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Perspective Article

Hylonome

Downregulation of SOST/Sclerostin by PTH: A novel mechanism of hormonal control of bone formation mediated by osteocytes

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Regulation of osteoblast number by PTH. Apoptosis versus genesis

Both chronic excess of PTH, as in hyperparathyroidism, and intermittent elevation of PTH (by daily injections) increase the number of osteoblasts. However, whereas the former condition can lead to bone catabolism[1], intermittent administration of PTH causes bone anabolism[2,3]. The striking difference between bone loss and bone gain in the two conditions might result from a negative vs. positive balance between formation and resorption within each bone remodeling unit, or from *de novo* bone formation not coupled to previous resorption in the case of intermittent PTH administration. In any event, increased osteoblast number can be achieved by increased osteoblast production from progenitors, or decreased osteoblast apoptosis, or a combination of the two events[4]. Studies in mice indicate that chronic and intermittent PTH increase osteoblast number by distinct mechanisms (Figure 1). Thus, whereas the increase in osteoblast number and the anabolic effect of intermittent PTH in cancellous bone can be accounted for by attenuation of osteoblast apoptosis[5,6], chronic elevation of endogenous PTH had no effect on osteoblast survival[6]. The osteoblast specific transcription factor Runx2 is required for the anti-apoptotic effect of PTH; however, PTH also stimulates proteasomal proteolysis of Runx2[6]. Based on this, we have reasoned that repeated injections of the hormone are needed to inhibit osteoblast apoptosis because the duration of the PTH-induced survival signaling is self-limited by downregulation of Runx2; and that the inability of chronic elevation of PTH to attenuate osteoblast apoptosis may be due to a decrease in Runx2 levels below the threshold needed for survival signaling. Nevertheless, the increase in osteoblasts seen with chronic PTH elevation cannot be accounted for by inhibition of osteoblast apoptosis and therefore must result from increased osteoblast production.

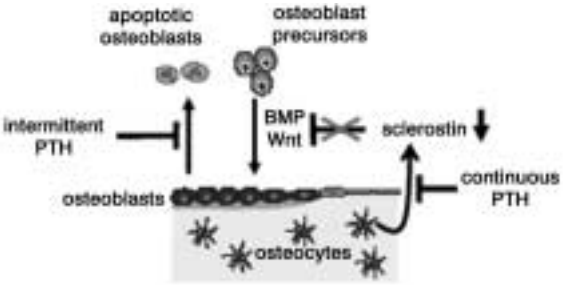

Figure 1. Intermittent and continuous elevation of PTH increases osteoblast number via distinct mechanisms.

Recent studies indicate that the osteoblastogenic action of chronic elevation of PTH may result from actions of the hormone on osteocytes via changes in Sost expression. Consistent with evidence that Sost is upregulated by Runx2[7] and that PTH induces proteasomal degradation of Runx2 protein[6], continuous elevation of PTH dramatically reduces the expression of Sost mRNA and sclerostin in osteocytes *in vivo* and *in vitro*[8]. These findings demonstrate a direct effect of PTH on osteocytes and were independently confirmed by other investigators[9]. PTH also acts on stromal/osteoblastic cells to stimulate the production of growth factors[10] and

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increases osteoclastic bone resorption which releases TGFβ from the bone matrix[11]. Therefore, it is possible that the Sost-mediated effects of PTH on osteoblastogenesis are amplified by these other actions.

Activation of PTH Receptor 1 specifically in osteocytes is sufficient for Sost inhibition and increases bone mass in transgenic mice

Recent findings demonstrate that PTHrP, the other ligand of the PTH/PTHrP receptor (PTHR1), also decreased potently Sost mRNA expression in osteocyte-containing cultures of murine calvaria cells. To determine whether activation of the PTHR1 in osteocytes is sufficient for Sost inhibition, we generated transgenic mice expressing a constitutively active PTHR1 specifically in osteocytes. The transgene consisted of the DNA sequence of one of the constitutively active receptors described in Jansen's metaphyseal chondrodysplasia (H223R mutant)[12,13] driven by the 8 kB portion of the promoter of the dentin matrix protein 1 (DMP1) gene. This promoter was previously shown to direct osteocyte specific expression of genes in transgenic mice. DMP1-caPTH1R transgenic mice express significantly reduced levels of Sost mRNA in vertebral and tibial bone as compared to wild type littermates at 10 weeks of age. Reduced Sost mRNA expression in vertebral bone lysates was also found in transgenic mice expressing the caPTH1R in both osteoblasts and osteocytes under the control of the 2.3kb-collagen 1 promoter (2.3 col-caPTH1R mice)[13]. On the other hand, the expression of Axin 2 and SMAD 6 – Wnt and BMP target genes, respectively – and the osteoblast specific genes osteocalcin and collagen1a1 was elevated DMP1-caPTH1R mice. Strikingly, DMP1-caPTHR1 mice exhibit a remarkable increase in BMD, as measured by Dexa (Piximus) and micro-CT, and strength in both the axial and appendicular skeleton. We conclude that PTHR1 signaling in osteocytes is sufficient for inhibition of Sost expression and leads to a concomitant increase in bone mass. These findings are consistent with a direct action of PTH on osteocytes and suggest that the increased osteoblast number induced by PTH or PTHrP results, in part, from decreased Sost expression in osteocytes.

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