

Postnatal role of the PTH/PTHrP receptor

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In fetal life parathyroid hormone (PTH)-related protein (PTHrP) is produced by cells at the ends of long bones and acts on the PTH/PTHrP receptor as chondrocytes decide to either keep dividing or instead stop dividing and differentiate into hypertrophic chondrocytes. The actions of PTHrP serve to keep chondrocytes dividing. In the absence of the PTH/PTHrP receptor, proliferating chondrocytes rapidly differentiate instead of continuing to proliferate, and bones fail to lengthen normally. As a result mice all die at the time of birth or earlier. As a result, possible roles for the PTH/PTHrP receptor in the growth plate after birth have been uncertain.

Here we use the cre-lox approach to ablate the PTH/PTHrP receptor gene after birth. We use the collagen II-creERT mouse constructed by Susan Mackem. In this mouse, cre is produced in collagen II-producing chondrocytes but is inactive because it is covalently bound to a mutant form of the ligand-binding domain of the estrogen receptor α that responds only to tamoxifen. In the absence of tamoxifen, this fusion protein is cytoplasmic and only moves to the nucleus where it is active in response to tamoxifen administration. Mice expressing this gene as well as a floxed PTH/PTHrP receptor gene were treated with tamoxifen at various times after birth. Remarkably, within 10 days of tamoxifen administration, the growth plates of these mice disappear (growth plate "fusion"). At times prior to the disappearance of the growth plate, studies of gene expression suggest that the flat proliferating chondrocytes rapidly stop proliferating and instead produce Indian hedgehog and then collagen, type X in an accelerated fashion. Apoptosis is also accelerated, not just in the morphologically late hypertrophic chondrocytes as in normal growth plates, but also in chondrocytes throughout the distal growth plate.

To determine whether this apoptosis is required for the disappearance of the growth plate, we put mice on a low phosphate diet the day before tamoxifen administration. Low phosphate diet was used because this diet has been reported to suppress apoptosis of late hypertrophic chondrocytes, resulting in the rachitic expansion of the hypertrophic chondrocytes. When the coll II-creERT; floxed PTH/PTHrP receptor mice were put on a low phosphate diet and then given tamoxifen, the growth plate persists for a prolonged time, with suppression of both normal and ectopic apoptosis. Thus, apoptosis is an important mechanism of growth plate fusion in this model.

The findings in these studies suggest that PTH/PTHrP receptor signaling postnatally is required for continued presence of the growth plate and raises the question of the role of PTH/PTHrP receptor signaling in human growth plate fusion. Unfortunately, since mice do not fuse their growth plates at the time of puberty in an estrogen-dependent fashion as humans do, we cannot test the possible involvement in this estrogen-dependent process in the mouse. However, people with Albright's hereditary osteodystrophy are known to have premature growth plate fusion. Since the defect in these people, mutation of one copy of the $G_s \alpha$ gene, involves one of the mediators of PTH/PTHrP receptor function, it is possible that PTH/PTHrP receptor action is required during human childhood to maintain normal growth plate function and prevent premature growth plate closure.