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Achondroplasia: Development, Pathogenesis, and Therapy

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Abstract

Autosomal dominant mutations in Fibroblast Growth Factor Receptor 3 (*FGFR3*) cause Achondroplasia (Ach), the most common form of dwarfism in humans, and related chondrodysplasia syndromes that include Hypochondroplasia (Hch), Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans (SADDAN), and Thanatophoric dysplasia (TD). FGFR3 is expressed in chondrocytes and mature osteoblasts where it functions to regulate bone growth. Analysis of the mutations in *FGFR3* revealed increased signaling through a combination of mechanisms that include stabilization of the receptor, enhanced dimerization, and enhanced tyrosine kinase activity. Paradoxically, increased FGFR3 signaling profoundly suppresses proliferation and maturation of growth plate chondrocytes resulting in decreased growth plate size, reduced trabecular bone volume, and resulting decreased bone elongation. In this review we discuss the molecular mechanisms that regulate growth plate chondrocytes, the pathogenesis of Ach, and therapeutic approaches that are being evaluated to improve endochondral bone growth in people with Ach and related conditions.

Keywords

Achondroplasia; Hypochondroplasia; Thanatophoric dysplasia; Fibroblast Growth Factor Receptor; FGF; FGFR3; chondrogenesis; growth plate; endochondral ossification; therapy; skeletal dysplasia

Introduction

Achondroplasia (Ach) is the most common form of dwarfism in humans. It occurs with a frequency of 1 in 15–25,000 and 80% of cases are sporadic. Ach is an autosomal dominant genetic disease that has 100% penetrance. The short stature in Ach mainly results from shortening of the limbs with proximal segments affected disproportionally, a phenotype referred as rhizomelia. The head is large with frontal bossing and the midface is hypoplastic resulting from cartilage growth defects at the skull base. Narrowing of the foramen magnum

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and spinal stenosis are relatively common and often require neurosurgical corrections. The size of the trunk is relatively normal but is often deformed by excessive lumbar lordosis (Horton et al., 2007; Baujat et al., 2008).

Genetic linkage studies placed the Ach gene on the short arm of chromosome 4 and mutation analysis identified an arginine to glycine substitution at residue 380 (p.Gly380Arg) in Fibroblast Growth Factor Receptor 3 (*FGFR3*) in almost all Ach patients in Caucasian, African, and Asian populations (Rousseau et al., 1994; Shiang et al., 1994). Expression of FGFR3 in growth plate chondrocytes suggested a direct causal relationship between mutation in FGFR3 and growth plate function. Comparison of wild type and mutant *FGFR3* showed that the mutant receptors had increased signaling that could be further enhanced in the presence of Fibroblast Growth Factor (FGF) ligands (Naski et al., 1996; Legeai-Mallet et al., 1998). This increased signaling may be due in part to increased protein stability resulting from decreased lysosomal degradation of the mutant receptor (Cho et al., 2004).

FGFs are signaling molecules that function during embryonic and postnatal development. In the adult, FGFs have roles in homeostasis and tissue repair (Ornitz and Itoh, 2015; Li et al., 2016). Eighteen FGF ligands have the capacity to activate four FGFR tyrosine kinase molecules. Alternative mRNA splicing of immunoglobulin-like domain III of FGFRs 1–3 produce b and c splice variants. In many tissues, b splice variants are expressed in epithelial cell types and c splice variants are expressed in mesenchymal derived cells (Belov and Mohammadi, 2013; Ornitz and Itoh, 2015; Li et al., 2016). These FGFR splice variants and cofactor molecules, which include heparan sulfate proteoglycans and Klotho-family proteins, also determine the strength and specificity of ligand binding and receptor activation (Ornitz, 2000; Polanska et al., 2009; Itoh et al., 2015). Binding to heparan sulfate also serves to limit FGF diffusion through tissue (Sun et al., 2016).

The identification of activating mutations in FGFR3 as the etiology of Ach and the related milder form of dwarfism, Hch, the severe and rare dwarfism, SADDAN, and the severe lethal chondrodysplasia, TD, immediately suggested that inhibitor therapies could be developed to lessen the severity of these diseases. Research over the past two decades has identified some of the mechanisms used by FGFR3 to regulate chondrocyte proliferation and differentiation in the growth plate. Also identified are signaling molecules and pathways that interact with FGFR3 that could be exploited to counteract the effects of hyperactivated FGFR3. Here, we review local signaling pathways acting on the growth plate, the mechanisms used by FGFR3 and interacting signaling pathways to regulate chondrogenesis, and the current efforts to develop therapies to treat patients with Ach and Hch, and potentially other forms of short-limbed dwarfism.

Growth plate structure and function

Longitudinal bone growth is driven by the proliferation and differentiation of chondrocytes in the growth plate, a structure located between the metaphysis and epiphysis of long bones. The definitive growth plate consists of three principal layers of cells that temporally and spatially follow a highly regulated developmental program (Figure 1) (Caplan and Pechak, 1987; Hall and Miyake, 1992; Hunziker, 1994; Olsen et al., 2000; Wagner and Karsenty,

2001; Karsenty and Wagner, 2002; Ornitz and Marie, 2002; Ornitz and Marie, 2015). Reserve (or resting) zone chondrocytes serve as a renewing population of progenitors that gives rise to proliferating chondrocytes. Proliferating chondrocytes form clonal columns of cells that differentiate into prehypertrophic and then hypertrophic chondrocytes. At the distal end of the growth plate, the extracellular matrix produced by hypertrophic chondrocytes begins to mineralize and the hypertrophic chondrocytes either die or further differentiate into osteoblasts that populate the primary spongiosa (Yang et al., 2014a; Yang et al., 2014b; Yeung Tsang et al., 2014; Zhou et al., 2014; Park et al., 2015). In this manner the growth plate functions as a template for trabecular (primary spongiosa or spongy) bone.

The growth plate is surrounded by the perichondrium, a structure contiguous with the periosteum. The inner layer of the perichondrium is populated by densely packed cells in the groove of Ranvier and surrounding perichondrial ring of LaCroix (Ranvier, 1873; Ranvier, 1889; Shapiro et al., 1977). This structure is important for regulating longitudinal bone growth and serves as a source of progenitor cells that populate the periosteum and cortical bone (Robinson et al., 1999; Fenichel et al., 2006; Karlsson et al., 2009). The perichondrium thus serves as a template for the formation of cortical bone.

Chondrocyte hypertrophy accounts for approximately 60% of longitudinal bone growth (Hunziker et al., 1987; Hunziker and Schenk, 1989; Hunziker, 1994; Wilsman et al., 1996; Noonan et al., 1998). The rate of longitudinal bone growth is determined by chondrocyte proliferation, the rate of hypertrophic differentiation, the change in height of hypertrophic chondrocytes, and the amount of extracellular matrix produced by hypertrophic chondrocytes (Breur et al., 1991; Wilsman et al., 1996). Although the force driving bone elongation requires chondrocyte proliferation and hypertrophy, longitudinal bone growth also requires elongation of the perichondrium/periosteum, which must be synchronized with growth plate chondrogenesis.

Overview of signaling pathways regulating the growth plate

Proliferation and differentiation of chondrocytes in the growth plate is regulated by locally acting secreted growth factors, by endocrine factors, and by mechanical forces. Locally acting signals include Parathyroid hormone-like peptide (PTHLH or PTHRP), Indian hedgehog (IHH), Bone morphogenetic proteins (BMPs), Transforming growth factor β (TGFβ), Wingless-type MMTV integration site family members (WNTs), Notch, C-natriuretic peptide (CNP encoded by *Nccp*), Insulin-like growth factor 1 (IGF-1), Epidermal growth factor (EGF), Transforming growth factor α (TGFα), Vascular endothelial growth factor A (VEGFA), and FGFs. The functions of these pathways in skeletal growth and development have been extensively reviewed (reviewed in Long and Ornitz, 2013; Lui et al., 2014; Kozhemyakina et al., 2015; Rosello-Diez and Joyner, 2015; Maes, 2016). Endocrine factors include growth hormone (GH), Thyroid hormone (T_3), Parathyroid hormone (PTH), FGF23, and sex steroids (reviewed in Perry et al., 2008; Rosello-Diez and Joyner, 2015; Maes, 2016; Yakar and Isaksson, 2016)]. Mechanical forces include those generated by hydrostatic forces, muscle contraction, and gravity. Hydrostatic compression of growth plate chondrocytes directly increases IHH signaling and chondrocyte proliferation (Shao et al., 2012). Chondrocyte proliferation and hypertrophy are also modulated by static and dynamic

loading (Villemure and Stokes, 2009). For example, in the absence of muscle forces, proliferation decreased in embryonic chick growth plate (Germiller and Goldstein, 1997) and in mice lacking skeletal muscle, formation of the primary ossification center was delayed (Nowlan et al., 2010).

Focusing on local signals, IHH, PTHLH, BMP2, Wnt, CNP and FGFR3 are central factors for growth plate regulation (Figure 2). IHH and PTHLH form a negative feedback loop that controls chondrocyte proliferation and differentiation. IHH is made by prehypertrophic and early hypertrophic chondrocytes. During postnatal bone growth, after formation of the secondary ossification center, IHH signals to its receptor, PTCH1, in reserve zone chondrocytes to regulate expression of PTHLH (Chau et al., 2011). PTHLH, in turn, signals to its receptor, PTH1R (PTH type 1 receptor) in prehypertrophic chondrocytes and inhibits IHH expression and chondrocyte hypertrophy. BMP2 and BMP4 are expressed in prehypertrophic and hypertrophic chondrocytes and signal to BMPR1a (Bone Morphogenetic Protein Receptor Type 1A) in proximal proliferating chondrocytes and prehypertrophic chondrocytes to regulate chondrocyte proliferation (Feng et al., 2003; Nilsson et al., 2007; Shu et al., 2011). Inhibition of Wnt signaling by inactivating the Wintless (Wls) gene in chondrocytes or osteoblasts results in reduced chondrocyte hypertrophy and a smaller skeleton (Lu et al., 2013). CNP is expressed in proliferating and prehypertrophic chondrocytes and signals to natriuretic peptide receptor 2 (NPR2 or NPR-B) in proliferating and prehypertrophic chondrocytes (Chusho et al., 2001; Potter et al., 2006). Like BMP, IHH, PTHLH, and CNP promote chondrocyte proliferation (Karp et al., 2000; Chusho et al., 2001; Long et al., 2001; Hirai et al., 2011).

Fgfr3 is expressed in proliferating and prehypertrophic chondrocytes during embryonic and postnatal development (Figure 1C) (Peters et al., 1993; Delezoide et al., 1998; Monsonego-Ornan et al., 2000; Pandit et al., 2002; Barnard et al., 2005; Karuppaiah et al., 2016). During establishment of the growth plate before formation of the secondary ossification center, FGFR3 signaling promotes chondrocyte proliferation (Iwata et al., 2000; Iwata et al., 2001; Havens et al., 2008). However, during postnatal skeletal growth, FGFR3 signaling inhibits chondrocyte proliferation and differentiation. The inhibition of chondrogenesis by FGFR3 underlies the etiology of Ach and related disorders in which activating mutations in *FGFR3* suppress chondrogenesis during pre-pubertal skeletal growth (Colvin et al., 1996; Deng et al., 1996; Naski et al., 1996; Naski et al., 1998; Chen et al., 1999; Li et al., 1999; Pannier et al., 2010).

FGFR3 signaling in the growth plate

Mice expressing the FGFR3(p.Gly374Arg) activating mutation, which corresponds to the human FGFR3(p.Gly380Arg) mutation, develop an Ach-like phenotype with reduced chondrocyte proliferation and reduced hypertrophic differentiation and matrix production (Naski et al., 1998; Wang et al., 1999). The intracellular signaling mechanisms that mediate these phenotypes have revealed a complex network of signals that integrate FGFR3 signaling with several other signaling pathways.

FGFR signaling activates at least four downstream intracellular signaling pathways including, MAPK, PI3K/AKT, PLCγ, and STATs (reviewed in Ornitz and Itoh, 2015; Brewer et al., 2016). In the growth plate, FGFR3 activates STAT1 and the ERK1/2 and p38 branches of the MAPK pathway (Figure 2) (Su et al., 1997; Chen et al., 1999; Li et al., 1999; Chen et al., 2001; Legeai-Mallet et al., 2004; Raucci et al., 2004; de Frutos et al., 2007; Parafioriti et al., 2009). Activation and overexpression of STAT1 is a strong candidate for regulation (suppression) of chondrocyte proliferation downstream of FGFR3, as inactivation of the *Stat1* gene rescued the chondrocyte proliferation defect in FGFR3(p.Gly374Arg) mice. However, these mice still developed an Ach-like phenotype, demonstrating that STAT1 is not sufficient to mediate the overall growth inhibitory effects of activated FGFR3 (Murakami et al., 2004). In contrast, expression of an activated MEK1 allele in chondrocytes of mice that lack a functional *Stat1* gene resulted in an Ach-like phenotype with a prominently reduced hypertrophic chondrocyte zone, but no decrease in chondrocyte proliferation. This is consistent with chondrocyte hypertrophy contributing to bone elongation to a greater extent than chondrocyte proliferation (Murakami et al., 2004). The separation between regulation of proliferation and differentiation was further supported by the observation that CNP signaling enhances bone growth by increasing hypertrophic differentiation and matrix production through inhibition of MAPK signaling (Yasoda et al., 2004).

SNAIL1 is a transcription factor that has been shown to regulate chondrocyte differentiation through repression of Collagen II and Aggrecan transcription (Seki et al., 2003). Several studies have demonstrated that Snail1 functions downstream of FGFR3 and is essential for FGFR3 regulation of both chondrocyte proliferation and differentiation (de Frutos et al., 2007; Karuppaiah et al., 2016). Forced activation of SNAIL1 in mice suppressed chondrocyte proliferation and hypertrophy at late embryonic stages, a phenotype that resembled Ach (de Frutos et al., 2007). Further analysis revealed significantly reduced chondrocyte proliferation and a correlation between *Snail1* expression and nuclear localization of STAT1. In addition to regulating STAT1, SNAIL1 activation also increases phosphorylated Erk1/2 and may enhance its nuclear localization (de Frutos et al., 2007; Smith et al., 2014). This function of SNAIL1 may be reinforced by a feed forward mechanism whereby activation of ERK2 phosphorylates and stabilizes SNAIL1 and increases its nuclear localization (Zhang et al., 2013). Downstream of SNAIL1, STAT1 and ERK1/2 activation results in suppression of chondrocyte proliferation and differentiation, respectively. Suppression of proliferation is mediated by activation of p107 (and p130) and expression of the cell cycle inhibitor, $p21^{Waf1/Cip1}$ (Figure 2B) (Cobrinik et al., 1996; Su et al., 1997; Aikawa et al., 2001; Laplantine et al., 2002; Dailey et al., 2003; Legeai-Mallet et al., 2004; Kolupaeva et al., 2008; Kolupaeva et al., 2013). Chondrocyte differentiation is mediated in part by ERK1/2 (MAPK) regulation of Sox9, which must be suppressed to allow terminal hypertrophic differentiation and endochondral ossification (Hattori et al., 2010; Ikegami et al., 2011; Kim et al., 2011; Shung et al., 2012; Zhou et al., 2015b).

FGFR3 signaling also affects surrounding bone, directly and through the regulation of other growth factor signaling pathways in chondrocytes. For example, inactivation of FGFR3 globally or in chondrocytes results in increased expression of *Ihh, Bmps 2, 4, 7, Tgfβ1*, and *Wnt4*, and decreased expression of *Noggin*, resulting in increased bone mass (Naski et al.,

1998; Zhou et al., 2015a; Wen et al., 2016), while activation of FGFR3 in chondrocytes results in decreased *Ihh, BMP4*, and *Pthlh* and leads to decreased bone mass (Figure 2A) (Naski et al., 1998; Chen et al., 2001; Su et al., 2010; Mugniery et al., 2012; Qi et al., 2014). Direct effects of FGFR3 on osteoblasts are supported by conditional knockouts of *Fgfr3* in osteoblasts (OC-Cre), which result in impaired bone formation and remodeling (Xie et al., 2014). The function of osteoblasts is coupled to osteoclasts during bone formation and resorption, and recently it was demonstrated that *Fgfr3* inactivation in osteoclasts (LysM-Cre) impaired bone resorption (Su et al., 2016).

Regulation of *Fgfr3* expression

FGFR3 signaling is controlled in part by regulating the level of *Fgfr3* mRNA and protein expression. Activating mutations in FGFR3 lead to increased FGFR3 protein expression, possibly through reduced receptor internalization and degradation (Cho et al., 2004; Legeai-Mallet et al., 2004; Qi et al., 2014). Paracrine and endocrine signals also regulate *Fgfr3* expression in growth plate chondrocytes. These signals include FGF, Thyroid hormone (T_3), and PTHLH. Overexpression of FGF9 in the perichondrium/periosteum activates a feed forward pathway that increases *Fgfr3* expression and suppresses chondrocyte proliferation (Karuppaiah et al., 2016).

Mice lacking Thyroid Receptor α (*TRα*$^{o/o}$), which is expressed in skeletal tissues, have skeletal hypothyroidism (reduced hypertrophic chondrocyte differentiation, delayed ossification, disorganized growth plate structure) (Gauthier et al., 2001). Mice with a mutant thyroid hormone receptor β (*TRβ*$^{pv/pv}$), which is expressed in the pituitary gland, have increased expression of TSH and develop thyrotoxicosis (elevated levels of T_3 and T_4) (O'Shea et al., 2003). These mice have reduced linear growth, advanced endochondral ossification, and craniosynostosis. These phenotypes can be explained in part through regulation of *Fgfr3* in chondrocytes (Bassett and Williams, 2016). *TRα*$^{o/o}$ mice have reduced levels of *Fgfr3* expression in growth plate chondrocytes, while hyperthyroid *TRβ*$^{pv/pv}$ mice showed increased levels of *Fgfr3* in growth plate chondrocytes (Barnard et al., 2005). This signaling could be direct (Figure 2), as analysis of the *Fgfr3* promoter identified a putative thyroid hormone response element (McEwen et al., 1999). Additionally, treatment of cultured chondrocytes with T_3 induced the expression of *Fgfr3* (Barnard et al., 2005).

PTHLH signaling may directly regulate *Fgfr3* by controlling a transcriptional regulatory element, which can be repressed by PTH through binding to a cAMP response element in the *Fgfr3* promoter (McEwen et al., 1999). Treatment of primary chondrocytes with PTH(1-34) suppressed expression of *Fgfr3* (Zhang et al., 2016) as did injection of PTH(1-34) *in vivo* (Karuppaiah et al., 2016). Although not investigated in chondrocytes, *Fgfr3* expression was induced by hypoxia in a transcriptional and HIF1α-dependent manner in bladder cancer cells (Blick et al., 2013). Similar regulation could occur in the relatively hypoxic growth plate. Additionally, BMP2 induced expression of *Fgfr3* through chromatin remodeling and SP1 sites in the *Fgfr3* promoter (McEwen and Ornitz, 1998; Sun et al., 2009).

FGF ligands that regulate endochondral bone growth

Several FGFs are expressed in the growth plate and in the surrounding perichondrium and periosteum. During development, *Fgf2*, *Fgf9,* and *Fgf18* are expressed in the perichondrium/periosteum and presumptive joint space and have been shown to regulate bone growth *in vivo* (Gonzalez et al., 1996; Liu et al., 2002; Ohbayashi et al., 2002; Hung et al., 2007; Reinhold and Naski, 2007). *Fgf1, Fgf2, Fgf17* and *Fgf19* are present in growth plate chondrocytes (Logan et al., 1991; Krejci et al., 2007), but of these, only *Fgf2* has been shown to regulate bone growth *in vivo*. Mice congenitally lacking *Fgf2* (*Fgf2*$^{-/-}$ mice) show normal growth plate morphology and function but have decreased bone mass, primarily seen in trabecular bone (Montero et al., 2000).

Mice that congenitally lack *Fgf9* (*Fgf9*$^{-/-}$ mice) have decreased growth of long bones that affects the proximal skeletal elements to a greater extent than the distal elements (rhizomelia) (Hung et al., 2007). Mice that lack *Fgf18* (*Fgf18*$^{-/-}$) show a more uniform decrease in skeletal growth (Liu et al., 2007). For both of these ligands, chondrocyte proliferation is decreased, which is consistent with observed phenotypes in *Fgfr3*$^{-/-}$ mice during embryonic stages of bone growth, where FGFR3 signaling functions to promote chondrocyte proliferation (Iwata et al., 2000; Iwata et al., 2001; Hung et al., 2007; Liu et al., 2007). Mice that lack both *Fgf9* and *Fgf18* have a severe defect in bone growth that affects all skeletal elements (Hung et al., 2016). At late stages of development, *Fgf9*$^{-/-}$ and *Fgf18*$^{-/-}$ mice show an increase in the size of the hypertrophic chondrocyte zone. This phenotype closely matches that of *Fgfr3*$^{-/-}$ mice, which is consistent with FGFR3 functioning to suppress chondrocyte proliferation and differentiation at late stages of development and in the postnatal growth plate (Liu et al., 2002; Ohbayashi et al., 2002; Hung et al., 2007).

Autophagy in the growth plate

Macroautophagy is a lysosomal-dependant degradation process that maintains cellular homeostasis in response to cellular stress. The initiation of autophagosome formation requires the interactions of a subset of at least 18 autophagy related genes (Atg) (Feng et al., 2014). During growth plate development, autophagy regulates the maturation and the hypertrophy of chondrocytes (Shapiro et al., 2014). Autophagy is protective in articular cartilage and mice lacking Atg5 in chondrocytes develop age-related osteoarthritis (Bouderlique et al., 2016).

Genome-wide association studies have identified potential links between autophagy and human stature (Pan et al., 2010). Targeted genetic ablations of autophagy-related genes, *Atg5* or *Atg7,* in chondrocytes results in mild growth retardation with reduced chondrocyte proliferation (Vuppalapati et al., 2015) and impairment of the secretion of collagen type 2, a major component of the cartilage extracellular matrix (Cinque et al., 2015).

A role for autophagy in FGF-regulation of chondrogenesis has recently been identified by several groups. Mice haploinsufficient or null for *Fgf18* exhibited a low level of autophagy in chondrocytes resulting in decreased levels of Col2 in the growth plate (Cinque et al.,

2015). Interestingly, this phenotype was attributed to signaling through FGFR4 rather than FGFR3. In contrast, Wang et al. showed that mice lacking *Fgfr3* in growth plate chondrocytes had increased autophagy and mice expressing a constitutively active FGFR3 had reduced autophagy (Wang et al., 2015).

Diseases caused by mutations in FGFR3

Achondroplasia

The diagnosis of Ach is usually made at birth and 80% of cases of Ach arise as sporadic mutations in *FGFR3*. Ach is the most frequent form of dwarfism, characterized by short long bones, disproportional shortening of the proximal skeletal segments (rhizomelia), impaired elbow extension, tibial bowing, exaggerated lumbar lordosis, shortening of the vertebral pedicles and narrowing of the lumbar interpedicular distance, shortening of the femoral head, macrocephaly, midface hypoplasia, frontal bossing, hearing loss and a reduced size of the foramen magnum (Figure 3) (Horton et al., 2007; Baujat et al., 2008). Ach can also include partial premature fusion of the coronal and sagittal sutures, suggesting a role for FGFR3 in membranous ossification (Twigg et al., 2009; Di Rocco et al., 2014). Ach is a progressive disease and the severity of the phenotype is correlated with age. For example, with age, there is progressive disorganization of the skeletal growth plate (Legeai-Mallet et al., 2004). Bone age (a assessment of skeletal maturation based on comparisons of radiographs of the wrist, hand, and fingers with standardized radiographs) is delayed in the newborn Ach patient; however, during adolescence bone maturation accelerates and the bone age approaches the chronological age (Pannier et al., 2010). Ach patients have a significant kyphosis that leads to a progressive deformity. With age, Ach patients develop an excessive lumbar lordosis. A major complication, narrowing of the spinal canal due to degenerative changes of the spinal canal, can lead to nerve root compression and often requires surgical decompression (Baujat et al., 2008).

The Ach gene locus was mapped to *FGFR3* in 1994 (Le Merrer et al., 1994; Velinov et al., 1994). Over 97% of cases result from an autosomal dominant missense mutation (p.Gly380Arg) localized in the transmembrane domain of FGFR3 (Figure 4) (Shiang et al., 1994; Wilkin et al., 1998; Vajo et al., 2000). Ach patients that do not have a p.Gly380Arg mutation are usually found to have other less common *FGFR3* mutations such as p.Ser217Cys, Ser279Cys, p.Ser344Cys and p.Gly375Cys (Superti-Furga et al., 1995; Zhang et al., 2007; Xue et al., 2014; Takagi et al., 2015). These less common mutations in *FGFR3,* that add a cysteine residue, are likely to result in constitutive receptor activation, similar to that seen in TDI; however, their mechanism of action will need to be further investigated. Ach mutations show a penetrance of 100 percent. Rare homozygous cases of Ach are lethal with phenotypes resembling that of TD (Stanescu et al., 1990; Tavormina et al., 1995).

Mutation analysis of Ach patients showed that nearly all mutations arise on the paternal chromosome. The paternal origin of Ach mutations in *FGFR3* correlates with advanced paternal age in all cases examined (Wilkin et al., 1998). The paternal origin of activating mutations in FGF receptors is attributed to positive selection and clonal expansion of spermatogonial stem cells with age (Goriely and Wilkie, 2012; Shinde et al., 2013).

Mutations causing Ach result in activation of FGFR3 and its signaling pathways that can be further enhanced in the presence of FGF ligands (Naski et al., 1996; Webster and Donoghue, 1996; Komla-Ebri et al., 2016). Increased activity may result from impaired receptor internalization and degradation (Monsonego-Ornan et al., 2000; Cho et al., 2004). Biochemical analysis shows that the Ach mutations increase the efficiency of receptor phosphorylation in the absence of ligand (He et al., 2012). Ach phenotypes have been modeled in mice by expressing the mutant *Fgfr3* in chondrocytes or directly introducing Ach mutations into the *Fgfr3* gene (Naski et al., 1998; Chen et al., 1999; Wang et al., 1999; Pannier et al., 2009a).

Thanatophoric Dysplasia type I and II

Thanatophoric Dysplasia type I and II (TDI and TDII) are sporadic more severe forms of dwarfism that are usually lethal. TD is characterized by short limbs (Figure 3), narrow thorax with short ribs, macrocephaly, and brain malformation with temporal lobe enlargement (Rousseau et al., 1995; Tavormina et al., 1995). The radiologic features that distinguish TDII are the frequent observation of straight femurs and a cloverleaf skull.

TDI and TDII are attributed to various mutations in *FGFR3* (Figure 4). The most frequent (75%) TDI missense mutations introduce a cysteine residue in the extracellular (p.Arg248Cys, p.Ser249Cys) or transmembrane (p.Tyr373Cys, p.Gly370Cys) domain of the receptor. Less commonly, mutations that introduce a stop codon (p.X807Ser, X807Arg, X807Cys) have been observed in 20% of case of TDI (Rousseau et al., 1995). TDII results from a *FGFR3* mutation (p.Lys650Glu) localized in the tyrosine kinase domain of the receptor. Both TDI and TDII mutations result in ligand-independent constitutive activation of the receptor (Naski et al., 1996); however, only the TDII mutation impedes complete maturation of FGFR3 and induces premature phosphorylation of the receptor (Lievens and Liboi, 2003; Gibbs and Legeai-Mallet, 2007). Analysis of downstream signaling showed that the TDI mutation strongly activates ERK1/2 and STAT1 (Legeai-Mallet et al., 2004; Krejci et al., 2008). Mouse models expressing TDI and TDII mutations all display a severe dwarf phenotype (Li et al., 1999; Iwata et al., 2001; Pannier et al., 2009b).

Hypochondroplasia

Hypochondroplasia (Hch) is a relatively mild form of dwarfism that shares many phenotypic features with Ach. Most cases of Hch develop as *de novo* mutations in the *FGFR3* gene, but in some cases there is a positive family history for this condition. In the sporadic cases, the diagnosis of this milder form of dwarfism is frequently not made at birth but later during childhood when an inflection in the growth curve is observed. Hch is caused by the *FGFR3* missense mutation, p.Asn540Lys, localized in tyrosine kinase domain I and is the most common Hch mutation, occurring in ~60% of cases (Figure 4). Other less common missense mutations have been identified in the tyrosine kinase domain II of FGFR3 (e.g. p.Lys650Asn) (Bellus et al., 1995; Tavormina et al., 1995; Bonaventure et al., 1996; Bellus et al., 2000) and in the extracellular domain (Heuertz et al., 2006). *In vitro* analyses of the p.Lys650Asn mutation showed weak activation of the FGFR3 kinase domain (Lievens et al., 2004; Gibbs and Legeai-Mallet, 2007). Analysis of the p.Asn540Lys mutation showed activation of ERK1/2 but not STAT1 (Krejci et al., 2008).

SADDAN syndrome and Platyspondylic lethal skeletal dysplasia, San Diego type (PLSD-SD)

Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans (SADDAN) and Platyspondylic Lethal Skeletal Dysplasia, San Diego Type (PLSD-SD) are very rare lethal chondrodysplasias that are accompanied by acanthosis nigricans (hyperpigmentation and thickening of the skin), and brain malformations. These syndromes and classical TDI are all caused by a p.Lys650Met mutation in FGFR3 (Figure 4) (Bellus et al., 1999; Brodie et al., 1999; Tavormina et al., 1999; Farmakis et al., 2015). Analysis of the p.Lys650Met mutation showed strong activation of ERK1/2 and STAT1 (Krejci et al., 2008). A mouse model expressing the SADDAN mutation displays a phenotype similar to the human pathology in SADDAN syndrome (Iwata et al., 2001).

Proportionate short stature

A dominant mutation (p.Met528Ile) that causes proportionate short stature (PSS) was identified in *FGFR3* (Figure 4) (Kant et al., 2015). Functional studies suggest that this mutation is activating, similar to that of the p.Gly380Arg mutation that causes Ach; however, the mechanisms that determine proportionate vs. rhizomelic limb shortening are not known.

Patients with tall stature

Rare pathogenic FGFR3 mutations cause tall stature. CATSHL (camptodactyly, tall stature, and hearing loss) syndrome results from a dominant *FGFR3* loss of function mutation (p.Arg621His) (Figure 4). These patients are characterized by skeletal overgrowth, sensorineural hearing loss and microcephaly (Toydemir et al., 2006; Makrythanasis et al., 2014; Escobar et al., 2016). It is hypothesized that this mutation results in loss of function or expression of a dominant negative protein. A rare recessive FGFR3 loss of function mutation (p.Thr546Lys) was also reported in patients that exhibited tall stature, microcephaly, moderate hearing loss and intellectual disability (Makrythanasis et al., 2014).

These phenotypes are consitent with those of mice that lack *Fgfr3*, which show skeletal overgrowth (Colvin et al., 1996; Deng et al., 1996; Eswarakumar and Schlessinger, 2007) and deafness (Colvin et al., 1996), and sheep with a recessive mutation in FGFR3 (p.Val700Glu) that results in spider lamb syndrome (SLS), characterized by long limbs, kyphoscoliosis, malformed ribs and sternebrae, Roman nose, lack of body fat, and muscular atrophy (Beever et al., 2006). Heterozygous sheep with this mutation show mild increased skeletal growth (Smith et al., 2006).

Craniosynostosis and hearing loss associated with FGFR3 mutations

Pathogenic dominant *FGFR3* mutations also cause craniosynostosis (premature fusion of cranial sutures). Muenke syndrome (MS) is the most common craniosynostosis syndrome (Sabatino et al., 2004). This autosomal dominant disorder is characterized by premature fusion of the coronal sutures, hearing loss, developmental delay and intellectual disability (Kruszka et al., 2016). Muenke syndrome is caused by a missense mutation (p.Pro250Arg) localized in the extracellular domain of *FGFR3* in the linker between immunoglobulin-like domains II and III (Figure 4) (Bellus et al., 1996; Gripp et al., 1998). Interestingly, this

mutation changes the specificity of both the FGFR3b and FGFR3c splice variants, allowing activation by FGF10 (Mansour et al., 2013). This is similar to the effects of corresponding mutations in FGFR2c that cause Apert syndrome (Yu et al., 2000). Paternal origin associated with advanced paternal age is also reported in Muenke syndrome (Rannan-Eliya et al., 2004). Mouse models with the p.Pro244Arg mutation also display craniosynostosis and hearing loss (Mansour et al., 2009; Twigg et al., 2009; Laurita et al., 2011; Nah et al., 2012; Mansour et al., 2013).

Crouzon syndrome associated with acanthosis nigricans (CAN) is a rare syndrome characterized by craniosynostoses, ocular ptosis, midface hypoplasia and hyperkeratosis, and hyperpigmentation of the skin. Patients with this syndrome carry a dominant missense mutation (p.Ala391Glu) in *FGFR3* (Meyers et al., 1995; Wilkes et al., 1996). This mutation is localized in the transmembrane domain of the receptor distal to the recurrent Ach mutation (p.Gly380Arg). Differences in phenotypes (craniosynostoses vs chondrodysplasia) of the p.Ala391Glu and p.Gly380Arg mutations may be attributed to relative increased formation of FGFR3 heterodimers with the p.Ala391Glu mutation (He et al., 2011).

Therapeutic approaches

In 1994, the chondrodysplasia research field made significant progress with the discovery that activating mutations in the *FGFR3* gene are the etiology of a broad clinical spectrum of chondrodysplasias, including Hch, Ach, SADDAN and TD. Potential therapeutic approaches to treat these conditions have been emerging over the past decade. To be effective, therapies for Ach need to be administered within a time window extending from birth to puberty (Figure 5A).

Surgical approaches

Surgical intervention is a common form of therapy for both proportional and disproportional dwarfism (e.g. Ach, Hch). Surgical limb lengthening classically uses the Ilizerov procedure in which cortical long bones are cut (osteotomy), external fixators are placed proximal and distal to the osteotomy and distraction is applied gradually over many months to extend bone length (Paley, 1988; Schiedel and Rodl, 2012). The average length gained is ~20.5 cm after multiple procedures (applied to the femurs and tibias) (Kim et al., 2014; Donaldson et al., 2015). This surgical treatment allows functional gains and quality of life improvements. However, this procedure is painful and is associated with complications that include infection, muscle contractures, and increased risk of fracture (Paley, 1990; Donaldson et al., 2015). Recent innovations, such as the use of intramedullary fixation (Figure 5B), may improve outcome and lessen risk (Paley, 2015). Limb lengthening, involving the surgical breaking of a bone, fixation, and distraction during the healing process remains controversial and is associated with a high degree of risk. A pre-operative psychological assessment is required before surgery to evaluate the high risk of complications vs. the improvement of short stature. In the future, the combination of surgical limb lengthening with pharmacological strategies (see below) could further improve outcomes.

Approaches to treat Hypochondroplasia

The primary therapies that are proposed to patients with Hch include treatment with recombinant human growth hormone (r-hGH) or surgical intervention (see surgical approaches section) (Tanaka et al., 2003; Kim et al., 2014; Burghardt et al., 2015; Massart et al., 2015). R-hGH is indicated for the treatment of short stature in children with other skeletal dysplasias, such as Léri-Weill dyschondrosteosis and Idiopathic Short Stature, which are associated with mutations in the *SHOX* gene (Fukami et al., 2016). In clinical trials, treatment with r-hGH improved growth velocity in these patients (Blum et al., 2007; Blum et al., 2013). R-hGH therapy is also effective for Hch patients and the benefits of this treatment are reported in many studies (Ramaswami et al., 1998; Tanaka et al., 2003). R-hGH is well tolerated and effective in improving growth in Hch patients, particularly when started early (Pinto et al., 2014; Massart et al., 2015). The mechanism of action of r-hGH does not directly act on FGFR3 signaling pathways; rather, r-hGH stimulates the growth of the cartilage through its pro-anabolic properties (Figure 5C-7) (Wang et al., 2004). Additional studies are necessary to establish safety of r-hGH and its benefits to achieving adult height and body proportion.

Approaches to treat Achondroplasia

Treatment of the developmental complications of Ach involves symptomatic management, surgical intervention, and lifelong follow-up care. Health problems commonly associated with Ach include: cervico medullary compression, which can present in the first few months of life due to a reduced size of the foramen magnum; recurrent otitis media, which is common in young patients and needs to be treated to prevent conductive hearing loss; restrictive respiratory insufficiency, due to small chest size; and in adults, lumbar spinal compression (Figure 3).

To treat the short stature and the impairment of linear growth, several surgical procedures (described above) have been used, and nonsurgical strategies are being evaluated. The first therapeutic strategy offered to Ach patients was treatment with r-hGH. An increase in growth (height) velocity was reported following short term r-hGH treatment, but no clear benefit was established for long term treatment (Miccoli et al., 2016). However, the effect on body proportion is still unknown and currently the use of r-hGH to treat Ach is not routinely recommended. Current pharmacological approaches are aimed at directly blocking FGFR3 activation or regulating other signaling pathways that control chondrocyte proliferation and differentiation.

Therapies aimed at FGFR3 signaling

Many nonsurgical strategies aimed at reducing excessive activation of FGFR3 have been proposed to stimulate linear bone growth in Ach. Many strategies have been borrowed conceptually from the oncological field, which is not surprising because the genetic lesions leading to FGFR3-related skeletal disorders are identical to those found in FGFR3-driven cancers (e.g. bladder tumors, multiple myeloma) (Chesi et al., 1997; Cappellen et al., 1999; Turner and Grose, 2010; Patani et al., 2016). Several studies have focused on FGFR-selective small molecule tyrosine kinase inhibitors (TKI) to directly reduce the high tyrosine kinase activity resulting from mutations in *FGFR3* (Figure 5C-3). Therapeutic efficacy of

the TKI CHIR-258 was demonstrated in a xenograft mouse model of FGFR3-induced multiple myeloma (MM) (Trudel et al., 2005) and A31 was effective in increasing the growth of femur explants from FGFR3(p.Tyr367Cys) mutant mice (Jonquoy et al., 2012). Two other FGFR TKIs, PD173074 and SU5402, are also able to inhibit the growth and induce apoptosis of MM cells. However, these TKIs are not selective for FGFR3 (Mohammadi et al., 1997; Dimitroff et al., 1999). Recently, NVP-BGJ398, a TKI more selective for FGFR3 over others FGFRs (Gudernova et al., 2016) was used in preclinical murine models for treating several FGFR-related cancers such as malignant rhabdoid tumors (Wohrle et al., 2013b), hepatocellular carcinoma (Scheller et al., 2015) and skeletal disorders including FGF23-mediated hypophosphatemic rickets (Wohrle et al., 2013a) and Ach (Komla-Ebri et al., 2016). Importantly, NVP-BGJ398 was shown *in vivo* to reduce FGFR3(p.Tyr367Cys) activation and improve the skeletal phenotype of Ach-like mice (Komla-Ebri et al., 2016). Following safety and pharmacokinetic studies, this compound may be appropriate for evaluation in clinical trials with Ach patients.

Another approach to inhibit FGFR3 consists of using monoclonal antibodies to target the extracellular part of the receptor to block ligand binding or to use soluble decoy receptors which can bind and sequester FGF ligands, preventing them from interacting with endogenous receptors (Figure 5C-2). Several studies demonstrated that FGFR3-specific monoclonal antibodies were highly efficient in slowing the growth of various bladder cancer cell lines and were able to reduce the growth of FGFR3-dependent tumors in mice and FGFR3-expressing tumor xenografts (Rauchenberger et al., 2003; Martinez-Torrecuadrada et al., 2005; Trudel et al., 2006; Gorbenko et al., 2009; Qing et al., 2009; Gust et al., 2013; Yin et al., 2016). FGFR3-specific monoclonal antibodies have not yet been evaluated *in vivo* in mouse models for Ach.

Soluble FGFR3 extracellular domain decoy receptors (sFGFR3) were recently designed with the objective of binding and sequestering available FGF to compete with endogenous FGFR3 binding to FGF ligands that functionally regulate chondrogenesis (Figure 5C-1) (Liu et al., 2002; Ohbayashi et al., 2002; Hung et al., 2007; Liu et al., 2007; Garcia et al., 2013). Subcutaneous injections of recombinant sFGFR3 into a transgenic mouse model for Ach (*Col2a1* promoter driving expression of FGFR3(p.Gly380Arg), $Fgfr3^{Ach/+}$ mice) (Naski et al., 1998), was found to decrease mortality and improve skeletal growth (Garcia et al., 2013).

Targeting non-FGF signaling pathways that control chondrocyte proliferation and differentiation

Many signaling molecules and transcription factors are involved during growth plate development and maturation stages (Figure 2). In Ach, the balance between chondrocyte proliferation and differentiation is severely disrupted. Among the factors playing a crucial role, PTH/PTHrP (PTHLH) is a well-studied regulator of growth plate chondrocyte proliferation and differentiation (Figure 5C-6). To correct the proliferation and differentiation defect in Ach, systemic intermittent PTH (1-34) injections were administered to $Fgfr3^{K544E/+}$ mice. These pre-clinical studies showed rescue of the retarded skeletal development in these mice (Xie et al., 2012). However, clinical use of PTH (1-34) (Teriparatide) is limited to two years in humans for treatment of osteoporosis (Hodsman et

al., 2005). Use of Teriparatide humans to treat Ach will require long-term administration and thus new clinical trials to evaluate safety and efficacy.

Recently, others strategies have emerged using drugs currently used for non-skeletal disorders. The first example is Meclozine, an over the-counter H1 receptor inhibitor used to treat motion sickness. In various cell lines, Meclozine is able to promote chondrocyte proliferation and differentiation and attenuate ERK1/2 phosphorylation (Figure 5C-5) (Matsushita et al., 2013). In *ex vivo* culture, Meclozine increases longitudinal growth of embryonic normal and $Fgfr3^{Ach/+}$ tibiae explants. Oral administration of Meclozine to $Fgfr3^{Ach/+}$ mice increased longitudinal bone growth but failed to increase the size of the foramen magnum and lumbar spinal canal (Matsushita et al., 2015). Future studies will require histological analyses of the growth plate to confirm rescue of the growth plate defect. A second example is statins, a class of cholesterol-lowering drugs (Figure 5C-8). Addition of statins to culture media rescued the defective chondrogenesis seen in chondrocytes derived from induced pluripotent stem cells (iPS) from Ach patients, and corrected the skeletal phenotype of $Fgfr3^{Ach/+}$ mice *in vivo* (Yamashita et al., 2014). However, controversy remains regarding the use of statins as a therapeutic approach for Ach, as recent studies showed that statin treatment retarded cartilage development and reduced the expression of the principal regulators of growth plate cartilage (Wu and De Luca, 2004; Woods et al., 2009). The mechanism by which statins could modify bone growth in Ach needs further investigation (Bush et al., 2015).

C-type natriuretic peptide

The most promising therapy thus far for treatment of Ach is the use of a stabilized form of C-type natriuretic peptide (CNP) called BMN-111 (Lorget et al., 2012; Wendt et al., 2015). CNP and its receptor, natriuretic peptide receptor B (*Npr2,* guanylyl cyclase B) are recognized as important regulators of longitudinal bone growth (Chusho et al., 2001). Loss-of-function mutations in *Npr2* are responsible for acromesomelic dysplasia Maroteaux type, a disproportionate dwarfism in humans (Bartels et al., 2004) and heterozygous inactivating mutations in *Npr2* are associated with short stature (Olney et al., 2006). Mutant mice with a disruption of CNP ($Nppc^{-/-}$) also show disproportionate dwarfism with short limbs (Chusho et al., 2001). Conversely, tall stature has been reported in a patient heterozygous for an activating NPR2 mutation (Hannema et al., 2013) and skeletal overgrowth has been observed in patients that overexpress CNP caused by a balanced translocation (Bocciardi et al., 2007; Moncla et al., 2007). The same phenotype was reported in transgenic mice overexpressing brain natriuretic peptide (BNP) (Suda et al., 1998). Interestingly, CNP over-expression in cartilage or continuous delivery of CNP through intravenous infusion normalizes the dwarfism of $Fgfr3^{Ach/+}$ mice (Yasoda et al., 2004; Yasoda et al., 2009), suggesting that CNP administration is a potential strategy to treat Ach.

CNP signals through NPR2 in chondrocytes and inhibits the MAPK signaling pathway at the level of RAF1 (Figure 5C-4) (Yasoda et al., 2004; Krejci et al., 2005; Geister et al., 2013). The role of the MAPK pathway in mediating FGFR3 activity is illustrated by the dwarfism of mice with constitutive activation of extracellular signal regulated kinases 1 (ERK1/MEK1) and conversely by the overgrowth of long bones of mice with ERK1/2 inactivation

(Sebastian et al., 2011). Several studies have attempted to explain the signaling cascades triggered by CNP in the growth plate. NPR2/CNP-induced cGMP activates cyclic GMP-dependent protein kinase II (cGKII, encoded by *PRKG2*) and p38 (*MAPK14*). *MAPK14* functionally antagonizes RAF1 activation of MEK (*MAP2K1*), which is a critical pathway that regulates chondrocyte hypertrophy (Murakami et al., 2004; Ozasa et al., 2005; Agoston et al., 2007; Hutchison, 2012; Peake et al., 2014). Signaling by FGF ligands through FGFR3 is functionally antagonized by CNP (BMN-111) signaling through NPR2, which decreases ERK1/2 phosphorylation in human chondrocytes and enhances the rate of chondrocyte hypertrophy and skeletal growth in a mouse model of Ach (*Fgfr3*$^{Y367C/+}$) (Lorget et al., 2012). The putative hemodynamic effects of BMN-111 were tested in normal juvenile cynomolgus monkeys. Echocardiographic parameters were unaffected at any dose of BMN-111, and there were no clinical signs of hypotension or distress at any time during the treatment (Wendt et al., 2015). A phase 2 clinical trial with BMN-111 (Vosoritide) is currently underway for the treatment of Ach (https://clinicaltrials.gov/ct2/show/NCT02055157).

Conclusion and future directions

Considerable progress has been made during the past twenty years in understanding FGFR3-related disorders as well in developing a rationale for effective therapeutic strategies to treat FGFR3-associated bone growth defects. Although there has been some success in developing therapies, a clear challenge for the future will be to further improve the care and treatment of children and adults with Ach. As reviewed here, there are several novel therapeutic strategies that need to be considered in the future. Additionally, it will be important to investigate the potential for synergy of two or more pharmacological inhibitors of FGFR3 and its signaling pathways, which could lead to more effective treatments for Ach patients. Progress in developing therapies for Ach will also contribute to the treatment of other diseases such as cancer (multiple myeloma, lung adenocarcinoma, bladder, gastric, colorectal cancers), ostheoarthitis, and aging that result from activation of FGF signaling pathways.

Further analyses and understanding of FGFR3 downstream signaling pathways in the growth plate, of mechanisms that regulate communication between cortical and trabecular bone and the growth plate, and mechanisms by which endocrine signals interact with FGFR3 signaling pathways will likely lead to additional therapeutic strategies. Finally, studies of the role of FGFR3 in extra skeletal tissue (e.g. heart, inner ear, lung) could explain some of the clinical features associated with mutations in *FGFR3* and will need to be considered during clinical trials for Ach.

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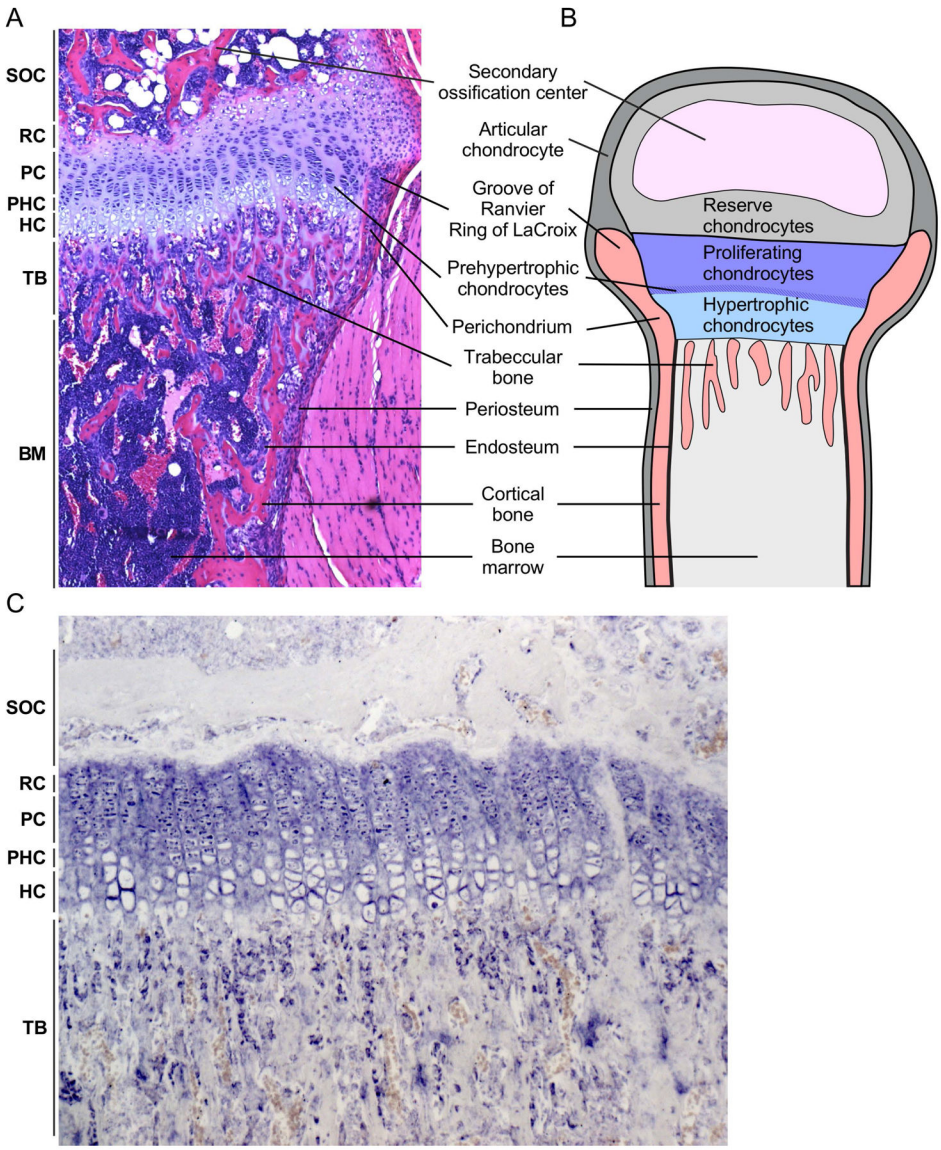


Figure 1. Histological organization of the postnatal growth plate

A. Histological section of the mouse proximal tibia showing growth plate chondrocytes at different stages of differentiation (resting, proliferating, prehypertrophic, and hypertrophic), perichondrium, and trabecular and cortical bone. B. Schematic of the postnatal growth plate showing progression of chondrocyte development and juxtaposition to trabecular and cortical bone, the groove of Ranvier and ring of LaCroix, and the secondary ossification center. C. *Fgfr3* expression (*in situ* hybridization) in proliferating and prehypertrophic chondrocytes and trabecular osteoblasts in a 21-day-old mouse tibia (image courtesy of K. Karuppaiah). SOC, secondary ossification center; RC, Reserve chondrocyte zone; PC, Proliferating chondrocyte zone; PHC, Prehypertrophic chondrocyte zone; HC, Hypertrophic chondrocyte zone; TB, trabecular bone.

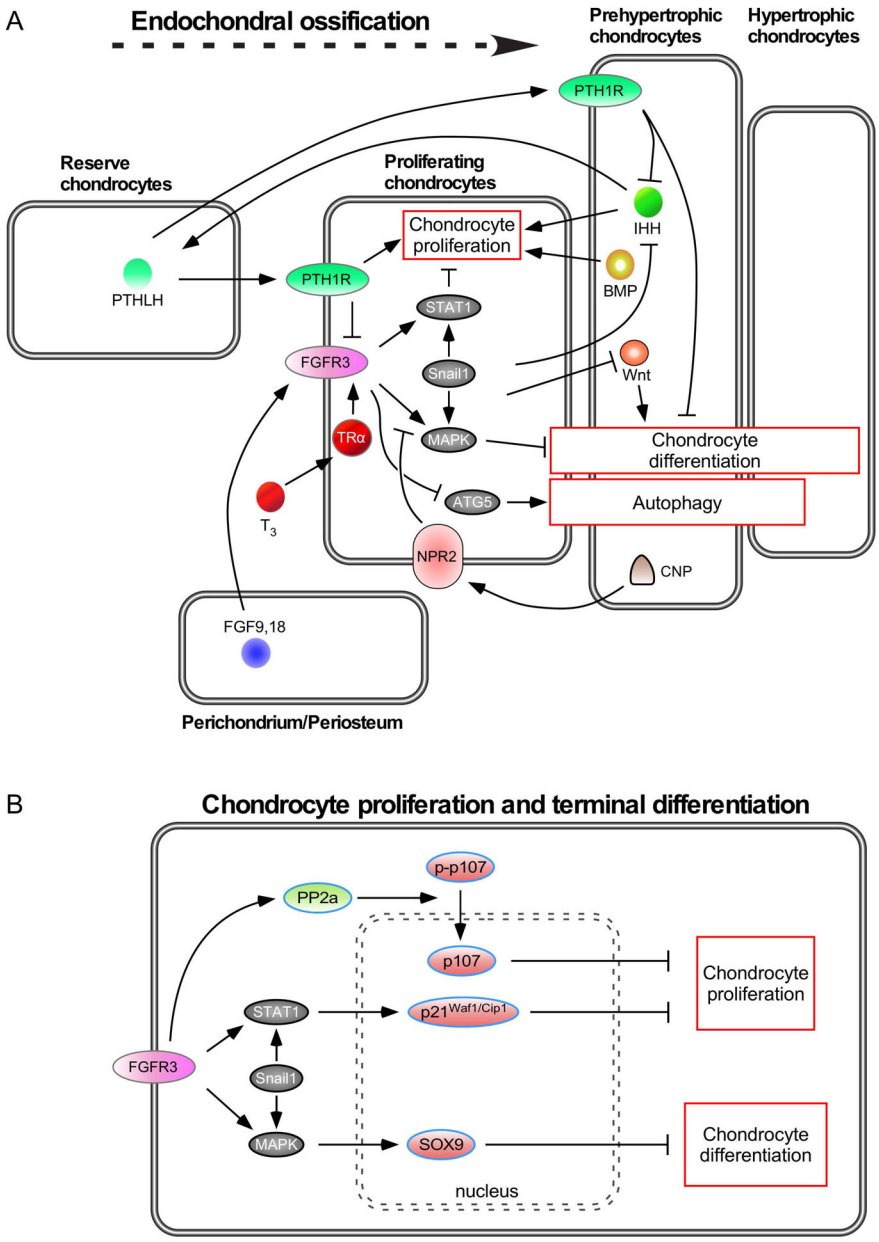


Figure 2. Signaling pathways in the postnatal growth plate

A. During endochondral bone development, FGF9 and FGF18, derived from the perichondrium and surrounding tissue, signal to FGFR3 in chondrocytes. The balance of chondrocyte proliferation and differentiation is controlled by crosstalk of several signaling pathways. Expression of FGFR3 is enhanced by thyroid hormone (T_3) and suppressed by PTHLH. FGFR3 signaling results in increased expression of Snail1, which is required for activation of STAT1 and MAPK signaling. Signaling from PTHLH, IHH and BMPs antagonizes the suppression of chondrocyte proliferation by FGFR3. Both FGFR3 and PTHLH function to suppress chondrocyte differentiation and antagonize the action of Wnt signaling, which promotes differentiation. FGFR3 negatively regulates the autophagy

protein, ATG5. B. Activation of downstream signals, PP2a and STAT1, regulate p107, $p21^{Waf1/Cip1}$ activation, respectively, which function to suppress chondrocyte proliferation. Activation of the MAPKs, ERK1 and ERK2, regulate Sox9 expression, which functions to suppress chondrocyte terminal differentiation and endochondral ossification.

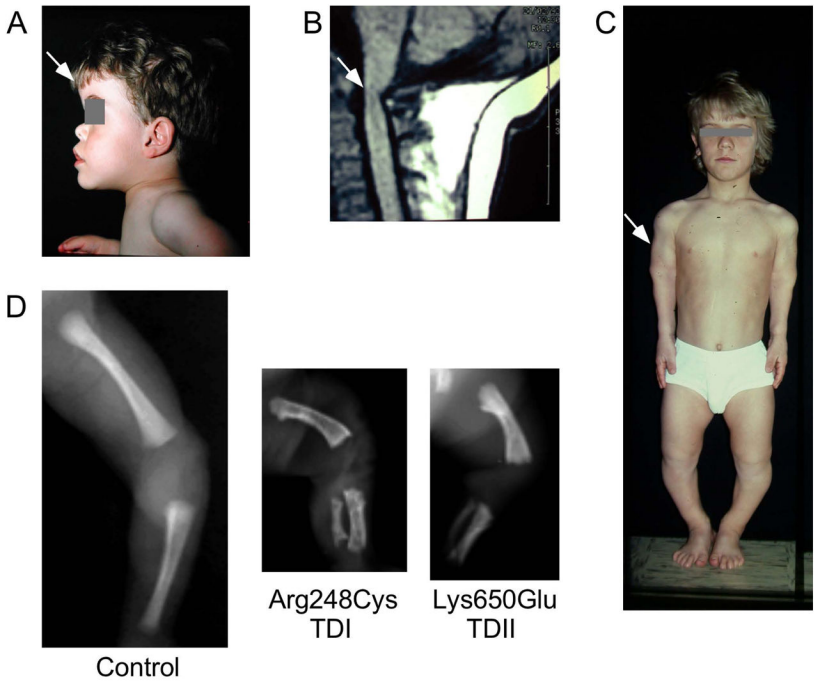
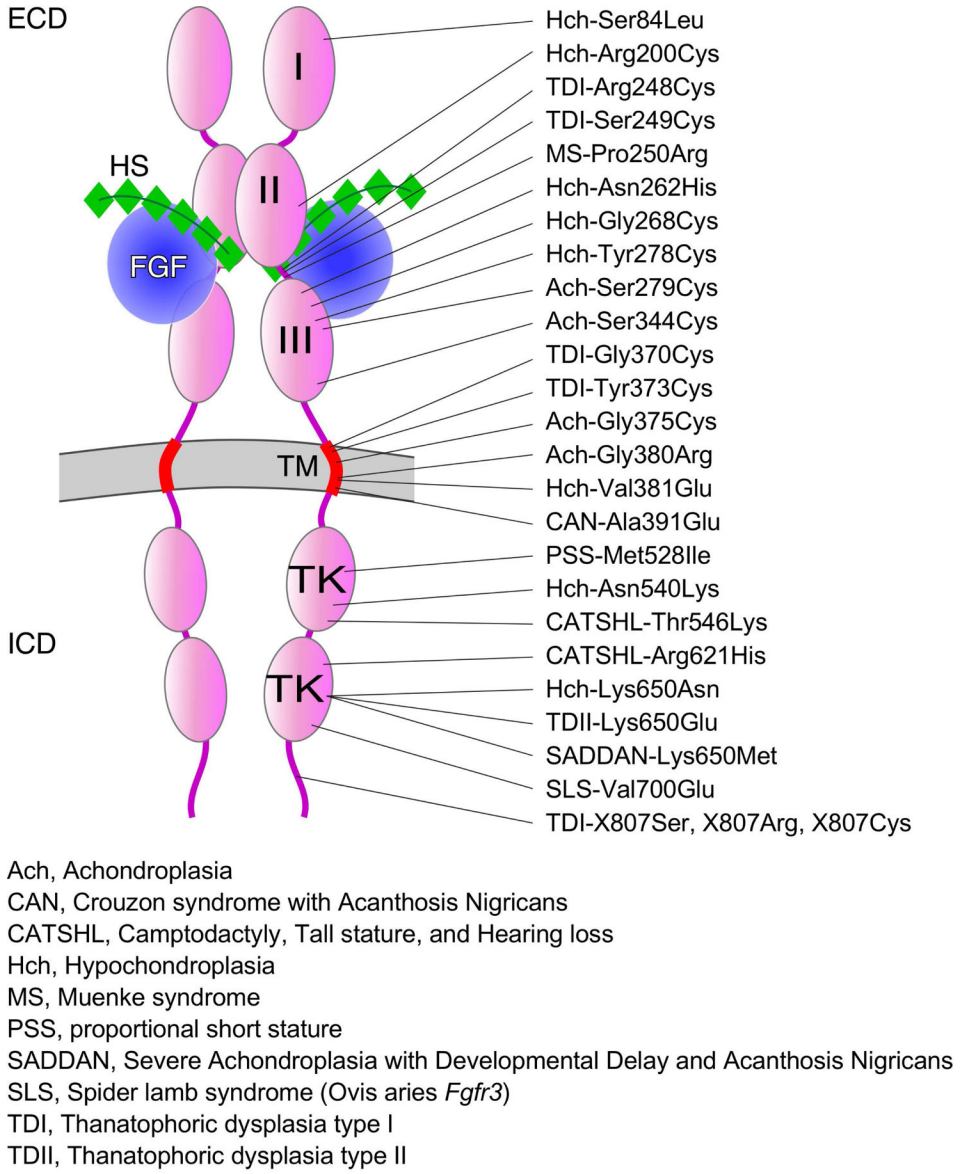


Figure 3. Clinical features of skeletal disorders resulting from activating mutations in *FGFR3*

A. The head of a patient with Ach is characterized by macrocephaly, frontal bossing (arrow), and hypoplasia of the midface. B. MRI (magnetic resonance imaging) showing the cervicomedullary compression at the foramen magnum (arrow). C. Rhizomelic short stature (arrow) of a patient with Ach (image courtesy of Dr. G. Finidori). D. X-rays of the lower limb (femur and tibia) of a 24 week-old normal fetus (control) and fetuses with TDI (p.Arg248Cyst) and TDII (p.Lys650Glu) *FGFR3* mutations. Note the short and curved femur compared to the age-matched control.



Ach, Achondroplasia
CAN, Crouzon syndrome with Acanthosis Nigricans
CATSHL, Camptodactyly, Tall stature, and Hearing loss
Hch, Hypochondroplasia
MS, Muenke syndrome
PSS, proportional short stature
SADDAN, Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans
SLS, Spider lamb syndrome (Ovis aries *Fgfr3*)
TDI, Thanatophoric dysplasia type I
TDII, Thanatophoric dysplasia type II

Figure 4. The mutational spectrum of *FGFR3*

The relative location of gain-of-function and loss-of-function mutations causing genetic skeletal disease in humans is shown distributed over the entire FGFR3 coding region. Abbreviations for different types of genetic diseases are shown. FGF ligands are shown in blue and heparan sulfate co-factors are shown in green. Some of the mutations in *FGFR3* change the affinity or specificity of the receptor for different FGF ligands, while others affect tyrosine kinase activity or receptor internalization and degradation. ECD, extracellular domain; ICD, intracellular domain; HS, heparan sulfate; I, II, III, immunoglobulin-like domains; TK, tyrosine kinase domains; TM, transmembrane domain (red).

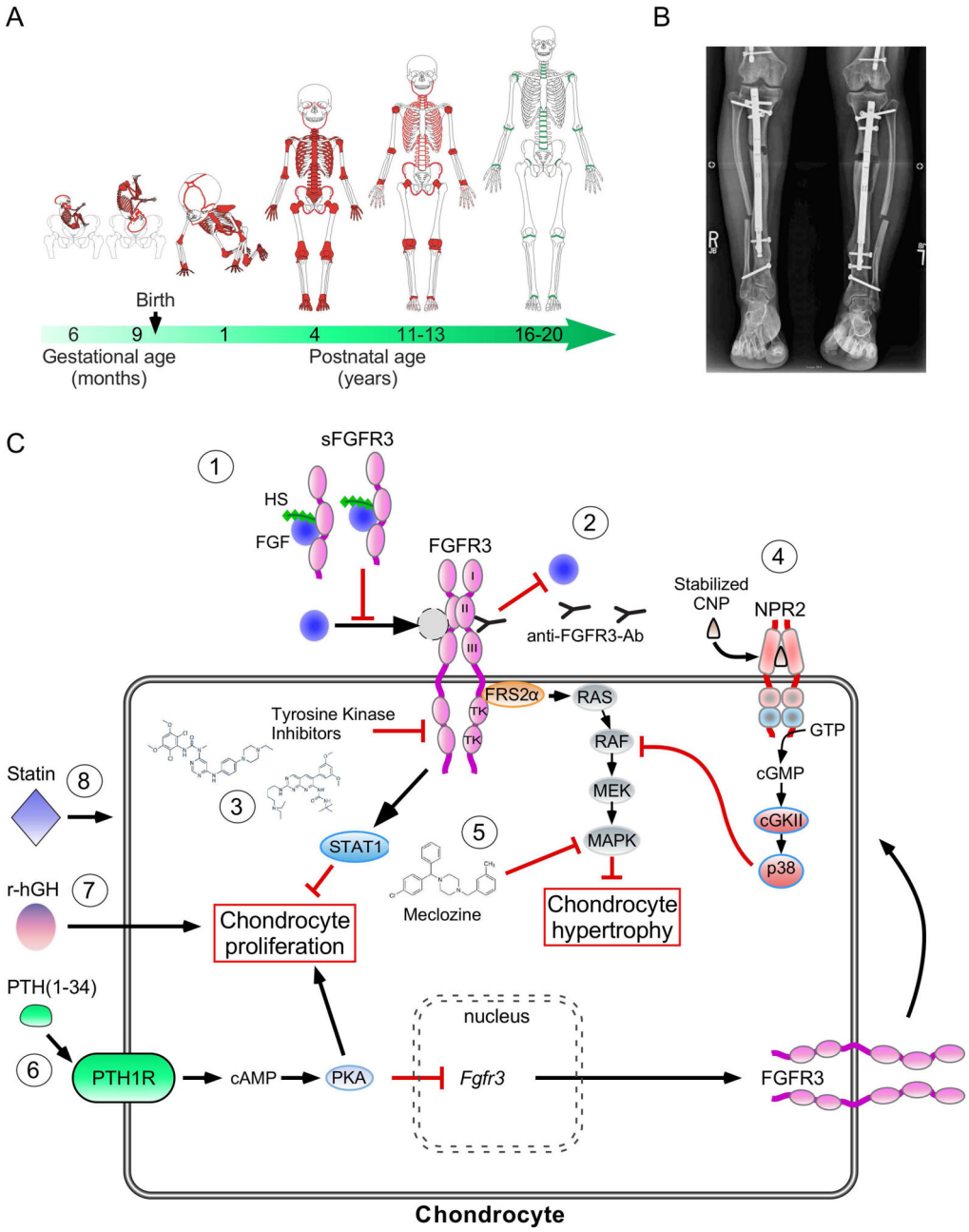


Figure 5. Therapeutic approaches for FGFR3-related disorders

A. Schematic representation of key milestones in bone and growth plate activity during skeletal development. The location of the active growth plates and bone sutures are shown in red, according to age. As skeletal development progresses, growth plates and skull sutures fuse (green). B. Tibia intramedullary lengthening in sixteen-year-old girl with Ach using the PRECICE system (image courtesy of Dr. D. Paley). C. Schematic representation of therapeutic approaches for Ach that are currently being evaluated. 1) Soluble FGFR3 bind and sequester FGF ligands, 2) Anti-FGFR3 antibodies block ligand binding to the receptor and subsequent downstream signaling pathways. 3) Tyrosine kinase inhibitors block receptor

phosphorylation of substrates. 4) Stabilized CNP (BMN-111) antagonizes RAF activation through the activation of the natriuretic peptide receptor 2 (NPR2), *a* guanylyl cyclase. cGMP activates cyclic GMP-dependent protein kinase II (cGKII) and p38 MAPK. 5) Meclozine, an anti-emetic drug, suppresses high ERK1/2 phosphorylation. 6) PTH(1-34) treatment leads to increased chondrocyte proliferation and suppression of *Fgfr3* expression. 7) Indirect effect of r-hGH on bone growth 8) Statin promotes degradation of FGFR3.