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The skeleton: stone bones and stoned heads?

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Introduction

In vertebrates, bone mass is maintained constant between the end of linear skeletal growth, when the peak bone mass is established, and gonadal failure, when accelerated bone loss begins. The bone mass is preserved by a continuous destruction/formation process termed bone remodeling [1]. This destruction/formation cycle occurs at the same time in multiple foci that in humans encompass approximately 5% of trabecular, endosteal, and Haversian system surfaces. A cycle consists initially of a relatively rapid (i.e. a few weeks) resorption of pre-existing bone by a bone-specific, bone marrow hematopoietic cell type, the osteoclast, derived from the monocyte/macrophage lineage [2]. It is then followed by a slower (i.e. a few months) step of *de novo* bone formation by another bone-specific cell type, the osteoblast [3], which belongs to the stromal cell lineage of bone marrow [4]. Although different foci present different phases of the cycle, the overall net effect is that of a balance between bone destruction and formation. The physiologic importance of bone remodeling is best illustrated in osteoporosis, the most frequent degenerative disease in developed countries, which results from impaired remodeling balance that leads to bone loss and increased fracture risk mainly in females but also in males.

The synchronized occurrence of multiple remodeling sites has long been viewed as suggestive of a complex, local, autocrine/paracrine [5] as well as endocrine regulation. Indeed, experiments in knockout (KO) and transgenic mice have demonstrated paracrine regulation of osteoclast differentiation and activity by factors such as receptor activator of NFκB (RANK) ligand, osteoprotegerin, macrophage colony-stimulating factor (M-CSF) and interleukin 6, which are derived from neighboring stromal cells, including osteoblasts and osteoblast precursors [6–11]. The most convincing evidence for local osteoblast regulation is by bone morphogenetic proteins [12]. Systemically, ablation of gonadal hormones in females and males has been repeatedly demonstrated to favor bone loss in humans, rats, and mice [13, 14]. In addition, parathyroid hormone [15, 16], calcitonin [17], insulin-like growth factor I [18], and the osteogenic growth peptide [19] have been shown to regulate bone formation. More recently, it has been demonstrated that bone remodeling is also subject to a potent central control consisting of hypothalamic leptin and neuropeptide Y