

## Indian hedgehog signaling in the embryonic growth plate

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**INTRODUCTION:** Endochondral ossification is a multistep process during which a cartilage template is successively replaced by bone tissue. Chondrocytes in the cartilage anlagen undergo several steps of differentiation until they become terminal hypertrophic and are subsequently replaced by bone. The secreted growth factor Indian hedgehog (Ihh) is expressed in a distinct population of chondrocytes that undergo hypertrophic differentiation. Ihh interacts with a second secreted molecule, Parathyroid Hormone related Protein (PTHrP), expressed in the distal ends of the cartilage elements in a negative feedback mechanism to regulate the onset of hypertrophic differentiation.

**RESULTS & DISCUSSION:** Analyzing a mouse line carrying a hypomorphic allele of *Ext1*, a glycosyltransferase necessary for the synthesis of heparan sulfates (HS), we have recently shown that HS negatively regulates the propagation of the Ihh signal in a concentration dependent manner. Our data strongly indicate that Ihh acts as a long range morphogen directly inducing the expression of PTHrP.

To further investigate the interaction between Ihh and PTHrP, we have started to analyze the role of the zinc finger transcription factor Gli3, which acts downstream of hedgehog signals in other organs. Ihh;Gli3 double mutants indicate that Gli3 acts as a repressor downstream of

Ihh in regulating chondrocyte proliferation and the expression of PTHrP, and, thus, the onset of hypertrophic differentiation. Furthermore, our studies revealed that Gli3 negatively regulates the differentiation of distal, low proliferating (zone I) into central, high proliferating (zone II) chondrocytes. Whereas the domain of zone II chondrocytes is determined by the level of PTHrP, the transition of zone I into zone II chondrocytes is regulated by Gli3 independent of PTHrP. We have thus identified a new function for the Ihh/Gli3 system in regulating the differentiation of distal chondrocytes.