NOT TO BE MISSED

Clinical and Basic Research Papers – September and October 2004 Selections

Ego Seeman, Clinical Editor
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Bone Modeling and Remodeling


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 osteoclastogenesis; 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


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


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


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 XbaI 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


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


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


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


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


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


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


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


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

*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**


**Other Work of Potential Interest**


