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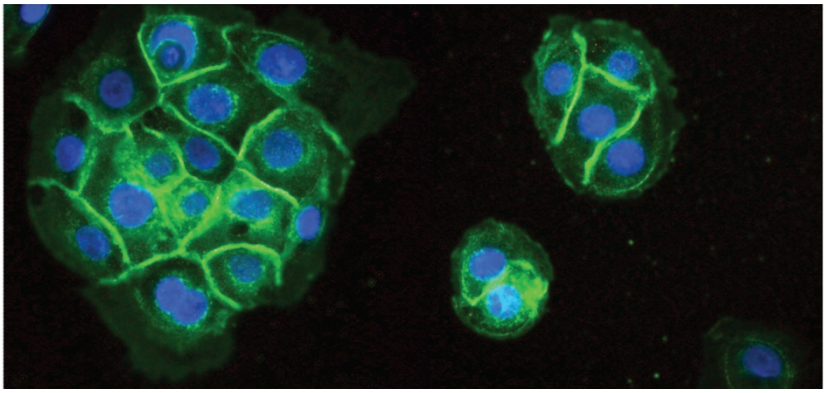

NOTCH1 maintains keratinocyte differentiation

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NOTCH1 is a transmembrane receptor with important functions in normal cellular signaling as well as in cancer. Gain-of-function *NOTCH1* mutations are common in human T-cell acute lymphoblastic leukemia. NOTCH1 activation is also thought to be important in the pathogenesis of squamous cell carcinoma of the cervix. However, mouse models that either ablate *Notch1* or harbor a transgene that expresses a pan-Notch inhibitor are prone to squamous cell dysplasia and squamous cell carcinoma. These contradictory findings prompted Sakamoto *et al* to study patterns of NOTCH1 expression in various squamous epithelial tissues.

Using immunohistochemistry, the authors localized NOTCH1 expression predominantly to the basal cells of stratified squamous epithelium. Examination of squamous cell dysplasia and squamous cell carcinomas from different anatomic locations revealed that NOTCH1 expression was lost in both dysplasia and squamous cell carcinoma of noncornified squamous epithelium, suggesting that loss of NOTCH1 expression is an early event in the development of squamous cell carcinoma. Further analysis revealed that NOTCH1 expression maintained a more differentiated basal cell phenotype whereas loss of NOTCH1 expression resulted in an immature or hyperplastic phenotype. Based on their results, the authors proposed a model in which NOTCH signaling maintains the correct balance of basal cells and more differentiated squamous cells. Pathological states such as regenerative squamous epithelium, dysplasia, and carcinoma shift the balance toward a more immature or hyperplastic phenotype through loss of NOTCH1 expression and cessation of terminal differentiation.

A critical role for caspase 1 in diet-induced steatohepatitis

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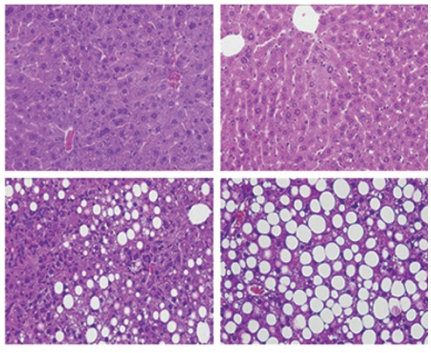

Nonalcoholic fatty liver disease (NAFLD) is due to metabolic syndrome and insulin resistance. Nonalcoholic steatohepatitis (NASH) is an extreme form of NAFLD that progresses to cirrhosis in 25% of patients. There is significant evidence suggesting that caspase-mediated hepatocyte apoptosis plays an important role in the development of NASH. Pan-caspase inhibition protects against diet-induced steatohepatitis in murine models. Because there are many caspases, it is not clear which are integral to NASH pathogenesis. To determine whether caspase 1, a proinflammatory initiator caspase, is involved in NASH pathogenesis, Dixon *et al* examined caspase 1 in a mouse model of steatohepatitis induced by a methionine choline–deficient (MCD) diet.

The authors demonstrated that MCD-fed mice had dramatically elevated levels of caspase 1. Caspase 1 knockout (*Casp1*$^{-/-}$) mice fed an MCD diet developed more pronounced macrovesicular steatosis than did MCD-fed wild-type mice. However, MCD-fed *Casp1*$^{-/-}$ mice had fewer markers of inflammation and less hepatic collagen deposition as compared with MCD-fed wild-type mice. A surprising finding was that caspase 3 activation and hepatocyte apoptosis were not elevated in MCD-fed *Casp1*$^{-/-}$ mice as compared with MCD-fed wild-type mice, implying that caspase 3 activation and apoptosis are not required for hepatic collagen deposition/cirrhosis. Examination of Kupffer cells suggested that they were the source of caspase 1. These results indicate that Kupffer cell caspase 1 plays an important role in NASH development in MCD-fed mice. Further studies are indicated to determine the mechanism of caspase 1 activation and whether caspase 1 is integral to the development of NASH in humans.

Podocyte Gα12 expression may contribute to chronic kidney disease

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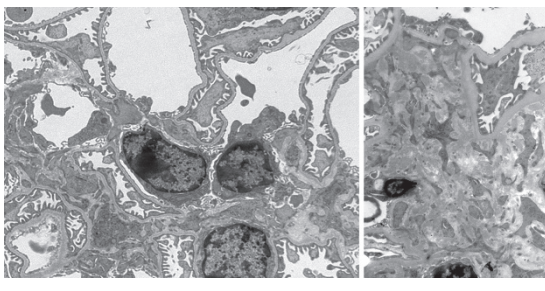
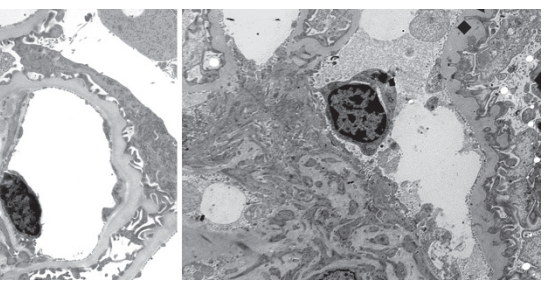
Glomerulosclerosis (GS), a common finding in chronic renal disease, contributes to end-



stage renal disease. However, little is known about the pathogenesis of GS. Podocytes are exposed to 180 liters per day of ultrafiltrate that contains a wide variety of biologically active compounds, including reactive oxygen species, lipid mediators, cytokines, and hormones. All of these molecules can activate G-coupled-protein receptors. Gα12 is expressed in podocytes and thus could mediate G-protein signaling–mediated glomerular damage. Based on these findings, Boucher and colleagues hypothesized that hyperactivation of Gα12 signaling in podocytes might lead to glomerulosclerosis.

The authors performed detailed analysis of Gα12 expression by immunohistochemistry and immunogold electron microscopy to confirm the presence of Gα12 on podocytes. They subsequently established a genetically engineered mouse model that expressed constitutively activated Gα12 in podocytes. Analysis of the mice demonstrated that approximately 50% of podocytes expressed constitutively activated Gα12. Importantly, mice expressing podocyte-specific constitutively activated Gα12 developed proteinuria that worsened as the mice aged. Electron microscopic examination revealed several podocyte abnormalities, and these mice had a greater than sixfold increase in sclerosed glomeruli. Further experiments revealed that constitutively active Gα12 signaling deregulated collagen α(IV) expression, implicating it in the pathogenesis of podocyte damage in this model. The results suggest that this mouse model with podocyte-specific constitutively activated Gα12 will be a valid model for elucidating chronic kidney disease in humans.



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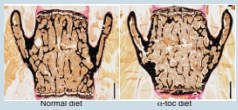
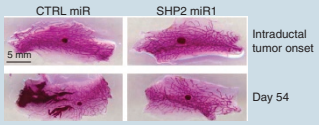


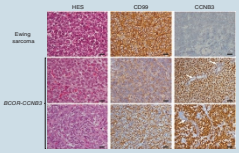
Loss of bone mass: an unintended consequence of vitamin E therapy Vitamins A, D, and K are well characterized with respect to their effects on bone metabolism. However, much less is known about the effects of vitamin E. In a recent letter in *Nature Medicine,* Fujita *et al* describe the effects of vitamin E on bone. They found that vitamin E potently stimulated osteoclast formation. Because osteoclasts resorb bone, this resulted in loss of bone mass in mice and rats treated at levels equivalent to those taken by humans during vitamin E supplementation. The authors demonstrated that stimulation of osteoclast formation was independent of the antioxidant effects of vitamin E. These results suggest that vitamin E supplementation may contribute to loss of bone mass in humans and clearly warrant further study.

Nature Medicine, published online 4 March 2012; doi:10.1038/nm.2659



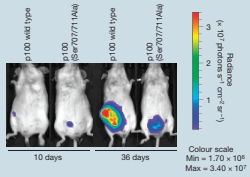
SHP2 phosphatase plays critical roles in breast cancer SHP2, a tyrosine phosphatase, is known to play important roles in several cancers, but its role in breast cancer has not been clearly defined. As described in a recent article in *Nature Medicine,* Aceto *et al* discovered that SHP2 is important for breast cancer tumor-initiating cells, tumor maintenance, and tumor progression. Mechanistically, they demonstrated that SHP2 activates extracellular signal–related kinase (ERK)1 and ERK2, which induces expression of oncogenes such as RAS and c-Myc. These results add to the evidence that phosphatases such as SHP2 play important roles in cancer development, maintenance, and progression. Given their critical role in cancer, development of selective inhibitors of SHP2 and other phosphatases is a therapeutic strategy that requires further investigation.

Nature Medicine, published online 4 March 2012; doi:10.1038/nm.2645



New genetically defined sarcoma identified Although many sarcomas have specific chromosomal translocations that can be used diagnostically and are important in defining their pathogenesis, there exists a subset of sarcomas without known consistent genetic aberrations. As reported in a recent letter in *Nature Genetics*, Pierron *et al* used deep transcriptome sequencing and bioinformatics to identify a novel *BCOR-CCNB3* gene fusion in a sarcoma with clinical and histological similarities to Ewing sarcoma but without the *EWSR1-ETS* family translocations that are characteristic of Ewing sarcoma. The *BCOR-CCNB3* translocation was identified in 24 of 594 sarcomas that lacked common translocations identified in other sarcomas. Gene profiling revealed that sarcomas harboring *BCOR-CCNB3* fusions were distinct from other sarcomas, confirming that they require correct classification. Because CCNB3 expression is not seen in other sarcomas, CCNB3 immunohistochemistry can be used as a surrogate to diagnose this new molecularly defined sarcoma.

Nature Genetics 2012;44:461–466; doi:10.1038/ng.1107



A novel therapeutic target in multiple myeloma Constitutive activation of the noncanonical nuclear factor (NF)-κB pathway is present in multiple myeloma, an aggressive B-cell neoplasm with a poor prognosis. Negative regulation of this pathway is achieved through p100. In a recent article in *Nature Cell Biology*, Busino *et al* describe the regulation of p100 and how it contributes to constitutive NF-κB activation in multiple myeloma. They discovered that Fbxw7α, an F-box protein that functions as a substrate-targeting subunit of an SCF (Skp1/Cul1/F-box protein) ubiquitin ligase complex, constitutively targets p100 for ubiquitin-mediated degradation, resulting in constitutive NF-κB activation. Fbxw7α binding is dependent on phosphorylation of p100 by GSK3. Inhibition of GSK3 resulted in diminished NF-κB activity and apoptosis *in vivo* in multiple myeloma xenotransplantation models. These results suggest a novel therapeutic strategy in which GSK3 is inhibited pharmacologically, resulting in stabilization of p100 and decreased NF-κB activity.

Nature Cell Biology, published online 4 March 2012; doi:10.1038/ncb2643