UKE Paper of the Month February 2013

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Canonical Wnt signaling inhibits osteoclastogenesis independent of osteoprotegerin

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ABSTRACT: Although Wnt signaling is considered a key regulatory pathway for bone formation, inactivation of ß-catenin in osteoblasts does not affect their activity but rather causes increased osteoclastogenesis due to insufficient production of osteoprotegerin (Opg). By monitoring the expression pattern of all known genes encoding Wnt receptors in mouse tissues and bone cells we identified Fzd8 as a candidate regulator of bone remodeling. Fzd8-deficient mice displayed osteopenia with normal bone formation and increased osteoclastogenesis, but this phenotype was not associated with impaired Wnt signaling or Opg production by osteoblasts. The deduced direct negative influence of canonical Wnt signaling on osteoclastogenesis was confirmed in vitro and through the generation of mice lacking ß-catenin in the osteoclast lineage. Here we observed increased bone resorption despite normal Opg production and a resistance to the anti-osteoclastogenic effect of Wnt3a. These results demonstrate that Fzd8 and ß-catenin negatively regulate osteoclast differentiation independent of osteoblasts and that canonical Wnt signaling controls bone resorption by two different mechanisms.

STATEMENT: *Since the discovery of the putative Wnt co-receptor LRP5 as a major determinant of bone formation in humans (Gong et al., Cell, 2001; Boyden et al., N. Engl. J. Med., 2001), several studies have been performed to address the role of Wnt signaling in bone-forming osteoblasts. These included the generation of mouse models lacking ß-catenin, the major intracellular mediator of canonical Wnt signalling, in osteoblasts, where results from three different groups have led to the consensus, that this pathway does not control bone formation, but bone resorption by activating expression of the osteoclastogenesis inhibitor osteoprotegerin.*
In our manuscript we provide in vitro- and in vivo-evidence demonstrating that ß-catenin-dependent Wnt signaling mediates a direct negative influence on osteoclastogenesis, independent of osteoprotegerin expression in osteoblasts. Importantly, we could also show that the Wnt receptor Fzd8 is involved in this process, which is particularly relevant, since Fzd receptors, based on their serpentine structure, are considered as excellent drug targets.

BACKGROUND: The Institute of Osteology and Biomechanics (IOBM) was founded in 2010 and is specialized on the osteologic assessment of patients and on research regarding the molecular mechanisms underlying skeletal development and remodeling as well as the pathogenic principles causing genetic and acquired skeletal disorders. This particular project was performed in the molecular biology unit of the IOBM, located in the Campus-Forschung building (N27) and received funding form the Deutsche Forschungsgemeinschaft as a subproject of the Research group FOR793 (Mechanisms of fracture healing and bone regeneration in osteoporosis).