

# OSTEOSCOOP

News on current events in osteoporosis and rheumatology

## Fat or bone? The answer is in the Wnt

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**A**dipocytes and osteoblasts derive from the same mesenchymal stem cells. During differentiation, gene expression programs decide the fate of these cells. One of the key mediators of adipogenesis is the nuclear hormone receptor PPAR- $\gamma$  (peroxisome proliferator activated receptor  $\gamma$ ). When stimulated by its ligand, PPAR- $\gamma$  enhances expression of target genes that force differentiation into adipocytes. By contrast, expression of the major osteogenic determinants, the transcription factors Runx2 and Osterix, produce osteoblasts. The control and signaling mechanisms that lead to an adipogenic or osteogenic cell-lineage decision remain largely elusive. Canonical Wnt signalling is crucial for bone formation. In the Wnt signaling cascade, Wnt family members bind to their receptors on the cell membrane, and LRP5 (low density lipoprotein receptor related protein 5) or LRP6 are required as coreceptors (see *Osteoscoop* entitled "PTH does not need Lrp5 to stimulate bone formation in mice"). Activation of the receptor complex leads to the intracellular accumulation of  $\beta$ -catenin, and this increase leads to translocation of  $\beta$ -catenin to the nucleus where it serves as a cofactor for a transcription factor. Disruption of the canonical Wnt signalling cascade severely impairs bone formation. For example, mutations in LRP5 result in altered bone mass in mice and humans. Deletion of  $\beta$ -catenin in osteoblasts also leads to multiple skeletal defects.

Another pathway involving Wnt, called non-canonical Wnt signaling, has been linked to bone formation only very recently. In a recent study [1], the authors identify new intracellular cascades for noncanonical Wnt signaling. They demonstrate that a member of the Wnt family, WNT5a, suppresses the expression of adipogenic PPAR- $\gamma$  target genes by activating the noncanonical Wnt signaling pathway. The authors show that WNT5a activates a complex involving several kinases (CaMKII, NLK), gives rise to a protein complex which binds to histones and methylates them at the PPAR- $\gamma$  target gene. This results in gene silencing and directs cell differentiation into osteoblasts [2].

It will be interesting to see whether the increase in adipocytes and decrease in osteoblasts in elderly humans is governed by alterations in noncanonical Wnt signaling. This would also open a new avenue for therapeutic strategies in the handling of osteoporosis.

1. Takada I et al. *Nat Cell Biol.* 2007;9:1273-1285.
2. Günther T et al. *Nat Cell Biol.* 2007;9:1229-1231.

### Differentiation of adipocytes and osteoblasts from a common bone marrow mesenchymal precursor [2].

Expression of PPAR- $\gamma$  target genes directs differentiation into adipocytes (a). Alternatively WNT5a stimulates a non-canonical Wnt signaling cascade (b), which, through a complex involving several kinases (CaMKII, NLK), gives rise to a protein complex which binds to histones and methylates them at the PPAR- $\gamma$  target gene. This results in gene silencing and directs cell differentiation into osteoblasts.

