Alternate delivery

Getting genes or drugs to the right place, without shedding bits in unintended tissues, remains a major challenge for gene therapy and drug delivery systems. In the August *Nature Biotechnology*, Yamada *et al.* cleanly deliver a gene encoding a human clotting factor to its intended target, liver cells. The authors bypassed conventional gene therapy vectors by loading the gene into hollow, engineered nanoparticles of recombinant hepatitis B virus (HBV) envelope proteins.

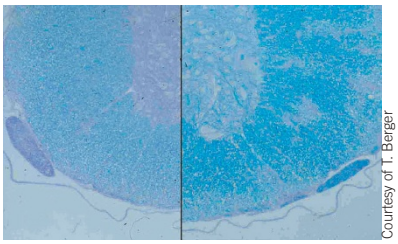
While working on HBV vaccines ten years ago, the investigators discovered that viral envelope proteins harvested from recombinant yeast cells formed spherical particles of envelope proteins embedded in a yeast-derived phospholipid vesicle. These nanoparticles were able to bind and fuse to liver cells.

In their current study, the researchers found that the particles withstood loading of the cargo gene by electroporation. Particles carrying the GFP gene homed to human hepatocellular carcinomas implanted into mice, but not to other carcinomas or mouse tissues. Delivery of the gene encoding human clotting factor IX into the xenograft resulted in factor IX production at levels relevant to the treatment of hemophilia B.

The nanoparticles seem adaptable to different targets. In cell culture, particles engineered to contain human epidermal growth factor homed to EGF receptor–containing cells. But the particles still have problems, including potentially high immunogenicity. Methods to eliminate immunogenic regions and increase transfection efficiency may be the next steps forward.

Managing multiple sclerosis

Up to 80% of patients with an initial single neurologic episode will progress to clinically definite multiple sclerosis. Magnetic resonance imaging (MRI) can now help predict who will progress, but determining when has seemed largely a matter of guesswork.



Courtesy of T. Berger

A study in the 10 July *New England Journal of Medicine* eliminates some of this guesswork. Berger *et al.* tested patients for the presence of serum antibodies against two proteins: myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP). A total of 103 patients with a clinically isolated syndrome, positive MRI findings and other indications of multiple sclerosis were followed for up to seven years.

Only 9 of 39 antibody-seronegative patients had a relapse, and the mean time to relapse was about 45 months. In contrast, the vast majority of patients with antibodies to both MOG and MBP (21 of 22 patients) had a relapse within a mean time of 7.5 months. The presence of antibodies to MOG alone was also associated with an increased risk of early relapse.

Whether the antibodies themselves are a cause or a consequence of the myelin destruction that occurs in multiple sclerosis is not clear. But they may interact with other components of the immune system to promote demyelination: on the left is an inflamed spinal-cord cross-section from a rat treated with MOG-specific T cells. Adding an antibody to MOG four days later induces demyelination (right). These new tools could ultimately help determine who might benefit from early interventions.

Charlotte Schubert & Pierrette Lo

Stopping senescence in carcinogenesis

The powerful oncoprotein MYC interacts with the gene behind a premature aging disease, reveals a study in the 2 May *Genes and Development*. Individuals lacking the human Werner syndrome gene, the DNA helicase *WRN*, not only age prematurely but also have an elevated risk of malignancy, and their cells are genetically unstable. MYC had previously been shown to upregulate the expression of genes involved in cellular senescence, such as the telomere-associated gene *TERT*. As a gene apparently central to senescence, *WRN* also seemed like a promising MYC target gene. Grandori *et al.* found that MYC, along with its binding partner, MAX, bound the *WRN* promoter and upregulated *WRN* in cultured cells. The investigators hypothesize that upregulation of *WRN* by oncogenic MYC could suppress cellular senescence, thereby promoting tumor formation. Indeed, the investigators found that they could induce cellular senescence in MYC-overexpressing cells by removing *WRN*. Consistent with their hypothesis, individuals with Werner syndrome do not typically display MYC-associated tumor types such as Burkitt lymphoma or large B-cell lymphomas.

Sensitized to stress

If life's stresses are getting you down, you might blame your coworkers, your partner, grant deadlines or bad traffic. Or you could blame your genes. In the 18 July *Science*, Caspi *et al.* reveal that individuals with certain 5′ polymorphisms in the serotonin transporter (5-HTT) gene seem particularly susceptible to stress-associated depression. Among the 847 study subjects, 17% were homozygous for the 'short' allele, which is transcribed with lower efficiency than the 'long' allele. Subjects between the ages of 21 and 26 were monitored for depression and stressful life events such as health, employment or relationship problems. Genotype did not seem to influence depression among the 30% of individuals who experienced no stressful events. But among study subjects with four or more stressful events and at least one copy of the short variant, 33% became depressed. By comparison, only 17% of subjects homozygous for the long variant became depressed after multiple stressful events. The authors speculate that depression and many other complex disorders might have a genetic influence that hinges on exposure to environmental risks—like stress.

Antibacterial aspirin

Staphylococcus aureus, a bacterium that is becoming increasingly resistant to conventional antibiotics, responds to an even older type of drug: aspirin. In animal models of S. _aureus_ infection, aspirin reduces bacterial numbers and tissue damage associated with the disease. In the July 2003 _Journal of Clinical Investigation_, Kupferwasser _et al._ show how this happens. They found that salicylic acid (SAL), the major metabolite of aspirin, erodes two bacterial systems of defense: the drug decreases expression of a-hemolysin, a toxin that causes tissue damage, and decreases binding of the pathogen to fibronectin, a necessary prerequisite for infection of host cells. SAL, it seems, does this by activating a bacterial stress-response gene, sigB, that downregulates sarA, a regulator of virulence genes. SAL treatment decreased the severity of _S. aureus_–induced disease in rabbits but had no effect in rabbits infected with sigB or sarA knockout strains. Now investigators know that SAL works by curtailing the virulence of the microbe, rather than inducing host antibacterial activity. Aspirin could be useful as an adjunct therapy in serious cases of _S. aureus_ infection.