UKE Paper of the Month Dezember 2018

Wnt1 is an Lrp5-independent bone-anabolic Wnt ligand

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ABSTRACT: *WNT1* mutations in humans are associated with a new form of osteogenesis imperfecta and with early-onset osteoporosis, suggesting a key role of WNT1 in bone mass regulation. However, the general mode of action and the therapeutic potential of Wnt1 in clinically-relevant situations such as aging remain to be established. Here, we report the high prevalence of heterozygous *WNT1* mutations in patients with early-onset of osteoporosis. We show that inactivation of Wnt1 in osteoblasts causes severe osteoporosis and spontaneous bone fractures in mice. In contrast, conditional Wnt1 expression in osteoblasts promoted rapid bone mass increase in developing young, adult, and aged mice by rapidly increasing osteoblast numbers and function. Contrary to current mechanistic models, loss of Lrp5 the co-receptor thought to transmit extracellular WNT signals during bone mass regulation, did not reduce the bone-anabolic effect of Wnt1, providing direct evidence that Wnt1 function does not require the LRP5 co-receptor. The identification of Wnt1 as a regulator of bone mass formation and remodeling provides the basis for development of Wnt1-targeting drugs for the treatment of osteoporosis.

STATEMENT: *The identification of gain- or loss-of-function mutations in components of the WNT signalling pathway that cause skeletal diseases in humans suggested a key role for WNT ligand(s) in regulating bone formation. However, until recently, the identity and the cellular origin of the bone-anabolic WNT ligand, among the 19 potential ones, was unknown. The discovery, by our clinic and by others, of mutations in WNT1 associated with early-onset osteoporosis or new form of osteogenesis imperfecta, suggested that WNT1 could be a good candidate. This hypothesis was tested in the present manuscript in a combined effort from bed to bench of the Institute for Osteology and Biomechanics. Our work revealed a high frequency of WNT1 mutation in patients with early-onset osteoporosis, and, using cell-specific Wnt1 loss of function in mice, demonstrated that Wnt1 production by bone-forming osteoblasts is required for post-natal maintenance of bone formation. To test the therapeutic potential of Wnt1, we used an inducible cell-specific transgenic mouse model, where Wnt1 expression by osteoblasts can be timely controlled. Using this model, we demonstrated the unmatched bone-anabolic effect of Wnt1 in young, adult and aging male and female mice and show that the Wnt1 bone-anabolic function does not require Lrp5 expression. Our data thereby open new opportunities for the treatment of low bone mass diseases such as osteoporosis.*

BACKGROUND: This translational application of the National Bone Board focusing on identifying and treating rare skeletal diseases coordinated by the Institute of Osteology and Biomechanics (IOBM, UKE) with the institute for Human Genetic(Berlin) is a joint effort of the clinic directed by Pr. Amling and two research groups of the IOBM (AG Schinke and AG David). It was mainly performed by Dr. Luther and Yorgan for the experimental part, Dr. Rolvien in the clinic, in collaboration with Pr. Trump (DKFZ, Heidelberg) and Dr. Bockamp (Mainz University). The IOBM was funded by the DFG (AM103/29, DA1067/5, SCHI 504/6), BMBF (DIMEOS), FP7-EU (SYBIL).