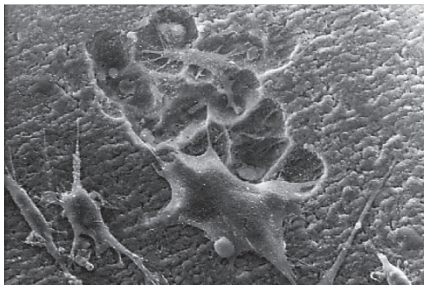
Laboratory Investigation (2012) 92, 486-487

INSIDE LI

doi:10.1038/labinvest.2012.51

Osteoclast differentiation in aneurysmal bone cyst

See page 600

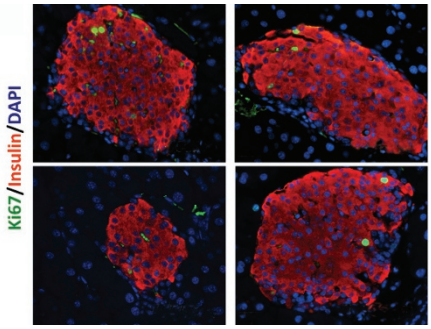


Aneurysmal bone cyst (ABC) is a benign bone lesion that tends to occur within the first two decades of life. Historically, there was vigorous debate over whether ABC is a true neoplasm. This debate was resolved several years ago with the identification of clonal cytogenetic rearrangements of the short arm of chromosome 17. Although ABC is benign, it is osteolytic and can cause extensive destruction of native bone. Treatment is surgical, relying on complete removal of the lesion. Occasionally there is recurrence, requiring additional surgery.

Histologically, ABC is composed of an admixture of mononuclear cells, multinucleated giant cells, and fibrous cyst walls that occasionally contain bone. Because the multinucleated cells are responsible for destroying bone, Taylor *et al* sought to characterize these cells and understand how they are formed, with the overall goal of identifying potential medical therapies for ABC. The authors found that the multinucleated cells expressed an osteoclast phenotype, which they demonstrated in culture. The phenotype was abolished by zoledronate, an aminobisphosphonate that inhibits osteoclast resorption activity and survival. Analysis of the mononuclear population of ABC demonstrated that CD14-mononuclear stromal cells express nuclear factor–κB ligand (RANKL) and macrophage-colony-stimulating factor (M-CSF), which stimulates $CD14^+$ mononuclear cells to form osteoclasts. Thus, osteoclasts form through a RANKL-dependent mechanism that can be exploited therapeutically. The anti-RANKL antibody denosumab is used to treat giant-cell tumor of bone, which is characterized by the presence of numerous osteoclasts that destroy bone. This suggests that denosumab may be useful in the medical treatment of ABC as well.

c-Kit signaling in pancreatic β-cells

See page 543



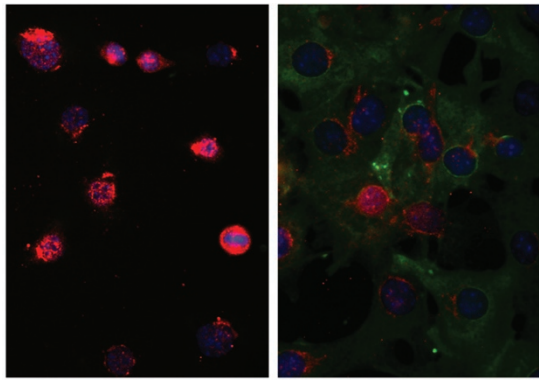
c-Kit plays a critical role in the development and maintenance of a number of cell types, including hematopoietic cells, germ cells, melanocytes, and pancreatic β-cells. c-Kit activation results in downstream signaling through a number of pathways, such as the phosphatidylinositol-3-kinase (PI3K)-Akt pathway. Recent work has demonstrated that *c-Kit*$^{Wv/+}$ male mice, which have partially defective c-Kit function, have loss of β-cell mass and function, resulting in diabetes. Glycogen synthase kinase 3β (Gsk3β) negatively regulates β-cell mass and is linked to diabetes. Because Akt negatively regulates Gsk3β, Feng *et al* hypothesized that loss of c-Kit function contributes to diabetes in c-*Kit*$^{Wv/+}$ male mice through loss of Akt activity and resultant increased Gsk3β activity.

The authors demonstrated that pancreatic islet cells from c-*Kit*$^{Wv/+}$ male mice not only had decreased activated Akt and increased activated Gsk3β but also had decreased cyclin D1 protein expression. Inhibition of Gsk3β by 1-azakenpaullone (1-AKP), a potent Gsk3β inhibitor, prevented early-onset diabetes in c-*Kit*$^{Wv/+}$ male mice. This was accompanied by an increase in β-cell mass. Additional analysis revealed that mRNA and protein levels of Pdx-1, an important pancreatic transcription factor, were higher in 1-AKP-treated c-*Kit*$^{Wv/+}$ male mice than in untreated controls. Together these results highlight c-Kit signaling in pancreatic β-cell maintenance and function and suggest that inhibition of Gsk3β is a potential therapy for diabetic patients, at least in some pathologic contexts. Further studies are required to understand the complexities of c-Kit signaling in different pathologic situations that result in diabetes so that more effective therapies that target specific diabetes-causing proteins and pathways can be developed.

Glomerular PECs need SSeCKS to sequester cyclin D1

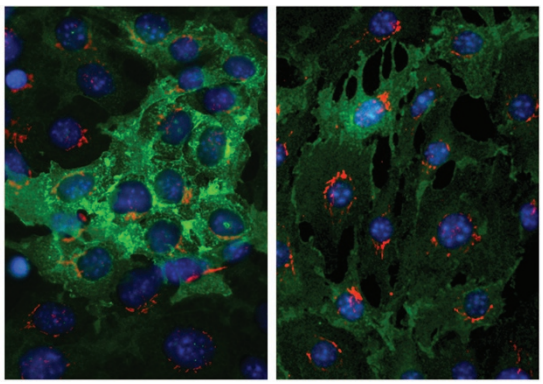
See page 499

Glomerular parietal epithelial cells (PECs) are renal tissue stem cells that differentiate into glomerular podocytes and are thus important for glomerular repair/replacement. Too few or too many podocytes result in a variety of glomerular diseases known collectively as podocytopathies. Fine control over PEC proliferation is therefore critical

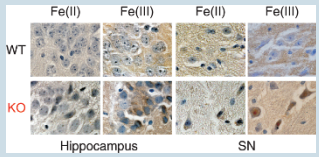


and could form the basis of therapeutic interventions to prevent or treat podocytopathies. Src-suppressed protein kinase C substrate (SSeCKS) is known to inhibit cell-cycle progression through binding cyclin D1 in the cytoplasm. The SSeCKS–cyclin D1 interaction is mediated by protein kinase C (PKC). Phosphorylation by PKC results in release of cyclin D1, which translocates to the nucleus and facilitates G_1-to-S cell-cycle progression. The finding in earlier studies that SSeCKS was strongly expressed in mature PECs but not in mature podocytes suggested to Burnworth *et al* that SSeCKS might control cell-cycle arrest in PECs.

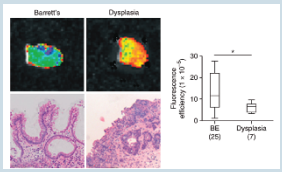
The investigators found that SSeCKS was phosphorylated by activated PKC, resulting in translocation of cyclin D1 to the nucleus in cultured PECs. SSeCKS$^{-/-}$ knockout mice developed PEC hyperplasia as would be expected if SSeCKS controls PEC proliferation. Examination of podocytopathic mouse and rat models revealed that proliferative podocytopathies were characterized by excessive numbers of SSeCKS-positive PECs. Finally, SSeCKS$^{-/-}$ knockout mice displayed more severe pathology in a model of crescentic glomerulonephritis in which proliferating PECs are major constituents of extracapillary lesions. Together, these results highlight the important role of SSeCKS in regulating PEC proliferation and suggest that control of SSeCKS may be useful in preventing or treating podocytopathies.



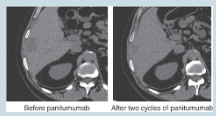
nature.com/pathology



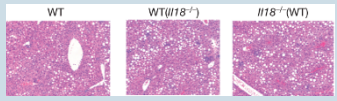
Tau deficiency linked to iron overload in tauopathies Neurofibrillary tangles composed partly of the microtubule-associated protein tau are a hallmark of neurodegenerative diseases such as Alzheimer's disease. Tau has risk alleles in Parkinson's disease, but little is known about this protein in Parkinson's disease. As recently described in a letter in *Nature Medicine*, Lei *et al* found that patients with Parkinson's disease had lower levels of soluble tau in the substantia nigra, which were similar to the levels found in affected brain regions in patients with Alzheimer's disease. This suggested a common pathogenesis. The authors demonstrated that tau-deficient mice developed iron accumulation and accompanying neuronal loss, which was reversed by iron chelation therapy. Mechanistically, soluble tau deficiency caused iron-transport abnormalities, suggesting that therapies aimed at solubilizing tau could prevent neuronal loss in tauopathies.
Nature Medicine 2012;18:291–295; doi:10.1038/nm.2613



Identification of Barrett's dysplasia before biopsy Barrett's esophagus is a nonneoplastic condition that precedes high-grade dysplasia and esophageal adenocarcinoma (EAC). Identification of EAC by surveillance programs before it is symptomatic is associated with improved prognosis. However, it is difficult to identify areas of high-grade dysplasia or asymptomatic EAC via endoscopic surveillance. In a recent technical report in *Nature Medicine*, Bird-Lieberman *et al* described the use of fluorescent lectins to highlight dysplasia and EAC. They demonstrated that wheat germ agglutinin (WGA) binding was lost during progression to EAC as a result of the loss of cell surface glycans that bind WGA. When fluorescently labeled WGA was sprayed onto the surface of Barrett's esophagectomy specimens, areas of high-grade dysplasia and EAC were readily identifiable. The next hurdle will be to test this technique *in vivo*, in patients with Barrett's esophagus.
Nature Medicine 2012;18:315–321; doi:10.1038/nm.2616



EGFR resistance mutation in colorectal carcinoma Metastatic colorectal carcinomas with epidermal growth factor receptor (EGFR) amplification respond to antibodies to EGFR. Two antibodies against EGFR are used clinically: cetuximab and panitumumab. In an effort to identify the mechanisms of resistance to cetuximab, Montagut *et al*, as described in a recent Brief Communication in *Nature Medicine*, cultured an EGFR-sensitive human colorectal carcinoma cell line continuously in the presence of cetuximab. Three resistant colonies were isolated with an identical S492R EGFR extracellular mutation that abrogated cetuximab binding. However, the cells were still sensitive to panitumumab. Examination of samples from patients who developed acquired resistance to cetuximab revealed that a proportion of the tumor cells had the identical S492 EGFR mutation found *in vitro*, showing that this mutation is important clinically.
Nature Medicine 2012;18:221–223; doi:10.1038/nm.2609



The enemy within: intestinal flora contribute to NASH Nonalcoholic fatty liver disease (NAFLD) is a common manifestation of metabolic syndrome, which has reached epidemic proportions in the developed world. About 20% of NAFLD patients progress to nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis. In a study recently reported in *Nature*, Henao-Mejia *et al* identified gut flora as a risk factor for progression of NAFLD to NASH. Using a variety of knockout mice, they demonstrated that mice with deficiencies in innate immunity developed gut flora that injured intestinal epithelium. Intestinal epithelium inflammation resulted in portal blood that was rich in Toll-like receptor agonists, which led to tumor necrosis factor–dependent hepatic injury when these agonists drained to the liver. This work may explain why some NAFLD patients progress to NASH and highlights the contribution of intestinal flora in the pathogenesis of another systemic illness.
Nature 2012;482:179–185; doi:10.1038/nature10809