

### In This Issue

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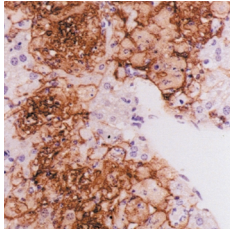
#### In this issue

Fibroleukin at fault in viral hepatitis. Fibrin deposition and thrombosis within the microvasculature play a pivotal role in the injury observed in viral hepatitis. Activated endothelial cells and macrophages express procoagulants including a novel prothrombinase, Fgl2/fibroleukin, important for the initiation and localization of fibrin deposition. Philip Marsden and colleagues show (pages 58–66) that mouse knockouts of Fgl2/fibroleukin fail to develop a procoagulant response to infection with hepatitis. In addition, the authors show that in humans with chronic HBV, expression of the Fgl2/fibroleukin gene is high and fibrin is deposited in the livers. Collectively, these studies indicate a critical role for Fgl2/fibroleukin in the pathophysiology of viral hepatitis and suggest that inhibition of this prothrombinase may be important for the treatment of inflammatory diseases not only of the liver but also of other tissues. Targeting the tubules. After transplantation of female human kidneys into male recipients, Y chromosome positive cells can be detected in the renal tubule of the transplanted kidney. In these studies, bone marrow–derived cells constitute a minor component of total tubular cell mass. Lloyd Cantley and colleagues now demonstrate (pages 42–49) that following ischemic renal injury in the mouse, bone marrow–derived stem cells home to the injured tubular segment, differentiate into a tubular cell phenotype specific for that tubular segment, and ultimately make up the majority of the cells [...]

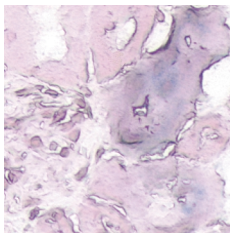
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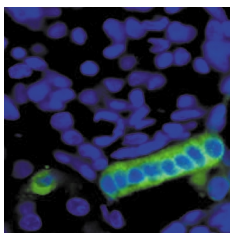




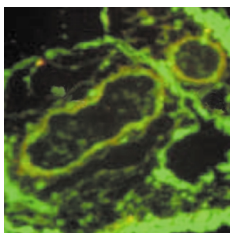
**Fibroleukin at fault in viral hepatitis.** Fibrin deposition and thrombosis within the microvasculature play a pivotal role in the injury observed in viral hepatitis. Activated endothelial cells and macrophages express procoagulants including a novel prothrombinase, Fgl2/fibroleukin, important for the initiation and localization of fibrin deposition. Philip Marsden and colleagues show (pages 58–66) that mouse knockouts of *Fgl2/fibroleukin* fail to develop a procoagulant response to infection with hepatitis. In addition, the authors show that in humans with chronic HBV, expression of the *Fgl2/fibroleukin* gene is high and fibrin is deposited in the livers. Collectively, these studies indicate a critical role for Fgl2/fibroleukin in the pathophysiology of viral hepatitis and suggest that inhibition of this prothrombinase may be important for the treatment of inflammatory diseases not only of the liver but also of other tissues.



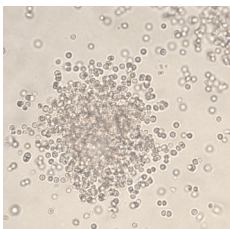
**Targeting the tubules.** After transplantation of female human kidneys into male recipients, Y chromosome positive cells can be detected in the renal tubule of the transplanted kidney. In these studies, bone marrow–derived cells constitute a minor component of total tubular cell mass. Lloyd Cantley and colleagues now demonstrate (pages 42–49) that following ischemic renal injury in the mouse, bone marrow–derived stem cells home to the injured tubular segment, differentiate into a tubular cell phenotype specific for that tubular segment, and ultimately make up the majority of the cells that repair the necrotic region of the tubule. This paper thus challenges the existing paradigm for repair of acute tubular necrosis and suggests that approaches aimed at bone marrow stem cell propagation and delivery to the kidney should be pursued in attempts to treat this disease.



**PGE<sub>2</sub> in control in the kidney.** Macula densa (MD) control of renin release is an important regulator of salt and water homeostasis in the kidney, particularly during volume depletion. However, details of the MD-signaling mechanism controlling renin release remained uncertain until János Peti-Peterdi and colleagues developed a novel biosensor tool to measure prostaglandin release from the MD (pages 76–82). This tool allowed direct functional evidence that intact MD cells release prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) through their basolateral membrane in response to low luminal NaCl concentrations. These studies provide the first direct evidence that intact MD cells synthesize and release PGE<sub>2</sub> during reduced luminal salt content and suggest that this response is important in the control of renin release and renal vascular resistance during salt deprivation.



**Del-1 drives angiogenesis.** The extracellular matrix protein Del-1 is one of several novel ECM proteins that accumulate around angiogenic blood vessels in embryonic and tumor tissue and promote angiogenesis in the absence of exogenous growth factors. Judith Varner and colleagues use Del-1 to enhance vessel development and accelerate functional recovery in two models of ischemic myopathy (pages 30–41). Del-1 binds to the integrin  $\alpha\beta 5$  on endothelial cells and induces the transcription factor Hox D3, which then serves as a master regulator of subsequent steps in angiogenesis, including induction of another receptor for Del-1, the integrin  $\alpha\beta 3$ . This process can be inhibited by antibodies against either integrin by genetic ablation of the integrin  $\beta 5$  subunit or by antisense mediated reduction in Hox D3 expression. This angiogenic matrix protein Del-1 may be a useful tool for the therapy of ischemic disease.



**Stem cells hold their breath.** Bone marrow (BM), hematopoietic stem, and progenitor cells are distributed along an oxygen (O<sub>2</sub>) gradient, with stem cells residing in the most hypoxic areas and proliferating progenitors found in O<sub>2</sub>-rich areas. As the reasons for the differential localization are unknown, Guénahel Danet and colleagues have evaluated the functional and molecular responses of human hematopoietic progenitors and stem cells to hypoxia (pages 126–135). The authors demonstrate that short-term culture under hypoxic conditions allows increased expansion of BM cells compared to normoxia, and that this is correlated with a preferential expansion of primitive BM cell subsets and arrest in the G1 phase. In response to hypoxia, HIF-1 $\alpha$  protein was stabilized, surface expression of angiogenic receptors was upregulated, and VEGF secretion was increased. These findings suggest the use of low O<sub>2</sub> levels could improve the expansion of human BM-repopulating cells.