

The mechanisms of estrogen regulation of bone resorption

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J Clin Invest. 2000;106(10):1203-1204. <https://doi.org/10.1172/JCI11468>.

Commentary

Estrogen (E) deficiency causes both the early and late forms of osteoporosis in postmenopausal women and contributes to the development of osteoporosis in elderly men (1). It is associated with large increases in bone resorption caused by increased osteoclast (OC) numbers (due to enhanced OC formation and reduced OC apoptosis) and by increased OC activity (2). Since the demonstration in 1988 that bone cells contain functional E receptors, progress on elucidating the molecular basis of E action has been rapid, albeit controversial and incomplete. Early studies on E's role in bone metabolism focused on the role of the proinflammatory cytokines — IL-1, IL-6, TNF- α , granulocyte macrophage colony-stimulating factor, macrophage colony-stimulating factor (M-CSF), and prostaglandin-E2 (PGE2). These factors increase bone resorption, mainly by increasing the pool size of pre-OCs in bone marrow (2, 3), and are downregulated by E. Moreover, ovariectomy-induced increases in OCs are attenuated or prevented by measures that impair the synthesis of or response to IL-1, IL-6, TNF- α , or PGE2 (2, 3). Other studies have found that E upregulates TGF- β , an inhibitor of bone resorption that acts directly on OC to decrease activity and increase apoptosis (2). However, E regulation of bone resorption must now be re-evaluated in the light of the recent discovery of three new members of the TNF ligand and receptor signaling family that serve [...]

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pages 1229–1237.

Estrogen (E) deficiency causes both the early and late forms of osteoporosis in postmenopausal women and contributes to the development of osteoporosis in elderly men (1). It is associated with large increases in bone resorption caused by increased osteoclast (OC) numbers (due to enhanced OC formation and reduced OC apoptosis) and by increased OC activity (2). Since the demonstration in 1988 that bone cells contain functional E receptors, progress on elucidating the molecular basis of E action has been rapid, albeit controversial and incomplete.

Early studies on E's role in bone metabolism focused on the role of the proinflammatory cytokines – IL-1, IL-6, TNF- α , granulocyte macrophage colony-stimulating factor (M-CSF), and prostaglandin-E₂ (PGE₂). These factors increase bone resorption, mainly by increasing the pool size of pre-OCs in bone marrow (2, 3), and are downregulated by E. Moreover, ovariectomy-induced increases in OCs are attenuated or prevented by measures that impair the synthesis of or response to IL-1, IL-6, TNF- α , or PGE₂ (2, 3). Other studies have found that E upregulates TGF- β , an inhibitor of bone resorption that acts directly on OC to decrease activity and increase apoptosis (2).

However, E regulation of bone resorption must now be re-evaluated in the light of the recent discovery of three new members of the TNF ligand and receptor signaling family that serve as the final effectors of OC differentiation and function (4, 5). The long-sought osteoblast-derived paracrine effector of OC differentiation has been identified as the receptor activator of NF- κ B ligand (RANKL, also called OPG ligand or OC differentiating factor), which is expressed by stromal-osteoblast lineage cells. Contact between these cells and cells of the OC lineage allows RANKL to bind its physiologic receptor, RANK,

potently stimulating all aspects of OC function: In response to RANKL signaling, OC differentiation and activity increase, and OC apoptosis decreases. Indeed, RANKL is both necessary and sufficient for OC formation, provided that permissive concentrations of M-CSF are present. The stromal-osteoblast lineage cells also secrete osteoprotegerin (OPG), a soluble decoy receptor that neutralizes RANKL. E increases OPG (5) and decreases M-CSF (3) and RANK (6). Part of the effect on this signaling system may be indirect, acting through E-responsive intermediaries. Thus, IL-1 and TNF- α increase RANKL, OPG, and M-CSF, whereas PGE₂ increases RANKL and decreases OPG (3, 5). E has not yet been shown to regulate RANKL directly.

In elegant studies published in this issue of the *JCI*, Cenci et al. (7) report

that increased production of TNF- α by T cells in bone marrow mediates the increased bone resorption and bone loss in ovariectomized (OVX) mice. These authors show that ovariectomy-induced bone loss can be prevented by administering either E, TNF- α binding protein, or an inactivating antibody specific for TNF- α , and that bone loss does not occur in OVX, T cell-deficient animals. OVX mice also increase production of TNF- α in their T cells, probably as a result of an increase in T cell numbers, rather than an increase in TNF- α production per cell. TNF- α is not upregulated in bone marrow monocytes (BMMs) under these conditions. TNF- α augments M-CSF- and RANKL-dependent OC formation. This appears to be a direct effect of TNF- α on OC precursors, rather than an indirect effect brought about by TNF- α

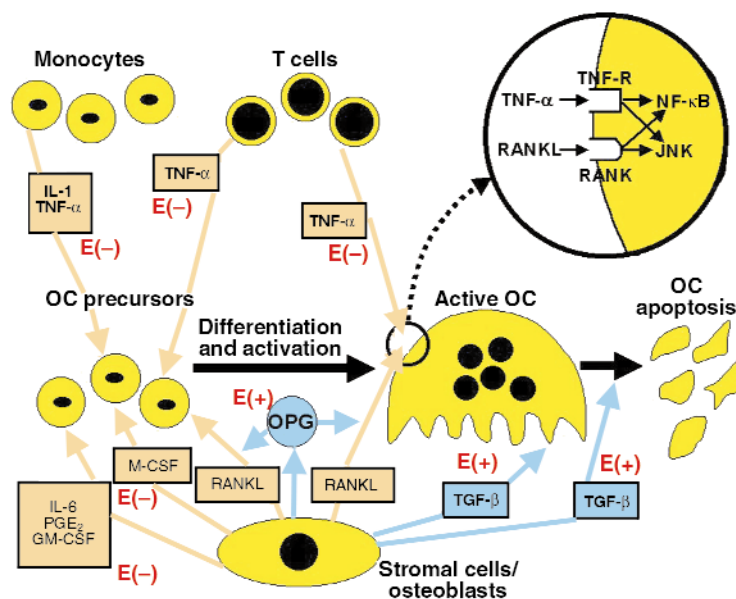


Figure 1

Major cytokines in the bone microenvironment that regulate OC function. Stimulatory factors are shown in orange and inhibitory factors are shown in blue. Positive (+) or negative (–) effects of E on these regulatory factors are shown in red. The blow-up circle shows that TNF- α and RANKL act through separate receptors, but both activate the NF- κ B and JNK intracellular signaling pathways. GM-CSF, granulocyte macrophage-colony-stimulating factor.

stimulation of RANKL production (3, 5), since TNF- α fails to induce OC formation in BMMs from OVX mice lacking the p55 TNF- α receptor (TNF-R1). Cenci et al. (7) note that both RANKL and TNF- α independently activate the NF- κ B and JNK intracellular signaling pathways in OC lineage cells, and they hypothesize that this convergence explains the additive effects of the two cytokines. They conclude that while M-CSF and RANKL are essential for physiologic OC renewal, TNF- α plays a key causal role in the bone loss associated with E deficiency.

Although these data are important, several caveats must be kept in mind. First, the regulation of bone metabolism varies widely among rodents of different ages, strains, and species, and varies even more between rodents and humans, raising serious questions about the generality of the findings. Indeed, Pacifici's laboratory has previously reported that TNF- α and IL-1 must be inhibited simultaneously if bone loss is to be prevented in OVX rats (8). Also, Miyaura et al. (9) found that the combined effect of IL-1 α , IL-6, and PGE₂ could account for the increase in resorption bioactivity from marrow of another strain of OVX mice. Also, prevention of postovariectomy bone loss by blocking the production or activity of a single cytokine does not establish per se that it is the sole causal agent.

Because bone-regulating cytokines, such as IL-1, TNF- α , and IL-6, synergize to stimulate their own and each other's synthesis, a small change in one cytokine in the bone microenvironment could dramatically alter the concentration of the others. Thus, the absence of any one cytokine may be sufficient to prevent this amplification from occurring. Finally, it seems unlikely that TNF- α is the sole mediator of the E effect on bone resorption, because genetically targeted mice deficient in TNF-R1 have normal bone histology (10). In contrast, M-CSF, OPG, and RANKL are potent final effectors that can induce the extremes of skeletal changes — osteoporosis or osteopetrosis — when their gene is overexpressed or deleted (4, 5). Thus, these factors should be able to compensate reciprocally for the effect of changes in upstream cytokines. That this does not occur suggests that E deficiency affects them as well.

It seems more likely that E inhibits bone resorption by inducing small but cumulative changes in multiple E-dependent regulatory factors, as shown in Figure 1. Of the E-dependent factors affecting OC formation, TNF- α and the OPG/RANKL/RANK system may be most important, whereas TGF- β and the OPG/RANKL/RANK system may have greater effects on OC activity and apoptosis. Clearly, more data are need-

ed, especially on cytokine changes in the bone microenvironment of women with early postmenopausal bone loss or postmenopausal osteoporosis.

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