NOT TO BE MISSED

Clinical and Basic Research Papers – April 2005 Selections

Ego Seeman, Clinical Editor
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Bone Modeling and Remodeling


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


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


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


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 IκB), 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**


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


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


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

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

- Delmas PD, Rizzoli R, Cooper C, Reginster JY. Treatment of patients with postmenopausal osteoporosis is worthwhile. The position of the International Osteoporosis Foundation. Osteoporos Int. 2005 Jan;16(1):1-5. [Info]

Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. *J Bone Miner Res.* 2005 Feb;20(2):177-84. [Abstract][Full Text]


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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Sambrook P. Vitamin D and fractures: quo vadis? *Lancet.* 2005 May 7;365(9471):1599-600. (GJS) [Info]


