Restrictions on HIV

The identity of a protein that is key to understanding why humans, but not monkeys, are susceptible to HIV-1 is revealed by Matthew Stemlau et al. in the 26 February Nature. This protein, TRIM-5α, counteracts HIV-1 infection in macaques but allows HIV-1 infection in humans. TRIM-5α is encoded by the gene Lv1, which was shown several years ago to shield monkey cells from infection. Until now, no one knew what Lv1 actually encoded. To find out, Stemlau et al. took a very straightforward approach: they transformed cells with a monkey cDNA library and selected for cells that were resistant to HIV-1 based on the production of reporter protein. Out came TRIM-5α.

Not much is known about TRIM proteins, but there are at least 36 of them in humans, many of which localize to discrete cellular compartments. TRIM-5α, for instance, forms speckles in the cytoplasm—consistent with the view that it could hijack HIV-1 before it enters the nucleus to undergo reverse transcription. Many other mechanisms could come into play: for instance, one well-known TRIM family member, PML, adds a ubiquitin-like moiety, SUMO, to target proteins. However it works, TRIM-5α appears to target the capsid protein of HIV-1.

Organ Orchestration

The regulatory networks that impinge on the development and daily upkeep of individual organs became more clear with a report from Duncan Odom et al. in the 27 February Science. Using a microarray approach, the researchers examined three HNF transcription factors central to the liver and pancreas—two organs that keep glucose levels stable.

The approach involved first enriching for DNA sequences that bind to chromatin by immunoprecipitation with HNF-specific antibodies. The DNA was then used to probe a microarray containing human promoter sequences.

Odom et al. found out how crucial HNF proteins are to these organs: HNF-4α bound to an extremely high percentage of promoters—about 12%. The researchers are beginning to tease out how HNFs can precisely respond to both long-term and short-term physiological input, paving the way for a detailed examination of the relationships between these central regulators and insulin. Since the mid-1990s, HNFs have been implicated in both type 1 and 2 diabetes. Certain polymorphisms in HNF-4α, for instance, are associated with increased insulin secretion and reduced risk of type 2 diabetes, whereas others increase risk.

Fat, in all the wrong places

Insulin resistance almost inevitably precedes type 2 diabetes, sometimes by several decades. This almost-silent problem has a compatriot in high levels of triglycerides in muscle. In the 12 February NEJM, Kitt Falk Petersen et al. examine the basis for the accumulation of triglycerides, and emerge with a well-studied culprit: the mitochondrion.

The researchers evaluated young, lean and insulin-resistant offspring of individuals with type 2 diabetes. Offspring from these individuals are often insulin resistant, presumably in part because of their genes. In contrast to many patients with type 2 diabetes, the subjects were lean and healthy, and thus ideal for analyzing the defects leading to insulin resistance.

Although the subjects may have been thin, their muscles were not. Insulin resistance in muscle was accompanied by an 80% increase in muscle lipids, compared with insulin-sensitive control subjects. That result is consistent with previous findings suggesting that dysregulated fat metabolism may contribute to insulin resistance.

What causes this dysregulation? In the insulin-resistant patients mitochondria lacked spark: the rate of mitochondrial ATP synthesis was 30% lower than in control subjects. The findings suggest that an inherited defect in oxidative phosphorylation could bump up lipid levels and lead to insulin resistance in muscle. The results also jibe with postmortem studies of type 2 diabetes patients, showing that their mitochondria are small and have impaired oxidative capacity.

SARS mouse

Ferrets, cats and monkeys are emerging as models for SARS, but a more familiar animal, the mouse, could also be on deck. In the April Journal of Virology, Kanta Subbarao et al. report that mice could be infected with the virus by delivery of high doses through the nose. The virus replicated efficiently in the respiratory tract, and the lungs on day 2 had mild inflammation. The virus, however, was cleared within a week, and the mice did not fall ill. Nonetheless, the mice could be useful for testing some drug leads and vaccines. For instance, the investigators were able to show that infected mice develop a robust neutralizing antibody response and a high degree of resistance to subsequent infection. This is in line with recent work in macaques showing that these animals can also produce a strong neutralizing antibody response against the virus. Such findings bode well for the development of a vaccine, although researchers caution that work on other coronaviruses has found evidence of ‘antibody-mediated enhancement,’ in which disease is exacerbated upon reinfection, as occurs with dengue virus.

Stay sharp

Keeping the mind limber can hold back the development of Alzheimer and Huntington disease in humans and in mouse models. In the 3 March Journal of Neuroscience, Tara Spires et al. show how an enriching environment can affect the brain in a mouse model of Huntington disease. The experiments were not gentle: one set of mice was kept in drab, boring cages and given nothing to do. Another set was kept in “enriched” conditions, and given new toys every two days. The second set of mice, in line with previous studies, fared better, holding their balance on a rotating cylinder. When the researchers examined the brains of both sets of mice, they found distinct differences. The mice from the enriched environment expressed higher levels of brain-derived neurotrophic factor (BDNF) in certain brain regions (the hippocampus and striatum). BDNF promotes neuronal growth and survival, and can regulate communication between neurons; levels of BDNF normally decline as the disease worsens. In addition to BDNF, the expression of other proteins wanes as symptoms develop; an enriched environment counteracted some of this decline. The findings buff up BDNF as a potential drug target.