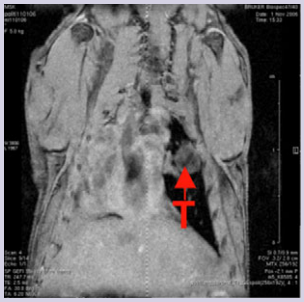
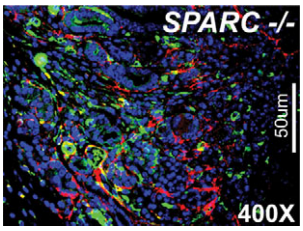


Drug-resistant lung cancers modeled in mice

The use of tyrosine kinase inhibitors (TKIs) to treat the 10-20% of lung adenocarcinomas with mutations in the *EGFR* gene is a recent success story in cancer medicine, but many tumors develop drug resistance after an initial response. Developing effective second-line therapy requires knowledge of the molecular basis of resistance, which is still unknown in many cases. Here, Katerina Politi and colleagues describe a mouse model of *EGFR*-induced lung tumors that, when treated with the TKI inhibitor erlotinib, become drug-resistant. This model will allow the mutations that cause resistance to be quickly identified and can also be used as a preclinical system to evaluate new therapeutic strategies. *This research report is freely accessible online.*
Page 111

SPARC and pancreatic cancer



SPARC, an extracellular protein involved in the deposition and modeling of the extracellular matrix, is dysregulated in many tumor types. Here, using a mouse model of pancreatic cancer, Arnold and colleagues show that loss of SPARC leads to an increase in the local spread and metastasis of tumors. These data position SPARC as a key component of the metastatic niche.
Page 57

Li-Fraumeni zebrafish mutants

Li-Fraumeni syndrome (LFS) is a hereditary disease that is often associated with germline mutation of the tumor suppressor gene *p53* and cancer. Parant and co-workers use a genetic screen in zebrafish to identify p53 mutant fish displaying a spectrum of tumors that closely mimics LFS. This approach may reveal new LFS genes, allow for whole-animal studies on the p53 pathway, and provide a rapid method for drug screening.
Page 45

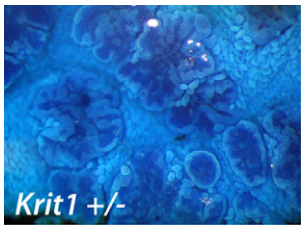
Notch and esophageal cancer

Barrett's esophagus, the first step in progression to esophageal adenocarcinoma, arises when chronic acid reflux causes the normal lining of the gullet to be replaced by aberrant epithelium resembling that of the lower gut. Menke et al. show that the Notch signaling pathway, normally silent in the esophageal lining, is highly activated in Barrett's biopsies and, when inhibited in a rat model, can halt proliferation of abnormal cells. These data suggest that anti-Notch therapeutics may have a role in the treatment of Barrett's.
Page 104

A fly model for Menkes disease

Menkes disease is an X-linked recessive defect in which the essential trace element copper cannot be properly metabolized by the gut, leading to brain damage and early death. Bahadorani and colleagues show that inhibiting the Drosophila version of the copper exporter gene that is mutated in Menkes patients causes a phenotype with similarities to the human disorder, with severe effects on brain development. This model provides a simple, fast and cheap way of identifying novel modifiers of the disease, and hence new treatment options.
Page 84

A KRITical gene in CCM



Cerebral cavernous malformations (CCM) are a leading cause of childhood stroke, and familial cases are linked to mutations in genes regulating blood vessel development and integrity. Glading and Ginsberg show that one of these genes, *KRIT1*, controls the subcellular distribution of the multifunctional protein β-catenin. Loss of KRIT1 drives β-catenin into the nucleus, activating multiple vasculogenic genes. In a further twist, reducing KRIT1 expression in mice that are prone to colon cancer increases adenoma formation, suggesting a wider role for CCM proteins in cancer.
Page 73

Kidney transplants: innate immunity matters

Chronic allograft dysfunction (CAD) is a major problem in kidney transplant rejection. Using a mouse renal transplant model, Wang and co-workers show that inhibiting the innate immune system of the acceptor mouse, by knocking out the Toll-like receptor pathway, results in significantly healthier grafts. This research highlights the innate immune system as a possible focus for anti-CAD therapies.
Page 92

Written by K.W.