Chapter 5

Calcium-sensing Receptor in Bone

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INTRODUCTION

Bone is intimately involved in systemic mineral ion homeostasis by virtue of its interplay with parathyroid gland and kidney (1). The extracellular calcium ion concentration ($Ca^{2+}_{o}$) underneath actively resorbing osteoclasts can rise as high as 8–40 mM (2). Therefore, it is likely that $Ca^{2+}_{o}$ within the immediate microenvironment of such osteoclasts would change substantially when this calcium is released. Indeed, during uncontrolled osteoclastic release of skeletal Ca$^{2+}_o$, as in cases where there is extensive skeletal metastases of certain malignancies promoting bone resorption via osteoclast-activating, hormonal factors, such as parathyroid hormone-related peptide (PTHrP) (e.g., breast), even the levels of systemic Ca$^{2+}_o$ can increase well above normal and become life-threatening (3). Ca$^{2+}_o$ in the local skeletal microenvironment is likely to be even higher in this setting. On the other hand, several hundred milligrams of Ca$^{2+}_o$ enter the skeleton owing to de novo formation of bone by osteoblasts on a daily basis. Local depletion of Ca$^{2+}_o$ will likely take place in the immediate vicinity of osteoblasts actively forming bone. Thus it is possible that the G protein-coupled, extracellular calcium (Ca$^{2+}_o$)-sensing receptor (CaR) (4,5) may also play some role within the skeleton by sensing such local changes in Ca$^{2+}_o$ caused by bone remodeling.

Bone formation during the normal process of skeletal remodeling is initiated by the migration of macrophage-like mononuclear cells to sites of osteoclastic bone resorption, during the "reversal" phase of skeletal turnover that precedes the laying down of new bone, which are then followed by preosteoblasts (6). These preosteoblasts subsequently differentiate into mature osteoblasts and eventually deposit and mineralize osteoid protein. The bone resorption-induced local increases in Ca$^{2+}_o$ within the immediate vicinity of osteoclasts could, therefore, provide both macrophage-like mononuclear cells and preosteoblasts with a signal that modulates their subsequent
physiological responses, such as migration and proliferation. In fact, *in vitro* studies showed that high Ca\(^{2+}\) induces chemotaxis of human peripheral blood monocytes (7) and chemotaxis as well as DNA synthesis of mouse osteoblastic MC3T3-E1 cells (7-10). These two cell types have the capacity, respectively, to differentiate into mature osteoclasts under specific culture conditions (11) and to differentiate from preosteoblasts to mature osteoblasts in culture (12). Several recent studies have shown that the CaR is expressed in a variety of bone cells including osteoblasts, stromal cells, monocytes-macrophages, osteoclasts, and chondrocytes, and, therefore, suggest that the receptor is involved in their physiological responses to the local high Ca\(^{2+}\) in the skeletal microenvironment (Figure 1).

**Figure 1**: The CaR’s expression in bone cells and its role in response to physiological reactions in the skeletal microenvironment.

Several recent studies have shown that the CaR is expressed in a variety of bone cells, including osteoblasts (9, 18,20-22), stromal cells (40), monocytes-macrophages (51-53), osteoclasts (22, 70), and chondrocytes (20, 48), and suggest that the receptor is involved in their physiological responses to the high local Ca\(^{2+}\) in the skeletal...