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INSIDE LAB INVEST

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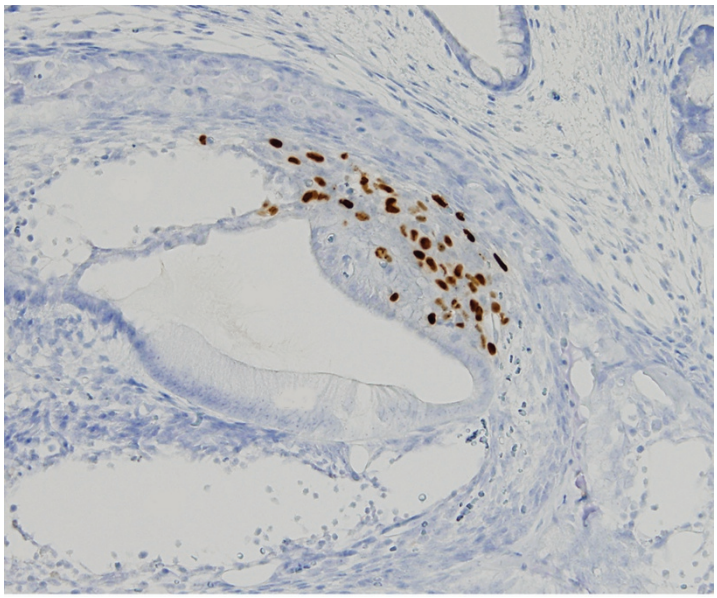


Say what? a model of CMV-associated hearing loss

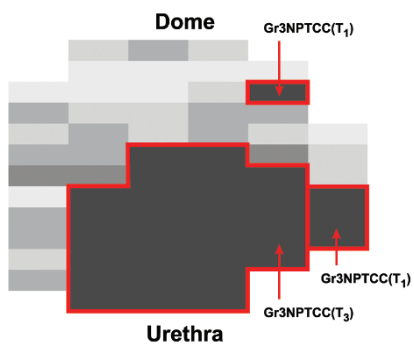
See page 723

Cytomegalovirus (CMV) is the most common intrauterine infection in the United States, and congenital CMV infection is believed to cause about one-third of all cases of sensory neural hearing loss in children. Very little is known about the mechanisms by which CMV damages hearing. In this issue, Li and colleagues present a new model of CMV-infectious labyrinthitis that is induced by lipopolysaccharide injection. Intraperitoneal injection of murine CMV into pregnant BALB/c mice resulted in very little brain infection and virtually no inner-ear involvement in the progeny. However, when intracranial injections of lipopolysaccharide were given to newborn mice that had been exposed to CMV *in utero*, they developed increased viral titers and inflammatory reactions in the brain and inner ears. CMV-infected cells were observed in the ependyma and subventricular zone in a pattern that was reminiscent of human CMV encephalitis. In addition, the authors present evidence that virus may spread to the inner ear along a pathway following the meninges, as well as hematogenously. This new model, which provides new insights into the pathobiology of a common cause of early sensory neural hearing loss, could lead to novel approaches to therapy. (I heard that!)

Forerunner genes in bladder cancer

See pages 686 and 694

Bladder cancer arises from the transitional cells of the mucosal urothelium. The solid, nonpapillary tumor form invades the bladder wall and has a high propensity for metastasis. A major paper by Majewski *et al* in this issue examines the genetic changes across the entire bladder mucosa in order to identify the earliest changes in the neoplastic sequence. An accompanying editorial perspective is provided by Crawford. Using whole-organ mapping of both morphology and genetic status, Majewski *et al* document genetic alterations in six chromosomal regions. These changes are found in histologically normal urothelial mucosa across broad expanses of the bladder. Target genes identified in these chromosomal regions are termed 'forerunner genes', based on the concept that these genes enable the initial clonal expansion of *in situ* urothelial dysplasia. The authors go on to characterize these genetic alterations in patient populations with bladder cancer, and they also examine familial clusters of cancers for evidence of mutations in forerunner genes. This research provides an important new opportunity for



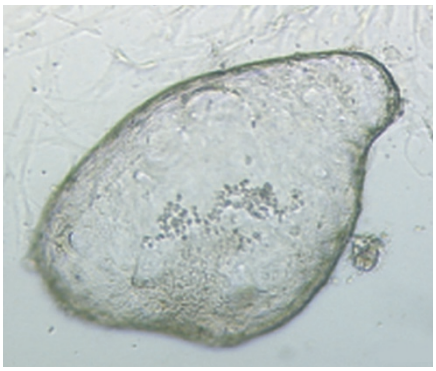
determining the origins of bladder cancer and for devising novel strategies for its detection and treatment.

Dedifferentiation of adult human islets

See page 762

Tantalizing recent evidence exists for *de novo* generation of insulin-producing cells in the adult pancreas. In keeping with pancreatic organogenesis, small clusters of β cells may potentially arise from duct-like intermediate structures; alternatively, it

has been suggested that pancreatic acinar tissue can be a direct source. However, there is controversy about the lineage relationships between adult human islet cells and cells of the exocrine pancreas. The uncertainty in these relationships makes interpretation of both *in vivo* and *in vitro* cell lineage experiments difficult.



On the basis of earlier work from this same group that demonstrated dedifferentiation of cultured adult human islets into proliferative precursor-type cells, Hanley *et al* have utilized adenoviral vectors to specifically label individual endocrine cell types. During culture of islets *in vitro*, cytokeratin expression indicative of an epithelial phenotype developed from α, δ, and pancreatic peptide cells, with minimal contribution from β cells. Conversely, β cells were the predominant cell acquiring nestin expression, more characteristic of a fibroblast-like phenotype. There was no transdifferentiation from one endocrine cell type to another. The findings were confirmed using targeted cell ablation studies. Collectively, these results raise the possibility that adult islet cells are not terminally differentiated but, rather, exhibit morphogenetic plasticity. Whether this phenomenon can be translated into regeneration of islet-cell capacity remains an open question.

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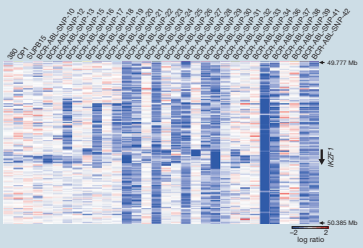
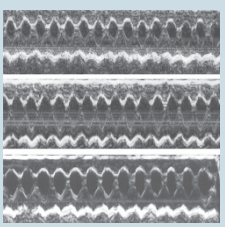
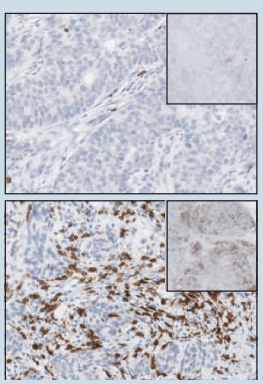


Ikaros deletion lets CML fly too close to the sun A genome-wide analysis of leukemia cases has identified deletions to the *IKZF1* gene encoding Ikaros that contribute to the transition of *BCR-ABL1*-associated chronic myelogenous leukemia (CML) lesions into acute lymphoblastic leukemia (ALL). Ikaros is a zinc-finger transcription factor essential for normal lymphoid development. More than 80% of Philadelphia chromosome–positive (*BCR-ABL1*-associated) ALL cases acquired *IKZF1* gene deletions that were not seen in CML. The data suggest that these recombination events may be mediated by the recombinase-activating gene *RAG*. These findings, which clarify the process by which CML can transform into ALL, may lead to both diagnostic and therapeutic opportunities.
Nature 2008;453:110–114; doi:10.1038/nature06866



Being insensitive is not always bad Blockade of β-adrenergic receptor (βAR) signaling is standard therapy in heart failure, because it prevents further damage as the sympathetic nervous system attempts to compensate for the failing heart. A multi-institutional group of investigators hypothesized that naturally occurring genetic variants of G protein–coupled receptor kinase (GRK) might desensitize βARs to sympathetic stimulation and therefore act somewhat like an endogenous β-blocker that modifies survival after cardiac events. Sequencing studies identified a polymorphism of GRK5 in which leucine is substituted for glutamine at position 41. This variant, which is common in African Americans, uncoupled isoproterenol-stimulated responses in transgenic mice. Moreover, transgenic mice carrying the GRK5-Leu41 variant were protected against catecholamine-induced cardiomyopathy. Perhaps most importantly, the presence of GRK5-Leu41 protected human subjects from death or the need for cardiac transplantation. The authors conclude that enhanced βAR desensitization by GRK5-Leu41 may provide a genetic βAR blockade that improves survival in African Americans with heart failure. This might explain conflicting results of clinical trials using pharmacological βAR-blockers in African Americans and also suggests that alternative therapeutic approaches will be more effective in individuals carrying the GRK5-Leu41 variant.
Nature Medicine 2008;14:510–517; doi:10.1038/nm1750



Molecular analysis of stromal reactions Pathologists are well aware of the importance of stromal response in assessing the biological properties of epithelial lesions. Desmoplasia is often the best indicator of invasion, and it is well recognized that the density of new tumor-associated vessels arising via angiogenesis is an important prognostic factor. A recently published study in *Nature Medicine* has taken this approach to a molecular level by evaluating gene expression within breast cancer tumor stroma. The authors developed a profile of 26 stromal genes whose expression correlates strongly with clinical outcome. As one might expect, mRNA-encoding proteins associated with angiogenic, hypoxic, and immune responses were all included within the prognostic stromal signature genes. A test application of this 26-stromal-gene array using published whole tumor–derived expression data sets was able to identify poor-outcome individuals from problematic clinical subtypes, including lymph node–negative tumors, and improve the accuracy of HER2-positive tumor evaluations. Thus, molecular diagnostics may be on its way to defining the stromal responses that skilled surgical pathologists have recognized for years.
Nature Medicine 2008;14:518–527; doi:10.1038/nm1764