Research News

Lost survival skills

Research into the role of huntingtin suggests that administration of the neuron survival factor BDNF may be useful in treating Huntington Disease (HD). HD is a dominantly inherited, incurable brain disorder that slowly diminishes motor and cognitive abilities. It is caused by polyglutamine expansions in huntingtin that confer a toxic gain-of-function. Huntingtin is highly expressed in cortical and striatal neurons, which degenerate during the course of disease. However, its normal function is unclear. In the 14 June issue of *Science*, Zuccato *et al.* report that mutant huntingtin causes a decrease in production of BDNF, but not other neurotrophic factors, in cultured neurons and in the cerebral cortex of transgenic mice. They report that BDNF expression is also reduced in human HD brain regions that project to the striatum, indicating reduced trophic support for striatal neurons during the course of the disease. Although wild-type huntingtin is usually a cytoplasmic protein, the authors suggest that small amounts or fragments of the protein might localize to the nucleus to induce transcription of this neuronal survival factor. Alternatively, huntingtin might act in the cytoplasm to recruit other transcription factors to the nucleus.

Matrix management

A human disease characterized by enhanced degradation of bone extracellular matrix has been unexpectedly found to be caused by mutations in the proteolytic enzyme MMP-2. Multicentric osteolyses is a rare bone disorder characterized by reduced growth and interphalangeal joint erosions that mimic severe juvenile rheumatoid arthritis. In the July issue of *Nature Genetics*, Martignetti *et al.* report a linkage analysis of four Saudi Arabian families, and identify mutations in *MMP2* as the genetic basis for this disease. Affected individuals carry nonsense mutations that delete *MMP2*'s substrate and catalytic binding sites, and lack fibroblast *MMP-2* activity. As *MMP-2* is a gelatinase/collagenase involved in bone and extracellular-matrix solubilization, it is surprising that loss of this enzyme increases bone resorption. The authors suggest that defects in osteoblast bone deposition are caused by incomplete degradation of this matrix. Further studies are required to determine how the imbalance between bone synthesis and resorption results in an osteolytic phenotype.

Motor defect disease

A defective molecular motor protein has been identified as the cause of Charcot-Marie-Tooth disease type 2A (CMT2A), the most common inherited peripheral neuropathy. The autosomal dominant disease, characterized by atrophy of peripheral muscles, maps to the 1p35-36 region of chromosome 1, but the gene that causes the disease is unknown. Zhao *et al.* realized that this region is near the gene encoding KIF1B, a member of the kinesin motor molecule family involved in intracellular transport. In the 1 June issue of *Cell*, they report cloning the mouse homolog *kif1B*. *Kif1B*-null mice die shortly after birth, and heterozygous mice develop multiple neurological abnormalities resembling those of people with CMT2A, such as muscle

weakness. These mice cannot even support their own body weight (Picture). The authors analyzed the genotype of patients, and found that four individuals carried heterozygous point mutations in *KIF1B*, whereas unaffected relatives did not. This mutation, Q98L, occurs in the middle of the consensus ATP binding site, and the authors demonstrated that it disrupts the ATPase and motor activity of the protein *in vitro*. The neurons of the *kif1B* heterozygous mice were impaired in axonal transport, and unable to deliver synaptic vesicle proteins along nerve axons. Zhao *et al.* suggest that the deficiency in transport of synaptic vesicles or other cargo causes degeneration of nerve endings, leading to distal-first axonal neuropathy.

T-cell rules of engagement

Immunologists have carefully detailed the mechanisms tumors use to avoid T-cell attack, providing valuable information for cancer vaccine design. Tumors avoid immune detection through a variety of techniques, such as mutation of immunogenic antigens, reduced expression of inhibitory molecules and downregulation of costimulatory molecules. However, even antigenic tumors can grow in a host with a fully functioning immune system by inducing T-cell immunity. Ochsenbein *et al.* investigated the mechanisms of T-cell evasion in greater detail, thoroughly analyzing the murine immune response to a variety of tumor types under several different immunological conditions. Based on these experiments, in the 28 June issue of *Nature*, the authors delineate the conditions required for tumor-specific T-cell induction. They found that the induction of a protective cytotoxic T-lymphocyte (CTL) response depends on the number and duration of tumor cells that have reached the secondary lymphatic organs. Tumors that invade secondary lymphatic organs in a diffuse manner delete CTLs, whereas those that remain outside are ignored by T cells, but do not delete them. Finally, they report that tumor antigen cross-priming of CTLs, mediated by the antigen-presenting cell's class I major histocompatibility complex, is inefficient and not protective. These findings should be considered in developing cancer immunotherapies.

Inducing clotting without viruses

An *ex vivo* gene therapy strategy appears to be safe and effective in treating patients with severe hemophilia A. Hemophilia A is an X-linked hemorrhagic disorder caused by mutations in the gene encoding coagulation factor VIII. Patients with severe disease must receive infusions of factor VIII to prevent spontaneous bleeding. This procedure is expensive and subject to contamination with infectious agents. The disease is a good candidate for gene therapy, because factor VIII is not regulated in response to bleeding, has a broad therapeutic index and does not require expression by a specific organ. Viral vectors have been used to deliver clotting factors to hemophilia B patients, but viral strategies also carry risks of immunoreactiv-

ity or viral mutation. In the 7 June issue of *NEJM*, Roth *et al.* report a successful non-viral approach to therapy. They isolated fibroblasts from patients, transfected them with a plasmid encoding factor VIII, subcloned and expanded expressing cells *in vitro*, and reinjected them into patients. A 12-month follow-up revealed no serious adverse events, and in 4 of 6 patients, plasma levels of factor VIII increased significantly. The increase in factor VIII activity coincided with a decrease in bleeding and a reduction in use of exogenous factor VIII. In one patient, the clinical effects lasted 10 months. The authors suggest this could be a safer approach to treating hemophilia.

By Kristine Novak