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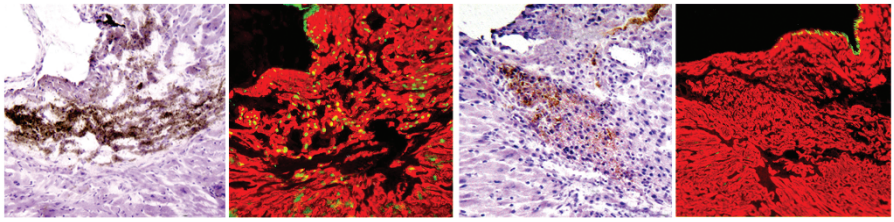

Deletion of Nkx2-5 in postnatal heart

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NKX2-5 is a cardiac transcription factor expressed in cardiomyocytes from development through adulthood. Heterozygous mutations in *NKX2-5* result in various cardiac anomalies in humans, including progressive conduction defects and left ventricular dysfunction. Homozygous deletion of *Nkx2-5* in mice results in embryonic lethality.

To understand the consequences of loss of *Nkx2-5* during various stages of development, Takeda and co-workers created a conditional *Nkx2-5* knockout mouse model. They specifically examined the consequences of deleting *Nkx2-5* two weeks after birth, which corresponds to a time when most cardiomyocytes are postmitotic and have lost the ability to proliferate. They found that mice exhibited both conduction and contraction defects, as well as left ventricular hypertrophy. Interestingly, the phenotype was less severe than that seen in mice that lost *Nkx2-5* at day 4 during the perinatal period. Examination of the atrioventricular node revealed that it was smaller and composed of cells of smaller width than those in control hearts. The cardiac defects were associated with expression of gene products important for cardiac conduction and contraction. Thus, Nkx2-5 plays an important role in the adult heart as well as during development and during the perinatal period. Many questions remain to be answered in futures studies, such as which genes downstream of *Nkx2-5* are responsible for specific defects. However, the current study illustrates how this elegant mouse model can be used to study the role of *Nkx2-5* in the developing and adult heart.

Adiponectin and liver regeneration

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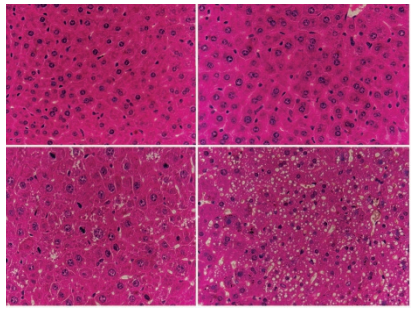

Obese patients with fatty livers tend to have a poor outcome following liver resection or transplantation. Furthermore, in experimental studies, both genetic and high-fat-diet models have shown that preexisting steatosis impairs liver regeneration after partial hepatectomy (PH). Adiponectin, an important adipocytokine produced by fat cells, plays important roles in energy homeostasis. It binds to at least two receptors, known as AdipoR1 and AdipoR2, both of which are expressed in the liver. To investigate the relationship among adiponectin, hepatocyte fat content, and liver regeneration, Shu and colleagues studied liver regeneration in a PH model in an adiponectin-knockout background. They found that liver regeneration was impaired in adiponectin-knockout mice, as illustrated by smaller regenerated livers that also exhibited decreased hepatocyte proliferation. Furthermore, hepatocyte fat content was higher in the livers of adiponectin-knockout mice as compared with controls. At the molecular level, adiponectin-deficient adipocytes manifest lower levels of mRNAs corresponding to proteins involved in fat metabolism. This suggests that the inability of the liver cells to utilize fat as an energy source compromises the ability of the liver to regenerate. They also found that suppressor of cytokine signaling 3 was not suppressed after PH, resulting in reduced signal transducer and activator of transcription protein 3 (STAT3) activation, suggesting that STAT3 activation is important in regulating hepatic fat accumulation. This study clearly shows that adiponectin is an important regulator of fat metabolism during regeneration. Future studies will likely focus on the precise molecular mechanisms that allow hepatocytes to use fat to power liver regeneration.

Critical regulator of intestinal inflammation

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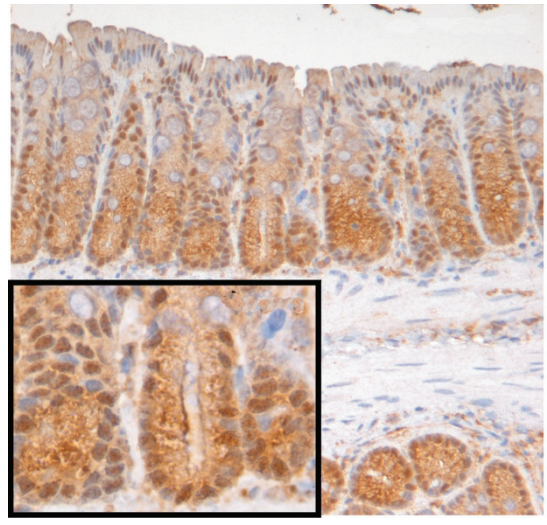
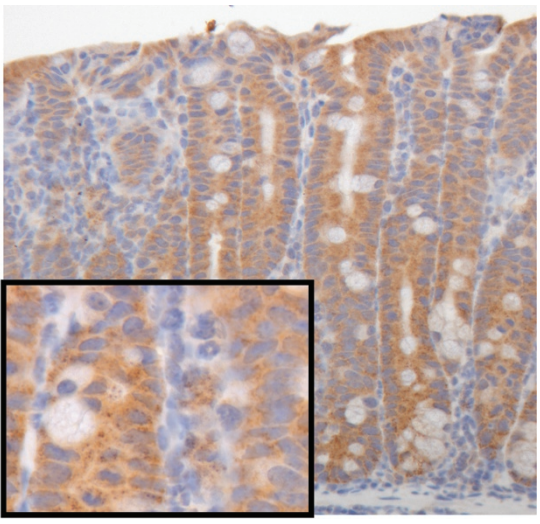
Inflammatory bowel disease (IBD) is composed of Crohn's disease (CD) and ulcerative colitis (UC). CD and UC are chronic illnesses that are responsible for considerable morbidity and health-care expense. Because chronic mucosal injury and infiltration of inflammatory cells are the hallmarks of



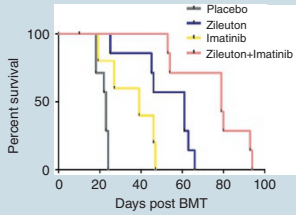
IBD, much IBD research has focused on inflammatory cell signaling pathways. Tumor necrosis factor-α (TNF-α), a cytokine that is known to activate inflammation in IBD, signals through the nuclear factor kappaB pathway. Recently, Snoeks and colleagues showed that FOXO3, a nuclear transcription factor regulated by phosphatidyl inositol-3 kinase (PI3K) and/or inhibitory kappaB (IκB) pathways, is inactivated in intestinal epithelia after bacterial infection. This led them to ask whether FOXO3 might be involved in the regulation of intestinal inflammation.

Using a human intestinal epithelial cell line, the authors found that FOXO3 translocated from the nucleus to the cytoplasm and was later degraded in response to TNF-α. Degradation of FOXO3 was shown to be dependent on PI3K and IκB kinase complex. Utilizing a mouse colonic inflammation model, they found that Foxo3 translocated from the nucleus to the cytoplasm in inflamed colonic mucosa. Finally, there was more severe intestinal inflammation and ulceration in the mouse inflammation model in a *Foxo3* knockout background as compared with wild-type controls. Together, their data make a compelling case for FOXO3 as a regulator of intestinal inflammation and highlight this tumor suppressor as a potential target for IBD treatment.

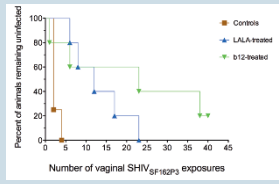


nature.com/pathology

Targeting stem cells in chronic myelogenous leukemia Imatinib mesylate, a small-molecule tyrosine kinase inhibitor, has been useful in treating patients with BCR-ABL-induced chronic myelogenous leukemia (CML). However, imatinib is not curative, as it fails to kill CML stem cells (LSCs). In a recent article in *Nature*, Chen and co-workers asked whether there might be targets specific to LSCs that would be amenable to targeted therapy without negatively impacting normal hematopoietic stem cells (HSCs). They identified the arachidonate 5-lipoxygenase (5-LO) gene (*Alox5*) as an important regulator of LSCs. They targeted *Alox5* in a mouse model of BCR-ABL-induced CML using either an *Alox5* knockout or Zileuton, a selective Alox5 inhibitor, which indicated that Alox5 is required for LSCs but not for HSCs. They also found that zileuton synergized with imatinib, suggesting a new therapeutic strategy for CML.



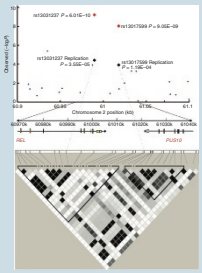
Nature Genetics 2009;41:783–792; doi:10.1038/ng.389



New HIV vaccine model Macaques have been used extensively to investigate HIV vaccines using a simian virus–HIV chimera (SHIV). Most studies use a high viral titer to ensure that all animals are infected. Since viral titers are high, a high serum antibody titer is required to confer protection. However, most human HIV infections result from repeated inoculation with low viral titers. Describing their efforts to more accurately model HIV vaccination and infection in a recent letter in *Nature Medicine*, Hessell and colleagues reported a macaque model that relies on low-titer antibody and repeated infection of low-dose SHIV. They found that low-titer human monoclonal antibodies were able to decrease the rate of transmission in this model, suggesting that antibody vaccines might be a useful protection strategy to prevent HIV infection.

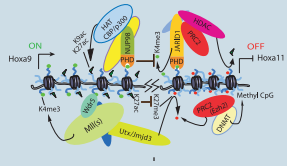
Nature Medicine, published online 7 June 2009; doi:10.1038/nm.1974

REL and rheumatoid arthritis Recent technological achievements have facilitated the genotyping of large numbers of patients with various diseases. These studies are shedding considerable light on once impenetrable diseases such as rheumatoid arthritis (RA). In a recent letter in *Nature Genetics*, Gregersen *et al* report their findings of a genotyping study involving 2,418 patients with RA. Their analysis identified an association of *REL*, which encodes c-Rel, a member of the NF-κB family of transcription factors, with RA. *REL* joins a growing list of other susceptibility genes associated with RA, including *CD40, TRAF1, TNFAIP3,* and *PRKCQ,* that suggests an important role for CD40 signaling pathways in the pathogenesis of RA and thus identify the CD40 pathway as an important therapeutic target. Further work will be required to elucidate the precise pathogenetic mechanisms involved in RA.



Nature Genetics 2009;41:820–823; doi:10.1038/ng.395

Chromatin modification and cancer Extensive indirect evidence implicates chromatin modification in the pathogenesis of various cancers, but direct evidence has been lacking. In a recent letter in *Nature*, Wang and colleagues provided direct evidence of a causative role for chromatin modification in the pathogenesis of acute myelogenous leukemia (AML). They showed that a chimeric protein composed of JARID1A, a plant homeodomain (PHD) finger protein, and NUP98, which contains transactivation activities, was sufficient to block differentiation of murine bone marrow–derived hematopoietic stem/progenitor cells and to induce AML *in vivo*. Mechanistically, the authors provided evidence that the PHD finger recognizes histone H3 lysine 4 methylation, protecting them from demethylation and inducing acetylation, which prevents silencing of several transcription factors involved in hematopoietic differentiation. Because there are many PHD finger–containing proteins, the authors suggest that the pathogenetic mechanism they have described may be of general importance in other diseases.



Nature 2009;459:847–851; doi:10.1038/nature08036