



The Free Fatty Acid Receptor GPR40 Protects from Bone Loss through Inhibition of Osteoclast Differentiation

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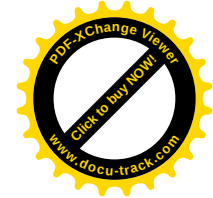
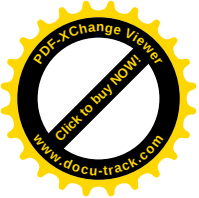
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Title: THE FREE FATTY ACID RECEPTOR GPR40 PROTECTS FROM BONE LOSS THROUGH INHIBITION OF OSTEOCLAST DIFFERENTIATION

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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 G-protein coupled 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.