

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

Expression of an estrogen receptor agonist in differentiating osteoblast cultures

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The skeleton is a well-recognized target for sex steroids. Bone fragility is notable when sex steroid levels fall in women after menopause, in elderly males, or after sex organ ablation. In such cases, bone loss follows a release from native constraints on bone resorption that largely result from changes in growth regulators expressed by osteoblasts and from opposing effects on osteoblast and osteoclast activation and apoptosis, leading to an overall increase in bone remodeling. Importantly, imbalances in bone remodeling are restored by sex hormone replacement therapy. Osteoblasts respond in direct and indirect ways to estrogens, and express the estrogen receptor.

In a recent study [1], the authors report the release and isolation of an estrogen receptor agonist from osteoblast cultures. This entity reprises many aspects of estradiol activity in isolated osteoblasts, but differs from authentic estradiol by several biochemical and physical criteria. At levels that occur in conditioned medium from differentiating osteoblast cultures, the agonist directly drives gene expression through estrogen-sensitive response elements, activates the obligate osteoblast transcription factor Runx2, and potentially enhances Smad-dependent gene expression in response to TGF- β , but exhibits relatively lesser suppressive effects on gene expression through C/EBP and AP-1-binding protein transcription factors. Mass spectrometry and molecular fragmentation analyses predict a molecular weight of 415.2 to 437.2 which, together with the physical and chemical properties, is consistent with a cholesterol-derived product.

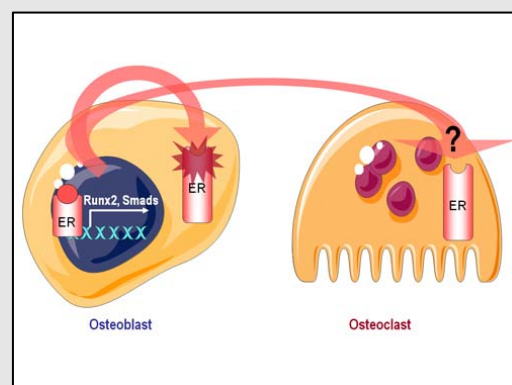
Therefore, in addition to earlier studies showing that osteoblasts readily respond to and metabolize various sex steroid-like substrates, this study shows that they also generate a potent estrogen receptor agonist during differentiation in vitro. Changes in the availability of a molecule like this within bone may relate to differences in skeletal integrity with aging or metabolic disease.

1. McCarthy TL et al. *Proc Natl Acad Sci USA*. 2008;105 :7022-7027.

Expression of an estrogen receptor agonist in differentiating osteoblast cultures

Both osteoblasts and osteoclasts express estrogen receptors. Estrogens exert opposite effects on these cells, promoting osteoblast differentiation and inducing osteoclast apoptosis. Osteoblasts were recently shown to synthesize a ligand of estrogen receptor with physical and chemical properties of a cholesterol-derived compound. Binding of this ligand to the estrogen receptor drives gene expression through estrogen-sensitive response elements and activates the obligate osteoblast transcription factor Runx2, and potentially enhances Smad-dependent gene expression in response to TGF- β , thus promoting osteoblast differentiation. Whether this ligand is also able to act on osteoclasts is not known.

Changes in the availability of a molecule like this within bone may relate to differences in skeletal integrity with aging or metabolic disease.



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