

Neurobiology

Hear hear

Cell 2006;127:277-89

Researchers have identified a mechanism that may underlie a recessive form of inherited deafness in human beings. This is linked to a protein called otoferlin, which is plugged into the plasma membrane of inner hair cells in the cochlea.

Upon stimulation by auditory signals, the inner hair cells release neurotransmitters to trigger the firing of auditory nerves. This release is only possible if the vesicles that contain the neurotransmitters fuse with the cell membrane of these hair cells. This mechanism, called exocytosis, requires calcium, and, the researchers have discovered using mice, otoferlin. Where otoferlin is defective, action potentials in auditory nerves never ensue and deafness results.

HIV/AIDS

The fighter within

Proc Natl Acad Sci USA 2006;103:17 372-7

Gene therapy has been in vogue for some time, and so the plausibility of using it to treat AIDS has been explored. And the first phase of a small non-randomised trial designed primarily to test the safety of this approach has had promising results.

Researchers recruited five patients who failed to respond to at least two conventional antiviral regimens and isolated and purified helper T cells from their blood. They stuffed these with a genetically modified HIV that carried the mirror image of a gene that enables the virus to multiply. When reintroduced into the patients, these T cells, now carrying the "antisense" gene, would inhibit further multiplication of virulent HIV within new T cells. Because the helper T cells are continuously replaced, infected T cells will be gradually removed from the body.

The immune system worked better in four of the five patients.

Infectious diseases

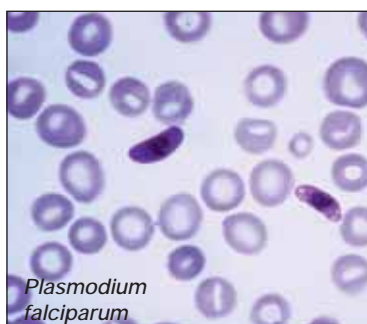
Africa

The problem of drug resistance, particularly in patients infected with HIV, has long complicated the management of tuberculosis and malaria in Africa.

Now researchers report that 6% of patients with culture confirmed tuberculosis in KwaZulu-Natal, South Africa, harbour strains of mycobacteria that are resistant to isoniazid, rifampicin, and at least two second line drugs.

This is worrying for two reasons. Firstly, a disease with resistance as high as this is bound to be rapidly and universally fatal—52 of the 53 affected people died within a month. All were co-infected with HIV. Secondly, this outbreak may not be an isolated event. Poor infection control, poor prescribing, low quality drugs, and low adherence are largely to blame.

Meanwhile, Malawi, which was the first country to abandon chloroquine in 1993 on grounds of resistance, has reported the re-emergence of chloroquine sensitive malarial strains, probably because of the role played by co-trimoxazole. A total of 210 infected children were recruited into a clinical trial. Co-trimoxazole cured only 21% of the children, but chloroquine cured 99%. This is good news considering the lethality of falciparum malaria and the relative merits of chloroquine. But reinstating chloroquine without wiping out resistance would be a mistake, the researchers argue.



This has prompted the move into the next phase of the study, which would involve more patients, including those with earlier stages of the disease. Where antiretroviral chemotherapy fails, gene therapy may come to the rescue.

Internal medicine

The kill switch for pemphigus

N Engl J Med 2006;355:1772-9

Pemphigus vulgaris, like many other autoimmune diseases, is currently treated by damping down the immune system with high doses of corticosteroids and other immunosuppressants. Rituximab, a monoclonal antibody that depletes the B lymphocytes associated with the disease, has been a potential alternative, and US researchers report promising results.

Eleven patients with extensive pemphigus vulgaris resistant to standard management were treated for six months

with rituximab and intravenous immunoglobulin. Sustained remission occurred in nine patients, and the other two had relapses after initial treatment, only to respond well to further infusions of rituximab. None of the patients reported serious side effects, but the long term effects of the drug are undocumented.

Obstetrics and gynaecology

Inducing danger

Lancet 2006;368:1444-8

Amniotic fluid embolism, although a rare complication of labour and delivery, can be catastrophic. Its incidence is unclear because no standard diagnostic test exists. The latest attempt to unpick the epidemiology comes from Canada, where researchers analysed routine hospital data covering 70% of all deliveries between 1991 and 2002. They found 180 recorded cases of

amniotic fluid embolism among almost three million singleton deliveries and five among nearly 34 000 multiple births. Twenty four of the women with singleton pregnancies died.

Because strong uterine contractions are thought to increase the risk, the researchers were particularly interested in women who had had labour induced. In this cohort, induction was associated with double the risk of an amniotic embolism compared with spontaneous labour. The absolute risks though remain small. The figures show that there would be an extra four or five cases of amniotic fluid embolism for every 100 000 women induced.

Molecular biology

Troublesome genes

Science 2006 Oct 26, doi: 10.1126/science.1135245

Inflammatory bowel disease, an umbrella term for Crohn's disease and ulcerative colitis, can cause severe abdominal pain, diarrhoea, and gastrointestinal bleeding. The involvement of genetic factors has long been suspected, and researchers have now identified a potential candidate.

The gene lies on the short arm of the first chromosome and codes for part of a receptor for the cell signalling molecule, interleukin 23, which has a role in causing inflammation. Researchers found a strong association between this gene (IL23R) and Crohn's disease. Although an uncommon variation in this gene conferred strong protection against Crohn's, additional portions of the IL23R gene, which do not code for the receptor, also seem to be involved.

This association has been further replicated in other cohorts of patients with inflammatory bowel disease, and association with ulcerative colitis also exists. Researchers will now have to further probe the operating mechanisms of interleukin 23 to see if they can target this pathway for therapeutic purposes.