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REVIEW ARTICLE

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

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Abstract Fibroblast growth factors (FGF) and their receptors serve many functions in both the developing and adult organism. Humans contain 18 FGF ligands and four FGF receptors (FGFR). FGF ligands are polypeptide growth factors that regulate several developmental processes including cellular proliferation, differentiation, and migration, morphogenesis, and patterning. FGF-FGFR signaling is also critical to the developing axial and craniofacial skeleton. In particular, the signaling cascade has been implicated in intramembranous ossification of cranial bones as well as cranial suture homeostasis. In the adult, FGFs and FGFRs are crucial for tissue repair. FGF signaling generally follows one of three transduction pathways: RAS/MAP kinase, PI3/AKT, or PLCγ. Each pathway likely regulates specific cellular behaviors. Inappropriate expression of FGF and improper activation of FGFRs are associated with various pathologic conditions, unregulated cell growth, and tumorigenesis. Additionally, aberrant signaling has been implicated in many skeletal abnormalities including achondroplasia and craniosynostosis. The biology and mechanisms of the FGF family have been the subject of significant research over the past 30 years. Recently, work has focused on the therapeutic targeting and potential of FGF ligands and their associated receptors. The majority of FGF-related therapy is aimed at age-related disorders. Increased understanding of FGF signaling and biology may reveal additional therapeutic roles, both in utero and postnatally. This review discusses the role of FGF signaling in general physiologic and pathologic embryogenesis and further explores it within the context of skeletal development.

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Introduction

The fibroblast growth factor (FGF) family consists of structurally related polypeptides involved in several physiologic processes. Highly conserved, these growth factors are found in thousands of animal species, ranging from nematode and zebra fish to mouse and human.[1] FGFs play a role in cellular proliferation, migration, and differentiation, mitogenesis, angiogenesis, embyrogenesis, and wound healing.[2] It is by the activation of various signal transduction pathways that FGFs mediate multiple developmental processes.[3]

Mammals contain 18 FGF types (FGF1—FGF10 and FGF16—FGF23), which have been grouped into six distinct subfamilies based on phylogeny and sequence homology.[4] FGFs share a similar internal core and have a characteristically high binding affinity for both heparin and fibroblast growth factor receptors (FGFRs). FGFRs are tyrosine kinase receptors that contain a heparin-binding sequence, three extracellular immunoglobulin-like domains (D1—D3), a hydrophobic transmembrane domain, and a split intracellular tyrosine kinase domain.[5–7] The mammalian FGFR family consists of four members (FGFR1—FGFR4). The amino acid sequences of each receptor are highly conserved, with differentiation occurring only in their ligand affinity and tissue distribution.[8] Characteristic of FGFRs is the acid box, which is a serine-rich, acidic sequence in the linker between D1 and D2.[4] The acid box and D1 domain are thought to play a role in receptor autoinhibition.[9] The D2—D3 fragment is required for ligand specificity and binding. In vertebrates, four genes encode the FGFRs (*FGFR1-4*), and undergo alternative splicing in their extracellular domain to produce many varieties of FGFR1-4 with varying affinities for their ligands.[10]

Many data suggest the role of FGF signaling in fundamental developmental pathways, including embryogenesis and the development of organ systems.[11] Aberrations in this pathway have been associated with human disease. Cancers from various tissue types have been linked to dysregulated FGF signaling.[12] Faulty signaling is also associated with many congenital syndromes. Many other conditions, including skeletal dysplasias,[13] deafness,[14] and lacrimo-auriculo-dento-digital syndrome,[15] result from FGF signaling errors. Pathological conditions are mostly due to gain- or loss-of-function mutations in the ligands themselves or their receptors.[4]

The degree of involvement of FGF signaling in both normal and pathologic development has led to considerable research on the therapeutic applications and targeting of the FGF family. Recombinant FGFs and small-molecule FGF receptor kinase inhibitors have been used in the treatment of cancer and cardiovascular disease. Emerging research has also demonstrated their potential pharmacologic role in preventing chemotherapeutic side effects as well as treating metabolic syndrome.[16] In this article, we review the current knowledge of FGF signaling in both physiologic and pathologic development and also address recent discoveries regarding its therapeutic potential.

The FGF signaling system

Positive regulation of signaling

The FGF signaling cascade is initiated by the binding of FGF ligands to FGFRs. Following FGF binding, a ligand-dependent dimerization event takes place in which a complex is formed that consists of two FGFs, two heparin sulfate chains, and two FGFRs. Each ligand binds to both receptors, and the receptors make contact with one another via a patch on the D2 domain.[4] This facilitates the transphosphorylation of each receptor monomer by an intrinsic tyrosine kinase domain. At least seven phosphorylation sites have been identified for FGFR1 (Tyr^{163}, Tyr^{583}, Tyr^{585}, Tyr^{653}, Tyr^{654}, Tyr^{730}, and Tyr^{766}).[17–19] Phosphotyrosine groups serve as docking sites for adaptor proteins that regulate downstream signaling.[20] The FGF system is associated with several downstream signaling pathways; the best understood are the RAS/mitogen-activating protein (MAP) kinase pathway, the phosphoinositide 3 (PI3) kinase/AKT pathway, and the phospholipase C gamma (PLCγ) pathway (Fig. 1).[21]

The main downstream pathway associated with FGF signaling is the RAS/MAP kinase pathway. This pathway is implicated during cellular proliferation and differentiation.[22] MAP kinases are serine/threonine-specific protein kinases that act in response to extracellular stimuli and regulate various cellular processes. Examples of MAP kinase effectors include c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 mitogen-activated kinase.[23] After an FGF ligand binds to its receptor, an integral step in the signaling pathway is the phosphorylation of the tyrosine residues on the docking protein fibroblast growth factor receptor substrate 2 alpha (FRS2α). This permits binding of adaptor proteins that are associated with signal activation.[24,25] An FRS2 complex consisting of FRS2α, guanine nucleotide exchange factor 2 (GRB2), GRB2-associated binding protein 1 (GAB1), the son of sevenless (SOS), and tyrosine phosphatase (SHP2) is then formed that facilitates activation of the RAS/MAP kinase[26] and also PI3 kinase/AKT pathways.[27]

The PI3 kinase/AKT pathway is associated with cellular survival and cell fate determination.[26,28] This pathway may also impact cell polarity.[29] Like the RAS/MAP kinase pathway, the PI3 kinase/AKT pathway is initiated when an FRS2 signaling complex forms. GAB1 protein then links activated FGFRs with PI3 kinase. Downstream of PI3 kinase, phosphoinositide-dependent kinase and AKT (an anti-apoptotic protein kinase) are activated.[21]

Another target molecule of activated FGFR is PLCγ. This pathway is activated upon the binding of the PLCγ molecule to the phosphorylated Tyr^{766} of the receptor.[21] Inositol triphosphate (IP3) and diacylglycerol (DAG) are then generated by the hydrolysis of activated PLCγ. DAG and cytoplasmic calcium released from the endoplasmic reticulum in response to IP3 together activate protein kinase C (PKC).[21] Though it has not been completely elucidated, the PLCγ kinase pathway influences cell morphology, migration, and adhesion.[26,28]

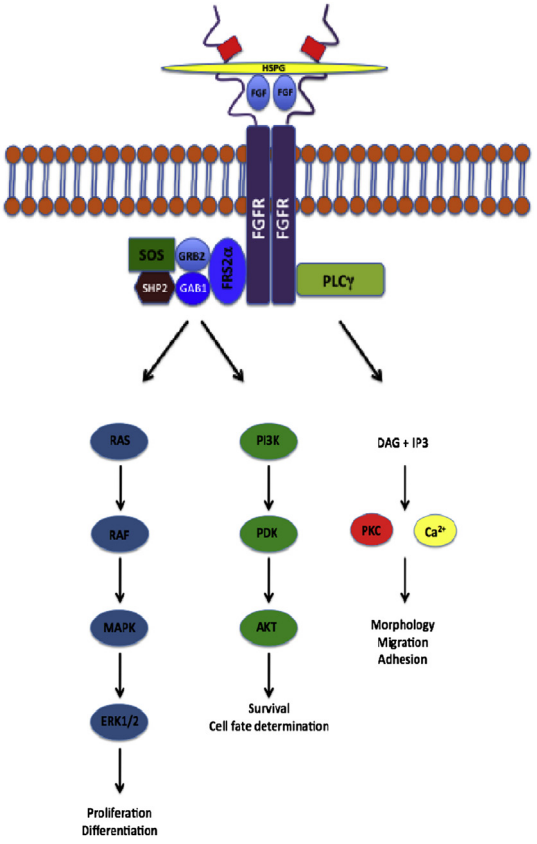

Figure 1 FGF-FGFR signaling pathway. The signaling cascade commences upon the formation of an FGF binding complex, consisting of two FGF ligands, two heparin sulfate chains, and two FGFRs. Signal transduction largely follows one of three pathways. The RAS/MAP kinase pathway, initiated upon the formation of an FRS2 complex, controls cell proliferation and differentiation. The PI3/AKT pathway is also initiated by the formation of an FRS2 complex, and regulates cell survival and fate determination. Finally, upon binding of PLCγ to the activated FGFR, DAG and IP3 are formed, activating PKC. The PLCγ pathway influences cell morphology, migration, and adhesion.

Negative regulation of signaling

Like signal activation, mechanisms that attenuate FGF-FGFR signaling are conserved among many animal species. These mechanisms, however, are less well understood than their positive regulation counterparts. In general, downstream signal attenuation occurs via the induction of MAPK phosphatases. First discovered in *Drosophilia melanogaster*,[30] the sprouty (SPRY) family of proteins, which are MAPK phosphatases, inhibit receptor tyrosine kinase signaling by directly binding to RAF and blocking subsequent MAPK signaling[31] or by competing for GRB2 binding, thereby preventing SOS-mediated RAS activation.[12] Interestingly, FGF signaling activates SPRY proteins, which may be an example of autoinhibition. Additional negative modulators include the phosphatases MAPK phosphatase 3 (MKP3)[32] and SEF.[33] MKP3 attenuates the FGF cascade by dephosphorylating ERK1 and ERK2, molecules important for MAPK downstream signaling.[34] SEF likely mediates its effects by inhibiting ERK phosphorylation and also by acting at various points along the signaling pathway to exert its function.[34] Further control of signaling takes place at the level of the receptors. Following activation, FGFRs may be internalized and subsequently degraded or recycled.[35]

FGF signaling in physiologic development

FGF signaling in general embryonic development

The FGF signaling pathway plays many diverse and essential roles in orchestrating human embryonic development. Numerous studies, conducted in model organisms over the past 25 years, have demonstrated that FGF signaling is a widely utilized regulatory system in early vertebrate development and has been conserved throughout chordate evolution.[36] FGFs control cell migration during gastrulation,[37–39] epithelio-mesenchymal interactions during limb morphogenesis,[11,40,41] and neural induction and patterning[42–48] in later stages of development.[49]

An interesting role of FGFs to organize the migratory events of gastrulation by functioning as both chemoattractants and repellents has been documented.[50–53] FGF signaling is associated with the coordinated cellular movements of convergent extension and in the epithelial to mesenchymal transition that marks the onset of gastrulation.[54,55] Convergent extension involves the reorganization of cytoskeletal elements to ensure that cells become polarized along a similar axis. Polarized cells intercalate amongst one another, which causes the overall tissue layer to extend along the perpendicular axis.[54] Both FGF and Wnt signaling have been shown to activate this planar cell polarity pathway and propagate the normal activities of convergent extension during gastrulation.[56]

In mammalian gastrulation, the process of epithelial-mesenchymal transition (EMT) takes place after formation of the primitive streak. During EMT, a fraction of tightly adherent cells of the epithelial layer lose contact with neighboring cells and migrate freely from this layer to enter the primitive streak in order to adopt a mesenchymal phenotype.[36,54] FGFR1 activation facilitates this transition by mediating down-regulation of E-cadherin-related cellular adhesions and stimulation of cell migration through the primitive streak.[37,38] This in part was elucidated by the fact that FGFR1$^{-/-}$ mice exhibit recessive embryonic lethality upon gastrulation[57,58] and display retarded migration of mesoderm precursor cells across the primitive streak.[38,59] Interestingly, FGF8-null mice also display embryonic lethality associated with a failure to develop through gastrulation.[60]

FGF signaling also contributes to tissue organization by directly promoting mesodermal formation while inhibiting endodermal development.[61] During specification of germ layers, vegetal cells release signals through nodal and activin pathways to mediate mesoderm identity and patterning.[62,63] FGF2, FGF4, and FGF8 may regulate transcription factors downstream of the nodal and activin pathways that activate and maintain expression of mesoderm-specifying genes.[64–67]

Neural induction is also mediated during gastrulation, marking a fundamental step of vertebrate central nervous

system development. During neural induction, a subset of cells within the pluripotent dorsal ectoderm is selected to adopt a neural fate rather than an epidermal fate.[49,68] FGF signaling has been shown to facilitate neural induction in these cells by inhibiting the expression of bone morphogenetic proteins (BMP) that stimulate epidermal development.[69] Specifically, FGF3 and FGF4 expression inhibits BMP4 and BMP7 in early neural tissues.[52,70,71] FGF signaling also indirectly inhibits BMP signaling. Expression of Noggin (NOG) protein, which is a negative inhibitor of BMP signaling, is increased by FGF stimulation. Furthermore, FGF signaling results in the inhibitory phosphorylation of the SMAD1, SMAD5, and SMAD8 transcription factors, which blocks their ability to travel to the nucleus and activate the transcription of BMP target genes.[36,72–75]

FGF ligands also serve as posteriorizing factors during pattering of the neural plate and directly activate the transcription of a set of posterior neural genes.[76] Studies manipulating ectopic FGF expression in developing central nervous systems demonstrate that FGFs convert anterior neural tissues to more posterior neural cell types.[77–84] Within the embryonic isthmic organizer, which is an important signaling center at the anatomical constriction of the vertebrate midbrain-hindbrain junction, expression of FGF8, FGF17, FGF18, and FGFR1 is observed.[36,85] There is strong evidence that FGF signaling modulates early patterning of the neural tissues via regulation of Hox genes, a family of homeobox transcription factors that dictate segmental identity.[86] Ectopic application and overexpression of various FGFs during and after gastrulation increase the expression of key posterior Hox genes and also inhibit anterior development.[75,87–96] Additionally, deficient FGFR1 expression is correlated with repression of posterior Hox genes.[87,97]

FGF signaling has also been implicated in limb bud development. In particular, FGF signaling mediates a positive feedback loop of paracrine signaling between mesenchymal and epithelial tissues that pattern the emerging limb bud and stimulate the outgrowth, morphogenesis, and maintenance of early limb structure.[55] Before the induction of the apical ectodermal ridge (AER), FGFR1 is expressed in the underlying mesenchyme; FGFR2 is found in both the mesenchyme and ectoderm of the presumed future limb site.[98–100] Expression of FGFR1 continues into the later stages of limb development, where it may play essential roles in mesodermal patterning of the distal limb fields and digit formation.[101] After induction, the AER expresses FGF2, FGF4, FGF8, and FGF9, while limb bud mesoderm expresses FGF2 and FGF10.[99] Upon the onset of limb development, FGF10 secreted by cells of the lateral plate mesoderm diffuses to the overlying surface ectoderm, and interacts with FGFR2b to induce formation of the AER superficially.[99,102] In response, the AER secretes FGF8, which acts upon the underlying mesenchymal cells through FGFR2c to maintain a proliferative state and continue FGF10 secretion.[101,103–106] Secretion of additional FGF10 by the mesenchymal cells maintains AER expression of FGF8.[107] This positive feedback loop drives further limb outgrowth by permitting the mesenchyme to maintain the organizational role of the AER at the propagating edge of the developing limb, while the AER reciprocally sustains the proximate mesenchyme of the progress zone in a mitotically active state.[108]

FGF signaling in cranial suture development

FGF signaling plays a critical role in the normal development and morphogenesis of the craniofacial skeleton during embryogenesis and postnatal growth.[109] In fact, many events of normal craniofacial development have been elucidated during studies examining the etiologic relationship between FGF and FGFR mutations and various skeletal dysplasias.[110,111] FGF signaling is complex and likely interacts with additional signaling pathways during craniofacial development.[109,110,112–116]

In mammals, embryonic tissues of the facial and cranial bones are derived from neural crest cells.[117–122] FGF signaling induces cranial neural crest formation and is present in both the epithelia and mesenchyme of the facial primordia.[112,123–127] At six weeks of development, mesenchymal condensations begin to foreshadow bones of the basicranium, followed soon thereafter by those of the cranial vault bones.[128] Delezoide et al observed FGFR1 gene expression throughout the entire mesenchyme in the head at this stage as well as strong FGFR2 expression in the epidermis, pre-bone mesenchymal condensations, and mesenchymal walls of the cranial vault.[128] From the eighth through thirteenth week of gestation, skull bones develop via intramembranous ossification. Condensations of mesenchymal cells located between the dermal mesenchyme and the developing meninges simultaneously differentiate into osteoblasts to give rise to the major cranial bones. Newly differentiated osteoblasts then synthesize and deposit osteoid matrix radially outwards from these ossification centers. This osteoid matrix is primarily composed of type I collagen.[129] During early intramembranous ossification, there is marked expression of FGFR1 and FGFR2 and, to a lesser extent, FGFR3 in the cells of the pre-bone mesenchyme and around the osteoid.[128] Indeed, intramembranous ossification of the skull vault is characterized by co-expression of FGFR1-3 in osteoblast precursors and osteoblasts.

As mineralization of newly deposited osteoid matrix progresses outward from ossification centers, the periphery of the extending bone fields (osteogenic front) develops as a wedge-shaped proliferation of cells that invade and recruit intervening mesenchymal tissue into these advancing edges to increase the size of each cranial bone.[112,115,129] By gestation week 18, bone fronts of adjacent cranial bones are in close proximity, and sutures develop along lines of approximation.[112] The osteogenic fronts of neighboring cranial bones, undifferentiated mesenchyme between them, and the adjacent pericranium and dura mater function as a complex to maintain normal development along the suture. Morriss-Kay et al demonstrated that in normal coronal suture development, the maintenance of proliferating osteogenic cells at the margins of membrane bones forming the suture requires relatively low FGF levels.[110] During normal development, cranial sutures remain in a patent, unossified state while new intramembranous bone is formed at the edges of osteogenic fronts. This requires mesenchymal cells within the suture to remain

undifferentiated while cells of the osteogenic layer that line the bony front differentiate into osteoblasts and produce additional new bone.[130–132] High FGF levels are associated with osteogenic differentiation. In other words, in the normal suture there is differential FGF expression with high levels found in the differentiated region and low levels found at the suture. At the time of suture fusion, increased FGF2 levels are observed.[133] Cross-talk also exists between osteoblasts and osteoclasts in maintaining suture homeostasis on a molecular level as FGF2 directly upregulates RANKL mRNA and indirectly inhibits M-CSF production, thereby inducing osteoclast differentiation.[134] In the setting of increased receptor activation, whether pathologic (see below) or experimental (by the addition of exogenous FGF), cellular proliferation ceases and suture fusion ensues.[110] Additionally, increased signaling through FGFR1 is associated with premature fusion while FGFR2 and FGFR3 signaling maintain osteoprecursor cell proliferation (Fig. 2).[130]

FGF signaling between dura mater and overlying cranial sutures during embryogenesis has implications on proper development of cranial sutures postnatally.[115,129,135] Before the suture complex can sustain itself through intrinsic signals, an inductive stimulus of soluble factors emanating from the dura mater is required during early suture morphogenesis.[129] Along these lines, Kim and colleagues found that signals from the dura mater regulate proper suture development prenatally, while signals within the osteogenic fronts dominate after birth.[115] Many of these signals have been identified as FGF ligands and receptors.

Aberrant FGF signaling during development

Given the many integral actions controlled by FGF signaling, it is no surprise that disruption of the normal cascade has been implicated in many disease states. Most mutations that are familial in nature are inherited in autosomal dominant fashion. New mutations can occur sporadically, however. Therefore, each mutation is subject to significant variability with respect to genotypic mutation and phenotypic expression.[8] Regarding FGFRs, many conditions are associated with mutations at specific gene locations. For example, craniosynostosis is often related to a mutation within the gene region responsible for the linker protein between the D2 and D3 extracellular domains of FGFRs. In addition, mutations around the N-terminal junction of the transmembrane domain are linked to skeletal disorders including thanatophoric dysplasia.[8] Achondroplasia and other disorders of long bone growth are associated with mutations to the gene responsible for the FGFR tyrosine kinase domain expressed by chondrocytes at the physis.[136] Several neoplastic conditions have also been linked to FGFR mutations.[136–147]

Numerous pathologic conditions are associated with mutated FGF ligands as well. FGF3, which plays a role in inner ear development, has been linked to inner ear agenesis and microtia.[14] Myogenesis is regulated in part by FGF6; when mutated, defective muscle regeneration is present.[148] An in depth discussion of the pathophysiology of mutations of each FGF ligand is beyond the scope of this review and has been reviewed elsewhere.[4] In the following

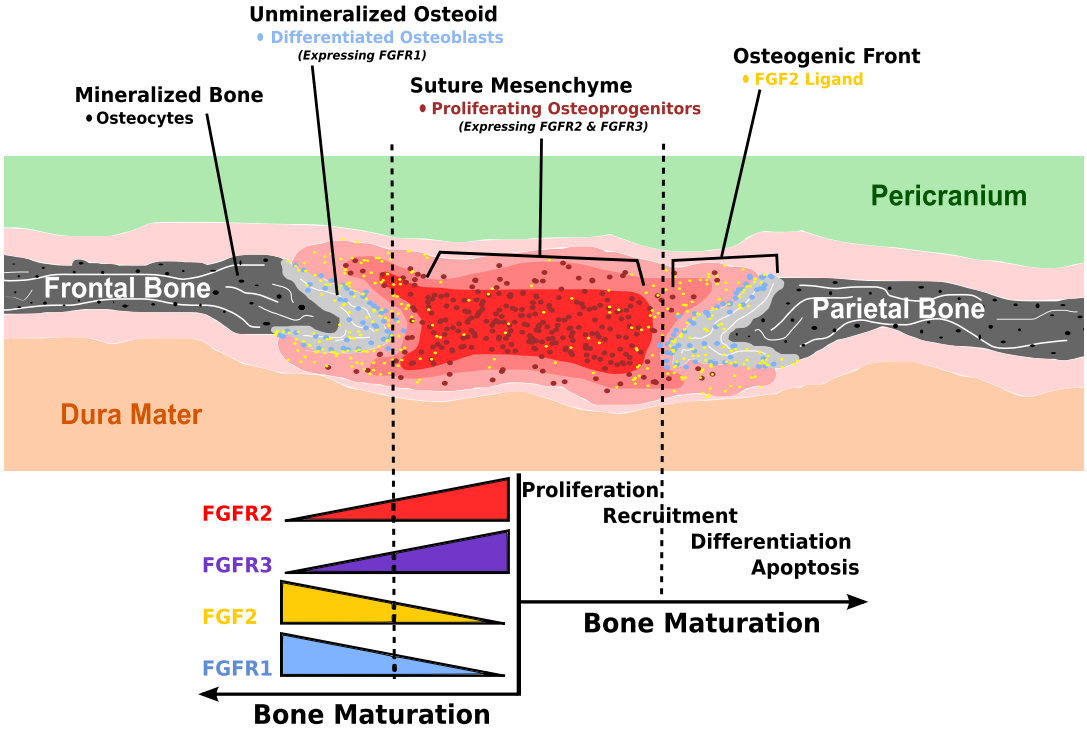

Figure 2 Schematic representation of developing coronal suture. In the presence of low concentrations of FGF2, undifferentiated osteoprogenitor cells expressing FGFR2 and FGFR3 proliferate within the suture mesenchyme between the two osteogenic fronts. At higher levels of FGF2, osteoprogenitor cells are recruited to differentiate into osteoblasts. This leads to increased of FGFR1 expression and deposition of osteoid matrix along the osteogenic fronts.

paragraphs, we detail aberrant FGF signaling in the context of skeletal disorders.

Achondroplasia

Achondroplasia is the commonest skeletal dysplasia and is characterized by short stature, rhizomelic limb shortening, limited elbow extension, frontal bossing, and midface deficiency. It is passed via autosomal dominant inheritance but can also occur sporadically. A gain-of-function mutation of the *FGFR3* gene results in decreased inhibition of endochondral ossification.[141] In the majority of patients, over activation of FGFR3 is due to substitution of arginine for glycine (G380R) within the transmembrane domain.[136] The introduction of a hydrophilic residue into the hydrophobic receptor domain results in alteration of the signal transduction pathway due to disruption of the alpha helical structure of the transmembrane protein.[140] Additionally, experimentally-induced under activation of FGFR3 results in elongation of the vertebral column and long bones.[149] It is thought that mutations causing over activation of FGFR-3 impair chondrocytes within growth plates.[136,149] Studies are now underway regarding whether attenuation of FGFR3 signaling of chondrocytes located within physes in cases of increased FGFR3 activation can increase bone growth. Lorget and colleagues demonstrated that an analogue of C-natriuretic peptide (CNP), which antagonizes downstream effects of mutated FGFR3, has been used to enhance bone growth in mice.[150,151]

Hypochondroplasia

Hypochondroplasia is essentially a milder form of achondroplasia that presents with similar radiographic findings in the limbs and spine.[139,141] It follows an autosomal dominant inheritance pattern. It is distinguished by normal facies and increased head circumference.[141] Greater than half of hypochondroplasia cases are due to an *FGFR3* gene missense mutation (N540K) in the first tyrosine kinase domain of the receptor.[139,142] This mutation causes a gain-of-function that results in premature fusion of the growth plates in the vertebral column and long bones.[152] Severe phenotypes are associated with missense mutations at nucleotides encoding the extracellular region of *FGFR3*.[139,140] The mild phenotype and clinical heterogeneity of hypochondroplasia are likely due to the fact that there are several potential mutations that may cause it.[140] Growth hormones have been used in an attempt to treat this condition but have been met with mixed results.[152] Because they share a similar pathogenesis, therapeutic options for achondroplasia may be of benefit for patients with hypochondroplasia.[150,151].

Thanatophoric dysplasia

Thanatophoric dysplasia is a skeletal dysplasia often incompatible with life. It is characterized by shortened limbs with normal trunk length, excessive skin folding, a narrow thorax with shortened ribs, disproportionate macrocephaly, frontal bossing, and protruding eyes.[141] Type I thanatophoric dysplasia is further characterized by micromelia with bowed femurs and a cloverleaf skull. Type II thanatophoric dysplasia is associated with micromelia with straight femurs, craniosynostosis, and a moderate-to-severe cloverleaf skull.[141,153] Patients with thanatophoric dysplasia often die of respiratory insufficiency soon after birth; however, survivors have been reported.[141,153] Though it follows an autosomal dominant inheritance pattern, virtually all cases are due to sporadic mutations.

Type I thanatophoric dysplasia can result from several different mutations affecting either extracellular or intracellular domains of FGFR-3. The most common mutation is the substitution of cysteine for arginine (R248C) in a polypeptide within the extracellular domain.[143,154,155] Mutations allow for unimpaired cysteine residues to create disulfide bonds that enable the receptor to dimerize independent of the ligand.[140] Type II thanatophoric dysplasia is caused by a point mutation (K650E) to the tyrosine kinase II domain of FGFR3 that is thought to also result in independent dimerization of the receptor.[140,143] The *FGFR3* mutations associated with the aforementioned skeletal dysplasias support the notion that FGFR3 signaling is critical for bone growth regulation (Table 1).

Craniosynostosis

Acrocephalosyndactyly, or craniosynostosis, was first described by Otto in 1830 as the premature fusion of the cranial sutures.[156] Craniosynostosis can be classified as simple (one fused suture) or complex (two or more fused sutures).[157] Simple or complex craniosynostosis can be further classified as primary (sutures prematurely fuse due to abnormal suture biology) or secondary (normal suture biology but sutures prematurely fuse due to abnormal external forces).[157] Additional classification as syndromic or sporadic is based on *FGFR* gene mutations and associated phenotype. Syndromic craniosynostosis follows autosomal dominant inheritance but nearly 75% of craniosynostosis cases are of the sporadic variety.[157] The overall incidence of craniosynostosis is one in 2500 live births.[112,156] In terms of nonsyndromic cases, sagittal suture synostosis occurs most frequently (scaphocephaly; 40–55% of cases) followed by coronal synostosis (anterior plagiocephaly; 20–25%), metopic synostosis (trigonocephaly; 5–15%), multiple synostoses (5–15%), and lambdoid synostosis (posterior plagiocephaly; 0–5%).[156–159]

Most syndromic cases are the result of a gain-of-function mutation within the gene region responsible for the linker between the D2 and D3 domains of the FGFR.[8] A mutation in this region may increase the receptor's affinity for its corresponding FGF ligand, resulting in increased signaling that stimulates cell differentiation and eventual suture fusion.[160] However, several additional gene mutations have also been implicated in syndromic craniosynostosis.[112,156] Several craniosynostosis syndromes will be discussed (Table 2).

Pfeiffer syndrome

Pfeiffer syndrome is characterized by craniosynostosis, proptosis, hypertelorism, maxillary deficiency, and a

Table 1 Skeletal dysplasias associated with *FGFR3* mutations.

Disorder	Mutation[a]	Mechanism	Key features	Inheritance[b]
Achondroplasia[136,140,141]	G380R (transmembrane domain)	Gain-of-function mutation results in decreased inhibition of endochondral ossification	Short stature, rhizomelic limb shortening, short fingers and toes, large head with prominent forehead, small midface with flattened nasal bridge, spinal kyphosis/lordosis, varus/valgus deformities	Autosomal dominant; sporadic
Hypochondroplasia[139,140,142,152]	N540K (first tyrosine kinase domain); missense mutations (extra-cellular domain)	Gain-of-function mutations result in premature fusion of growth plates in vertebral column and long bones	Short stature, short limbs, increased head circumference, normal facies	Autosomal dominant; sporadic
Thanatophoric dysplasia[140,141,143,153–155]	R248C (extra-cellular domain; type I) K650E (second tyrosine kinase domain; type II)	Gain-of-function mutations result in ligand-independent receptor activation	Early death, extremely short limbs, redundant skin folds, narrow chest with short ribs, underdeveloped lungs, large head, curved thigh bones (type I), cloverleaf skull (type II)	Autosomal dominant; sporadic

FGFR3, fibroblast growth factor receptor 3.
[a] Commonest mutation(s) is noted. Others may be documented.
[b] Virtually all cases of thanatophoric dysplasia result from sporadic mutations because of its early lethality.

beaked nose. Patients with Pfeiffer syndrome also have wide thumbs and great toes that bend away from other digits and may display brachydactyly or syndactyly. Three variants of Pfeiffer syndrome exist: type I is associated with *FGFR1* and *FGFR2* mutations; types II and III are associated with *FGFR2* mutations.[161] Significant genetic heterogeneity exists among patients with Pfeiffer syndrome. Approximately 5% of patients with type I Pfeiffer syndrome contain a gain-of-function P252R mutation of *FGFR1*.[161,162] This mutation occurs at the linker region between D2 and D3, resulting in a bulkier residue that increases the receptor's affinity for ligand binding and therefore excessive receptor activation.[112] The other 95% of cases are thought to be due to sequence variants in the *FGFR2* gene. Patients with type I Pfeiffer syndrome due to an *FGFR1* mutation usually display a more favorable phenotype than patients with a mutation of *FGFR2*.

Patients with types II or III Pfeiffer syndrome generally have a more severe phenotype and worse prognosis. These conditions result from an *FGFR2* mutation. The most common mutations occur in exons IIIa and IIIc, resulting in an unpaired cysteine residue that forms an intermolecular disulfide bond that causes ligand-independent receptor activation.[161,163]

Apert syndrome

Apert syndrome is characterized by bilateral premature fusion of the coronal suture, developmental delay, midface hypoplasia, syndactyly of fingers and toes, and potentially other anomolies.[160,164–168] Activating mutations (S252W and P253R) in FGFR2 are thought to be responsible for the majority of cases and resultant brain dysmorphologies.[160,165] These mutations result in increased ligand affinity for the receptor and therefore trigger excessive activation. Evidence supports that the P253R mutation results in an indiscriminate increase in affinity of FGFR2 toward any FGF. The S252W mutation, however, selectively enhances FGFR2 affinity toward a subset of FGFs.[169] These genotypic differences may also cause clinical variability in patient presentation.

Crouzon syndrome

Crouzon syndrome is due to a gain-of-function mutation in FGFR2 that results in ligand-independent, disulfide-mediated, covalent receptor dimerization and activation.[165] The disulfide bond is formed between a cysteine-cysteine

Table 2 Syndromic craniosynostoses associated with *FGFR* mutations.

Syndrome	Mutation[a,b]	Mechanism	Key features	Inheritance
Pfeiffer[112,161–163]	P252R (*FGFR1*); several sequence variants (*FGFR2*)	P252R gain-of-function mutation results in increased receptor affinity for ligand binding; *FGFR2*-related gain-of-function mutations result in ligand-independent receptor activation	Proptosis, hypertelorism, maxillary hypoplasia, beaked nose, developmental delay (types II and III), cloverleaf skull (type II), turribrachycephaly (type III)	Autosomal dominant; sporadic
Apert[160,165,169]	S252W and P253R (*FGFR2*)	Gain-of-function mutations result in increased receptor affinity for ligand binding	Turribrachycephaly, midface hypoplasia, syndactyly of fingers and toes, varying degrees of developmental delay	Autosomal dominant; sporadic
Crouzon[112,161,165]	Several missense mutations (*FGFR2*)	Gain-of-function mutations result in disulfide bond that stabilizes the D3 loop to allow for ligand-independent receptor activation	Proptosis, external strabismus, mandibular prognathism, normal extremities, normal intelligence	Autosomal dominant; sporadic
Beare-Stevenson cutis gyrata[112,161,174,175]	Y394C (*FGFR2*)	Gain-of-function mutation results in ligand-independent receptor activation	Midface hypoplasia, abnormal ears, natal teeth, widespread cutis gyrata, acanthosis nigricans, skin tags, developmental delay, pyloric stenosis, anterior anus	Autosomal dominant; sporadic
Jackson-Weiss[161,176]	C342S, C342R, Q289P, A344G (*FGFR2*)	Gain-of-function mutations result in ligand-dependent receptor overactivation	Mandibular prognathism, broad and medially deviated great toes, short first metatarsal, calcaneocuboid fusion, normal intellect	Autosomal dominant; sporadic
Muenke[112,170]	P250R (*FGFR3*)	Gain-of-function mutation results in increased receptor affinity for ligand binding	Uni- or bicoronal synostosis, megalencephaly, midface hypoplasia, hypertelorism, variable sensorineural hearing loss, osteochondroma	Autosomal dominant; sporadic

FGFR, fibroblast growth factor receptor.
[a] Commonest mutation(s) is noted. Others may be documented.
[b] Type I Pfeiffer syndrome is associated with a P252R mutation in *FGFR1* in 5% of cases. The majority of type I and all of types II and III Pfeiffer syndrome cases are associated with sequence variant mutations in *FGFR2*.

linkage that stabilizes the D3 loop, which allows for ligand-free activation of the receptor.[112] Patients with Crouzon syndrome chiefly present with premature fusion of the coronal sutures, mandibular prognathism, strabismus, and proptosis.[165] Unlike Apert syndrome, patients with Crouzon syndrome typically display normal cognitive development and normal-appearing extremities.[112,161,170–172]

A variant of Crouzon syndrome is Crouzonodermoskeletal syndrome. Patients present with many of the skeletal features of Crouzon syndrome but this condition is distinguished by the presence of acanthosis nigricans. Crouzonodermoskeletal syndrome is primarily associated with mutations to *FGFR3*. Specifically, an A391E mutation is thought to result in ligand-free activation of the receptor.[112,173]

Beare-Stevenson cutis gyrata syndrome

Beare-Stevenson cutis gyrata syndrome is also a syndromic form of craniosynostosis caused by an *FGFR2* mutation. It is characterized by cognitive impairment, moderate-to-severe

midface hypoplasia, abnormal ears, cutis gyrata, acanthosis nigricans, prominent umbilical stump, accessory nipples, pyloric stenosis, and an anterior anus.[112,174] A Y394C mutation leads to a cysteine-cysteine disulfide bond that initiates ligand-free activation of the receptor.[161,175]

Jackson-Weiss syndrome

Jackson-Weiss syndrome is characterized by mandibular prognathism, broad and medially deviated toes, short first metatarsals, calcaneocuboid fusions, and abnormal tarsals.[176] It has been associated with several missense mutations of *FGFR2*, including C342S, C342R, Q289P, and A344G.[161,176] In each case, an amino acid substitution triggers excessive receptor activation.

Muenke syndrome

Muenke syndrome is an FGFR3-related craniosynostosis that generates isolated coronal synostosis and overlaps phenotypically with Pfeiffer and Jackson-Weiss syndromes.[112,161,170] Patients have normal to mildly impaired intelligence, variable uni- or bicoronal synostosis, megalencephaly, midface hypoplasia, carpal-tarsal fusion, brachydactyly, sensorineural hearing loss, and osteochondroma.[170,177,178] An *FGFR3* P250R mutation occurs between the D2 and D3 domains, promoting excessive ligand binding through the substitution of a bulkier residue.[112] This causes over activation of the receptor.

Nonsyndromic craniosynostosis

Nonsyndromic craniosynostosis is characterized by isolated premature suture fusion and no additional extra-cranial abnormalities. Classification is based on which sutures are fused. The genetic mechanisms of nonsyndromic variants are less well understood than those associated with syndromic craniosynostosis.[179] It had been thought that mutations in *FGFR3* may be responsible for particular sporadic cases. However, many of these cases were determined to be mild syndromic variants.[157] Recently, evidence has shown a potential link between an A315Y mutation on *FGFR2* and isolated sagittal synostosis.[133,157] Additionally, in utero factors may play a role in isolated synostosis. Intrauterine cranial constraints have been observed to induce over expression of FGFR2 at the osteogenic fronts of calvarial bones in the dura and osteoblasts.[180]

Concluding remarks and future directions

FGFs and their associated receptors have been studied extensively for the past 30 years. Recently, significant research has focused on the therapeutic potential of FGF-FGFR signaling. Beenken and Mohammadi provide an excellent review of traditional therapeutic applications of recombinant FGFs and small-molecule FGFR kinase inhibitors.[4] Both *in vitro* and *in vivo* studies offer evidence as to the physiologic roles of each FGF ligand. Phenotypic studies of knockout mice in particular provide clues for the specific functions of each FGF ligand and whether a ligand is required for life. As discussed above, aberrant FGF-FGFR signaling is associated with many pathologic conditions including cancer and craniofacial and axial skeletal abnormalities. Aberrant signaling has also been implicated in cardiovascular disease, mood disorders, and potentially metabolic syndromes. To this end, the FGF-FGFR signaling system appears to an import therapeutic target.

To date, the therapeutic potential of FGFRs mostly relate to their role in tumorigenesis and cancer development. In particular, direct inhibition of FGFRs may improve outcomes of various cancers. Proof of principle with respect to effective treatment for malignancy comes from many lines of evidence. The small molecule inhibitors SU5402, PD173074, and nordihydroguaiaretic acid are efficacious in the treatment of multiple myeloma cell lines associated with deregulated FGFR3 expression.[181,182] PD173074 has also been shown to induce cell cycle arrest in FGFR2-mutated endometrial cancer cells.[183] In addition, sunitinib, a receptor tyrosine inhibitor with activity against FGFRs, has received approval from the Food and Drug Administration (FDA) for use in patients with renal cell carcinoma and gastrointestinal stromal tumors.[184] Interestingly, potential therapeutic targets have also been elucidated by experiments that involve the disruption of downstream signaling after FGFR activation. The blood cancer 8p11 myeloproliferative syndrome (EMS) is due to constitutive dimerization of the FGFR1 kinase domain in the setting of an inappropriate translocation.[185] A mutation in the PLCγ1 binding site at Tyr^{766} attenuates EMS.[186] A potential strategy in the treatment of EMS could therefore include the disruption of FGFR-PLCγ1 signaling. The interference of the interaction of FGFR and its downstream signaling pathways has become a conceivable therapeutic strategy.

Many potential roles for FGF ligands to be used as therapy also exist. FGF18 is key for physiologic bone growth and development. $FGF18^{-/-}$ mice demonstrate a wide variety of bone and cartilage malformations including a delay in osteogenic differentiation, closure of the calvarial sutures, and long-bone ossification; defective joint development; and enlargement of the proliferating and hypertrophic zones in long bone growth plates.[187,188] Recombinant FGF18 has been shown to stimulate growth of porcine and human articular chondrocytes and have an overall anabolic effect on cartilage.[189] Clinically, it may stimulate the repair of cartilage damaged in the setting of progressive osteoarthritis.[190]

Many additional therapeutic uses of FGF ligands have been documented. FGF1 treatment can stimulate nerve repair and may enhance nerve graft take.[191] FGF1, FGF2, and FGF4 have therapeutic promise in cardiovascular disease.[192–194] Recombinant FGF2 may also provide benefit to patients with mood disorders.[195] Recombinant FGF7 improves wound healing.[196] Additionally, although further investigation is needed, FGF19 and -21 and FGF20 have potential roles in the treatment of diabetes and Parkinson's disease, respectively.[197–199] Oppositely, inhibitors of FGF5 may aid in hair growth.[200]

Significant work has demonstrated the myriad developmental and homeostatic processes that involve FGF-FGFR signaling. Moving forward, ongoing research will almost certainly uncover additional functions of the FGF-FGFR

signaling system. It is hopeful that the discovery of additional therapies that involve this system will parallel such findings. These may come in the form of recombinant proteins, small molecules, and gene therapy. At this time, the majority of FGF-based therapies are aimed at age-related disorders including osteoarthritis, diabetes, cardiovascular disorders, and Parkinson's disease. A substantial challenge is the prevention and treatment of FGF-related disorders that are present at birth. To this end, an even greater understanding of FGF biology will unlock additional strategies to treat disease, both in utero and postnatally. Finally, a new frontier in the investigation of FGF signaling relates to our recent understanding of the role of FGFs and FGFRs in inducing stem cell self-renewal and inhibiting stem cell senescence.[201] Stem cells have tremendous potential in the treatment of human disease. The addition of targeted FGF therapy to this armamentarium could augment success.

Conflicts of interest

The authors declare no conflict of interest.

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