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NOT TO BE MISSED

Clinical and Basic Research Papers – November 2005 Selections

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

Bone Modeling and Remodeling

Clark WD, Smith EL, Linn KA, Paul-Murphy JR, Muir P, Cook ME. Osteocyte apoptosis and osteoclast presence in chicken radii 0-4 days following osteotomy. *Calcif Tissue Int*. 2005 Nov;77(5):327-36. [Abstract]

> *Osteocytes may be the leaders of the orchestra of local remodeling. The reason remodeling occurs at a given focal point on a bone surface is not known, but remodeling is thought to be induced by local damage, which in turn produces osteocyte apoptosis. The extent and anatomy of apoptosis may provide the road map needed to localize damage and then signal osteoclastogenesis and osteoblastogenesis for the removal of damaged bone and restoration with new bone. In this study, the incidence of osteocyte apoptosis and the presence of osteoclasts during the first 96 hours following osteotomy were assessed. Osteocyte apoptosis precedes an increase in osteoclast presence.* —ES

Hilton MJ, Tu X, Cook J, Hu H, Long F. Ihh controls cartilage development by antagonizing Gli3, but requires additional effectors to regulate osteoblast and vascular development. *Development* 2005 Oct 1;132(19):4339-51. [Abstract]

Koziel L, Wuelling M, Schneider S, Vortkamp A. Gli3 acts as a repressor downstream of Ihh in regulating two distinct steps of chondrocyte differentiation. *Development.* 2005 Dec;132 (23):5249-60. [Abstract]

> *Indian hedgehog (Ihh) is a regulator of cartilage maturation and endochondral ossification. In general, hedgehogs act on Gli family transcription factors, either by counteracting their repression of gene expression or by inducing their transcriptional activity. These two papers examine the results of removing the* Gli3 *gene from* Ihh*(-/-) embryos. Most of the cartilage phenotype of Ihh deficiency is restored by removing Gli3: chondrocytes proliferate relatively normally and no longer undergo premature hypertrophy. This indicates that Ihh acts in cartilage mainly by blocking repression of gene expression by Gli3. Koziel* et al. *report that restoration of normal chondrocyte hypertrophy is PTHrP dependent, but the switch from distal into columnar proliferating chondrocytes is PTHrP-independent. Hilton* et al. *concentrate on the persistent failure of bone collar formation in double knockouts and conclude that an activator activity of Gli3 and a vasculature-derived signal are required for osteoblast development.* —GJS

Kieslinger M, Folberth S, Dobreva G, Dorn T, Croci L, Erben R, Consalez GG, Grosschedl R. EBF2 Regulates Osteoblast-Dependent Differentiation of Osteoclasts. *Dev Cell*. 2005 Dec;9(6):757-67. [Abstract]

This paper implicates the transcription factor EBF2 in the regulation of osteoprotegerin expression by osteoblasts. Contrary to cbfa1/Runx2 *and O*sterix *KO mice,* EBF2 *KO mice have a normal skeletal morphology at birth, but develop dwarfism and a dramatic reduction of cortical thickness and trabecular volume by 3 weeks of age. Bone formation and osteoblast numbers are normal in these mice, and there is no evidence for an osteoblast-autonomous defect in vitro. In contrast, osteoclast numbers are increased, as well as biochemical indices of bone resorption.* OPG *mRNA expression is decreased and* RANKL *mRNA is more modestly increased in EBF2-deficient osteoblasts. Subsequently, EBF binding sites in the* OPG *promoter region were identified and, most interestingly, EBF2 was shown to synergize with beta-catenin, the mediator of the canonical Wnt signaling pathway, for the transcriptional control of* OPG*. —*SF

van der Eerden BC, Hoenderop JG, de Vries TJ, Schoenmaker T, Buurman CJ, Uitterlinden AG, Pols HA, Bindels RJ, van Leeuwen JP. The epithelial Ca2+ channel TRPV5 is essential for proper osteoclastic bone resorption. *Proc Natl Acad Sci U S A*. 2005 Nov 29;102(48):17507-12. [Abstract] [Full Text]

The epithelial calcium channel transient receptor potential-5 (TRPV5) is the PTH- and vitamin D-responsive channel through which calcium is reabsorbed in the distal nephron. This paper reports that osteoclasts display TRPV5 in the ruffled border, and that osteoclasts from which the TRPV5 *gene was removed are deficient in bone resorption. Impaired bone resorption in* TRPV5*(-/-) mice is not associated with full-blown osteopetrosis, however, perhaps because of markedly increased 1,25(OH)2D levels in* TRPV5*(-/-) mice, or because osteoclasts also express the vitamin D-sensitive intestinal brush border calcium channel TRPV6. Calcium transport through TRPV channels is physiologically significant in kidney, intestine and bone. —*GJS

Diagnosis

Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab*. 2005 Dec;90(12):6508-15. [Abstract] [Full Text]

*The use of high-resolution micro-computed tomography (HRmCT) to analyze tri-dimensional trabecular and cortical bone architecture in vivo is moving from rodents to humans. This seminal paper describes the excellent reproducibility of this technology in adults. Consistent with previous bone histomorphometrical analyses performed on iliac crest biopsies, HRmCT shows a rather large decrease in trabecular and cortical bone parameters at distal radius and tibia in osteopenic and osteoporotic women, as compared to premenopausal women. Most interestingly, trabecular architecture at the distal radius, but not tibia, was significantly decreased in a subgroup of osteopenic postmenopausal women with a history of non-vertebral fractures, compared to those without such history. It now remains to be seen whether non-invasive peripheral measurements of bone micro-architecture will be able to discriminate osteopenic women with or without vertebral fractures as well. —*SF

Pathophysiology

Sun L, Blair HC, Peng Y, Zaidi N, Adebanjo OA, Wu XB, Wu XY, Iqbal J, Epstein S, Abe E, Moonga BS, Zaidi M. Calcineurin regulates bone formation by the osteoblast. *Proc Natl Acad Sci U S A*. 2005 Nov 22;102(47):17130-35. [Abstract] [Full Text]

Calcium signals transmitted by the calcium-sensitive protein phosphatase calcineurin are essential for T-lymphocyte and osteoclast function. Immunosuppression with calcineurin inhibitors, such as cyclosporin A and tacrolimus (FK506), is associated with severe osteoporosis. Mice lacking the gene for the subunit calcineurin Aα have severe osteoporosis, with markedly reduced bone formation. Runx2, osteocalcin and bone sialoprotein expression are reduced in calcineurin Aα *(-/-) osteoblasts; transduction of calcineurin Aα into osteoblasts enhances their expression. Similar findings were reported in mice deficient in NFAT, a transcription factor that is downstream of calcineurin (Koga T, et al., Nat Med. 2005 Aug;11(8):880-5).* —GJS

Physiology and Metabolism

Perwad F, Azam N, Zhang MY, Yamashita T, Tenenhouse HS, Portale AA. Dietary and serum phosphorus regulate fibroblast growth factor 23 expression and 1,25-dihydroxyvitamin D metabolism in mice. *Endocrinology*. 2005 Dec;146(12):5358-64. [Abstract] [Full Text]

FGF-23 is one of the "phosphatonins" that promotes tubular excretion of phosphate and inhibits synthesis of calcitriol. Some human studies have shown that circulating FGF-23 increases upon introduction of a phosphate-rich diet, and conversely decreases upon phosphate deprivation, thereby demonstrating phosphate homeostasis regulation independent of PTH. This study now provides further evidence that dietary phosphate regulates circulating FGF-23 levels and that FGF-23 is directly correlated to serum phosphate levels in mice. Furthermore, FGF-23 mRNA abundance, in calvarial bone, followed the pattern of circulating FGF-23 in response to diet, indicating that bone may be an important source of FGF-23 in response to phosphate changes. —SF

Ryan MR, Shepherd R, Leavey JK, Gao Y, Grassi F, Schnell FJ, Qian WP, Kersh GJ, Weitzmann MN, Pacifici R. An IL-7-dependent rebound in thymic T cell output contributes to the bone loss induced by estrogen deficiency. *Proc Natl Acad Sci U S A*. 2005 Nov 15;102 (46):16735-40. [Abstract] [Full Text]

Estrogen deficiency causes rapid bone loss; however, the role of local and systemic cytokines in this phenomenon is uncertain. Here, it is reported that ovariectomy (OVX) leads to dysregulation of T-cell development, stimulating more thymic maturation of bone marrow-derived T-cell progenitors. The key signal to induce thymic T-cell maturation is interleukin-7 (IL-7). Thymectomy reduces post-OVX bone loss by about half, but blocking IL-7 completely prevents it, suggesting that IL-7 has both thymic and extrathymic actions to induce immune functions related to estrogen-responsive bone loss. —GJS

Treatment and Drug Effects

Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. *JAMA*. Nov 2005;294(18):2336-41. [Abstract]

That vitamin D insufficiency causes secondary hyperparathyroidism is now well-established. This large cross-sectional study in Iceland shows the expected inverse relationship of 25-hydroxyvitamin D [25(OH)D] and PTH, but also shows that at 25(OH)D levels <10 ng/ml, subjects with estimated calcium intakes <800 mg/day had secondary hyperparathyroidism, but those with intakes >1200 mg/day did not. In subjects with 25(OH)D levels >18 ng/ml, there was no relationship between calcium intake and PTH, suggesting that when vitamin D intake is adequate, calcium intake levels of more than

800 mg/day may be unnecessary to maintain calcium homeostasis. Vitamin D supplementation is required to maintain these levels, however, in this northern climate. — GJS

Reviews, Perspectives and Editorials

Balemans W, Van Wesenbeeck L, Van Hul W. A clinical and molecular overview of the human osteopetroses. *Calcif Tissue Int*. 2005 Nov;77(5):263-74. [Abstract]

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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.