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New gastric carcinoma mouse model

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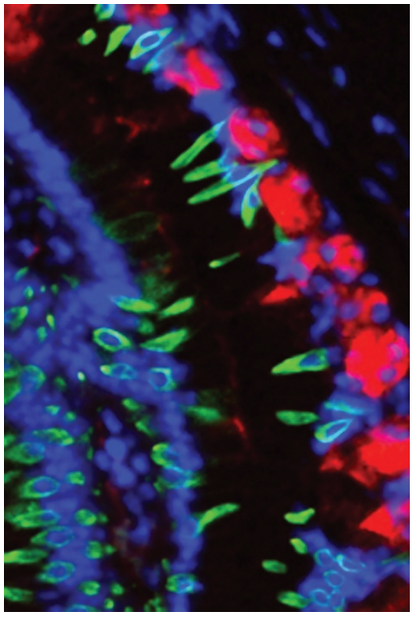

Gastric carcinoma is the fourth most commonly diagnosed cancer worldwide but the second most common cause of cancer mortality. In the Western world, gastric adenocarcinomas of the proximal stomach are on the rise. Animal models of gastric carcinoma of the proximal stomach are therefore needed to elucidate its pathogenesis. Smads—downstream effectors of the transforming growth factor–β signaling pathway—have been directly implicated in a variety of cancers. A recent report showed that Smad3 is suppressed in human gastric carcinomas and gastric carcinoma cell lines, most likely owing to aberrant expression of Smad3 inhibitors. On the basis of these results, Nam *et al* asked whether *Smad3* knockout mice develop gastric carcinoma.

The authors utilized a germline *Smad3* knockout mouse to carefully study morphologic changes that developed over time. At 6 months after birth, homozygous $Smad^{-/-}$ mice developed metaplastic columnar glands at the junction of the squamous mucosa of the forestomach and the glandular epithelium of the lesser curvature. These changes were not observed at the junction of the forestomach and the greater curvature. Furthermore, no histological changes were observed in heterozygous $Smad3^{+/-}$ heterozygotes or age-matched wild-type littermate controls. At 10 months, metaplastic lesions in $Smad^{-/-}$ mice progressed to high-grade dysplasia. Interestingly, there was also an association between the areas of metaplasia and gastritis cystica profunda, which the authors interpreted as invading glands, although the relationship to gastric carcinoma was unclear. In summary, the authors have developed a novel *Smad* knockout mouse model in which to study the pathogenesis of adenocarcinoma of the proximal stomach.

Determinants of tooth decay in type 1 diabetic mice

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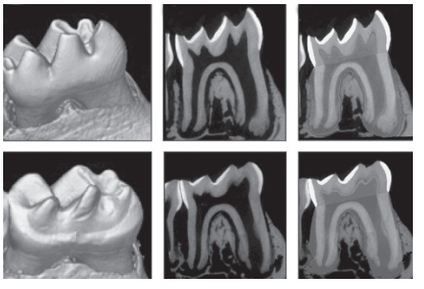
Together, types 1 and 2 diabetes affect more than 20 million people in the United States. Many of the complications of diabetes, such as cardiovascular complications, are well publicized, but less is known concerning the disorder's effects on oral health. An excellent model of type 1 diabetes is the $Akita^{-/-}$ mouse, which harbors a mutation of *Ins2* that results in insulin deficiency at birth. These mice exhibit reduced growth rate and body fat, polyuria, polydipsia, retinopathy, neurological defects, and, if untreated, death within 4 months due to extreme hyperglycemia. Yeh *et al* took advantage of the $Akita^{-/-}$ mouse model of type 1 diabetes to examine the effects of uncontrolled hyperglycemia on oral health.



The investigators demonstrated that, although teeth develop normally in these mice, they exhibit significant oral pathology after birth. Beginning at 4 weeks after birth, the mice began to show increased wearing of enamel characterized by a modest reduction of enamel and dentin. Hypomineralization and enamel attrition were accompanied by microabscesses that progressed to significant tooth destruction and bone loss around the roots of affected teeth. Mechanistically, $Akita^{-/-}$ mice were found to have impaired saliva production, probably due to a neurologic defect. Cell culture experiments using pulp cells showed that high glucose inhibited both proliferation and differentiation. These results have practical implications for diabetic patients; they suggest that early detection and treatment of hyperglycemia and hyposalivation may provide a strategy for maintaining excellent oral health in diabetics.

Notch signaling and CDx2 expression in Barrett's esophagus

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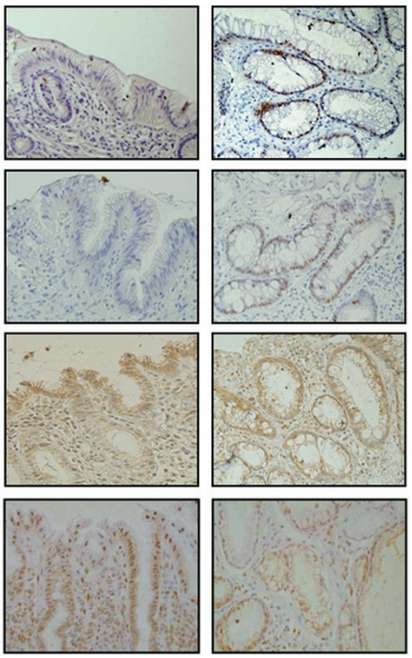
Barrett's esophagus, which is characterized by a metaplastic transformation of the squamous mucosa of the distal esophagus into intestinal-type columnar epithelium with goblet cells, is caused by chronic gastroesophageal reflux. The condition is a risk factor for the development of gastroesophageal adenocarcinoma—approximately 0.5% of patients progress to adenocarcinoma each year. Because of this risk, and the fact that the incidence of Barrett's esophagus has increased steadily over the past two decades, it is important to understand its pathogenesis. Upregulation of Cdx2, an intestine-specific transcription factor, is known to play a role in intestinal differentiation in Barrett's esophagus. Recently, a relationship



between Notch signaling and Cdx2 expression has been demonstrated. On the basis of these results, Tamagawa *et al* wondered whether Notch signaling and Cdx2 expression were related in the pathogenesis of Barrett's esophagus.

The authors demonstrated that ATOH1, which is associated with Notch signaling and is also known to be a transcriptional activator of the intestine-specific gene *MUC2,* was upregulated in Barrett's esophagus. Experiments in Barrett's adenocarcinoma cell lines revealed that inhibition of Notch signaling by a gamma secretase inhibitor resulted in increased Cdx2 and MUC2 expression. Mechanistic studies revealed that bile acids induced ATOH1 and Cdx2 expression *in vitro* in a concentration- and time-dependent manner, thus tying exposure to bile acids to expression of factors that are directly related to the development of the histological changes associated with Barrett's epithelium. Further studies will be required to determine how these factors relate to the eventual development of adenocarcinoma in a minority of patients with Barrett's esophagus.

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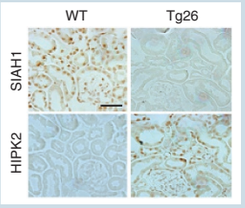

***HIPK2* is a key regulator of kidney fibrosis** As described in a recent article in *Nature Medicine*, Jin *et al*, using a systems approach, have identified *HIPK2* as an important mediator of fibrosis. They used a mouse model of HIV-associated nephropathy (HIVAN), which is characterized by renal fibrosis, and measured renal gene expression to define a fibrosis gene signature. Powerful bioinformatics programs enabled them to work their way backward to identify a network of transcription factors, which they linked to upstream regulatory mechanisms and eventually to a small group of kinases that were the proximal events deregulated by HIV infection. This analysis led them to HIPK2, a serine/threonine nuclear kinase that regulates gene expression by phosphorylating transcription factors. In addition to HIVAN, they found that *HIPK2* was deregulated in a variety of renal diseases characterized by fibrosis. Given that kinases are targetable by small-molecule tyrosine kinase inhibitors, the authors suggest that HIPK2 is a potential target for antifibrosis therapy.

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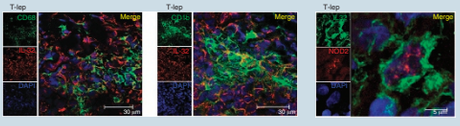
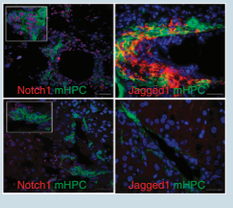


NOD2 has a central role in host defense against leprosy Leprosy is caused by the intracellular pathogen *Mycobacterium leprae*. There is a spectrum of the disease that correlates with the immune response. At one end of the spectrum, tuberculoid leprosy (T-lep), infection is limited; at the other end, lepromatous leprosy (L-lep), infection is disseminated. As recently reported in *Nature Medicine,* Schenk *et al* tested the hypothesis that specific pattern-recognition receptors (PRRs) induce distinct innate immune responses in response to *M. leprae* infection, which result in either T-lep or L-lep. They demonstrated that activation of monocytes via NOD2, a cytoplasmic PRR belonging to the NOD-like receptor family, triggered dendritic cell differentiation, which correlated with a more limited *M. leprae* infection. Mechanistically, NOD2 induced interleukin-32 (IL-32) production. The authors demonstrated that monocytes from patients with L-lep did not respond to NOD2 by producing IL-32 or differentiating into dendritic cells, suggesting that therapy with recombinant IL-32 may help limit disease manifestations in patients with L-lep.

Nature Medicine 2012;18:555–563; doi:10.1038/nm.2650



Determinants of hepatic progenitor cell fate during regeneration Chronic liver damage causes the liver to regenerate damaged hepatic tissue. Eventually, regeneration may fail to keep up with ongoing chronic liver damage, resulting in end-stage liver disease (ESLD). The only cure for ESLD is liver transplantation. However, as has been well publicized, the number of livers available for transplantation is severely limited, and many potential transplant recipients die while waiting for donor livers to become available. Because failure of the liver to regenerate properly is at the core of ESLD, it is necessary to understand the mechanisms that control liver regeneration in chronic liver disease and to identify pathways that can be manipulated therapeutically. In a study recently published in *Nature Medicine,* Boulter *et al* sought to understand the mechanisms that govern whether hepatic progenitor cells (HPCs) differentiate into bile duct epithelium or hepatocytes. They found that activation of Notch signaling was required for biliary epithelium regeneration from HPCs and for adult biliary repair in chronic liver injury. In addition, they demonstrated that canonical Wnt-dependent action for the ubiquitin ligase Numb was required for HPCs to adopt a hepatocyte fate. They showed that Wnt pathway activation could occur by production of Wnt3a by macrophages after they ingested hepatocyte debris. Thus, the inflammatory microenvironment was found to influence differentiation of HPCs into hepatocytes. Because bile duct proliferations are seen in abnormal liver regeneration in chronic liver disease, these results provide a mechanistic framework for stimulating productive liver regeneration.

Nature Medicine 2012;18:572–579; doi:10.1038/nm.2667