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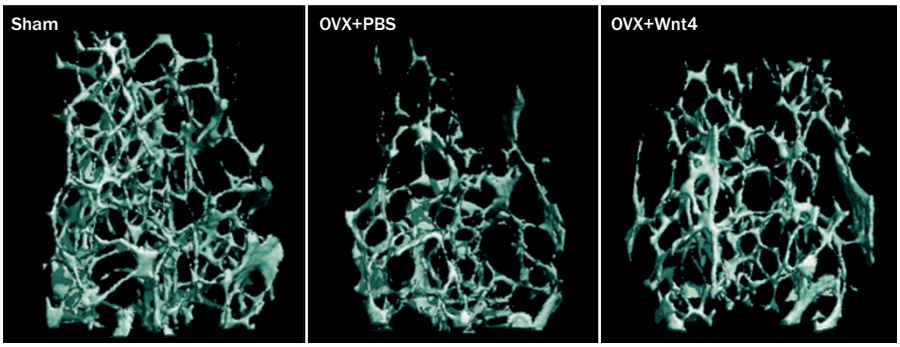
OSTEOIMMUNOLOGY

Dual role for Wnt4: bone formation and bone resorption

"While the roles of canonical Wnt proteins in bone metabolism have been extensively studied, noncanonical Wnt signalling in bone formation and resorption is poorly understood," says Prof. Cun-Yu Wang. "This prompted us to create transgenic mice overexpressing *Wnt4* in mature osteoblasts to determine whether Wnt4 regulates bone metabolism," he adds. The findings from this study, which confirm and extend previous research from the same authors, identify a dual role for Wnt4 in promoting bone formation and, novelly, in inhibiting bone resorption.

At birth, *OB-Wnt4* transgenic mice had phenotypically normal skeletons, but by 1 month of age these mice had considerably higher bone mineral density than wild-type littermates. The authors then studied the effect of Wnt4 in three models of bone loss—ovariectomy, chronic inflammation, and ageing—and in all three scenarios, overexpression of *Wnt4* provided protection against bone loss and inflammation. Bone formation rates and osteoblast counts were higher and osteoclast activity was lower in the *OB-Wnt4* mice than in wild-type littermates. Levels of serum proinflammatory cytokines were lower in transgenic mice than in wild-type mice; with additional *in vitro* experiments Wang *et al.* showed that this defect was probably due to Wnt4 inhibiting NFκB signalling in macrophages and osteoclast precursors.



μCT reconstructions of distal femoral metaphyses from 3-month-old wild-type mice 2 months after sham surgery or ovariectomy (OVX). Wnt4 protein or PBS control were administered 1 month after surgery when bone loss was established.

"Our finding is the first report that noncanonical Wnt signalling can inhibit osteoclast differentiation and, importantly, NFκB activation and inflammation," concludes Wang.

Jenny Buckland

Original article Yu, B. *et al.* Wnt4 signaling prevents skeletal aging and inflammation by inhibiting nuclear factor-κB. *Nat. Med.* doi:10.1038/nm.3586

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