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## **GPR40: a new relevant target for nutraceutical-based prevention of bone loss**

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**Keywords:** GPR40, fatty acids, osteoporosis, osteoclast, NF- $\kappa$ B

### **Background:**

Industrialized countries face an amplified prevalence of metabolic disorders as a consequence of increased amount of fat in daily food intake. The main social and economic burdens of these pathologies lay in their complications including cardio-vascular diseases, cancers and osteoporosis. However, from a “bone” point of view, mechanisms linking fat intake to bone alteration remain quite controversial.

### **Objectives:**

By demonstrating the expression of the free fatty acid receptor G-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.

### **Methods and Results:**

Using  $\mu$ CT analysis, we showed that GPR40<sup>-/-</sup> mice exhibit osteoporotic features suggesting a positive role of GPR40 on bone density. In primary cultures of bone marrow, we revealed that GW9508, a GPR40 agonist, abolished bone resorbing cell differentiation. This alteration of the Receptor Activator of NF- $\kappa$ B Ligand (RANKL)-induced osteoclast differentiation occurred via the inhibition of the Nuclear Factor  $\kappa$ B (NF- $\kappa$ B) signalling pathway as demonstrated by decrease in gene reporter activity, inhibitor of  $\kappa$ B kinase (IKK $\alpha/\beta$ ) activation, inhibitor of  $\kappa$ B (I $\kappa$ B $\alpha$ ) 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<sup>-/-</sup> primary cell cultures. In addition, *in vivo* administration of GW9508 counteracted ovariectomy-induced bone loss in wild-type but not GPR40<sup>-/-</sup> mice enlightening the obligatory role of the GPR40 receptor.

### **Conclusions:**

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.

### **Funding:**

N/A

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