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MOLECULAR PATHOGENESIS OF ACHONDROPLASIA

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INTRODUCTION

Achondroplasia (OMIM 100800) is by far the most common chondrodysplasia in humans with an estimated prevalence to be one in 15 000 to 40 000 live births. It is the prototype of short-limbed dwarfism and the archetype of a group of disorders that range from the much more severe thanatophoric dysplasia (TD) to the less severe hypochondroplasia.¹ These disorders share a common qualitative clinical phenotype dominated by short limbs, long trunk, large head with frontal bossing, and midfacial hypoplasia.²

Infants with achondroplasia typically present with mild-to-moderate limb

shortening, moderate craniofacial manifestations, and a lumbar gibbis. These features typically become more noticeable over time. The gibbis usually gives way to a lumbar lordosis, and infants and children with achondroplasia are at risk for spinal cord compression at the foramen magnum, as well as obesity. Average adult height for men with achondroplasia is 131 ± 5.6 cm; for women it is 124 ± 5.9 cm.

Thanatophoric dysplasia is much more severe in general. It is usually lethal in the perinatal period, but on rare occasions infants survive with a poor prognosis. Craniofacial abnormalities are much more dramatic. The thorax appears long but narrow and is associated with severe respiratory distress. Two types of TD (TDI and TDII: OMIM 18700 and 18760) can be distinguished radiographically. SADDAN dysplasia refers to a clinical phenotype

From The Editor's Desk

Dear Colleague:

The latest issue of GGH includes the highlights of 2 important annual meetings in our field. The printed journal contains the highlights of the Endocrine Society's meeting held in June in Boston. The online journal also contains highlights from the European Society of Pediatric Endocrinology meeting held in July in Rotterdam. The lead article by Dr. William A. Horton, "Molecular Pathogenesis of Achondroplasia," elucidates the advances that have occurred in the understanding of the mechanisms of growth alterations of these patients. A look at the future with potential therapeutic considerations adds value to the clarification of the pathophysiology of the disease. Additionally, there are 17 reviews of recent papers that were selected by the Editorial Board. Altogether, the journal will stimulate you and enhance your continuous medical education efforts. I am very pleased to note that we continue to expand the content and size of the e-reviews; for example, this issue contains 11 reviews of papers with editorial comments. As well, new clinical practice guidelines continue to be added to the website. In order to provide more reviews, the index of volume 22 (2006) is now only online. Moreover, all issues and subjects are searchable online.

Finally, it is the time of year that I take the opportunity to wish you all the best for the holiday season and best wishes for the New Year.

Sincerely,
Fima Lifshitz, MD

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intermediate in severity between TD and achondroplasia accompanied by developmental delay and acanthosis nigricans.³ Patients with hypochondroplasia (OMIM 146000) typically present in mid childhood with mild short stature and a stocky build; the craniofacial manifestations may be minimal. Patients with hypochondroplasia blend in to the lower range of normal stature; many go undiagnosed or may be considered idiopathic short stature or be confused with another bone dysplasia.

GENETICS

Achondroplasia was mapped to chromosome 4p16.3 in 1994, and heterozygous mutations of Fibroblast Growth Factor Receptor 3 (*FGFR3*) were identified shortly afterwards.⁴⁻⁶ *FGFR3* mutations were subsequently discovered for the TDs and hypochondroplasia (Figure 1).⁷⁻⁹ Remarkable degrees of genetic homogeneity and genotype:phenotype correlation soon became apparent as virtually all patients with classic achondroplasia were found to have the same Gly380Arg mutation in the transmembrane domain of this tyrosine kinase receptor.^{1,8} Similarly, all infants with TDII had the identical Lys650Glu mutation in the distal kinase domain, whereas an Asn540Lys mutation in the proximal kinase domain was detected in most patients with hypochondroplasia.⁷⁻⁹ Almost all infants with TDI have mutations that introduce free cysteine residues in the proximal extracellular ligand-binding domain of the receptor. Of note is that mutation of lysine 650 can produce 3 different clinical phenotypes: conversion to glutamic acid results in TDII, conversion to methionine causes SADDAN, and conversion to serine leads to hypochondroplasia.^{10,11}

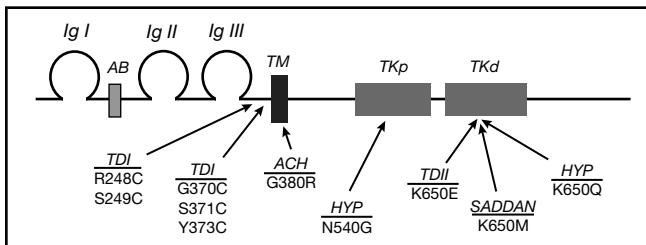


Figure 1. Domain structure of *FGFR3* and major sites of mutations. *Ig*: immunoglobulin, *AB*: acid box, *TM*: transmembrane, *TKp/d*: proximal and distal tyrosine kinase domains, *ACH*: achondroplasia, *HYP*: hypochondroplasia, *TD*: thanatophoric dysplasia, *SADDAN*: severe achondroplasia with developmental delay and acanthosis nigricans.

The penetrance of the achondroplasia mutation is 100%, meaning that individuals with *FGFR3* Gly380Arg mutation have achondroplasia. The vast majority of infants with *FGFR3* mutations are born to parents without *FGFR3* mutations, although there is a strong correlation with advanced paternal age (over 35 years). These findings were initially attributed to increased mutability of *FGFR3* during spermatogenesis. However, recent observations, including the detection of *FGFR3* in all germ cells except for elongated spermatids in adult men and failure to detect sufficiently high mutation rates in sperm from older males, have led to the alternative explanation that

sperm bearing mutant *FGFR3* have a selective advantage over sperm bearing normal *FGFR3* receptors.¹²⁻¹⁴

MOLECULAR PATHOGENESIS

a) Receptors

The *FGFR3* encodes one of 4 closely related FGF receptors (*FGFR1-4*) in mammals.¹⁵ All have an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain that contains a split tyrosine kinase subdomain. The receptors differ in their temporal and spatial distribution of expression. Additional diversity is generated by alternative splicing that influences ligand specificity. Mutations similar to those in *FGFR3* have been observed in *FGFR1* and *FGFR2* in human craniosynostosis syndromes.¹⁶

After initial speculation that achondroplasia mutations cause loss-of-receptor function, it soon became evident they actually result in gain of *FGFR3* function, and the extent of this gain was found to correlate with the severity of the clinical phenotype.¹⁷ The most compelling evidence came from genetic engineering experiments in mice in whom *FGFR3* was either inactivated or the receptor activated in cartilage by introducing achondroplasia or TD mutations, or by overexpressing ligands that activate *FGFR3*.¹⁸⁻²³ Mice in whom *FGFR3* was inactivated had long bones, while mice with excess *FGFR3* activation had short bones. Accordingly, *FGFR3* mutations associated with achondroplasia are often referred to as activating mutations.

Of interest is the fact that functions which are gained by activating mutations differ, depending on the cell type in which the *FGFR3* receptor is expressed. For instance, *FGFR3* activation promotes mitosis and blocks differentiation in many non-chondrocytic cell types. In fact, activating TD mutations have been found in colon and bladder carcinoma and multiple myeloma, as well as in benign adenoid seborrhic keratoses.²⁴⁻²⁷ In growth plate chondrocytes, however, activation of *FGFR3* has the opposite effect as discussed below.

b) Dimerization

The binding of FGF ligands to *FGFR3* monomers leads to receptor dimerization. Which of the 22 known FGFs is (are) the physiologic ligand(s) for *FGFR3* is (are) not known, although FGFs 2, 4, 9 and 18 are probably the best candidates based on the distribution of expression and ability to bind and activate *FGFR3* in *in vitro* assays.^{28,29} It is also conceivable that different FGF ligands activate *FGFR3* in different physiologic situations. Heparin sulfate-bearing proteoglycans on the cell surface, such as syndecans, as well as alternative splicing of ligand-binding subdomains, influence binding specificity.³⁰⁻³²

Dimerization activates the intrinsic tyrosine kinase activity of the receptor and promotes transphosphorylation of

key tyrosine residues in the cytoplasmic domain. These residues serve as docking sites for adapter proteins and signal effectors that are recruited to the activated receptors and which propagate FGFR3 signals.³³⁻³⁶

c) Signaling pathways

FGFR3 signals influence a variety of cellular events and processes largely through inducing or repressing expression of target genes in a cell-specific context. Four main signaling pathways have been identified to date to propagate FGFR3 signals: STAT, MAPK, PLC- γ , and PI3K-AKT (signal transducer and activator of transcription 1, mitogen-activated protein kinase, phospholipase C gamma, phosphatidylinositol phosphate-3-kinase-serine/threonine kinase [protein kinase B]) with the first 2 receiving the most attention.^{31,37-42} The most relevant signaling pathways are illustrated in Figure 2. STAT1 signals are thought to induce expression of mitotic inhibitors, such as the cdk inhibitor p21.⁴⁰ Using microarrays to assess changes in gene expression in chondrocytic cells, Dailey et al⁴³ showed that FGFs initiate signals in multiple pathways that result in the induction of antiproliferative functions and down regulation of growth-promoting molecules.

Two MAPK pathways have been implicated, the strongest evidence coming from transgenic mice in whom expression of constitutively active members of the 2 pathways was targeted to cartilage, including growth plate cartilage. Expression of activated MKK6, which specifically activates the MAPK-p38 pathway, inhibits chondrocyte proliferation in part through induction of the

transcription factor Sox 9.⁴⁴ Chondrocyte hypertrophy was also inhibited in these dwarf mice. Expression of constitutively active MEK1, which specifically activates the MAPK-ERK pathway, produced a similar dwarf phenotype, but through inhibition of terminal chondrocyte differentiation with no inhibitory effect on cell proliferation.⁴⁵ These observations underscore the importance of both chondrocyte proliferation and terminal (hypertrophic) differentiation in linear bone growth and the central role of FGFR3 in negatively regulating these events.

It is important to emphasize that FGFR3 is one of many physiologic regulators that modulate linear bone growth. Its normal function is as a negative regulator. The mutations associated with achondroplasia and related conditions are thought to act through exaggeration or enhancement of this normal physiologic function rather than through acquisition of new functions.

d) Consequences of mutations

Several mutation-specific mechanisms have been proposed to explain how activating mutations of FGFR3 enhance FGFR3 signals (Figure 3).^{1,46} The transmembrane achondroplasia mutation is thought to stabilize FGFR3 dimers following ligand-induced dimerization, although this mechanism has recently been challenged.^{47,48} Monsonego-Ornan et al⁴⁹ have suggested that this mutation slows receptor internalization, leaving it on the surface to signal. The free cysteine residues introduced by the TDI mutations are believed to form disulfide bonds resulting in dimerization, which in turn activates the receptor.³³

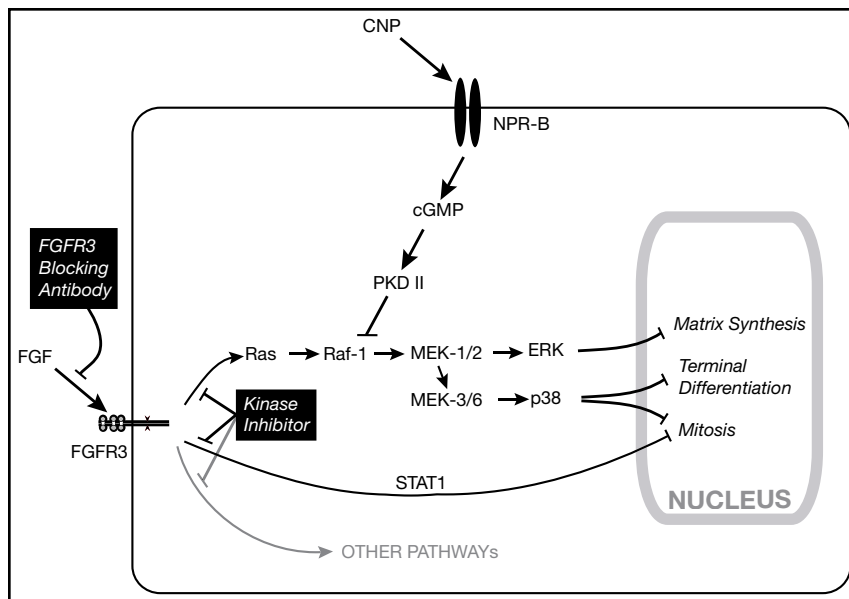


Figure 2. Signaling pathways and potential therapeutic strategies. FGFR3 signals are propagated through STAT1, MAPK-ERK, MAPK-p38 and probably other pathways which inhibit growth plate chondrocyte proliferation, post-mitotic matrix synthesis and terminal (hypertrophic) differentiation. The CNP-NPR-B pathway inhibits the MAPK pathways. Proposed therapeutic strategies include chemical inhibition of FGFR3 tyrosine kinase, antibody blockade of ligand-induced receptor activation, and enhancement of CNP-NPR-B signals.

The mutations of lysine 650 alter the conformation of the kinase domain, constitutively activating the intrinsic enzyme activity to different extents, corresponding with the severity of the clinical phenotype.^{34,46,47} It is not clear if receptors carrying the lysine 650 mutations reach the cell surface to become activated by ligand. The receptor tyrosine kinase is also activated by the common (Asn540Lys) hypochondroplasia mutation, but presumably to a relatively low degree, ie, comparable to the Lys650Ser mutation that is associated with a hypochondroplasia phenotype.

A mechanism that seems to be relevant to all of the mutation types is delayed turnover of activated receptor, which increases the overall FGFR3 signal output.⁵⁰ Like most other transmembrane receptors, FGFR3 is internalized within endosomes relatively soon after

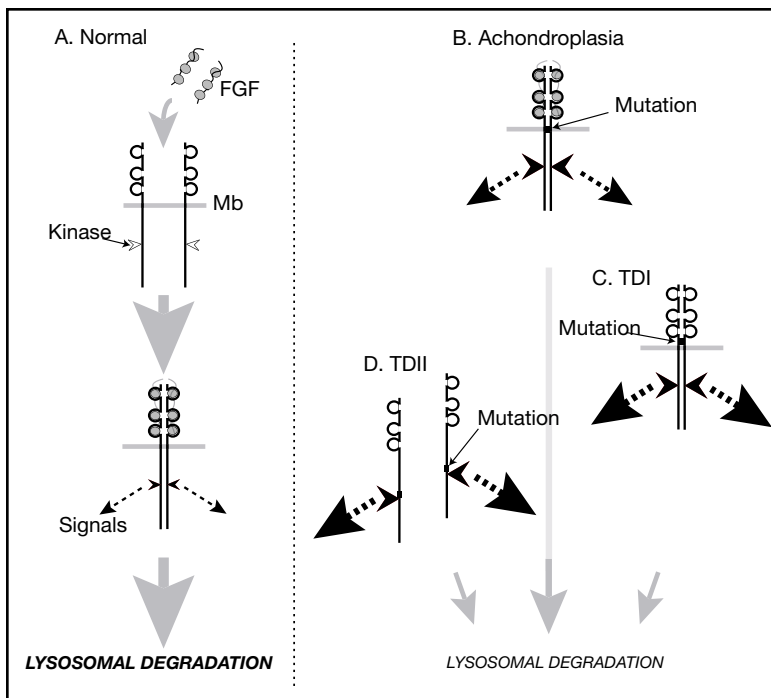


Figure 3. Proposed mechanisms by which mutations lead to gain of FGFR3 function. (A) Normally, ligand induces dimerization of receptor monomers, which activates kinase and initiates propagation of FGFR3 signals. Activated FGFR3 is targeted to and degraded by lysosomes relatively soon after activation. (B) FGFR3 dimers are stabilized by mutation (arrow) in transmembrane domain of the receptor in achondroplasia. (C) FGFR3 dimers are induced by formation of disulfide bonds in the proximal extracellular domain (arrow) in TDI. (D) Kinase is constitutively activated by mutation in TDII (and to lesser extent, in SADDAN and hypochondroplasia). (E) Lysosomal degradation is slowed in all 3 conditions. Mb: membrane.

activation. Since the intracellular “signaling” domain of the receptor has access to cytoplasmic signaling molecules, the endosomal-bound receptor continues to propagate signals until it is eventually degraded in lysosomes. Lysosomal targeting of receptors is mediated by the addition of multiple ubiquitin molecules to the activated receptor; the ubiquitin serves as a “lysosomal targeting signal.” FGFR3 ubiquitination is directed by the adapter protein c-Cbl, which functions as a ubiquitin ligase. c-Cbl activation occurs following FGFR3 activation; accordingly, the activated receptor directs its own degradation presumably as a negative feedback mechanism to keep its signaling output in check. In achondroplasia and related disorders, however, there is a defect in c-Cbl-mediated FGFR3 ubiquitination that leads to slowed receptor degradation and consequently, increased signal output.⁵⁰

Another pathway that down modulates FGFR3 signaling involves C-type natriuretic peptide (CNP).⁵¹ Through interaction with its receptor, natriuretic peptide receptor B (NPR-B), CNP induces accumulation of intracellular cGMP (Figure 2). Of interest is that mutations of NPR-B are responsible for acromesomelic dysplasia, type Maroteaux (OMIM 602875).⁵² Both CNP and NPR-B are expressed in the proliferative and prehypertrophic zones of the growth plate, setting up a potential autocrine or

paracrine regulatory circuit.⁵² Considerable evidence suggests that downstream signals from NPR-B antagonize FGFR3 downstream signals. More specifically, an increase in cGMP is known to activate a number of signaling mediators, including cGMP-dependent protein kinases (cGKs, or alternatively PKGs), one of which—cGKII (PKGII)—is thought to inhibit MAPK-ERK signaling at the level of Raf-1.^{53,54} Probably most telling is a genetic study in which mice exhibiting dwarfism due to expression of the achondroplasia mutant *FGFR3* transgene in cartilage were mated to mice in whom CNP expression was also targeted to cartilage.⁵⁵ The dwarfism of the “achondroplasia” mice was rescued by expression of CNP in cartilage.

THERAPEUTIC CONSIDERATIONS

As the molecular pathways involved in the pathogenesis of achondroplasia and related disorders have become clearer, a number of potential therapeutic strategies have emerged. Most of these approaches are similar to those used to treat cancer. This may seem odd, since the physiologic disturbances are in opposite directions, ie, too much growth in cancer, too little in achondroplasia. However, at the molecular level, the mechanisms are quite similar, ie, too much tyrosine kinase activity.

The most attention in achondroplasia has gone to inhibiting the FGFR3 tyrosine kinase through small chemical inhibitors. This approach has a strong rationale because essentially all of the cellular and higher level physiologic disturbances that interfere with bone growth seem to be driven by the excess in tyrosine kinase activity. For example, even the defect in lysosomal targeting and degradation of the activated receptor appears to be a downstream consequence of increased kinase activity. Selective FGFR3 kinase inhibitors have been developed and show promise in cell and organ culture experiments, but to date none has shown success in whole animals.⁵⁶

An alternative approach has involved generating antibodies to block FGFR3 activation. Although highly specific humanized antibodies have been developed, there have been no reports to date of success beyond cell culture experiments in which they block receptor activation well.⁵⁶

The therapeutic use of CNP or a CNP analog that could activate NPR-B signaling pathway to counter excessive FGFR3 signals transmitted through the MAPK-ERK and possibly MAPK-p38 pathways has been proposed.^{55,57} This approach is appealing because other natriuretic peptides have been used clinically for their hemodynamic

effects in adults and even in children.^{57,58} While they appear to be safe at least in the short term, a major drawback is their very short half-life requiring them to be administered by infusion, which would not be satisfactory for long-term treatment of achondroplasia.

A variation of this approach involves therapeutically targeting the NPR-C, another natriuretic peptide receptor that binds to CNP. The NPR-C, which is present on hypertrophic chondrocytes in the growth plate,⁵² lacks the ability to increase intracellular cGMP and has been proposed to function as a clearance receptor to down regulate the effects of natriuretic peptides.⁵⁷ Theoretically, blocking NPR-C would lead to an increase in available CNP to bind to NPR-B in the growth plate, which in turn would be expected to antagonize FGFR3-MAPK-ERK/p38 signals as discussed above.

There are 2 considerations regarding molecular treatment of achondroplasia that deserve special attention. The first is that treatment would need to be long term, probably starting soon after birth when the diagnosis is made and lasting through puberty. This adds challenges to any form of treatment.

The second consideration relates to the difficulty in targeting therapeutic agents to the cartilaginous growth plate. Compared to most tissues, cartilage is avascular and the dense and highly charged extracellular matrix that surrounds chondrocytes represents a formidable barrier for drug delivery. Indeed, these factors may explain at least in part why treatments that have worked in cell and organ culture experiments, have failed in whole animals. Agents given systemically may need to be administered in higher doses than those used for most other tissues in order to achieve therapeutic levels in the growth plate, and this could create a predisposition to side effects in the other tissues. Accordingly, it may be necessary to develop means to target agents to growth plate chondrocytes to reach effective doses of drugs and to avoid adverse effects in other tissues. Concern over such adverse effects may be especially relevant to the central nervous system where FGFR3 is known to be expressed postnatally.⁵⁹

GENETIC IMPLICATIONS

The diagnosis of achondroplasia can usually be made clinically. In rare instances in which the patient is too young or exhibits atypical findings, it can be established by molecular genetic testing for the achondroplasia mutation.⁶⁰ There are a number of laboratories that carry out such testing, and these can be accessed through the GeneTest Laboratory Directory at www.genetests.org. Given the virtual 100% penetrance of achondroplasia, the risk to family members who do not display clinical features of achondroplasia, ie, siblings and offspring of affected individuals, as well as siblings of parents,

is extremely low and testing is not ordinarily indicated. However, prenatal genetic testing may be useful in situations in which both parents have achondroplasia to identify fetuses with homozygous, or double-dose, achondroplasia. Such matings are at 25% risk for this much more severe form of achondroplasia.

Molecular genetic testing for hypochondroplasia may confirm a suspected diagnosis. However, only about 70% of individuals with typical findings of this condition are heterozygous for a mutation of FGFR3, presumably because mutations in genes other than *FGFR3* can result in the hypochondroplasia clinical phenotype.⁶¹

The position statement of the Little People of America regarding genetic discoveries in dwarfism may be reviewed online.⁶²

CONCLUSION

The tyrosine kinase-mediated transmembrane receptor FGFR3 is an important negative regulator of linear bone growth acting mainly through the STAT1, MAPK-p38, and MAPK-ERK signaling pathways to inhibit chondrocyte proliferation and terminal differentiation in the growth plate. Mutations that enhance these actions produce the qualitative achondroplasia clinical phenotype; the extent of this enhancement correlates with the severity of this phenotype. The mutations act through promoting or stabilizing the dimerization required for receptor activation, by directly activating kinase activity through conformational change of the receptor and by slowing of receptor degradation. Several strategies have been proposed to therapeutically counter the increased FGFR3 signal output, including chemical tyrosine kinase inhibitors and blocking antibodies, both selective for FGFR3 and activation of the CNP-NPR-B-cGMP pathway, which antagonizes MAPK-ERK/p38 signals downstream of FGFR3. All 3 strategies have shown success in cell and organ culture systems, but not yet in whole animal trials, perhaps because they may need to be targeted directly to growth plate chondrocytes to achieve therapeutic effect restricted to growing bones.

Research on achondroplasia and mutations of *FGFR3* has stimulated much interest in the molecular and cellular biology of both normal and abnormal linear bone growth. Indeed, many new genes whose products influence bone growth have been discovered or better delineated in the past several years, as have pathways that contribute to the regulation of bone growth. The hope is that these discoveries will lead to novel, safe, and effective therapies for disorders of linear bone growth within the next several years.

Acknowledgement

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