FATP2 Promotes Osteoclastogenesis by Regulating Lipid Metabolism and ROS production

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INTRODUCTION: The maintenance of bone homeostasis is dependent on a delicate balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Disruption of this equilibrium can result in various bone-related disorders, including pathological fractures, osteosclerosis and osteoporosis. Obese patients and HFD mice both exhibited decreased bone mass and density, as well as increased numbers and activity of osteoclasts, indicating that excessive lipid intake can enhance osteoclastic activity. Current clinical treatments for osteoporosis primarily focus on inhibiting OCs to reduce bone loss through the use of bisphosphonates; however, effective therapeutic strategies specifically targeting lipid accumulation-induced osteoporosis are currently lacking. FATP2, which is encoded by the Slc27a2 gene, belongs to the family of fatty acid transport proteins. It is primarily located on the endoplasmic reticulum membrane, cell membrane and peroxisome membrane where it functions as a transporter for long-chain and very-long-fatty acids while also serving as a long-chain and very-long-chain fatty acyl-CoA synthetase. However, the precise role of FATP2 in osteoclastogenesis remains unclear. The objective of this investigation is to explore the correlation between FATP2 and lipid metabolism in osteoclasts, with the aim of devising effective clinical strategies for preventing and treating osteoporosis.

METHODS: Murine bone marrow-derived macrophages (BMMs) were isolated for osteoclastogenesis, followed by protein and gene analysis as well as TRAP staining to evaluate osteoclast differentiation. To mimic the phenotype of obesity-induced osteoporosis, mice were fed a high-fat diet for 12 weeks. Lipopolysaccharide (LPS) and ovariectomy (OVX) were employed to establish models of osteoporosis, with intervention performed via intraperitoneal injection of the FATP2 inhibitor Lipofemata. Micro-CT was utilized for bone mass measurement, while immunofluorescence staining was employed to detect protein expression.

RESULTS: Lipid metabolism plays a crucial role in maintaining bone homeostasis, particularly in osteoclasts (OCs) formation. Here, we found the expression level of FATP2, a transporter for long-chain and very-long-chain fatty acids, was significantly upregulated during OC differentiation and in the bone marrow of mice fed a high-fat diet (HFD). Notably, the use of FATP2 siRNA or a specific inhibitor (Lipofemata) resulted in significant inhibition of OC differentiation while only slightly affecting osteoblasts (OBs). In pathological models of bone loss induced by LPS or OVX, in vivo treatment with Lipofemata was able to rescue the loss of bone mass by inhibiting OC differentiation. RNA sequencing (RNA-seq) revealed that Lipofemata reduced fatty acid β-oxidation and inhibited energy metabolism, while regulating reactive oxygen species (ROS) metabolism to decrease ROS production, ultimately inhibiting OC differentiation. Treatment with Lipofemata, either in vivo or in vitro, effectively rescued the overactivation of OCs, indicating that FATP2 regulated OC differentiation by modulating fatty acid uptake and energy metabolism. These findings suggested that targeting FATP2 may represent a promising therapeutic approach for pathological osteoporosis.

DISCUSSION: The inhibition of osteoclastogenesis by Lipofemata, a FATP2 inhibitor, was achieved through the reprogramming of energy metabolism and regulation of ROS levels. In both pathological bone loss and HFD-induced osteoporosis models, the expression levels of FATP2 were significantly upregulated and Lipofemata demonstrated potential therapeutic effects in the pathological bone loss model.

SIGNIFICANCE/CLINICAL RELEVANCE: FATP2 may be a novel therapeutic target for osteogenesis and osteoporosis treatment.