UKE Paper of the Month March 2011

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Control of bone formation by the serpentine receptor Frizzled-9

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Abstract: Although Wnt signaling in osteoblasts is of critical importance for the regulation of bone remodeling, it is not yet known which specific Wnt receptors of the Frizzled family are functionally relevant in this process. Here, we show that Fzd9 is induced upon osteoblast differentiation and that $Fzd9^{-/-}$ mice display low bone mass caused by impaired bone formation. Our analysis of $Fzd9^{-/-}$ primary osteoblasts demonstrated defects in matrix mineralization in spite of normal expression of established differentiation markers. In contrast, we observed reduced expression of chemokines and interferon-regulated genes in $Fzd9^{-/-}$ osteoblasts. We also identified the ubiquitin-like modifier Isg15 as one potential downstream mediator of Fzd9 in these cells. Importantly, our molecular analysis further revealed that canonical Wnt signaling is not impaired in the absence of Fzd9, thus explaining the absence of a bone resorption phenotype. Taken together, our results reveal a previously unknown function of Fzd9 in osteoblasts, a finding which may have therapeutic implications for bone loss disorders.

Statement: Albeit osteoporosis is one of the most common disorders in the aged population, the therapeutic options are still limited. In our manuscript we have identified the first receptor of the Frizzled family that specifically controls bone formation, at least in mice, and possibly in humans. Since Fzd9, as a serpentine receptor, belongs to the major class of target proteins for currently available drugs, it is reasonable to speculate that a Fzd9-specifiic agonist can be used for osteoanabolic therapy.

This study was done in the newly formed Department of Osteology and Biomechanics, which is led by Prof. Dr. Michael Amling and PD Dr. Thorsten Schinke. The project is funded as a part of the DFG transregional research group 793 “Mechanisms of Fracture Healing and Bone Regeneration”. Within the UKE we have collaborated with several other departments in terms of bone histology (Trauma, Hand and Reconstructive Surgery), retroviral transfection (Stem Cell Transplantaion), Gene Chip Hybridization (Clinical Chemistry) and immunohistochemistry (Pathology). This can be seen as a positive result of the raising amount of scientific interactions within the new Campus-Forschung building N27.