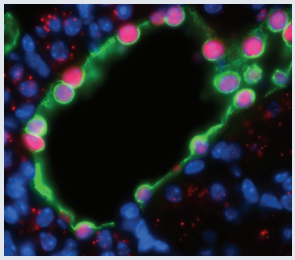
Loss of *MAT1A* lets the liver down

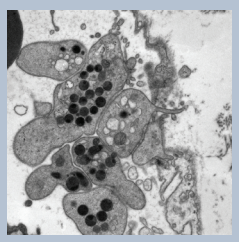
TNF-α signaling can elicit multiple responses including proliferation, inflammation, or cell death. Recently, acidic sphingomyelinase (ASMase) has been shown to play a significant role in hepatocellular apoptosis and liver damage induced by TNF-α. José Fernández-Checa and colleagues further these findings to show that ASMase exerts its ill effects by downregulating methionine adenosyltransferase 1A (MAT1A) levels in the liver (pages 895–904). Generation of ceramide by human placenta ASMase decreased MAT1/III protein levels in cultured rat hepatocytes. Using an in vivo mouse model of lethal hepatitis, the authors observed depletion of *S*-adenosy-L-methionine (SAM), the synthesized product of MATs, before fatal liver damage ensued. However, *ASMase*$^{-/-}$ mice maintained higher levels of SAM and experienced minimal liver damage. Furthermore, SAM administration prevented lethal liver failure in *ASMase*$^{+/+}$ mice. These studies identify a novel function for ASMase in TNF-α mediated cytotoxicity and suggest a therapeutic use for SAM in the treatment of liver diseases and liver failure.

Cystic diseases get linked



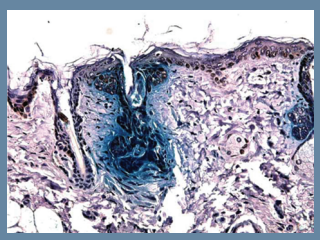
Maturity-onset diabetes of the young type 5 (MODY5) and autosomal recessive polycystic kidney disease (ARPKD) are caused by mutations in two distinct genes, *HNF1β* and *PKHD1*, respectively. Both diseases affect the kidney and result in renal cystogenesis. Peter Igarashi and colleagues have determined a link between these genetic diseases by identifying an evolutionarily conserved *HNF1β* binding site on the proximal promoter of *PKHD1* (pages 814–825). In vitro studies demonstrated that wild-type *HNF1β* activated transcription of the *PKHD1* promoter, whereas a dominant negative form could not. Moreover, specific mutations and deletions of the binding site on the *PKHD1* promoter abolished promoter activity as assayed by a gene reporter system. To relay this information in vivo, the authors generated transgenic mice expressing a dominant negative form of HNF1β. As expected, *PKHD1* gene expression was decreased in the kidneys of transgenic mice. Examination of renal histology revealed renal cysts in these mice. Finding a commonality in the mechanism of these diseases may enable shared treatment strategies for renal cyst diseases.

Src is the myocardial shark



Within hours following ischemic injury, VEGF expression increases, leading to changes in the vasculature including increased permeability, angiogenesis, and endothelial cell survival. However, David Cheresh and colleagues now report that, in addition to the potential positive effects VEGF may have following acute myocardial infarction (MI), VEGF also has a dark side. The authors showed that the VEGF-induced vascular permeability (VP) response led to edema and extensive cardiac tissue injury following MI (pages 885–894). However, they demonstrated that mice deficient in pp60Src or normal mice treated with pharmacological Src inhibitors showed minimal VP, edema, and platelet microthrombi following MI. These animals exhibited not only dramatically reduced infarct volume early on, but also a decrease in fibrosis and mortality months after the injury. Importantly, a single dose of an Src inhibitor given up to 6 hours after injury still provided cardiac protection. Furthermore, the biochemical mechanism responsible for this protection is the stabilization of an endothelial cell Flk/cadherin complex, which normally dissociates upon VEGF-mediated Src signaling. These data suggest that important consideration must be exercised in the use of VEGF clinically to promote angiogenesis, and they support Src blockade as a therapy to limit tissue injury following MI and perhaps other ischemic diseases.

Patching up skin cancer



Mutations in the tumor suppressor gene *patched* (*Ptch*) are responsible for most basal cell carcinomas (BCCs). *Ptch*$^{+/-}$ mice provide a good model for the study of BCCs, since their skin appears normal until exposure to radiation accelerates the induction of BCCs. Ornithine decarboxylase (ODC) catalyzes conversion of ornithine to putrescine and is induced by solar ultraviolet B (UVB) rays. This enzymatic reaction leads to the production of higher levels of polyamines, which are critical for normal and neoplastic cell growth. As ODC activity is higher in BCCs than in normal human skin, Mohammad Athar and colleagues sought to evaluate the potential for ODC inhibition as a therapeutic target for these tumors (pages 867–875). They generated *Ptc1*$^{+/-}$ mice that constitutively expressed ODC in the skin and observed an even greater acceleration of BCC induction. To block ODC activity in *Ptc1*$^{+/-}$ mice, the group generated mice overexpressing antizyme, which controls ODC by posttranslational modifications and suppresses ODC activity. These mice were less susceptible to UVB-induced photocarcinogenesis and had fewer visible BCCs and reduced tumor volume. In addition, administration of a suicidal ODC inhibitor to *Ptc1*$^{+/-}$ mice diminished BCC-like lesions by more than 80%. This article proposes that ODC inhibitors might be useful for the chemoprevention of BCCs.