Research News

Brain stems

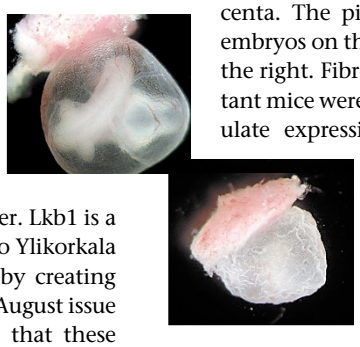
Neural stem cells (NSCs) are widely sought-after for their potential to replace damaged neural tissue. These cells, however, are rare and their exact location and features are unclear. In the 16 August issue of *Nature*, Rietze *et al*. report the purification of NSCs from adult mouse brain using flow cytometry. The authors initially isolated cells from the two brain areas with the highest reported stem-cell content (the ependymal and subventricular zones), sorted them into different populations based on cell-surface markers, and tested the ability of these populations to generate multipotent neurospheres. One population was found to contain 63% of the NSC activity present in the unsorted population. When the authors searched for these cells in mutant mice that cannot produce olfactory neurons, they found that this NSC population was depleted, supporting a central functional role for these cells. This NSC population was also able to differentiate into myocytes. These cells will facilitate the study of neural differentiation, and allow their therapeutic potential to be compared directly with that of embryonic stem cells.

How to grow a glioma

A new mouse model of glioma has provided some insight into the pathogenesis of the most common form of primary brain tumors. Several human gliomas have mutations that induce constitutive activation of receptor tyrosine signaling pathways such as the PDGF pathway. PDGF signaling normally occurs during glial cell development, and keeps glial precursors in an undifferentiated and proliferating state. In the 1 August issue of *Genes and Development*, Dai *et al*. show that overexpression of PDGF in astrocytes caused them to proliferate and dedifferentiate into glial progenitor-like cells. The authors developed transgenic mice that overexpressed PDGF in astrocytes or in central nervous system progenitor cells, leading to the formation of oligoastrocytomas and oligodendrogliomas, respectively. These findings indicate that PDGF signaling alone is sufficient to induce low-grade glioma formation, and that some gliomas might arise from glial progenitors that are trapped in an undifferentiated and proliferating state. The authors suggest that these types of tumors might respond well to drugs that promote differentiation, such as histone deacetylase inhibitors and retinoic acid derivatives, and also to PDGF receptor kinase inhibitors.

A new vasculogenesis gene

A human cancer-causing mutation might confer increased angiogenic potential by upregulating vascular endothelial growth factor (VEGF). Germline mutations in the gene encoding Lkb1 cause Peutz–Jeghers syndrome, characterized by gastrointestinal polyposis, abnormal melanin pigmentation and an increased incidence of cancer. Lkb1 is a kinase of unknown function, so Ylikorkala *et al*. investigated its activity by creating Lkb1-deficient mice. In the 17 August issue of *Science*, the authors report that these mice die at midgestation, showing defects in neural tube closure and vascular development. Aortas of the mutant embryos were thin and discontinuous, the yolk sacs failed to develop large vitelline vessels, and fetal blood vessels failed to invade the placenta. The picture shows control embryos on the left and mutant on the right. Fibroblasts from the mutant mice were also found to upregulate expression of VEGF under both normoxic and hypoxic conditions. These findings indicate that Lkb1 regulates embryonic vascular development, and possibly increases cancer risk in Peutz-Jeghers patients, through regulation of VEGF expression.



Inheritance of phobia … and flexibility

Researchers have discovered a clue to the genetic basis for anxiety disorders, which affect several million people worldwide. Although studies have suggested an autosomal dominant pattern of inheritance for this complex disorder, genome-wide scans have failed to identify a major susceptibility locus. Joint laxity is reportedly 16-fold more common in patients with panic or agoraphobia than controls. In the 10 August issue of *Cell*, Gratacos *et al*. analyzed co-segregation of these traits to identify candidate chromosome regions. By studying the pedigrees of seven families affected by panic/phobic disorders with joint laxity, they found an interstitial duplication of chromosome 15q24–26, named DUP25, that is significantly associated with these traits. The authors suggest a non-mendelian mechanism of inheritance. Several candidate genes for both anxiety disorders and joint flexibility lie within the DUP25 region. One gene encodes the neurotrophin-3 receptor, which mediates changes in neural connections associated with learning and memory. Genes encoding three subunits of the nicotinic acetylcholine receptor, which also regulates behavior, lie at the proximal end of the duplication. Finally, the authors also suggest that overexpression of the lysyl oxidase-like gene, which encodes an extracellular matrix-associated protein, might affect collagen or elastin extension and increase joint flexibility. Detailed epidemiological studies should reveal more about the clinical effects of this genomic duplication.

Hair removal

A toxic fusion protein is effective in treating chemotherapy-resistant hairy-cell leukemia. This B-cell neoplasm is characterized by the accumulation of white blood cells that possess hair-like projections, which disrupt normal blood flow and production. In most patients, the disease can be treated with cytokine therapy or chemotherapy, but many cases are resistant to these treatments and have poor prognosis. Hairy cells express high levels of CD22, a B-cell–specific adhesion molecule. In the 26 July issue of *The New England Journal of Medicine*, Kreitman *et al*. report targeting CD22-expressing cells with a recombinant immunotoxin named BL22. BL22 contains an anti-CD22 variable domain fused to truncated *Pseudomonas* exotoxin. The authors had previously shown that BL22 treatment induced complete remission in mice with a B-cell lymphoma and killed human malignant B cells in culture. They performed a dose-escalation trial of 16 patients with hairy-cell leukemia who were resistant to treatment with purine analogs. Strikingly, BL22 induced complete remission in 11 of the 16 patients, as demonstrated by an absence of tumor cells in the peripheral blood and bone marrow for four weeks. Spleen size was also reduced in these patients, and neutrophil and platelet numbers increased, along with hemoglobin levels. Additional studies are required to determine whether additional cycles of therapy have any affect on relapsing patients and to collect dose-response data.

By Kristine Novak