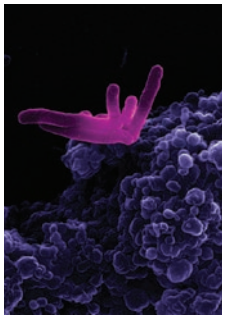
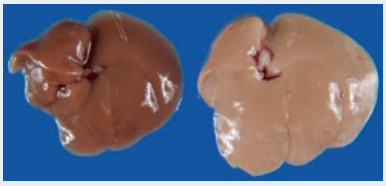
Beating tuberculosis with a beefed up BCG



Tuberculosis is a major global health threat. Although more than 3 billion doses of the BCG vaccine have been administered to fight tuberculosis, the ability of the vaccine to protect adults is limited as is its efficacy against newly emerging isolates. In this issue, Grode et al. (pages 2472–2479) boost the immunogenicity of BCG by creating a novel vaccine strain with high efficacy against tuberculosis. The researchers engineered a BCG strain that secretes the listeriolysin protein, which punches holes in the membranes of phagosomes where *M. tuberculosis* is located, allowing better T cell–mediated immunity. Because listeriolysin works optimally at a pH of 5.8, the researchers also deleted the urease C gene of BCG, which normally plays a role in pH neutralization of the phagosome. The lack of urease C allowed phagosomal acidification and provided an ideal pH environment for listeriolysin. The new vaccine strain protected mice against tuberculosis significantly better than the parental BCG strain. Superior protection was induced not only against the laboratory strain of *M. tuberculosis* but also against a clinical isolate of the Beijing/W family, a strain of tuberculosis that is spreading all over the world, is drug resistant, and is responsible for the most threatening disease outbreaks.

Solving a 72-year-old dietary cholesterol puzzle

End-product feedback regulation of a biosynthetic pathway was first demonstrated 72 years ago when Rudolph Shoenheimer observed that mice synthesized large amounts of cholesterol when fed a low-cholesterol diet but that this synthesis stopped when the mice were fed cholesterol. Many details of this cholesterol feedback have since been worked out, but the main mechanism by which cells in the liver sense cholesterol and thus regulate cholesterol production has remained unknown. In this issue, Engelking et al. (pages 2489–2498) finally solve the mystery of the Shoenheimer effect. Through studies of mice lacking the 2 mammalian *Insig* genes — *Insig1* and *Insig2* — in the liver, they show that Insig proteins are essential components of this cholesterol feedback. On a normal diet, the mice overaccumulated cholesterol and fats in the liver, but levels of SREBPs — molecules that sense cholesterol and regulate its synthesis — and SREBP target genes were not reduced. Normally, cholesterol intake reduces levels of SREBP and the genes that synthesize cholesterol and fat, but this response was blunted in the knockout mice, and fat and cholesterol synthesis was not suppressed. The mice also had elevated levels of HMG-CoA reductase, a key enzyme for cholesterol synthesis. The data indicate that the entire pathway for SREBP processing functions in the liver. Further, this pathway is responsible for the synthesis of cholesterol as well as the feedback suppression of synthesis when cholesterol is absorbed from the diet.



Insulin sensitivity gets a kick out of SOCS-7

Insulin resistance is a fundamental factor in noninsulin-dependent diabetes. Prolonged activation of the insulin receptor, inflammation, and excessive insulin levels can induce insulin resistance by decreasing levels of insulin receptor substrate (IRS) proteins. However, the mechanism underlying the destruction of IRS proteins and subsequent resistance to insulin has not been well defined. Proteins of the SOCS family have been implicated in the negative regulation of insulin signaling and are known to regulate cytokine signaling by targeting proteins for degradation by the proteosome. In particular, the function of the SOCS-7 protein was previously unclear. In this issue, Banks et al. (pages 2462–2471) demonstrate that SOCS-7 regulates insulin signaling by associating with several components of the insulin-signaling cascade. The researchers generated SOCS-7–deficient mice, one of the only mouse knockout models featuring increased insulin sensitivity, and showed that cells lacking SOCS-7 have increased IRS protein levels and prolonged IRS activation. SOCS-7–deficient mice were more insulin sensitive as measured by a glucose tolerance test and an insulin tolerance test. In addition, SOCS-7–deficient mice exhibited increased growth of pancreatic islets with increased fasting insulin levels and hypoglycemia. These data suggest that SOCS-7 is a potent regulator of glucose homeostasis and insulin signaling.

Effective Alzheimer treatment: the nose knows

Alzheimer disease (AD) is the most common form of senile dementia, with no effective treatment available. Previous studies utilizing immunization against the Aβ peptide, a key pathogenic player in AD, to generate antibodies against Aβ were discontinued because of unacceptable side effects in patients. Now Frenkel et al. (pages 2423–2433) describe a novel immunologic approach for the treatment of AD. The researchers used a specific nasal vaccination to decrease AD burden in mice. The vaccine consisted of an FDA-approved drug currently used to treat multiple sclerosis plus a recently developed nasal adjuvant that has been shown to be safe in humans. The vaccine activated microglia cells, which then cleared amyloid in the brain without evidence of toxic effects. These findings have basic and clinically relevant implications. The discovery of a nonantibody-mediated method to clear Aβ could lead to a treatment for patients who show signs and symptoms of AD. Moreover, the compounds used have already been tested in humans and shown to be safe.