OSTEOPOROSIS

Elucidating the role of the glucocorticoid receptor in glucocorticoid-induced osteoporosis

Glucocorticoids are commonly used to treat patients with autoimmune diseases, but are known to induce osteoporosis. These agents are thought to reduce bone mass via induction of apoptosis and/or suppression of osteoblast differentiation, effects that are mediated by the glucocorticoid receptor (GR), a nuclear receptor that is expressed in many cell types. Dimerized GR can induce transcription of hormone-responsive genes, and as a monomer the GR interacts with several DNA-bound transcription factors, such as nuclear factor κB (NFκB). The dimerized form is thought to be mainly responsible for glucocorticoid-induced osteoporosis. Rauch *et al.* performed a range of experiments in mice to try to form a better understanding of the mechanisms by which the GR mediates bone loss in response to glucocorticoids.

They found that prednisolone failed to induce reductions in bone formation rate, bone mass and trabecular thickness in mice lacking GR expression in osteoblasts ($GR^{Runx2Cre}$ mice). Osteoblast numbers were also unaffected by prednisolone in $GR^{Runx2Cre}$ mice, whereas they were diminished in prednisolone-treated wild-type animals. Notably, the researchers did not detect increased osteoblast apoptosis in these wild-type mice, suggesting that this mechanism might not explain the observed dramatic decrease in mature osteoblast numbers.

> “... dimerized GR is not required for glucocorticoid-induced osteoporosis...”

Mice with a dimerization-deficient mutant GR (GR^{dim} mice) showed a decrease in bone formation following prednisolone treatment similar to that observed in wild-type mice, indicating that dimerized GR is not required for glucocorticoid-induced osteoporosis. Dimerized GR was found to be necessary for osteoblast proliferation; however, it was not shown to be required for osteoblastogenesis.

The authors showed that monomeric GR was capable of suppressing cytokines under the transcriptional control of AP-1, which ultimately led to decreased osteoblast differentiation. Repression of NFκB-associated genes—which is an important anti-inflammatory effect of glucocorticoids—had no effect on bone loss. The authors suggest, therefore, that selective GR agonists that do not interfere with AP-1 activity might show the required anti-inflammatory properties without inducing osteoporosis.

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Original article Rauch, A. *et al.* Glucocorticoids suppress bone formation by attenuating osteoblast differentiation via the monomeric glucocorticoid receptor. *Cell Metab.* **11**, 517–531 (2010)