FGF3 gain-of-function mutations and short stature syndromes

The fibroblast growth factors (FGFs) are major regulators of embryonic development. Recently, mutations in the FGF receptor 3 (FGFR3), a family of tyrosine kinases, have been found to underlie several developmental diseases. Mutations in three different FGFRs have been identified in craniosynostosis syndromes, and mutations in FGFR3 are associated with several forms of classic short stature syndrome. Additionally, several recurrent, dominant mutations in FGFR3 also cause achondroplasia, hypochondroplasia or thanatophoric dysplasia.

Previous knockout mouse models of Fgfr3 showed overgrowth and not dwarfism, suggesting that FGFR3 is a negative regulator of bone growth and that the human disorders are caused by gain-of-function mutations. In fact, constitutive activation of the FGFRs is thought to underlie all the FGFR syndromes. Two papers now describe mouse models that express two different mutant forms of Fgfr3 and finally confirm that they indeed lead to a gain of function. These two mutants harbour mutations that are recurrent in achondroplasia (G250R) and thanatophoric dysplasia (K650E). The heterozygotes showed either no phenotype (G250R) or mild bone dysplasia (K650E) but the homozygotes exhibited phenotypes almost identical to their human counterparts. Although these mutations are dominant in humans, expression from the mutant mouse alleles is reduced. It has been suggested that the quantity of mutant FGFR3 determines the severity of the phenotype, which is supported by these results.

Dramatically reduced proliferation in the growth plate cartilage was found to underlie reduced bone growth in the mutant mice. Furthermore, Li et al. showed that the constitutive activation of Fgfr3 caused the activation of several STAT transcription factors and the upregulation of the Ink4 cell-cycle inhibitors (p16, p18 and p19), causing cell-cycle arrest and an expansion of the number of chondrocytes in the resting zone, leaving too few in the proliferating zone.

Tasimova et al. have identified an FGF3 mutation in an individual with thanatophoric dysplasia, developmental delay and acanthosis nigricans. Acanthosis nigricans is a thickening and abnormal pigmentation of the skin that is associated with diabetes, obesity and other endocrine disorders and that is indicative of hyperten cinurneia. Interestingly, this phenotype is occasionally found in several of the FGFR syndromes. The individual reported in this paper is a novel skeletal dysplasia with developmental delay and acanthosis nigricans in an individual with thanatophoric dysplasia. The arrowhead shows facial shortening and the arrow points to thoracic kyphosis at the craniocervical junction. The arrow points to thoracic kyphosis at the craniocervical junction.

A deletion of a gain-of-function FGF3 mutant mouse shows a phenotype distinct from that of the wild-type littermates. The homozygous animals exhibit reduced bone growth and skeletal delay in the development of the distal skeleton, resulting in dwarfism; insight into this associated phenotype is sure to follow.


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Gene transfer to liver

Several hematological and metabolic disorders are caused by dysfunctioning liver proteins, making the liver an important gene therapy target. Two recent studies describe the correction of hemophilia B, a bleeding disorder, and citrullinemia, a urea-cycle disorder, in animal models via liver transgene expression. In the first, an adenovirus-associated virus (AAV) vector was constructed that carried the canine Factor IX (FIX) cDNA driven by a liver-specific promoter. The vector was introduced into hemophilia B mice via the portal vein, and canine FIX was detected in serum up to four months after treatment. The highest dose of AAV-FIX gave the highest level of functional FIX (within the mouse normal range) as measured by clotting time. All treated mice survived tail clipping 15–22 weeks post-injection. Episomal maintenance of the AAV-FIX genome might be responsible for sustained restoration of coagulation.

Lee et al. used a bovine model of citrullinemia caused by a homonymous mutation in the argininosuccinate synthetase (ASS) gene, and calves received a replication-defective adenoviral vector that expressed the normal ASS gene. To determine the effect of ASS expression, the incorporation of 15N into urea was assayed. No 15N was detected in untreated controls but was enriched in the urea of treated animals. 15N-labeled urea was detected only in the liver and transduction was accomplished by an improved clinical condition. Plasma citrulline levels remained elevated as there was no effect on renal ASS activity; plasma glutamine levels decreased to normal levels after vector administration. In both studies, transgene expression was detected only in the liver and transduction rates were ~10%2. The fact that these relatively low rates of transduction resulted in clinical improvement is encouraging.


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