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BONE

Hedgehog signalling linked to heterotopic ossification in POH

"We set out to ask how bone formation is spatially regulated by studying the molecular mechanisms underlying a genetic disease of ectopic bone formation, progressive osseous heteroplasia (POH)", explains Yingzi Yang, from the National Human Genome Research Institute at the NIH. This research, now published in *Nature Medicine,* found that loss of *GNAS* expression in POH results in activation of Hedgehog signalling, which leads to the formation of extraskeletal bone (heterotopic ossification).

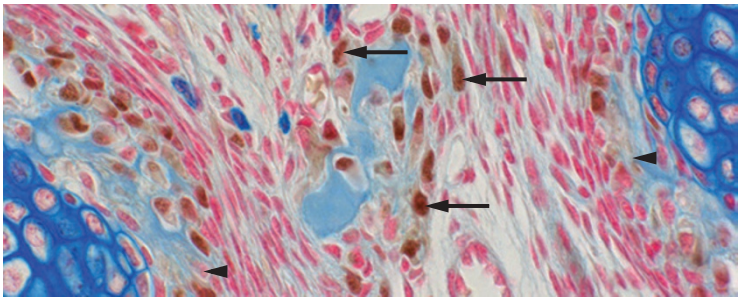
Frederick Kaplan and Eileen Shore (University of Pennsylvania), also coauthors on this paper, found that POH is caused by a defect in GNAS, the gene encoding $G\alpha_s$, which is a downstream mediator of signalling via G protein-coupled receptors; however, the molecular mechanisms responsible for the pathogenesis of this disease remain poorly understood. Here, the researchers generated mice that lacked expression of both alleles of *Gnas* in limb mesenchymal progenitor cells (*Prrx1-cre;Gnas*$^{fl/-}$ and *Prrx1-cre; Gnas*$^{fl/fl}$ mice). Homozygous loss of *Gnas* expression resulted in progressive heterotopic ossification and POH-like phenotypes in these mice. The authors established that this phenotype resulted from ectopic osteoblast differentiation resulting in progressive noncartilaginous intramembranous bone formation and that these mice, therefore, represent a model of POH.

Previous work by Yang and colleagues demonstrated a link between $G\alpha_s$ and the Wnt-β-catenin pathway, which led them to investigate whether $G\alpha_s$ regulates bone formation in POH by influencing the Wnt-related Hedgehog signalling pathways. First, they demonstrated that Hedgehog target genes were expressed at a higher level in *Prrx1-cre;Gnas*$^{fl/-}$ limbs at embryonic day 14.5 in comparison with control embryos. Next they showed that $G\alpha_s$ modulates the strength of Hedgehog signalling pathways by regulating the activation of the Gli family of zinc-finger transcription factors in embryonic limbs, through cAMP and PKA. Finally, the authors showed that activation of Hedgehog signalling is necessary and sufficient to result in heterotopic ossification.

"The significance of our work is that we have figured out a fundamental mechanism that restricts bone formation to its normal location, which has to be strictly controlled in skeletal development and regeneration", says Yang. "We plan to test whether inhibition of Hedgehog signalling could lead to suppression of heterotopic ossification caused by nongenetic causes, such as occurs after trauma or surgery".

Jenny Buckland

Original article Regard, J. B. *et al.* Activation of Hedgehog signaling by loss of GNAS causes heterotopic ossification. *Nat. Med.* doi:10.1038/nm.3314



Bone-forming cells (brown nuclear staining, arrows) in the ossicles (light blue) between two ossifying digits (arrowheads) in *Prrx1-cre; Gnas*$^{fl/fl}$ mice. Image courtesy of Y. Yang.