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Review Article

Hylonome

Calcium-sensing receptors in bone cells

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Extracellular calcium (Ca^{2+}_o) homeostasis is maintained through the coordinated actions of cells that sense Ca^{2+}_o as well as those that translocate calcium ions into or out of the extracellular fluid compartment. Key Ca^{2+}_o-sensing cells participating in mineral ion homeostasis are the parathyroid chief cells, the C-cells of the thyroid gland and several epithelial cells along the nephron. All of these cell types express the G protein-coupled, Ca^{2+}_o -sensing receptor (CaR) originally cloned from parathyroid that is capable of detecting changes in Ca^{2+}_o on the order of a few percent and then modulating the functions of the aforementioned cell types in ways that will restore Ca^{2+}_o to normal[1]. In response to hypercalcemia, for example, activation of the CaR leads to inhibition of PTH secretion, stimulation of calcitonin secretion and promotion of renal calcium excretion -actions that would tend to reduce Ca^{2+}_o toward normal. In addition to parathyroid cells, C-cells and kidney cells, the other two tissues that are important participants in the maintenance of Ca^{2+}_o homeostasis are intestine and bone. The former regulates influx of calcium from the external environment, while the latter can serve as either a source or sink for extracellular calcium ions. There has been only limited work on the physiological relevance of Ca^{2+}_o -sensing in the intestine to overall calcium metabolism, but in the duodenum Ca^{2+}_o and $1.25(OH)_2D_3$ increase the expression of the calcium-binding protein, calbindin D_{9K}[2], which participates in the transcellular transport of calcium ions from the apical to the basolateral membrane of the enterocyte. It is clear that calcium sensing is an important attribute of both osteoclasts[3] and osteoblasts[4], but the molecular basis for Ca^{2+}_o-sensing in these two types of bone cells is far from clear. Some studies suggest that the capacity of these cells to sense Ca^{2+}_o can be accounted for by one molecular species, the CaR, while others indicate that at least three different Ca^{2+}_o-sensors contribute to cation sensing in osteoblasts and osteoclasts. This presentation reviewed the evidence supporting the existence of one or several Ca^{2+}_o-sensors in bone cells, discussed the future use of cellular, molecular and genetic tools that could elucidate this issue further in future studies, and briefly addressed the possible therapeutic implications of the existence of Ca^{2+}_o-sensors in bone cells.

Some studies have identified the existence of the CaR in both osteoblasts[5,6] and osteoclasts[7] as well as in cells related to or earlier in their cellular lineages[8]. Studies in CaR knockout mice "rescued" by ablation of their parathyroid glands, however, show apparently normal bone histomorphometry[9]. It remains to be determined, therefore, whether the CaR identified by some groups in osteoblasts and osteoclasts plays a role in states with normal or pathological bone turnover. What, therefore, are additional candidates for Ca^{2+}_o -sensors in bone cells? In the osteoclast, Zaidi et al. have suggested that an isoform of the type II ryanodine receptor may serve as both a Ca^{2+}_o -sensor and influx pathway[3]. In the osteoblast, Quarles and co-workers have identified one intracellular protein, calcyclin, that confers Ca^{2+}_o -sensing properties upon cells expressing it[10], and have provided evidence in CaSR knockout osteoblasts for a G protein-coupled receptor unrelated to the CaR that senses Ca^{2+}_o and Sr^{2+}_o[11]. Clearly, further studies will be needed utilizing *in vitro* and *in vivo* knockout of these genes to determine their physiological relevance in health and disease. Additional studies, therefore, should clarify the number and identities of Ca^{2+}_o -sensing proteins that participate in bone biology. Furthermore, this information should sharpen our understanding of the relative importance of these various molecules as therapeutic targets in the treatment of osteoporosis and other metabolic bone diseases.

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References

1. Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. Physiol Rev 2001;

81:239-297.
2. Brehier A, Thomasset M. Stimulation of calbindin-D9K (CaBP9K) gene expression by calcium and 1,25-dihydroxycholecalciferol in fetal rat duodenal organ culture. Endocrinology 1990; 127:580-587.
3. Zaidi M, Moonga BS, Huang CL. Calcium sensing and cell signaling processes in the local regulation of osteoclastic bone resorption. Biol Rev Camb Philos Soc 2004; 79:79-100.
4. Quarles LD. Cation sensing receptors in bone: a novel paradigm for regulating bone remodeling? J Bone Miner Res 1997; 12:1971-1974.
5. Dvorak MM, Siddiqua A, Ward DT, Carter DH, Dallas SL, Nemeth EF, Riccardi D. Physiological changes in extracellular calcium concentration directly control osteoblast function in the absence of calciotropic hormones. Proc Natl Acad Sci USA 2004; 101:5140-5145.
6. Chattopadhyay N, Yano S, Tfelt-Hansen J, Rooney P, Kanuparthi D, Bandyopadhyay S, Ren X, Terwilliger E, Brown EM. Mitogenic action of calcium-sensing receptor on rat calvarial osteoblasts. Endocrinology 2004; 145:3451-3462.
7. Kameda T, Mano H, Yamada Y, Takai H, Amizuka N, Kobori M, Izumi N, Kawashima H, Ozawa H, Ikeda K, Kameda A, Hakeda Y, Kumegawa M. Calcium-sensing receptor in mature osteoclasts, which are bone resorbing cells. Biochem Biophys Res Commun 1998; 245:419-422.
8. Yamaguchi T, Chattopadhyay N, Kifor O, Brown EM. Extracellular calcium ($Ca^{2+}_{(o)}$)-sensing receptor in a murine bone marrow-derived stromal cell line (ST2): potential mediator of the actions of $Ca^{2+}_{(o)}$ on the function of ST2 cells. Endocrinology 1998; 139:3561-3568.
9. Tu Q, Pi M, Karsenty G, Simpson L, Liu S, Quarles LD. Rescue of the skeletal phenotype in CasR-deficient mice by transfer onto the Gcm2 null background. J Clin Invest 2003; 111:1029-1037.
10. Tu Q, Pi M, Quarles LD. Calcyclin mediates serum response element (SRE) activation by an osteoblastic extracellular cation-sensing mechanism. J Bone Miner Res 2003; 18:1825-1833.
11. Pi M, Quarles LD. A novel cation-sensing mechanism in osteoblasts is a molecular target for strontium. J Bone Miner Res 2004; 19:862-869.