Taking on tuberculosis

An experimental compound against tuberculosis has more power against the disease than any drug now available, according to studies in mice by Koen Andries *et al.* in the 9 December online issue of *Science* (doi:10.1126/science.1106753). What's more, experiments in animals and a small number of people suggest that the compound is safe.

More than a billion people are infected with *Mycobacterium tuberculosis* worldwide, drug-resistant strains are on the rise, and antibiotic regimens can take months to complete. When administered with a combination of three commonly used drugs against tuberculosis, the new compound cleared *M. tuberculosis* from infected mice in half the time of the triple combination alone. The new compound was also effective against drug-resistant strains. The drug seems to work by a unique mechanism; sequence analysis of strains that had become resistant to the drug suggested that the drug targets the proton pump of ATP synthase. —*CS*

Deconstructing depression

Xiaodong Zhang *et al.* have pinned a gene variant to major depression in people; the gene encodes tryptophan hydroxylase–2, a rate-limiting enzyme for the synthesis of the neurotransmitter serotonin. A single nucleotide polymorphism (SNP) in this gene could help explain why some individuals respond poorly to serotonin-reuptake inhibitors such as Prozac.

In the 9 December online issue of *Neuron* (doi:10.1016/neuron.2004.12.014) the researchers show that the SNP was present in nine of 87 patients with major unipolar depression. In contrast, the SNP was present in none of 60 patients with bipolar disorder and only three of 219 controls who did not have major depression—although these three individuals had either mild depression or generalized anxiety symptoms.

Cell culture data suggest that the brains of individuals with the variant might produce less serotonin. These studies revealed that the gene variant with the SNP encodes an enzyme with sharply decreased activity in cells. That result dovetails with the finding that the nine individuals with the SNP and major depression responded poorly to serotonin-reuptake inhibitors; presumably there would be less serotonin available to manipulate with the drugs.

Genetic studies have suggested that depression has a hereditary component but the genes involved have been hard to pin down. Work earlier this year showed that a SNP in the tryptophan hydroxylase–2 gene in mice is associated with symptoms of depression in the animals. —*CS*

Cholesterol on the brain

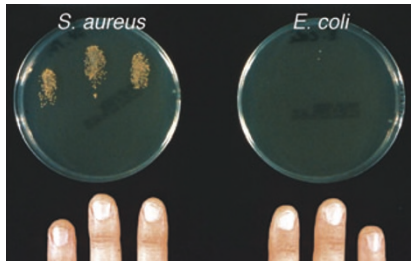
Cholesterol-lowering drugs, such as the statins, reduce the risk of developing Alzheimer disease, according to retrospective epidemiological studies. But reducing cholesterol levels in the brains of rodents seems to promote neurodegeneration.

In an attempt to resolve this apparent inconsistency, Jose Abad-Rodríguez *et al.* examine how cholesterol levels in neuronal membranes influence the production of amyloid-β (Aβ)—the main constituent of the amyloid plaques that form in the brains of patients with Alzheimer disease. The findings show that cholesterol reduction in the brain could do more harm than good (*J. Cell Biol.* **167**, 953–960; 2004).

Aβ production was previously thought to occur mainly in cholesterol-rich microdomains of the neuronal membrane, known as rafts. The evidence for this model, however, came largely from experiments that overexpressed amyloid precursor protein (APP) and the secretase enzymes that cleave APP to generate Aβ. Abad-Rodríguez *et al.* found that when APP and the β-secretase BACE1 were expressed at physiological levels, APP was almost entirely excluded from the rafts, whereas BACE1 was present in both raft and nonraft domains. If the membrane fluidity was increased by lowering the cholesterol level in cultured hippocampal neurons, APP and BACE1 were colocalized more frequently, leading to a rise in Aβ production. Therefore, cholesterol seems to create a barrier to APP–BACE1 interaction.

How can these observations be reconciled with the effects of statins in humans? As the researchers point out, most of the commonly used statins are poor penetrators of the blood-brain barrier, so it is unlikely that they act directly on brain neurons. Instead, their benefits might derive from anti-inflammatory or antioxidant properties. These new findings indicate that, far from trying to reduce brain cholesterol, care should be taken to preserve the cholesterol content of brain neurons. —*HW*

Killer Skin



Courtesy of R.Gläser

S. aureus survives on fingertips whereas *E. coli* does not.

An antimicrobial compound on human skin fights off infection with *Escherichia coli*, a common microbe in the intestine, report Regine Gläser *et al.* in the January *Nature Immunology* (6, 57-64; 2005). Previous studies had identified a host of different compounds that fight off microbes on the skin, such as lysozyme and β-defensin. The *E. coli*-fighting compound, psoriasin, is unique in that it seems to be aimed specifically at *E. coli* instead of a broad range of microbes. That was apparent in experiments in which fingers were inoculated with either *E. coli* or another bacterium such as *Staphylococcus aureus*: *E. coli* was killed while other bacteria survived. Survival of *E. coli* could be blocked by antibodies against psoriasin. Previous work has shown that individuals with psoriasis have high levels of psoriasin in skin lesions, and other studies have found several related proteins of unknown function expressed in several cell types, including epithelial tissues. The authors provide evidence that psoriasin might work through sequestering zinc ions; it is possible, speculate the authors, that alterations in psoriasin activity could help explain the susceptibility to infection of individuals with disorders of zinc metabolism. —*CS*

The best responders

Research on a small population of asthma patients has found a gene variant that seems to be associated with high responsiveness to inhaled corticosteroids, a common treatment for asthma. Kelan Tantisira *et al.* (*Proc. Natl. Acad. Sci. USA* **52**, 18099–18104; 2004) evaluated children with asthma for a polymorphism in the gene encoding the transcription factor T-bet, which controls T-cell development. About five percent of patients had the polymorphism, about the same frequency as the general population. About 210 patients received corticosteroids as part of a larger, four-year trial. At the end of the trial, treated patients with the variant performed up to the level of nonasthmatics on a measure of airway responsiveness to allergens, and outperformed patients who did not have the polymorphism. The biological basis for this apparent enhanced response remains unknown. The work suggests that it might be possible to genetically stratify asthma patients based on their likelihood to respond well to corticosteroids. —*CS*

Written by Charlotte Schubert and Heather Wood, Senior Editor, *Nature Reviews Neuroscience*