Exposing HIV

On page 1407, Decker and colleagues trick HIV into exposing itself. This trick revealed that a majority of infected individuals have broadly cross-reactive neutralizing antibodies against HIV in their circulation.

Antibodies that neutralize diverse strains of HIV have been difficult to find, despite decades of searching. Several gp120-specific neutralizing antibodies have been cloned. Some of them target the binding site for the HIV coreceptor C-C chemokine receptor 5 (CCR5), which is exposed only when gp120 engages the CD4 receptor on target cells. Many strains of HIV require CCR5 to infect cells, but this binding site was thought to be weakly antigenic as it is normally hidden from the immune system.

Decker and colleagues now prove this idea wrong and show that the coreceptor binding site is one of the most highly immunogenic regions of gp120. The authors incubated various strains of HIV-2 with soluble CD4 (sCD4) to induce exposure of the coreceptor binding site. They then tested whether plasma from HIV-1 infected individuals could neutralize the CD4-induced virus. To their surprise, they found that >90% of individuals infected with HIV-1 had antibodies that could neutralize highly divergent strains of HIV-2 and SIV, but only when the viruses were first treated with sCD4. This suggested that the coreceptor binding site is not only immunogenic, but also antigenically conserved among different HIV strains.

The authors suggest that antibodies against this well-concealed epitope may be elicited in vivo by shed gp120 proteins—prevalent during HIV infection—that bind to CD4-expressing cells causing the gp120 molecules to reveal their coreceptor binding sites to antibody-producing B cells. Thus, antibodies are generated, but are probably helpless to attack their real target: the still hidden sites on the gp120 of the intact virus.

Whether it will be possible to take advantage of this antigenic site for vaccine development remains to be seen. Providing sCD4 in vivo is unlikely to work, as previous clinical trials showed that sCD4 actually enhanced virus replication at low concentrations. One possibility, the authors suggest, is to create a vaccine that elicits two kinds of antibodies: one that mimics CD4 and exposes the coreceptor binding site and another that binds the exposed site and prevents HIV from getting into cells.

Relief from IL-1

The cytokine interleukin-1 (IL-1) is primarily to blame for a severe type of juvenile arthritis, according to Pascual and colleagues on page 1479. Blocking IL-1 activity in children with systemic onset juvenile idiopathic arthritis (SoJIA) completely resolved disease symptoms in a majority of children who had failed to respond to conventional treatments.

SoJIA is a systemic inflammatory disease of unknown etiology that can cause long-term arthritis in children. The pathogenesis of the disease is unclear, although increases in the inflammatory cytokine IL-6 have been reported in the blood of these patients. Currently the most effective therapy for SoJIA is long-term treatment with steroids, which carries with it the risk of growth retardation, osteoporosis, and obesity.

Pascual and colleagues now reveal a central role for IL-1—a cytokine that plays a major role in many inflammatory and autoimmune diseases—in the pathology of SoJIA. They show that serum from SoJIA patients provokes healthy cells to increase expression of IL-1, but no other cytokines. In addition, stimulated peripheral blood cells from children with SoJIA produced more IL-1, but not IL-6 or TNF, compared with cells from healthy children.

These results prompted Pascual and colleagues to treat these patients with an IL-1 receptor antagonist (Anakinra). The results were remarkable—symptoms were completely resolved or significantly improved in all children with active arthritis, with only one later case of relapse.

The mechanism behind the increased IL-1 production in SoJIA is unknown. As SoJIA is not an inherited disease, the defect is likely to be different from familial IL-1–triggered inflammatory diseases in which a mutated NALP3 can no longer control the activation of caspase-1, which cleaves the IL-1β precursor into the active cytokine. The authors are now looking for the serum component that turns on IL-1.
Boosting innate immunity in cancer

Mature DCs and the NKT cell ligand α-galactosyl ceramide (α-GalCer) are a promising combination for boosting immunity in humans, according to a study on page 1503. Chang and colleagues used α-GalCer-pulsed DCs to immunize cancer patients and showed that the treatment resulted in long-term expansion of both NKT cells and virus-specific CD8+ T cells.

α-GalCer, a glycolipid derived from marine sponges, was identified based on its antitumor properties. This foreign glycolipid was later found to be presented to NKT cells by DCs. NKT cells activated by this glycolipid can promote tumor regression in mice. Attempts to extend this work to humans, however, have met with limited success. α-GalCer treatment alone decreased NKT cell numbers in patients with solid tumors, and vaccination with α-GalCer-pulsed immature DCs induced only modest and transient NKT cell expansion.

Maturation of the DCs—treatment with cytokines that enhance the expression of MHC and costimulatory molecules—was the key to the approach used by Chang and colleagues. They immunized five advanced cancer patients, none of whom had detectable NKT cells in their blood before treatment. But with α-GalCer-pulsed mature DCs, all patients had a rapid and sustained increase in NKT cell numbers.

Surprisingly, CD8+ T cells specific for cytomegalovirus were also expanded by the treatment, suggesting that this approach might also be useful to boost immunity to chronic viral infections like HIV or hepatitis C virus, or to enhance the efficacy of T cell–based vaccines. JEM

Turning fat into muscle

Stem cells from fat tissue have the potential to become muscle, bone, or fat, according to a study by Rodriguez and colleagues on page 1397. These stem cells rescued the production of the muscle protein dystrophin in a mouse model of Duchenne muscular dystrophy (DMD), a fatal muscle wasting disease of children. The authors think that these cells may eventually be promising for treatment of children with this deadly, and thus far untreatable, disease.

DMD is caused by a lack of the cytoskeletal protein dystrophin, which provides muscle cells with structural stability. Several treatment strategies for DMD are under investigation, including gene therapy to replace the defective dystrophin gene, and stem cell transplantation to generate new dystrophin-producing muscle cells.

Previous work by this group and others revealed the presence of stem cells in human fat tissue, but their longevity in vitro and capacity to differentiate in vivo had not been explored. Rodriguez et al. now show that fat tissue from young donors yielded self-renewing stem cells that could differentiate into muscle, bone, or fat cells in culture, even after 100 or more cell divisions. Similar stem cells have been found previously in bone marrow, but fat, the authors point out, provides a more plentiful and easily accessible source of these cells.

Injection of the stem cells into the muscles of dystrophin-deficient mice restored dystrophin production and decreased muscle cell necrosis, without eliciting an immune response against the human dystrophin protein—a protein that is normally highly immunogenic in mice. Why the immune system does not respond to this foreign protein is not known.

Another unknown is how these stem cells become dystrophin-producing muscle cells. One possibility—illustrated in recent reports of stem cell therapy in mice—is that the stem cells fuse with local tissue cells rather than differentiating de novo into new cells. JEM

Stem cells from human fat differentiate into muscle cells and produce dystrophin (green) when injected into mice.