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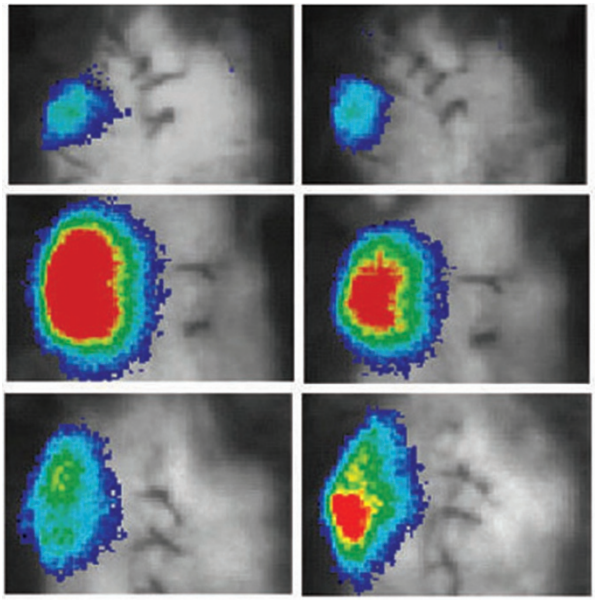

Mechanism of impaired liver regeneration in aged mice

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As a result of advances in sanitation and medical care, populations in the developed world are reaching dramatically higher ages. In aging populations, there is an increase in liver disease, which is frequently treated by partial hepatic resection. The procedure is dependent on liver regeneration for success. The liver exhibits remarkable regenerative capacity, but as patients age, their capacity to regenerate hepatic tissues diminishes. To determine why regenerative capacity declines in the aging liver, Haga *et al* utilized a mouse partial hepatectomy (PH) model to evaluate candidate proteins and processes that might be responsible.

The authors identified $p66^{Shc}$, an Src homology 2 domain–containing (Shc) protein that is known to inhibit Ras/MAP kinase pathway activation and to regulate oxidative stress (OS) and apoptosis, which play important roles in loss of hepatic regenerative capacity. The severity of acute liver injury following PH was greater in aged mice. The injury was caused predominantly by OS and was accompanied by marked $p66^{Shc}$ phosphorylation at serine 36. Ablation of $p66^{Shc}$ in aging mice resulted in a hepatic regenerative capacity equivalent to that in young mice, as well as a decrease in OS and apoptosis. While this result requires confirmation in other animal models and in humans, identification of the role of $p66^{Shc}$ in impairment of liver regeneration in the aged liver is a significant step in the development of rational-based therapies to address this important clinical problem.

Mouse model of autoimmune pancreatitis

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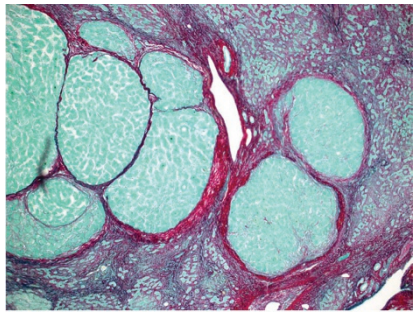
Autoimmune pancreatitis (AIP) is defined by a constellation of histological and clinical findings, including occasional association with extrapancreatic lesions such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis. There are two histological subtypes: (i) lymphoplasmacytic sclerosing pancreatitis (LPSP), or type 1 AIP, which is characterized by lymphoplasmacytic infiltration and idiopathic duct–centric pancreatitis (IDCP), and (ii) type 2 AIP, which is characterized by granulocyte epithelial lesions. Given that bacterial cell wall components have been implicated in the pathogenesis of AIP, Haruta *et al* hypothesized that repeated inoculation of avirulent, heat-killed *Escherichia coli* might induce AIP in mice and created a mouse model of AIP to be used in dissecting the pathogenesis of this interesting disease.



The authors showed that shortly after completion of inoculations the pathology in the pancreas resembled that of IDCP but later it resembled that of LPSP, suggesting that the two types of AIP are related. Moreover, mice developed sclerosing sialadenitis, further supporting their model. They also demonstrated that mice inoculated with *E. coli* developed autoantibodies characteristic of AIP. Finally, adoptive transfer of *E. coli*–inoculated spleen cells to $Rag2^{-/-}$ mice resulted in AIP-like pancreatitis in recipient mice, indicating that autoimmune mechanisms are probably involved in the pathogenesis of AIP in this mouse model. Because this model parallels the clinical and pathological features of AIP in humans, it will undoubtedly be useful in understanding the pathogenesis of AIP in humans.

Hedgehog signaling links hepatitis to cirrhosis/ hepatocellular carcinoma

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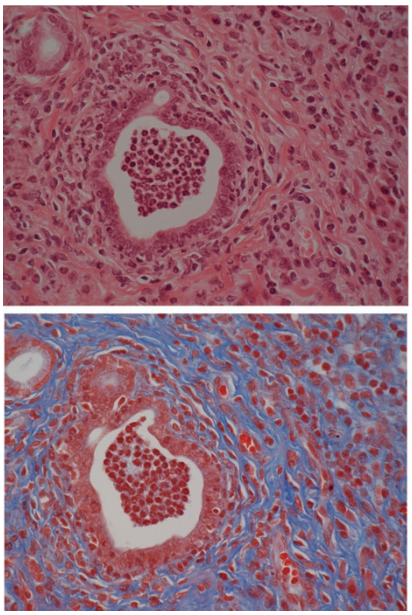
The majority of cirrhosis and hepatocellular carcinomas (HCCs) arise in the setting of chronic hepatitis B (HBV) or hepatitis C (HCV). However, not all patients with HBV or HCV infection develop cirrhosis and subsequently HCC. Recent evidence has implicated the Hedgehog (Hh) signaling pathway in the pathogenesis of cirrhosis and HCC. Activation of Hh signaling promotes many processes that occur during liver repair, such as the growth of myofibroblasts that contribute



to fibrosis, epithelial-to-mesenchymal transitions that have the potential to supply additional myofibroblasts, vascular remodeling, accumulation of inflammatory cells that supply additional Hh morphogens, and an increase in liver progenitors that could be the precursors to HCC. Because infection by HBV or HCV initiates cirrhosis and HCC, Diehl and colleagues asked whether HBV or HCV infection could directly upregulate Hh signaling.

Using human liver samples from patients infected with HBV or HCV, the authors observed that Hh signaling was increased in all patients with chronic hepatitis infection. Interestingly, Sonic Hedgehog was produced mainly by hepatocytes whereas stromal cells were the primary source of Indian Hedgehog. The downstream ligands Patched and Gli were also abundant in samples from patients infected with HBV or HCV. Levels of Hh signaling proteins correlated with stage of cirrhosis. To determine whether induction of Hh signaling was caused by HBV/HCV infection, the investigators infected hepatocytes with HCV, which led to the production of Hh ligands. Together, the data suggest that inhibition of Hh signaling at an early point in the development of hepatic fibrosis may delay or inhibit progression to fibrosis/cirrhosis and HCC.

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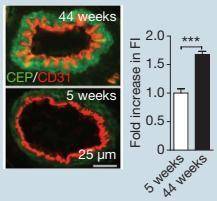
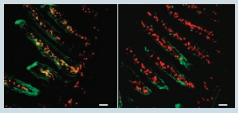


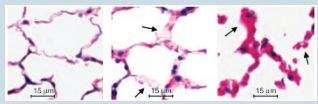
Novel inflammation-stimulated angiogenesis pathway The mechanism of hypoxia-induced angiogenesis is understood. However, less is known about how inflammation induces angiogenesis. This relationship is important because inflammation-initiated angiogenesis is key to many pathological processes. In a recent letter in *Nature*, Byzova and colleagues describe the mechanism underlying inflammation-induced angiogenesis. They focused their attention on ω-(2-carboxyethyl) pyrroles (CEPs), end products of lipid oxidation that are present at high levels during inflammation. They found that, in contrast to hypoxia-induced angiogenesis, CEPs did not act through vascular endothelial growth factor receptor 2 signaling. Instead, they identified Toll-like receptor 2, which plays important roles in innate immunity, as the CEP receptor involved in angiogenesis. They demonstrated that CEPs activate vascularization in a variety of inflammatory and neoplastic contexts, suggesting a general role for this pathway in various normal and pathologic states.

Nature 2010;467:972–976; doi:10.1038/nature09421



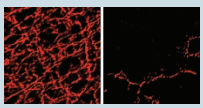
Preventive strategy to alleviate food-induced systemic anaphylaxis To better understand the mechanism of food-induced anaphylaxis and to develop strategies for inducing oral tolerance, Zhou *et al*, as reported in a recent article in *Nature Medicine*, tested the hypothesis that targeting gastrointestinal lamina propria dendritic cells (LPDCs) with neoglyco-antigen mimicking highly mannosylated structures on pathogens leads to induction of oral tolerance by C-type lectin receptors in a prophylactic model of food allergy. They demonstrated that mice treated with mannosylated bovine serum albumin (BSA) with 51 molecules of mannosides (Man_{51}-BSA) showed a significant decrease in the severity of anaphylaxis after challenge with BSA. They also showed that SIGNR-1, a C-type lectin receptor present on LPDCs, binds Man_{51}-BSA, leading to production of interleukin-10 and generating Tr1-like T cells that confer suppressive activity on antigen-induced anaphylaxis. The results suggest that this approach could be generalized to treat humans with food-induced anaphylaxis.

Nature Medicine 2010;16:1128–1133; doi:10.1038/nm.2201



Cardiolipin implicated in pathogenesis of pneumonia Cardiolipin levels are low in lung fluid under healthy conditions but elevated in patients with pneumonia. Patients with familial intrahepatic cholestasis type 1 (PFIC1) are prone to pneumonia and have mutations in ATP8b1, an ATPase that maintains lipid balance by translocating phospholipids from the outer to the inner leaflets of membrane bilayers. On the basis of these data, Ray *et al*, hypothesized that ATP8b1 is a cardiolipin import protein. In their study, recently published in *Nature Medicine*, they demonstrated that Atp8b1 is a cardiolipin import protein, but that cardiolipin severely impairs lung function. They concluded that the capacity of Atp8b1 to remove cardiolipin from the extracellular fluid is exceeded during inflammation, suggesting that removal of cardiolipin from the extracellular fluid would be useful in the treatment of pneumonia.

Nature Medicine 2010;16:1120–1127; doi:10.1038/nm.2213



ETV1 in gastrointestinal stromal tumor Gastrointestinal stromal tumor (GIST), the most common sarcoma of the gut, is characterized by activating mutations in *KIT* or *PDGFRA*. GIST is a paradigm for targeted therapy with small-molecule tyrosine kinase inhibitors; KIT inhibitors such as imatinib mesylate (Gleevec; Novartis) are very effective in the control of recurrent/metastatic GIST. In a study examining transcription factors in GIST described in a recent letter in *Nature*, Chi *et al* identified ETV1 as being GIST-specific. They also showed that ETV1 is essential in the development of a subset of interstitial cells of Cajal, pacemaker cells within the gut wall that are the putative cells of origin of GIST. Furthermore, they demonstrated that ETV1 cooperates with KIT in GIST tumorigenesis; ETV1 unleashes a KIT-dependent transcriptional program that drives tumorigenesis.

Nature 2010;467:849–853; doi:10.1038/nature09409