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In This Issue

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Osteoclast survival and steroid-induced bone loss (See article on pages 1041–1048.) In people receiving high doses of glucocorticoids, a shifting balance between osteoblast-mediated deposition and osteoclast-mediated resorption plays out in bone loss and increased risk of fractures. Weinstein and coworkers note that the underlying changes in osteoclast and osteoblast population are not fully understood and appear to involve different mechanisms at different times during treatment. Based on their work in intact animals and in osteoclast culture, they show that bone loss during short-term glucocorticoid treatment reflects a drop in the osteoclast apoptosis rate and occurs despite a decline in the rate of osteoclast formation over the same period. Weinstein et al. have also examined the effects on bone cell populations of a different class of drugs, the bisphosphonates, which are used to maintain bone density and to ameliorate the effects of glucocorticoids. Bisphosphonates become incorporated into the bone matrix and are taken up by osteoclasts, where they increase caspase levels and thereby promote apoptosis. However, Weinstein and colleagues show, glucocorticoids not only increase osteoclast longevity under baseline conditions, but also abrogate the pro-apoptotic effect of bisphosphonates, raising the question as to why the latter are helpful in patients with glucocorticoid-induced osteoporosis. The authors suggest, among several possible explanations, that bisphosphonates allow for a rise in the osteoblast population, an effect […]

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Osteoclast survival and steroid-induced bone loss

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Transcriptional control of podocyte form and function

(See articles on pages 1065–1072 and 1073–1082.)

The filtration function of the kidney depends in part on the adhesive contacts made by podocytes with each other and with the glomerular basement membrane (GBM). Several genetic diseases involving defective renal filtration arise from defects in structural components of the podocyte foot processes or of the adjacent slit diaphragm or in the adhesive molecules that allow these structures to form. However, the molecular lesion in the nail-patella syndrome, a multisystem developmental disorder that leads to kidney dysfunction, is in the gene for the transcription factor LMX1B. In this issue, Miner et al. and Rohr et al. show that this protein interacts directly with the promoters of several genes whose products localize to the GBM or slit diaphragm. These structural genes are themselves implicated in other heritable filtration disorders affecting podocyte foot processes, such as the steroid-resistant nephrotic syndrome, which is caused by defects in the LMX1B target gene *NPHS2*. Nephropathy in humans occurs in some but not all *LMX1B* heterozygotes, and human homozygotes have not been described. Curiously, in mice — at least in the strains studied — *Lmx1b* heterozygotes are healthy, and only homozygotes show evidence of filtration defects. This discrepancy, as well as the inconsistent presentation of renal symptoms in the human patients, may be explained by variable local loss of expression of the target genes, which may be sensitive to genetic background. For this reason the homozygous null mouse strains described here may offer both a more extreme and a more reproducible view of glomerular dysfunction than is possible in human patients.

Vitamin D receptor signaling in hematopoiesis

(See article on pages 1091–1099.)

Vitamin D in its active form [$1,25(OH)_2D_3$] is a steroid hormone that binds a specific nuclear receptor (VDR) to regulate expression of numerous target genes. Mice lacking this receptor, like humans with vitamin D–resistant rickets, are subject to a variety of metabolic and developmental defects, notably in their bones and reproductive organs. In their present analysis of hematopoiesis in wild-type and $Vdr^{-/-}$ mice, O'Kelly et al. identify several responses to $1,25(OH)_2D_3$ signaling that are clearly absent in the mutants, such as the ability of myeloid precursor cells to generate excess monocytes following treatment with this compound. However, as in previous descriptions of *VDR* mutant animals and humans, it also appears that the effects of VDR-deficiency can be qualitatively different from those of Vitamin D deprivation. Hair loss, which is seen in models of VDR-deficiency but not in dietary rickets, provides one well-studied example. Here, O'Kelly and coworkers observe that $Vdr^{-/-}$ mice can mount only a poor Th1 response — an unexpected finding, given evidence that Th1 formation in wild-type animals can be inhibited by $1,25(OH)_2D_3$. The reduced ability of $Vdr^{-/-}$ mutant T cells to adopt the Th1 phenotype seems to be due to their low levels of Stat4, which transduces cytokine signals that favor Th1 development. The authors suggest that this defect represents another instance in which the effect of VDR expression is distinct from that of $1,25(OH)_2D_3$ signaling, consistent with the idea that the VDR plays both ligand-dependent and -independent roles in lymphocytes.