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NOT TO BE MISSED

Clinical and Basic Research Papers – March and April 2004 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Akune T, Ohba S, Kamekura S, Yamaguchi M, Chung UI, Kubota N, Terauchi Y, Harada Y, Azuma Y, Nakamura K, Kadowaki T, Kawaguchi H. PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. *J Clin Invest.* 2004 Mar;113(6):846-55. [Abstract] [Full Text]

> *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*

Ivaska KK, Hentunen TA, Vaaraniemi J, Ylipahkala H, Pettersson K, Vaananen HK. Release of intact and fragmented osteocalcin molecules from bone matrix during bone resorption in vitro. *J Biol Chem.* 2004 Apr 30;279(18):18361-9. [Abstract] [Full Text]

> *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*

Koga T, Inui M, Inoue K, Kim S, Suematsu A, Kobayashi E, Iwata T, Ohnishi H, Matozaki T, Kodama T, Taniguchi T, Takayanagi H, Takai T. Costimulatory signals mediated by the ITAM motif cooperate with RANKL for bone homeostasis. *Nature.* 2004 Apr 15;428(6984):758-63. [Abstract]

> *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 factorNFATc1. 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*

Liu Z, Shi W, Ji X, Sun C, Jee WS, Wu Y, Mao Z, Nagy TR, Li Q, Cao X. Molecules mimicking Smad1 interacting with Hox stimulate bone formation. *J Biol Chem.* 2004 Mar 19;279(12):11313-9. [Abstract] [Full Text]

Recommended. —ES

Smits P, Dy P, Mitra S, Lefebvre V. Sox5 and Sox6 are needed to develop and maintain source, columnar, and hypertrophic chondrocytes in the cartilage growth plate. *J Cell Biol.* 2004 Mar 1;164(5):747-58. [Abstract] [Full Text]

Recommended. —ES

Wang G, Woods A, Sabari S, Pagnotta L, Stanton LA, Beier F. RhoA/ROCK signaling suppresses hypertrophic chondrocyte differentiation. *J Biol Chem.* 2004 Mar 26;279(13):13205-14. [Abstract] [Full Text]

Recommended. —ES

Zhao M, Qiao M, Harris SE, Oyajobi BO, Mundy GR, Chen D. Smurf1 inhibits osteoblast differentiation and bone formation in vitro and in vivo. *J Biol Chem.* 2004 Mar 26;279(13):12854-9. [Abstract] [Full Text]

Recommended. —ES

Genetics

Ferrari SL, Deutsch S, Choudhury U, Chevalley T, Bonjour JP, Dermitzakis ET, Rizzoli R, Antonarakis SE. Polymorphisms in the low-density lipoprotein receptor-related protein 5 (LRP5) gene are associated with variation in vertebral bone mass, vertebral bone size, and stature in whites. *Am J Hum Genet.* 2004 May;74(5):866-75. [Abstract]

*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*

Sun LQ, Lee DW, Zhang Q, Xiao W, Raabe EH, Meeker A, Miao D, Huso DL, Arceci RJ. Growth retardation and premature aging phenotypes in mice with disruption of the SNF2-like gene, PASG. *Genes Dev.* 2004 May 1;18(9):1035-46. [Abstract] [Full Text]

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

Akkus O, Adar F, Schaffler MB. Age-related changes in physicochemical properties of mineral crystals are related to impaired mechanical function of cortical bone. *Bone.* 2004 Mar;34(3):443-53. [Abstract]

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

deformation capacity of aged rats was impaired at the tissue and organ level with increasing age. With age, increasing mineralization, crystallinity, and typeB carbonate substitution were correlated with decreasing elastic deformation capacity. —ES

Qi X, Li TG, Hao J, Hu J, Wang J, Simmons H, Miura S, Mishina Y, Zhao GQ. BMP4 supports self-renewal of embryonic stem cells by inhibiting mitogen-activated protein kinase pathways. *Proc Natl Acad Sci U S A.* 2004 Apr 20;101(16):6027-32. [Abstract] [Full Text]

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

Usui M, Yoshida Y, Tsuji K, Oikawa K, Miyazono K, Ishikawa I, Yamamoto T, Nifuji A, Noda M. Tob deficiency superenhances osteoblastic activity after ovariectomy to block estrogen deficiency-induced osteoporosis. *Proc Natl Acad Sci USA.* 2004 Apr 27;101(17):6653-8. [Abstract] [Full Text]

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*

Yang X, Matsuda K, Bialek P, Jacquot S, Masuoka HC, Schinke T, Li L, Brancorsini S, Sassone-Corsi P, Townes TM, Hanauer A, Karsenty G. ATF4 is a substrate of RSK2 and an essential regulator of osteoblast biology; implication for Coffin-Lowry Syndrome. *Cell.* 2004 Apr 30;117(3):387-98. [Abstract]

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

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 Apr 6;101(14):5140-45. [Abstract] [Full Text]

Pi M, Quarles LD. A novel cation-sensing mechanism in osteoblasts is a molecular target for strontium. *J Bone Miner Res.* 2004 May;19(5):862-9. [Abstract]

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

Elefteriou F, Takeda S, Ebihara K, Magre J, Patano N, Kim CA, Ogawa Y, Liu X, Ware SM, Craigen WJ, Robert JJ, Vinson C, Nakao K, Capeau J, Karsenty G. Serum leptin level is a regulator of bone mass. *Proc Natl Acad Sci USA.* 2004 Mar 2;101(9):3258-63. [Abstract] [Full Text]

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

Hashimoto-Gotoh T, Ohnishi H, Tsujimura A, Tsunezuka H, Imai K, Masuda H, Nakamura T. Bone mass increase specific to the female in a line of transgenic mice overexpressing human osteoblast stimulating factor-1. *J Bone Miner Metab.* 2004;22(3):278-82. [Abstract]

Recommended. —ES

Mocsai A, Humphrey MB, Van Ziffle JA, Hu Y, Burghardt A, Spusta SC, Majumdar S, Lanier LL, Lowell CA, Nakamura MC. The immunomodulatory adapter proteins DAP12 and Fc receptor gamma-chain (FcRgamma) regulate development of functional osteoclasts through the Syk tyrosine kinase. *Proc Natl Acad Sci USA.* 2004 Apr 20;101(16):6158-63. [Abstract] [Full Text]

Recommended. —ES

Nampei A, Hashimoto J, Hayashida K, Tsuboi H, Shi K, Tsuji I, Miyashita H, Yamada T, Matsukawa N, Matsumoto M, Morimoto S, Ogihara T, Ochi T, Yoshikawa H. Matrix extracellular phosphoglycoprotein (MEPE) is highly expressed in osteocytes in human bone. *J Bone Miner Metab.* 2004;22(3):176-84. [Abstract]

Recommended. —ES

Xiao ZS, Hjelmeland AB, Quarles LD. Selective deficiency of the "bone-related" Runx2-II unexpectedly preserves osteoblast-mediated skeletogenesis. *J Biol Chem.* 2004 May 7;279(19):20307-13. [Abstract] [Full Text]

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

density in older men with low serum testosterone. *J Clin Endocrinol Metab.* 2004 Feb;89(2):503-10. [Abstract] [Full Text]

> *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*

Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, Hercz G, Cunningham J, Abu-Alfa AK, Messa P, Coyne DW, Locatelli F, Cohen RM, Evenepoel P, Moe SM, Fournier A, Braun J, McCary LC, Zani VJ, Olson KA, Drueke TB, Goodman WG. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med.* 2004 Apr 8;350(15):1516-25. [Abstract] [Full Text]

> *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*

Hosfield DJ, Zhang Y, Dougan DR, Broun A, Tari LW, Swanson RV, Finn J. Structural basis for bisphosphonate-mediated inhibition of isoprenoid biosynthesis. *J Biol Chem.* 2004 Mar 5;279(10):8526-9. [Abstract] [Full Text]

> *Recommended. —ES*

Martin TJ. Does bone resorption inhibition affect the anabolic response to parathyroid hormone? *Trends Endocrinol Metab.* 2004 Mar;15(2):49-50. [Abstract]

> *Recommended. —ES*