

Growth Hormone and Estrogen Receptors

One of the major hormones involved in growth control is, of course, growth hormone (GH). Growth hormone usually acts indirectly, instructing the liver to synthesize insulin-like growth factor-I (IGF-I). IGF-I stimulates the production and division of the cartilage cells. In most giants, there is an increase in the production of growth hormone. Among African Pygmies, a people noted for short stature, there appears to be a severe reduction in the number of growth hormone receptors, resulting in a reduction of liver IGF-I and small limbs (Bozzola et al. 2009). Similarly, certain small breeds of dogs (such as Pomeranians and toy poodles) are characterized by a reduced-function allele of *Igf1*, whereas large breeds (such as Newfoundlands and St. Bernards) are characterized by different allele of this gene (Sutter et al. 2007; Parker et al. 2010).

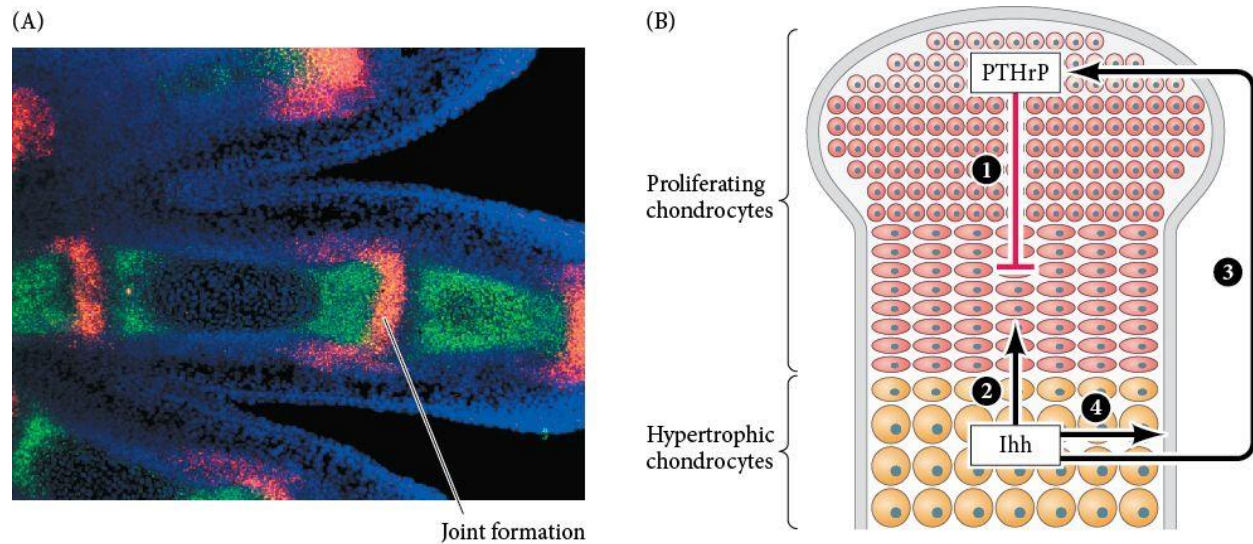
The pubertal growth spurt and subsequent cessation of growth are induced by increased growth hormone production regulated by the gonadal steroid hormones (Kaplan and Grumbach 1990). Estrogen appears to be important for bone growth in both men and women. Relatively low levels of estrogen stimulate skeletal growth in men and women, whereas the higher levels that occur at the end of puberty induce apoptosis in the hypertrophic chondrocytes and stimulate the invasion of bone-forming osteoblasts into the growth plate. There have been several documented cases of men who do not produce estrogen (Smith 1994; Juul 2001). These men continue to grow even in adulthood and may approach 7 feet in height. Their epiphyseal growth plates do not mature and thus remain full of dividing chondroblasts. In most cases, this deficiency is due to a loss-of-function mutation in the gene encoding aromatase, the enzyme that converts testosterone into estrogen; in such instances, therapy with estrogens is able to stop the excessive growth.

Estrogen receptors are found in the cells that regulate growth hormone production, as well as in all the cells of the human growth plate. Thus, the effects of estrogen on growth may involve both the regulation of growth hormone and more local effects on the growth plate itself (Juul 2001; Karimian and Sävendahl 2011). Both growth hormone and estrogen antagonists (such as aromatase) can increase final height of young boys and girls, but there are often severe side-effects (Karimian and Sävendahl 2011; Mauras 2011). It is even possible that estrogen ensures that all the growth plates of the body close at about the same time (Nilsson and Baron 2004).

Parathyroid hormone-related peptide and Indian hedgehog

The growth plate is a rapidly changing population of cells. In young rats, for instance, there are about 40 cells in a column of chondrocytes. During peak growth, about eight cells per day die and are replaced by bone, and another eight chondrocytes replace them (Wilsman et al. 1996). The length of these proliferating chondrocyte columns is controlled largely by parathyroid hormone-related peptide (PTHrP) and Indian hedgehog (Ihh). Ihh maintains chondrocyte cell division directly (by activating cyclin D1 synthesis) and prevents the chondrocytes' immediate hypertrophy. Ihh is made by the cartilage at the "bottom" of the column as the chondrocytes begin to hypertrophy. This Ihh diffuses "upward," stimulating cell division and increasing the number of new chondrocytes in the column. PTHrP, which is stimulated by Ihh, prevents premature hypertrophic differentiation in the young

chondrocytes at the base of the growth plate. As the chondrocytes leave the influence of PTHrP, they begin to hypertrophy, die, and are replaced by bone. In this way, Ihh and PTHrP regulate the length of the chondrocyte columns (Figure 1; Vortkamp et al. 1996; Kobayashi et al. 2005). In humans, mild loss-of-function mutations in the protein encoding PTHrP result in short stature and short fingers (Provot and Schipiani 2005).



A courtesy of Dr. P. Tylzanowski. B after H. M. Kronenberg. 2003. *Nature* 423: 332–336.

Figure 1 Model for endochondral ossification in the limb. (A) In situ hybridization in the limb of a 14.5-day mouse embryo shows collagen-2 mRNA (green) in the proliferative growth plate cartilage and Gdf5 mRNA (red) in the region destined to become a joint. Nuclei are stained blue. (B) Regulation of cartilage cell proliferation by PTHrP and Indian hedgehog. (1) PTHrP acts on receptors on proliferating chondrocytes to keep them dividing and thereby delays the production of Ihh. (2) When the source of PTHrP production becomes sufficiently far away, then Ihh is synthesized. Indian hedgehog acts on its receptor on chondrocytes to increase the rate of proliferation and (3) to stimulate the production of PTHrP at the ends of bones. (4) Ihh also acts on the perichondrial cells enveloping the cartilage to convert them into the osteoblasts of the bone collar. (A courtesy of Dr. P. Tylzanowski; B after Kronenberg 2003.)

Literature Cited

Bozzola M. and 12 others. 2009. The shortness of Pygmies is associated with severe under-expression of the growth hormone receptor. *Mol. Genet. Metab.* 98: 310–313.

[PubMed Link](#)

Juul, A. 2001. The effects of oestrogens on linear bone growth. *Hum. Reprod. Updates* 7: 303–313.

[PubMed Link](#)

Kaplan, S. L. and M. M. Grumbach. 1990. Pathophysiology and treatment of sexual precocity. *J. Clin. Endocrinol. Metab.* 71: 785–789.

[PubMed Link](#)

Karimian E and L. Sävendahl. 2011. Estrogen signaling in growth plate cartilage. *Endocr. Dev.* 21: 42–51.

[PubMed Link](#)

Kobayashi T. and 6 others. 2005. Indian hedgehog stimulates periarticular chondrocyte differentiation to regulate growth plate length independently of PTHrP. *J. Clin. Invest.* 115: 1734–1742.

[PubMed Link](#)

Kronenberg, H. M. 2003. Developmental regulation of the growth plate. *Nature* 423: 332–336.

[PubMed Link](#)

Mauras N. 2011. Strategies for maximizing growth in puberty in children with short stature. *Pediatr. Clin North Am.* 58: 1167–1779.

[PubMed Link](#)

Nilsson, O. and J. Baron. 2004. Fundamental limits on longitudinal bone growth: Growth plate senescence and epiphyseal fusion. *Trends Endocrinol. Metab.* 15: 370–374.

[PubMed Link](#)

Parker, H. G., A. L. Shearin and E. A. Ostrander E. 2010. Man's best friend becomes biology's best in show: Genome analyses in the domestic dog. *Ann. Rev. Genet.* 44: 309–336.

[PubMed Link](#)

Provot, S. and E. Schipiani. 2005. Molecular mechanisms of endochondral bone development. *Bioch. Biophys. Res. Comm.* 328: 658–665.

[PubMed Link](#)

Smith, E. P. and 8 others. 1994. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N. Engl. J. Med.* 331: 1056–1061.

[PubMed Link](#)

Sutter, N. B. and 20 others. 2007. A single *IGF1* allele is a major determinant of small size in dogs. *Science* 316: 112–115.

[PubMed Link](#)

Vortkamp, A, K. Lee, B. Lanske, G. V. Segre, H. M. Kronenberg and C. J. Tabin. 1996. Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein. *Science* 273: 613–622.

[PubMed Link](#)

Wilsman, N. J., C. E. Farnum, E. M. Green, E. M. Leiferman, and M. K. Clayton. 1996. Cell cycle analysis of proliferative zone chondrocytes in growth plates elongating at different rates. *J. Orthop. Res.* 14: 562–572.

[PubMed Link](#)

All the material on this website is protected by copyright. It may not be reproduced in any form without permission from the copyright holder.

© 2023 Oxford University Press