Nature Reviews Rheumatology **7**, 373 (2011); published online 21 June 2011; doi:10.1038/nrrheum.2011.84

BONE

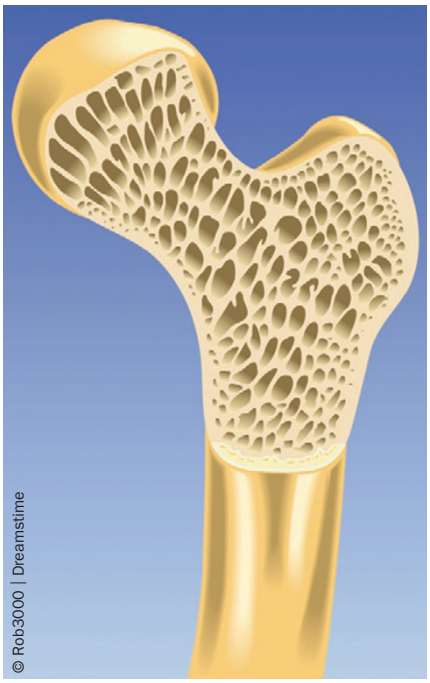
Evidence for local effects of LRP5 on bone mass

The question of how LRP5 (LDL receptor-related protein 5) exerts its effects on bone formation has come under debate. New findings published by Cui *et al.* in *Nature Medicine* support a local role for LRP5 signaling in bone.

LRP5 was first implicated in the regulation of bone mass through studies of two human genetic diseases: heterozygous missense mutations in *LRP5* were shown to produce a dominantly inherited high bone mass (HBM) phenotype, whereas loss-of-function *LRP5* mutations were shown to cause osteoporosis-pseudoglioma syndrome (OPPG), which is associated with low bone mass. "What excited the bone research community was that LRP5 appeared to function in the Wnt signaling pathway, which had previously not been implicated in regulating bone strength," says Matthew Warman, one of the authors of the *Nature Medicine* paper. Data from other lines of investigation supported a direct role for Wnt signaling in bone mass accrual; however, direct proof that LRP5 functioned locally in bone cells or that it was a transducer of Wnt signaling in bone cells was lacking.

It has since been hypothesized that, surprisingly, LRP5 influences bone formation not through its role as a Wnt co-receptor on osteoblasts, but indirectly, via its effects on the production of serotonin (5-hydroxytryptophan) in the gut. Cui *et al.* sought to independently test this serotonin hypothesis and also determine where and how LRP5 functioned to regulate bone mass. Instead of confirming a serotonin-based mechanisms, however, their data suggest that LRP5 functions locally in bone cells.

The researchers were able to determine the site of Lrp5 function in mouse models by generating conditional alleles that could be activated or inactivated in different cell types, in animals of different ages or in cells at different stages of differentiation. This approach



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enabled them to compare the effect of inheriting *Lrp5* HBM alleles with the effect of activating *Lrp5* HBM alleles in specific cell types. "Perhaps the most intriguing result from our present study is that activating an *Lrp5* HBM allele in the most mature bone cells, the osteocytes, appears as effective at increasing bone mass as inheriting the active *Lrp5* HBM in all cells," says Warman. In addition, mice with conditional inactivation of *Lrp5* in osteocytes had decreased bone mass in comparison with their wild-type littermates.

Together, the findings indicate that bone mass is regulated by Lrp5 signaling in mature cells. "The importance of this observation is that it might not be necessary to find therapies that target uncommitted cells to become bone-forming cells," continues Warman. "Instead, therapies that can mimic what the HBM mutations in LRP5 do in osteocytes can be just as effective at increasing bone mass and bone strength."

Cui *et al.* found no effect of *Lrp5* genotype on serotonin synthesis in the gut. Activation of *Lrp5* HBM alleles, or inactivation of wild-type *Lrp5,* in serotonin-producing cells in the duodenum did not affect bone mass. In addition, bone mass did not seem to be affected by inhibition of tryptophan hydroxylase 1, the rate-limiting enzyme of peripheral serotonin synthesis, whether induced genetically or pharmacologically. The reasons for the discrepancy between the findings of this study and earlier work that led to the serotonin hypothesis are unknown, but could be related to differences in the mice studied or to other technical aspects of the research.

Although the data from Cui *et al.* does not support the model of Lrp5 expression in the gut having a major influence on bone mass, they do not exclude the possibility that Lrp5 could regulate bone mass indirectly through its function at other sites. Investigating this possibility, the researchers conducted further tests that showed that selectively activating *Lrp5* HBM alleles in cells that form bone in the appendicular skeleton but not in cells that form the bone in axial skeleton led to increased bone mass in the limbs but not in the vertebrae.

In summary, the data presented by Cui *et al.* indicate that Lrp5 functions to regulate bone mass in mice via Wnt signaling in osteocytes, thereby acting locally rather than via other sites.

The researchers are now keen to determine whether increasing the activity of LRP5 in older mice is as effective as it is in younger mice at increasing bone mass and strength. If this proves to be the case, LRP5-targeted interventions might be applicable to the treatment of age-related osteoporosis in humans.

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Original article Cui, Y. *et al.* Lrp5 functions in bone to regulate bone mass. *Nat. Med.* doi:10.1038/nm.2388

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