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Oral mucosal damage in murine graft-versus-host disease

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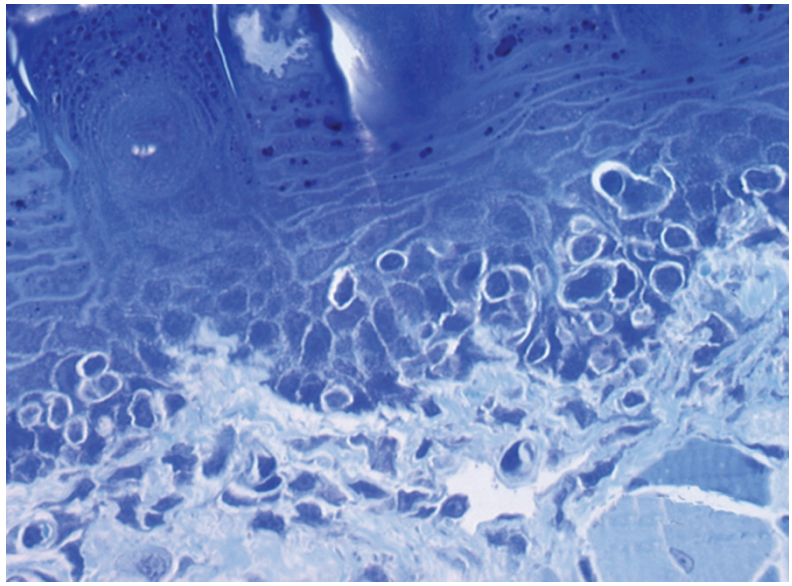

A major complication of allogeneic bone marrow transplantation is acute graft-versus-host disease (aGVHD), including development of oral mucosal lesions characterized by apoptosis induction in the basal keratinocytes. Mature T lymphocytes of donor origin play a key role in immune-cell infiltration into the mucosa. However, the pathogenesis is not altogether clear, owing to potential contribution from the conditioning regimens of radiation and/or chemotherapy. In this issue, Deschaumes *et al* use a murine model of aGVHD (which does not involve conditioning treatment) to demonstrate that the earliest detectable change in the oral mucosa is apoptosis of the endothelial cells from chorion capillaries. This precedes induction of basal keratinocyte apoptosis. Importantly, mice deficient in CD95 ligand (CD95L) exhibit neither vascular damage nor epithelial cell death upon allogeneic transplantation. Hence, an early and major event in the pathogenesis of oral mucosal damage of aGVHD is endothelial cell death, and requires CD95L expression by the allogeneic lymphocytes. Further mucosal damage would then result from hypoxia and vascular leakage of alloreactive immune cells or soluble pro-apoptotic mediators. Over and above implications for understanding the pathogenesis of aGVHD, it will be interesting to determine whether early endothelial cell death is involved in other oral conditions featuring basal and para-basal keratinocyte death.

Genomic analysis of adenoid cystic carcinoma: little lost but insight gained

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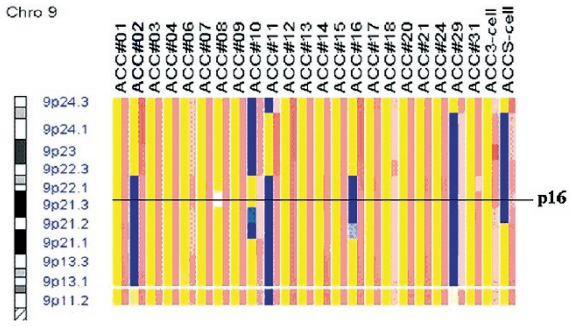
Adenoid cystic carcinoma (ACC) is a slow-growing but highly malignant salivary gland tumor that may also arise in extra-salivary locations. The neoplasm is well known for its characteristic cribriform growth pattern with pseudo-glandular structures, an almost pathognomonic tendency for perineural invasion, and high risk of local recurrence after surgery. Despite the rather well described pathology and biologic behavior of this entity, the molecular alterations relating to pathogenesis remain largely unknown. In a study described in this issue, Yu and colleagues performed genome-wide loss of heterozygosity analysis on 22 primary ACCs and two ACC cell lines using high-density oligonucleotide single-nucleotide polymorphism (SNP) genotyping arrays. Analysis of the data using the Haplotype Correction version of the Linkage Disequilibrium Hidden Markov Model (HC/LD-HMM) allows for accurate identification of chromosomal deletion in tumors without the need for paired normal samples. Copy number analysis of primary hybridization data was also performed, and the authors validated their SNP array findings using conventional microsatellite analysis. This carefully performed study shows that LOH and copy number alterations are relatively rare in ACC compared with other forms of neoplasia (such as squamous cell carcinoma). The authors conclude that gene mutations or epigenetic events other than major genetic loss or amplification underlie the pathogenesis of ACC.



Reactivating Hedgehog in response to bile duct ligation

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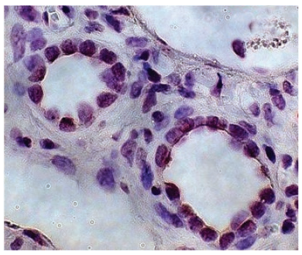
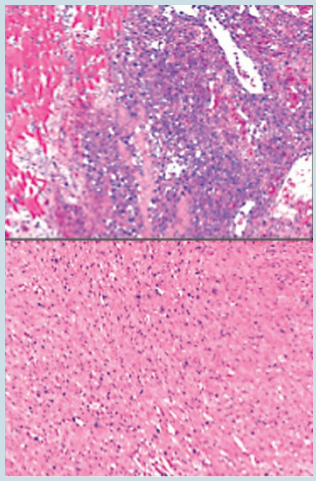


Bile duct obstruction leads to rapid proliferation of intrahepatic bile duct structures and to brisk deposition of fibrous tissue around intrahepatic bile ducts and ductules. In particular, periductular myofibroblasts become active and proliferate. The immediate proximity of the myofibroblasts and bile duct epithelial cells—cholangiocytes—suggests that mesenchymal-epithelial cross-talk promotes the fibroproliferative hepatic response to cholestatic liver injury. In this issue, Omenetti and co-workers document that bile duct obstruction in mice induces activity of the Hedgehog (Hh) pathway, a system that regulates the viability and differentiation of various progenitor cells during embryogenesis. Both proliferating cholangiocytes and myofibroblasts express Hh ligands, receptors, and/or target genes. Importantly, *in vitro* experiments demonstrate that each cell type is capable of enhancing the others' viability and proliferation via Hh activation. PtcLacZ mice have an impaired ability to constrain Hedgehog signaling because of a heterozygous deficiency of Patched. In these mice, the hepatic response to bile duct ligation exhibited more fibrogenesis and bile ductular proliferation, as well as more severe patchy necrosis of the parenchyma. These findings indicate that adult livers resurrect the Hedgehog developmental signaling systems in response to cholestatic injury, possibly as a guide for remodeling and restoration of the biliary epithelia and stroma.

nature.com/pathology

p53 restoration causes tumor suppression The activation of oncogenes and the inactivation of tumor suppressor genes are both necessary for tumorigenesis. Mutations in p53, a tumor suppressor gene, are a common feature of human cancers. Two recent letters in *Nature* reported that the reactivation of p53 leads to tumor regression *in vivo*. One research team reported that the tumor regression was caused by either apoptosis or cellular senescence, depending on tumor type. Another study found that p53 caused cellular senescence and triggered an innate immune response that targeted tumor cells. The activation of tumor suppressor genes may be the next development in anticancer drugs.

Nature 2007; 445: 656–660; doi:10.1038/nature05529
Nature 2007; 445: 661–665; doi:10.1038/nature05541



Virus alters immune response A recent letter in *Nature* reported that the virus from the 1918 influenza pandemic caused atypical immune responses in infected primates. This dysregulated antiviral response was insufficient for protection and may contribute to the virus' lethality. The interference in host immune responses by influenza viruses has also been demonstrated in the avian H5N1 influenza virus.

Nature 2007; 445: 319–323; doi:10.1038/nature05495

Liver regeneration and degeneration The liver's ability to regenerate mass after injury or partial removal has been recognized for millennia. But what limits the ultimate size of the liver and other organs? This question was recently addressed from a developmental perspective, as reported in *Nature*. When pancreatic progenitor cells were ablated, the final size of the pancreas was reduced. In contrast, ablation of hepatic progenitor cells had no impact on adult liver size. It remains to be seen whether this unique regenerative capacity of hepatic progenitors is related to nodule formation in cirrhosis. However, insight into a different process in cirrhosis was recently reported in *Nature Medicine*. In Wilson's disease, a genetic liver disease, regenerative nodules and cirrhosis follow hepatocellular Cu^{2+} accumulation and hepatocyte apoptosis. Researchers found that Cu^{2+} accumulation triggers hepatocyte apoptosis through activation of acid sphingomyelinase. Indeed, either genetic or pharmacological acid sphingomyelinase inhibition prevented Cu^{2+}-induced hepatocyte apoptosis and protected rats prone to develop Wilson's disease from liver failure and early death. Thus, rather than Cu^{2+} depletion, pharmacological inhibitors of acid sphingomyelinase hold promise as a treatment to prevent cirrhosis and anemia in Wilson's disease. (Photo courtesy of James M. Crawford.)

Nature 2007; 445: 886–891; doi: 10.1038/nature05537
Nature Medicine 2007; 13: 164–170; doi:10.1038/nm1539