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NOT TO BE MISSED

Clinical and Basic Research Papers – December 2009

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Toshio Matsumoto, Associate Editor

Bone Modeling, Remodeling, and Repair

Bonnet N, Standley KN, Bianchi EN, Stadelmann V, Foti M, Conway SJ, Ferrari SL. The matricellular protein periostin is required for sclerostin inhibition and the anabolic response to mechanical loading and physical activity. *J Biol Chem*. 2009 Oct 16. [Epub ahead of print]

> *Periostin is expressed in the periosteum. Exercise and axial compression increased BMD, trabecular and cortical microarchitecture and biomechanical properties of the long bones in Postn(+/+) mice by increasing periosteal bone formation, changes that correlated with an increase of periostin expression and a decrease of Sost. Mechanical stimuli had no effect in Postn(-/-) mice where baseline expression of Sost was higher than in Postn(+/+) mice and remained unchanged following axial compression. Injection of Sost-Ab rescued the bone biomechanical response in Postn(-/-) mice.* —ES

Burghardt AJ, Kazakia GJ, Ramachandran S, Link TM, Majumdar S. Age and gender related differences in the geometric properties and biomechanical significance of intra-cortical porosity in the distal radius and tibia. *J Bone Miner Res*. 2009 Nov 5. [Epub ahead of print] [Abstract]

> *The distal radius and tibia of 57 male and 94 females were imaged using HR-pQCT. Intra-cortical porosity (Ct.Po) was calculated. Micro-finite element analysis (μFE) was used to simulate 1% uniaxial compression for the structure with and without porosity artificially occluded. Stiffness (ΔK), modulus (ΔE), failure load (ΔF), and cortical load fraction (ΔCt.LF) were calculated as the difference between original and occluded values. Porosity correlated with age for males and females (radius: ρ=0.7; tibia: ρ=0.5; $p < 0.001$). Ct.Th, Ct.Ar, and Ct.vBMD were weakly correlated with age. The biomechanical deficit (ΔK) associated with porosity was higher for post- than pre-menopausal women.* —ES

Clinical Studies and Drug Effects

Bolland MJ, Bacon CJ, Horne AM, Mason BH, Ames RW, Wang TK, Grey AB, Gamble GD, Reid IR. Vitamin D insufficiency and health outcomes over 5 y in older women. *Am J Clin Nutr*. 2009 Nov 11. [Epub ahead of print] [Abstract]

> *In 1471 healthy community-dwelling women, mean age 74 y and followed for 5 y, 50% had 25(OH)D <50 nmol/L. These women had more comorbidities and increased incidence of stroke and cardiovascular events that did not persist after adjustment for age or comorbidities, compared to women with 25(OH)D ≥50 nmol/L. Nor were they at increased risk of fracture, falls, or other adverse events. Vitamin D 'insufficiency' is*

more common in older, frailer women but there is no evidence of a causal link. —ES

Johannesen J, Briody J, McQuade M, Little DG, Cowell CT, Munns CF. Systemic effects of zoledronic acid in children with traumatic femoral head avascular necrosis and Legg-Calve-Perthes disease. *Bone*. 2009 Nov;45(5):898-902. [Abstract]

This study adds evidence to the benefits and safety of zoledronic acid (18 months) in children with avascular necrosis of the femoral head. —SF

Pilz S, Dobnig H, Nijpels G, Heine RJ, Stehouwer CD, Snijder MB, van Dam RM, Dekker JM. Vitamin D and mortality in older men and women. *Clin Endocrinol (Oxf)*. 2009 Nov;71(5):666-72. [Abstract]

In 614 subjects followed 6.2 years, all-cause and cardiovascular mortality hazard ratios in the first compared with the upper three 25(OH)D quartiles were 2.24 (1.28-3.92; P = 0.005) and 4.78 (1.95-11.69; P = 0.001), respectively. After adjustment for confounding variables, the hazard ratios for all-cause [1.97 (1.08-3.58; P = 0.027)] and for cardiovascular mortality [5.38 (2.02-14.34; P = 0.001)] remained significant. Is vitamin D deficiency a cause or a consequence of a poor health? —ES

Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, Krege JH, Krohn K, Warner MR. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. *Arthritis Rheum*. 2009 Nov;60(11):3346-55. [Abstract]

In a 36-month, randomized, double-blind, controlled trial in 428 subjects with OP who received ≥5 mg/day of prednisone equivalent for ≥3 months, increases in BMD were greater with teriparatide than with alendronate (11.0 v 5.3% spine, 5.2 v 2.7% total hip, 6.3 v 3.4% femoral neck (P < 0.001 all). Fewer subjects had vertebral fractures in the teriparatide than alendronate group (3/173 [1.7%] vs. 13/169 [7.7%], P = 0.007). There was no difference in nonvertebral fractures: 16/214 (7.5%) in the teriparatide group vs. 15/214 (7.0%) in the alendronate group. —ES

Genetics

Grundberg E, Kwan T, Ge B, Lam KC, Koka V, Kindmark A, Mallmin H, Dias J, Verlaan DJ, Ouimet M, Sinnett D, Rivadeneira F, Estrada K, Hofman A, van Meurs JM, Uitterlinden A, Beaulieu P, Graziani A, Harmsen E, Ljunggren O, Ohlsson C, Mellström D, Karlsson MK, Nilsson O, Pastinen T. Population genomics in a disease targeted primary cell model. *Genome Res*. 2009 Nov;19(11):1942-52. [Abstract]

Genetic variants that influence gene expression levels may represent the most directly causal genetic factors for common diseases. These so-called eSNPs remain poorly investigated. This study reports on gene expression level related to SNPs in primary human osteoblasts from 95 donors. About 2000 cis-QTLs (i.e., SNPs associated with gene expression in cis, not trans) were identified and replicated in a second biological sample, showing the consistency of this approach. Moreover, the authors report the convergence between eSNPs and SNPs identified as related to BMD in a recent GWAS study. Interestingly, this combined approach allowed for the identification of a new gene locus for osteoporosis. —SF

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Molecular and Cell Biology

Cackowski FC, Anderson JL, Patrene KD, Choksi RJ, Shapiro SD, Windle JJ, Blair HC, Roodman GD. Osteoclasts are important for bone angiogenesis. *Blood*. 2009 Nov 3. [Epub ahead of print]

> *Studies in MMP-9(-/-) mice suggest that osteoclasts stimulate angiogenesis by secretion of MMP-9. The authors demonstrate that suppression of osteoclast formation with OPG inhibits angiogenesis. Treatment with RANKL or PTHrP increases calvarial vessel density in vivo, whereas the proangiogenic effects of RANKL and PTHrP were absent in MMP-9(-/-) mice. Osteoclast differentiation was normal but osteoclast migration at angiogenic sites appeared to be reduced in MMP-9(-/-) mice. These results suggest that MMP-9 modulates angiogenesis by affecting osteoclast migration.* —TM

Ferrandon S, Feinstein TN, Castro M, Wang B, Bouley R, Potts JT, Gardella TJ, Vilardaga JP. Sustained cyclic AMP production by parathyroid hormone receptor endocytosis. *Nat Chem Biol*. 2009 Oct,5(10):734-42. [Abstract]

> *Although PTH and PTHrP act through the same receptor, PTHR1, they trigger different durations of the cAMP response. This study demonstrates that, during $G_s\alpha$ coupling and cAMP production, PTHrP action is restricted to the cell membrane, whereas PTH(1-34) is internalized rapidly into Rab5-positive endosomes where PTH(1-34) is associated with PTHR1, $G_s\alpha$ and adenylyl cyclases. Internalization of PTHR1 is not associated with desensitization of the cAMP response, and blockade of internalization prevents the sustained cAMP response. Such marked differences may explain why continuous infusion of PTH(1-34) causes more prolonged elevation in serum 1,25(OH)$_2$D and bone resorption than PTHrP.* —TM

Koizumi K, Saitoh Y, Minami T, Takeno N, Tsuneyama K, Miyahara T, Nakayama T, Sakurai H, Takano Y, Nishimura M, Imai T, Yoshie O, Saiki I. Role of CXCL1/fractalkine in osteoclast differentiation and bone resorption. *J Immunol*. 2009 Nov 18. [Epub ahead of print] [Abstract]

> *The authors show that CX3CL1/fractalkine is expressed by osteoblasts, whereas osteoclast precursors selectively express its receptor, CX3CR1. Soluble CX3CL1 induces migration of osteoclast precursors, and immobilized CX3CL1 mediates firm adhesion of these cells. Blocking anti-CX3CL1 mAb inhibits osteoclast formation in vitro and suppresses bone resorption in vivo. These results demonstrate an important role for CX3CL1 on osteoblasts and CX3CR1 on osteoclast precursors in osteoclastogenesis, and suggest that the CX3CL1-CX3CR1 axis may become a new target for the treatment of diseases with enhanced bone resorption.* —TM

Park H, No AL, Lee JM, Chen L, Lee SY, Lee DS, Yim M. PDE4 inhibitor upregulates PTH-induced osteoclast formation via CRE-mediated COX-2 expression in osteoblasts. *FEBS Lett*. 2009 Nov 17. [Epub ahead of print] [Abstract]

> *This study confirms the importance of controlling cAMP signaling through phosphodiesterases, in order to limit PTH catabolic effects through the expression of RANKL promoting osteoclastogenesis – also see Perspective in this issue on β-arrestins – and the role of COX-2 (hence prostaglandin production) therein.* —SF

Wang W, Lian N, Li L, Moss HE, Wang W, Perrien DS, Elefteriou F, Yang X. Atf4 regulates chondrocyte proliferation and differentiation during endochondral ossification by activating Ihh transcription. *Development*. 2009 Dec;136(24):4143-53. [Abstract]

> *ATF4 is a transcription factor that regulates osteoblast terminal differentiation and function and is implicated in the pathophysiology of Coffin-Lowry syndrome (an X-linked mental retardation condition associated with skeletal abnormalities). This study now demonstrates the essential role of ATF4 in chondrogenesis by regulating the expression and function of Indian hedgehog (Ihh).* —SF

Physiology

Meir T, Levi R, Lieben L, Libutti S, Carmeliet G, Bouillon R, Silver J, Naveh-Many T. Deletion of the vitamin D receptor specifically in the parathyroid demonstrates a limited role for the receptor in parathyroid physiology. *Am J Physiol Renal Physiol*. 2009 Nov;297(5):F1192-8. [Abstract]

> *PTH production by the parathyroids has a number of negative regulators, including serum calcium, of course, and calcitriol, the latter being the base for treatment of secondary hyperparathyroidism in renal failure. Yet this study, by investigating a parathyroid-targeted VDR KO mouse, reveals that PTH levels and bone turnover markers in these mice were only moderately increased – which differs from total VDR KOs – suggesting a limited role for direct vitamin D effects on the parathyroid glands. A quite provocative finding.* —SF

Public Health

Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *JAMA*. 2009 Oct 14;302(14):1573-9. [Abstract]

> *Between 1986 and 2005, there were 957.3 per 100,000 hip fractures in women and 414.4 per 100,000 in men. In women, incidence increased 9.0%, from 964.2 in 1986 to 1050.9 in 1995, with a decline of 24.5% to 793.5 in 2005. In men, the increase in incidence from 1986 to 1995 was 16.4%, from 392.4 to 456.6 and the decrease to 2005 was 19.2%, to 369. Mortality in women declined by 11.9%, 14.9%, and 8.8% at 30-, 180-, and 360-days, respectively. For men, mortality decreased by 21.8%, 25.4%, and 20.0% for 30-, 180-, and 360-days, respectively. The incidence decrease is coincident with increased use of bisphosphonates.* —ES

Danese MD, Badamgarav E, Bauer DC. Effect of adherence on lifetime fractures in osteoporotic women treated with daily and weekly bisphosphonates. *J Bone Miner Res*. 2009 Nov;24(11):1819-26. [Abstract]

> *About 258 lifetime fractures can be prevented with adherence per 1,000 bisphosphonate-treated women. This translates to a lifetime medication cost of $3,800 and a lifetime savings in fracture-related costs of $2,100, for a net cost of $1,700 per woman over her life. These results suggest a substantial number of fractures occur that are attributable to suboptimal adherence.* —ES

Reviews, Perspectives and Editorials

Kuhn NZ, Tuan RS. Regulation of stemness and stem cell niche of mesenchymal stem cells: Implications in tumorigenesis and metastasis. *J Cell Physiol*. 2010 Feb;222(2):268-77. [Abstract]

Riccardi D, Brown EM. Physiology and pathophysiology of the calcium-sensing receptor in the kidney. *Am J Physiol Renal Physiol*. 2009 Nov 18. [Epub ahead of print]

Other Studies of Potential Interest

Balkan W, Martinez AF, Fernandez I, Rodriguez MA, Pang M, Troen BR. Identification of NFAT binding sites that mediate stimulation of cathepsin K promoter activity by RANK ligand. *Gene*. 2009 Oct 15;446(2):90-8. [Abstract]

Bahtiar A, Matsumoto T, Nakamura T, Akiyama M, Yogo K, Ishida-Kitagawa N, Ogawa T, Takeya T. Identification of a novel L-serine analog that suppresses osteoclastogenesis in vitro and bone turnover in vivo. *J Biol Chem*. 2009 Dec 4;284(49):34157-66. [Abstract] [Full Text]

Baud'huin M, Duplomb L, Téletchéa S, Charrier C, Maillasson M, Fouassier M, Heymann D. Factor VIII-von Willebrand factor complex inhibits osteoclastogenesis and controls cell survival. *J Biol Chem*. 2009 Nov 13;284(46):31704-13. [Abstract] [Full Text]

Chang CL, Park JI, Hsu SY. Activation of calcitonin receptor and calcitonin receptor-like receptor by membrane-anchored ligands. *J Biol Chem*. 2009 Nov 10. [Epub ahead of print]

Fazenda C, Simões B, Kelsh RN, Cancela ML, Conceição N. Dual transcriptional regulation by runx2 of matrix Gla protein in Xenopus laevis. *Gene*. 2009 Nov 4. [Epub ahead of print] [Abstract]

Hesaraki S, Alizadeh M, Nazarian H, Sharifi D. Physico-chemical and in vitro biological evaluation of strontium/calcium silicophosphate glass. *J Mater Sci Mater Med*. 2009 Oct 29. [Epub ahead of print] [Abstract]

Hoeppner LH, Secreto F, Jensen ED, Li X, Kahler RA, Westendorf JJ. Runx2 and bone morphogenic protein 2 regulate the expression of an alternative Lef1 transcript during osteoblast maturation. *J Cell Physiol*. 2009 Nov;221(2):480-9. [Abstract]

Kim MS, Kondo T, Takada I, Youn MY, Yamamoto Y, Takahashi S, Matsumoto T, Fujiyama S, Shirode Y, Yamaoka I, Kitagawa H, Takeyama K, Shibuya H, Ohtake F, Kato S. DNA demethylation in hormone-induced transcriptional derepression. *Nature*. 2009 Oct 15;461(7266):1007-12. [Abstract]

Lee DY, Li YS, Chang SF, Zhou J, Ho HM, Chiu JJ, Chien S. Oscillatory flow-induced proliferation of osteoblast-like cells is mediated by alphavbeta3 and beta1 integrins through synergistic interactions of FAK and Shc with PI3K and the Akt/mTOR/p70S6K pathway. *J Biol Chem*. 2009 Nov 4. [Epub ahead of print]

Lekva T, Bollerslev J, Kristo C, Olstad OK, Ueland T, Jemtland R. The glucocorticoid-induced leucine zipper gene (GILZ) expression decreases after successful treatment of patients with endogenous Cushing's syndrome and may play a role in glucocorticoid-induced osteoporosis. *J Clin Endocrinol Metab*. 2009 Oct 29. [Epub ahead of print] [Abstract]

Mitrofan LM, Castells FB, Pelkonen J, Monkkonen J. Lysosomal-mitochondrial axis in zoledronic acid induced apoptosis in human follicular lymphoma cells. *J Biol Chem*. 2009 Oct 29. [Epub ahead of print]

Nagase Y, Iwasawa M, Akiyama T, Kadono Y, Nakamura M, Oshima Y, Yasui T, Matsumoto T, Hirose J, Nakamura H, Miyamoto T, Bouillet P, Nakamura K, Tanaka S. The anti-apoptotic molecule Bcl-2 regulates the differentiation, activation and survival of both osteoblasts and

osteoclasts. *J Biol Chem*. 2009 Oct 21. [Epub ahead of print]

Nakatani T, Ohnishi M, Razzaque MS. Inactivation of klotho function induces hyperphosphatemia even in presence of high serum fibroblast growth factor 23 levels in a genetically engineered hypophosphatemic (Hyp) mouse model. *FASEB J*. 2009 Nov;23(11):3702-11. [Abstract]

Piscopo DM, Johansen EB, Derynck R. Identification of the GATA factor TRPS1 as a repressor of the osteocalcin promoter. *J Biol Chem*. 2009 Nov 13;284(46):31690-703. [Abstract] [Full Text]

Rifas L, Weitzmann MN. A novel T cell cytokine, secreted osteoclastogenic factor of activated T cells, induces osteoclast formation in a RANKL-Independent manner. *Arthritis Rheum*. 2009 Nov;60(11):3324-35. [Abstract]

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Shen Q, Little SC, Xu M, Haupt J, Ast C, Katagiri T, Mundlos S, Seemann P, Kaplan FS, Mullins MC, Shore EM. The fibrodysplasia ossificans progressiva R206H ACVR1 mutation activates BMP-independent chondrogenesis and zebrafish embryo ventralization. *J Clin Invest*. 2009 Nov;119(11):3462-72. [Abstract]

Utriainen P, Jääskeläinen J, Saarinen A, Vanninen E, Mäkitie O, Voutilainen R. Body composition and bone mineral density in children with premature adrenarche and the association of LRP5 gene polymorphisms with bone mineral density. *J Clin Endocrinol Metab*. 2009 Nov;94(11):4144-51. [Abstract]

Xiao Z, Zhang S, Cao L, Qiu N, David V, Quarles LD. Conditional disruption of Pkd1 in osteoblasts results in osteopenia due to direct impairment of bone formation. *J Biol Chem*. 2009 Nov 3. [Epub ahead of print]

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Zauli G, Rimondi E, Celeghini C, Milani D, Secchiero P. Dexamethasone counteracts the anti-osteoclastic, but not the anti-leukemic, activity of TNF-related apoptosis inducing ligand (TRAIL). *J Cell Physiol*. 2010 Feb;222(2):357-64. [Abstract]

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and is an advisory committee member and lectures occasionally at conference symposia for Merck Sharp & Dohme, the Alliance for Better Bone Health (sanofi aventis/P&G), Amgen, Eli Lilly (Switzerland), Servier (Switzerland), and Novartis (Switzerland). 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.