NOT TO BE MISSED

Clinical and Basic Research Papers - January and February Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling


Recommended. —ES


Vascular endothelial growth factor (VEGF) has been shown to be important for vascular invasion of the metaphysis and formation of the primary spongiosa. This paper focuses attention on the epiphysis, wherein a large body of avascular cartilage resides until the secondary ossification center forms. Mice that express only VEGF_{188}, a matrix-associated isotype, develop massive apoptosis of epiphyseal chondrocytes and exhibit markedly impaired linear growth. It is likely that hypoxic chondrocytes in the interior of the epiphysis activate HIF_{1α} dependent secretion of soluble forms of VEGF. These molecules diffuse to the perichondrium and induce vascular invasion to form centers of secondary ossification and simultaneously rescue central chondrocytes from hypoxia. —GJS


Bone length and volume are independently regulated. The gp130-dependent cytokines regulate osteoclast and osteoblast formation. Attenuation of the signal transducer and activator of transcription (STAT) 1/3 signaling pathway (gp130[ΔSTAT/ΔSTAT]) produces reduced bone length caused by premature growth plate closure, but normal trabecular bone volume (BV/TV), indicating an essential role for gp130-STAT1/3 signaling in chondrocyte differentiation. SHP2/ras/MAPK (gp130[Y757F/Y757F]) pathway attenuation produces high remodeling and low BV/TV, thus SHP2/Ras/MAPK inhibits osteoclastogenesis. —ES

Genetics

The authors disrupted dominant-negative mutant COL1A1 collagen genes in mesenchymal stem cells from individuals with osteogenesis imperfecta, demonstrating successful gene targeting in adult human stem cells. —ES


The MEN1 gene is a tumor suppressor, loss of which causes multiple endocrine neoplasia type 1 (MEN 1), but the cellular basis of tumor suppression is unknown. This paper reports that menin, the protein product of the MEN1 gene, is associated with a histone methyltransferase complex and is required for histone methylation. Several (but not all) menin point mutants in MEN 1 tumors lack histone methyltransferase activity. Histone methylation is an important epigenetic mechanism of gene regulation, and Hoxc8 is among the genes that bind menin and are transcriptionally regulated. —GJS


Recommended. —ES

Pathophysiology


The fibroblast growth factor receptor FGFR3 signals both through Stat1 and the mitogen-activated protein (MAP) kinase pathway and is constitutively activated in achondroplasia. Constitutive activation of MEK1 causes achondroplasia-like dwarfism in wild-type and Stat1-deficient mice and rescues the phenotype of FGFR3 deficiency, suggesting that bone growth is mediated by the MAP kinase pathway. Loss of Stat1 rescues the proliferative defect in achondroplasia, but does not rescue the short stature phenotype. Proliferative effects of FGFR3 are mediated by Stat1 but effects on chondrocyte hypertrophy and bone growth are mediated by the MAP kinase pathway. The results fit well with a recent report that C-type natriuretic peptide inhibits MAP kinase activity and suppresses the achondroplastic phenotype (Nat Med. 2004 Jan;10(1):80-6). —GJS


This long-awaited paper reports that removal of the Fgf23 gene from the mouse produces hyperphosphatemia and high 1,25(OH)2vitaminD levels, with eventual hypercalcemia, nephrocalcinosis, and renal failure. The physiological role of FGF23 in phosphate and vitamin D metabolism is established by these data. Notable also are severe growth retardation, rickets, osteomalacia, hypoglycemia, and hypotriglyceridemia, findings that suggest hitherto unpredicted new roles of FGF23. —GJS
Physiology and Metabolism

Bharti AC, Takada Y, Shishodia S, Aggarwal BB. Evidence that receptor activator of nuclear factor (NF)-κB ligand can suppress cell proliferation and induce apoptosis through activation of a NF-κB-independent and TRAF6-dependent mechanism. *J Biol Chem.* 2004 Feb 13;279(7):6065-76. [Abstract] [Full Text]

Recommended. —ES


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The mammary gland is a calcium-sensing organ! In response to a low medium calcium concentration or to direct activators of the parathyroid-type calcium-sensing receptor, mammary epithelial cells secrete more parathyroid hormone–related protein; high extracellular calcium also stimulates transcellular calcium secretion. Intact mice on a low calcium diet display significant changes in milk composition, which can also be mimicked by calcium receptor activators. This is convincing evidence of a new role of the calcium sensor to adapt both mother and child to a low maternal calcium intake, but much remains to be understood. As the authors write, “Milking mice is imprecise.” —GJS


Recommended. —ES


Recommended. —ES

Treatment and Drug Effects


A mimic of osteoprotegerin inhibits osteoclast formation in vitro and limits bone loss in an animal model. OP3-4 inhibits osteoclast formation and bone loss and modulates RANK-TRANCE signaling pathways and alters the biological functions of the RANK-TRANCE receptor complex. —ES


Strontium is incorporated by ionic substitution into bone mineral and increases bone mineral density (even after correction for its own atomic weight). This study reports a 42% decrease in vertebral fractures over 36 months of strontium ranelate treatment. The accompanying editorial raises several interesting questions: What is the mechanism by which strontium treatment uncouples bone formation and resorption, as indicated in this study by biochemical markers? Would lower doses have similar effects? Serum calcium and parathyroid hormone levels fall and serum phosphate levels rise during therapy; does strontium activate the calcium receptor in parathyroid cells, or indeed in bone cells? —GJS


Osteoporosis is common in cardiac transplant candidates, and rapid bone loss occurs posttransplant, because treatment with cyclosporine or other calcineurin inhibitors increases bone resorption, and glucocorticoid therapy impairs the osteoblast response. It is reported here that both alendronate and calcitriol reduced the otherwise alarming loss of bone mineral density at the spine and hip. Alendronate treatment was simpler because calcitriol therapy required frequent monitoring to prevent hypercalcemia or hypercalciuria. —GJS