BoneKEy-Osteovision. 2004 July;1(7):1-3
http://www.bonekey-ibms.org/cgi/content/full/ibmske;1/7/1
DOI: 10.1138/20040130

NOT TO BE MISSED

Clinical and Basic Research Papers – May and June 2004 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Gorski JP, Wang A, Lovitch D, Law D, Powell K, Midura RJ. Extracellular bone acidic glycoprotein-75 defines condensed mesenchyme regions to be mineralized and localizes with bone sialoprotein during intramembranous bone formation. *J Biol Chem.* 2004 Jun 11;279(24):25455-63. [Abstract] [Full Text]

> *The molecular events that regulate mineralization of matrix are still understood poorly. Bone acidic glycoprotein-75 (BAG-75) is localized in regions of the bone matrix destined to be mineralized; bone sialoprotein is subsequently colocalized in the same regions. The spatiotemporal sequence suggests that these molecules may regulate mineralization. —GJS*

Horiki M, Imamura T, Okamoto M, Hayashi M, Murai J, Myoui A, Ochi T, Miyazono K, Yoshikawa H, Tsumaki N. Smad6/Smurf1 overexpression in cartilage delays chondrocyte hypertrophy and causes dwarfism with osteopenia.
J Cell Biol. 2004 May 10;165(3):433-45. [Abstract] [Full Text]

> *Recommended. —ES*

Diagnosis

Binkley N, Krueger D, Cowgill CS, Plum L, Lake E, Hansen KE, DeLuca HF, Drezner MK. Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3152-7. [Abstract] [Full Text]

> *Those who care for patients know that diagnosing vitamin D insufficiency is problematic. Part of the problem has to do with marked variation between the various commercial assays for 25-hydroxyvitamin D in common clinical use. —GJS*

Genetics

Topaz O, Shurman DL, Bergman R, Indelman M, Ratajczak P, Mizrachi M, Khamaysi Z, Behar D, Petronius D, Friedman V, Zelikovic I, Raimer S, Metzker A, Richard G, Sprecher E. Mutations in GALNT3, encoding a protein involved in O-linked glycosylation, cause familial tumoral calcinosis. *Nat Genet.* 2004 Jun;36(6):579-81. [Abstract]

> *Familial tumoral calcinosis (FTC) is a recessively inherited disorder of phosphate metabolism, with hyperphosphatemia and massive subcutaneous deposition of calcium phosphate. In two families, mutations were identified in GALNT3, which encodes a glycosyltransferase responsible for initiating mucin-type O-glycosylation. Serum FGF-23 levels are markedly increased in subjects with FTC, but this could be compensatory for marked hyperphosphatemia. FGF-23 has potential O-linked glycosylation sites, but the skeletal phenotype of FGF-23-null mice is not present in FTC. —GJS*

Pathophysiology

van Meurs JB, Dhonukshe-Rutten RA, Pluijm SM, van der Klift M, de Jonge R, Lindemans J, de Groot LC, Hofman A, Witteman JC, van Leeuwen JP, Breteler MM, Lips P, Pols HA, Uitterlinden AG. Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med.* 2004 May 13;350(20):2033-41. *N. Engl. J. Med.* 2004 May 13; 350 (20):2033-2041. [Abstract]

McLean RR, Jacques PF, Selhub J, Tucker KL, Samelson EJ, Broe KE, Hannan MT, Cupples LA, Kiel DP. Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med.* 2004 May 13;350(20):2042-9. [Abstract]

Raisz LG. Homocysteine and osteoporotic fractures--culprit or bystander?
N Engl J Med. 2004 May 13;350(20):2089-90.

> *These two papers, one from the Netherlands and the other from the Framingham Study, show an association between plasma homocysteine levels and fracture that is comparable in magnitude to known risk factors, such as age and BMD. Does homocysteine interfere with collagen cross-linking, as it does in homocystinuria, or is it a marker for differences in vitamin intake, nutrition, estrogen level, or for genetic differences (e.g., in the methyltetrahydrofolate reductase gene)? —GJS*

Yang CM, Chien CS, Yao CC, Hsiao LD, Huang YC, Wu CB. Mechanical strain induces collagenase-3 (MMP-13) expression in MC3T3-E1 osteoblastic cells. *J Biol Chem.* 2004 May 21;279(21):22158-65. [Abstract] [Full Text]

> *Recommended. —ES*

Physiology and Metabolism

Akiyama H, Lyons JP, Mori-Akiyama Y, Yang X, Zhang R, Zhang Z, Deng JM, Taketo MM, Nakamura T, Behringer RR, McCrea PD, de Crombrugghe B. Interactions between Sox9 and beta-catenin control chondrocyte differentiation.
Genes Dev. 2004 May 1;18(9):1072-87. [Abstract]

> *Overexpression of β-catenin inhibits chondrocyte differentiation and accelerates chondrocyte hypertrophy, opposite of the effects of* Sox-9 *deletion. The converse is also true: deficiency of β-catenin has effects similar to overexpression of* Sox-9*. It is shown here that the two factors interact directly, and that the interaction prevents their nuclear actions and leads to proteosome-mediated degradation. Chondrogenesis may be controlled by these interactions, but the specific implications are hard to parse out, because β-catenin is downstream of multiple wnt proteins and of the cadherins.—GJS*

Fitzgerald JB, Jin M, Dean D, Wood DJ, Zheng MH, Grodzinsky AJ. Mechanical compression of cartilage explants induces multiple time-dependent gene expression patterns and involves intracellular calcium and cyclic AMP. *J Biol Chem.* 2004 May 7;279(19):19502-11. [Abstract] [Full Text]

> *Recommended. —ES*

Kisiday JD, Jin M, DiMicco MA, Kurz B, Grodzinsky AJ. Effects of dynamic compressive loading on chondrocyte biosynthesis in self-assembling peptide scaffolds. *J Biomech.* 2004 May;37(5):595-604. [Abstract]

> *Recommended. —ES*

MacLean HE, Guo J, Knight MC, Zhang P, Cobrinik D, Kronenberg HM. The cyclin-dependent kinase inhibitor p57(Kip2) mediates proliferative actions of PTHrP in chondrocytes. *J Clin Invest.* 2004 May;113(9):1334-43. [Abstract] [Full Text]

> *PTHrP regulates cartilage development at the junction between proliferative and hypertrophic zones by controlling exit of proliferating chondrocytes from the cell cycle and their subsequent hypertrophy. This paper shows that many aspects of the* PTHrP*-null phenotype -- both reduced proliferation and premature differentiation -- are rescued by removal of the cell cycle inhibitory protein p57. It may be that PTHrP regulates chondrocyte hypertrophy mainly by regulating the cell cycle, although additional effects on differentiation are possible.—GJS*

Pfander D, Kobayashi T, Knight MC, Zelzer E, Chan DA, Olsen BR, Giaccia AJ, Johnson RS, Haase VH, Schipani E. Deletion of Vhlh in chondrocytes reduces cell proliferation and increases matrix deposition during growth plate development. *Development.* 2004 May;131(10):2497-508. [Abstract]

> *Chondrocytes live in a relatively hypoxic environment because cartilage is avascular, and it was previously shown that removal of the hypoxia-inducible transcription factor HIF1a leads to massive chondrocyte death. Here* Vhlh*, the gene that encodes the von Hippel Lindau tumor suppressor protein, was removed from cartilage. The von Hippel-Lindau protein is a ubiquitin ligase that targets HIF1α for degradation. The marked reduction in proliferation and increase in matrix deposition that were observed may be the consequences of increased HIFα, because* Vhlh/HIF1α *double knockout mice have the HIF1α–null phenotype. —GJS*

Treatment and Drug Effects

Hwang R, Lee EJ, Kim MH, Li SZ, Jin YJ, Rhee Y, Kim YM, Lim SK. Calcyclin, a Ca^{2+} ion-binding protein, contributes to the anabolic effects of simvastatin on bone. *J Biol Chem.* 2004 May 14;279(20):21239-47. [Abstract] [Full Text]

> *Recommended. —ES*

Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* May 2004; 62 (5):527-34. [Abstract]

> *Osteonecrosis of the jaw, usually following dental procedures, is a newly described and significant complication of bisphosphonate therapy. Most cases reported here were in cancer patients treated with intravenous bisphosphonates; but six were under treatment with oral alendronate. We need to know how frequent the syndrome is, what the risk factors for it are, and what we can do to prevent it. Are other skeletal sites also subject to osteonecrosis? —GJS*

Reviews

Vanderschueren D, Vandenput L, Boonen S, Lindberg MK, Bouillon R, Ohlsson C. Androgens and bone. *Endocr Rev.* 2004 Jun;25(3):389-425. [Abstract] [Full Text]

Vattikuti R, Towler DA. Osteogenic regulation of vascular calcification: an early perspective. *Am J Physiol Endocrinol Metab*. 2004 May;286(5):E686-96. [Abstract]