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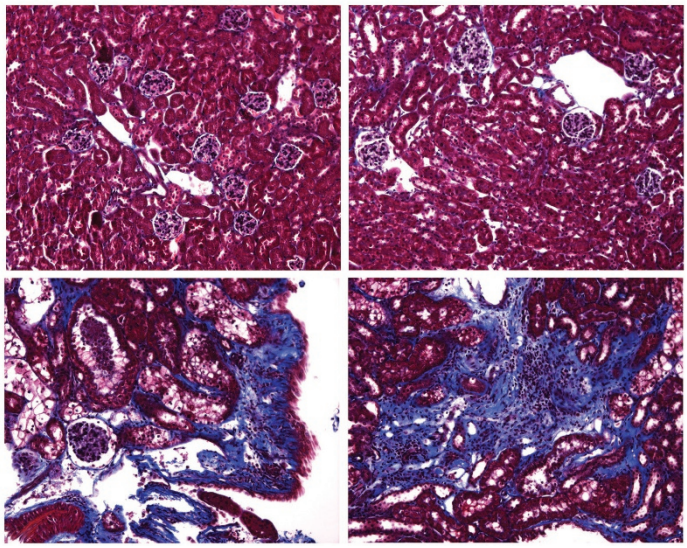

Mechanism of nephropathy in type Ia glycogen storage disease

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Glycogen storage disease type Ia (GSD-Ia) is an autosomal recessive disorder characterized by aberrant glucose homeostasis due to inactivating mutations in endoplasmic reticulum–bound glucose-6-phosphatase-α (G6Pase-α). Clinical findings include fasting hypoglycemia, hepatomegaly, nephromegaly, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, lactic academia, and growth retardation. There is no cure, but the disease manifestations can be managed using dietary therapies that normalize sugar levels. Chronic renal disease is a major complication of GSD-Ia with histologic findings of tubular atrophy, focal segmental glomerulosclerosis, and interstitial fibrosis. Renal insufficiency is delayed but still occurs in metabolically compensated patients.

To understand the pathophysiology of GSD-Ia, Yiu and colleagues have developed a G6Pase-α knockout mouse that recapitulates the salient features of GSD-Ia. They had previously shown that angiotensin II (AngII) and transforming growth factor-β1 (TGF-β1) play important roles in the development of renal fibrosis in GSD-1a-deficient mice. Because AngII and TGF-β1 can promote renal damage through the generation of reactive oxygen species (ROS), Yiu *et al* evaluated whether ROS might be involved in the pathogenesis of renal damage in GSD-Ia. They demonstrated that several mediators of ROS were elevated in GSD-Ia mice. Furthermore, they showed that renal DNA exhibited signs of oxidative damage. Finally, renal dysfunction in GSD-Ia was improved in mice treated with tempol, an antioxidant drug. These results suggest that treatment with antioxidant drugs will improve the benefits of dietary therapy in GST-Ia patients.

Potential mechanism of myocardial dysfunction in sepsis

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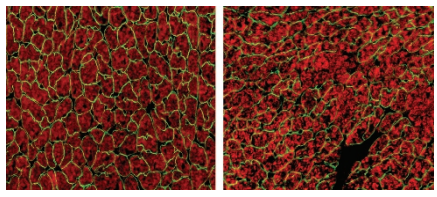

Myocardial contractility can, via an unknown mechanism, become severely dysfunctional during sepsis. The concomitant mortality rate is high, in the range of 70–90%. The dystrophin–glycoprotein complex (DGC), a protein complex, is located within cardiac muscle cells in classic Z-band structures. The DGC has several functions, including transmission of force between the sarcomere and plasma membrane as well as conferring structural stability to the plasma membrane. Recent studies implicate myocyte structural changes in sepsis-induced myocardial dysfunction.

Using a mouse model of sepsis with clinical and biological features identical to those of human sepsis, Celes and colleagues sought to refine their understanding of the pathogenesis of sepsis-induced myocardial dysfunction by examining the role of the DGC in this process. They showed that dystrophin and β-dystroglycan, two important components of the DGC, were markedly decreased in hearts from mice with severe sepsis as compared to sham-operated controls. Furthermore, depressed dystrophin and β-dystroglycan correlated with hypotension, circulatory shock, and increased sarcolemmal permeability. In addition, antioxidant therapy with peroxide dismutase decreased the loss of dystrophin and increased sarcolemmal membrane permeability, indicating that oxidative damage is involved in the loss of dystrophin. These findings provide a concrete framework in which to address mechanistic experiments that address the relationship among sepsis, oxidative damage, structural changes in cardiomyocytes, and depressed cardiac contractility. Overall, these studies have the potential to identify several therapeutic targets that can be used to treat cardiac dysfunction associated with sepsis.

RegI accelerates gastric ulcer healing

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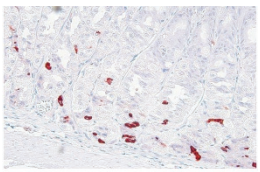
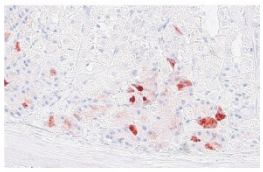
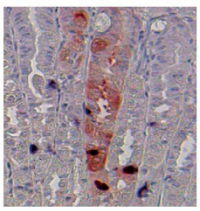
Gastric ulcers are a common problem. They are associated with several potential complications, including perforation with subsequent peritonitis. Gastric ulcer healing is a complicated process that serves as an excellent model of wound healing and tissue regeneration. A model established predominantly from

descriptive data and *in vitro* data postulates that interleukin 8 (IL-8) is secreted from injured gastric mucosal epithelial cells at the ulcer margin. Enterochromaffin-like cells—neuroendocrine cells located in the basal portion of the gastric gland—respond to IL-8 by producing RegI (regenerating gene I). RegI, which was originally identified as a growth factor crucial for pancreatic regeneration, interacts with gastric progenitor cells to trigger their proliferation, a critical step in gastric ulcer healing.

Recently, Fukuhara and colleagues developed a RegI-transgenic mouse, which they have used to test directly whether RegI is involved in gastric ulcer healing *in vivo*. Using both water-immersion stress







and hydrochloric acid/ethanol-induced gastric ulcer models, they showed that RegI transgenic mice had shorter healing times. Furthermore, their data support the idea that RegI functions predominantly in the regeneration phase to stimulate gastric progenitor cells and not in the injury phase to protect gastric cells. In fact, ulcers were initially larger in RegI transgenic mice in comparison with their wild-type littermates. These results establish RegI as a critical molecule in gastric ulcer healing and lay the groundwork for further studies that will examine the precise progenitor cell targets of RegI.

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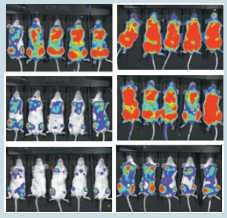
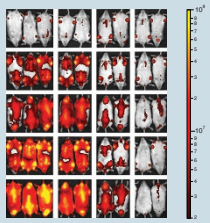
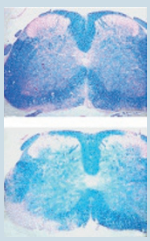
Deep sequencing of renal cell carcinoma Most renal cell carcinomas (RCCs) are characterized by inactivating mutations of the *VHL* gene. To determine the complete spectrum of mutations seen in RCC, as reported in a recent letter in *Nature*, Dalgliesh and colleagues sequenced the exons from 3,544 genes in 101 RCCs. Genes with two or more nonsynonymous mutations were sequenced in a follow-up series of 311 RCCs. Of particular interest, they identified truncating mutations in *SETD2*, a histone H3K36 methyltransferase, and *JARID1C*, a histone H3K4 demethylase, in 3% of RCCs each, indicating a role for histone modification in the pathogenesis of RCC. Among cases harboring these mutations, 88% also had *VHL* mutations or a hypoxia-expression phenotype, suggesting that mutations in *SETD2* or *JARID1C* collaborate with *VHL* mutations.
Nature 2010;463:360–363; doi:10.1038/nature08672



Combination Bcr-Abl inhibition by allosteric and ATP-binding-site inhibitors in CML Chronic myelogenous leukemia (CML) characteristically harbors a chromosomal rearrangement resulting in a Bcr-Abl fusion protein that drives oncogenesis. Inhibition of Bcr-Abl by imatinib mesylate, which targets the adenosine triphosphate (ATP)-binding site, usually results in clinical remission. However, the emergence of imatinib-resistant clones results in relapse. In a recent article in *Nature*, Zhang and colleagues show that GNF-2, an allosteric Bcr-Abl inhibitor that binds to the myristate-binding site, inducing changes in the ATP-binding site, synergizes with imatinib to inhibit the most recalcitrant imatinib-resistant Bcr-Abl mutant, the T315I "gatekeeper" mutation, which commonly emerges in clinical isolates. Using GNF-5, an analog of GNF-2, they demonstrated impressive tumor inhibition in a murine bone marrow–transplantation model. Thus, by targeting Bcr-Abl with two mechanistically different types of inhibitors, they were able to inhibit the previously untreatable T315I mutant.
Nature 2010;463:501–506; doi:10.1038/nature08675



"Active-site" mTOR inhibition suppresses growth of leukemia cells without immunosuppression Rapamycin suppresses mammalian target of rapamycin (mTOR) through allosteric inhibition. Rapamycin has impressive immunomodulatory activity, but it has been less successful in the treatment of cancer. mTOR kinase is present in two separate complexes: TORC1 and TORC2. Rapamycin selectively targets TORC1, which blocks a feedback inhibitory loop, resulting in activation of phosphoinositide 3-kinase–AKT signaling. Recently, "active-site" mTOR inhibitors have been developed that target both TORC1 and TORC2. In a recent article in *Nature Medicine*, Janes and colleagues examined the efficacy of one of these inhibitors, PP242, in targeting leukemia cells. Using models of Philadelphia chromosome–positive acute lymphoblastic leukemia, they found that PP242 augmented the antineoplastic effects of imatinib mesylate. Surprisingly, they also discovered that PP242 was less immunosuppressive than rapamycin, suggesting that it may be a better choice in cancer therapy.
Nature Medicine 2010;16:205–213; doi:10.1038/nm.2091



Interleukin-7 plays a critical role in proliferation of Th17 cells in autoimmune disease T helper type 17 (Th17) cells are thought to play an important role in the pathogenesis of multiple sclerosis (MS), a chronic demyelinating disease with a proposed autoimmune etiology. Recently, an important clue in the pathogenesis of MS was identified with the finding that a single-nucleotide polymorphism in the *Il7r* gene, which encodes the interleukin-7 receptor (IL-7R), was associated with MS. In a recent article in *Nature Medicine*, Liu and colleagues sought to determine a mechanistic link between IL-7 signaling and the development of pathogenic Th17 cells. They demonstrated that IL-7 signaling was responsible for the expansion of pathogenic Th17 cells, suggesting that inhibition of IL-7 signaling might be useful for the treatment of MS.
Nature Medicine 2010; 16:191–197; doi:10.1038/nm.2077