Effects of miRNA-125b on Bone Morphometry in Ovariectomized Mice

ABSTRACT

Objective: MicroRNAs (miRNAs) are small non-coding RNAs involved in the regulation of gene expression. Previously our group demonstrated that miRNAs are enriched in matrix vesicles (MVs) secreted from osteoblasts and accumulate in the bone matrix. Of miRNAs identified, miRNA-125b (miR-125b) inhibits osteoclast formation by targeting the transcription repressor *Prdm1*, resulting in increased expression of anti-osteoclastogenic genes. To demonstrate the potential of miR-125b as a therapeutic target for skeletal diseases, we quantified bone morphometry in transgenic (Tg) mice overexpressing miR-125b with and without ovariectomy (OVX).

Methods & Results: Tg mice overexpressing mmu-miR-125b-5p were generated under the control of the human osteocalcin promoter. miR-125b levels were higher in bones and osteoblasts in Tg mice *vs.* wild type (WT) counterparts and *vs.* bone marrow macrophages with and without RANKL/M-CSF and extra-skeletal tissues in both genotypes. Tg mice were born at normal Mendelian ratios and grew normally, while they had high bone mass as determined by micro computed tomography (μCT). Calcein double-labeling revealed no difference in bone formation rate in Tg *vs.* WT mice. μCT analysis of long bones and vertebrae showed that the high bone mass in Tg mice arose as a result of increased trabecular bones extending over the medullary cavity, independent of gender. We then performed OVX in 10-week-old female mice. After 8 weeks, OVX caused weight gain equally in both genotypes, while OVX-dependent bone loss was significantly reduced in Tg mice.

Conclusion: These findings indicate that osteoblasts may regulate osteoclast formation though the mechanism underlying MV-mediated transport of miR-125b. This pathway may serve a potential therapeutic target for OVX-induced bone loss.

Keywords: miRNA 125b, Matrix vesicles, Osteoclast formation, Ovariectomy