Thiazolidinediones Induce Osteocyte Apoptosis by a G Protein-coupled Receptor 40-dependent Mechanism

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Résumé en anglais	Thiazolidinediones (TZDs) represent an interesting treatment of type 2 diabetes mellitus. However, adverse effects such as heart problems and bone fractures have already been reported. Previously, we reported that pioglitazone and rosiglitazone induce osteocyte apoptosis and sclerostin up-regulation; however, the molecular mechanisms leading to such effects are unknown. In this study, we found that TZDs rapidly activated Erk1/2 and p38. These activations were mediated through Ras proteins and GPR40, a receptor expressed on the surface of osteocytes. Activation of this pathway led only to osteocyte apoptosis but not sclerostin up-regulation. On the other hand, TZDs were capable of activating peroxisome proliferator-activated receptor-γ, and activation of this signaling pathway led to sclerostin up-regulation but not osteocyte apoptosis. This study demonstrates two distinct signaling pathways activated in osteocytes in response to TZDs that could participate in the observed increase in fractures in TZD-treated patients.
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Liens

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