Research News

Gene therapy sees the light

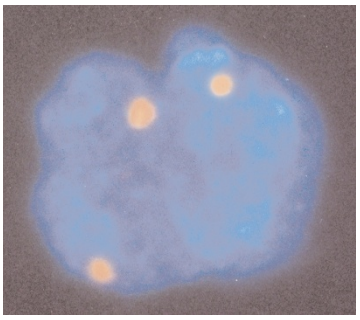
A light-activated vector offers a new strategy for a targeted and inducible gene delivery. Although gene therapy has advanced from proof of principle to early stage clinical trials, it has not proven to be the medical panacea that many had hoped, due to problems associated with efficiency and precision of gene delivery. Viral vectors are the current delivery method of choice, but these friendly Trojan horses can infect a wide range of tissues *in vivo*. In the December issue of *Gene Therapy*, Pandori and Sano report the construction of a photo-activated vector whose infectivity can be controlled temporally and spatially. Attachment of a biotin derivative to an amphotropic murine retrovirus containing the *lacZ* reporter gene inhibited infectivity of the retrovirus vector while in transit. Upon reaching the target site, the biotin molecule was cleaved by exposure to light of wavelengths between 300–365 nm, allowing the vector to infect cells. Thus, infectivity can be inhibited and then activated under controlled conditions, making this vector construct a potentially safer and more efficient gene delivery vehicle.

At last, a ligand for RXR

A long-sought ligand for the orphan retinoid-X receptor (RXR) been identified as a polyunsaturated fatty acid involved in brain development. RXR is a nuclear receptor that heterodimerizes with other proteins, such as the retinoic acid receptor, to function as a ligand-activated transcription factor. Although RXR is activated by the vitamin A metabolite *in vitro*, little is known about ligands that can activate RXR *in vivo*. In the 15 December issue of *Science*, Mata de Urquiza *et al*. report the isolation of an endogenous RXR ligand from mouse brain tissue. Mass spectrometry analysis revealed the ligand to be the polyunsaturated fatty acid DHA. The authors show that DHA specifically binds and activates RXR, but does not activate other similar receptors such as the retinoic acid receptor. DHA is expressed in mammalian brain during early stages of development, and has been shown to be required for brain maturation in rodents and people. DHA-deficient rats and humans develop learning defects, and the fatty acid is also known to influence metabolism and energy homeostasis. The authors suggest that DHA influences neural function through activation of the RXR signaling pathway.

Fetal FISH

Researchers in Hong Kong have developed a non-invasive prenatal diagnostic test for Down syndrome. Fetal chromosomal abnormalities such as trisomy 21, the cause of Down syndrome, are currently detected through invasive procedures such as amniocentesis. In the 25 November issue of *The Lancet*, Poon *et al*. report that intact fetal cells are present in the plasma of pregnant women, and that these cells can be harvested and genetically analyzed. Using fluorescent *in situ* hybridization (FISH), the authors were able to detect the presence (picture) or absence of fetal trisomy 21 in fetal cells isolated from ten maternal plasma samples. These results are surprising, as plasma was believed to be acellular, although fetal DNA has been previously detected in maternal blood. The authors were also able to use the test to determine the sex of the fetuses as early as the end of the first trimester of pregnancy. All results were confirmed by karyotypic analysis of amniotic fluid. Ultimately, with further technical refinements, prenatal diagnosis by maternal plasma DNA analysis may be a safe approach for detecting genetic defects and chromosomal abnormalities.



Power beads

Forget healing crystals—drug-releasing beads may be the next therapeutic delivery method. In the January issue of *Nature Biotechnology*, two studies describe the creation of a protein-producing matrix by mixing genetically-engineered kidney epithelial cells with a copolymer derived from seaweed. This mixture forms a beadlike matrix that allows free exchange of proteins, nutrients and oxygen. Read *et al*. and Joki *et al*. created encapsulated cells that constitutively overexpress endostatin, an anti-angiogeneic protein fragment that is currently being tested in clinical trials as an anti-cancer drug. Read *et al*. report that intracerebral implantation of these cells prevents tumor formation and growth in the brains of immunocompetent rats, while Joki *et al*. report that the implanted capsules reduce the growth of existing tumors by 70%. Studies have shown that continuous administration improves endostatin efficacy in mice, but would require patients to receive frequent injections or carry a delivery apparatus. The encapsulated cells survive and maintain endostatin production for at least four months after intracerebral implantation. They also exclude inflammatory cells, protecting the cells from rejection. These beads may be developed as a simplified method to continuously deliver anti-angiogenics and other therapeutic proteins to people.

Diabetes signals

Two studies published in recent issues of *Nature* shed light on the signal transduction pathways underlying Type II diabetes mellitus. In the 14 December issue, Hart *et al*. report that pancreatic β cells express fibroblast growth factor receptors and ligands. Transgenic mice that produce a mutant form of the FGF receptor FGFR1c developed a phenotype resembling type II diabetes in humans, including fewer β cells, deficits in glucose homeostasis, and impaired insulin processing. The homeobox gene Ipf1 has been genetically linked to diabetes and the authors show that this gene regulates FGFR1c expression. Thus, the FGF pathway may mediate the nutritional and mitogenic control of β-cell expansion and function, and future studies should determine whether aberrant FGF signaling also contributes to human diabetes. In a second study published in the 21/28 December issue, Pende *et al*. show that mice deficient in S6 kinase (S6K1), a member of the PI3-kinase signaling pathway, develop a phenotype resembling malnutrition-induced type II diabetes. S6K1-deficient mice develop hypoinsulinemia and glucose intolerance, due to a decrease in β-cell size and decreased insulin secretion. Thus, S6K is involved in glucose homeostasis, and may underlie the link between early malnutrition and diabetes.

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