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Estrogen receptor-β confers isoflavone induced expression of osteoprotegrin, a potent inhibitor of osteoclast differentiation.

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The treatment of isoflavones, especially genistein (10^{-9}M) and daidzein (10^{-6}M), increases estrogen receptor-α (ERα) expression and proliferation of MG-63 osteoblastic cells. In contrast, the increase of estrogen receptor-β (ERβ) expression in proliferating MG-63 cells with isoflavone treatment is less pronounced, which suggested that ERβ may play a role rather in the regulation of osteoclast differentiation. To determine the role of ERβ in isoflavone-mediated regulation of osteoclast differentiation, we established MG-63 cell lines stably expressing ERβ. Constitutive expression of ERβ did not affect ERα expression and proliferation of MG-63 cells. However expressing ERβ in MG-63 cells (ERβ-MG-63 cells) significantly enhanced the isoflavone induced expression of osteoprotegrin (OPG), a novel soluble glycoprotein which is secreted from osteoblasts and mediates the signal for osteoclast differentiation. In addition, the treatment of ERβ-MG-63 cells with yak-kong extracts, which contained low levels of genistein and daidzein (genistein 0.4 x 10^{-14}M; daidzein 0.2 x 10^{-14}M), further enhanced the expression of OPG. The increased effect of yak-kong treatment on OPG expression was comparable to the combined treatment of daidzein and genistein standards (10^{-14}M + 10^{-14}M). Together, coupled with low level of ER in osteoclasts, our data demonstrate that ERβ in osteoblasts plays an important role in isoflavone mediated inhibition of osteoclast differentiation indirectly by enhancing the expression of OPG. The greater expression of OPG with yak-kong treatment is mediated by the synergistic effect of low leveled isoflavones in extracts.