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NOT TO BE MISSED

Clinical and Basic Research Papers - January and February Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Dacquin R, Davey RA, Laplace C, Levasseur R, Morris HA, Goldring SR, Gebre-Medhin S, Galson DL, Zajac JD, Karsenty G. Amylin inhibits bone resorption while the calcitonin receptor controls bone formation *in vivo*. *J Cell Biol.* 2004 16;164(4):509-14. [Abstract] [Full Text]

Recommended. —ES

Maes C, Stockmans I, Moermans K, Van Looveren R, Smets N, Carmeliet P, Bouillon R, Carmeliet G. Soluble VEGF isoforms are essential for establishing epiphyseal vascularization and regulating chondrocyte development and survival. *J Clin Invest.* 2004 Jan 15;113(2):188-199. [Abstract] [Full Text]

Vascular endothelial growth factor (VEGF) has been shown to be important for vascular invasion of the metaphysis and formation of the primary spongiosa. This paper focuses attention on the epiphysis, wherein a large body of avascular cartilage resides until the secondary ossification center forms. Mice that express only $VEGF_{188}$, a matrix-associated isotype, develop massive apoptosis of epiphyseal chondrocytes and exhibit markedly impaired linear growth. It is likely that hypoxic chondrocytes in the interior of the epiphysis activate HIF1α dependent secretion of soluble forms of VEGF. These molecules diffuse to the perichondrium and induce vascular invasion to form centers of secondary ossification and simultaneously rescue central chondrocytes from hypoxia. —GJS

Sims NA, Jenkins BJ, Quinn JM, Nakamura A, Glatt M, Gillespie MT, Ernst M, Martin TJ. Glycoprotein 130 regulates bone turnover and bone size by distinct downstream signaling pathways. *J Clin Invest.* 2004 Feb;113(3):379-89. [Abstract] [Full Text]

Bone length and volume are independently regulated. The gp130-dependent cytokines regulate osteoclast and osteoblast formation. Attenuation of the signal transducer and activator of transcription (STAT) 1/3 signaling pathway (gp130[DeltaSTAT/DeltaSTAT]) produces reduced bone length caused by premature growth plate closure, but normal trabecular bone volume (BV/TV), indicating an essential role for gp130-STAT1/3 signaling in chondrocyte differentiation. SHP2/ras/MAPK (gp130[Y757F/Y757F]) pathway attenuation produces high remodeling and low BV/TV, thus SHP2/Ras/MAPK inhibits osteoclastogenesis. —ES

Genetics

Chamberlain JR, Schwarze U, Wang PR, Hirata RK, Hankenson KD, Pace JM, Underwood RA, Song KM, Sussman M, Byers PH, Russell DW. Gene targeting in stem cells from individuals with osteogenesis imperfecta. *Science.* 2004 Feb 20;303(5661):1198-201. [Abstract] [Full Text]

The authors disrupted dominant-negative mutant COL1A1 *collagen genes in mesenchymal stem cells from individuals with osteogenesis imperfecta, demonstrating successful gene targeting in adult human stem cells. —ES*

Hughes CM, Rozenblatt-Rosen O, Milne TA, Copeland TD, Levine SS, Lee JC, Hayes DN, Shanmugam KS, Bhattacharjee A, Biondi CA, Kay GF, Hayward NK, Hess JL, Meyerson M**.** Menin associates with a trithorax family histone methyltransferase complex and with the hoxc8 locus. *Mol Cell* Feb 2004;13(4):587-97. [Abstract]

The MEN1 *gene is a tumor suppressor, loss of which causes multiple endocrine neoplasia type 1 (MEN 1), but the cellular basis of tumor suppression is unknown. This paper reports that menin, the protein product of the* MEN1 *gene, is associated with a histone methyltransferase complex and is required for histone methylation. Several (but not all) menin point mutants in MEN 1 tumors lack histone methyltransferase activity. Histone methylation is an important epigenetic mechanism of gene regulation, and* Hoxc8 *is among the genes that bind menin and are transcriptionally regulated. —GJS*

Krakow D, Robertson SP, King LM, Morgan T, Sebald ET, Bertolotto C, Wachsmann-Hogiu S, Acuna D, Shapiro SS, Takafuta T, Aftimos S, Kim CA, Firth H, Steiner CE, Cormier-Daire V, Superti-Furga A, Bonafe L, Graham JM Jr, Grix A, Bacino CA, Allanson J, Bialer MG, Lachman RS, Rimoin DL, Cohn DH. Mutations in the gene encoding filamin B disrupt vertebral segmentation, joint formation and skeletogenesis. *Nat Genet.* 2004 Apr;36(4):405-10. [Abstract]

Recommended. —ES

Pathophysiology

Murakami S, Balmes G, McKinney S, Zhang Z, Givol D, de Crombrugghe B. Constitutive activation of MEK1 in chondrocytes causes Stat1-independent achondroplasia-like dwarfism and rescues the *Fgfr3*-deficient mouse phenotype. *Genes & Dev.* 2004 Feb 1;18(3):290-305. [Abstract]

*The fibroblast growth factor receptor FGFR3 signals both through Stat1 and the mitogen-activated protein (MAP) kinase pathway and is constitutively activated in achondroplasia. Constitutive activation of MEK1 causes achondroplasia-like dwarfism in wild-type and Stat1-deficient mice and rescues the phenotype of FGFR3 deficiency, suggesting that bone growth is mediated by the MAP kinase pathway. Loss of Stat1 rescues the proliferative defect in achondroplasia, but does not rescue the short stature phenotype. Proliferative effects of FGFR3 are mediated by Stat,1 but effects on chondrocyte hypertrophy and bone growth are mediated by the MAP kinase pathway. The results fit well with a recent report that C-type natriuretic peptide inhibits MAP kinase activity and suppresses the achondroplastic phenotype (*Nat Med. 2004 Jan;10(1):80-6). *—GJS*

Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, Yamashita T. Targeted ablation of *Fgf23* demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *J Clin Invest.* 2004 Feb 15;113(4):561-568. [Abstract] [Full Text]

This long-awaited paper reports that removal of the Fgf23 *gene from the mouse produces hyperphosphatemia and high 1,25(OH)$_2$vitaminD levels, with eventual hypercalcemia, nephrocalcinosis, and renal failure. The physiological role of FGF23 in phosphate and vitamin D metabolism is established by these data. Notable also are severe growth retardation, rickets, osteomalacia, hypoglycemia, and hypotriglyceridemia, findings that suggest hitherto unpredicted new roles of FGF23. —GJS*

Physiology and Metabolism

Bharti AC, Takada Y, Shishodia S, Aggarwal BB. Evidence that receptor activator of nuclear factor (NF)-kappaB ligand can suppress cell proliferation and induce apoptosis through activation of a NF-kappaB-independent and TRAF6-dependent mechanism. *J Biol Chem.* 2004 Feb 13;279(7):6065-76. [Abstract] [Full Text]

Recommended. —ES

Roman-Roman S, Shi DL, Stiot V, Hay E, Vayssiere B, Garcia T, Baron R, Rawadi G. Murine Frizzled-1 behaves as an antagonist of the canonical Wnt/beta-catenin signaling. *J Biol Chem.* 2004 Feb 13;279(7):5725-33. [Abstract] [Full Text]

Recommended. —ES

VanHouten J, Dann P, McGeoch G, Brown EM, Krapcho K, Neville M, Wysolmerski JJ. The calcium-sensing receptor regulates mammary gland parathyroid hormone–related protein production and calcium transport. *J Clin Invest.* 2004 Feb 15; 113(4):598-608. [Abstract] [Full Text]

The mammary gland is a calcium-sensing organ! In response to a low medium calcium concentration or to direct activators of the parathyroid-type calcium-sensing receptor, mammary epithelial cells secrete more parathyroid hormone-related protein; high extracellular calcium also stimulates transcellular calcium secretion. Intact mice on a low calcium diet display significant changes in milk composition, which can also be mimicked by calcium receptor activators. This is convincing evidence of a new role of the calcium sensor to adapt both mother and child to a low maternal calcium intake, but much remains to be understood. As the authors write, "Milking mice is imprecise." —GJS

Viviano BL, Paine-Saunders S, Gasiunas N, Gallagher J, Saunders S. Domain-specific modification of heparan sulfate by Qsulf1 modulates the binding of the bone morphogenetic protein antagonist Noggin. *J Biol Chem.* 2004 Feb 13;279(7):5604-11. [Abstract] [Full Text]

Recommended. —ES

Wu S, De Luca F. Role of cholesterol in the regulation of growth plate chondrogenesis and longitudinal bone growth. *J Biol Chem.* 2004 Feb 6;279(6):4642-7. [Abstract] [Full Text]

Recommended. —ES

Treatment and Drug Effects

Cheng X, Kinosaki M, Takami M, Choi Y, Zhang H, Murali R. Disabling of receptor activator of nuclear factor-kappaB (RANK) receptor complex by novel osteoprotegerin-like peptidomimetics restores bone loss in vivo. *J Biol Chem.* 2004 Feb 27;279(9):8269-77. [Abstract] [Full Text]

A mimic of osteoprotegerin inhibits osteoclast formation in vitro *and limits bone loss in an animal model. OP3-4 inhibits osteoclast formation and bone loss and modulates RANK-TRANCE signaling pathways and alters the biological functions of the RANK-TRANCE receptor complex. —ES*

Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, Cannata J, Balogh A, Lemmel EM, Pors-Nielsen S, Rizzoli R, Genant HK, Reginster JY. The effects of strontium

ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med.* 2004 Jan 29; 350(5):459-468. [Abstract]
El-Hajj Fuleihan G. Strontium Ranelate — A Novel Therapy for Osteoporosis or a Permutation of the Same? *N Engl J Med.* 2004 Jan 29;350(5):504-506.

> *Strontium is incorporated by ionic substitution into bone mineral and increases bone mineral density (even after correction for its own atomic weight). This study reports a 42% decrease in vertebral fractures over 36 months of strontium ranelate treatment. The accompanying editorial raises several interesting questions: What is the mechanism by which strontium treatment uncouples bone formation and resorption, as indicated in this study by biochemical markers? Would lower doses have similar effects? Serum calcium and parathyroid hormone levels fall and serum phosphate levels rise during therapy; does strontium activate the calcium receptor in parathyroid cells, or indeed in bone cells? —GJS*

Shane E, Addesso V, Namerow PB, McMahon DJ, Lo SH, Staron RB, Zucker M, Pardi S, Maybaum S, Mancini D. Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. *N Engl J Med.* 2004 Feb 19; 350 (8): 767-776. [Abstract]
Lindsay R. Bone loss after cardiac transplantation. *N. Engl J Med.* 2004 Feb 19;350(8):751-754.

> *Osteoporosis is common in cardiac transplant candidates, and rapid bone loss occurs posttransplant, because treatment with cyclosporine or other calcineurin inhibitors increases bone resorption, and glucocorticoid therapy impairs the osteoblast response. It is reported here that both alendronate and calcitriol reduced the otherwise alarming loss of bone mineral density at the spine and hip. Alendronate treatment was simpler because calcitriol therapy required frequent monitoring to prevent hypercalcemia or hypercalciuria. —GJS*