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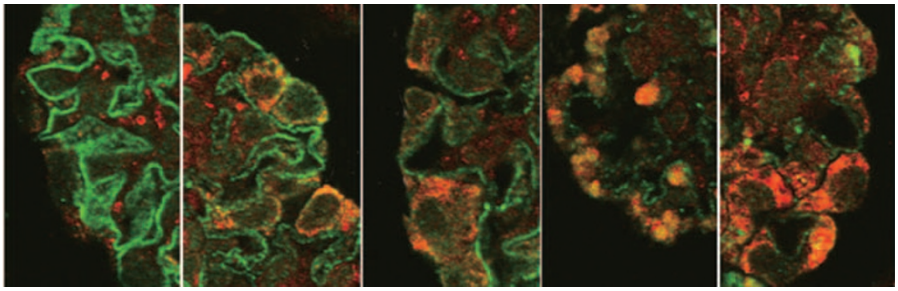

ER stress causes minimal-change disease

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Minimal-change disease (MCD) is the most common cause of nephritic syndrome in pediatric patients. It is characterized by diffuse loss of podocyte foot processes that can be seen only under electron microscopy. There are minimal glomerular changes that can be seen under the microscope, hence the name. Recently, endoplasmic reticulum (ER) stress, as characterized by an increase in the unfolded protein response (UPR), has been shown to be associated with proteinuria in a rat model of MCD. In a study described in this issue, Ito *et al* sought to determine whether ER stress/UPR was a cause or an effect of MCD.

Using a puromycin aminonucleoside (PAN) rat model of MCD, the authors found that after PAN injection there was diffuse activation of the mammalian target of rapamycin 1 (mTORC1) pathway, which presaged the UPR. Treatment with the mTORC1 inhibitor everolimus prior to PAN injection eliminated PAN nephrosis and was associated with decreased glomerular mTORC1 and UPR activation. This result runs counter to what is seen in other systems, in which mTORC1 inactivation leads to UPR activation. The authors observed that adenosine triphosphate was depleted after mTORC1 activation, suggesting that energy depletion due to mTORC1 activation led to UPR activation. They also demonstrated that one consequence of ER stress is a mislocalization of nephrin to the cytoplasm; nephrin is important in permselective barrier function within the glomerulus. The authors hypothesized that ER stress might interfere with posttranslational modification of nephrin, leading to mislocalization. Overall, this work links mTORC1 activation to ER stress in MCD, providing provocative new data about the pathogenesis of nephritic syndrome.

Role of TGF-β signaling in cerebral vascular development

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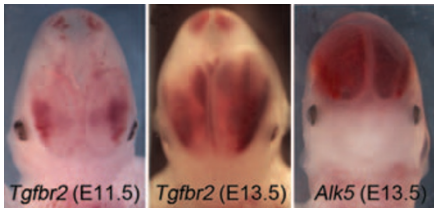

Cerebral vascular development is orchestrated by an assortment of proteins that induce the development of new blood vessels via endothelial cell growth and sprouting. Mouse knockouts of various transcription factors, signaling molecules, and integrins exhibit intracerebral hemorrhage phenotypes without vascular defects in other organs, suggesting that brain vascular development is regulated via specific signaling pathways. Integrins—heterodimeric receptors composed of α- and β-subunits—are expressed in both neural and endothelial cells in the brain. αvβ8 integrin is essential for cerebral vascular development. Both αv and β8 knockouts develop abnormal cerebral vasculature and intracerebral hemorrhage during development. αvβ8 integrin can activate TGF-β1 or TGF-β3. Mice harboring mutations in transforming growth factor (TGF)-β1 and TGF-β3 also develop intracerebral hemorrhage, suggesting that αvβ8 integrin talks to TGF-β1 and TGF-β3 during cerebral vascular development. Selective deletion of αv or β8 integrin genes in neuroepithelial cells, but not endothelial cells, showed cerebral vascular phenotypes that were similar to the germline knockouts, demonstrating that neuroepithelial cells were responsible for producing αvβ8 integrin during cerebral vascular development. However, it is still an open question whether TGF-β1 and TGF-β3 are produced by neuroepithelial cells or endothelial cells during cerebral vascular development. Because TGF-β type I and II receptors transduce TGF-β signals in various cell types, Nguyen *et al* used endothelial cell and neuroepithelial cell lineage–specific Cre-recombinase drivers and conditional TGF-β type I and II receptors to show that only endothelial cell–specific deletion of either TGF-β type I or TGF-β type II receptors resulted in abnormalities of cerebral vascular development. The findings indicate that integrins produced on neuroepithelial cells talk to integrin receptors on endothelial cells during brain vascular development.

CAR is essential for driving DDC-induced liver injury

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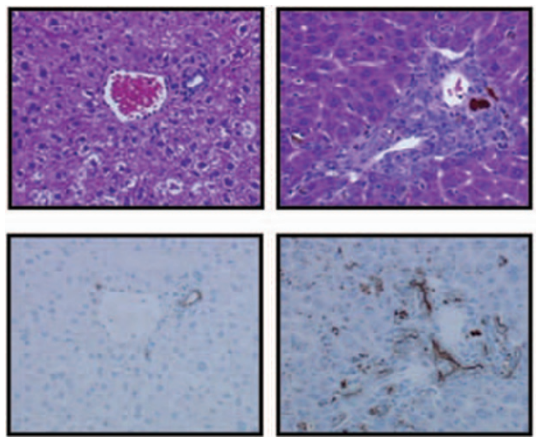
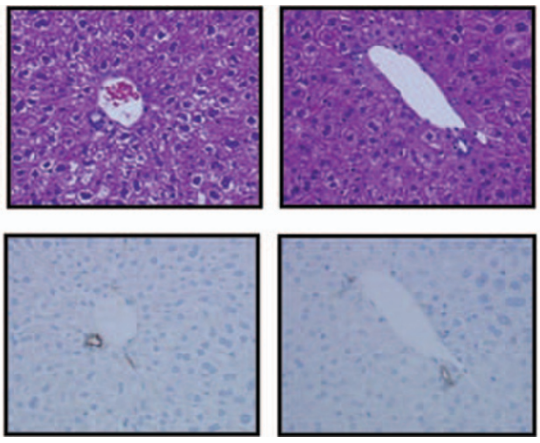
Regeneration is of fundamental importance to the maintenance of liver mass and function. When liver regeneration is impaired,



postnatal progenitor cells known as oval cells are thought to pick up the slack. They have also been implicated as hepatocellular carcinoma cancer stem cells. An understanding of oval cell biology is therefore necessary to harnessing the potential for regeneration without stimulating hepatocellular carcinoma. Constitutive androstane receptor (CAR), a member of the nuclear steroid/thyroid hormone receptor superfamily, is known to play important roles in regulating hepatic drug metabolism through regulation of the cytochrome P450 2B (*CYP2B)* gene. It has recently been demonstrated that liver regeneration is more efficient in the presence of CAR. Therefore, Yamazaki *et al* investigated whether CAR might also influence oval cell proliferation.

When mice were given 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC), a compound known to strongly induce oval cell proliferation, the authors observed that oval cell proliferation was absent in the $Car^{-/-}$ mice but not in *Car* wild-type mice, implicating CAR in the proliferation of oval cells. Furthermore, in contrast to other compounds that cause liver hypertrophy in the centrilobular regions, DDC caused liver hypertrophy in the periportal regions where oval cells proliferate; this was ablated in $Car^{-/-}$ mice. Thus, periportal activation of CAR appears to be important in causing oval cell proliferation. The authors plan to leverage this exciting observation as a tool to study the roles of oval cells in liver regeneration and cancer.



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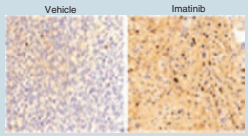
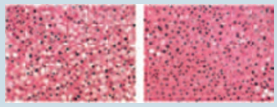
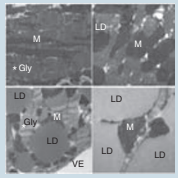


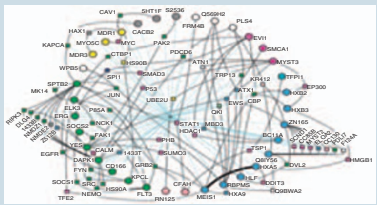
Imatinib augments immune-mediated response to gastrointestinal stromal tumors Imatinib mesylate is a small-molecule tyrosine kinase inhibitor that targets KIT and platelet-derived growth factor-α (PDGFRA) and is first-line therapy for the treatment of gastrointestinal stromal tumors (GISTs) that are driven by KIT or PDGFRA. Surprisingly, as described in a recent article in *Nature Medicine,* Balachandran *et al* found that imatinib enhances the immune-mediated response to GISTs in addition to the direct effect of KIT inhibition in GIST cells. They demonstrated that KIT inhibition reduced GIST cell expression of indoleamine 2,3-dioxygenase, an enzyme that suppresses immune function. This resulted in increased $CD8^+$ T cells in imatinib-sensitive GISTs. Importantly, immune therapy with cytotoxic T lymphocyte–associated antigen 4 significantly augmented the effect of imatinib in a genetically engineered mouse model.
Nature Medicine 2011;17:1094–1100; doi:10.1038/nm.2438



Focus on pancreatic β-cell dysfunction in diabetes A variety of factors contribute to type 2 diabetes, which is characterized by impaired glucose homeostasis. A mouse model of type 2 diabetes lacks the GnT-4a glycosyltransferase encoded by the *Mgat4a* gene. This gene fosters cell surface localization of glucose transporter-2 (Glut-2), which is required for glucose uptake and glucose-stimulated insulin secretion. As recently reported in *Nature Medicine*, Ohtsubo *et al* undertook to determine whether defects in GnT-4a and Glut-2 function cause type 2 diabetes. Elevated free fatty acids resulted in decreased GnT-4a glycosyltransferase expression in pancreatic β-cells, which produced all the signs and symptoms of type 2 diabetes. Notably, disease symptoms were prevented by enforced β-cell expression of GnT-4a glycosyltransferase, suggesting that interventions that maintain GnT-4a activity and glucose transporter expression may be useful in the prevention and treatment of diabetes.
Nature Medicine 2011;17:1067–1075; doi:10.1038/nm.2414



Fat catabolic defects linked to cardiac mitochondrial dysfunction Neutral lipid storage disease (NLSD), which is caused by mutations in the adipose triglyceride lipase (*ATGL*) gene, is characterized by massive lipid accumulation in multiple tissues, severe skeletal and cardiomyopathies, and premature death. Mice harboring deletions of *Atgl* (*Atgl*KO) have symptoms similar to those in humans with NLSD. As recently reported in *Nature Medicine*, Haemmerle *et al* studied *Atgl*KO mice to investigate the relationship between loss of Atgl function and cardiomyopathy. They discovered that loss of Atgl results in decreased lipid ligands for peroxisome proliferator–activated receptor (PPAR)-α and PPAR-δ, leading to decreased PPAR-α and PPAR-δ target gene expression, which in turn caused defective mitochondrial substrate oxidation, cardiac lipid accumulation, and cardiomyopathy. Interestingly, PPAR-α agonists bypassed the Atgl deficiency, resolving all the clinical findings in *Atgl*KO mice.
Nature Medicine 2011;17:1076–1085; doi:10.1038/nm.2439



"Stemness" is prognostic in AML The cancer stem cell (CSC) model predicts that patient outcome depends more on CSCs than on non-CSCs. To test the CSC model, Eppert *et al*, in a study published recently in *Nature Medicine*, asked whether the stem cell gene expression program in acute myelogenous leukemia (AML) was predictive of clinical behavior. They found that human leukemia stem cells (LSCs), as defined by functional characteristics in a xenotransplant assay, had a gene expression program similar to that of hematopoietic stem cells. The LSC expression signature correlated with cytogenetically poor-prognosis AML and even identified a poor-prognosis group within a cytogenetically normal overall good-prognosis AML group. Overall, this study suggests that eradication of LSCs would improve overall survival in AML patients.
Nature Medicine 2011;17:1086–1093; doi:10.1038/nm.2415