**NOT TO BE MISSED**

Clinical and Basic Research Papers – May and June 2004 Selections

Ego Seeman, Clinical Editor
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Bone Modeling and Remodeling


*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*


*Recommended. —ES*

Diagnosis


*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


*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


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 methylenetetrahydrofolate reductase gene)? —GJS


Recommended. —ES

Physiology and Metabolism


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


Recommended. —ES


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


Chondrocytes live in a relatively hypoxic environment because cartilage is avascular, and it was previously shown that removal of the hypoxia-inducible transcription factor HIF1α 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 HIF1α, because Vhlh/HIF1α double knockout mice have the HIF1α−null phenotype. —GJS

Treatment and Drug Effects


Recommended. —ES


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
