## Barring the door to HIV

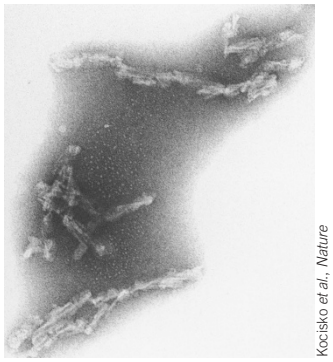
Before HIV can do damage, it must get in. Much effort has therefore focused on how HIV recognizes and enters target cells. The identity of the primary HIV receptor, CD4, was described in the mid-1980s, but HIV entry clearly required other cellular factors. In 1996, the elusive coreceptors were chased down. First, Edward Berger and colleagues identified as a coreceptor a G-protein-coupled receptor, since found to act as a chemokine receptor and named CXCR4 (*Science* **272**, 872–877; 1996). This work paved the way for the rapid identification of the other major coreceptor, the chemokine receptor CCR5.

With the discovery that HIV-1 isolates use either one or the other of these coreceptors, it became apparent that the distinction between the two has important consequences for disease transmission and progression. Transmitted viruses generally use CCR5, and a switch to CXCR4 is associated with disease progression.

The identification of these coreceptors has set the stage for new classes of AIDS drugs. CXCR4 may be more critical for normal immune function, but CCR5 may be the preferred coreceptor target, as homozygous mutations in CCR5 confer protection from HIV-1 in humans, without serious deleterious effects. Indeed, in pilot studies CCR5 inhibitors could reduce the levels of circulating virus in HIV-infected patients. Another strategy targets gp41, a protein that mediates the final steps of HIV entry; this strategy led to the FDA approval of the first HIV entry inhibitor in 2003. —*MB*

## The prion propagates

A prion protein can propagate disease by shifting the conformation of the native, noninfectious protein to the shape of the prion, so turning a nonlethal protein into an infectious agent—that is the crux of the prion hypothesis. David Kocisko *et al.* gave this hypothesis a big lift with experiments in 1994, showing that the prion form of the PrP protein could change the shape of the native form in a test tube (*Nature* **370**, 471–474).



Kocisko *et al.*, *Nature*

Scrapie-associated fibrils from hamster brains. Such fibrils can drive conversion of the native PrP protein.

The work showed that the prion itself was sufficient for conversion of the native protein and nailed down ideas generated from earlier, *in vivo* work: that protein conversion occurs post-translationally and involves no covalent changes. The research also came on the heels of key *in vivo* experiments, showing that mice lacking the PrP protein were resistant to scrapie (*Cell* **73**, 1339–1347;1993; *Cell* **77**, 967–968;1994). All this lab work emerged against a tumultuous backdrop. In 1996, a new variant form of Creutzfeldt-Jakob disease was identified in Great Britain and widely held to be transmitted through beef consumption (*Lancet* **347**, 921–925)

A criticism of the experiments of David Kocisko *et al.* was that the infectious prion had to be present in vast excess over the native form to seed conversion. Moreover, one critical aspect of the hypothesis has yet to be proven: the generation in a test tube of a prion that causes infection upon injection into animals. —*CS*

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## Host-virus battle lines redrawn

Human cells have long been known to use interferons to fend off viruses. In 2002, a new intracellular defense mechanism began to see the light, opening a new vista in innate immunity. Ann Sheehy *et al.*, trying to work out why a protein called virion infectivity factor (Vif) is required for HIV replication, identified a cellular antiviral factor they called CEM15 (*Nature* **418**, 646–650; 2002).

Now known as ApoBEC3G, this protein is a member of the ApoBEC family of nucleic acid–editing proteins, and it exerts its effect against a broad range of retroviruses by triggering G-to-A mutations in nascent retroviral DNA. HIV has evolved a counter-response: Vif targets ApoBEC3G for degradation by the proteasome.

The research on ApoBEC3G has offered insight into virus evolution, opened the possibility of a new therapeutic target for HIV infection and prompted a fruitful search for other cellular antiviral 'restriction factors.' These now include other members of the ApoBEC family and a second type of restriction factor, TRIM5, which targets the virus capsid and seems to work by blocking virus uncoating (*Nature* **427**, 848–853; 2004). —*CT*

## Malaria maneuvers

The most effective parasites change like chameleons, rapidly shifting antigens to avoid the host immune response. Malaria parasites do this from within the red blood cell, where they orchestrate the expression of different parasite proteins expressed on the cell surface. This concept hit the mainstream in 1995 with the identification of a set of genes that underlie this process, the var genes. Three studies (*Cell* **82**, 77–89, 89–100, 101–110) showed that the var genes encode a large family of variant antigens on the cell surface, and that they are tightly regulated. A single infected red blood cell may express only one or at most a few var genes, and the rate at which var gene expression shifts is as high as 2.4% per generation.

Why would the parasite even make itself so vulnerable by expressing its proteins on the host cell surface? The var genes encode proteins that make red blood cells stick to the vascular endothelium. This keeps the cells clear of the spleen, which senses and destroys abnormal red blood cells.

More recent work has hinted that the invasive form of the parasite, the merozoite, might also undergo such phenotypic variation. All of this complicates vaccine development efforts. —*CS*

## KSHV and cancer

The identification of disease agents has often been assisted by emerging technologies. In 1994, Yuan Chan *et al.* (*Science* **266**, 1865–1869) identified a herpes-like virus associated with Kaposi sarcoma (KS), using a PCR technique described the year before. KS, a cancer prevalent in HIV-infected patients in the 1990s, had been variously attributed to hepatitis B virus, cytomegalovirus and HIV—as well as nitrite inhalants.

Chan *et al.* sought to put these arguments to rest. The technique enabled the researchers to identify unique sequences in KS tissue from HIV-infected patients that were absent from normal tissue in the same patients. The investigators found that the herpes-like sequences were present in more than 90% of AIDS-associated KS. Although this study did not prove that a new virus was the cause of KS, the findings were swiftly confirmed by other groups. With its sequencing two years later, Kaposi sarcoma–associated herpes virus joined the ranks of viruses linked to cancer, such as HTLV, EBV and HPV. —*AF*