).

Garre, J. M., Yang, G., Bukauskas, F. & Bennett, M. V. FGF-1 triggers Pannexin-1 hemichannel opening in spinal astrocytes of rodents and promotes inflammatory responses in acute spinal cord slices. J. Neurosci. 36, 4785–4801 (2016).

Huang, Z. et al. Uncoupling the mitogenic and metabolic functions of FGF1 by tuning FGF1-FGF receptor dimer stability. Cell Rep. 20, 1717–1728 (2017).

Wang, D. et al. FGFR1(DeltaHBS) ameliorates chronic kidney disease via P38/KAT mediated suppression of oxidative stress and inflammation. Cell Death Dis. 10, 464 (2019).

Li, H. et al. FGF1 ameliorates diabetic nephropathy by an anti-inflammatory mechanism. Kidney Int. 93, 95–109 (2018).

Harada, M. et al. Temporal expression of growth factors triggered by epiregulin regulates inflammation development. J. Immunol. 194, 1039–1046 (2015).

Shao, X. et al. FGF2 cooperates with IL-17 to promote autoinmune inflammation. Sci. Rep. 7, 7024 (2017).

Song, X. et al. Growth factor FGF2 cooperates with interleukin-17 to repair intestinal epithelial damage. Immunity 43, 488–501 (2015).
494. Boehme, K. A. & Roluffs, B. Onset and progression of human osteoarthritis—
can growth factors, inflammatory cytokines, or differential miRNA expression
concomitantly induce proliferation, ECM degradation, and inflammation in
articular cartilage? Int. J. Mol. Sci. 19, 2282 (2018).

495. Lappegard, K. T. et al. The artificial surface-induced whole blood inflammatory
reaction revealed by increases in a series of chemokines and growth factors is
largely complement dependent. J. Biomed. Mater. Res. A 879, 142–135 (2008).

496. Keating, S. M. et al. The effect of HIV infection and HAART on inflammatory
biomarkers in a population-based cohort of women. AIDS 25, 1823–1832 (2011).

497. Bocelli-Tyndall, C. et al. FGF2 induces RANKL gene expression as well as IL-1beta
regulated MHC class II in human bone marrow-derived mesenchymal
progenitor stromal cells. Ann. Rheum. Dis. 74, 260–266 (2015).

498. Fedowski, P. et al. Markers of inflammation and fibrosis in the orbital fat
connective tissue of patients with Graves’ ophthalmopathy: clinical implications.
Mediat. Inflamm. 2014, 412158 (2014).

499. Presta, M. et al. Inflammatory cells and chemokines sustain FGF-2-induced
angiogenesis. Eur. Cytokine Netw. 20, 39–50 (2009).

500. Schultz, K., Murthy, V., Tatro, J. B. & Beasley, D. Endogenous interleukin-1 alpha
promotes a proliferative and proinflammatory phenotype in human vascular
smooth muscle cells. Am. J. Physiol. Heart Circ. Physiol. 292, H2927–H2934 (2007).

501. Bovolenta, R. et al. Hippocampal FGF-2 and BDNF overexpression attenuates
epileptogenesis-associated neuronal inflammation and reduces spontaneous
recurrent seizures. J. Neuroinflamm. 7, 81 (2010).

502. Kim, Y. S. et al. The role of FGF-2 in smoke-induced emphysema and the
therapeutic potential of recombinant FGF-2 in patients with COPD. Exp. Mol.
Pharmacol. 80, 1–10 (2011).

503. Leon, S. G. et al. Recombinant basic fibroblast growth factor inhibits the airway
hyperresponsiveness, mucus production, and lung inflammation induced by an
allergen challenge. J. Allergy Clin. Immunol. 119, 831–837 (2007).

504. Sautter, N. B., Delaney, K. L., Hausman, F. A. & Trune, D. R. Tissue remodeling
gene expression in a murine model of chronic rhinosinusitis. Laryngoscope 122,
711–717 (2012).

505. Sautter, N. B., Delaney, K. L. & Trune, D. R. Altered expression of tissue
remodeling genes in a mouse model of acute allergic rhinitis. Int. Forum Allergy
Rhinitol. 1, 262–267 (2011).

506. Sautter, N. B., Delaney, K. L., Hausman, F. A. & Trune, D. R. Tissue remodeling
in the acute otitis media mouse model. Int. J. Pediatr. Otorhinolaryngol. 75,
1368–1371 (2011).

507. Feingold, K. R. et al. FGF21 is increased by inflammatory stimuli and protects
leptin-deficient ob/ob mice from the toxicity of sepsis. Endocrinology 153,
2689–2700 (2012).

508. Gariani, K. et al. Increased FGF21 plasma levels in humans with sepsis and SIRS.
Endocr. Connect. 2, 146–153 (2013).

509. Refsgaard Holm, M. et al. Fibroblast growth factor 21 in patients with cardiac
cachexia: a possible role of chronic inflammation. ESC Heart Fail. 6, 985–991 (2019).

510. Planavila, A. et al. Fibroblast growth factor 21 protects the heart from oxidative
stress. Cardiovasc. Res. 106, 19–31 (2015).

511. Zhang, C. et al. Attenuation of hyperlipidemia- and diabetes-induced early-stage
apoptosis and late-stage renal dysfunction via administration of fibroblast
growth factor-21 is associated with suppression of renal inflammation. PLoS ONE
9, (2014), e82275.

512. Lee, K. J. et al. Expression of fibroblast growth factor 21 and beta-Klotho regu-
lates hepatic fibrosis through the nuclear factor-kappaB and c-Jun N-terminal
kinase pathways. Gut Liver 12, 449–456 (2018).

513. Mindur, J. E. & Swirski, F. K. Growth factors as immunotherapeutic targets in
cardiovascular disease. Arterioscler. Thromb. Vasc. Biol. 39, 1275–1287 (2019).

514. Wang, N. et al. Fibroblast growth factor 21 ameliorates pancreatic fibrogenesis
via regulating polarization of macrophages. Exp. Cell Res. 382, 111457 (2019).

515. Li, J. Y. et al. FGF-21 elevated IL-10 production to correct LPS-induced inflam-
mation. Inflammation 41, 751–759 (2018).

516. Wang, N. et al. Fibroblast growth factor 21 regulates foam cells formation and
inflammatory response in Ox-LDL-induced THP-1 macrophages. Biomod. Phar-
macotherapeut. 50, 1–10 (2018).

517. Wang, N. et al. Improving hyperglycemic effect of FGF-21 is associated with
alleviating inflammatory state in diabetes. Int. Immunopharmacol. 56, 301–309
(2018).

518. Wang, N. et al. Fibroblast growth factor 21 exerts its anti-inflammatory effects on
multiple cell types of adipose tissue in obesity. Obesity (Silver Spring) 27,
399–408 (2019).

519. Liu, M. H. FGF-21 alleviates diabetes-associated vascular complications: Inhibit-
ing NF-kappaB/NIK/NFJP3 inflammasome-mediated inflammation? Int. J. Cardiol. 185,
320–321 (2015).

520. Holecki, M. et al. Inflammation but not obesity or insulin resistance is associated
with increased plasma fibroblast growth factor 23 concentration in the elderly.
Clin. Endocrinol. 82, 90 (2015).
Owen, B. M. et al. FGF21 acts centrally to induce sympathetic nerve activity, and
Tan, B. K. et al. Fibroblast growth factor 21 (FGF21) in human cerebrospinal
Hu, M. C., Shi, M. & Moe, O. W. Role of alphaKlotho and FGF23 in regulation of
Wu, A. L. et al. Amelioration of type 2 diabetes by antibody-mediated activation
Yoshiko, Y. et al. Mineralized tissue cells are a principal source of FGF23.
Beck, L. et al. Targeted inactivation of Npt2 in mice leads to severe renal
Madjdpour, C. et al. Segment-specific expression of sodium-phosphate cotrans-
Gattinoni, J. et al. FGF23 decreases renal NaPi-2a and NaPi-2c expression and
Adv. Chronic Kidney Dis. 18, 85–90 (2011).
Miyamoto, K. et al. Inhibition of intestinal sodium-dependent inorganic phosphate transport by fibroblast growth factor 23. Ther. Apher. Dial. 9, 331–335 (2005).
Fukumoto, S. Phosphate metabolism and vitamin D. Bonekey Rep. 3, 497 (2014).
Shimada, T. et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis (2008).
Potthoff, M. J. et al. FGF21 induces PGC-1alpha and regulates carbohydrate and
of FGF21 on glucose homeostasis and insulin sensitivity in mice. Cell Metab. 17, 779–789 (2013).
Badman, M. K. et al. Hepatic fibroblast growth factor 21 is regulated by PPAR-
alpha and is a key mediator of hepatic lipid metabolism in ketotic states. Cell Metab. 5, 426–437 (2007).
Inagaki, T. et al. Endocine regulation of the fasting response by PPARalpha-
mediated induction of fibroblast growth factor 21. Cell Metab. 5, 415–425 (2007).
Potthoff, M. J. et al. FGF21 induces PGC-1alpha and regulates carbohydrate and
acid metabolism during the adaptive starvation response. Proc. Natl Acad. Sci. USA 106, 10853–10858 (2009).
Bai, X. et al. Transgenic mice overexpressing human
of FGF21 and metabolic disease in 2016: a new frontier in FGF21 biology. Nat. Rev. Endocrinol. 13, 74–76 (2017).
Lin, Z. et al. Adiponectin mediates the metabolic effects of FGF21 on glucose
Matsumoto, M. & Nishida, M. FGF21 is released into the circulation upon brown adipose tissue lipolysis. J. Biol. Chem. 284, 12543–12550 (2009).
Feng, J. Q. et al. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nat. Genet. 38, 1310–1315 (2006).
Fukumoto, S. Phosphate metabolism and vitamin D. Nutr. Metab. 10, 505–506 (2003).
author reply 505–506.
Strom, T. M. et al. Pex gene deletions in Gy and Hyp mice provide mouse models for X-linked hypophosphataemia. Hum. Mol. Genet. 6, 165–171 (1997).
Liu, S. et al. Regulation of fibroblast growth factor 23 expression but not degradation by PHEX. J. Biol. Chem. 278, 37419–37426 (2003).
Saito, H. et al. Circulating FGF-23 is regulated by 1alpha,25-dihydroxyvitamin D3 and phosphorus in vivo. J. Biol. Chem. 280, 2543–2549 (2005).
Collins, M. T. et al. Fibroblast growth factor-23 is regulated by 1alpha,25-dihydroxyvitamin D. J. Bone Miner. Res. 20, 1944–1950 (2005).
Ito, N. et al. Extracellular phosphate modulates the effect of 1alpha,25-dihydroxy vitamin D3 (1,25D) on osteocyte like cells. J. Steroid Biochem. Mol. Biol. 136, 183–186 (2013).
Olauson, H. et al. Parathyroid-specific deletion of Klotho unravels a novel calcineurin-dependent FGF23 signaling pathway that regulates PTH secretion. PLoS Genet. 9, e1003975 (2013).
Ben-Dov, I. Z. et al. The parathyroid is a target organ for FGF23 in rats. J. Clin. Invest. 117, 4003–4008 (2007).
Kobayashi, K. et al. Regulation of plasma fibroblast growth factor 23 by calcium in primary hyperparathyroidism. Eur. J. Endocrinol. 154, 93–99 (2006).
Meiri, T. et al. Parathyroid hormone activates the orphan nuclear receptor Nurr1 and induces FGF23 transcription. Kidney Int. 86, 1106–1115 (2014).
Rhee, Y. et al. Parathyroid hormone receptor signaling in osteocytes increases the expression of fibroblast growth factor-23 in vitro and in vivo. Bone 49, 636–643 (2013).
Lewerin, C. et al. Low serum iron is associated with high serum intact FGF23 in elderly men: the Swedish MrOS study. Bone 98, 1–8 (2017).
Farrow, E. G. et al. Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (FGF23) knock-in mice. Proc. Natl Acad. Sci. USA 108, E1146–E1155 (2011).
Huang, Y., Wang, H. & Yang, Y. Expression of fibroblast growth factor 5 (FGF5) and its influence on survival of breast cancer patients. Med. Sci. Monit. 24, 3524–3530 (2018).
Guo, S. et al. A gene-based recessive diplotye exon scan discovers FGF6, a novel hedgehog-regulating iron-metabolism gene. Blood 133, 1888–1898 (2019).
Shaoul, R. et al. Elevated expression of FGF7 protein is common in human parathyroid cancer. Blood 108, 3096–3100 (2006).
Leutenegger, M., Wigger, A., Bartl, D. & Egger, B. FGF23 is a bone-derived hormone that regulates phosphorus and vitamin D metabolism. J. Clin. Invest. 114, 1501–1509 (2004).
Larsson, S. et al. Transgenic mice expressing fibroblast growth factor 23 under the control of the alpha1(I) collagen promoter exhibit growth retardation, osteomalacia, and disturbed phosphate homeostasis. Endocrinology 145, 3087–3094 (2004).
Bai, X. et al. Transgenic mice overexpressing human fibroblast growth factor 23 (R176Q) delineate a putative role for parathyroid hormone in renal phosphate wasting disorders. Endocrinology 145, 5269–5279 (2004).
Hu, M. C., Shi, M. & Moe, O. W. Role of alphaKlotho and FGF23 in regulation of type II Na-dependent phosphate co-transporters. Pflug. Arch. 471, 99–108 (2019).
Beck, L. et al. Targeted inactivation of Npt2 in mice leads to severe renal phosphate wasting, hypercalcuria, and skeletal abnormalities. Proc. Natl Acad. Sci. USA 95, 5372–5377 (1998).
Madjdpour, C. et al. Segment-specific expression of sodium-phosphate cotrans-
transporters NaPi-IIa and -IIc and interacting proteins in mouse renal proximal tubules. Pflug. Arch. 448, 402–410 (2004).
Gattinoni, J. et al. FGF23 decreases renal NaPi-2a and NaPi-2c expression and induces hypophosphatemia in vivo predominantly via FGF receptor 1. Am. J. Physiol. Renal Physiol. 297, F282–F291 (2009).
Fibroblast growth factor receptors as treatment targets in clinical oncology.
Gaich, G. et al. The effects of LY2405319, an FGF21 analog, in obese human subjects. Bioconjug. Chem. 24, 915–925 (2013).

Song, L. et al. A solid-phase PEGylation strategy for protein therapeutics using a potent FGF21 analog. Biomaterials 35, 5206–5215 (2014).

Veniant, M. M. et al. Long-acting FGF21 has enhanced efficacy in diet-induced obese mice and in obese rhesus monkeys. Endocrinology 153, 4192–4203 (2012).

Hecht, R. et al. Rationale-based engineering of a potent long-acting FGF21 analog for the treatment of type 2 diabetes. PLoS ONE 7, e94395 (2012).

Huang, J. et al. Development of a novel long-acting antidiabetic FGF21 mimetic by targeted conjugation to a scaffold antibody. J. Pharm. Exp. Ther. 346, 270–280 (2013).

Weng, Y. et al. Pharmacokinetics (PK), pharmacodynamics (PD) and integrated PK/PD modeling of a novel long acting FGF21 clinical candidate PF-05231023 in diet-induced obese and leptin-deficient obese mice. PLoS ONE 10, e0119104 (2015).

Soria, J. C. et al. Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lutiCanabin in advanced solid tumors. Ann. Oncol. 25, 2244–2251 (2014).

Awwad, N. & Schwarz, R. E. Profile of nintedanib in the treatment of solid tumors: the evidence to date. Onco Targets Ther. 8, 3691–3701 (2015).

Carter, E. P., Fearon, A. E. & Grose, R. P. Careless talk costs lives: fibroblast growth factor receptor signalling and the consequences of pathway malfunction. Trends Cell Biol. 25, 221–233 (2015).

Porta, C., Gligone, P., Liguigi, W. & Paglino, C. Dovitinib (CHIR258, TK258): structure, development and preclinical and clinical activity. Fut. Oncol. 11, 39–50 (2015).

André, F. et al. Targeting FGFR with dovitinib (TK258): preclinical and clinical data in breast cancer. Clin. Cancer Res. 19, 3639–3702 (2013).

Trudel, S. et al. CHIR-258, a novel, multitargeted tyrosine kinase inhibitor, for the potential treatment of t(4;14) multiple myeloma. Blood 105, 2941–2948 (2005).

Porta, R. et al. FGFR a promising druggable target in cancer: molecular biology and new drugs. Crit. Rev. Oncol. Hematol. 113, 256–267 (2017).

Gavine, P. R. et al. AZD4547: an orally bioavailable, potent, and selective inhibitor of the fibroblast growth factor receptor tyrosine kinase family. Cancer Res. 72, 2045–2056 (2012).

Maehara, O. et al. Fibroblast growth factor-2-mediated FGF/Erk signaling supports maintenance of cancer stem-like cells in esophageal squamous cell carcinoma. Carcinogenesis 38, 1073–1083 (2017).

Zhao, Q. et al. FGFR inhibitor, AZD4547, impedes the stemness of mammary epithelial cells in the premalignant stages of MMTV-ErbB2 transgenic mice. Sci. Rep. 7, 11306 (2017).

Nogova, L. et al. Evaluation of BGJ398, a fibroblast growth factor receptor 1–3 kinase inhibitor, in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors: results of a global phase I dose-escalation and dose-expansion study. J. Clin. Oncol. 35, 156–165 (2017).

Perera, T. P. S. et al. Discovery and pharmacological characterization of JNJ-42756493 (Erdafitinib), a functionally selective small-molecule FGF family inhibitor. Mol. Cancer Ther. 16, 1010–1020 (2017).

Tabernero, J. et al. Phase I dose-escalation study of JNJ-42756493, an oral pan-fibroblast growth factor receptor inhibitor, in patients with advanced solid tumors. J. Clin. Oncol. 33, 1020–1027 (2015).

Di Stefano, A. L. et al. Detection, characterization, and inhibition of FGRF-TACC fusions in IDH wild-type glioma. Clin. Cancer Res. 21, 3307–3317 (2015).

Sohl, C. D. et al. Illuminating the molecular mechanisms of tyrosine kinase inhibitor resistance for the FGFR1 gatekeeper mutation: the Achilles’ heel of targeted therapy. ACS Chem. Biol. 10, 1319–1329 (2015).

Liu, K. et al. Opposing effects of Sca-1+ cell-based systemic FGFR gene transfer strategy on lumbar versus caudal vertebrae in the mouse. Gene Ther. 23, 500–509 (2016).

Byron, S. A. et al. The N550K/II mutations in FGFR2 confer differential resistance to PD173074, dovitinib, and ponatinib ATP-competitive inhibitors. Neoplasia 15, 975–988 (2013).

Talbot, C. et al. Phase I dose-escalation study of FGFR2 fusion inhibitors. J. Clin. Oncol. 33, 3501–3507 (2015).

Sigal, L. et al. Oncogenic FGFR2 mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion-positive cholangiocarcinoma. Cancer Discov. 7, 252–263 (2017).

Aono, Y. et al. Therapeutic effects of anti-FGFR3 antibodies in hypophosphatemic rickets/osteomalacia. J. Bone Miner. Res. 24, 1879–1888 (2009).

Tocher, A. W. et al. A Phase I, first in human study of FP-1039 (GSK3502320), a novel FGFR ligand trap, in patients with advanced solid tumors. Ann. Oncol. 27, 526–532 (2016).

Urakawa, I. et al. Klotho converts canonical FGF receptor into a specific FGF receptor signaling. J. Bone Miner. Res. 24, 770–774 (2009).

Giorgio, C. et al. Pharmacological evaluation of new bioavailable small molecules targeting Eph/ephrin interaction. Biochem. Pharmacol. 147, 21–29 (2018).
728. Colombo, G. et al. Non-peptidic thrombospondin-1 mimics as fibroblast growth factor-2 inhibitors: an integrated strategy for the development of new anti-angiogenic compounds. J. Biol. Chem. 285, 8733–8742 (2010).

729. Pagano, K. et al. Direct and allosteric inhibition of the FGF2/HSPGs/FGFR1 ternary complex formation by an antiangiogenic, thrombospondin-1-mimic small molecule. PLoS ONE 7, e36990 (2012).

730. Camozzi, M. et al. Identification of an antiangiogenic FGF2-binding site in the N terminus of the soluble pattern recognition receptor PTX3. J. Biol. Chem. 281, 22605–22613 (2006).

731. Leali, D. et al. Fibroblast growth factor 2-antagonist activity of a long-pentraxin 3-derived anti-angiogenic pentapeptide. J. Cell Mol. Med. 14, 2109–2121 (2010).

732. Castelli, R. et al. Synthesis, structural elucidation, and biological evaluation of NSC12, an orally available fibroblast growth factor (FGF) ligand Trap for the treatment of FGF-dependent lung tumors. J. Med. Chem. 59, 4651–4663 (2016).

733. Yokota, M. et al. Therapeutic effect of nanogel-based delivery of soluble FGFR2 with S252W mutation on craniosynostosis. PLoS ONE 9, e101693 (2014).

734. Morita, J. et al. Soluble form of FGFR2 with S252W partially prevents craniosynostosis of the apert mouse model. Dev. Dyn. 243, 560–567 (2014).

735. Garcia, S. et al. Postnatal soluble FGFR3 therapy rescues achondroplasia symptoms and restores bone growth in mice. Sci. Transl. Med. 5, 203ra124 (2013).

736. Jin, M. et al. A novel FGFR3-binding peptide inhibits FGFR3 signaling and reverses the lethal phenotype of mice mimicking human thanatophoric dysplasia. Hum. Mol. Genet. 21, 5443–5455 (2012).

737. Whitsett, J. A. et al. Fibroblast growth factor 18 influences proximal programming during lung morphogenesis. J. Biol. Chem. 277, 22743–22749 (2002).

738. Nikol, S. et al. Therapeutic angiogenesis with intramuscular NV1/FGF improves amputation-free survival in patients with critical limb ischemia. Mol. Ther. 16, 972–978 (2008).

739. Shukla, V. et al. RNA interference and inhibition of MEK-ERK signaling prevent abnormal skeletal phenotypes in a mouse model of craniosynostosis. Nat. Genet. 39, 1145–1150 (2007).

740. McDowell, L. M. et al. Inhibition or activation of Apert syndrome FGFR2 (S252W) signaling by specific glycosaminoglycans. J. Biol. Chem. 281, 6924–6930 (2006).

741. Valdimenis, P. N. & Kay, M. A. Future of rAAV gene therapy: platform for RNAi, gene editing, and beyond. Hum. Gene Ther. 28, 361–372 (2017).

742. Rotterman, M. A. & Schaffer, D. V. Engineering adeno-associated viruses for clinical gene therapy. Nat. Rev. Genet. 15, 445–451 (2014).

743. Luo, F. et al. Adeno-associated virus-mediated RNAi against mutant alleles attenuates abnormal calvarial phenotypes in an Apert Syndrome Mouse Model. Mol. Ther. Nucleic Acids 13, 291–302 (2018).

744. Yang, Y. et al. A dual AAV system enables the Cas9-mediated correction of a metabolic liver disease in newborn mice. Nat. Biotechnol. 34, 334–338 (2016).

745. Wu, Y. et al. Correction of a genetic disease in mouse via use of CRISPR-Cas9. Cell Stem Cell 13, 659–662 (2013).

746. Nelson, C. E. et al. In vivo genome editing improves muscle function in a mouse model of Duchenne muscular dystrophy. Science 351, 403–407 (2016).

747. Yin, H. et al. Genome editing with Cas9 in adult mice corrects a disease mutation and phenotype. Nat. Biotechnol. 32, 551–553 (2014).

748. Ou, Z. et al. The combination of CRISPR/Cas9 and iPSC technologies in the gene therapy of human beta-thalassemia in mice. Sci. Rep. 6, 32463 (2016).

749. Miao, K. et al. Optimizing CRISPR/Cas9 technology for precise correction of the Fgfr3-G374R mutation in achondroplasia in mice. J. Biol. Chem. 294, 1142–1151 (2019).

750. Vasudevan, H. N. & Soriano, P. A Thousand and One Receptor Tyrosine Kinases: Wherein the Specificity? Curr. Top. Dev. Biol. 117, 393–404 (2016).

751. Xie, Y. et al. Intermittent PTH (1-34) injection rescues the retarded skeletal development and postnatal lethality of mice mimicking human achondroplasia and thanatophoric dysplasia. Hum. Mol. Genet. 21, 3941–3955 (2012).