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NOT TO BE MISSED

Clinical and Basic Research Papers – April 2006 Selections

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

Bone Modeling and Remodeling

Aguirre JI, Plotkin LI, Stewart SA, Weinstein RS, Parfitt AM, Manolagas SC, Bellido T. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. *J Bone Miner Res*. 2006 Apr;21(4):605–15. [Abstract]

> *A reduction in bone mass with immobilization is attributed to reduced bone formation – not quite so it seems. In this experiment, mice were tail-suspended and within 3 days osteocyte apoptosis was followed in 2 weeks by increased osteoclast number and cortical porosity, reduced trabecular and cortical width, and decreased vertebral strength. Apoptotic osteocytes were preferentially sequestered in endosteal cortical bone, an effect reproduced in transgenic mice with osteocytes refractory to glucocorticoids. Diminished mechanical forces eliminate signals that maintain osteocyte viability, leading to apoptosis and signaling resorptive activity.* —ES

Kurata K, Heino TJ, Higaki H, Vaananen HK. Bone marrow cell differentiation induced by mechanically damaged osteocytes in 3D gel-embedded culture. *J Bone Miner Res*. 2006 Apr;21(4):616–25. [Abstract]

> *The initiating event in remodeling is unlikely to be bone resorption. Damage to osteocytes, the guardians of the material and structural integrity of the bone, signals the location and magnitude of the damage to then contribute to osteoclastogenesis and removal of damage, and osteoblastogenesis and reconstruction of the excavated site. This study shows that damaged osteocytes induce the initial resorptive stage. Osteocyte-like cell line MLO-Y4 cells in 3D cultures were subjected to scratching and the formation of $TRACP^+$ in cocultured bone marrow cells was assayed. Scratching induced the death of MLO-Y4 cells and induced $TRACP^+$ cell differentiation in the restricted region along the scratching path. Damaged osteocytes secreted M-CSF and RANKL, activating osteoclastic cell formation.* —ES

Maes C, Coenegrachts L, Stockmans I, Daci E, Luttun A, Petryk A, Gopalakrishnan R, Moermans K, Smets N, Verfaillie CM, Carmeliet P, Bouillon R, Carmeliet G. Placental growth factor mediates mesenchymal cell development, cartilage turnover, and bone remodeling during fracture repair. *J Clin Invest*. 2006 May 1;116(5):1230-42. [Abstract] [Full Text]

> *Placental growth factor (PlGF) is a homolog of vascular endothelial growth factor (VEGF) which is redundant with VEGF during development but important in the response to injury. PlGF expression is increased in normal fracture healing, and experimental fracture healing in* PlGF(-/-) *mice is impaired, with massive accumulation of cartilage in a soft callus and increased fibrous tissue at the fracture line. Analysis of these changes showed impairment of the inflammatory response to fracture, reduced recruitment of osteochondroprogenitor cells, impaired release of the proteases MMP-13 and MT1-MMP,*

and altered bone remodeling in PlGF(-/-) *mice. Treatment with PlGF may improve fracture healing and prevent nonunion.* —GJS

Sun L, Peng Y, Sharrow AC, Iqbal J, Zhang Z, Papachristou DJ, Zaidi S, Zhu LL, Yaroslavskiy BB, Zhou H, Zallone A, Sairam MR, Kumar TR, Bo W, Braun J, Cardoso-Landa L, Schaffler MB, Moonga BS, Blair HC, Zaidi M. FSH directly regulates bone mass. *Cell*. 2006 Apr 21;125(2):247-60. [Abstract]

Baron R. FSH versus estrogen: Who's guilty of breaking bones? *Cell Metab.* 2006 May; 3(5):302-5. [Abstract]

This provocative paper reports that FSH receptors are present on the osteoclast surface and signal for osteoclast differentiation and bone resorption. In two models of deficient FSH action, the FSH receptor knockout mouse and the FSHβ knockout mouse, bone mass is either unchanged or increased in the face of ovarian failure. It is therefore suggested that FSH is a primary signal for postmenopausal bone loss. Estrogen deficiency must also be important; for example, increased bone resorption and bone loss are observed when gonadotropin secretion is inhibited by long-acting GnRH analogs. Additionally, previous reports indicate bone loss and osteoporotic changes in aging FSH receptor knockout mice (Danilovich et al. Endocrinology. 2000 Nov;141(11):4295-308), contrasting with the preservation of bone mass observed here. It is important to know that FSH could be a direct signal to the osteoclast, but many crucial experiments, such as measurement of estrogen and androgen levels in mutant animals, are missing, as outlined in the editorial by Baron, and the role of FSH in osteoporosis is not resolved by this work. —GJS

Genetics

Ichikawa S, Koller DL, Johnson ML, Lai D, Xuei X, Edenberg HJ, Klein RF, Orwoll ES, Hui SL, Foroud TM, Peacock M, Econs MJ. Human ALOX12, but not ALOX15, is associated with BMD in white men and women. *J Bone Miner Res*. 2006 Apr;21(4):556-64. [Abstract]

*The arachidonate 15-lipoxygenase (*Alox15*) gene is a negative regulator of peak BMD in mice.* ALOX15*, the human homolog of mouse* Alox15*, and* ALOX12 *were studied by genotyping SNPs across the two genes in 411 men 18-61 years of age and 1291 premenopausal women 20-50 years of age. Association was found between spine BMD and six SNPs in the* ALOX12 *gene in men and women. The most common SNP haplotype in* ALOX12 *showed evidence of association with high spine BMD in men, whereas the second most common haplotype was associated with high spine BMD in women. Polymorphisms in the* ALOX12 *gene may contribute to normal variation in spine BMD.* —ES

Service S, Deyoung J, Karayiorgou M, Roos JL, Pretorious H, Bedoya G, Ospina J, Ruiz-Linares A, Macedo A, Palha JA, Heutink P, Aulchenko Y, Oostra B, van Duijn C, Jarvelin MR, Varilo T, Peddle L, Rahman P, Piras G, Monne M, Murray S, Galver L, Peltonen L, Sabatti C, Collins A, Freimer N. Magnitude and distribution of linkage disequilibrium in population isolates and implications for genome-wide association studies. *Nat Genet*. 2006 May;38(5):556-60.

How many SNPs does it take to map susceptibility to a disease? By analyzing nearly 25 hundred markers on chromosome 22 in 200 individuals from each of 11 population isolates from around the world, such as Finns from Kuusano and Sardinians, this study demonstrates that the extent of linkage disequilibrium (LD) decreases when the number of founders increases and the rate of expansion of the population is lower. The worst

case scenario is for an outbred European population, which shows an LD map 20-45% shorter than the population isolates mentioned above, i.e. larger "holes" in the genome flanked by non-linked SNPs (that is black boxes with no genomic information available). Hence, linkage mapping for common disorders in broad population samples from Europe or the US is more likely to miss the genomic region where susceptibility for the disease is located than similar studies led in isolated populations. Conversely, the number of SNP markers required in outbred populations to map a disease is likely to be as much as 3-fold larger compared to isolated populations. —SF

Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Brown MA, Kaplan FS. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. *Nat Genet*. 2006 May;38(5):525-7. [Abstract]

*Fibrodysplasia ossificans progressiva (FOP) is a devastating inherited (autosomal dominant) or sporadic disease characterized by extra-skeletal ossifications that can eventually become of extraordinary proportions and completely prevent mobility of the affected subjects. A previous attempt of linkage analysis in affected families had failed to identify gene mutations responsible for FOP. This time linkage analysis in 5 affected families led to the identification of a single gene mutation in the activin Type 1 receptor gene (*ACVR1*). The same de novo mutation was then also identified in 32 sporadic cases of FOP.* ACVR1 *codes for a BMP receptor family member. Although no functional assays were performed in this study to demonstrate whether this mutation altered receptor signaling and/or activity, in silico protein modeling suggests that it would lead to a constitutive BMP-like activity, a plausible mechanism for the process of heterotopic ossifications in FOP. This discovery may potentially pave the way to develop ACVR1 inhibitors (reverse agonists) to treat FOP.* —SF

Pathophysiology

Ruppel ME, Burr DB, Miller LM. Chemical makeup of microdamaged bone differs from undamaged bone. *Bone*. 2006 Mar 31; [Epub ahead of print]

Microdamaged areas of bone are chemically different than the undamaged areas, the mineral stoichiometry was altered in microdamaged bone, where the carbonate/protein ratio and carbonate/phosphate ratio were lower in areas of microdamage, and the acid phosphate content was higher. No differences were observed in tissue mineralization (phosphate/protein ratio) or crystallinity between the microdamaged and undamaged bone, indicating that the microdamaged regions of bone were not over-mineralized. The collagen cross-linking structure was also different in microdamaged areas of bone, consistent with ruptured cross-links. All differences had well-defined boundaries in the microcrack region, suggesting that they occurred after microcrack formation. —ES

Physiology and Metabolism

Hoffmann A, Pelled G, Turgeman G, Eberle P, Zilberman Y, Shinar H, Keinan-Adamsky K, Winkel A, Shahab S, Navon G, Gross G, Gazit D. Neotendon formation induced by manipulation of the Smad8 signalling pathway in mesenchymal stem cells. *J Clin Invest*. 2006 Apr;116(4):940-52. [Abstract] [Full Text]

Towler DA, Gelberman RH. The alchemy of tendon repair: a primer for the (S)mad scientist. *J Clin Invest*. 2006 Apr;116(4):863-6. [Abstract] [Full Text]

Cotransfection of BMP2 and a truncated form of Smad8 into C3H10T1/2 cells induced them to differentiate into tendon-like cells. Transfected cells maintained this phenotype when grown in nude mice and were incorporated into an experimental tendon defect, suggesting that this strategy could produce cells useful for tendon repairs in humans. —GJS

Venken K, De Gendt K, Boonen S, Ophoff J, Bouillon R, Swinnen JV, Verhoeven G, Vanderschueren D. Relative impact of androgen and estrogen receptor activation in the effects of androgens on trabecular and cortical bone in growing male mice: a study in the androgen receptor knockout mouse model. *J Bone Miner Res*. 2006 Apr;21(4):576-85. [Abstract]

How important the role of testosterone is, as compared to its aromatization into estrogens, on bone mass acquisition in males remains uncertain. Pursuing their seminal work on androgen receptor deficient mice (ARKO), the authors demonstrate in a series of elegant experiments that testosterone (T) and a non-aromatizable androgen (DHT) have similar ability to restore trabecular bone density and trabecular number as well as cortical area and periosteal bone formation in orchidectomized (ORX) mice, but not ARKO mice. These results clearly indicate a direct and predominant role of androgen acting through its cognate nuclear receptor on bone mass regulation in males. Intriguingly, however, combination with an aromatase inhibitor partially prevented T effects on cortical bone in ORX wild-type mice, but not in ARKO mice. This inhibition was accompanied by a decrease in systemic IGF-1 levels, suggesting that T aromatization into estrogens raises IGF-1 and thereby (and/or directly) contributes to periosteal bone formation in males. So, is it androgen or estrogen that makes up the male bone size and mass? Likely both, albeit in different proportions. —SF

Reviews, Perspectives and Editorials

Boonen S, Bischoff-Ferrari HA, Cooper C, Lips P, Ljunggren O, Meunier PJ, Reginster JY. Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. *Calcif Tissue Int*. 2006 May;78(5):257-70. [Abstract]

Chattopadhyay N. Effects of calcium-sensing receptor on the secretion of parathyroid hormone-related peptide and its impact on humoral hypercalcemia of malignancy. *Am J Physiol Endocrinol Metab*. 2006 May;290(5):E761-70. [Abstract]

Daftary GS, Taylor HS. Endocrine regulation of HOX genes. *Endocr Rev*. 2006 Apr 21; [Epub ahead of print]

Krishnan V, Bryant HU, MacDougald OA. Regulation of bone mass by Wnt signaling. J *Clin Invest*. 2006 May;116(5):1202-9. [Abstract] [Full Text]

Valdivielso JM, Fernandez E. Vitamin D receptor polymorphisms and diseases. *Clin Chim Acta*. 2006 Mar 6; [Epub ahead of print] [Abstract]

Weitzmann MN, Pacifici R. Estrogen deficiency and bone loss: an inflammatory tale. *J Clin Invest*. 2006 May;116(5):1186-94. [Abstract] [Full Text]

Yin T, Li L. The stem cell niches in bone. *J Clin Invest*. 2006 May;116(5):1195-201. [Abstract] [Full Text]

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Other Studies of Potential Interest

Amin S, Zhang Y, Felson DT, Sawin CT, Hannan MT, Wilson PW, Kiel DP. Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study. *Am J Med*. 2006 May;119(5):426-33. [Abstract]

Guo J, Chung UI, Yang D, Karsenty G, Bringhurst FR, Kronenberg HM. PTH/PTHrP receptor delays chondrocyte hypertrophy via both Runx2-dependent and -independent pathways. *Dev Biol*. 2006 Apr 1;292(1):116-28. [Abstract]

Jiang Z, Asplin JR, Evan AP, Rajendran VM, Velazquez H, Nottoli TP, Binder HJ, Aronson PS. Calcium oxalate urolithiasis in mice lacking anion transporter Slc26a6. *Nat Genet*. 2006 Apr;38(4):474-8. [Abstract]

Maruyama R, Aoki F, Toyota M, Sasaki Y, Akashi H, Mita H, Suzuki H, Akino K, Ohe-Toyota M, Maruyama Y, Tatsumi H, Imai K, Shinomura Y, Tokino T. Comparative genome analysis identifies the vitamin D receptor gene as a direct target of p53-mediated transcriptional activation. *Cancer Res*. 2006 May 1;66(9):4574-83. [Abstract]

Rohmann E, Brunner HG, Kayserili H, Uyguner O, Nurnberg G, Lew ED, Dobbie A, Eswarakumar VP, Uzumcu A, Ulubil-Emeroglu M, Leroy JG, Li Y, Becker C, Lehnerdt K, Cremers CW, Yuksel-Apak M, Nurnberg P, Kubisch C, Schlessinger J, van Bokhoven H, Wollnik B. Mutations in different components of FGF signaling in LADD syndrome. *Nat Genet*. 2006 Apr;38(4):414-7. [Abstract]

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.