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NOT TO BE MISSED

Clinical and Basic Research Papers – May 2009

Serge Ferrari, Editor-in-Chief
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Toshio Matsumoto, Associate Editor

Genetics

Timpson NJ, Tobias JH, Richards JB, Soranzo N, Duncan EL, Sims AM, Whittaker P, Kumanduri V, Zhai G, Glaser B, Eisman J, Jones G, Nicholson G, Prince R, Seeman E, Spector TD, Brown MA, Peltonen L, Smith GD, Deloukas P, Evans DM. Common variants in the region around Osterix are associated with bone mineral density and growth in childhood. *Hum Mol Genet*. 2009 Apr 15;18(8):1510-7. [Abstract]

> *A genome-wide association study of BMD and related traits was performed in children from a large population-based cohort in which BMD was assessed by total DXA. The results were compared to a scan of adults with extreme high or low hip BMD. Associations with BMD were identified in an area of chromosome 12 containing the Osterix (SP7) locus in both cohorts. A meta-analysis of studies with similar association with adult BMD revealed strong association between SNPs in the Osterix region and adult lumbar BMD. Genotyping of additional individuals confirmed the association with whole body BMD in children as well. All SNPs were related to height in children, but not weight or body mass index. These results demonstrate that genetic variants in the Osterix region are associated with BMD in children and adults probably through primary effects on growth.* —TM

Molecular and Cell Biology

Binder NB, Niederreiter B, Hoffmann O, Stange R, Pap T, Stulnig TM, Mack M, Erben RG, Smolen JS, Redlich K. Estrogen-dependent and C-C chemokine receptor-2-dependent pathways determine osteoclast behavior in osteoporosis. *Nat Med*. 2009 Apr;15(4):417-24. [Abstract]

> *MCP-1 and -3 bind to their receptor, CCR2, and enhance RANK expression in preosteoclasts. Ovariectomy (OVX) leads to an increase in CCR2 expression in preosteoclasts. OVX upregulates MCP-1 expression on CD3+ T cells, but does not upregulate the other bone resorptive chemokines. CCR2(-/-) mice exhibit increased bone mass due to impaired osteoclast development and function resulting from suppressed RANK expression, and are protected from OVX-induced increases in bone resorption or BMD loss. This study unveils a hitherto unrecognized mechanism of estrogen deficiency-induced bone loss occurring through upregulation of RANK expression in preosteoclasts via enhanced CCR2 signaling. Thus, targeting the CCR2 pathway to inhibit only the pathological bone resorptive process may become a new modality of therapy for postmenopausal osteoporosis.* —TM

Ishii KA, Fumoto T, Iwai K, Takeshita S, Ito M, Shimohata N, Aburatani H, Taketani S, Lelliott CJ, Vidal-Puig A, Ikeda K. Coordination of PGC-1beta and iron uptake in mitochondrial biogenesis and osteoclast activation. *Nat Med*. 2009 Mar;15(3):259-66. [Abstract]

PGC-1β, but not PGC-1α, expression is induced during osteoclastogenesis. PGC-1β is a regulator of mitochondrial biogenesis, and mitochondrial DNA/protein content increases in parallel with PGC-1β. The PGC-1β gene promoter contains CREB binding sites, and reactive oxygen species (ROS) enhance PGC-1β gene transcription by CREB. Iron demands increase along with mitochondrial biogenesis, which enhances transferrin receptor 1 (TfR1) expression and cellular heme content during osteoclastogenesis. Transferrin enhances osteoclastogenesis, mitochondrial gene expression, ROS production, CREB phosphorylation, and PGC-1β expression. Thus, there is a positive feedback loop between iron uptake and PGC-1β, thereby accelerating osteoclastogenesis. —TM

Kim H, Choi HK, Shin JH, Kim KH, Huh JY, Lee SA, Ko CY, Kim HS, Shin HI, Lee HJ, Jeong D, Kim N, Choi Y, Lee SY. Selective inhibition of RANK blocks osteoclast maturation and function and prevents bone loss in mice. *J Clin Invest*. 2009 Apr;119(4):813-25. [Abstract]

RANKL inhibitors, such as OPG and specific antibodies, have been proven efficient in preventing osteoclastogenesis and bone resorption in pre-clinical models and in humans. Considering the impact of the RANKL/RANK pathway on immune functions (see recent Perspective by Ferrari-Lacraz et al.), alternate strategies to block RANK signaling specifically in osteoclast (precursors) have some appeal. This study demonstrates the ability of a cell-permeable RANK inhibitor targeting a specific RANK cytoplasmic motif to do so. —SF

Pathophysiology

Kansara M, Tsang M, Kodjabachian L, Sims NA, Trivett MK, Ehrich M, Dobrovic A, Slavin J, Choong PF, Simmons PJ, Dawid IB, Thomas DM. Wnt inhibitory factor 1 is epigenetically silenced in human osteosarcoma, and targeted disruption accelerates osteosarcomagenesis in mice. *J Clin Invest*. 2009 Apr;119(4):837-51. [Abstract]

While focusing on Wnt-LRP5/LRP6-β-catenin signaling as a major pathway for bone formation, we should not forget that Wnts also have a major impact on the oncogenic process. Wnt inhibitory factor 1 (WIF1) was found to be epigenetically silenced in 5 human osteosarcoma cell lines, including SaOS2. In turn, WIF1 induced osteoblast cell differentiation and suppressed osteosarcoma tumor cell growth in vitro. In the adult mouse, Wif1 was highly expressed in the skeleton and a limited range of additional tissues, but bone mass was not significantly altered in Wif 1-deleted mice. However, some of these mice developed osteosarcoma, either spontaneously or in response to radiation. Whether or not these findings should raise further concerns with regard to the development of pharmacological agonists of the Wnt pathway for bone remains to be seen, considering that SOST KO mice, for instance, were not reported to develop osteosarcoma spontaneously. —SF

Physiology and Metabolism

Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med*. 2009 Apr 9;360(15):1509-17. [Abstract]

Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerbäck S, Nuutila P. Functional brown adipose tissue in healthy adults. *N Engl J Med*. 2009 Apr 9;360(15):1518-25. [Abstract]

It is not about bone, but fat, more precisely metabolically active brown adipose tissue, a major source of energy expenditure, which was supposed to vanish quickly after birth. The common message from these studies is that brown adipose tissue is present and active in adult humans, and its presence and activity are inversely associated with BMI, adiposity and indexes of the metabolic syndrome. One can only start to think about its potential influence on bone homeostasis as well. —SF

Tamma R, Colaianni G, Zhu LL, Dibenedetto A, Greco G, Montemurro G, Patano N, Strippoli M, Vergari R, Mancini L, Colucci S, Grano M, Faccio R, Liu X, Li J, Usmani S, Bachar M, Bab I, Nishimori K, Young LJ, Buettner C, Iqbal J, Sun L, Zaidi M, Zallone A. Oxytocin is an anabolic bone hormone. *Proc Natl Acad Sci U S A*. 2009 Apr 28;106(17):7149-54. [Abstract] [Full Text]

This study describes a new role for oxytocin, beyond lactation: the direct stimulation of osteoblast differentiation and the complex modulation of osteoclastogenesis and activity. Oxytocin and oxytocin receptor KO mice have markedly reduced trabecular bone volume and a decline in osteoblast number and bone formation, whereas haploinsufficient mice also have a trabecular bone defect. Central injections of oxytocin did not modify bone turnover, indicating that its effects on bone are peripheral. —SF

Public Health

Gillespie LD, Robertson MC, Gillespie WJ, Lamb SE, Gates S, Cumming RG, Rowe BH. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2009 Apr 15;(2):CD007146. [Abstract]

Since osteoporosis treatment has shown clear limitations in reducing non-vertebral fractures, clinicians should be aware of concomitant strategies to reduce falls in order to prevent peripheral fractures. This state-of-the art review and meta-analysis identifies exercise, Tai Chi, cataract surgery and withdrawal of psychotropic medications as significantly reducing falls. Overall vitamin D did not, but could potentially in vitamin D-deficient subjects. Subtle differences are identified between reducing risk of falls, and reducing or not reducing risk of falling. —SF

Reviews, Perspectives and Editorials

Bilezikian JP, Matsumoto T, Bellido T, Khosla S, Martin J, Recker RR, Heaney R, Seeman E, Papapoulos S, Goldring SR. Targeting bone remodeling for the treatment of osteoporosis: summary of the proceedings of an ASBMR workshop. *J Bone Miner Res*. 2009 Mar;24(3):373-85. [Info]

Chudyk AM, Jutai JW, Petrella RJ, Speechley M. Systematic review of hip fracture rehabilitation practices in the elderly. *Arch Phys Med Rehabil*. 2009 Feb;90(2):246-62. [Abstract]

Lefterova MI, Lazar MA. New developments in adipogenesis. *Trends Endocrinol Metab*. 2009 Apr;20(3):107-14. [Abstract]

Rosen CJ. Breaking into bone biology: serotonin's secrets. *Nat Med*. 2009 Feb;15(2):145-6. [Info]

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Other Studies of Potential Interest

Bessette L, Jean S, Davison KS, Roy S, Ste-Marie LG, Brown JP. Factors influencing the treatment of osteoporosis following fragility fracture. *Osteoporos Int*. 2009 Mar 31. [Epub ahead of print] [Abstract]

Binkley N, Ringe JD, Reed JI, Ljunggren O, Holick MF, Minne HW, Liu M, Lamotta A, West JA, Santora AC. Alendronate/vitamin D3 70 mg/2800 IU with and without additional 2800 IU vitamin D3 for osteoporosis: results from the 24-week extension of a 15-week randomized, controlled trial. *Bone*. 2009 Apr;44(4):639-47. [Abstract]

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*. 2009 Jan;136(1):123-30. [Abstract]

Galli C, Fu Q, Wang W, Olsen BR, Manolagas SC, Jilka RL, O'Brien CA. Commitment to the osteoblast lineage is not required for RANKL gene expression. *J Biol Chem*. 2009 May 8;284(19):12654-62. [Abstract] [Full Text]

Samee N, Geoffroy V, Marty C, Schiltz C, Vieux-Rochas M, Clément-Lacroix P, Belleville C, Levi G, de Vernejoul MC. Increased bone resorption and osteopenia in Dlx5 heterozygous mice. *J Cell Biochem*. 2009 May 4. [Epub ahead of print] [Abstract]

Wadhwa VK, Weston R, Mistry R, Parr NJ. Long-term changes in bone mineral density and predicted fracture risk in patients receiving androgen-deprivation therapy for prostate cancer, with stratification of treatment based on presenting values. *BJU Int*. 2009 Mar 10. [Epub ahead of print] [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.