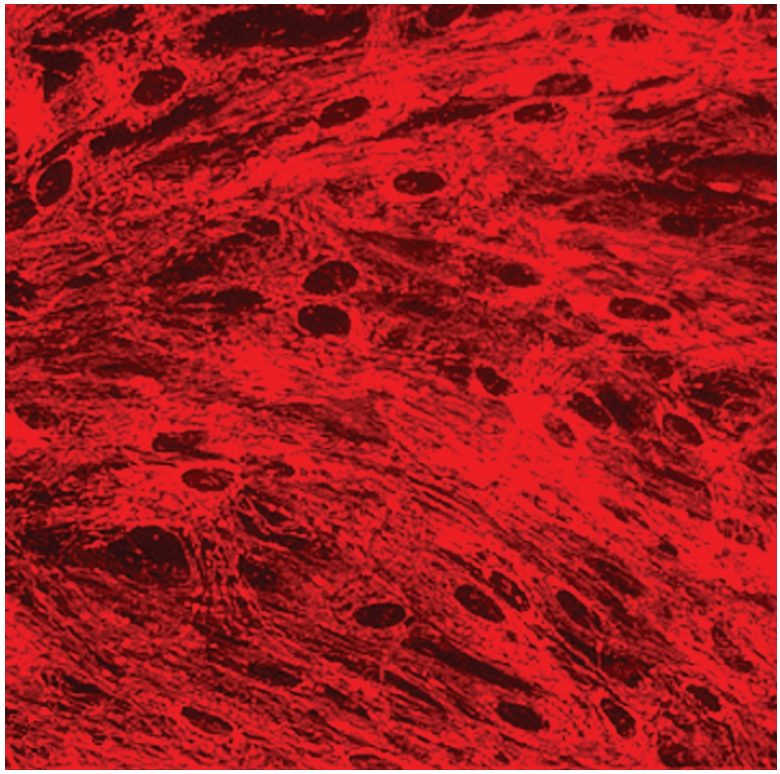
Laboratory Investigation (2008) 88, 794-795

INSIDE LAB INVEST

doi:10.1038/labinvest.2008.68



Copper excess and the mitochondrial permeability transition in astrocytes

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Copper is an essential trace element for proper enzyme function in proteins such as Cu/Zn superoxide dismutase, cytochrome c oxidase, dopamine-β hydroxylase, and monoamine oxidase. However, elevated concentrations in the brain are associated with neurodegenerative conditions ranging from inborn errors of copper metabolism (Wilson's disease) to more common nervous system degenerations, including Alzheimer's and Parkinson's diseases. Although mechanisms of copper neurotoxicity are not completely understood, roles for oxidative stress and mitochondrial dysfunction have been suggested. One effect of oxidative stress is induction of a mitochondrial permeability transition (mPT), which refers to increased permeability of mitochondrial membranes to molecules of less than 1,500 Daltons. This change in permeability is due to opening of pores in the inner mitochondrial membrane that results in dissipation of membrane potential, defective energy production, and ultimately cell death.

Reddy *et al* report the effects of elevated copper (20 μM $CuSO_4$ for 12–24 h) on primary cultures of astrocytes and neurons. In astrocytes, mPT was induced by copper with an observed dissipation of membrane potential and delayed death occurring within 48 h after treatment. This effect was blocked by cyclosporin A, a known inhibitor of mPT. In contrast, neurons were very sensitive to copper under these conditions, suffering early and severe injury/death that could not be blocked by cyclosporin A but could be blocked by antioxidants, suggesting little involvement of mPT. This study provides novel insights into the mechanisms of copper toxicity in brain cells and suggests a novel role for mPT in astrocytic injury.

Transcriptional regulation of liver regeneration

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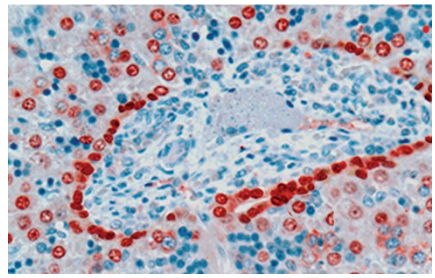
Expression of nuclear transcription factors plays a critical role in determining cellular differentiation pathways. Transcription factors impart specificity to gene expression and determine the developing cellular phenotype. In chronic disease conditions, aberrant expression of transcription factors can lead to promiscuous expression of cellular proteins, raising the possibility of cellular reprogramming and eventual transdifferentiation into different cell types. A key example is the phenotypic programming of the regenerating liver in chronic liver disease. In the setting of liver injury, mature adult hepatocytes can undergo division and generate new hepatocytes, just as mature bile duct epithelial cells (BECs) can generate their own progeny. However, proliferation of progenitor cells with expression of both hepatocyte and BEC markers with evidence of transdifferentiation from one cell type to the other has been well documented in rodent models of liver disease.



In this issue, Limaye *et al* examine in detail the expression of transcription factors in human livers, with the goal of providing a comparison standard to rodent-based experimental studies. Their analysis was first of human fetal and normal adult liver, and then of liver diseases characterized by phenotypic plasticity of hepatocytes and BEC. They demonstrate that hepatocyte-associated transcription factors appear in biliary cells prior to emergence of an "oval cell" population, which then function as progenitor cells for hepatocytes when the regenerative capacity of the latter is

compromised. These data from human livers are critically important for validating the extensive ongoing effort being put into experimental animal studies of liver regeneration and repair.

Growth inhibition of melanoma

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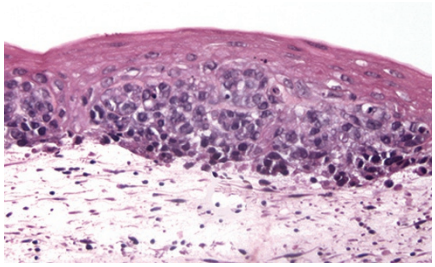

Bone morphogenetic proteins (BMPs) are members of the TGF-β superfamily. Like TFG-β, BMPs can have different roles in regulating the biology of normal and tumor cells and are able to either promote or inhibit tumorigenesis. Investigating the intracellular molecular effectors of BMPs, and the mechanism by which cells respond to them, will help to elucidate the role of BMP signaling in cancer suppression or progression. Identification of potential targets for therapeutic intervention might also be possible. In this report Hsu *et al* examine the role of BMP7 expression in malignant melanoma. Their experiments demonstrate that BMP7 inhibits the growth of primary melanomas but not the growth of metastatic lesions. Overexpression of BMP7 causes G0/G1 arrest and induction of apoptosis in primary melanomas. Moreover, their data show that the expression of the BMP antagonist Noggin allows melanoma cells to overcome the growth-inhibiting effect of BMP7.

These results provide new insights into the mechanisms of BMP7 resistance in metastatic melanoma through concomitant aberrant expression of Noggin. Such insights may lead to the development of new biomarkers for melanoma detection. Strategies for primary melanoma prevention and therapy might take advantage of the autocrine-inhibiting effects of BMP7.

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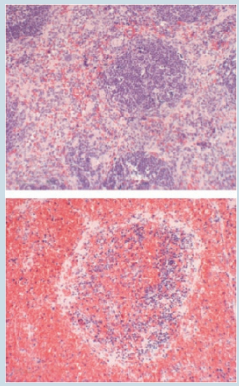
Indeterminate colitis? Maybe it's genetic Crohn's disease (CD) and ulcerative colitis (UC) are related diseases with a great deal of phenotypic overlap. This often makes it difficult to distinguish between these diseases clinically, and treatments are often similar. Thus, it is not surprising that there is also significant overlap in our mechanistic understanding of these diseases. The rate of disease concordance in monozygotic twins is far greater in CD than in UC, and this is one reason for the greater progress in identifying genetic determinants of CD. One consequence of the advances in molecular screening techniques is the ability to scan entire genomes of large numbers of patients. A recent paper in *Nature Genetics* presents a large-scale scan of 10,886 nonsynonymous and major histocompatibility complex tag single-nucleotide polymorphisms in 905 UC patients and 1,465 control subjects. Thirty-three markers were identified, and five of these, representing three distinct loci, were replicated in a second set of 936 UC patients and 1,470 controls. The strongest association was with the *ECM1* locus. Remarkably, unlike other identified UC-associated genes, *ECM1* was not associated with CD. The massive patient population available also allowed the authors to screen known CD loci. Interestingly, immune-related genes, such as *IL23R*, *IL12B*, *HLA*, *NKX2-3*, and *MST1*, were common to both diseases, whereas autophagy genes, such as *ATG16L1* and *IRGM*, as well as *NOD2/CARD15*, were unique to CD. Although they only begin to crack the surface, these observations may lead to new progress in understanding the shared pathogenesis of UC and CD as well as the mechanistic differences between these diseases.

Nature Genetics 2008; 40:710–712; doi:10.1038/ng.145

Interfering with neurological damage The extent of edema and generalized neurologic damage is a major determinant of the clinical course of glioma patients. While not completely understood, one factor thought to contribute to peritumoral cell death is the secretion of neurotoxic quantities of glutamate by glioma cells. A recent Brief Communication in *Nature Medicine* tested this hypothesis. After determining that the glutamate transporter xCT was responsible for glutamate secretion from gliomas, the authors inhibited xCT using siRNA or pharmacological agents. Although tumor growth was not affected, peritumoral neurodegeneration and edema were markedly reduced and survival enhanced by xCT inhibition. In addition to demonstrating the pathogenic role of glutamate, this relatively simple pharmacological approach may have benefits for current glioma patients.

Nature Medicine 2008; 14:629–632; doi:10.1038/nm1772



Right over here, sugar… Ashwell receptors (ARs) are asialoglycoprotein receptors of hepatocytes. They capture galactose- and N-acetylgalactosamine-bearing glycoproteins from the circulation and complicate development of glycoprotein pharmaceuticals, but their biological role has remained unknown. A new study in *Nature Medicine* shows that ARs clear von Willebrand factor (vWF) and platelets, thereby maintaining homeostasis. Bacterial neuraminidase desialylates platelets, allowing ARs to clear platelets and cause the thrombocytopenia associated with *Streptococcus pneumoniae* sepsis. Studies of genetically modified bacteria and mice demonstrated the importance of this adaptive reduction of prothrombotic factors. Severity of disseminated intravascular coagulation was increased and host survival decreased following infection of wild-type mice with neuraminidase-deficient *Streptococcus* or infection of AR knockout mice with wild-type *Streptococcus*.

Nature Medicine 2008; 14:648–655; doi:10.1038/nm1760