<Barresi13e, Further Development_c21_06>

Fibroblast Growth Factor Receptors: Dwarfism

The rate of growth appears to be intrinsic to each bone. Each growth plate is controlled locally (probably by differences in the sensitivity to growth factors), but the coordinated growth of the entire skeleton is maintained by circulating factors. Thus, when transplantations are made between growth plates of old and young mammals, the growth rate of the transplanted growth plate depends on the age of the donor animal, not that of the host animal (Wolpert 2010). However, discoveries of human and mouse mutations resulting in abnormal skeletal development have provided remarkable insights into how hormones and paracrine factors can control the eventual size of the limbs.

Fibroblast growth factors are critically important in halting the growth of the epiphyseal plates, telling the cells to differentiate rather than divide (Deng et al. 1996; Webster and Donoghue 1996). In humans, mutations of the receptors for FGFs can cause these receptors to become active prior to receiving the normal FGF signal. Such mutations give rise to the major types of human dwarfism. Achondroplasia is a dominant condition caused by mutations in the transmembrane region of FGF receptor 3 (FgfR3). Roughly 95% of achondroplastic dwarfs have the same mutation of the *FgfR3* gene: a base-pair substitution that converts glycine to arginine at position 380 in the transmembrane region of the protein. In addition, mutations in the extracellular portion of the FgfR3 protein or in the tyrosine kinase intracellular domain may result in thanatophoric dysplasia, a lethal form of dwarfism that resembles homozygous achondroplasia (Bellus et al. 1995; Tavormina et al. 1995).

As mentioned in Chapter 1, dachshunds have an achondroplastic mutation, but its cause is slightly different than that of the human form. Dachshunds have an extra copy of the *Fgf4* gene, which is also expressed in the developing limb. This extra copy causes excess production of Fgf4, activating FgfR3 and accelerating the pathway that stops the growth of chondroblasts and hastens their differentiation. The same extra copy of *Fgf4* has been found in other short-limbed dogs, such as corgis and basset hounds (Parker et al. 2009).