BONE

Anabolic Wnt/ β -catenin signalling: osteocytes are key

“Activation of canonical Wnt/ β -catenin signalling exclusively in osteocytes increases both osteoclasts and osteoblasts leading to bone gain, and is sufficient to activate the Notch pathway without affecting survival,” explains Teresita Bellido, lead author on a new *Proceedings of the National Academy of Sciences* paper.

The Wnt/ β -catenin pathway is essential for bone homeostasis: anabolic stimuli activate Wnt signalling leading to bone maintenance and accrual. Until now, the cells responsible for mediating these anabolic signals were unknown. This paper identifies osteocytes as the key cells in this process.

The researchers generated a new knock-in mouse model, *da β cat^{Ox}* mice, in which a dominant active β -catenin is expressed specifically in osteocytes, resulting in activation of canonical Wnt signalling in these cells. Mice expressing the same dominant active β -catenin specifically in osteoblasts had been generated previously.

“...expression of β -catenin in osteocytes favours bone formation over bone resorption”

Bone mineral density of both the axial and the appendicular skeleton was higher in the *da β cat^{Ox}* mice than in wildtype littermates, as was cancellous bone volume. *da β cat^{Ox}* mice also had increased levels of periosteal bone formation, more cancellous and cortical bone osteoblasts, and higher levels of osteoblast activity than wildtype littermates. In addition, numbers of cancellous osteoclasts and levels of bone resorption were increased in the *da β cat^{Ox}* mice. Finally, Notch and Wnt signalling pathway target genes were expressed at higher levels in bones from the *da β cat^{Ox}* mice than in bones from wildtype littermates.

As Bellido explains, “These findings contrast with previous evidence in the literature showing that canonical

Wnt/ β -catenin signalling in osteoblasts decreased bone resorption and induced perinatal death from leukaemia.”

Despite affecting both osteoclasts and osteoblasts, expression of β -catenin in osteocytes favours bone formation over bone resorption. “Future studies are needed to fully understand the downstream mechanisms and molecular mediators of osteocyte-driven regulation of osteoblasts and osteoclasts,” says Bellido. “Long-lived osteocytes constitute more than 90% of bone cells, so these cells represent a more logical and effective target cell to induce bone anabolism than scarce short-lived osteoblasts.”

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Original article Tu, X. *et al.* Osteocytes mediate the anabolic actions of canonical Wnt/ β -catenin signaling in bone.

Proc. Natl Acad. Sci. USA doi:10.1073/pnas.1409857112

Further reading Kode, A. *et al.* Leukaemogenesis induced by an activating β -catenin mutation in osteoblasts. *Nature* doi:10.1038/nature12883