Research News

But what do normal prions do?

Although many studies have focused on how conformational changes in prion proteins lead to neurodegenerative diseases such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease, new findings have emerged about the biological functions of the non-infectious cellular form of prion (PrP^c). PrP^c is a cell surface glycoprotein that is highly expressed in neurons. In the 15 September issue of *Science*, Mouillet-Richard *et al.* report that prions are involved in neuronal signal transduction. Using an *in vitro* neuronal differentiation model, the authors found that inhibition of PrP^c function through antibody cross-linking reduced phosphorylation of the tyrosine kinase Fyn in differentiating cells. The authors also show that Fyn phosphorylation depends on a functional interaction between PrP^c and the membrane signaling molecule caveolin-1. The next steps will be to identify other members of this signaling cascade and to determine whether the infectious prion protein interferes with the normal signaling activity of PrP^c.

Prostate protection

The diabetes drug troglitazone may also be useful in treatment of prostate cancer, the most common malignancy in American men. Despite advances in early detection and treatment, new treatment strategies are needed. Activation of the peroxisome proliferator-activated receptor- γ (PPAR γ), a nuclear hormone receptor, inhibits cell growth and differentiation in liposarcomas, breast and colon cancer cells. In the 12 September issue of *PNAS*, Mueller *et al.* report that PPAR γ is expressed in normal prostate tissue and prostatic adenocarcinomas. Furthermore, activation of the receptor through ligand binding caused growth inhibition in prostate cell lines. In a phase II prospective clinical study, treatment with the PPAR γ ligand troglitazone decreased production of prostate-specific antigen (PSA), a widely used diagnostic marker for prostate cancer, in 20% of patients with metastatic prostate cancer, and stabilized PSA production in 39%. Treatment with troglitazone was also associated with absence of new metastases. Troglitazone has been prescribed for more than one million diabetes patients in the US, and is generally well tolerated at the doses tested in this clinical trial.

KSHV monkey business

The great apes of central Africa may provide a reservoir of new Kaposi sarcoma-associated herpesvirus (KSHV) that is potentially transmissible to humans. KSHV may be involved in the pathogenesis of Kaposi sarcoma, a malignant neoplasm that often occurs in immunocompromised patients. As KSHV is endemic to central Africa, Lacoste *et al.* tested for KSHV-related viruses in chimpanzees and great apes from Cameroon and Gabon. In the 14 September *Nature*, the authors report that 20 of 25 chimpanzees and two of five gorillas expressed KSHV antigens. This is unexpected, as γ 2-herpesviruses have been identified in New and Old World monkeys, but never before

in apes. Comparative analysis of γ 2-herpesvirus DNA isolated from the apes to other herpesvirus sequences demonstrated the existence of two new chimpanzee KSHV-like viruses and a new gorilla KSHV-like virus. Phylogenetic analysis indicated that there are five separate lineages among γ 2-herpesviruses: one for New World monkeys, two for macaque/African green monkeys, one for the new chimpanzee strain and one that includes the new gorilla strain. As the contact between great apes and humans increases in central Africa through hunting and commercial logging, so do the opportunities for interspecies viral transmission to humans.

Sweet success for diabetes gene hunters

Positional cloning of a gene for susceptibility to type 2 diabetes has led to the unexpected discovery that the calpain proteases are involved in the regulation of blood glucose levels. Type 2 diabetes is a multifactorial disorder characterized by defects in insulin function and secretion. In previous studies, a genome-wide screen for type 2 diabetes genes localized a susceptibility gene, called *NIDDM1*, to chromosome 2. In the October issue of *Nature Genetics*, Horikawa *et al.* report that the gene for cysteine protease calpain 10 (*CAPN10*), located in the *NIDDM1* region, is associated with type 2 diabetes in Mexican-Americans and a Northern European population. The authors found a complex relationship between susceptibility to type 2 diabetes and polymorphisms in *CAPN10*, in that susceptibility was not attributable to a single polymorphism or allele, but to multiple polymorphisms. Calpain proteases are involved in intracellular signaling and downregulate insulin receptor substrate 1, a mediator of insulin action. Furthermore, *CAPN10* is expressed in pancreatic islets, muscle and liver, three tissues involved in controlling glucose homeostasis. The authors suggest that high-risk haplotypes affect expression of *CAPN10* in insulin-secreting pancreatic β -cells or insulin-responsive tissues, leading to defects in insulin secretion, signaling and/or glucose production.

Blood stem cells to the rescue

Blood stem cells show promise in treating metastatic renal cell carcinoma, which is resistant to chemotherapy and is usually fatal in less than a year. Renal cell carcinoma is unusual among solid tumors because of its immunogenic properties—disease regression sometimes occurs in response to cytokine treatment, indicating that the cancer is susceptible to immunologic control. In the 14 September issue of *The New England Journal of Medicine*, Childs *et al.* report that nonmyeloablative allogeneic peripheral blood stem cell transplantation caused regression of metastatic disease in 53% of patients and total regression of all metastases in 16% of patients. Nineteen patients were

given blood stem cells and lymphocytes from a tissue-matched sibling donor, along with short-term cyclosporine treatment to prevent the initial rejection of donor cells and graft-versus-host disease. Although one patient died from graft-versus-host disease, in other patients metastatic tumor regression was seen at multiple sites, including lymph nodes, adrenal glands, bones and lung. The fact that patients who had no response to conventional cytokine-based therapy did respond to transplantation therapy indicates that this approach is a more effective means of inducing anti-tumor immunity.

By Kristine Novak