CDB SEMINAR

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16:00~17:00 Seminar Room A7F

Smad-dependent BMP signaling through type IA receptor in cranial neural crest cells directs their cell fate towards chondrocytes to cause craniosynostosis

Summary
My laboratory is interested in functions of bone morphogenetic protein (BMP) signaling during bone development/remodeling and craniofacial development. We recently developed several mouse lines to conditionally decrease or increase levels of BMP signaling using a Cre-loxP system. Using these systems, we have found that BMP signaling in osteoblasts is critical for maintenance of bone mass and biomechanical properties, that BMP signaling in early embryos is critical for ciliogenesis that is essential to establish a left-right asymmetry, and that BMP signaling in cardiac neural crest cells is important for valve functions during heart development. In this seminar, I would like to talk about our recent findings how BMP signaling is critically involved in skull morphogenesis through a tight regulation of its signaling activity.

Craniosynostosis refers to conditions in which one or more sutures of the infant skull are prematurely fused, resulting in facial deformity and delayed brain development. Approximately 20% of human craniosynostoses are thought to result from gene mutations altering growth factor signaling; however, the molecular mechanisms by which these mutations cause craniosynostosis are incompletely characterized, and the causative genes for diverse types of syndromic craniosynostosis have yet to be identified.

We recently found that enhanced BMP signaling through the BMP type IA receptor (BMPR1A) in cranial neural crest cells, but not in osteoblasts, causes premature suture fusion in mice. In support of a requirement for precisely regulated BMP signaling, this defect was rescued on a *Bmpr1a* haploinsufficient background, with corresponding normalization of Smad phosphorylation. Moreover, in vivo treatment with LDN-193189, a selective chemical inhibitor of BMP type I receptor kinases resulted in rescue of craniosynostosis. The finding that relatively modest augmentation of Smad-dependent BMP signaling leads to premature cranial suture fusion suggests an important contribution of dysregulated BMP signaling to syndromic craniosynostoses, and potential strategies for early intervention.

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