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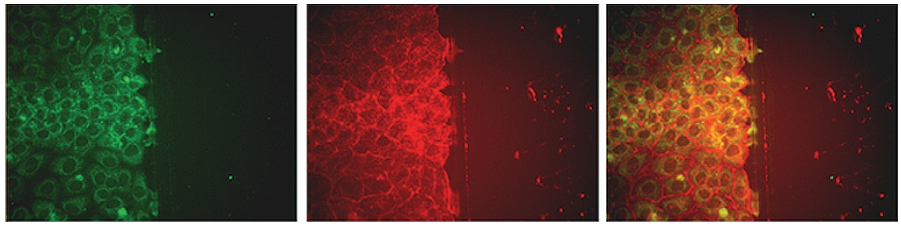

Epithelial restitution for intestinal wound healing

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Epithelial damage is a common occurrence in nearly all gastrointestinal diseases, including gastritis, infectious enteritis, and inflammatory bowel disease. In each case, histologically apparent epithelial wounds may lead to defects in water transport and nutrient absorption as well as blood loss; they may also allow luminal microbes and antigens to access the lamina propria. Thus it is critical that these wounds heal rapidly. In the intestine, epithelial cells migrate and spread rapidly, prior to cell division, in a process known as restitution. While restitution is well recognized, the mechanisms that regulate this process are not.

In this issue, Moyer and co-workers demonstrate that the CXC chemokine CXCL12 acts directly on epithelial cells through its receptor, CXCR4, to promote restitution. Treatment of intestinal epithelial sheets with CXCL12 leads to increased Rho activation, actin polymerization, and myosin light-chain phosphorylation through both myosin light-chain kinase and Rho kinase–mediated pathways. These actomyosin alterations lead to increased epithelial migration and accelerated wound closure. Thus, CXCL12 signaling via CXCR4 may play an important role in intestinal epithelial wound healing and reverse disease progression in patients. In addition to this new role for CXCL12-CXCR4, these data suggest the novel hypothesis that differing subsets of chemokines may either exacerbate tissue injury, through leukocyte migration, or promote healing, via epithelial restitution.

Optimizing proteomics through tissue surrogates

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In the post-genomic era, the use of high-throughput proteomic techniques on proteins extracted from formalin-fixed paraffin-embedded (FFPE) tissues is destined to become essential for the delineation of disease biomarkers. Although much progress has been made, key problems need to be circumvented. To date, the extraction process suffers from incomplete and selective recovery of protein, incomplete reversal of formaldehyde modifications, and protein degradation. Since analysis of protein extracts from whole tissues is possible only through mass spectrometry or two-dimensional gel electrophoresis, optimization and validation of the protocols are daunting tasks.

Fowler *et al* take a step back in order to make a leap forward; they describe simple, well-defined 'tissue surrogates' for the systematic study of the recovery of proteins from FFPE samples. The surrogates were formed by fixation of lysozyme, RNase A, or a mixture of carbonic anhydrase and lysozyme in buffered formalin; dehydration in graded alcohols; incubation in xylene; and embedding of the resultant gels in paraffin. Various extraction protocols were then screened in order to identify the most effective conditions for recovering proteins from the surrogates. The protein compositions of the extracts were easily visualized by SDS-PAGE. The authors were able to develop an efficient protein-recovery protocol from the tissue surrogates by use of heat, a protein denaturant, and detergent. In future studies, RNA, DNA, lipids, and carbohydrates could be added to the surrogates to more closely mimic real tissue. These studies are of critical importance in validating the methodologies with which proteomic analysis of fixed tissues is to be performed.

The fatty liver: steatotic but not necessarily insulin-resistant

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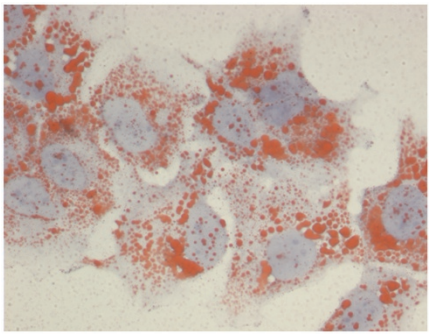
Accumulation of fat in the liver—steatosis—has become a major health problem in the Western world, owing to the epidemic of obesity. While steatosis has long been associated with excessive alcohol consumption, it is 'nonalcoholic fatty liver disease' that poses a new health threat. The systemic manifestations of the altered metabolic state of obesity center on 'insulin-resistance', whereby tissue responsiveness to insulin—including the liver—is reduced. The liver is itself at risk for inflammatory injury (nonalcoholic steatohepatitis), which may lead to cirrhosis. Animal models of nonalcoholic fatty liver disease are few in number, and they are yielding their secrets reluctantly. Hence, there is value in taking a totally separate approach to mechanistic

evaluation of hepatocyte steatosis, through comprehensive genomic analysis of human hepatocytes subjected to steatotic insult.

De Gottardi *et al* used human hepatocytes immortalized by lentiviral transduction and exposed to oleic acid as a cellular model of steatosis. Intracellular lipid status, differential gene expression, and activation of the highly relevant insulin-receptor-dependent intracellular signaling pathways were explored. The



major hypothesis of this study was that lipid accumulation in steatosis directly affects the gene-expression programming of hepatocytes. The authors found that immortalized human hepatocytes are an excellent cellular model with which to study steatosis because they are virtually fat-free under basal conditions. They accumulate intracellular fat when exposed to oleic acid, so there is an excellent ratio of 'signal-to-noise' for genomic analysis. The intracellular triglyceride synthesis caused by oleic acid exposure induces changes in gene expression for the redox, apoptosis, and proliferation systems, similar to those observed in humans with hepatic steatosis. Of interest is the fact that triglyceride accumulation did not appear to alter intracellular insulin signaling. Over and above providing valuable information on a new model of hepatic steatosis; these findings suggest that hepatic steatosis and insulin resistance are not always associated.

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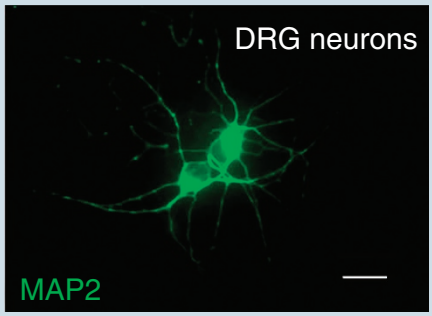
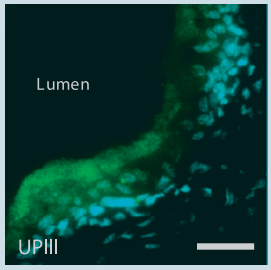
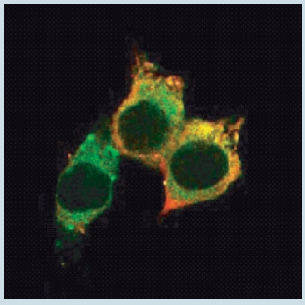


Astrocytes' role in ALS Amyotrophic lateral sclerosis, an adult-onset fatal motor-neuron disease, is caused by mutations in the enzyme superoxide dismutase-1 (SOD1). A recent study in *Nature Neuroscience* found that while expression of mutated SOD1 in primary mouse spinal motor neurons did not result in motor neuron degeneration, expression of mutated SOD1 in mouse astrocytes did cause the death of spinal primary and embryonic mouse stem cell–derived motor neurons. The neuronal death was mediated by the release of soluble toxic factor(s) from astrocytes, resulting in the recruitment of a Bax-dependent death mechanism in motor neurons.
Nature Neuroscience 2007;10:615–622; doi:10.1038/nn1876

***E. coli* plays hide-and-seek in the urothelium** Uropathogenic *E. coli* (UPEC), which causes 90% of urinary tract infections, is the most effective pathogen at overcoming the mucosal barrier in the urinary tract. *E. coli's* expression of filamentous appendages called type 1 fimbriae enables UPEC to bind to and invade superficial bladder epithelial cells. Using a mouse model, researchers recently found that type 1 fimbriated UPEC circumvents the mucosal barrier by hiding in specialized fusiform vesicles within bladder epithelial cells (BECs) that regulate bladder volume. UPEC thus avoids elimination during voiding via incorporation into BEC fusiform vesicles. Following micturition, UPEC re-emerges in the urine as the bladder distends and fusiform vesicles are exocytosed to increased plasma membrane area. As predicted, treatment of UPEC-infected mice with a drug that induces fusiform vesicle exocytosis reduced the number of intracellular *E. coli*. This may provide a means of interrupting UPEC's stealthy game of hide-and-seek.
Nature Medicine 2007;13:625–630; doi:10.1038/nm1572



Antielastin autoimmunity in emphysema A recent study in *Nature Medicine* found that, in response to elastin peptides, peripheral blood $CD4^+$ T cells from emphysema patients proliferated and released the inflammatory cytokines interferon (IFN)-γ and interleukin (IL)-10. The severity of emphysema was positively associated with the increase in T-cell secretion of IFN-γ and IL-10. Thus, in addition to being a destructive inflammatory disease, emphysema is an autoimmune disease characterized by the presence of antielastin antibodies and T-helper type 1–polarized immune activation.
Nature Medicine 2007;13:567–569; doi:10.1038/nm1583



MIF in inflammatory diseases The cytokine macrophage migration inhibitory factor (MIF), a highly conserved and evolutionarily ancient molecule, plays an important role in atherogenesis and acute and chronic inflammatory diseases. In a recent issue of *Nature Medicine*, researchers shed light on the largely unknown mechanisms underlying MIF-regulated cell migration. MIF was found to control inflammatory and atherogenic leukocyte recruitment by binding to the chemokine receptors CXCR2 and CXCR4.
Nature Medicine 2007;13:587–596; doi:10.1038/nm1567