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In This Issue

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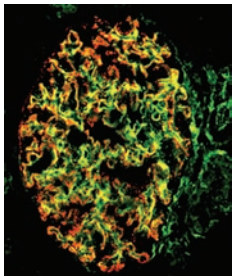
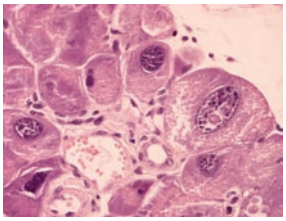
B7-1 beyond the immune system Proteinuria is a hallmark of nephrotic disease and results from dysfunction in the podocyte structure of kidney glomeruli. While a great deal has been discovered in the last several years about the molecular underpinnings of proteinuria, Peter Mundel and colleagues have identified an unexpected player in the development of this disease: B7-1, a transmembrane protein primarily known for its role in the immune system (pages 1390–1397). B7-1 is expressed on antigen-presenting cells, where it acts as a T cell costimulatory molecule. In this study, using an RNA differential display screen, the authors found increased expression of B7-1 in podocytes from α3-integrin–deficient mice, which have abnormal podocyte structures. They further observed induction of podocyte B7-1 expression in other models of nephrotic syndrome and found a correlation between podocyte B7-1 levels and the clinical severity of human lupus nephritis. Additionally, the absence of B7-1 protected mice from LPS-induced proteinuria. These results point to a novel role for B7-1 in the kidney in response to damage in this organ and offer new insights into the mechanism of kidney dysfunction. See figure Pancreatic maturity lost with E2F loss The E2F transcription factor family is known to be important in regulating cell growth and differentiation. Phenotypes of single- and double-mutant mice of the six gene family members display varied defects […]



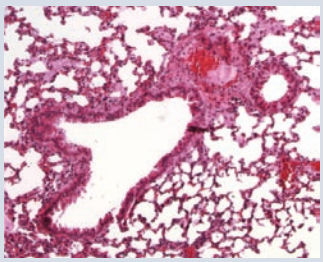
B7-1 beyond the immune system

Proteinuria is a hallmark of nephrotic disease and results from dysfunction in the podocyte structure of kidney glomeruli. While a great deal has been discovered in the last several years about the molecular underpinnings of proteinuria, Peter Mundel and colleagues have identified an unexpected player in the development of this disease: B7-1, a transmembrane protein primarily known for its role in the immune system (pages 1390–1397). B7-1 is expressed on antigen-presenting cells, where it acts as a T cell costimulatory molecule. In this study, using an RNA differential display screen, the authors found increased expression of *B7-1* in podocytes from α3-integrin–deficient mice, which have abnormal podocyte structures. They further observed induction of podocyte *B7-1* expression in other models of nephrotic syndrome and found a correlation between podocyte *B7-1* levels and the clinical severity of human lupus nephritis. Additionally, the absence of *B7-1* protected mice from LPS-induced proteinuria. These results point to a novel role for B7-1 in the kidney in response to damage in this organ and offer new insights into the mechanism of kidney dysfunction.



Pancreatic maturity lost with E2F loss

The E2F transcription factor family is known to be important in regulating cell growth and differentiation. Phenotypes of single- and double-mutant mice of the six gene family members display varied defects in systemic and cellular function. Ana Zubiaga and colleagues previously characterized E2F1 and E2F2 single-knockout mice and concluded that these two members have distinct roles in T lymphocyte homeostasis. They now show that E2F1 an E2F2 are critical for proper pancreatic development and function, as mice deficient in both these genes develop diabetes and exocrine gland dysfunction (pages 1398–1407). Loss of both these factors results in gross abnormalities in pancreatic function as the mice age, and disease manifests as diabetes due to lack of insulin. Cell cycle assays showed increased proliferation and apoptosis in the double-knockout mouse cells. These results suggest the involvement of E2F1 and E2F2 in the maintenance of differentiated cells in the pancreas and support their distinct role as transcriptional repressors that cannot be compensated for by other members of the gene family.



CD39 thins out thrombosis

Vascular thrombosis results from platelet recruitment and aggregation at a site of vascular injury. CD39 converts ATP and ADP to AMP, which can be further degraded to adenosine, an antithrombotic mediator. Anthony d'Apice and colleagues pursued CD39 as a potential antithrombosis agent in disease and in transplantation using mice transgenic for human CD39 (pages 1440–1446). *hCD39*-transgenic mice had increased bleeding times and were also protected from collagen-induced thrombosis. Moreover, the study showed that *hCD39* expression in either endothelial cells alone or blood components alone was sufficient to increase bleeding times. To test CD39's potential in improving xenotransplantation, the researchers performed cardiac grafts from the transgenic mice and promoted transplant rejection by immune system induction. Transgenic hearts were protected from rejection that is manifested as widespread intravascular thrombosis and platelet infiltration in small blood vessels of wild-type mice. Thus, *CD39*-transgenic cells may aid in improving xenotransplantation protocols as well as other clinical problems involving vascular injury and thrombosis.

Bile keeps triglycerides down

Elevated triglyceride (TG) levels have been shown to be a cardiovascular disease risk factor. TG production is controlled largely at the transcriptional level by the transcription factor SREBP-1c, which governs fatty acid synthesis. TG levels are also inversely affected by bile acids, although the mechanism underlying this relationship is unknown. Johan Auwerx and collaborators traced this elusive pathway through experiments with a diet-inducible hypertriglyceridemic mouse model and showed that bile acid–related TG level reduction occurs through transcriptional regulation (pages 1408–1418). TG levels were significantly lowered in mice receiving either a natural or a synthetic agonist for the bile acid receptor FXR. Mice treated with cholic acid, a type of bile acid, also had increased *SHP* expression levels. SHP, an FXR target, represses the nuclear receptor LXR. LXR is essential for a basal transcription level of *SREBP-1c*. The authors analyzed the *SREBP-1c* promoter using luciferase assays to show that SREBP-1c expression was attenuated via the FXR/SHP cascade. Finally, $SHP^{-/-}$ mice as well as $LXR\alpha/\beta^{-/-}$ mice showed no decrease in TG levels upon cholic acid treatment, further supporting this transcription pathway as the link between bile acid presence and TG levels.