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NOT TO BE MISSED

Clinical and Basic Research Papers – September and October 2004 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Kukita T, Wada N, Kukita A, Kakimoto T, Sandra F, Toh K, Nagata K, Iijima T, Horiuchi M, Matsusaki H, Hieshima K, Yoshie O, Nomiyama H. RANKL-induced DC-STAMP is essential for osteoclastogenesis. *J Exp Med.* 2004 Oct 4;200(7):941-6.

> *By screening RAW264 cells deficient in responsiveness to receptor activator of NFκB ligand (RANKL), the seven-spanning membrane protein DC-STAMP was identified as a possible coreceptor involved in osteoclastogenesis. DC-STAMP is expressed on osteoclasts and RAW264 cells. A neutralizing antibody or small interfering RNA to DC-STAMP blocks RANKL-dependent osteoclasto-genesis; forced expression of DC-STAMP amplifies the response to RANKL. There may be a DC-STAMP receptor on RAW264 cells. Is this another costimulatory system similar to the immunoreceptor tyrosine-based activation motif system? —GJS*

Nilsson O, Baron J. Fundamental limits on longitudinal bone growth: growth plate senescence and epiphyseal fusion. *Trends Endocrinol Metab.* 2004 Oct;15(8):370-4.

> *The decline in growth rate is caused by a programmed decrease in the rate of chondrocyte proliferation intrinsic to the growth plate itself, because stem-like cells in the resting zone have a finite proliferative capacity. —ES*

Sutherland MK, Geoghegan JC, Yu C, Turcott E, Skonier JE, Winkler DG, Latham JA. Sclerostin promotes the apoptosis of human osteoblastic cells: a novel regulation of bone formation. *Bone.* 2004 Oct;35(4):828-35.

> *Consistent with report from van Bezooijen et al. J Exp Med. 2004 Mar 15;199(6):805-14, treatment with sclerostin induces osteoblast apoptosis, an effect not shared by other BMP antagonists. —GJS*

van Bezooijen RL, Roelen BA, Visser A, van der Wee-Pals L, de Wilt E, Karperien M, Hamersma H, Papapoulos SE, ten Dijke P, Lowik CW. Sclerostin is an osteocyte-expressed negative regulator of bone formation, but not a classical BMP antagonist. *J Exp Med.* 2004 Mar 15;199(6):805-14.

> *Sclerostin, the product of the* SOST *gene, is a negative regulator of bone formation; loss of sclerostin function causes the osteosclerotic disorder sclerosteosis. In postnatal mouse and human bone, sclerostin is exclusively expressed in osteocytes and their canaliculi. Although it has structural features of a bone morphogenetic protein (BMP) antagonist, sclerostin, in contrast to noggin, does not acutely inhibit BMP actions. It is proposed that sclerostin is transported from osteocytes to the bone surface to inhibit the osteoblast, perhaps by antagonizing a BMP-dependent signal. —GJS*

Genetics

Ioannidis JP, Ralston SH, Bennett ST, Brandi ML, Grinberg D, Karassa FB, Langdahl B, van Meurs JB, Mosekilde L, Scollen S, Albagha OM, Bustamante M, Carey AH, Dunning AM, Enjuanes A, van Leeuwen JP, Mavilia C, Masi L, McGuigan FE, Nogues X, Pols HA, Reid DM, Schuit SC, Sherlock RE, Uitterlinden AG; GENOMOS Study. Differential genetic effects of ESR1 gene polymorphisms on osteoporosis outcomes. *JAMA.* 2004 Nov 3;292(17):2105-14.

> *Statistical power is everything in human genetics. Small studies have shown conflicting results about the genetic role of the estrogen receptor-a gene,* ESR1*, in osteoporosis. A European consortium pooled and reanalyzed data on 18,917 individuals. In women homozygous for the absence of an* Xba*I recognition site in intron 1 of* ESR1*, the adjusted odds of all fractures were reduced by 19% (odds ratio [OR], 0.81; 95% confidence interval [CI], 0.71–0.93]) and vertebral fractures by 35% (OR, 0.65; 95% CI, 0.49–0.87). Fracture risk was also reduced in men and was independent of BMD. —GJS*

Hellemans J, Preobrazhenska O, Willaert A, Debeer P, Verdonk PC, Costa T, Janssens K, Menten B, Van Roy N, Vermeulen SJ, Savarirayan R, Van Hul W, Vanhoenacker F, Huylebroeck D, De Paepe A, Naeyaert JM, Vandesompele J, Speleman F, Verschueren K, Coucke PJ, Mortier GR. Loss-of-function mutations in LEMD3 result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis. *Nat Genet.* 2004 Nov;36(11):1213-8.

> *Osteopoikilosis, melorheostosis, and the Buschke-Ollendorff syndrome are allelic osteosclerotic disorders with dominant inheritance. Positional cloning localized the loss-of-function mutations responsible for the three disorders to the LEMD3 (aka MAN1) gene, which encodes an inner nuclear membrane protein. In Xenopus, LEMD3 binds smads and antagonizes bone morphogenetic protein (BMP) signaling. In this paper, LEMD3 is shown to bind smads in a yeast two-hybrid system and to inhibit BMP signaling. Another BMP-dependent osteosclerotic syndrome? See van Bezooijen et al. J Exp Med. 2004 Mar 15;199(6):805-14. —GJS*

Kokubu C, Heinzmann U, Kokubu T, Sakai N, Kubota T, Kawai M, Wahl MB, Galceran J, Grosschedl R, Ozono K, Imai K. Skeletal defects in *ringelschwanz* mutant mice reveal that Lrp6 is required for proper somitogenesis and osteogenesis. *Development.* 2004 Nov;131(21):5469-80.

> Ringelschwanz *is a spontaneous mouse mutation that causes a curled tail (ringelschwanz), vertebral and neural tube defects, delayed ossification, and osteoporosis. It is shown here that* ringelschwanz *is a hypomorphic allele of the* Lrp6 *gene. The contribution of* Lrp6 *to bone development and remodeling was previously uncertain, because of prenatal lethality of* Lrp6*(-/-) mice.* Lrp5 *and* Lrp6 *make independent contributions to skeletal development and consolidation. —GJS*

Treatment and Drug Effects

Cameron MA, Paton LM, Nowson CA, Margerison C, Frame M, Wark JD. The effect of calcium supplementation on bone density in premenarcheal females: a co-twin approach. *J Clin Endocrinol Metab.* 2004 Oct;89(10):4916-22.

> *Pairs of premenarcheal twins, supplemented with calcium in a randomized, single-blind, placebo-controlled trial, increased BMD by a couple of percentage points, all gone by 24 months. This is another study challenging the role of dietary calcium supplementation in skeletal growth. These tiny effects seem to be temporary remodeling changes induced by intervention, which reverse on cessation of the supplement. The trial needed is one done*

in kids taking less than 200 mg/day, but of course, this must be unethical. Or is it unethical not to conduct such a trial? —ES

Delmas PD, Recker RR, Chesnut CH 3rd, Skag A, Stakkestad JA, Emkey R, Gilbride J, Schimmer RC, Christiansen C. Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study. *Osteoporos Int.* 2004 Oct;15(10):792-8.

Ibandronate joins the other antiresorptive agents in demonstrating antispine fracture efficacy. Daily and intermittent treatment reduced the risk of vertebral fractures by 62% and 50%, respectively. Remodeling was suppressed by more than 50% within three months of treatment. —ES

Frediani B, Spreafico A, Capperucci C, Chellini F, Gambera D, Ferrata P, Baldi F, Falsetti P, Santucci A, Bocchi L, Marcolongo R. Long-term effects of neridronate on human osteoblastic cell cultures. *Bone.* 2004 Oct;35(4):859-69.

A missing link in bisphosphonate therapy seems to be whether these drugs influence the volume of bone formed in the basic multicellular unit by affecting the production, work, or lifespan of osteoblasts. Neridronate seems to enhance the differentiation of cultured osteoblasts in mature bone-forming cells. —ES

Kanis JA, Borgstrom F, Johnell O, Jonsson B. Cost-effectiveness of risedronate for the treatment of osteoporosis and prevention of fractures in postmenopausal women. *Osteoporos Int* 2004:15:862-71.

*A Markov model assessed the cost effectiveness of intervention by age and other factors. Risedronate was used in the modeling and was cost effective in women aged 60 years and older. Cost savings were found for postmenopausal women aged 70 years and older with established osteoporosis, in women 65 years and older with a prior vertebral fracture and a T score = -2.5 SD, and in women with a T score ≤ -2.5 SD without a prior vertebral fracture. In women aged 60-80 years at the threshold of osteoporosis (T score = -2.5 SD), but without a prior vertebral fracture, treatment exceeded the threshold for cost effectiveness. An additional independent risk factor (*e.g.*, corticosteroid use) made treatment cost effective. —ES*

Lindsay R, Scheele WH, Neer R, Pohl G, Adami S, Mautalen C, Reginster JY, Stepan JJ, Myers SL, Mitlak BH. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med.* 2004 Oct 11;164(18):2024-30.

PTH reduces fracture risk, but after stopping PTH, bone loss resumes, and it is likely that antiresorptives will be needed. Lindsay et al. *suggest that the 40% fracture risk reduction was maintained during an 18-month follow-up period. Osteoporosis drugs were used by 47% of women during follow-up, making the data difficult to interpret. —ES*

McClung MR, Wasnich RD, Hosking DJ, Christiansen C, Ravn P, Wu M, Mantz AM, Yates J, Ross PD, Santora AC 2nd; Early Postmenopausal Intervention Cohort Study. Prevention of postmenopausal bone loss: six-year results from the Early Postmenopausal Intervention Cohort Study. *J Clin Endocrinol Metab.* 2004 Oct;89(10):4879-85.

In this study, 585 women were given placebo or alendronate (2.5 or 5 mg/day) for six years. Women receiving placebo lost bone, whereas those receiving alendronate gained BMD (not bone mass) that was maintained through the sixth year. Fractures occurred in 11.5%, 10.3%, and 8.9% of women taking placebo, alendronate (2.5 mg/day), and alendronate (5 mg day), respectively. No difference in fracture rate, so why treat with any drug, if few fractures occur in the early postmenopausal years? Now read the paper by

Kanis et al. Osteoporos Int 2004:15:862-71. —ES

- van Staa TP, Bishop N, Leufkens HG, Cooper C. Are inhaled corticosteroids associated with an increased risk of fracture in children? *Osteoporos Int.* 2004 Oct;15(10):785-91.

Big studies must be true. This is big. Inhaled corticosteroids in 97,387 asthmatics, bronchodilators in 70,984 asthmatics, and a reference group of 345,758. The increased risk of fracture associated with use of inhaled corticosteroids seems to be explained by disease. —ES

Reviews, Perspectives, and Editorials

- Eng-Wong J, Zujewski JA. Raloxifene and its role in breast cancer prevention. *Expert Rev Anticancer Ther.* 2004 Aug;4(4):523-32.

- Friedman PA. PTH revisited. *Kidney Int Suppl.* 2004 Oct(91):S13-9.

- Fromigue O, Modrowski D, Marie PJ. Growth factors and bone formation in osteoporosis: roles for fibroblast growth factor and transforming growth factor-□. *Curr Pharm Des.* 2004;10(21):2593-603.

- Iwamoto J, Takeda T, Sato Y. Effects of vitamin K2 on osteoporosis. *Curr Pharm Des.* 2004;10(21):2557-76.

- Lane NE. Parathyroid hormone: evolving therapeutic concepts. *Curr Opin Rheumatol.* 2004 Jul;16(4):457-63.

- Manolagas SC, Kousteni S, Chen JR, Schuller M, Plotkin L, Bellido T. Kinase-mediated transcription, activators of nongenotropic estrogen-like signaling (ANGELS), and osteoporosis: a different perspective on the HRT dilemma. *Kidney Int Suppl.* 2004 Oct(91):S41-9.

- Miyakoshi N. Effects of parathyroid hormone on cancellous bone mass and structure in osteoporosis. *Curr Pharm Des.* 2004;10(21):2615-27.

- Qin L, Raggatt LJ, Partridge NC. Parathyroid hormone: a double-edged sword for bone metabolism. *Trends Endocrinol Metab.* 2004 Mar;15(2):60-5.

- Silver J, Bushinsky D. Harnessing the parathyroids to create stronger bones. *Curr Opin Nephrol Hypertens.* 2004 Jul;13(4):471-6.

Other Work of Potential Interest

- Bastepe M, Weinstein LS, Ogata N, Kawaguchi H, Juppner H, Kronenberg HM, Chung UI. Stimulatory G protein directly regulates hypertrophic differentiation of growth plate cartilage in vivo. *Proc Natl Acad Sci U S A.* 2004 Oct 12;101(41):14794-9.

- Buevich AV, Silva T, Brodsky B, Baum J. Transformation of the Mechanism of Triple-helix Peptide Folding in the Absence of a C-terminal Nucleation Domain and Its Implications for Mutations in Collagen Disorders. *J Biol Chem.* 2004 Nov 5;279(45):46890-5.

- Colopy SA, Benz-Dean J, Barrett JG, Sample SJ, Lu Y, Danova NA, Kalscheur VL, Vanderby R Jr, Markel MD, Muir P. Response of the osteocyte syncytium adjacent to and distant from linear microcracks during adaptation to cyclic fatigue loading. *Bone.* 2004 Oct;35(4):881-91.

Gruber HE, Ingram JA, Leslie K, Hanley EN Jr. Cellular, but not matrix, immunolocalization of SPARC in the human intervertebral disc: decreasing localization with aging and disc degeneration. *Spine.* 2004 Oct 15;29(20):2223-8.

Guo X, Day TF, Jiang X, Garrett-Beal L, Topol L, Yang Y. Wnt/beta-catenin signaling is sufficient and necessary for synovial joint formation. *Genes Dev.* 2004 Oct 1;18(19):2404-17.

Loveridge N, Power J, Reeve J, Boyde A. Bone mineralization density and femoral neck fragility. *Bone.* 2004 Oct;35(4):929-41.

Matsumoto M, Kogawa M, Wada S, Takayanagi H, Tsujimoto M, Katayama S, Hisatake K, Nogi Y. Essential role of p38 mitogen-activated protein kinase in cathepsin K gene expression during osteoclastogenesis through association of NFATc1 and PU.1. *J Biol Chem.* 2004 Oct 29;279(44):45969-79.

Schroeder TM, Kahler RA, Li X, Westendorf JJ. Histone deacetylase 3 interacts with runx2 to repress the osteocalcin promoter and regulate osteoblast differentiation. *J Biol Chem.* 2004 Oct 1;279(40):41998-2007.

Tavella S, Biticchi R, Schito A, Minina E, Di Martino D, Pagano A, Vortkamp A, Horton WA, Cancedda R, Garofalo S. Targeted expression of SHH affects chondrocyte differentiation, growth plate organization, and Sox9 expression. *J Bone Miner Res.* 2004 Oct;19(10):1678-88.

Van Pottelbergh I, Goemaere S, Zmierczak H, Kaufman JM. Perturbed sex steroid status in men with idiopathic osteoporosis and their sons. *J Clin Endocrinol Metab.* 2004 Oct;89(10):4949-53.