

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

Estrogens prevent osteoporotic bone loss by inducing osteoclast apoptosis?

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Estrogens are key hormones in bone remodeling. Estrogen deficiency in postmenopausal women frequently leads to osteoporosis, the most common skeletal disorder. Osteoporotic bone loss is the result of high bone turnover in which bone resorption outpaces bone formation. This imbalance can be ameliorated with bioavailable estrogens. Estrogens primarily act by regulating gene transcription via estrogen receptors (ER α , ER β). In mice, though ER α appears to be the major estrogen receptor, neither bone loss nor high bone turnover is detectable in ER α knock-out females. This unexpected maintenance of bone mass in female mutants is presumed to be due to unphysiologically elevated levels of other osteoprotective hormones, like androgens. Systemic defects in the hypothalamus caused by ER inactivation appear to impair the negative feedback system of hormone production. This leads to an excess in estrogen precursors, notably androgens. Thus, irrespective of the accumulating clinical and basic research data on the osteoprotective actions of estrogens, the molecular basis of this osteoprotection in females remains elusive. In this study [1], the authors report a critical role for ER α in mediating estrogen-dependent bone maintenance in female mice.

In mice, ER α were selectively ablated in differentiated osteoclasts. Females, but not males, exhibited trabecular bone loss, similar to the osteoporotic bone phenotype in postmenopausal women. Further, estrogens induced apoptosis (programmed cell death) and upregulation of Fas ligand (FasL), a proapoptotic mediator expression in osteoclasts of the trabecular bones of wild type but not transgenic mice lacking ER α in their osteoclasts. The expression of ER α was also required for the induction of apoptosis in cultured osteoclasts.

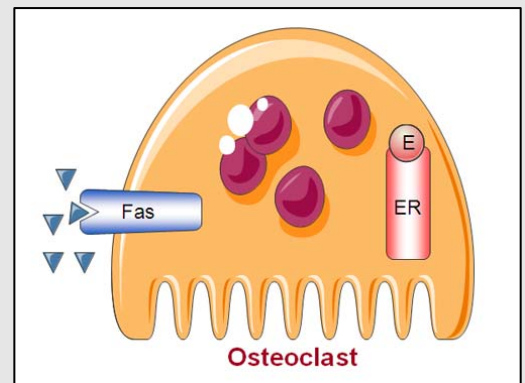
These results support a model in which estrogen regulates the life span of mature osteoclasts via the induction of the Fas/FasL system, thereby providing an explanation for the osteoprotective function of estrogens. However, osteoporosis involves also a deficit in bone formation, which is an important therapeutic target.

1. Nakamura T et al. *Cell*. 2007;130:811-823.

Estrogens prevent osteoporotic bone loss by inducing osteoclast apoptosis

Osteoporotic bone loss is the result of high bone turnover in which bone resorption, performed by osteoclasts, outpaces bone formation. Osteoclasts are a target for estrogens because they express the estrogen receptor (ER). Binding of estrogens to their receptors triggers the transcription of several genes. One of them is Fas ligand (FasL) which is then secreted by osteoclasts. Fas ligand is then able to bind a membrane receptor called Fas which triggers programmed cell death or apoptosis.

In the absence of estrogens, osteoclast apoptosis is deficient and numerous active osteoclasts are responsible for postmenopausal osteoporosis.



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