**NOT TO BE MISSED**

Clinical and Basic Research Papers – March and April 2004 Selections

Ego Seeman, Clinical Editor
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**Bone Modeling and Remodeling**


This study investigated the role of PPARγ, a regulator of adipocyte differentiation, in bone metabolism. Homozygous PPARγ-deficient embryonic stem cells failed to differentiate into adipocytes, but differentiated into osteoblasts, and adipogenesis was restored by reintroduction of the PPARγ gene. Heterozygous PPARγ-deficient mice exhibited high bone mass with increased osteoblastogenesis. The osteogenic effect of PPARγ haploinsufficiency became prominent with aging and was confirmed to enhance osteoblastogenesis in marrow cell culture. PPARγ regulated bone metabolism in vivo, and PPARγ insufficiency increased bone mass by stimulating osteoblastogenesis from bone marrow progenitors. —ES


Osteocalcin in matrix is released in resorption. The amount of osteocalcin in the medium is correlated with cross-linked C-telopeptide of bone collagen (CTX) (r > 0.9) and may contribute to circulating osteocalcin, suggesting that serum osteocalcin should be considered a marker of bone turnover, not bone formation. —ES


Costimulatory signals are standard operating procedure in the immune system. This paper reports that RANKL and M-CSF likewise require costimulators to induce formation of osteoclasts. Mice lacking the immunoreceptor tyrosine-based activation motif (ITAM)-harboring adaptors, Fc receptor common γ subunit (FcRγ) and DNAX-activating protein 12 (DAP12), have osteopetrosis, owing to impaired osteoclast differentiation. In osteoclast precursor cells, FcRγ and DAP12 associate with multiple immunoreceptors and activate calcium signaling through phospholipase Cγ to autoamplify activation of the transcription factor NFATc1. These results reveal that RANKL and M-CSF are not sufficient to activate the signals required for osteoclastogenesis. Costimulatory signaling is a major new level of complexity in the control of osteoclast formation. —ES &GJS


*Genetics*


The low-density lipoprotein receptor-related protein 5 (LRP5) gene is an important determinant of bone mass, but does allelic variation account for variation in bone mass in the general population? In adult men in Geneva, Switzerland, a missense mutation in exon 9 of the LRP5 gene is associated with reduced spinal bone mineral content (BMC) and a 2-cm reduction in stature. Furthermore, growing boys with the exon 9 mutation had a reduction in vertebral BMC and area. —GJS


Disruption of PASG, a SNF2-like gene that facilitates DNA methylation, caused global hypomethylation, growth retardation, and premature aging. Fibroblasts from PASG mutant embryos showed a replicative senescence phenotype with increased expression of senescence-associated tumor suppressor genes, such as p16(INK4a), which are associated with downregulation of bmi-1, a negative regulator of p16(INK4a). PASG maintains DNA methylation and gene expression patterns required for growth and longevity. —ES

*Pathophysiology*


In this study, age-related changes in physicochemical properties of mineral crystals were found to be related to impaired elastic deformability of cortical bone tissue. Elastic
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deformation capacity of aged rats was impaired at the tissue and organ level with increasing age. With age, increasing mineralization, crystallinity, and type B carbonate substitution were correlated with decreasing elastic deformation capacity. —ES


The derivation and maintenance of embryonic stem cells (ES cells) in vitro depend on feeder cell-derived growth factors that are as yet unidentified. The authors conducted a screen to identify factors produced by mouse embryonic fibroblast STO cells that maintain the pluripotency of ES cells. The major effect of bone morphogenetic protein 4 (BMP4) on the self-renewal of ES cells was accomplished by the inhibition of extracellular receptor kinase (ERK) and p38 mitogen-activated protein kinase (MAPK) pathways, and inhibitors of ERK and p38 MAPKs mimic the effect of BMP4 on ES cells. Inhibition of the p38 MAPK pathway by SB203580 overcomes the block in deriving ES cells from blastocysts lacking functional Alk3, the BMP type IA receptor. —ES


Transducer of erbB2 (Tob) proteins inhibit bone morphogenetic protein (BMP) and suppress T-cell proliferation. In Tob(-/-) mice, ovariectomy reduces bone volume, but trabecular bone volume and bone mineral density are comparable to sham-operated WT because bone formation is higher in Tob(-/-) than in WT mice, whereas resorption is similar to that found in WT mice. Ex vivo nodule formation is higher in the marrow cells of Tob-deficient mice than in those of WT mice. Tob and estrogen signaling pathways converge at BMP activation of alkaline phosphatase and GCCG reporter gene expression in osteoblasts, revealing an interaction between the two signals. Tob deficiency prevents ovariectomy-induced bone loss through enhancement of osteoblastic activities. —ES


Coffin-Lowry syndrome is associated with skeletal abnormalities and is caused by a mutation in RSK2, a gene that encodes a growth factor-regulated kinase. RSK2 is required for osteoblast differentiation and function and phosphorylates the transcription factor ATF4 for this purpose. Knockout of the latter produces a skeletal phenotype more severe than RSK2 deficiency, one that features a marked reduction in collagen synthesis because of impaired amino acid transport. It seems that ATF4 is downstream of RSK2 in a pathway that regulates late stages of osteoblast differentiation and osteoblast function. The extracellular signals that activate this pathway have not been identified. —ES&GJS

Physiology and Metabolism


Whether osteoblasts harbor the calcium-sensing receptor has been a controversial issue. In the Dvorak study, receptor mRNA and protein were present in rat calvarial osteoblasts and murine 2T3 cells. In fetal rat calvarial cells, increasing extracellular calcium or gadolinium stimulated multiple signaling pathways and induced cell growth; these effects were blocked by the calcium receptor antagonist NPS 89636. In contrast, the Pi study finds a calcium-sensing mechanism that is distinct from the calcium-sensing receptor that responds to strontium in osteoblasts (of interest, of course, because of the therapeutic effect of strontium in osteoporosis. —GJS


The latest chapter in the leptin story from the Karsenty laboratory. The antiosteogenic effect of leptin was previously demonstrated by infusing leptin into the CNS. In this paper, the afferent arm of the leptin signaling pathway is addressed. Leptin is not demonstrable in the CNS, but raising serum levels by overexpressing leptin in liver leads to decreased bone mass. Conversely, decreasing free serum levels of leptin with a decoy leptin receptor increases bone mass. The probable source of serum leptin is adipose tissue. Lipodystrophic mice have increased bone mass, which is reversed by increasing leptin levels in serum. —GJS


Recommended. —ES


Recommended. —ES


Recommended. —ES


Recommended. —ES

Treatment and Drug Effects

Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL. Exogenous testosterone or testosterone with finasteride increases bone mineral
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http://www.bonekey-ibms.org/cgi/content/full/ibmske;1/6/1
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The treatment of older men with borderline testosterone (T) levels is a vexatious issue. In this study, 70 men with T < 350 ng/dL and normal bone mineral density (BMD) for age were randomized to treatment with intramuscular T, T plus the 5α-reductase inhibitor finasteride, or placebo. Men treated for 36 months with either T alone or T plus finasteride experienced an approximately 10% increase in lumbar spine BMD, compared with men treated with placebo. Treatment with T plus finasteride resulted in a smaller increase in prostate volume than occurred with T alone and no change in prostate-specific antigen (PSA) levels. —GJS


Combined results are reported of two placebo-controlled trials of cinacalcet, an agonist of the parathyroid calcium-sensing receptor. In dialysis patients with moderate secondary hyperparathyroidism, addition of cinacalcet reduced parathyroid hormone and serum calcium levels and improved the calcium-phosphate product. Bone alkaline phosphatase was significantly reduced, and cinacalcet was well tolerated. Cinacalcet has now been released in the United States for this indication. —GJS


Recommended. —ES


Recommended. —ES