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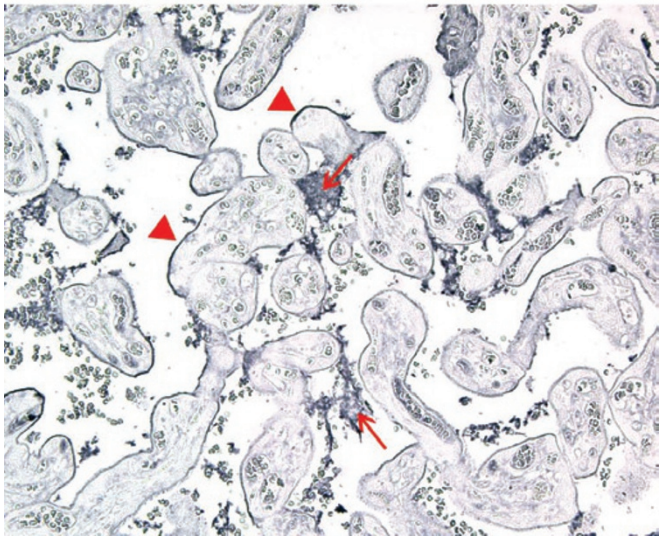

Hypoxia-induced ceruloplasmin in severe preeclampsia: friend or foe?

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Preeclampsia is the acute onset of hypertension, proteinuria, and edema during the second half of gestation. It occurs in 1% of all pregnancies but particularly affects nulliparous women (5% incidence). Patients with severe preeclampsia may develop seizures (eclampsia), with further risk to mother and child. Clinical management often walks a fine line between immediate delivery, which is curative for the mother, and allowing the pregnancy to continue in order to reduce perinatal morbidity and mortality by delivery of a more mature fetus. Although the underlying pathophysiology is unknown, placental ischemia and reperfusion injury are associated with severe preeclampsia and promote placental damage with the release of factors that lead to maternal endothelial dysfunction, a hallmark of the disorder. In this issue, Guller *et al* report increased expression of ceruloplasmin in placentas of patients with preeclampsia. Identifying syncytiotrophoblasts as the source of ceruloplasmin, the authors show that hypoxia results in a striking upregulation of the enzyme by cultured syncytiotrophoblasts. Better known for its ability to bind copper, ceruloplasmin has been shown to have ferroxidase activity and can convert potentially toxic ferrous ions into less damaging ferric ions. The authors suggest a mechanism whereby increased ceruloplasmin expression may be a host response to protect the placenta against the adverse effects of hypoxia and reperfusion injury in severe preeclampsia.

Molecular mimicry in dengue fever

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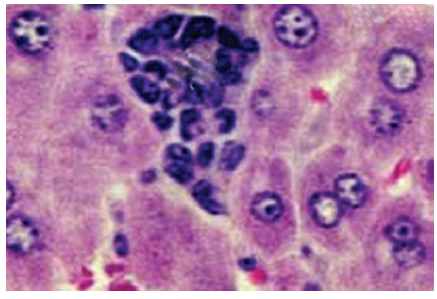
For more than a century, the unique susceptibility of the liver to destruction by pathogenic viruses has been known. Indeed, the demonstration of a viral agent as the cause of yellow fever was a major public health breakthrough at the dawn of the twentieth century. We are now in an era of "emerging pathogens," in which known infectious agents are found to have unexpected potency and previously unknown infectious agents are being discovered. Elucidating the pathogenesis of tissue injury for emerging pathogens has become even more important if effective public health and therapeutic measures are to be devised. In the case of dengue virus, infection of a human host can cause mild to severe dengue fever or a devastating "dengue shock syndrome," in which fulminant hepatic failure features prominently. Human dengue viral infection is now endemic in more than 100 countries, affecting at least 50 million individuals. There are several thousand cases of severe dengue hemorrhagic fever per year.

In this issue, Lin *et al* use a murine model to examine the liver injury caused by host antibodies against the dengue virus nonstructural protein 1 (DV NS1). They have previously demonstrated that such host antibodies cross-react with hepatic endothelial cells to cause their inflammatory activation and apoptosis. In this study, anti-DV NS1 antibodies were shown to bind to naive hepatic



endothelium in portal and central veins. Binding activity could be inhibited by pre-absorption of host antibodies with DV NS1. Conversely, immunization of mice with DV NS1 resulted in host antibody deposition on hepatic endothelium, followed by apoptotic cell death and onset of clinically measurable hepatic injury. This same effect could be produced by passive immunization of mice with purified IgG from human dengue patients.

Demonstration of this molecular mimicry effect *in vivo* helps further understanding of dengue virus infection and may eventually help in the public health effort to reduce the devastating effects of this disease.

Picture yourself at a scope with dysplasia, a girl with colitis goes by...

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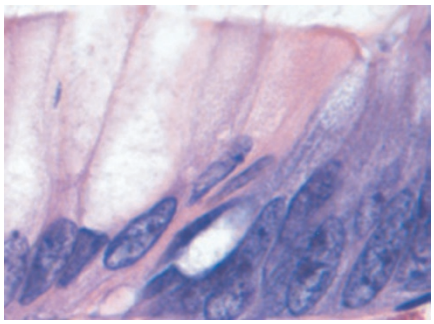

Intestinal barrier loss is commonly associated with inflammatory bowel disease (IBD) and may even be a risk factor for development of disease. The molecular structure that forms the barrier is the epithelial tight junction. Thus, it is not surprising that expression of tight junction proteins is abnormal in IBD. Given that the tight junction is also instrumental in determining cell polarity, Weber *et al* asked whether altered tight junction protein expression might be related to the increased risk of neoplasia in IBD patients. The authors show that expression of two tight junction proteins, claudin-1 and claudin-2, is increased in IBD. Claudin-1 and claudin-2 expression was also increased in IBD-associated and sporadic colonic dysplasia. The similarities between nondysplastic IBD, IBD-associated dysplasia, and sporadic dysplasia suggest that alterations in the protein composition of this polarity- and barrier function–determining protein complex may contribute to neoplastic transformation. Apologies to John, Paul, George, and Ringo...

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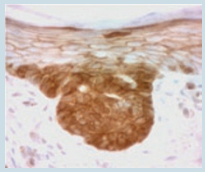
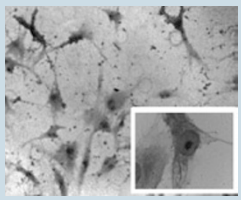
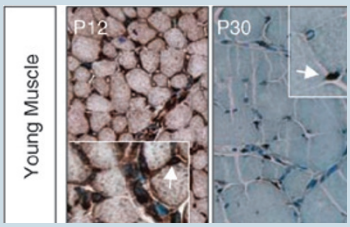


Basal cell carcinoma: a wild hair More than half a century ago, it was noted that early basal cell carcinomas (BCCs) resemble embryonic hair germs. Decades later, it was shown that that hair bud formation is regulated by canonical Wnt/β-catenin signaling, and that Hedgehog (Hh) signaling followed during maturation of the follicle. In BCC, mutations leading to the constitutive expression of Hh are common. Accordingly, Yang *et al* sought to determine whether Wnt signaling has a role in the pathology in BCC. The authors found that in mice *de novo* epithelial buds could be formed in response to ectopic Hh expression. Furthermore, conditional overexpression of an antagonist of the Wnt pathway in these mice inhibited epithelial bud development without affecting Hh signaling; thus, the animals' response to uncontrolled Hh expression was mediated through the Wnt pathway. Interestingly, in this model of BCC, the temporal relationship between Hh and Wnt is reversed compared with normal hair follicle development. This study is the first to define the biochemical basis of the similarity between early superficial BCCs and embryonic hair germs, and it indicates that blockade of Wnt signaling might be a treatment for Hh-dependent tumors.
Nature Genetics 2008;40:1130–1135; doi:10.1038/ng.192



Mesenchymal stem cells in tumor angiogenesis: accessories after the fact Mesenchymal stem cells (MSCs) migrate to areas of injury and contribute to tissue regeneration by differentiation into various cell types. Whether MSCs can evolve into endothelial cells remains controversial. Of interest to cancer biologists, MSCs migrate to tumors as well. Beckermann *et al* set out to determine the mechanism by which MSC recruitment promotes tumor angiogenesis in pancreatic carcinomas, which contain exceptionally poorly vascularized regions. The authors determined that, *in vitro*, MSCs migrated toward growth factors found in pancreatic tumors, and specific inhibitors of these factors interfered with migration. MSCs also migrated into spheroids consisting of pancreatic cancer cells, fibroblasts, and endothelial cells. Additionally, the MSCs themselves produced vascular endothelial growth factor (VEGF) in response to hypoxia. The MSCs did not, however, differentiate into endothelial cells *in vitro*. *In vivo* studies using an orthotopic mouse model of pancreatic carcinoma revealed MSC migration to and interaction with endothelium of blood vessels, and an increase in vessel density was observed after the arrival of MSCs. Differentiation of the MSCs to endothelium was not observed *in vivo*. Therefore, production of VEGF by MSCs is the main mechanism by which MSCs promote angiogenesis in this model.
British Journal of Cancer 2008;99:622–631; doi:10.1038/sj.bjc.6604508



Progress in the ARMS race Alveolar rhabdomyosarcoma (ARMS) is an aggressive pediatric malignancy of myogenic lineage, and the prognosis for metastatic disease is poor. ARMS is associated with chromosomal translocations that result in fusion of a *PAX* gene to the *FKHR* gene, creating an oncogenic chimeric transcription factor. Additionally, mutations in the tumor suppressors Cdkn2a or p53 are also frequently found. Gene expression analysis of patient biopsies revealed that increased levels of platelet-derived growth factor receptor A (PDGFR-A) correlate with decreased patient survival. In a new paper by Taniguchi *et al*, the authors employed a mouse model of ARMS in which *Pax3:Fkhr* is activated and Cdkn2a or p53 is inactivated, which caused the mice to develop tumors resembling advanced-stage human ARMS. By careful and thorough dissection of the PDGF-A signaling pathway *in vitro* and *in vivo*, they found that PDGFR-A and its downstream effectors were highly activated in primary and metastatic tumors. Inhibition of PDGF-A by imatinib, short interfering RNA treatment, and neutralizing antibodies each greatly decreased tumor cell growth *in vivo*. Unfortunately, imatinib resistance developed in about one-third of the tumors. Nevertheless, PGDFR-A may be a therapeutic target in ARMS.
Oncogene, advance online publication 4 August 2008; doi:10.1038/onc.2008.255