Control of bone formation by the serpentine receptor Frizzled-9.

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. In this paper, 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 a 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. Collectively, our results reveal a previously unknown function of Fzd9 in osteoblasts, a finding that may have therapeutic implications for bone loss disorders.

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