feeding or satiation or to assess the ability of glucose to alter neuronal activity or the release of peptides (Levin et al., 2004; Parton et al., 2007).

Such nonphysiological glucose levels provide little useful evidence for a physiological role of glucose in vitro or in vivo in the regulation of neuronal function or energy and glucose homeostasis. Thus, after more than 50 years, we are still in search of a direct link between neuronal glucose sensing and the physiological regulation of food intake and other facets of energy and glucose homeostasis. However, the Claret et al. (2007) and Parton et al. (2007) studies do point to important glucose-sensing-independent roles for both AMPK and the KATP channel in POMC neurons in the control of these physiological processes, which should be the focus of future studies in this field.

REFERENCES


---

**Estrogen and Bone: Osteoclasts Take Center Stage**

Deborah V. Novack1,*

1Department of Internal Medicine and Department of Pathology and Immunology, Division of Bone and Mineral Diseases, Washington University School of Medicine, St. Louis, MO 63110, USA

*Correspondence: novack@wustl.edu

DOI 10.1016/j.cmet.2007.09.007

Loss of estrogen at menopause causes osteoporosis in many women, but estrogen’s relevant cellular target in this process has remained unclear. In a recent study in Cell, Kato and colleagues (Nakamura et al., 2007) selectively ablate estrogen receptor α in osteoclasts and demonstrate that estrogen directly induces osteoclast apoptosis.

Estrogen plays a central role in the control of bone strength, and its loss at menopause causes osteoporosis in millions of women. In healthy individuals, bone mass is maintained by the balanced activity of bone-forming osteoblasts and bone-resorbing osteoclasts. These two cell types, although derived from mesenchymal and hematopoietic precursors, respectively, affect each other’s differentiation and activity. In addition, bone, particularly the trabecular component closely associated with bone marrow, is a rich microenvironment in which many cell types have the opportunity to influence osteoblast/osteoclast dynamics.

Osteoporosis, at the outset, is a disease of increased bone turnover in which the bone-resorbing activity of osteoclasts outpaces the bone-forming activity of osteoblasts, leading to loss of predominantly trabecular bone. Both of these cell types are reported to respond to estrogen. However, many studies suggest that bone’s response to estrogen withdrawal is at least in part mediated by a network of inflammatory and osteoclastogenic cytokines including TNFα and IL-1, released by stromal/osteoblast lineage cells and T cells (Figure 1A) (Clowes et al., 2005). Thus, the critical estrogen target cell has been of considerable debate.

Most estrogenic effects are mediated by the nuclear hormone receptor transcription factors estrogen receptor α and β (ERα and ERβ); some actions are attributed to an unidentified membrane receptor that signals through JNK or ERK kinases. Mice lacking ERα, ERβ, or both do not show the expected low bone mass but have abnormally high levels of either testosterone or estradiol, leading to confounding effects on the androgen receptor (Sims et al., 2002). Further studies in which sex steroid levels were controlled by gonadectomy and
Several groups have reported direct induction of osteoclast apoptosis by estrogen in vitro, but whether this occurs in vivo was left unclear. Nakamura et al. (2007) find apoptotic, Fasl-expressing osteoclasts in the bones of estrogen-treated ovariectomized wild-type mice. Osteoclasts lacking ERα do not upregulate Fasl, either in vivo or in vitro, and do not undergo apoptosis following estrogen treatment. Fas, the death receptor required for an apoptotic response to Fasl, is also expressed by osteoclasts but is not regulated by estrogen. Thus, estrogen-mediated upregulation of Fasl appears to control osteoclast life span in an autocrine manner (Figure 1B). Although in most instances Fas and Fasl are expressed in different cells, apoptosis of single T cells expressing both proteins has been described (Brunner et al., 1995). However, the mechanism by which Fas and Fasl expressed by the same cell might interact remains unknown.

One puzzling finding is that, in the ovariectomized ERαΔOC/ΔOC mice, TNF levels are increased, but there is no effect on osteoclast numbers or bone mass. TNF is a potent osteoclastostogenic factor that induces RANKL on osteoblast lineage cells and also acts directly on osteoclasts and their precursors. It is not clear why TNF and the RANKL it induces locally do not act on ERα-deficient osteoclast lineage cells to enhance bone resorption, since the response to these cytokines is independent of estrogen. Are the ERαΔOC/ΔOC mice already at the upper limit of their osteoclastogenic response prior to ovariectomy?

In isolation, the data derived from the osteoclast-specific deletion of ERα convincingly indicate that the osteoclast is the key estrogen target for the maintenance of bone mass. However, it is difficult to ignore myriad other studies in both mice and humans suggesting that the immune system and a host of inflammatory cytokines are activated upon estrogen withdrawal, with adverse effects on bone mass (Clowes et al., 2005). In many studies using genetically modified mice, removal of response to a single factor (such as TNF, IL-6, IL-7, or IL-11) has been found to block bone loss following ovariectomy. It is difficult to envision how each factor could
exert such a dominant effect when the normal physiological response involves upregulation of so many distinct factors. Most investigators have concluded that several cytokines have unique yet interconnected roles in the pathogenesis of osteoporosis. Similarly, although removal of ERα only from the osteoclast ablates the response to changes in estrogen, it is likely that deleting the receptor from other estrogen-responsive cells will reveal additional critical cellular targets for estrogen, generating a more complete picture of the complex process of postmenopausal bone loss.

REFERENCES


