UKE Paper of the Month März 2018

Lrp1 in osteoblasts controls osteoclast activity and protects against osteoporosis by limiting PDGF–RANKL signaling

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ABSTRACT: Skeletal health relies on architectural integrity and sufficient bone mass, which are maintained through a tightly regulated equilibrium of bone resorption by osteoclasts and bone formation by osteoblasts. Genetic studies have linked the gene coding for low-density lipoprotein receptor-related protein1 (Lrp1) to bone traits but whether these associations are based on a causal molecular relationship is unknown. Here we show that Lrp1 in osteoblasts is a novel regulator of osteoclast activity and bone mass. Mice lacking Lrp1 specifically in the osteoblast lineage displayed normal osteoblast function but severe osteoporosis due to highly increased osteoclast numbers and bone resorption. Osteoblast Lrp1 limited receptor activator of NF-κB ligand (RANKL) expression *in vivo* and *in vitro* through attenuation of platelet-derived growth factor (PDGF-BB) signaling. In co-culture, Lrp1-deficient osteoblasts stimulated osteoclastogenesis in a PDGFRβ-dependent manner and *in vivo* treatment with the PDGFR tyrosine kinase inhibitor imatinib mesylate limited RANKL production and led to complete remission of the osteoporotic phenotype. These results identify osteoblast Lrp1 as a key regulator of osteoblast−to−osteoclast communication and bone mass through a PDGF-RANKL signaling axis in osteoblasts and open perspectives to further explore the potential of PDGF signaling inhibitors in counteracting bone loss as well as to evaluate the importance of functional *LRP1* gene variants in the control of bone mass in humans.

STATEMENT: *We discovered that the lipoprotein receptor Lrp1 expressed by osteoblasts regulates bone mass through a novel PDGF RANKL signalling pathway, and demonstrate that this mechanism can be therapeutically exploited to treat osteoporosis in preclinical models.*

BACKGROUND: This work is the result of an interdisciplinary research approach of the Departments of Orthopaedics, Biochemistry and Molecular Cell Biology, and Department of Osteology and Biomechanics with help from additional international expert leaders. Drs. Bartelt, Heeren and Niemeier have a long-standing interest in understanding the interaction of systemic energy metabolism and bone, with the ultimate goal of developing novel therapeutics for obesity-related diseases and skeletal disorders. This study was supported by grants from DFG and BMBF “Metabolic Impact on Joint and Bone Diseases”.