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Cytokine Growth Factor Rev. Author manuscript; available in PMC 2011 April 27.

Published in final edited form as:
Cytokine Growth Factor Rev. 2005 April ; 16(2): 205–213. doi:10.1016/j.cytogfr.2005.02.003.

FGF signaling in the developing endochondral skeleton

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Abstract

Mutations in fibroblast growth factor receptors (*Fgfrs*) are the etiology of many craniosynostosis and chondrodysplasia syndromes in humans. The phenotypes associated with these human syndromes and the phenotypes resulting from targeted mutagenesis in the mouse have defined essential roles for FGF signaling in both endochondral and intramembranous bone development. In this review, I will focus on the role of FGF signaling in chondrocytes and osteoblasts and how FGFs regulate the growth and development of endochondral bone.

Keywords

FGF; Skeletal development; Craniosynostosis; Achondroplasia; Receptor tyrosine kinase

1. Human skeletal disease syndromes: the FGF connection

Fgfrs were known to be expressed in the developing skeleton. However, a functional link between FGF signaling and skeletal development was not appreciated until the discovery that achondroplasia (ACH), the most common form of skeletal dwarfism in humans, was caused by a missense mutation in *Fgfr3* [1–5]. Following this initial discovery, a milder form of dwarfism, hypochondroplasia (HCH) [6,7], and a more severe form of dwarfism, thanatophoric dysplasia (TD) [3,8–10], were also found to result from mutations in *Fgfr3*.

In addition to the chondrodysplasia syndromes, many other human skeletal dysplasias have been attributed to mutations in *Fgfrs 1, 2* and *3* [11–17]. These disorders have in common craniosynostosis (premature fusion of the cranial sutures) and variably other phenotypes that affect the appendicular skeleton and other organ systems. The craniosynostosis syndromes involving *Fgfr2* include Apert syndrome (AS) [18], Beare-Stevenson cutis gyrata [19], Crouzon syndrome (CS) [20–32], Pfeiffer syndrome (PS) [33–37,23,28,29], Jackson-Weiss syndrome (JWS) [22,23,26] and a non-syndromic craniosynostosis (NSC) [38]. Recently a family has been described with a double mutation in *Fgfr2* (S2521, A315S) that is associated with syndactyly but not craniosynostosis [39]. However, individually, these mutations are associated with low-penetrance craniosynostosis.

In addition to the single mutation in *Fgfr1* (P252R) that causes Pfeiffer syndrome [40–42,29], a rare mutation has been identified that causes osteoglophonic dysplasia (OD), a disease characterized by craniosynostosis, prominent supraorbital ridge, and depressed nasal bridge, as well as the rhizomelic dwarfism and nonossifying bone lesions [43]. One patient has also been described with Jackson-Weiss syndrome and a P252R mutation in *Fgfr1*

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(P252R) [44]. Loss of function mutations in *Fgfr1* are associated with one form of Kalmann syndrome (KS), a disease that does not directly affect skeletal development [45].

Recently, a mutation in *Fgfr3* (P250R) has been described that causes Muenke syndrome (MS), which is characterized by craniosynostosis and variably other skeletal and neurological phenotypes [38,46,47]. Another mutation in *Fgfr3* (A391E) causes Crouzon syndrome with acanthosis nigricans, now referred to as crouzonodermoskeletal syndrome [48–52,24].

All of the skeletal disease syndromes are caused by autosomal dominant mutations and frequently arise sporadically. The mutations in *Fgfrs* are shown in Fig. 1. The genetics and pathophysiology of these diseases are discussed in the need to refer to article by Andrew Wilkie.

2. Endochondral bone development

Endochondral ossification is responsible for the formation of the appendicular skeleton, facial bones, vertebrae and the medial clavicles. Appendicular skeletal development initiates shortly after the formation of the limb bud with the formation of a histologically identifiable mesenchymal condensation, marked by the expression of type II collagen and Sox9 [53–56]. This condensing mesenchyme forms an anlage for the endochondral skeleton and can either branch or segment to form individual skeletal elements [57,58].

Condensing mesenchyme gives rise to a highly proliferative population of cells. The centrally localized cells express type II collagen and will give rise to chondrocytes. The more peripherally localized cells transiently express type II collagen and then adopt an osteoblast fate characterized by the expression of alkaline phosphatase and eventually type I collagen [53].

As development progresses, the condensation elongates. Medially localized cells proliferate, while more distal cells form a slowly growing pool of reserve chondrocytes. Midway between the ends of this elongated cartilaginous template, chondrocytes exit the cell cycle, downregulate type II collagen expression and begin to differentiate into hypertrophic chondrocytes, characterized by the synthesis of high levels of type X collagen [59]. The process of chondrocyte hypertrophy is thought to contribute to the force driving bone elongation [60].

Developing and mature bone is highly vascularized, whereas cartilage is an avascular structure. The conversion of the cartilaginous template into bone involves several developmental events. An early and essential step in the formation of bone requires neovascularization of the avascular hypertrophic zone chondrocytes. Vascular invasion allows the influx of periosteal-derived osteoblast precursors and hematopoietic derived osteo(chondro)clasts. At this stage of development, distal hypertrophic chondrocytes begin to ossify while the extracellular cartilaginous matrix is degraded by matrix metalloproteases produced by the osteoclasts. Osteoblasts, osteoclasts and the newly developed vasculature form a center of ossification that propagates toward the distal ends of the nascent bone. This process converts cartilaginous matrix into trabecular bone. The trabecular ossification region (primary and secondary spongiosa) and chondrocytes at various stages of differentiation constitute a developmental structure called the epiphyseal growth plate. These well-demarcated zones of cells follow an elegant developmental program that extends through puberty and the closure of the growth plate [57,61–65].

Surrounding the growth plate is the perichondrium, a fibrous structure containing osteoprogenitor cells. Centrally, the perichondrium forms a structure called the bone collar

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(periosteum), the precursor of cortical bone [61]. The periosteum is a well-vascularized structure and contains precursor pools of cells that give rise to the mature osteoblasts that line the endosteal (inner) surface of cortical bone. As mineralization proceeds, osteoblasts become postmitotic (osteocytes) as they become embedded within cortical bone. A large number of signaling pathways are required to coordinate chondrogenesis and osteogenesis. This review will focus on the role of FGF signaling pathways in this process.

3. FGF and FGF receptor expression and signaling in condensing mesenchyme

The formation of the mesenchymal condensation is associated with changes in gene expression. *Fgfr2, type II collagen* and *Sox9* are among the earliest genes upregulated in condensing mesenchyme [53–56,66]. *Fgfr1* continues to be expressed in surrounding loose mesenchyme and is also expressed along with *Fgfr2* in the periphery of the condensation [66–69].

The physiologic ligands that activate FGFRs in the mesenchymal condensation have been difficult to identify. *Fgf9* is expressed within condensing mesenchyme early in development [70]. *Fgf2, Fgf5, Fgf6* and *Fgf7* expression has been observed in mesenchyme surrounding the condensation [71–75]. However, knockout mice lacking these FGFs have no apparent defects in skeletal development [76–78]. It is possible that a combination of these and other FGFs may constitute the complete FGF signal to the developing condensation.

The role of FGF signaling in condensing mesenchyme is poorly understood. In primary chondrocytes and in undifferentiated mesenchymal cells, FGF signaling pathways induce the expression of *Sox9*, an essential transcription factor for chondrocyte differentiation [79,55]. Additionally, FGFR3 signaling may enhance chondrocyte proliferation in the mesenchymal condensation, even though it is well established that FGFR3 limits chondrocyte proliferation in the mature growth plate [80,81]. Consistent with this, FGF2 and to a greater extent, FGF9 can stimulate proliferation of chondrocytes [82]. Defects in FGF signaling in the mesenchymal condensation can result in skeletal abnormalities. For example, in the case of Apert Syndrome, mutations in FGFR2 allow for inappropriate activation of FGFR2 in the mesenchymal condensation by mesenchymally expressed ligands, such as FGF7 and FGF10, that normally do not signal to this receptor [83,84]. Although ligand-binding specificity is also lost for epithelial forms of FGFR2, the recent identification of mutations within the mesenchymal-specific c exon of *Fgfr2* (A315S) that allow binding to FGF10, suggests that the primary etiology of Apert syndrome results from inappropriate activation of the mesenchymal receptor [85,39]. The soft tissue and bony syndactyly characteristic of Apert syndrome suggests that the phenotype may originate at the mesenchymal condensation stage of development.

4. FGF and FGF receptor expression and signaling in endochondral bone

4.1. Fgf receptors expressed in developing bone

Shortly after formation of a mesenchymal condensation, *Fgfr3* expression is activated in chondrocytes located in the central core of the mesenchymal condensation (Fig. 2) [86]. At this stage of development, overlap in expression may exist with *Fgfr2* and *Fgfr3*. As the epiphyseal growth plate develops, *Fgfr1* expression is upregulated as chondrocytes hypertrophy. *Fgfr1* and *Fgfr3* have very distinct domains of expression with little overlap; *Fgfr3* is expressed in proliferating chondrocytes, whereas *Fgfr1* is expressed in prehypertrophic and hypertrophic chondrocytes [87,88,66]. This juxtaposition of FGFR1 and FGFR3 expression domains suggests unique functions. Expression of *Fgfr3* in the reserve and proliferating zone suggests a direct role for FGFR3 in regulating chondrocyte

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proliferation and possibly differentiation [67,89,88]. In contrast, the expression of *Fgfr1* in hypertrophic chondrocytes [67,66] suggests a role for FGFR1 in regulating cell survival, cell differentiation, extracellular matrix production and cell death. Interestingly, immunohistochemical localization of FGFR3 in costal cartilage identifies FGFR3 extracellular domains within the extracellular matrix of hypertrophic chondrocytes. This suggests that proteolytic processing could regulate the activity of FGFR3 and that the FGFR3 ectodomain could compete with FGFR1 for ligand-binding [90]. In mature bone, *Fgfr1* and *Fgfr2* continue to be expressed in osteoblasts. Interestingly, immunohistochemistry has also identified FGFR3 expression in mature osteoblasts and in osteocytes [86].

4.2. Fgf ligands expressed in developing bone

Several FGFs are expressed in developing endochondral bone [16]. FGF2 (basic FGF) was first isolated from growth plate chondrocytes [91]. Subsequently, *Fgf2* expression has also been observed in periosteal cells and in osteoblasts [92–95]. Targeted deletion of FGF2 caused a relatively subtle defect in osteoblastogenesis leading to decreased bone growth and bone density. However, no defects in chondrogenesis were observed [94]. Further analysis of $Fgf2^{-/-}$ mice revealed decreased osteoclastogenesis [96], which may in part compensate for the observed mild phenotype in $Fgf2^{-/-}$ bones. *Fgf9* is also expressed in immature chondrocytes in condensing mesenchyme [70,97].

In the perichondrium, expression of *Fgf7*, *Fgf8*, *Fgf9*, *Fgf17* and *Fgf18* has been observed ([72,74,98–100] I. Hung and DMO, unpublished data), suggesting a possible paracrine signal to the growth plate. Recent genetic studies have identified a defect in chondrogenesis and osteogenesis in mice lacking FGF 18 [98,99]. Mice lacking FGF7, FGF8 and FGF17 have apparently normal chondrogenesis, or in the case of FGF8, die prior to skeletal development [77,101,102]. The skeletons of newborn $Fgf9^{-/-}$ mice are slightly smaller than of wild type littermates and their proximal skeletal elements are disproportionately short (I. Hung and DMO, unpublished observation). Issues of functional redundancy among these and other FGFs will need to be addressed in the future.

4.3. FGF signaling pathways in the growth plate

Mice either lacking *Fgfr3* or expressing an activated form of *Fgfr3* develop skeletal pathology in the perinatal and young adult stages of development. Mice lacking *Fgfr3* develop skeletal overgrowth, while mice overexpressing an activated form of *Fgfr3* develop skeletal dwarfism. These phenotypes demonstrate that the primary effect of signaling through FGFR3 is to negatively regulate chondrocyte proliferation and differentiation [103–106,81,89,14,15]. This effect is mediated in part by direct signaling in chondrocytes [107–109] and in part indirectly, by regulating the expression of the IHH/PTHrP/BMP signaling pathways [107,63,110,89]. Mice harboring an activating mutation in FGFR3 have decreased expression of *Ihh*, *Ptc* and *Bmp4* [104,105,89], whereas in mice lacking FGFR3, *Ihh*, *Ptc* and *Bmp4* expression are upregulated ([89] and data not shown). The overall function of FGFR3 is consistent with a direct action of FGFR3 on proliferating chondrocytes (see below) and an indirect consequence of modulating Hedgehog and BMP signaling.

Ligands that signal to FGFR3 during skeletal development should fit the criteria of expression proximal to zones of proliferating chondrocytes (but not within proliferating chondrocytes) and should produce a phenotype similar to that of $Fgfr3^{-/-}$ mice when knocked out. *Fgf18*, and more recently, *Fgf9* expression has been observed in the perichondrium and periosteum of developing bone ([98,99] and I. Hung, unpublished data). Growth plate histology of mice lacking *Fgf18* is similar to that of mice lacking *Fgfr3*. Both knockout mice show an upregulation of *Ihh* and *Ptc* expression and increased chondrocyte

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proliferation. These phenotypic similarities strongly suggest that FGF18 is a physiological ligand for FGFR3 in chondrocytes [98,99]. In vitro studies show that FGF18 can activate FGFR3c [102] and stimulate the proliferation of cultured articular chondrocytes [111]. However, mice lacking *Fgf18* have a more severe phenotype than mice lacking *Fgfr3* [98]. Unlike *Fgfr3*$^{-/-}$ mice, *Fgf18*$^{-/-}$ mice exhibit delayed ossification which may be due to direct signaling to osteoblasts or hypertrophic chondrocytes or to a delay in vascular invasion of the growth plate. The simplest explanation is that FGF18 is signaling bi-directionally to osteoblasts in the endosteum and primary spongiosa, and to periosteal mesenchyme. Signals to periosteal mesenchyme could either directly or indirectly regulate vasculogenesis. With the recent observation that *Fgfr3* is expressed in mature osteoblasts [86], it is not clear which FGFR (FGFR1, FGFR2 or FGFR3) is actually responding to FGF 18 in osteoblasts.

4.4. Signaling pathways regulating chondrocyte and osteoblast proliferation and differentiation

During early embryonic development, constitutive FGFR3 activation enhances proliferation of immature chondrocytes [80,81]. However, as chondrocytes mature, the primary role of FGFR3 is to restrain chondrocyte proliferation and differentiation [89]. The signaling pathways regulating chondrocyte proliferation and differentiation are not unique to FGFR3, even though FGFR1 and FGFR3 appear to have different signaling properties in some cell types in vitro [112–114]. Both FGFR1 and FGFR3 kinase domains appear to have similar activities when expressed in growth plate chondrocytes in vivo [115]. Therefore, observed differences between these receptors must be attributable to differences in the strength of the tyrosine kinase signal rather than the specific signaling pathway activated [116]. This property of FGF signaling in chondrocytes supports the hypothesis that the proliferating chondrocyte itself is uniquely responsive to an FGFR signal.

Endochondral bone growth requires regulated chondrocyte proliferation, differentiation to hypertrophic chondrocytes, and ossification. The signaling pathways mediating growth arrest in mature proliferating chondrocytes are thought to require activation of the MAP kinase pathway [117]. In vivo, activation of MEK1 in chondrocytes caused a dwarfism phenotype but did not affect chondrocyte proliferation [118]. A clue to the signaling mechanism downstream of FGFR3 comes from studies that show that activation of FGF signaling in chondrocytes can increase expression and induce nuclear translocation of STATs 1, 3 and 5 and induce the expression of the cell-cycle inhibitor p21 (WAF1/CIP1) in chondrocyte cell lines [119–122]. Furthermore, chondrocytes isolated from patients with Thanatophoric dysplasia (constitutive activation of FGFR3) exhibited nuclear localized STAT1 [123]. In vivo, the dwarfism phenotype observed in mice expressing activating mutations in FGFR3 correlated with the activation of STAT proteins and upregulation of cell-cycle inhibitors (pl6, pl8 and pl9) [103,105]. Additionally, mating FGF2-expressing transgenic mice into a *Stat1* null background corrected the chondrodysplasia phenotype characteristic of this transgenic line [124]. These data support a model in which STAT1 activation acts either downstream or in parallel to the MAP kinase pathway in chondrocytes to mediate inhibition of endochondral growth by FGFR3.

Interestingly, in primary chondrocytes derived from mice lacking STAT1, FGF signaling failed to induce chondrocyte growth inhibition [121]. Furthermore, constitutive activation of MEK1 in chondrocytes resulted in a dwarfism phenotype in mice without affecting chondrocyte proliferation [118]. Mating MEK1 mice to Achondroplasia mice or to mice lacking FGFR3 suggests a model in which FGFR3 signaling inhibits bone growth by inhibiting chondrocyte differentiation through the MAPK pathway and by inhibiting chondrocyte proliferation through a STAT1 pathway [118].

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In a chondrocyte cell line, FGF signaling induces differentiation and inhibits proliferation, as demonstrated by inhibition of growth promoting molecules, such as Rb and p107, and up-regulation of genes associated with hypertrophic differentiation, such as MMP13, osteopontin and FGFR1 [107]. The relationship between STAT1 and the regulation of these molecules remains to be determined.

Another role for FGF signaling in chondrocytes may be to promote cell death. Overexpression of *Fgf2* or activating mutations in *Fgfr3* in chondrocytes promoted apoptosis [124,125]. This is consistent with the observed decrease in AKT phosphorylation in chondrocytes in response to FGF [117,124]. Also consistent with this signaling pathway, treatment of *Fgfr3(ACH)* cells with growth hormone or IGF-1, which activates PI3 kinase, or with PTHrP, which induces *Bcl-2*, blocked the apoptosis [125]. Furthermore, in patients with thanatophoric dysplasia, there is an increased expression of *Bax*, decreased expression of *Bcl2* and an increase in the number of apoptotic chondrocytes [123]. In achondroplasia mice, however, no increase in chondrocyte cell death was observed during embryonic development [14].

FGF signaling is also an important regulator of osteoblast function. Mice conditionally lacking FGFR2 or harboring a mutation in the mesenchymal splice form of FGFR2 develop skeletal dwarfism and decreased bone mineral density [126,127]. Examination of the bones of these mice revealed decreased osteoblast proliferation and quiescent osteoblast morphology but otherwise normal differentiation. Thus in osteoblasts, FGFR2 signaling positively regulates bone growth. Interestingly, mice lacking FGF2 also show osteopenia, though much later in development than in FGFR2-deficient mice [94]. This suggests that FGF2 may be a homeostatic factor that replaces the developmental growth factor, FGF18, in adult bones. Osteoblasts also express FGFR3, and mice lacking FGFR3, have decreased bone mineral density and osteopenia [128,86]. In osteoblasts lacking STAT1, FGFR3 and the cell cycle inhibitor, p21WAF/CIP, expression are down regulated and FGF18 expression is increased [86]. Thus STAT1 may regulate the balance between osteoblast proliferation and differentiation by modulating an FGF2/FGF18 to FGFR3 autocrine signal in osteoblasts.

Acknowledgments

This work was supported by NIH grant HD39952 and a gift from the Virginia Friedhofer Charitable Trust.

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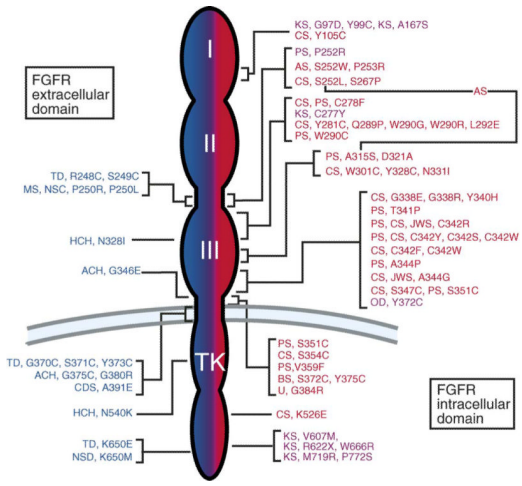

Fig. 1.

FGF receptor mutations in humans. Left (Blue): Mutations in FGFR3 – achondroplasia (ACH), thanatophoric dysplasia (TD), hypochondroplasia (HCH), crouzonodermoskeletal syndrome syndrome (Crouzon syndrome with acanthosis nigricans) (CDS), non-syndromic craniosynostosis (NSC), Muenke syndrome (MS). Right (Red): Mutations in FGFR2 – Crouzon syndrome (CS), Jackson-Weiss syndrome (JWS), Pfeiffer syndrome (PS), Apert syndrome (AS), Beare-Stevenson cutis gyrata (BS), unclassified (U). The line connecting S252L and A315S indicates the double mutation found in patients with Apert syndrome-like syndactyly without craniosynostosis. Right (Pink): A single mutation in FGFR1 causes Pfeiffer syndrome (PS) and osteoglophonic dysplasia (OD). Multiple mutations in FGFR1 cause Kallmann syndrome (KS). The numbers represent the position of the mutant amino acid in the human coding sequence. Amino acids are abbreviated using standard single letter abbreviations (adapted from [16]).

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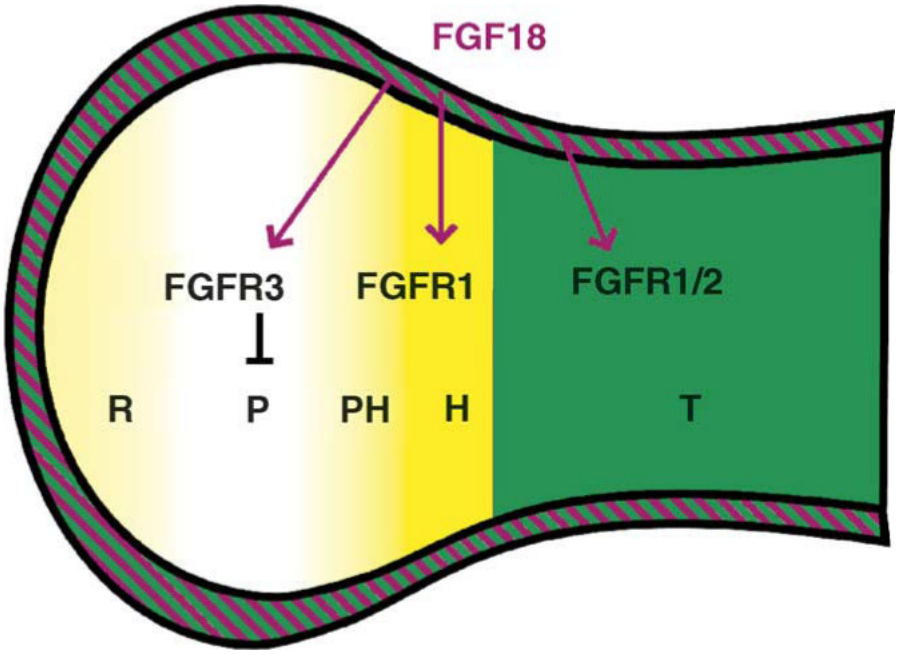

Fig. 2.

FGF and FGFR expression patterns in the growth plate. Chondrocytes progress through reserve (R), proliferating (P), prehypertrophic (PH) and hypertrophic (H) stages. Hypertrophic chondrocytes are then replaced by trabecular bone (T). FGF 18 is expressed in the perichondrium and may signal to FGFRs in both osteoblasts and chondrocytes.