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NOT TO BE MISSED

Clinical and Basic Research Papers – May 2006 Selections

Serge Ferrari, Associate Editor
Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Dobreva G, Chahrour M, Dautzenberg M, Chirivella L, Kanzler B, Farinas I, Karsenty G, Grosschedl R. SATB2 is a multifunctional determinant of craniofacial patterning and osteoblast differentiation. *Cell*. 2006 Jun 2;125(5):971-86. [Abstract]

Ellies DL, Krumlauf R. Bone formation: The nuclear matrix reloaded. *Cell*. 2006 Jun 2;125(5):840-2. [Abstract]

> *SATB2 is a protein that attaches transcription factors to the nuclear matrix. Mice deficient in the* Satb2 *gene have a cleft palate and other craniofacial patterning defects but also have profoundly impaired osteoblast function.* Hoxa2 *expression is markedly increased both in the developmental field of the palate and in osteoblasts. Biochemical experiments show that SATB2 binds to the* Hoxa2 *gene and represses its expression and genetic experiments show rescue of the calvarial osteoblast phenotype in* Satb2(-/-)/Hoxa2(-/-) *mice. SATB2 interacts physically with both Runx2 and Atf4, and double heterozygotes for* Satb2/Atf4 and Satb2/Runx2 *have marked impairment in bone formation. It is suggested that SATB2 is multifunctional, acting both by DNA binding and as a scaffolding protein, which in particular recruits ATF4 to Runx2-containing protein complexes in osteoblasts.* —GJS

Jones DC, Wein MN, Oukka M, Hofstaetter JG, Glimcher MJ, Glimcher LH. Regulation of adult bone mass by the zinc finger adapter protein Schnurri-3. *Science*. 2006 May 26;312(5777):1223-7. [Abstract] [Full Text]

> *This paper is a major new insight into the processes that regulate bone remodeling. The adapter protein Schnurri-3 promotes degradation of Runx2 through physical association between these molecules, which targets Runx2 to ubiquitination. In turn, mice lacking Schnurri-3 develop high bone mass and trabecular bone volume, with increased bone formation but normal osteoclastic function, i.e. a sclerosing bone dysplasia. Most interestingly, the process of excessive bone formation develops in mature mice, leading the authors to propose that Schnurri-3 belongs to the small group of factors that regulate postnatal osteoblast activity. A potential new target for anabolic therapy.* —SF

Takegahara N, Takamatsu H, Toyofuku T, Tsujimura T, Okuno T, Yukawa K, Mizui M, Yamamoto M, Prasad DV, Suzuki K, Ishii M, Terai K, Moriya M, Nakatsuji Y, Sakoda S, Sato S, Akira S, Takeda K, Inui M, Takai T, Ikawa M, Okabe M, Kumanogoh A, Kikutani H. Plexin-A1 and its interaction with DAP12 in immune responses and bone homeostasis. *Nat Cell Biol*. 2006 Jun;8(6):615-22. [Abstract]

Tamagnone L, Giordano S. Semaphorin pathways orchestrate osteogenesis. *Nat Cell Biol*. 2006 Jun;8(6):545-7. [Abstract]

> *Semaphorins were identified as axon guidance molecules but also function in cardiovascular development and the immune system. Removal of the gene for the semaphorin receptor plexin A1 produces osteopetrosis as well as mild impairment of dendritic cell function. The semaphorin sema6D is expressed on osteoclasts and addition of soluble sema6D promotes osteoclast differentiation. Semaphorin receptors employ several signaling pathways; Trem2 and DAP12 were identified as partners of plexin A1 in dendritic cells and osteoclasts and were shown to be essential for semaphorin effects on dendritic cells, but not shown to be essential to the development of osteoclasts. It is not clear what cells in bone besides osteoclasts express semaphorins; if semaphorins are flags, waving to guide osteoclasts, what are they trying to say?* —GJS

Winslow MM, Pan M, Starbuck M, Gallo EM, Deng L, Karsenty G, Crabtree GR. Calcineurin/NFAT signaling in osteoblasts regulates bone mass. *Dev Cell*. 2006 Jun;10(6):771-82.

> *The calcineurin inhibitors cyclosporine and tacrolimus are bad for osteoblasts; both the phosphatase calcineurin and its principal substrate NFAT are required for normal osteoblast development. NFATc1 binds to and activates the Col1a1 promoter cooperatively with Osterix (Koga T, et al. Nat Med. 2005 Aug;11(8):880-5.) Winslow et al. report that mice that express a constitutively active form of nuclear NFAT have massive osteosclerosis and increased osteoblast number as well as increased osteoclast number. They find increased expression of members of the Wnt signaling pathway and suggest this may account for increased osteoblastogenesis but do not examine cooperativity with Osterix. They detect no changes in RANKL or OPG and suggest that osteoclast number and bone resorption may be increased because of monocyte chemotaxis mediated by CCL8. Calcium signaling through calcineurin and NFAT is essential for normal osteoblast function; what is the first messenger that induces this calcium signal?* —GJS

Pathophysiology

McNamara LM, Ederveen AG, Lyons CG, Price C, Schaffler MB, Weinans H, Prendergast PJ. Strength of cancellous bone trabecular tissue from normal, ovariectomized and drug-treated rats over the course of ageing. *Bone*. 2006 Apr 25; [Epub ahead of print] [Abstract]

> *The authors report very counterintuitive and provocative data; that ovariectomy in rats increases the stiffness, yield strength, yield strain and ultimate stress of the mineralized trabecular bone and increase in the mineral content at the tissue level although overall bone mineral density and mass decrease. The higher bone strength in the OVX group may cause the trabecular architecture to adapt or compensate for loss of trabecular architecture.* —ES

Physiology and Metabolism

Nabeshima Y. Toward a better understanding of Klotho. *Sci Aging Knowledge Environ*. 2006 May 3;2006(8):pe11. [Abstract]

Razzaque MS, Lanske B. Hypervitaminosis D and premature aging: lessons learned from Fgf23 and Klotho mutant mice. *Trends Mol Med*. 2006 May 25; [Epub ahead of print] [Abstract]

Current reviews of a field that's moving with lightning speed. Klotho is a partner of FGF23, thereby regulating phosphate and vitamin D homeostasis; it regulates renal calcium transport; and it's apparently involved in PTH secretion. Klotho has a central role in mineral ion homeostasis but is also an authentic aging gene -- Klotho overexpression extends the lifespan of mice. Are vitamin D and phosphate levels determinants of longevity? —GJS

Treatment and Drug Effects

Plotkin LI, Manolagas SC, Bellido T. Dissociation of the pro-apoptotic effects of bisphosphonates on osteoclasts from their anti-apoptotic effects on osteoblasts/osteocytes with novel analogs. *Bone*. 2006 Apr 17; [Epub ahead of print]

Bisphosphonates induce osteoclast apoptosis by inhibition of the mevalonate pathway or from conversion to toxic ATP analogs and prevent osteoblast apoptosis by connexin43 hemichannel opening and activation of the extracellular signal-regulated kinases (ERKs). Bisphosphonates act on the two cell types by distinct mechanisms. Preservation of osteoblast and osteocyte viability without inducing osteoclast apoptosis as found with some analogs opens new possibilities for the treatment of bone fragility in conditions in which a decrease in bone remodeling is not desirable. —ES

Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med*. 2006 May 16;144(10):753-61. [Abstract]

It is "only" a systematic review, nothing new, but very much needed in the face of the growing anxiety concerning the complications of bisphosphonates therapy. The number of published ONJ cases recapitulated in this review is 390, and the prevalence data in cancer patients, available from 3 studies only, could be as high as 3-10%. In contrast, with only 15 published cases in patients treated for osteoporosis, ONJ problems might be vanishingly small in this context. An anti-angiogenic mechanism of bisphosphonates is proposed to explain the pathophysiology of ONJ. Some guidelines for dental care in patients receiving these drugs are provided which, although not revolutionary, might represent the current standard of care. Still waiting for true incidence data and elucidation of pathophysiological mechanisms. —SF

Reviews, Perspectives and Editorials

Kuro-O M. Klotho as a regulator of fibroblast growth factor signaling and phosphate/calcium metabolism. *Curr Opin Nephrol Hypertens*. 2006 Jul;15(4):437-41.

Nayak S, Olkin I, Liu H, Grabe M, Gould MK, Allen IE, Owens DK, Bravata DM. Meta-analysis: accuracy of quantitative ultrasound for identifying patients with osteoporosis. *Ann Intern Med*. 2006 Jun 6;144(11):832-41. [Abstract]

Seeman E, Delmas PD. Bone quality--the material and structural basis of bone strength and fragility. *N Engl J Med*. 2006 May 25;354(21):2250-61. [Info]

Other Studies of Potential Interest

Aoki K, Saito H, Itzstein C, Ishiguro M, Shibata T, Blanque R, Mian AH, Takahashi M, Suzuki Y, Yoshimatsu M, Yamaguchi A, Deprez P, Mollat P, Murali R, Ohya K, Horne WC, Baron R. A TNF

receptor loop peptide mimic blocks RANK ligand-induced signaling, bone resorption, and bone loss. *J Clin Invest*. 2006 Jun 1;116(6):1525-34. [Abstract] [Full Text]

Banziger C, Soldini D, Schutt C, Zipperlen P, Hausmann G, Basler K. Wntless, a conserved membrane protein dedicated to the secretion of Wnt proteins from signaling cells. *Cell*. 2006 May 5;125(3):509-22. [Abstract]

Berman E, Nicolaides M, Maki RG, Fleisher M, Chanel S, Scheu K, Wilson BA, Heller G, Sauter NP. Altered bone and mineral metabolism in patients receiving imatinib mesylate. *N Engl J Med*. 2006 May 11;354(19):2006-13. [Abstract]

Gori F, Friedman LG, Demay MB. Wdr5, a WD-40 protein, regulates osteoblast differentiation during embryonic bone development. *Dev Biol*. 2006 May 25; [Epub ahead of print] [Abstract]

Kavanagh KL, Dunford JE, Bunkoczi G, Russell RG, Oppermann U. The crystal structure of human geranylgeranyl pyrophosphate synthase reveals a novel hexameric arrangement and inhibitory product binding. *J Biol Chem*. 2006 May 11; [Epub ahead of print]

Kavanagh KL, Guo K, Dunford JE, Wu X, Knapp S, Ebetino FH, Rogers MJ, Russell RG, Oppermann U. The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. *Proc Natl Acad Sci U S A*. 2006 May 16;103(20):7829-34. [Abstract] [Full Text]

Kollet O, Dar A, Shivtiel S, Kalinkovich A, Lapid K, Sztainberg Y, Tesio M, Samstein RM, Goichberg P, Spiegel A, Elson A, Lapidot T. Osteoclasts degrade endosteal components and promote mobilization of hematopoietic progenitor cells. *Nat Med*. 2006 Jun;12(6):657-64. [Abstract]

Prahalad AK, Hickey RJ, Huang J, Hoelz DJ, Dobrolecki L, Murthy S, Winata T, Hock JM. Serum proteome profiles identifies parathyroid hormone physiologic response. *Proteomics*. 2006 Jun;6(12):3482-93. [Abstract]

Weber M, Roschger P, Fratzl-Zelman N, Schoberl T, Rauch F, Glorieux FH, Fratzl P, Klaushofer K. Pamidronate does not adversely affect bone intrinsic material properties in children with osteogenesis imperfecta. *Bone*. 2006 Apr 24; [Epub ahead of print] [Abstract]

Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, Saito T, Ikeda T, Kawasaki Y, Azuma Y, Ikegawa S, Hoshi K, Chung UI, Nakamura K, Kato S, Kawaguchi H. Carminerin contributes to chondrocyte calcification during endochondral ossification. *Nat Med*. 2006 Jun;12(6):665-70. [Abstract]

Zhou C, Assem M, Tay JC, Watkins PB, Blumberg B, Schuetz EG, Thummel KE. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. *J Clin Invest*. 2006 Jun 1;116(6):1703-12. [Abstract] [Full Text]

Conflict of Interest: Dr. Ferrari and Dr. Strewler report that no conflicts of interest exist. Dr. Seeman reports that he is an advisory committee member for Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme, Novartis, and Servier, and that he lectures occasionally at conference symposia for those companies.