NOT TO BE MISSED

Clinical and Basic Research Papers – August 2005 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling


*The clock genes Per and Cry are expressed in osteoblasts and block the osteoblast cell cycle via cyclin D1. Deletion of clock genes leads to a high bone mass phenotype attributed to increased osteoblast activity. Intraventricular leptin, which leads to bone loss in WT mice, increases bone mass in mice with an osteoblast-specific deletion of Per. Thus, clock genes mediate the osteoblast effects of leptin, and their deletion uncovers an anabolic effect of leptin that is mediated by stimulation of AP-1 via the sympathetic nervous system. The diurnal rhythm in bone remodeling has been attributed to gut hormones and the role of clock genes is presently unknown. —GJS*


*Mesenchymal stem cells in bone can differentiate into osteoblasts, chondrocytes or adipocytes, and the control of cell fate is complex. This paper reports that TAZ, a 14-3-3 binding protein, coactivates Runx2-dependent gene expression while repressing PPAR-γ-dependent gene expression. Depletion of TAZ enhances the adipocyte potential of mesenchymal cell lines. TAZ-depleted zebrafish embryos display severe defects in osteogenesis, suggesting a critical role for TAZ in switching cells to an osteoblast cell fate. —GJS*


*Post-transplant bone disease has a component of impaired osteoblast function that is attributed to the use of calcineurin inhibitors like cyclosporine A and FK506 for immunosuppression. In the mouse, administration of FK506 reduces bone mass, despite negatively affecting osteoclast differentiation, by severely impairing bone formation. In culture, bone formation is inhibited in Nfatc1- and Nfatc2-deficient cells as well as in FK506-treated osteoblasts. Thus, NFAT transcription factors, which are important in osteoclast differentiation, also have an important role in the transcriptional program of osteoblasts. —GJS*

Martin T.J. Osteoblast-derived PTHrP is a physiological regulator of bone formation. J Clin Invest. 2005 Sep 1;115(9):2322-2324. [Abstract] [Full Text]

**Pathophysiology**


Interferon-β (IFN-β) is one hundred fold more potent than IFN-α as an inhibitor of osteoclastogenesis. Gene profiling shows that CXCL11 responds to IFN-β but not IFN-α. While addition of CXCL11 inhibits osteoclast formation in vitro, the responsible receptor has not been identified. Possible CXCL11 receptors include CCR2 and DC-STAMP, which was recently shown to be required for fusion of osteoclast precursors (Yagi M, et al. J Exp Med 2005 Aug 1;202(3):345-51.) —GJS


Osteoporosis seems to be a neurological disorder. Once again, we have work demonstrating the role of the sympathetic nervous system in the control of bone mass. Treatment with propranolol suppressed the unloading-induced reduction in bone mass. Conversely, isoproterenol reduced bone mass in loaded mice. Reduction in mineral apposition rate, mineralizing surface, and bone formation rate by unloading was suppressed by propranolol. Unloading-induced increases in osteoclast number and surface, as well as urinary deoxypyridinoline, were all suppressed by propranolol. —ES

Lotinun S, Sibonga JD, Turner RT. Evidence that the cells responsible for marrow fibrosis in a rat model for hyperparathyroidism are preosteoblasts. Endocrinology. 2005 Sep;146(9):4074-81. [Abstract] [Full Text]

Marrow fibrosis is an important element of severe hyperparathyroidism. This paper explores the fate of marrow fibroblasts in rats infused with continuous PTH. The fibroblasts express osteoblast genes and, at the conclusion of the PTH infusion, they differentiate into osteoblasts on the bone surface. Explosive new bone formation by such cells is the probable basis for hypocalcemia in the “hungry bones syndrome” following successful parathyroidectomy. —GJS

**Physiology and Metabolism**

Direct measurement of solute movement in intact bone was achieved by visualizing the movement of sodium fluorescein among lacunae in situ beneath the periosteal surface of mouse cortical bone at depths up to 50 µm with laser scanning confocal microscopy. The diffusion of fluorescein in bone is consistent with the presence of an osteocyte pericellular matrix whose structure resembles that proposed for the endothelial glycocalyx. —ES

Treatment and Drug Effects


Women receiving PTH (1-84, 100 µg/d) for 1 year received placebo or alendronate. Subject receiving both PTH and alendronate in year 1, received alendronate only in year 2. Those taking alendronate only in year 1, continued it in year 2. Over 2 years, alendronate after PTH increased BMD relative to placebo after PTH (an increase of 31% in the PTH-alendronate group compared to 14% in the PTH-placebo group). During year 2, subjects receiving placebo lost BMD. After one year of PTH (1-84), gains in BMD appear to be maintained or increased with alendronate but lost if not followed by an antiresorptive agent. —ES


Of 126 women with osteoporosis who had been taking alendronate for 1 year, one group continued alendronate, another took PTH (1-34) daily, and a third group took PTH daily for 3 months on and 3 months off. During the subsequent 15 months, markers of bone formation increased in PTH-treated subjects and cycled up in the PTH “on” cycles and down in the PTH “off” cycles. Bone resorption markers increased more in the daily-treatment group than in the cyclic-therapy group. Spinal BMD rose similarly (~5-6%) for each parathyroid hormone group compared with the alendronate group. The authors infer there is an early stage of “pure stimulation of bone formation” by PTH. —ES

Reviews, Perspectives, and Editorials


Diffey B. Do white British children and adolescents get enough sunlight? BMJ. 2005 Jul 2;331(7507):3-4. [Full Text]

Hamerman D. Osteoporosis and atherosclerosis: biological linkages and the emergence of dual-purpose therapies. QJM. 2005 Jul;98(7):467-84. [Abstract]


Kalaitzidis D, Gilmore TD. Transcription factor cross-talk: the estrogen receptor and NF-κB Trends Endocrinol Metab. 2005 Mar;16(2):46-52. [Abstract]


Other Studies of Potential Interests


Celil AB, Campbell PG. BMP-2 and insulin-like growth factor-I mediate Osterix (Osx) expression in human mesenchymal stem cells via the MAPK and protein kinase D signaling pathways. J Biol Chem. 2005 Sep 9;280(36):31353-9. [Abstract] [Full Text]


