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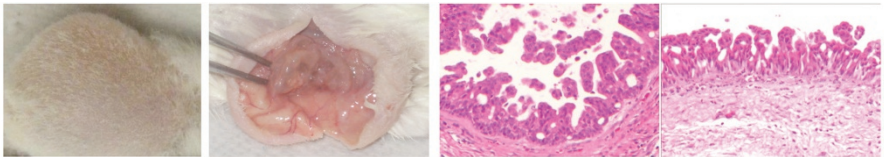

New models of pancreatic intraductal papillary neoplasms

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Pancreatic ductal carcinoma (PDAC) is an aggressive cancer, with approximately 37,000 new cases and 34,000 deaths in 2008 and a worldwide 5-year survival estimated at only 4%. There is therefore a great need to understand the pathogenesis of this disease. Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing pancreatic epithelial neoplasms that definitionally involve the main and/or branch pancreatic ducts and often have a papillary architecture. IPMNs are one of three precursor lesions known to give rise to PDAC. Whereas much has been learned about one of the other PDAC precursors—pancreatic intraepithelial neoplasia, which is characterized by the progressive accumulation of mutations in *KRAS2*, *TP53*, *p16/cdkn2a*, and *DPC4* genes—a similar neoplastic sequence has not been identified in IPMNs.

To develop cell-based model systems to fully explore the pathogenesis of IPMNs and their progression to PDAC, Kamiyama and colleagues asked whether IPMNs might grow in different types of murine xenograft models. They showed that IPMNs that were implanted grew as tumors in a variety of immunocompromised mice, including athymic (nude), severe combined immunodeficient, and NOD/SCID/IL2Rγ^{null} (NOG) mice. Two cell lines were obtained from cyst fluid and a solid area of one of the xenografts. One of the tumors was successfully re-implanted serially in NOG mice and maintained pathological features that were virtually identical to those of the original tumor. This study demonstrates that these lesions can grow and propagate in immunocompromised mice and that cell lines can be established from xenografts. These newly developed resources will undoubtedly accelerate research in this important area.

VEGFR2 depletion leads to unexpectedly aggressive phenotype in ovarian carcinoma

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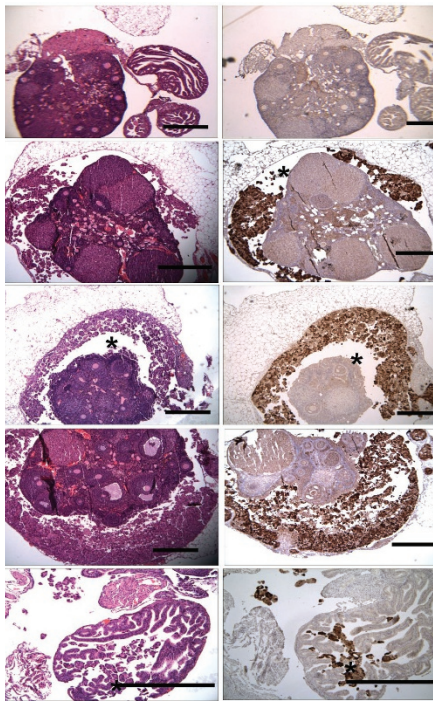
Epithelial ovarian carcinoma (EOC) accounts for more than 90% of all ovarian tumors and has a dismal prognosis because most patients are diagnosed at an advanced stage and have tumors that are refractory to available therapies. Inhibition of angiogenesis through vascular endothelial growth factor (VEGF) blockade by bevacizumab (Avastin) has demonstrated activity in phase II clinical trials and in mouse models of EOC. Recently, short-term pharmacologic inhibition of VEGF receptor-2 (VEGFR2) signaling was shown to reduce EOC cell survival *in vitro*.



To understand the long-term effects of VEGFR2 inhibition on EOC, Adham and colleagues performed short hairpin RNA–mediated stable knockdown of kinase domain protein receptor (*KDR*), which encodes VEGFR2. Unexpectedly, they discovered that stable depletion of VEGFR2 in EOC cell lines led to more successful growth instead of impairing growth as was anticipated. Furthermore, they showed that downregulation of VEGFR let to upregulation of neuropilin-1 (NRP-1). NRP-1 is a co-receptor for VEGFR2 that is known to enhance angiogenic signaling, and high levels of NRP-1 had previously been shown to correlate with increasing aggressiveness in EOC. They further examined the relationship between NRP-1 and VEGFR2 in a large cohort of EOCs and found that the NRP-1:VEGFR2 ratio correlated well with tumor grade; high-grade tumors had a significantly higher NRP-1:VEGFR2 ratio than lower-grade tumors. The unexpected finding that VEGFR2 depletion leads to upregulation of NRP-1 and an aggressive clinical phenotype warrants further preclinical evaluation of VEGFR2 inhibition as a therapeutic strategy in EOC.

Differences in mouse strains' susceptibility to experimentally induced acute pancreatitis

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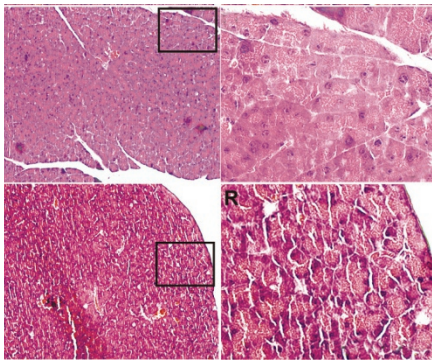
Acute pancreatitis is an important and often life-threatening disease that can be triggered by a variety of factors, including excessive alcohol consumption,

obstruction of the ampulla of Vater by gallstones, and genetic factors. Two genes that have been linked to acute pancreatitis are protease, serine, 1 (*PRSS1*), which encodes trypsinogen and serine protease inhibitor, Kazal type 1 (*SPINK1*). Mutation in *PRSS1* leads to an amino acid substitution in the autolytic domain of trypsin, which blocks autolysis and leads to constitutive trypsin activity. *SPINK1* is also involved in trypsin inhibition. Thus uncontrolled activation of trypsin appears to be a key mediator of pancreatitis.

It has long been appreciated that different strains of mice are more susceptible to certain diseases. These susceptibility loci have been the basis of genetic mapping experiments that have identified several disease-related genes with direct relevance to human disease. To identify factors associated with



susceptibility to acute pancreatitis, Wang *et al* evaluated five mouse strains for their sensitivity to two established models of acute pancreatitis. They found that the strains varied in their susceptibility to acute pancreatitis, and that the susceptibility correlated with increased trypsin activity. Nucleotide variation was found in the promoter regions of both *Prss1* and *Spink1*, leading to the hypothesis that promoter differences might lead to differences in expression related to the various susceptibility phenotypes. Further work will be required to test this hypothesis.

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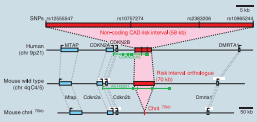
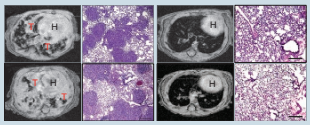
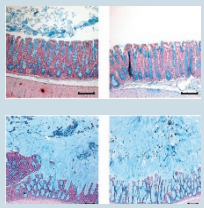


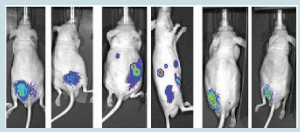
Noncoding coronary artery disease risk interval on 9p21 is involved in control of *Cdkn2a* and *Cdkn2b* expression Genome-wide association studies have identified sequence variants in a 58-kilobase region that confers an increased risk in coronary artery disease (CAD). Interestingly, the sequence variants are not associated with classic CAD risk factors such as plasma lipoprotein levels. To understand the association between this region and increased risk of CAD, as described in a recent letter in *Nature*, Visel and colleagues deleted the orthologous region in mice, which resulted in reduced expression of *Cdkn2A* and *Cdkn2b* in heart tissue. Analysis of aortic smooth muscle cells revealed that they had increased proliferation and decreased senescence, two phenotypes that correlate with CAD. Disruption of *CDKN2A* and *CDKN2B* regulatory sequences provides a plausible model for the increased risk of CAD associated with sequence variants on 9p21.
Nature, published online 21 February 2010; doi:10.1038/nature08801



Chromosome instability mediates lung tumor relapse after oncogene withdrawal Oncogene addiction, in which a tumor is dependent on a single oncogene for tumor cell proliferation, has been documented in a variety of solid tumors. Targeting these oncogenes has been shown to be highly effective, but such therapies are rarely curative. In a recent letter in *Nature*, Sotillo and colleagues asked whether chromosomal instability (CIN) might contribute to tumor recurrence in oncogene-addicted cancers. Using genetically engineered mice harboring a lung-specific tetracycline-inducible form of oncogenic Kras in combination with a tetracycline-inducible Mad2-overexpression allele known to induce CIN, they showed that Kras-driven tumors that had been generated with or without CIN were still dependent on Kras because turning off Kras and Mad2 led to tumor regression. However, recurrences arose only in the setting of Mad2-overexpressing tumors, indicating that CIN can lead to Kras/oncogene independence. These results have significant relevance to targeted cancer therapies.
Nature, published online 21 February 2010; doi:10.1038/nature08803



Identification of a defect in PPAR-γ signaling in a mouse model of cystic fibrosis Cystic fibrosis (CF) is characterized by mutations in the cystic fibrosis transmembrane regulator (*Cftr*), a chloride channel that supports bicarbonate transport. CF patients have thickened mucus, which plugs airways and obstructs luminal organs. To characterize the defect in a mouse CF model, Harmon and colleagues, reporting in a recent letter in *Nature Medicine*, performed transcriptome analysis and found that genes involved in lipid metabolism, including peroxisome proliferator–activated receptor-γ (PPAR-γ), were decreased. Treatment of *Cftr*-deficient mice with rosiglitazone, a synthetic PPAR-γ ligand, reduced mucus retention and decreased disease severity. This study suggests that modulation of PPAR-γ signaling can be used to decrease the severity of CF.
Nature Medicine 2010;16:313–318; doi:10.1038/nm.2101



Identification of a prostate cancer tumor suppressor that directs metastasis Currently, there is no cure for metastatic prostate cancer. It is therefore imperative to identify determinants of metastasis. In a recent article in *Nature Medicine*, Min and colleagues describe the identification of *DAB2IP*, a Ras GTPase–activating protein (RasGAP) that, when inactivated, is able to induce metastasis. When *DAB2IP*-depleted primary human prostate epithelial cells were injected orthotopically into mouse prostates, the lesions invaded and metastasized in all cases. Inhibition of *DAB2IP* activates both Ras and nuclear factor-κB (NF-κB) in a parallel pathway. Interestingly, NF-κB appears to underlie the metastatic phenotype induced by *DAB2IP* inactivation. Inactivation of *DAB2IP* appears to occur through epigenetic silencing mediated by EZH2, a histone methyltransferase that has been associated with aggressive prostate cancer. This study suggests that EZH2 inhibitors may be useful in treating aggressive prostate cancer.
Nature Medicine 2010;16:286–294; doi:10.1038/nm.2100