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Too much TNF? Drink your milk or FLIP out!

See pages 540 and 572

Tumor necrosis factor (TNF)-mediated diseases have a major impact on human health. While canonical TNF signaling pathways have been well described, the complex ancillary pathways that play important roles in specific cell types have not been completely defined. Two studies in this issue describe inhibition of TNF signaling by vitamin D_3 and c-FLIP, respectively. Chung *et al* elegantly describe how vitamin D_3 can inhibit TNF-induced AP-1 and NF-κB signaling to prevent transcriptional activation of tissue factor (TF), a coagulation factor, in monocytes. TNF-induced TF secretion plays an important role in thrombotic disease. Takai *et al* describe how genetic background modulates susceptibility to TNF- or Fas-mediated hepatocyte apoptosis and acute liver failure in inbred mice. The study showed that Imperial Cancer Research (ICR) mice were protected from TNF-mediated liver failure, relative to NOD or B6 mice, owing to increased expression of c-FLIP, an endogenous caspase-8 inhibitor. This is of general pathogenic importance, as TNF-induced apoptosis contributes to ischemia/reperfusion injury as well as alcoholic and viral hepatitis. These reports emphasize the complexities of TNF signaling in disease and highlight the therapeutic modulation of TNF signaling in disease. While a long way from clinical application, therapies could not be proposed without careful dissection of TNF signaling pathways as described here.

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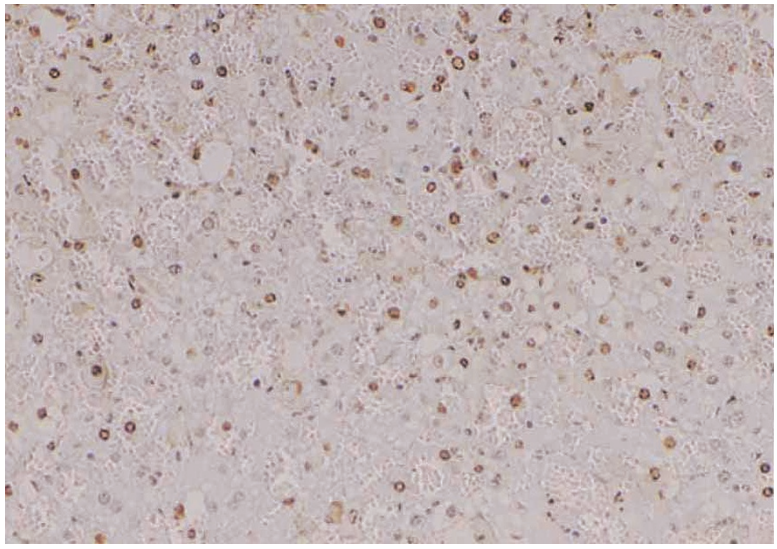
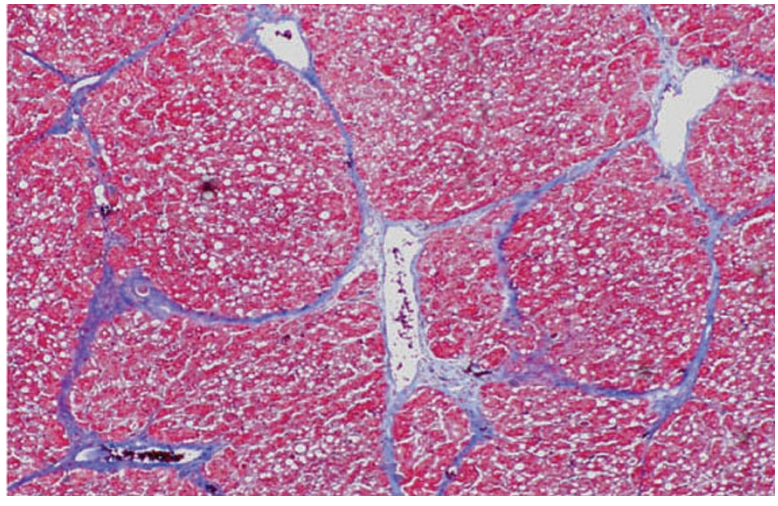


Kinase inhibitor therapy raises hope for prevention of cirrhosis

See page 591

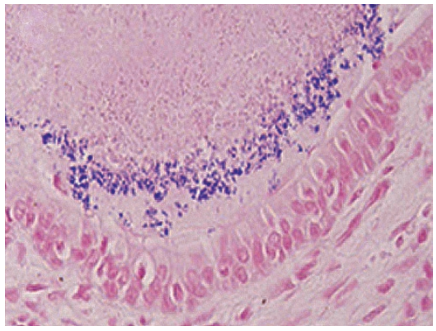
Liver cirrhosis—the fibrous scars and regenerative nodules that form following cycles of hepatocellular damage and regeneration—is among the leading causes of death in developed countries. Hepatic stellate cells, which are critical to progression of fibrosis, respond to cytokines and growth factors induced by hepatic damage. However, the intracellular signaling pathways that lead to *in vivo* hepatic fibrogenesis are not clear. One clue may be the observation that p38 MAP kinase may participate in renal, cardiac, and pulmonary fibrosis. Hattori *et al* tested whether p38 MAP kinase is necessary for cirrhosis. Using a carbon tetrachloride (CCl_4)-induced cirrhosis model in rats, Hattori *et al* showed that a selective p38 MAP kinase inhibitor, FR-167653, can reverse CCl_4-induced p38 MAP kinase activation and prevent increases in serum liver enzyme levels. FR-167653 also reduced collagen fiber deposition and myofibroblast functions. Moreover, it reduced expression of Runx2, a transcription factor that promotes profibrogenic myofibroblast differentiation. These data support a critical role of p38 MAP kinase in cirrhosis and further suggest that p38 MAP kinase inhibition may prevent hepatic fibrogenesis in patients. *Le Shen, MD, PhD, The University of Chicago, Chicago, IL*



Toll-like receptor signaling induces intestinal metaplasia

See page 559

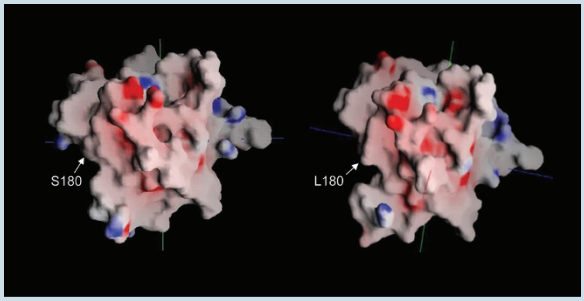
Intestinal metaplasia within biliary epithelium is thought to be an important step in pathogenesis of biliary neoplasia. Such metaplasia is associated with MUC2 expression, which, in turn, is regulated by the CDX2 transcription factor. In this issue, Ikeda *et al* provide data supporting a role for Toll-like receptor (TLR) signaling in this metaplasia. CDX2 expression, MUC2 expression, and biliary intestinal metaplasia developed in parallel in the polycystic rat *in vivo* model of chronic suppurative cholangitis. Similar changes



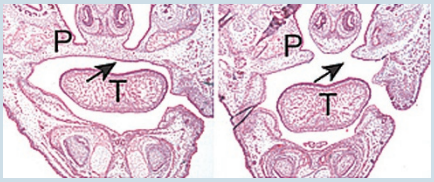
were induced by culture of biliary epithelia with bacterial components, such as peptidoglycan or lipopolysaccharide. The *in vitro* changes were prevented by anti-TLR2 or anti-TLR4 antibodies, suggesting that signaling through these TLRs was involved in biliary intestinal metaplasia. Treatment of cultured biliary epithelia with these bacterial components induced NF-κB activation, and the NF-κB inhibitor MG132 also prevented CDX2 and MUC2 expression. Finally, siRNA-mediated CDX2 knockdown prevented MUC2 expression. This study provides a mechanistic link between biliary infection and CDX2-dependent biliary intestinal metaplasia, thereby illuminating the pathogenesis of biliary neoplasia in chronic cholestatic diseases with superimposed biliary infection. *Liping Su, MD, PhD, The University of Chicago, Chicago, IL*

nature.com/pathology

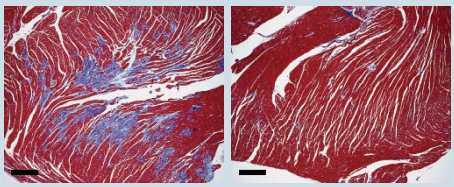
Gene mutation affects susceptibility to infectious diseases Toll-like receptors (TLRs) play a key role in the body's immune response by recognizing pathogens and then initiating intracellular signaling via their Toll/interleukin-1 (TIR) receptor domains. The TIR domain-containing adaptor protein Mal, or TIRAP, mediates downstream signaling of TLR2 and TLR4. *Nature Genetics* recently published a study of the Mal gene that identified a single nucleotide polymorphism encoding a single amino acid substitution that attenuates TLR2 signal transduction. The homozygous carriage of this variant was associated with increased susceptibility to invasive pneumococcal disease, bacteremia, malaria, and tuberculosis. In contrast, heterozygous carriage had a protective effect against these diseases.
Nature Genetics 2007;39:523–528; doi:10.1038/ng1976



The many roles of GSK-3β Glycogen synthase kinase-3β (GSK-3β) is involved in a variety of biological processes. A recent study published in *Nature* found that *GSK-3β* is a genetic requirement for normal midline development. *GSK-3β*-null mice exhibited cleft palate and incomplete fusion of the ribs at the midline. A chemically regulated allele of *GSK-3β* was used to identify discrete temporal windows in palatogenesis and skeletogenesis in which GSK-3β activity is necessary.



GSK-3β was also recently identified as a regulatory factor in cardiac disease. Congestive heart failure (CHF) is characterized by reactivation of a "fetal gene program" that is associated with cardiac hypertrophy. The histone deacetylase (HDAC) gene *Hdac2* mediates these this reactivation via a GSK-3β-dependent pathway. In *Hdac2*-null mice, constitutive GSK-3β activation prevented the fetal gene program and normal hypertrophic responses. This suggests that Hdac2 and GSK-3β may be good therapeutic targets for preventing cardiac hypertrophy in heart failure.



Nature 2007;446:79–82; doi:10.1038/nature05557
Nature Medicine 2007;13:324–331; doi:10.1038/nm1552

Novel risk loci for type 2 diabetes Type 2 diabetes mellitus results from both environmental and genetic factors, but the genetic variants contributing to this disease have largely remained unknown. The identification of genetic factors that contribute to type 2 diabetes mellitus was recently reported in *Nature*. Using high-density arrays, researchers confirmed the known association with the *TCFTL2* gene and also identified genes not previously known to confer type 2 diabetes risk. The novel loci include a zinc transporter that is expressed exclusively in β-cells as well as several other genes that may be involved in β-cell development or function.
Nature 2007;445:881–885; doi:10.1038/nature05616