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NOT TO BE MISSED

Clinical and Basic Research Papers – January 2009

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Bone Modeling, Remodeling and Repair

Ascenzi MG, Gill J, Lomovtsev A. Orientation of collagen at the osteocyte lacunae in human secondary osteons. *J Biomech*. 2008 Dec 5;41(16):3426-35. [Abstract]

> *This is a masterly piece of work. The authors examine collagen orientation around osteocyte lacunae and examine stress and strain patterns suggesting that microcrack initiation and diversion depend on lamellar type and fiber orientation at the lacunar apices. Interesting reading.* —ES

Izu Y, Mizoguchi F, Kawamata A, Hayata T, Nakamoto T, Nakashima K, Inagami T, Ezura Y, Noda M. Angiotensin II type 2 receptor blockade increases bone mass. *J Biol Chem*. 2008 Nov 11; [Epub ahead of print]

> *Angiotensin II type 2 (AT2) receptor protein is expressed in osteoblasts and osteoclasts. Renin and angiotensin II converting enzyme (ACE) are expressed in bone cells in vivo. Treatment with AT2 receptor blocker enhances bone mass and osteoblastic activity and suppresses osteoclastic activity in vivo.* —ES

Zhu S, Barbe MF, Liu C, Hadjiargyrou M, Popoff SN, Rani S, Safadi FF, Litvin J. Periostin-like-factor in osteogenesis. *J Cell Physiol*. 2008 Nov 12;218(3):584-92. [Abstract]

> *An isoform related to periostin is present in mesenchymal cells in the periosteum and in osteoblasts lining trabecular bone. Over-expression increased cell proliferation in vitro, activity of alkaline phosphatase and calcium deposition. Over-expression increased bone formation in the marrow and increased callus osteoblasts post-fracture. If this is a source of anabolism, it might be a target for therapy.* —ES

Genetics

Cheung CL, Sham PC, Chan V, Paterson AD, Luk KD, Kung AW. Identification of LTBP2 on chromosome 14q as a novel candidate gene for bone mineral density variation and fracture risk association. *J Clin Endocrinol Metab*. 2008 Nov;93(11):4448-55. [Abstract] [Full Text]

> *Chromosome 14q has previously been linked to BMD variation in several genome-wide linkage scans in Caucasian populations. This study replicates and identifies the novel candidate genes in this region. Among the five top-ranked candidate genes identified by use of a gene prioritization approach for the validated QTL in 1459 Chinese subjects, ESR2 and latent TGF-β binding protein 2 (LTBP2) had significant associations with trochanter and total hip BMD. In vitro studies revealed differential expression of the LTBP2 gene in MC3T3-E1 mouse preosteoblastic cells in culture.* —HWD

Donnelly P. Progress and challenges in genome-wide association studies in humans. *Nature*. 2008 Dec 11;456(7223):728-31.

Rockman MV. Reverse engineering the genotype-phenotype map with natural genetic variation. *Nature*. 2008 Dec 11;456(7223):738-44.

> *These two papers are part of an 'Insight' with several papers on quantitative genetics. This Insight highlights progress in teasing apart the basis of complex traits from genome-wide association studies (GWAS) to the building of molecular networks (such as gene expression) in a cell or organism.* —SF

Styrkarsdottir U, Halldorsson BV, Gretarsdottir S, Gudbjartsson DF, Walters GB, Ingvarsson T, Jonsdottir T, Saemundsdottir J, Snorradóttir S, Center JR, Nguyen TV, Alexandersen P, Gulcher JR, Eisman JA, Christiansen C, Sigurdsson G, Kong A, Thorsteinsdottir U, Stefansson K. New sequence variants associated with bone mineral density. *Nat Genet*. 2008 Dec 14; [Epub ahead of print] [Abstract]

> *Expanding their GWAS on bone density and fractures (recently published in N Engl J Med. 2008 May 29;358(22):2355-65), the authors analyze more subjects from the original and replication cohorts in Iceland, Denmark and Australia, to identify additional SNPs and genes associated with these phenotypes. Among them are markers close to the SOST gene. More original is the identification of MARK3, a gene coding for MAP/microtubule affinity-regulating kinase 3, and of non-synonymous (potentially functional) SNPs in five other genes, including the IBSP (integrin-binding sialoprotein) gene. At last a GWAS provides some new and interesting targets in osteoporosis!* —SF

Zmuda JM, Yerges LM, Kammerer CM, Cauley JA, Wang X, Nestlerode CS, Wheeler VW, Patrick AL, Bunker CH, Moffett SP, Ferrell RE. Association analysis of WNT10B with bone mass and structure among individuals of African ancestry. *J Bone Miner Res*. 2008 Nov 18; [Epub ahead of print] [Abstract]

> *This study reports replicable associations of two WNT10B polymorphisms with hip BMD in three Afro-Caribbean samples. Further analysis revealed that these two SNPs were also associated with cortical cross-sectional area, periosteal circumference and bone mineral content in the radius. Together with other functional evidence, this study offers insight into the role of the WNT pathway in bone phenotypes.* —HWD

Molecular and Cell Biology

Chan CK, Chen CC, Luppen CA, Kim JB, Deboer AT, Wei K, Helms JA, Kuo CJ, Kraft DL, Weissman IL. Endochondral ossification is required for haematopoietic stem-cell niche formation. *Nature*. 2008 Dec 10; [Epub ahead of print] [Abstract]

> *This study describes a new in vivo model allowing the identification of a population of fetal bone-derived progenitor cells capable of generating ectopic endochondral bone containing a bone marrow cavity. In turn, this new bone was capable of supporting the homing of hematopoietic stem cells. To form, the HSC niche requires osterix and VEGF.* —SF

Oskowitz AZ, Lu J, Penfornis P, Ylostalo J, McBride J, Flemington EK, Prockop DJ, Pochampally R. Human multipotent stromal cells from bone marrow and microRNA: Regulation of differentiation and leukemia inhibitory factor expression. *Proc Natl Acad Sci U S A*. 2008 Nov 25;105(47):18372-7. [Abstract] [Full Text]

Differentiation of human marrow multipotent stromal cells (hMSCs) to osteoblasts and adipocytes was inhibited by suppression of Dicer and Drosha, two essential enzymes for processing early transcripts to miRNA. Expression of 11 miRNAs was commonly up-regulated in both osteoblastic and adipocytic differentiation. Five of the up-regulated miRNAs during hMSC differentiation were predicted to target leukemia inhibitory factor (LIF), and this was confirmed for two of the miRNAs, overexpression of which decreased LIF secretion by hMSCs. Because LIF is a marker for hMSC multipotentiality, the results suggest that hMSC differentiation is regulated by miRNAs that decrease LIF expression. —TM

Wan M, Yang C, Li J, Wu X, Yuan H, Ma H, He X, Nie S, Chang C, Cao X. Parathyroid hormone signaling through low-density lipoprotein-related protein 6. *Genes Dev*. 2008 Nov 1;22(21):2968-79. [Abstract]

Binding of PTH to its receptor PTH1R induced association of LRP6, a coreceptor of Wnt, with PTH1R. The formation of the ternary complex containing PTH, PTH1R, and LRP6 promoted rapid phosphorylation of LRP6, which resulted in the recruitment of axin to LRP6, and stabilization of β-catenin. Activation of PKA is essential for PTH-induced β-catenin stabilization, but not for Wnt signaling. These observations suggest that ternary complex formation among PTH, PTH1R and LRP6 is a key element of PTH signaling to enhance osteoblastic bone formation. —TM

Yadav VK, Ryu JH, Suda N, Tanaka KF, Gingrich JA, Schütz G, Glorieux FH, Chiang CY, Zajac JD, Insogna KL, Mann JJ, Hen R, Ducy P, Karsenty G. Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. *Cell*. 2008 Nov 28;135(5):825-37. [Abstract]

The identification of Wnt-LRP5-β-catenin signaling as the canonical pathway for osteoblast proliferation and bone formation is one the most important recent discoveries in bone biology. Yet, starting with the observation of some discordant results from genetic models previously used to dissect this pathway, such as the absence of a cell autonomous osteoblastic phenotype in β-catenin-invalidated cells, the authors reanalyzed gene expression maps from LRP5 KO mice and found increased expression of Tph1, a serotonin-synthesizing enzyme. Invalidation of LRP5 in intestinal cells, but not osteoblasts, led to low bone formation and decreased trabecular bone volume, whereas expression of the high bone mass LRP5 mutant in the gut, but not in osteoblasts, increased bone mass. Through an impressive series of experiments, the authors further demonstrate that non-canonical signaling by LRP5 controls trabecular bone mass by inhibiting serotonin synthesis in the gut, thereby preventing activation of the Htr1b (serotonin) receptor on osteoblasts and inhibition of CREB signaling downstream. Hence, Wnt-LRP5 could regulate bone formation in an endocrine, rather than in a paracrine-autocrine mode, as previously thought. Whether the LRP5-serotonin pathway exerts similar (or opposite?) effects on cortical bone remains to be clarified. —SF

Reviews, Perspectives and Editorials

Ober C, Loisel DA, Gilad Y. Sex-specific genetic architecture of human disease. *Nat Rev Genet*. 2008 Dec;9(12):911-22. [Abstract]

Other Studies of Potential Interest

Dubner SE, Shults J, Baldassano RN, Zemel BS, Thayu M, Burnham JM, Herskovitz RM, Howard KM, Leonard MB. Longitudinal assessment of bone density and structure in an incident

cohort of children with Crohn's disease. *Gastroenterology*. 2008 Nov 1; [Epub ahead of print] [Abstract]

Gutierrez GM, Kong E, Sabbagh Y, Brown NE, Lee JS, Demay MB, Thomas DM, Hinds PW. Impaired bone development and increased mesenchymal progenitor cells in calvaria of RB1-/- mice. *Proc Natl Acad Sci U S A*. 2008 Nov 25;105(47):18402-7. [Abstract] [Full Text]

Hohenester E, Sasaki T, Giudici C, Farndale RW, Bächinger HP. Structural basis of sequence-specific collagen recognition by SPARC. *Proc Natl Acad Sci U S A*. 2008 Nov 25;105(47):18273-7. [Abstract] [Full Text]

Ordóñez-Morán P, Larriba MJ, Pálmer HG, Valero RA, Barbáchano A, Duñach M, de Herreros AG, Villalobos C, Berciano MT, Lafarga M, Muñoz A. RhoA-ROCK and p38MAPK-MSK1 mediate vitamin D effects on gene expression, phenotype, and Wnt pathway in colon cancer cells. *J Cell Biol*. 2008 Nov 17;183(4):697-710. [Abstract] [Full Text]

Oskowitz AZ, Lu J, Penfornis P, Ylostalo J, McBride J, Flemington EK, Prockop DJ, Pochampally R. Human multipotent stromal cells from bone marrow and microRNA: regulation of differentiation and leukemia inhibitory factor expression. *Proc Natl Acad Sci U S A*. 2008 Nov 25;105(47):18372-7. [Abstract] [Full Text]

Sharff KA, Song WX, Luo X, Tang N, Luo J, Chen J, Bi Y, He BC, Huang J, Li X, Jiang W, Zhu GH, Su Y, He Y, Shen J, Wang Y, Chen L, Zuo GW, Liu B, Pan X, Reid RR, Luu HH, Haydon RC, He TC. Hey1 basic helix-loop-helix (bHLH) protein plays an important role in mediating BMP9 induced osteogenic differentiation of mesenchymal progenitor cells. *J Biol Chem*. 2008 Nov 5; [Epub ahead of print]

Wan M, Yang C, Li J, Wu X, Yuan H, Ma H, He X, Nie S, Chang C, Cao X. Parathyroid hormone signaling through low-density lipoprotein-related protein 6. *Genes Dev*. 2008 Nov 1;22(21):2968-79. [Abstract]

Wu J, Glimcher LH, Aliprantis AO. HCO3-/Cl- anion exchanger SLC4A2 is required for proper osteoclast differentiation and function. *Proc Natl Acad Sci U S A*. 2008 Nov 4;105(44):16934-9. [Abstract] [Full Text]

Wu JY, Purton LE, Rodda SJ, Chen M, Weinstein LS, McMahon AP, Scadden DT, Kronenberg HM. Osteoblastic regulation of B lymphopoiesis is mediated by Gsalpha-dependent signaling pathways. *Proc Natl Acad Sci U S A*. 2008 Nov 4;105(44):16976-81. [Abstract] [Full Text]

Zhang Y, Hassan MQ, Xie RL, Hawse J, Spelsberg TC, Montecino M, Stein JL, Lian JB, van Wijnen AJ, Stein GS. Co-stimulation of the bone-related Runx2 P1 promoter in mesenchymal cells by Sp1 and Ets transcription factors at polymorphic purine-rich DNA sequences (Y-repeats). *J Biol Chem*. 2008 Nov 18; [Epub ahead of print]

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and consultancy/speaker's fees from Merck Sharp & Dohme, Eli Lilly, and Amgen. Dr. Little reports that he receives royalties, research funds and consultancy fees from Novartis Pharma, as well as research support from Stryker Biotech. 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. Dr. Matsumoto and Dr. Deng report no conflicts of interest.