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NOT TO BE MISSED

Clinical and Basic Research Papers – December 2006 Selections

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

Bone Modeling and Remodeling

Gao Y, Grassi F, Ryan MR, Terauchi M, Page K, Yang X, Weitzmann MN, Pacifici R. IFN-gamma stimulates osteoclast formation and bone loss in vivo via antigen-driven T cell activation. *J Clin Invest*. 2007 Jan;117(1):122-32. [Abstract] [Full Text]

> *The role of interferon-γ on bone resorption is complex and somewhat controversial. Numerous experiments in mice and humans indicate that on one side IFN-γ promotes osteoclastogenesis, on the other that IFN-γ inhibits RANKL effects on osteoclast formation. Through a series of elegant experiments in vitro and in vivo, the authors demonstrate here that IFN-γ may exert dual (both positive and negative) effects on bone resorption via direct inhibition of osteoclastogenesis, and indirect stimulation of osteoclastogenesis through T cell activation. Yet, IFN-γ receptor KO mice were only partially resistant against bone loss induced by ovariectomy or LPS, suggesting that IFN-γ acts as a modulator, rather than as a key factor, for bone resorption.* —SF

Haycraft CJ, Zhang Q, Song B, Jackson WS, Detloff PJ, Serra R, Yoder BK. Intraflagellar transport is essential for endochondral bone formation. *Development*. 2007 Jan;134(2):307-16. [Abstract]

> *The finding that cilia are important to bone remodeling has caused a considerable flurry (see BoneKEy-Osteovision. 2006 December;3(12):7-10). Haycroft et al. used a conditional allele of the polaris gene product to disrupt cilia within the developing limb. Deletion of cilia from ectoderm had no overt effect, but removal of cilia from the mesenchyme caused aberrant sonic hedgehog and Indian hedgehog signaling, with digit patterning and limb outgrowth abnormalities, respectively. Moreover, elements of the perichondrium differentiate abnormally into chondrocyte-like cells. Cilia are important in limb patterning and endochondral bone formation.* —GJS

Valcourt U, Merle B, Gineyts E, Viguet-Carrin S, Delmas PD, Garnero P. Non-enzymatic glycations of bone collagen modify osteoclastic activity and differentiation. *J Biol Chem*. 2006 Dec 1; [Epub ahead of print]

> *It is interesting when the result is diametrically opposite to that hypothesized. Advanced glycation end products (AGEs) appear to inhibit bone resorption. Mature osteoclasts seeded on slices containing an AGE result in a reduction in resorbed area, and decreased release of type I collagen fragments.* —ES

Genetics

Barnes AM, Chang W, Morello R, Cabral WA, Weis M, Eyre DR, Leikin S, Makareeva E, Kuznetsova N, Uveges TE, Ashok A, Flor AW, Mulvihill JJ, Wilson PL, Sundaram UT, Lee B,

Marini JC. Deficiency of cartilage-associated protein in recessive lethal osteogenesis imperfecta. *N Engl J Med*. 2006 Dec 28;355(26):2757-64. [Abstract]

> *Three children with lethal or severe osteogenesis imperfecta but no primary collagen mutations were shown to have mutations in the gene for cartilage-associated protein (CRTAP), part of the prolyl 3-hydroxylase complex. All had deficient 3-hydroxylation of Pro986 and excessive posttranslational modification of collagen, consistent with delayed folding of the collagen gene. A similar syndrome results from deletion of the mouse gene for CRTAP (see Morello et al. Cell. 2006 Oct;127(2):291-304). Though the obvious conclusion would be that 3-hydroxylation is essential for normal collagen folding, in a recent Commentary (see BoneKEy-Osteovision. 2006 November;3(11):10-13), Stephen Krane discusses the pathogenesis of osteogenesis imperfecta in these syndromes and suggests that deficient 3-hydroxylation of Pro986 may not be the whole story.* —GJS

Pathophysiology

Park BK, Zhang H, Zeng Q, Dai J, Keller ET, Giordano T, Gu K, Shah V, Pei L, Zarbo RJ, McCauley L, Shi S, Chen S, Wang CY. NF-kappaB in breast cancer cells promotes osteolytic bone metastasis by inducing osteoclastogenesis via GM-CSF. *Nat Med*. 2007 Jan;13(1):62-9. [Abstract]

> *Metastatic MDA-MB-231 breast cancer cells express NF-κB, and inhibiting the NF-κB pathway by expression of a super-repressor (MDA/I cells) or with IKK2 inhibitors prevents osteolytic bone metastasis. A principal target gene of the NF-κB pathway in MDA cells is GM-CSF; restoration of GM-CSF expression in MDA/I cells restores their ability to metastasize to bone. It is GM-CSF produced by MDA cells that is responsible for osteoclastogenesis in vitro; knockdown of GM-CSF reduces osteolytic bone metastasis, and also inhibits osteolysis by MDA cells injected directly into bone. Importantly, 75% of bone metastatic human breast cancers display nuclear localization of NF-κB and express GM-CSF. Though there are many candidate mediators of tumor osteolysis, the GM-CSF story told here is remarkably complete.* —GJS

Sornay-Rendu E, Boutroy S, Munoz F, Delmas PD. Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased bone mineral density measured by DXA. The OFELY study. *J Bone Miner Res*. 2006 Dec 20; [Epub ahead of print] [Abstract]

> *These authors previously reported in a smaller sample of postmenopausal women that volumetric bone density and trabecular structure at the distal radius, as evaluated by high-resolution computed tomography, was decreased in women with fractures compared to women without fractures, despite similar levels of BMD. In this study, they compared a larger sample of women with and without fractures prospectively assessed for up to 13 years, confirming their previous data and further indicating that some parameters of bone microarchitecture, such as trabecular density at the distal radius and cortical thickness at the distal tibia, remain lower among fractured women after adjusting for BMD values at ultradistal radius and total hip, respectively.* —SF

Treatment and Drug Effects

Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR; FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture

Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006 Dec 27;296(24):2927-38. [Abstract]

Colon-Emeric CS. Ten vs five years of bisphosphonate treatment for postmenopausal osteoporosis: enough of a good thing. *JAMA*. 2006 Dec 27;296(24):2968-9. [Info]

> *1099 postmenopausal women were randomized to alendronate or placebo for 5 years after 5 years of alendronate. Despite declines in BMD and increases in markers of turnover, non-vertebral and morphometric vertebral fractures were no greater in the placebo group. There was a lower risk of clinical vertebral fractures with continued alendronate. The null observation is interpreted as being consistent with a sustained protective effect after discontinuation of alendronate for up to 5 years. A per protocol analysis would be interesting given use of drug therapy including alendronate in 83 of 428 subjects in the placebo arm and cessation of alendronate in 63 of 321 (5mg) and 71 of 322 (10 mg) in the treatment arm.* —ES

Deane A, Constancio L, Fogelman I, Hampson G. The impact of vitamin D status on changes in bone mineral density during treatment with bisphosphonates and after discontinuation following long-term use in post-menopausal osteoporosis. *BMC Musculoskelet Disord*. 2007 Jan 10;8(1):3 [Epub ahead of print] [Abstract]

> *Do vitamin D and/or PTH levels influence the BMD response to bisphosphonates? Considering that at least 50% of osteoporosis patients still taking bisphosphonates after one year may have dropped their vitaminD/calcium supplements, the question is of importance. This small, observational study in 112 post-menopausal women receiving alendronate, risedronate or etidronate suggests that 4-yr BMD changes at the spine were unaffected by PTH levels and vitamin D status, whereas at the hip, no BMD gain was observed in the group with higher PTH levels, nor in those with 25OHD values below 70 nmol/L, i.e. the currently recommended threshold. Although not definitive, these results are intriguing.* —SF

Reviews, Perspectives and Editorials

Berenson JR, Rajdev L, Broder M. Managing bone complications of solid tumors. *Cancer Biol Ther*. 2006 Sep;5(9):1086-9. [Abstract]

Bischoff-Ferrari HA. How to select the doses of vitamin D in the management of osteoporosis. *Osteoporos Int*. 2006 Dec 7; [Epub ahead of print] [Abstract]

Boyce BF, Xing L. Osteoclasts, no longer osteoblast slaves. *Nat Med*. 2006 Dec;12(12):1356-8. [Info]

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Dunstan CR, Felsenberg D, Seibel MJ. Therapy insight: the risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease. *Nat Clin Pract Oncol*. 2007 Jan;4(1):42-55. [Abstract]

Harrison RA, Siminoski K, Vethanayagam D, Majumdar SR. Osteoporosis-related kyphosis and impairments in pulmonary function: a systematic review. *J Bone Miner Res*. 2006 Dec 20; [Epub ahead of print] [Abstract]

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Martin TJ, Seeman E. New mechanisms and targets in the treatment of bone fragility. *Clin Sci (Lond)*. 2007 Feb;112(2):77-91. [Abstract]

Mbalaviele G, Shin CS, Civitelli R. Cell-cell adhesion and signaling through cadherins: connecting bone cells in their microenvironment. *J Bone Miner Res*. 2006 Dec;21(12):1821-7. [Info]

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Poole KE, Compston JE. Osteoporosis and its management. *BMJ*. 2006 Dec 16;333(7581):1251-6. [Info] [Full Text]

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Zhao Q, Shao J, Chen W, Li YP. Osteoclast differentiation and gene regulation. *Front Biosci*. 2007 Jan 1;12:2519-29. [Abstract]

Other Studies of Potential Interest

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Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2006 Dec 4; [Epub ahead of print] [Abstract]

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Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and consultancy/speaker's fees from Merck Sharp & Dohme, Eli Lilly, and Amgen. 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. Dr. Strewler reports that no conflict of interest exists.