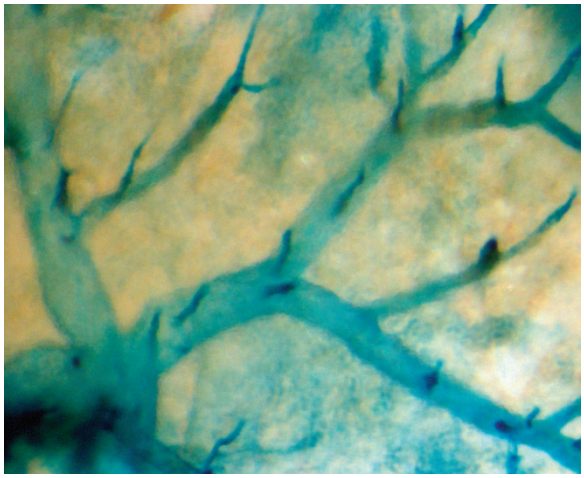
Laboratory Investigation (2007) 87, 626-627

INSIDE LAB INVEST

doi: 10.1038/labinvest.3700589



ALK1 in placental vasculogenesis

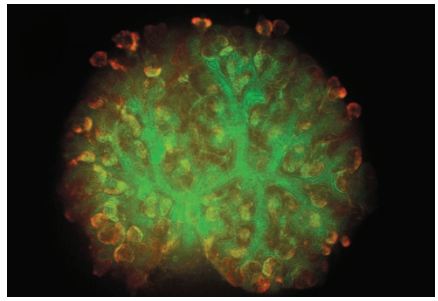
See page 670

Hereditary hemorrhagic telangiectasia (HHT) is a genetic vascular disorder. Typical symptoms of HHT patients are recurrent nosebleeds and telangiectasia (focal dilation of blood vessels). More than 70% of HHT patients have one or more arteriovenous malformations (direct connections of arterial and venous vessels without intervening capillaries) in their brain, lungs, or visceral organs. Despite the identification more than a decade ago of activin receptor-like kinase 1 (ALK1) and endoglin (transforming growth factor-β family signaling receptors) as HHT-causing genes, the underlying mechanism for the pathogenesis of HHT is still largely unknown. Previously, ALK1 expression was predominant in the endothelial cells of embryonic arterial (as opposed to venous) blood vessels. The arterial-predominant ALK1 expression suggests a role for ALK1 in arteriogenesis, as well as in the pathogenesis of HHT.

Hong and Oh examined whether the differential arterial:venous *Alk1* expression pattern in embryonic vessels is conserved in extraembryonic vessels, where the oxygen tension is reversed. They also evaluated the functional consequence of ALK1 deletion for umbilical and placental development using various *lacZ*-reporter strains. They show that differential *Alk1* expression is established after onset of circulation in arterial endothelium of umbilical vessels, and that depletion of ALK1 resulted in fused, instead of distinctive, umbilical arteries and veins. In the placenta, *Alk1* was detected only in the endothelial lineages. ALK1 depletion did not affect trophoblast invasion but caused severe dilation of placental vessels. These results further support the role of ALK1 in arteriogenesis and provide better guidelines for the use of *Alk1*-null embryos in studying pathogenesis of HHT and other related vascular disorders.

Fetal nephrogenesis in diabetic mothers

See page 680



The high blood-glucose levels present during diabetes are deleterious to fetal development, resulting in a high incidence of congenital malformations including urogenital abnormalities. Lelievre-Pegorier and colleagues previously demonstrated a 30% reduction in nephron numbers in rats born from diabetic mothers. Nephrogenesis is a complex process that requires a constant matrix metalloproteinases (MMP)-mediated extracellular matrix (ECM) remodeling. In this issue, Duong Van Huyen *et al* show that expression of MMP-2 and MMP-9 is regulated during normal nephrogenesis and that it was dramatically reduced in the kidneys of fetal rats from diabetic mothers, as compared with normoglycemic ones. *In vivo* and *in vitro* experiments strongly suggested that this was due to increased TGF-β1 and connective tissue growth factor levels, which are known to be induced by hyperglycemia. Impaired type IV collagenase activity has already been implicated in adult diabetic glomerulosclerosis. The present study clearly shows that the same enzymatic system is responsible for altered diabetic nephrogenesis, through abnormal ECM turnover leading to decreased uteric branching. High blood-glucose levels may adversely affect the kidney through the same mechanism both during development and in the adult.

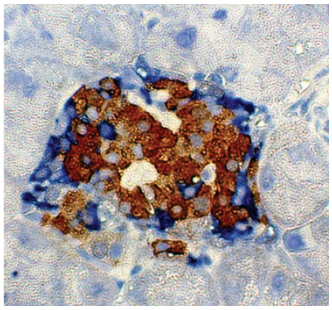
Partners in transdifferentiation

See page 702

Mounting *in vitro* experimental evidence indicates that insulin-producing cells can be derived from liver stem cells, either by manipulating cell culture conditions or by reprogramming through ectopic expression of one or more key pancreatic genes. Even so, *in vivo* animal models are likely to be more informative of the pathophysiology and the clinical sequelae of diabetes. In particular, there is a lack of understanding about the role of endogenous liver stem cells in restoring blood-glucose homeostasis in diabetic animals. One well-established liver-injury model for investigating liver

stem cell regeneration and differentiation involves feeding mice a liver toxin (3,5-diethoxycarbonyl-1,4-dihydrocollidine; DDC) for 30 days, resulting in massive liver stem cell proliferation. Similarly, a well-established mouse diabetic model for studying pancreatic β-cell regeneration relies on injection of the β-cell toxin streptozotocin (STZ), causing massive β-cell death and subsequent hyperglycemia.

In this issue, Kim *et al* offer a combined DDC-STZ treatment model for examining the dynamic interplay of liver stem cell transdifferentiation and pancreatic endocrine regeneration in regulating blood-glucose levels. Mice are first treated with DDC to induce liver stem cell proliferation and then with STZ to bring

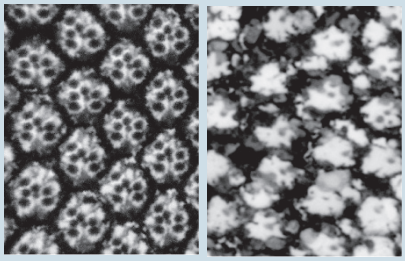


about β-cell death. Surprisingly, the DDC-treated mice were resistant to becoming diabetic after STZ treatment. Measurement of insulin content in both mouse liver and pancreas tissues suggests that the liver stem cells in the DDC-treated mice may play an important role in promoting pancreatic β-cell regeneration, perhaps by secreting liver-derived insulin in a timely manner. The study of Kim *et al* therefore has important implications for *in vivo* investigation of the interplay of the liver-cell transdifferentiation and β-cell regeneration in restoring glucose homeostasis under hyperglycemic conditions. If anything, their paper underscores the need for those investigating *in vivo* cell transdifferentiation to examine both liver and pancreas tissues rather than focus solely on one organ.

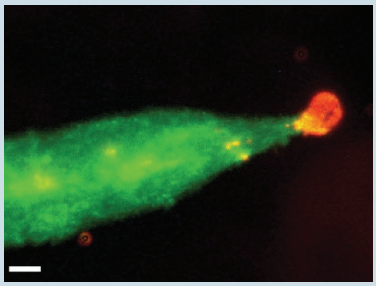
Li-Jun Yang, MD, University of Florida

nature.com/pathology

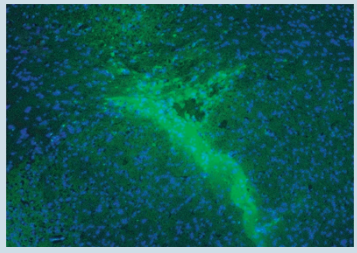
Myc deletion rescues Apc deficiency Both the *APC* tumor suppressor gene and the proto-oncogene *c-MYC* participate in colorectal neoplasia, but interactions between *APC* and *c-MYC* have been difficult to discern. By deleting both *APC* and *MYC* in the adult mouse intestine, a recent study showed that effects of *APC* gene inactivation require functional Myc protein. Thus, Myc is the critical mediator of the early stages of neoplasia that follow Apc loss. These data also suggest that Myc inhibition may be a future means of preventing tumor progression following *APC* mutation.
Nature 2007;446:676–679; doi:10.1038/nature05674
http://www.nature.com/ncb/journal/v9/n4/abs/ncb1553.html



Regulating polyglutamine diseases Huntington's disease and spinocerebellar ataxia are among nine neurodegenerative disorders caused by expanding CAG repeats coding for polyglutamine, but the mechanisms of cellular toxicity are unknown. A recent proteome analysis of neurons expressing mutant ataxin-1 (AT1) or huntingtin (Htt) showed that mutant AT1 and Htt reduced the concentration of soluble high-mobility group B (HMGB) 1/2 chromatin proteins. Conversely, HMGB1/2 overexpression reduced the toxicity of mutant AT1 and Htt. These results suggest that HMGBs are key regulators of disease and may represent therapeutic targets.
Nature Cell Biology 2007;9:402–414; doi:10.1038/ncb1553
http://www.nature.com/nm/journal/v13/n4/full/nm1565.html



Platelet TLR4 in sepsis A recent *Nature Medicine* study shows that platelet Toll-like receptor 4 (TLR4) is engaged by the presence of bacterial components in serum. These platelets activate adherent neutrophils and cause release of web-like structures—neutrophil extracellular traps (NETs)—that can trap and kill microbes in tissue and vasculature. This suggests that platelet TLR4 is the switch that triggers NET bacterial trapping. Perhaps because NET release causes tissue and endothelial injury, this mechanism is employed only under extreme conditions, such as severe sepsis.
Nature Medicine 2007;13:463-469; doi:10.1038/nm1565
http://www.nature.com/nm/journal/v13/n4/full/nm1555.html



Microglia in Alzheimer disease Senile plaques of Alzheimer disease are composed of β-amyloid (Aβ), activated microglia, and degenerating neurons. A recent study in ***Nature Medicine*** used a transgenic mouse model to study the role of the chemokine receptor Ccr2 in Alzheimer disease. Ccr2 deficiency caused earlier accumulation of Aβ and premature death, and data from heterozygous mice missing only one copy of Ccr2 suggested a role for Ccr2 gene dosage. Early accumulation of microglia, which express Ccr2, was defective in Ccr2-deficient mice, suggesting that Ccr2-dependent microglial accumulation may promote Aβ clearance in the early stages of disease. Studies of Ccr2 expression in autopsy specimens will be important to determine whether these observations translate to Alzheimer disease in humans.
Nature Medicine 2007;13:432–438; doi:10.1038/nm1555