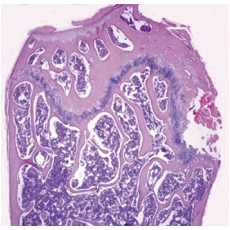
JCI The Journal of Clinical Investigation

In This Issue

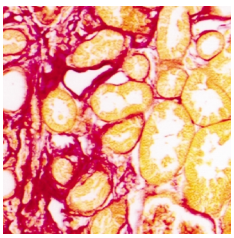
J Clin Invest. 2003;112(6):809-809. https://doi.org/10.1172/JCI119983.

In this issue

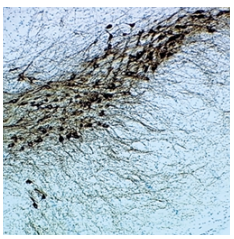
BMPs get it through their noggin. Bone morphogenetic proteins (BMPs) 2 and 4 are known to regulate hair follicle growth, neuronal differentiation, cardiomyogenesis, thymocyte differentiation, and fusion of cranial sutures. All of these effects are inhibited by a protein called noggin, yet little was known about the role of noggin in osteoblast differentiation and adult skeletal remodeling. Etsuko Abe and colleagues have found that noggin is expressed in vivo in osteoblasts, chondrocytes, and macrophages (pages 924–934). Infection of preosteoblastic cells with a retrovirus containing noggin inhibited osteoblast differentiation and osteoclast-supporting activity. A transgenic mouse that overexpressed noggin in mature osteoblasts displayed dramatic osteoporosis, decreased trabecular and calvarial bone, diminished bone formation rates, and reduced osteoblast differentiation in ex vivo cultures. These studies provide strong evidence that the balance between the expression of BMPs and noggin may determine the extent of osteoblast differentiation, osteoclast formation, skeletal remodeling, and ultimately bone mass in adult mice. (Figure)JunD protects the kidney. The transcription factor AP-1 is composed of Jun and Fos proteins and plays a crucial role in the fine-tuning of cell proliferation. Fabiola Terzi and colleagues used JunD–/– mice to define a key role for this transcription factor in preventing renal lesions following nephron reduction (pages 843–852). The model showed that nephron reduction induced a bimodal proliferative response. JunD was dispensable for […]



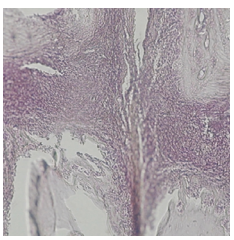
BMPs get it through their *noggin*. Bone morphogenetic proteins (BMPs) 2 and 4 are known to regulate hair follicle growth, neuronal differentiation, cardiomyogenesis, thymocyte differentiation, and fusion of cranial sutures. All of these effects are inhibited by a protein called noggin, yet little was known about the role of noggin in osteoblast differentiation and adult skeletal remodeling. Etsuko Abe and colleagues have found that *noggin* is expressed in vivo in osteoblasts, chondrocytes, and macrophages (pages 924–934). Infection of preosteoblastic cells with a retrovirus containing *noggin* inhibited osteoblast differentiation and osteoclast-supporting activity. A transgenic mouse that overexpressed *noggin* in mature osteoblasts displayed dramatic osteoporosis, decreased trabecular and calvarial bone, diminished bone formation rates, and reduced osteoblast differentiation in ex vivo cultures. These studies provide strong evidence that the balance between the expression of BMPs and noggin may determine the extent of osteoblast differentiation, osteoclast formation, skeletal remodeling, and ultimately bone mass in adult mice.



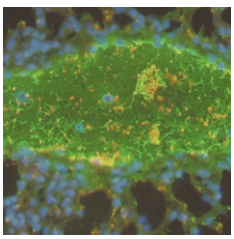
JunD protects the kidney. The transcription factor AP-1 is composed of Jun and Fos proteins and plays a crucial role in the fine-tuning of cell proliferation. Fabiola Terzi and colleagues used *JunD*$^{-/-}$ mice to define a key role for this transcription factor in preventing renal lesions following nephron reduction (pages 843–852). The model showed that nephron reduction induced a bimodal proliferative response. JunD was dispensable for the initial proliferative phase but essential for preventing a late phase that leads to kidney lesions. The regulation by JunD was found to act via a paracrine mechanism involving the TGF-α mitogen, and expression of a transgene encoding a dominant-negative isoform of EGF receptor prevented hyperplasia and development of renal lesions in *JunD*$^{-/-}$ mice. Dissection of these regulatory networks opens avenues for identifying genes involved in the susceptibility to renal disease.



A cheap and easy way to treat Parkinson disease. Parkinson disease (PD) is a neurodegenerative disorder characterized by loss of the nigrostriatal dopaminergic neurons accompanied by a deficit in mitochondrial respiration. Serge Przedborski and colleagues used a neurotoxin (MPTP) that causes dopaminergic neurodegeneration and a mitochondrial deficit reminiscent of PD (pages 892–901). Using this model of PD, the authors showed that the infusion of the ketone body D-β-hydroxybutyrate (DβHB) to mice restored mitochondrial respiration impaired by MPTP and protected against MPTP-induced neurodegeneration and motor deficits. The beneficial effect of DβHB was mediated through succinate and complex II of the mitochondrial respiratory chain. This study supports a critical role for mitochondrial defect in the pathogenesis of PD and suggests a novel target for intervention.



CD69 and TGF-β: double trouble in arthritis. The CD69 receptor is induced following activation of leukocytes at inflammatory sites, but its physiological role during inflammation remains unknown. Francisco Sánchez-Madrid and colleagues explored the role of CD69 in autoimmune reactivity by analyzing a model of collagen-induced arthritis (CIA) in CD69-deficient mice (pages 872–882). CD69$^{-/-}$ mice showed increased CIA, with exacerbated T and B cell immune responses to type II collagen. TGF-β1 and -β2, which are protective in CIA, were reduced in the inflamed joints of CD69$^{-/-}$ mice, correlating with the increase in other proinflammatory cytokines. Local injection of blocking anti–TGF-β antibodies increased CIA severity and proinflammatory cytokines in control but not CD69$^{-/-}$ mice. These results show that CD69 is a negative modulator of autoimmune reactivity and inflammation through synthesis of TGF-β, a cytokine that in turn downregulates the production of various proinflammatory mediators.



Mucins make microthrombi. Trousseau syndrome involves the formation of platelet-rich microthrombi in individuals with mucinous adenocarcinomas. However, no molecular link between carcinoma mucins and thrombosis has been made. Adenocarcinomas produce abnormally glycosylated mucins that present pathological binding sites for P- and L-selectins. Hypothesizing that selectin interactions with circulating mucins might trigger the syndrome, Ajit Varki and colleagues (pages 853–862) injected purified carcinoma mucin preparations into mice, rapidly inducing platelet-rich microthrombi. These were diminished in P- and L-selectin–deficient mice and by the anticoagulant heparin. Inhibition of endogenous thrombin did not block platelet aggregation. Thus, heparin was likely working by directly inhibiting P- and L-selectin interactions. This may also explain why Trousseau syndrome is ameliorated by heparin but not by other antithrombotic agents.