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NOT TO BE MISSED

Clinical and Basic Research Papers – April 2005 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Eghbali-Fatourechi GZ, Lamsam J, Fraser D, Nagel D, Riggs BL, Khosla S. Circulating osteoblast-lineage cells in humans. N Engl J Med. 2005 May 12;352(19):1959-66. [Abstract]
Canalis E. The fate of circulating osteoblasts. *N Engl J Med.* 2005 May 12;352(19):2014-6. [Info]

> *Osteoblast-lineage cells have previously been found in bone marrow and peripheral blood, but this report shows that the recovery of nonadherent cells with an osteoblast phenotype from peripheral blood is about 10^6-fold greater than the previously reported recovery of adherent cells -- although it is difficult to ascertain their absolute number from the report. The number of circulating osteoblast-lineage cells is markedly increased in two states of high bone turnover, adolescence and fracture. Where do these cells come from? What is their fate? —GJS*

Murshed M, Harmey D, Millan JL, McKee MD, Karsenty G. Unique coexpression in osteoblasts of broadly expressed genes accounts for the spatial restriction of ECM mineralization to bone. *Genes Dev.* 2005 May 1;19(9):1093-104. [Abstract]

> *Why is mineralization of the extracellular matrix normally unique to bone, teeth, and hypertrophic cartilage? This paper argues from a series of genetic and in vitro experiments that the simultaneous presence of three things is both necessary and sufficient for mineralization: an adequate concentration of phosphate; cellular expression of type I collagen, the substrate for mineralization; and the enzyme alkaline phosphatase, which serves to remove pyrophosphate, an inhibitor of mineralization. Ectopic expression of alkaline phosphatase is sufficient to mineralize the matrix of fibroblasts that express type I collagen. —GJS*

Yamashita M, Ying SX, Zhang GM, Li C, Cheng SY, Deng CX, Zhang YE. Ubiquitin ligase Smurf1 controls osteoblast activity and bone homeostasis by targeting MEKK2 for degradation. *Cell.* 2005 Apr 8;121(1):101-13. [Abstract]

> *Smurf1 is a ubiquitin ligase that targets for destruction SMADs in the BMP signaling pathway. Smurf1(-/-) mice have increased osteoblast function and bone mass, but the primary target of Smurf1 in osteoblasts seems not to be a SMAD. Instead, the phosphorylated form of the protein kinase MEK kinase2 is directly bound by Smurf1 and targeted for degradation. MEK kinase2 is upstream of Jun-kinase and thereby regulates the transcription complex AP-1. —GJS*

Pathophysiology

Wada T, Nakashima T, Oliveira-dos-Santos AJ, Gasser J, Hara H, Schett G, Penninger JM. The molecular scaffold Gab2 is a crucial component of RANK signaling and osteoclastogenesis. *Nat Med*. 2005 Apr;11(4):394-9. [Abstract]

> *Gab2 is a scaffolding protein that binds to receptor complexes, often via Grb; it is a target for phosphorylation and thereafter assembles other signaling molecules. The authors*

observed mild osteopetrosis in Gab2(-/-) mice and found decreased osteoclast numbers. Unexpectedly, Gab2 seems to be downstream of RANK: RANKL-induced osteoclastogenesis is impaired in Gab2(-/-) macrophages, and Gab2 associates with RANK and is phosphorylated upon exposure to RANKL. Gab2(-/-) osteoclasts have impaired signaling in some of the pathways downstream of RANK (e.g., JNK, AKT, and I□B□), but not all of them -- phosphorylation of p38 and induction of NFAT are unaffected. It is not clear how Gab2 binds to RANK (e.g., does binding involve tumor necrosis factor receptor-associated factors?), how it is phosphorylated, or how it interacts with downstream signaling pathways. —GJS

Treatment and Drug Effects

Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA.* 2005 May 11;293(18):2257-64. [Abstract]

The epidemiologist Alvin Feinstein once observed that meta-analysis is to analysis as metaphysics is to physics. This meta-analysis, however, arrives at an important conclusion: a vitamin D supplement of at least 800 IU is required for prevention of fractures. Useful as it is, the conclusion is immediately challenged by a clinical trial that we also note this month (Lancet May 2005; 365 (9471) : 1621-8.) —GJS

Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, Anderson FH, Cooper C, Francis RM, Donaldson C, Gillespie WJ, Robinson CM, Torgerson DJ, Wallace WA; RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet.* 2005 May 7;365(9471):1621-8. [Abstract]

Current data suggest that supplementation of elderly persons with vitamin D (800 IU) can prevent fractures (see Bischoff-Ferrari JAMA May 2005; 293 (18): 2257-64, noted elsewhere in this feature, and a recent review [link to Dawson-Hughes]). In this study, 5292 people aged 70 years or older with a low-trauma fracture were randomly assigned vitamin D3 (800 IU), calcium (1000 mg), the combination, or placebo. After at least 24 months of followup the incidence of fractures in the treatment groups was not different from placebo. Only 54.5% of patients were still taking their medication at 24 months, and the mean 25OHD level achieved with supplements (in a small subset of subjects) was lower than in previous studies. The final word is still out on vitamin D supplementation to prevent fractures. —GJS

Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, Lindsay R, Mitlak BH. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporos Int.* 2005 May;16(5):510-6. [Abstract]

*Stopping PTH is associated with bone loss. Antiresorptives prevent the decline. Of 279 men, 11.7% assigned to placebo, 5.4% treated with teriparatide (20 µg), and 6.0% treated with teriparatide (40 µg) had vertebral fractures. In treatment groups combined vs. placebo, risk of vertebral fracture was reduced by 51% (*p = *0.07). The incidence of moderate or severe fractures was reduced by 83% (*p = *0.01). —ES*

McCombs JS, Thiebaud P, McLaughlin-Miley C, Shi J. Compliance with drug therapies for the treatment and prevention of osteoporosis. *Maturitas.* 2004 Jul 15;48(3):271-87. [Abstract]

There is no point in effective therapy if compliance is poor. In 58,109 patients with osteoporosis initiating therapy, one-year compliance rates were less than 25%. Mean duration of therapy was 221 days for raloxifene, 245 days for bisphosphonates, 262 for estrogen-only, and 292 days for estrogen plus progestin. Poor compliance was associated with higher fracture rates at the hip and use of more physicians and outpatient services. General patient-, drug-, and doctor-related factors causing poor compliance are not well defined, nor are methods of improving compliance. However, whether higher morbidity or mortality rates in poor compliers is actually caused by omission of therapy is uncertain, as poor compliance with placebo is associated with twice the mortality of compliers with placebo (Lancet 1990;336:542, NEJM 1980;303:1038) —ES

Reviews, Perspectives, and Editorials

Ariyoshi W, Takahashi T, Kanno T, Ichimiya H, Takano H, Koseki T, Nishihara T. Mechanisms involved in enhancement of osteoclast formation and function by low molecular weight hyaluronic acid. *J Biol Chem.* 2005 May 13;280(19):18967-72. [Abstract][Full Text]

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Delmas PD. Clinical effects of strontium ranelate in women with postmenopausal osteoporosis. *Osteoporos Int*. 2005 Jan;16 Suppl 1:S16-9. [Abstract]

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Egermann M, Schneider E, Evans CH, Baltzer AW. The potential of gene therapy for fracture healing in osteoporosis. *Osteoporos Int.* 2005 Mar;16 Suppl 2:S120-8. [Abstract]

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Other Studies of Potential Interest

Acheson LS. Bone density and the risk of fractures: should treatment thresholds vary by race? *JAMA.* 2005 May 4;293(17):2151-4. (GJS) [Info]

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