

Doctoral dissertation

Overexpression of miR-125b in osteoblasts inhibits bone resorption without affecting skeletal development and improves age-related changes in bone mass and quality

(miR-125b の骨芽細胞特異的過剰発現は骨格成長への影響なく骨吸収を阻害し、加齢性の骨量や骨質への変化を改善する)

Shota Ito

Biomedical Sciences Major, Doctoral Course
Graduate School of Biomedical and Health Sciences
Hiroshima University

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Chief academic supervisor: Professor Kotaro Tanimoto
(Department of Orthodontics and Craniofacial Developmental Biology)

Abstract

Recently, we identified an expected role of matrix vesicles (MVs), budding from osteoblasts, in delivery of microRNAs to bone matrix. Of these, miR-125b inhibits osteoclast formation by targeting *Prdm1*, a transcriptional repressor of anti-osteoclastogenesis factors. Transgenic (Tg) mice overexpressing miR-125b in osteoblasts grow normally but exhibit high trabecular bone mass. We then determined whether miR-125b overexpression in osteoblasts affects bone development, aging, and fracture healing in mice. There were no significant differences in primary ossification center and lateral (periosteal) bone formation and mineral apposition rate between Tg and wild type (WT) mice during early bone development (from embryonic day 16.5). However, medial (endosteal) bone resorption and osteoclast number were less in Tg than WT mice, in parallel with increased trabecular bone mass. When compared with WT mice, Tg mice retained bone mass, phosphate/amide I ratio and mechanical strength even at 77 weeks old. During fracture healing, callus formation progressed equally in Tg and WT mice, while callus resorption was delayed in Tg mice with decreased number of osteoclasts. Taken together, our data suggest that miR-125b overexpression

in osteoblasts may increase bone mass and strength with decreased number of osteoclasts while keeping bone formation and bone quality. These findings may provide a novel therapeutic target for bone loss.