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Hypothetical multiple-hit model of platelet apoptosis. Adapted with permission from V Leytin *et al*, Pathologic high shear stress induces apoptosis events in human platelets, *Biochem Biophys Res Comm* 2004;320:303–310.

How platelets die

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It might surprise scientists who do not normally think about platelets—anucleate cells with a critical role in coagulation—that platelets are capable of dying by apoptosis, just like cells with nuclei. The role of mitochondria in apoptosis of nucleated cells is well known, but it has been largely unexplored in platelets, which do have mitochondria. Using cyclosporin A (CsA), a potent inhibitor of the mitochondrial permeability transition pore (MPTP), Leytin *et al* dissected the functions of the MPTP in platelet apoptosis. When stimulated with A23187, a calcium ionophore that strongly stimulates apoptosis in platelets, they underwent a series of events, including depolarization of the mitochondrial membrane potential, activation of caspase-3, phosphatidylserine (PS) exposure on the membrane surface, platelet shrinkage, and microparticle formation. Blockage of the MPTP by CsA essentially ablated all these events with the exception of PS exposure on the membrane surface, which appeared to be only partially dependent on the

MPTP. Thus, CsA appears to have potential as an inhibitor of apoptosis in platelets. Beyond contributing to our understanding of basic mechanisms of apoptosis, these results have practical importance. Given its long history of use in transplant medicine, CsA is well poised for application to human thrombocytopenias that are characterized by increased platelet apoptosis.

Putting a stop to glomerular damage

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The many forms of glomerulonephritis are responsible for significant human morbidity, often requiring dialysis or renal transplant. Therefore, strategies to halt

the progression of glomerulonephritis are sorely needed. Macrophages play an important part in the renal injury associated with anti-glomerular basement membrane (GBM) glomerulonephritis, which is thought to be due to pro-inflammatory mediators such as tumor necrosis factor- α produced by the macrophage infiltrate. The macrophage pro-inflammatory response appears to be dependent on c-Jun amino terminal kinase (JNK) signaling. To test the hypothesis that inhibition of JNK signaling might stop progression of established anti-GBM glomerulonephritis, Ma and colleagues used CC-401, an orally administered, small-molecule JNK inhibitor, in a rat model of aggressive anti-GBM glomerulonephritis. Remarkably, there was a profound decrease in renal pathology, proteinuria, and creatinine in mice that were treated with CC-401 compared with the untreated control group. CC-401 treatment correlated with suppression of JNK signaling and a decrease in pro-inflammatory molecules. This interesting work has obvious implications for the treatment of anti-GBM glomerulonephritis. Given a more generalized role for JNK in inflammatory-mediated diseases, inhibition of the JNK pathway by small-molecule inhibitors may have applications well beyond anti-GBM glomerulonephritis.

CAP1 is associated with aggressive behavior in pancreatic cancer

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Adenocarcinoma of the pancreas has a terrible prognosis; the 5-year survival rate has not changed in decades and is still less than 5%. To investigate why

pancreatic cancers are so aggressive, Yamazaki *et al* used expression profiling of pancreatic tumor xenografts to identify 57 candidate genes that were overexpressed in pancreatic cancer; about half of these had previously been described. Based on the reasonable assumption that aggressive behavior was associated with metastasis, and the realization that rapid actin-filament turnover is necessary for cell migration, the authors focused their attention on *CAP1*, which encodes an actin-binding protein and had not previously been studied in pancreatic cancer. Using immunohistochemistry, they found CAP1 protein in all cases of a group of 73 adenocarcinomas of the pancreas. CAP1 was not seen in normal pancreatic ductal cells. The pancreatic cancers with higher numbers of positive cells had a dramatically worse prognosis. When CAP1 was depleted by siRNA in pancreatic cancer cell lines, filopodia formation and cell motility were impaired. These results support the hypothesis that CAP1 is involved in pancreatic cancer cell movement and metastasis. Given that cell movement and metastasis are general features of aggressive cancers, it will be interesting to see whether CAP1 is overexpressed in other cancers as might be expected.

nature.com/pathology

New method to hunt for gene fusions in cancer Recurrent gene fusions have typically been found in hematological cancers and sarcomas. More recently, however, they have been described in common epithelial malignancies. In a recent letter in *Nature*, Maher and colleagues described a clever method for identifying gene fusions. The new method relies on massively parallel transcriptome cDNA sequencing to identify noncontiguous sequences that suggest gene fusions. The two types of sequencing that were used generated "long-read" and "short-read" sequencing data that were compared in order to filter out false positives. Examination of prostate cancer cell lines and tumor samples led to the identification of several new fusion genes. Furthermore, they identified a unique chimeric transcript generated by a read-through event from adjacent genes without a detectable DNA aberration. This powerful technology is certain to lead to many important new leads in the fight against cancer.

Nature, published online 11 January 2009; doi:10.1038/nature07638

Opening a door for HCV entry The development of small animal models, such as mouse models, that are susceptible to hepatitis C virus (HCV) infection is vital to battling HCV infection. However, mouse cells do not contain the host-cell factors that are critical for the coordinated entry of HCV. Although there has been strong evidence for scavenger receptor class B type I, claudin-1, and CD81 in this process, these are insufficient to permit entry into murine cells. Using a cDNA library derived from a highly susceptible human hepatocellular carcinoma cell line, Ploss and colleagues have identified occludin as the missing element that facilitates HCV entry. There are still many hurdles to overcome before a mouse model can be constructed, but defining the factors necessary for HCV entry is a huge step in the right direction.

Nature 2009;457:882–886; doi:10.1038/nature07684

Good news for spinal cord injury After spinal cord injury (SCI), there is secondary spread of hemorrhage/injury in a process known as "blossoming." In a recent article in *Nature Medicine*, Gerzanich and co-workers showed that transient receptor potential 4 (Trpm4), a nonselective cation channel, is upregulated in adjacent capillary endothelial cells near the SCI site. This is followed by capillary fragmentation and hemorrhage formation, which is toxic to spinal tissues. Importantly, blockage of Trpm4, either by antisense RNA in a rat

model or by knockout in a mouse model, limited SCI-induced secondary hemorrhage and resulted in significantly better functional outcomes. These results lay an important foundation for further studies aimed at exploiting these findings therapeutically.

Nature Medicine 2009;15, 185–19; doi:10.1038/nm.1899

Feedback circuit in breast cancer Notch1 has increasingly been implicated as playing a role in signaling in various cancers. After binding to its ligands, Notch1 undergoes extracellular cleavage followed by intracellular cleavage, which releases the Notch1 intracytoplasmic domain (NICD). The NICD translocates to the nucleus, where it modulates gene expression of various targets. In a recent article in *Nature Cell Biology*, Rustighi and colleagues show that intracellular cleavage of Notch1 is enhanced by the prolyl-isomerase Pin1.

They also show that Pin1 is a transcriptional target of Notch1, thereby creating a positive feedback circuit. Importantly, Pin1 and Notch1 are strongly coexpressed in a subset of breast cancers, and ablation of *Pin1* by shRNA impaired growth in a breast cancer xenograft mouse model. Thus, pharmacological inhibition of the Pin1–Notch1 feedback loop appears to be a promising target for breast cancer therapy.

Nature Cell Biology 2009;11:133–142; doi:10.1038/ncb1822