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In This Issue

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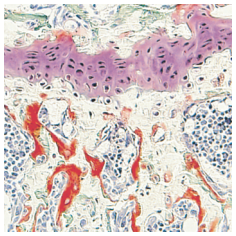
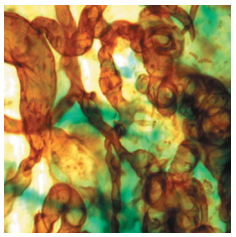
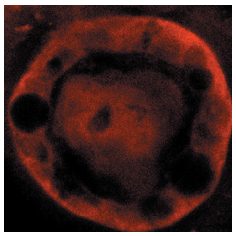
Central role for FGF-23 in mineral metabolism. Hypophosphatemic diseases are marked by renal phosphate wasting and impaired mineralization of bone. Regulation of phosphate serum levels is hormonally controlled, akin to the way the calcium-sensing receptor in the parathyroid gland regulates secretion of parathyroid hormone for calcium homeostasis. FGF-23 has been implicated as the factor that regulates serum phosphate, and Takeyoshi Yamashita and colleagues have now created Fgf23–/– mice to study this further (pages 561–568). Fgf23–/– mice had a shortened life span, hyperphosphatemia, enhanced renal phosphate reabsorption, and high serum levels of 1,25-dihydroxyvitamin D. However, mice heterozygous for the FGF-23 allele showed no abnormalities. Further studies with these mice will aid in better understanding mineral metabolism and hypophosphatemic diseases. See figure How much is too much VEGF? VEGF is a potent inducer of vascular growth and could be clinically valuable for proangiogenic gene therapy. However, the expression of VEGF needs to be tightly controlled in order to avoid excessive vascular growth and hemangiomas. To address this need, Helen Blau and colleagues investigated the relationship between VEGF dosage and blood vessel formation and distinguished overall dosage of VEGF administration from microenvironmental levels of VEGF secretion (pages 516–527). By implanting different clonal populations of VEGF-expressing myoblasts into mice and observing the resultant new vascular growth, the authors were able to identify a threshold […]



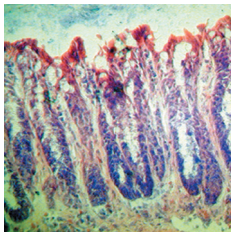
Central role for FGF-23 in mineral metabolism. Hypophosphatemic diseases are marked by renal phosphate wasting and impaired mineralization of bone. Regulation of phosphate serum levels is hormonally controlled, akin to the way the calcium-sensing receptor in the parathyroid gland regulates secretion of parathyroid hormone for calcium homeostasis. FGF-23 has been implicated as the factor that regulates serum phosphate, and Takeyoshi Yamashita and colleagues have now created *Fgf23*$^{-/-}$ mice to study this further (pages 561–568). *Fgf23*$^{-/-}$ mice had a shortened life span, hyperphosphatemia, enhanced renal phosphate reabsorption, and high serum levels of 1,25-dihydroxyvitamin D. However, mice heterozygous for the FGF-23 allele showed no abnormalities. Further studies with these mice will aid in better understanding mineral metabolism and hypophosphatemic diseases.



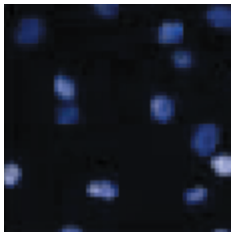
How much is too much VEGF? VEGF is a potent inducer of vascular growth and could be clinically valuable for proangiogenic gene therapy. However, the expression of VEGF needs to be tightly controlled in order to avoid excessive vascular growth and hemangiomas. To address this need, Helen Blau and colleagues investigated the relationship between VEGF dosage and blood vessel formation and distinguished overall dosage of VEGF administration from microenvironmental levels of VEGF secretion (pages 516–527). By implanting different clonal populations of VEGF-expressing myoblasts into mice and observing the resultant new vascular growth, the authors were able to identify a threshold level of VEGF that distinguished normal from aberrant angiogenesis. Furthermore, normal angiogenesis could not be achieved by simply reducing the total VEGF dose, emphasizing the importance of microenvironmental growth factor release. These findings may guide strategies for pro-angiogenic treatment.



Lactating mammary glands sense calcium. The calcium-sensing receptor (CaR) regulates cellular responses to changes in extracellular calcium levels. During reproduction in mammals, mothers require large amounts of calcium for transfer to offspring, and adaptive mechanisms are necessary for the maintenance of calcium homeostasis in the body. John Wysolmerski and colleagues show that the CaR is central to these adaptive mechanisms (pages 598–608). The authors observe that expression of the CaR on mammary epithelial cells is upregulated during lactation. Dietary restriction of calcium upregulates parathyroid hormone–related protein production during lactation, decreases the calcium content of milk, increases milk osmolality and protein concentration, and decreases overall milk production. Most of these effects are prevented by the infusion of calcimimetic compounds, implicating the CaR as the key mediator of these processes.



Vanin-1 regulates intestinal inflammation. Vanin-1 possesses the enzymatic ability to hydrolyze pantetheine to pantothenic acid (vitamin B5) and cysteamine. Cysteamine is thought to be a key factor in several metabolic pathways and putatively inhibits γ-glutamylcysteine synthetase (γ-GCS), which catalyzes a key step in glutathione (GSH) synthesis. To explore the physiological importance of cysteamine, Philippe Naquet, Bouchra Gharib, and colleagues generated *Vanin-1*–deficient mice that lack cysteamine (pages 591–597). They found that these mice were more tolerant of intestinal injury by NSAID administration or by *Schistosoma* infection. The inflammatory response in *Vanin-1*–deficient mice was reduced, and γ-GCS activity and GSH stores were increased. Oral administration of cysteamine reversed the protective effects of *Vanin-1* deficiency. These studies offer the enzymatic activity of Vanin-1 as a potential new target for anti-inflammatory treatments.



APOE and HDL target COX-2 expression. HDL and its associated apolipoprotein APOE play an important role in preventing atherosclerotic disease. This protective role is associated with the ability to modulate plasma lipid levels, but recent evidence also suggests that APOE and HDL have antimitogenic capabilities that contribute to cardioprotection. Richard Assoian and colleagues delve further into this notion by elucidating the mechanism by which HDL and APOE inhibit the proliferation of aortic smooth muscle cells (pages 609–618). In experiments using murine and human smooth muscle cells both in vitro and in vivo, the authors show that APOE and HDL exert their antimitogenic effects through induction of COX-2 gene expression and activation of prostacyclin receptor–signaling pathways. Activation of these pathways led to inhibition of cyclin A expression and blocked entry into S-phase. These studies identify a new target for intervention in the prevention of cardiovascular disease.