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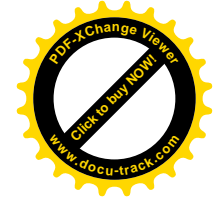
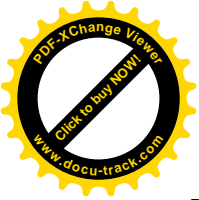
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PO21

Title: THE FREE FATTY ACID RECEPTOR GPR40 PROTECTS FROM BONE LOSS THROUGH INHIBITION OF OSTEOCLAST DIFFERENTIATION

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Abstract: The mechanisms linking fat intake to bone loss remain unclear. By demonstrating the expression of the free fatty acid receptor Gcoupled Protein Receptor 40 (GPR40) in bone cells, we hypothesized that this receptor may play a role in mediating the effects of fatty acids on bone remodeling. Using μ CT analysis, we showed that GPR40^{-/-} mice exhibit osteoporotic features suggesting a positive role of GPR40 on bone density. In primary cultures of bone marrow, we showed that GW9508, a GPR40 agonist, abolished bone resorbing cell differentiation. This alteration of the Receptor Activator of NF- κ B Ligand (RANKL)-induced osteoclast differentiation occurred via the inhibition of the Nuclear Factor κ B (NF- κ B) signalling pathway as demonstrated by decrease in gene reporter activity, inhibitor of κ B kinase (IKK α / β) activation, inhibitor of κ B (I κ B α) phosphorylation and Nuclear Factor of Activated T cells 1 (NFATc1) expression. The GPR40-dependent effect of GW9508 was confirmed using shRNA interference in osteoclast precursors and GPR40^{-/-} primary cell cultures. In addition, in vivo administration of GW9508 counteracted ovariectomy-induced bone loss in wild-type but not GPR40^{-/-} mice enlightening the obligatory role of the GPR40 receptor. Then, in a context of growing prevalence of metabolic and age-related bone disorders, our results demonstrate for the first time in translational approaches that GPR40 is a relevant target for the design of new nutritional and therapeutic strategies to counter bone complications.