Mood manager

Mood disorders affect serotonin-mediated neurotransmission, but the nature of the underlying defect is not understood. A recent study in *Science* (**311**, 77–80; 2006) identifies a new binding partner of serotonin receptors, pointing to a potential molecular mechanism to account for depression.

Per Svenningsson *et al.* searched for binding partners of the $5HT_{1B}$ serotonin receptor and found a poorly understood protein called p11. They report that p11 increased the localization of 5-HT_{1B} receptors at the cell surface. Looking at the brains of mice treated with antidepressants, they observed an increase in p11 levels. In contrast, the protein was decreased in a mouse model of depression and in brain from depressed patients.

The *in vivo* effects of manipulating p11 were striking. p11 knockout mice showed a depression-like phenotype and had reduced responses to serotonin agonists and to antidepressant. What's more, overexpressing p11 in mice elicited behaviors seen after antidepressant treatment. —*JCL*

Accomplice to angiogenesis

VEGF seems like the do-all molecule, turning on whenever the body issues a new call for blood vessels. But how does VEGF coordinate such a complicated job?

It seems that VEGF enlists some powerful helpers. VEGF recruits and retains bone marrow cells that in turn carry out some of the tasks of angiogenesis in adult organisms, report Myriam Grunewald *et al.* in the 13 January *Cell* (124, 175–189; 2006).

The researchers first observed that, in mice, VEGF summons hematopoietic cells from the bone marrow and coaxes them to settle down in areas of high VEGF expression. VEGF induces expression of another factor, SDF-1. SDF-1 helps retain a specialized population of recruited cells close to angiogenic vessels, where the cells pump out proangiogenic factors.

This mechanism is distinct from another, which involves the mobilization endothelial progenitor cells from the bone marrow—cells that can incorporate directly into the vasculature.

Previous work had suggested that accessory cells recruited from the bone marrow could promote vessel sprouting. The new findings begin to flesh out the players involved and add impetus to antiangiogenic therapeutic approaches that block SDF-1.—*CS*

Transport genes speed vaccines

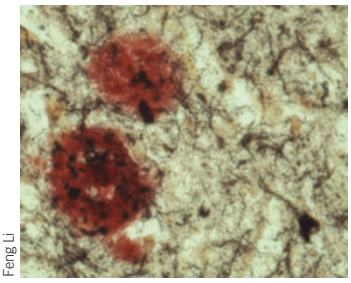
A new approach to improving vaccine potency harnesses a cellular pathway used to process antigen and stimulate T cells (*PLoS Pathog.* **1**, e36; 2005).

For a vaccine antigen to induce efficient cytotoxic T-cell responses, antigen-presenting cells must display antigen-derived peptides on their surface in conjunction with major histocompatability complex (MHC) class I molecules. Crucial to antigen presentation are the cellular proteins TAP1 and TAP2 (transporters associated with antigen processing), which transport the antigenic peptides to the MHC molecules.

Timothy Vitalis *et al*. engineered vaccinia viruses to express human TAP1 and TAP2 proteins. With this vaccine they were able to use 100-fold lower doses of virus to protect mice from lethal infection. Providing more TAP had allowed cells to display antigen more efficiently to T cells, the investigators found.

Many vaccines are protective only if they are administered with adjuvants, immune stimulatory molecules that boost the immune response to the vaccine. But many conventional adjuvants are toxic, which limits their use in people. The new work could offer an alternative strategy.—*CT*

Alzheimer protein protects



Feng Li

Two amyloid-β plaques (red) and a tangle (black, lower right) in the brain of an Alzheimer patient.

A pubmed search for 'β-amyloid precursor protein' pulls up more than 3,000 citations—yet the endogenous role of this protein, implicated in Alzheimer disease, remains unclear. Ping Han *et al.* propose one function in the *Journal of Neuroscience* (25, 11542–11552; 2005).

The researchers suggest that β-amyloid precursor protein (APP) protects neurons from death by inhibiting phosphorylation of tau. APP may thereby prevent the formation of the potentially toxic tau-protein aggregates characteristic of Alzheimer disease. The key intermediary between APP and tau seems to be cyclin-dependent kinase 5 (CDK5), a protein previously implicated in neuronal cell death.

The researchers came to these conclusions in part by comparing neurons from APP-deficient and wild-type mice. They found that that the APP-deficient neurons had increased activation of CDK5 and increased tau phosphorylation, and were more susceptible to excitotoxic cell death. In contrast, neurons from mice overexpressing APP had reduced levels of CDK5 and were less susceptible to cell death. The extracellular domain of APP, which is thought to be neuroprotective, seemed to be responsible for regulating CDK5.

Understanding whether the mechanism operates *in vivo* will require further studies. Meanwhile, the findings should bolster drug-development approaches that target APP and boost the formation of the extracellular form of the protein.—*CS*

Kidney killer goes nuclear

The transcription factor STAT-6, a molecule best known for helping regulate the immune response, is now implicated in autosomal-dominant polycystic kidney disease, a common inherited disease in humans.

More than 85 percent of human cases of the disease are due to mutations in the gene encoding polycystin-1. Little is known about how this protein operates, but it is known to be a large integral membrane protein expressed on the cilia of kidney epithelial cells.

Seng Hui Low *et al.* provide evidence that polycystin-1 undergoes proteolytic cleavage, leading to nuclear translocation of its cytoplasmic tail. This tail seems to interact with STAT-6 and a cofactor, and stimulate gene transcription—possibly leading to cysts.

In the January *Developmental Cell* (**10**, 57–69), the researchers report that the polycystin-1 tail and STAT-6 were both localized to the cilia in kidney cells in culture. But when the flow of fluid across the cells was stopped, the polycystin-1 tail and STAT-6 both entered the nucleus.

Elevated nuclear levels of polycystin-1 and STAT-6 also were observed in tissue of individuals with the disease. What's more, expression of the human polycystin-1 tail in zebrafish resulted in renal cyst formation. Exactly how mutations in polycystin-1 kick-start this mechanism and the consequences of STAT-6 gene activation in the kidney remain unclear.—*CS*

Written by Juan Carlos López, Charlotte Schubert and Clare Thomas