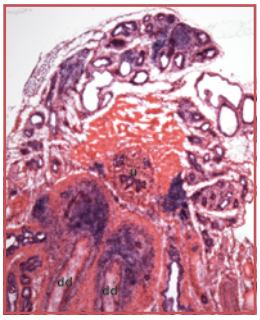
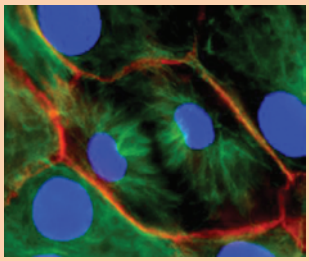
Chronic prostatitis: an autoimmune condition



Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a prevalent disease that causes pelvic pain in men. While acute prostatitis is caused by bacterial infection, the etiology of CPPS is unknown. However, Hou and colleagues have now determined that an autoimmune response can cause prostatitis in mice (2031–2041). Previous studies indicated that mice lacking autoimmune regulator (Aire), a transcriptional regulator with a key role in establishing central tolerance, develop prostatitis spontaneously. In this study, analysis of Aire-deficient mice revealed that they mount a spontaneous T and B cell response to seminal vesicle secretory protein 2 (SVS2). The importance of the SVS2-specific immune response was highlighted by the observation that wild-type mice immunized with SVS2 developed prostatitis. Of clinical relevance, antibodies specific for the human SVS2-like seminal vesicle protein semenogelin were detected in the serum of patients with CPPS. The authors therefore suggest that CPPS is an autoimmune disease and that if this is confirmed, it will open new avenues for diagnosing and treating CPPS, a condition for which there are currently no specific treatments.

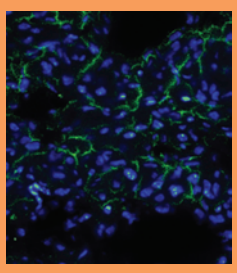
Insulin triggers hepatocyte polyploidy

The appearance of binucleated tetraploid hepatocytes, as a result of a failure in cytokinesis, is part of normal mammalian postnatal liver development. In this issue, Celton-Morizur and colleagues have identified a cellular signaling pathway that leads to cytokinesis failure and the formation of binucleated tetraploid hepatocytes in rodents (1880–1887). Initial analysis revealed that upon weaning, the proportion of dividing hepatocytes that failed to complete cytokinesis increased substantially in rats. As rats with low levels of circulating insulin and insulin-resistant mice both exhibited reduced formation of binucleated tetraploid cells, while rats injected with insulin exhibited increased formation of binucleated tetraploid cells, it seems likely that the aspect of the suckling-to-weaning transition that controls the initiation of cytokinesis failure is the increase in insulin levels that occurs upon weaning. Further in vitro analysis using pharmacological inhibitors indicated that insulin controlled cytokinesis failure via the PI3K/Akt signaling pathway. Future studies will investigate whether the deregulation of the insulin signaling pathway observed in various metabolic diseases alters the liver ploidy profile and whether any modifications in this have a role in disease pathophysiology.



Cell type–specific nonviral gene therapy

Hemophilia A is an inherited bleeding disease caused by a lack of Factor VIII (FVIII). It had been hoped that gene therapy would provide a treatment breakthrough, but gene replacement strategies using viral vectors have been unsuccessful in clinical hemophilia trials. However, Kren and colleagues have developed a nonviral, cell type–specific gene-targeting system and used it to achieve long-term expression of FVIII in hemophilia A mice, markedly reducing disease severity (2086–2099). Using a dispersion atomization method, the authors generated nanocapsules coated in asialoorosomucoid (ASOR) or hyaluronan (HA) — ligands for cell-surface receptors expressed uniquely by hepatocytes and liver sinusoidal endothelial cells, respectively — and demonstrated their ability to target encapsulated plasmids in a cell type–specific manner. Of therapeutic interest, when hemophilia A mice were injected intravenously with HA-coated nanocapsules containing the *Sleeping Beauty* (*SB*) transposon in *cis* with the gene encoding B domain–deleted canine FVIII, they exhibited plasma FVIII activity almost identical to that of wild-type mice through 50 weeks. As the hemophilia phenotype was markedly improved by treatment, the authors hope this combination of technologies, the cell-specific nanocapsule delivery system and the *SB* transposon, might constitute a viable gene therapy approach for treating hemophilia A.



Long-sought-after antitumor CD8$^+$ T cells found

Studying individuals with paraneoplastic neurologic disorders (PNDs) such as Hu syndrome, which can occur in individuals with small cell lung cancer (SCLC), provides insight into human antitumor immunity. SCLC cells express the neuronal protein HuD, and the presence of low-titer, HuD-specific antibodies correlates with improved prognosis for individuals with SCLC. In a small number of patients, HuD-specific antitumor immune responses also attack neurons, causing neurologic symptoms. As antigen-specific CTLs have been detected in another PND, it has been proposed that HuD-specific CD8$^+$ T cells contribute to Hu syndrome pathogenesis, but such cells have never been detected. However, Roberts and colleagues have identified, in Hu patients, HuD-specific CD8$^+$ T cells (2042–2051). Surprisingly, not all patients had the same type of HuD-specific CD8$^+$ T cells; some harbored classical IFN-γ–producing CTLs, whereas others had atypical type 2 cytokine–producing, noncytotoxic CD8$^+$ T cells, a finding that provides a potential explanation for why these cells have been difficult to detect. Further analysis indicated that SCLC cells produced type 2 cytokines and that these cytokines promoted naive CD8$^+$ T cell differentiation toward the atypical phenotype, leading the authors to suggest this might be a mechanism by which SCLC evades tumor immune surveillance.