BONE

Novel microRNA expressed in osteoblasts promotes bone formation

A microRNA (miRNA) expressed in mouse osteoblasts, miR-2861, promotes osteoblast differentiation by repressing expression of histone deacetylase 5 (HDAC5) at the post-translational level, thereby contributing to bone formation. Furthermore, evidence that a mutation in this miRNA causes primary osteoporosis in humans suggests that miR-2861 has an important role in the pathogenesis of this disease.

“In humans, a mutation in the precursor of miR-2861 ...could have an important role in the development of osteoporosis”

In a study published in *The Journal of Clinical Investigation*, Li *et al.* demonstrated in ST2 stromal cells that miR-2861 promotes osteogenic differentiation induced by bone morphogenetic protein 2 (BMP2). Overexpression of miR-2861 increased levels of AMP activity, osteocalcin secretion, and bone nodule formation in cultures. In addition, expression of runt-related transcription factor 2 (RUNX2) protein, but not *Runx2* messenger RNA

(mRNA), was increased in miR-2861-transfected cells compared with control cells. In contrast to these effects, silencing expression of miR-2861 attenuated BMP2-induced osteoblastogenesis.

The investigators identified HDAC5, which is involved in RUNX2 degradation, as the most important target of miR-2861. Overexpression of miR-2861 decreased levels of HDAC5 protein but not *Hdac5* mRNA, indicating that the effects of miR-2861 on osteoblastogenesis occur at the post-translational level.

In vivo administration of a chemically modified antisense nucleotide specific to miR-2861, which generated mice lacking miR-2861, affected markers of osteoblast activity but not markers of osteoclast activity. In comparison with control mice, treated mice demonstrated reduced bone mineral density, increased expression of HDAC5 protein and decreased expression of RUNX2 protein.

In humans, a mutation in the precursor of miR-2861 that prevents the expression of mature miR-2861 in bone could have an important role in the development of osteoporosis. A rare homozygous mutation in the miR-2861 precursor was found in two adolescent siblings with primary osteoporosis and no expression

of miR-2861. As expected, bone samples from the two patients revealed elevated levels of HDAC5 protein and decreased expression of RUNX2 protein compared with controls.

Together, the data from mouse and clinical studies suggest that miR-2861 has an important physiological role in the regulation of bone metabolism through its effects on osteoblast differentiation.

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Original article Li, H. *et al.* A novel microRNA targeting HDAC5 regulates osteoblast differentiation in mice and contributes to primary osteoporosis in humans. *J. Clin. Invest.* 119, 3666–3677 (2009)