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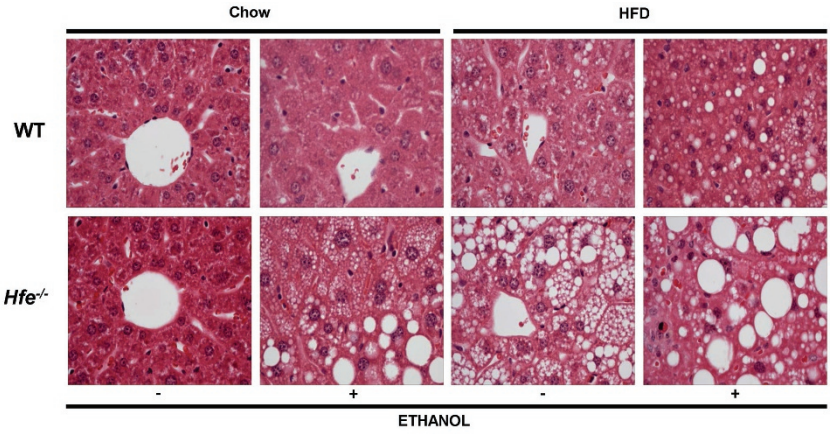

Osteopontin is profibrogenic and prolongs hepatic fibrosis

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Both iron and endoplasmic reticulum (ER) pathways play an important role in the progression and pathogenesis of alcoholic (ALD) and nonalcoholic fatty liver disease (NAFLD). Often, ALD and predisposing factors for NAFLD, such as hypertension, obesity, and the metabolic syndrome, coexist in a patient. Tan *et al* sought to determine whether there is a relationship between iron overload and ER stress. They fed transgenic mice with hemochromatosis a diet high in fat and ethanol to recapitulate the coexistence of ALD and NAFLD in humans. After 8 weeks, they observed profound steatohepatitis, fibrosis, and apoptosis in the hemochromatosis mice but not in wild-type controls. The findings indicate that iron loading may exacerbate the damage caused by dietary fats and ethanol. From a more mechanistic standpoint, they found that iron overload was associated with increased ER stress and activation of the unfolded protein response. Autophagy was muted.

It would thus seem that iron overload inhibits the ability to process a diet high in fat and ethanol, leading to an increase in hepatic injury. The authors also report increased expression of Toll-like receptors, which perhaps activates additional inflammatory hepatic injury. Further study of this model is likely to provide additional insights into human disease.

COX-2 activity contributes to gut barrier failure

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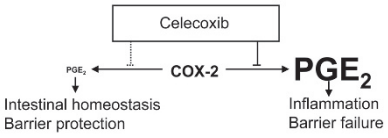

Maintenance of a physical barrier by the gut is a critical function that prevents seepage of intestinal contents, which often results in peritonitis and attendant morbidity. This can be a particular challenge in critically ill patients managed in acute-care settings, where sepsis is not uncommon. Indeed, sepsis associated with gut barrier failure can complicate a number of conditions and is recognized as part of multiple-organ dysfunction syndrome. An important cause of gut barrier failure in many settings is bowel inflammation. Short *et al* used two mouse models of peritonitis: one involving intraperitoneal injection of lipopolysaccharide, the other involving cecal ligation with puncture. They observed increased levels of both the inflammatory mediator prostaglandin E_2 (PGE_2) and the enzyme that produces it, cyclooxygenase-2 (COX-2), in ileal mucosa. Increased levels of COX-2 and PGE_2 were associated with sloughing of the intestinal epithelium and increased permeability across the gut barrier as assessed by an FITC-dextran diffusion assay. A partial, at least, explanation for this increased permeability could be internalization of the JAM-A and ZO-1 tight junction proteins.

To determine whether PGE_2 can induce such changes, it was luminally inoculated into physically isolated bowel segments; the result was an increase in bowel barrier permeability. The delivery of a low dose of a COX-2 inhibitor reduced permeability, but higher doses were associated with an increase in permeability independent of induced injury. Hence, mediation of the immune system by PGE_2 appears to be necessary for bowel barrier function at homeostasis, but overactivation may be counterproductive in some pathogenic situations. These results suggest that low-dose COX-2 inhibitors may have clinical efficacy in some settings.

Stem cell–like differentiation markers in HNSCC

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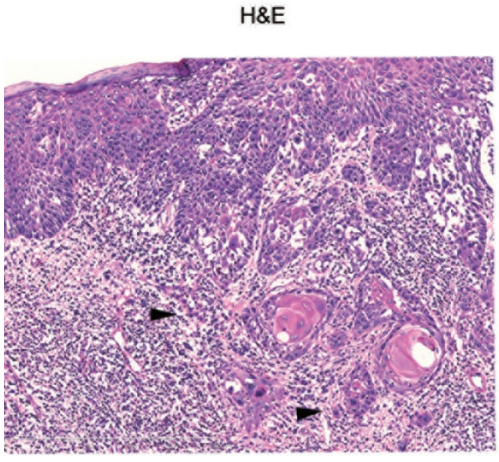
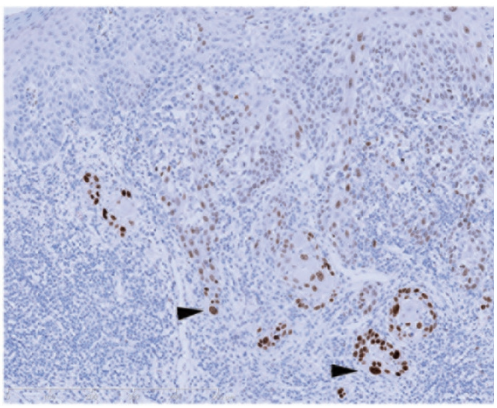
Head and neck squamous cell carcinoma (HNSCC) is associated with several etiologies, including viral infection, alcohol and tobacco use, and chronic inflammation. Significant mortality results from locoregional recurrence. Given the morphologic heterogeneity of HNSCC, Yamazaki *et al*



hypothesized that the cancer may have stem cell–like properties that further differentiate to create morphologic heterogeneity. Twelve HNSCC samples were analyzed on gene expression arrays for increased "stemness" factors relative to their cognate normal tissues. Ultimately four genes were identified as having significantly higher expression, and the authors focused on further characterization of two messenger RNAs (mRNAs): HMGA2 and Bmi-1. Both are chromatin regulators that promote stem cell self-renewal and have been shown to act as oncogenes in a variety of tumors.

HMGA2 mRNA levels were higher in human HNSCC tumors than in their corresponding normal controls in almost every paired case, and also when comparing groups of tumor versus normal, whereas Bmi-1 levels were not. With respect to protein expression, in an independent and larger group of HNSCC tumors, HMGA2 appeared to correlate with invasion, poorer histologic differentiation, and decreased overall survival. HMGA2 expression seemed particularly prominent in cells at the leading edge of invasion. Bmi-1 protein expression was more common in early-stage and well-differentiated HNSCC. In addition to suggesting stem cell–like properties in HNSCC, these markers were differentially expressed in tumor versus normal, suggesting their potential for both pathologic and diagnostic insights, with the latter perhaps most relevant for small samples.

HMGA2



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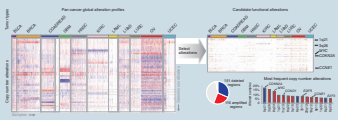
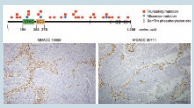


A meta-analysis of many cancer types shows common themes Drawing from a large database of 3,299 tumors representing 12 cancer types from the Cancer Genome Atlas project, researchers corralled many thousands of genetic and epigenetic events into approximately 500 groups termed selected functional events. This and other analyses were recently presented in *Nature Genetics* with commentaries and companion articles. The broad classes were dominated by either copy-number changes or somatic mutations. The most commonly copy-altered region included *CDKN2A*. The most commonly mutated gene was *TP53*, with *PIK3CA* and *PTEN* immediately following, showing the importance of the PI3K pathway in cancer. In fact, 4 of the 10 genes most commonly mutated in cancer (including *KRAS* and *NF1*) can, arguably, activate the PI3K pathway. The meta-analysis, which heralds the comprehensive cataloging of alterations in human cancer, identifies genetic groups of tumors that may be amenable to targeted treatments independent of histologic type.

Nature Genetics 2013;45:1127–1133; doi:10.1038/ng.2762



STAG2 may be an important tumor suppressor in bladder cancer In a recent article in *Nature Genetics*, Solomon *et al* demonstrated truncating mutations in *STAG2* in a significant subset of both noninvasive papillary urothelial carcinomas (36%) and invasive urothelial carcinomas (16%) of the bladder. These mutations would inactivate this cohesion complex gene and in other cancers are associated with defects in chromosomal segregation that result in aneuploidy. Consistent with this, the great majority of *STAG2*-mutated tumors in the study were aneuploid. Reintroduction of STAG2 into deficient cells did not reduce proliferation or chromosomal complexity. Immunohistochemistry demonstrated that loss of STAG2 expression in tumor nuclei was associated with lymph node metastases in a large series of surgically treated invasive urothelial carcinomas. Additional studies will further explore the connection of STAG2 status to clinical outcomes and other molecular determinants.

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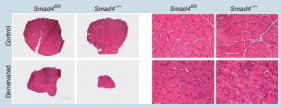
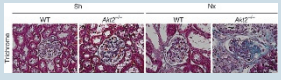


The BMP pathway promotes muscle hypertrophy at the cellular level Several factors influence cellular growth. The equilibrium between protein synthesis and degradation determines cell size and is governed by, among others, hormonal, nutritional, mechanical, and energy factors. It has been shown that inactivating mutations in myostatin lead to uncontrolled muscle growth, but the pathways mediating this effect are poorly understood. Work recently presented in *Nature Genetics* demonstrates that the bone morphogenetic protein (BMP) pathway mediates muscle-cell hypertrophy through particular Smad proteins. Additional and novel downstream regulators were also identified. Using a myostatin-deficient mouse model, the authors found that interruption of BMP signaling abrogates the muscle hypertrophy associated with the model. Lack of BMP signaling also exacerbates the atrophy and weakness seen with denervation and starvation. How this pathway regulates hypertrophy gains in resistance training will be of interest to many.

Nature Genetics 2013;45:1309–1318; doi:10.1038/ng.2772



Maintenance of residual podocytes is critical for renal function in chronic kidney disease In chronic kidney disease, nephron dropout stresses residual nephrons. In a recent *Nature Medicine* article, Canaude *et al* report that AKT2 is required to sustain podocytes. Transgenic mice deficient in AKT2 are more susceptible to renal damage; this was not the case for mice deficient in AKT1. Deletion of AKT2 demonstrated that Mdm2, GSK3, and Rac1 are regulated by AKT2 and promote survival of podocytes, probably through decreased apoptosis. Albuminuria is induced by sirolimus treatment in kidney-transplant patients with poor renal function. Although sirolimus is primarily an mTORC1 inhibitor, longer-term treatment results in mTORC2 inhibition. This untoward effect of sirolimus in the kidney appears to result from the longer-term mTORC2 inhibition that prevents the feedback activation of AKT2 and exposes podocytes to nephric damage.

Nature Medicine 2013;19:1288–1296; doi:10.1038/nm.3313