Research news

Pigmentation restoration

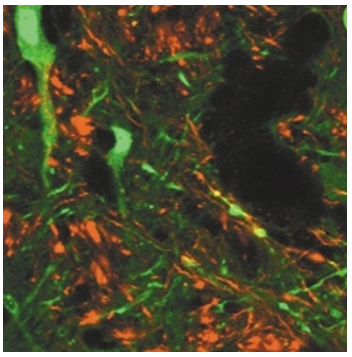
A gene therapy approach involving chimeric RNA–DNA oligonucleotides (RDOs) has been shown to correct a mutation that causes albinism in mice. Melanocytes derived from albino mice contain a point mutation in the gene encoding tyrosinase, a key enzyme in melanin synthesis. In the January issue of *Nature Biotechnology*, Alexeev *et al*. report that multiple rounds of topical application or intradermal injection of RDOs in depilated albino mice restored pigmentation in a localized area. RDOs penetrated hair melanocytes, restored tyrosinase enzymatic activity and introduced a single-base correction in the tyrosinase gene of melanogenic cells. Restored enzyme activity was detectable for up to three months after treatment, indicating that gene correction occurred in the melanocyte precursors that mature, migrate to the hair bulb and produce melanin during later hair cycles.

A purpose for perforin

What genetic defect could cause children to develop symptoms as diverse as fever, splenomegaly, hepatomegaly, pancytopenia, coagulation and neurological abnormalities? In the 3 December issue of *Science*, Stepp *et al*. report that this disorder, known as familial hemophagocytic lymphohistiocytosis (FHL), is associated with defects in the gene encoding perforin, an important mediator of lymphocyte cytotoxicity. After learning that FHL-linked loci mapped near the perforin gene, the researchers sequenced the perforin coding region of eight FHL patients. They found that half of the patients carried independent nonsense mutations in the perforin gene, whereas the other half carried missense mutations. $CD8^+$ T cells taken from these patients were severely impaired in perforin-dependent cytotoxic activity, and immunostaining showed little or no perforin in cytotoxic granules. The authors believe that perforin production may be involved in downregulation of the immune response, and that in FHL patients, perforin deficiency leads to the accumulation of T cells and macrophages, overproduction of inflammatory cytokines, and hematophagocytosis of the bone marrow, spleen, liver, lymph nodes and central nervous system.

A glowing report on poly-Q tracts

Although proteins containing long polyglutamine (poly-Q) tracts have been associated with inherited neurodegenerative disorders such as Huntington disease (HD), little is known about their role in the formation of the toxic intraneuronal aggregates that are commonly seen in poly-Q-related disorders. In the 1 January issue of *The Journal of Neuroscience*, Senut *et al*. provide direct *in vivo* evidence that poly-Q tracts themselves can mediate neurodegeneration. Using adeno-associated viral vectors the authors were able to locally express expanded poly-Q tracts fused to green fluorescent protein (97Q-GFP) in adult rat brain. Injection of the 97Q-GFP vector into adult rat striatum, the brain region typically affected in HD patients, induced the formation of brightly fluorescent neuronal cytoplasmic and nuclear aggregates (picture). GFP-expressing striatal neurons also underwent apoptosis. Low-level cumulative expression of poly-Q repeats throughout life did not cause neuronal cell death, whereas acute overexpression of poly-Q was toxic to adult neurons. This rat model will be useful in determining the molecular basis of poly-Q aggregate induction and the mechanism by which these aggregates induce neuronal apoptosis.



Taking a bite out of leishmaniasis

A new phase 2 clinical trial offers hope for an affordable and effective treatment for Indian visceral leishmaniasis, known also as 'kala azar' or 'black sickness'. Visceral leismaniasis is a potentially lethal parasitic disease acquired by sandfly bites, which affects an estimated 500,000 people per year. Current therapeutics are plagued by toxicity, high cost and the requirement of daily intravenous injections. In the 9 December issue of the *New England Journal of Medicine*, Jha *et al.* report that oral administration of the drug miltefosine led to complete elimination of parasites in all 120 patients tested within two weeks after completion of therapy. Although miltefosine caused some gastrointestinal side effects, these were tolerable and reversible. Initially developed as an anti-tumor compound, miltefosine, a close analog of phosphatidylcoline, acts by modifying cell signaling pathways and membrane synthesis. An accompanying editorial calls miltefosine "the fruit of careful basic-science and clinical research." Larger phase 3 clinical trials and phase 1 and 2 escalating-dose studies will determine whether miltefosine will fulfill its promise to be an effective, safe and affordable treatment for leishmaniasis in developing countries.

Proteasome defect in diabetes

A study published in the December issue of *Molecular and Cellular Biology* suggests that proteasome dysfunction may be involved in the development of autoimmunity in nonobese diabetic (NOD) mice, an animal model of human type I diabetes. The proteasome is a multiprotein complex involved in intracellular protein degradation and the generation of peptide fragments for class I MHC presentation. Hayashi and Faustman report that in adult NOD mice, granulocytes and macrophages stop expressing the proteasome subunit LMP2, leading to impaired processing of proteins such as the transcription factor NF-κB. NF-κB regulates the expression of genes involved in cytokine generation, lymphocyte maturation and MHC class I antigen processing and presentation. The authors propose that ablation of LMP2 in the immune system may impair antigen presentation, causing errors in lymphocyte development and regulation, and lead to autoimmunity. Genetic risk factors for type I diabetes map to the MHC region of the genome, where the *LMP2* gene is also located, indicating that tissue-specific loss of a proteasome subunit may be one more piece of this multi-gene puzzle.

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