In vivo anabolic effect of strontium on trabecular bone was associated with increased osteoblastogenesis of bone marrow stromal cells

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INTRODUCTION: The cellular and molecular mechanism for the dual action of strontium (Sr) remains poorly understood. In vitro studies from our and other groups demonstrated that Sr can increase osteogenic differentiation of bone marrow stromal cells (BMSCs)1, 2, 3, but the in vivo effect of Sr on BMSCs is not known.

MATERIALS AND METHODS: Thirty six 3-month old female Sprague-Dawley rats were randomly divided into the following four groups: Sham+Veh, Sham+Sr, OVX+Veh and OVX+Sr. Both Veh and Sr were orally administrated daily 7 days after the surgery and lasted for 12 weeks. Serum osteocalcin was measured at week 4, 8 and 12 after Sr treatment. The effect of Sr on trabecular bone microstructure and bone remodeling was analyzed by microCT and histomorphometry respectively on proximal tibiae. The effect of Sr on lineage differentiation of rat BMSCs was analyzed with colony formation assays and real-time PCR. Effect of Sr treatment on lineage differentiation of cultured human BMSCs cell line was assessed with biochemical analysis and real-time PCR.

RESULTS: Sr treatment resulted in a significant increase for serum osteocalcin compared with Veh treatment in Sham and OVX rats at week 12 (p<0.05). Bone volume (BV/TV), trabecular number (Tb. N) and connectivity density (Conn. D) assessed by microCT were significantly higher in Sr-treated versus Veh-treated OVX rats (p<0.05 for all) (Fig. 1). Histomorphometric analysis demonstrated that Sr significantly increased mineralizing surface (MS/BS), bone formation rate (BFR/BS) and osteoid surface (OS/BS) compared with that of Veh treatment in OVX rats (p<0.05 for all). Colony formation assays demonstrated that BMSCs from Sr-treated group exhibited higher osteogenic colony (CFU-Osteo, p<0.05) but lower adipogenic colony (CFU-Adipo, p<0.05) compared with that of Veh-treated OVX rats (Fig. 2). There was no significant difference for the proliferation of BMSCs between the two groups. Runx2 and osteocalcin mRNA level was higher while PPAR-γ mRNA level was lower in the bone marrow from Sr-treated versus Veh-treated Sham and OVX rats, respectively. Runx2 mRNA level, ALP activity was significantly higher while PPAR-γ mRNA level and adipocyte number was significantly lower in Sr-treated versus Veh-treated human BMSCs (Fig. 3).

CONCLUSIONS: This was the first study to evaluate the effect of Sr on in vivo bone formation at the progenitor cell level. The data indicated that the enhanced bone-forming effect of Sr on Sham and OVX rat bones was associated with increased osteoblastic differentiation of BMSCs. The modulation of in vivo and in vitro differentiation preferably towards osteoblast lineage of BMSCs by Sr provides a novel mechanism of the anabolic effect of anti-osteoporosis agent strontium ralenate on postmenopausal women.


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Fig. 1 Representative 3-D images of proximal tibiae trabecular bone by microCT.

Fig. 2 Effect of Sr treatment on rat BMSCs proliferation and differentiation.

Fig. 3 Effect of Sr on the osteogenic lineage differentiation of human BMSCs.