From discovery…

Four studies in *Nature*, *Science* and *Cell* unveil a cellular system of defense against HIV-1 that also seems to contribute to the high mutation rate of the virus.

The lynchpin of the antiviral system is CEM15, a cytoplasmic protein present in T lymphocytes and other HIV-1 target cells. CEM15 (also known as APOBEC3EG) is a cytidine deaminase, an enzyme that induces G-to-A mutations in DNA. The CEM15 protein was recently found to counteract HIV-1 infection, but exactly how had been unclear.

The new data reveal that CEM15 deaminates newly synthesized HIV-1 DNA. HIV-1 isolated from cells that lack CEM15 had a lower mutation rate than HIV-1 from cells with CEM15. When disarmed of zinc finger sequences thought critical for deamination, CEM15 lost much of its ability to induce viral G-to-A mutations.

HIV-1 has evolved a counterstrategy—deployment of the protein Vif, required for successful HIV-1 infection *in vivo*. In cell culture experiments, HIV-1 lacking Vif had a markedly higher rate of G-to-A mutations compared with intact HIV-1.

The new data show that murine leukemia virus similarly undergoes deamination by CEM15. Moreover, G-to-A hypermutation has been observed in other retroviruses and in the pararetrovirus hepatitis B virus. Deamination may initiate a system of repair that leads to viral destruction, or the accumulation of mutations may simply disable the virus. Whatever the mechanism, the new data begin to reveal how a weak flank for HIV-1, the Vif protein, operates.

…To therapy

A new antiretroviral drug effectively fights HIV-1 in patients with multidrug resistance infection, according to data from the first randomized controlled studies of enfuvirtide, a fusion inhibitor. The drug inhibits fusion of the HIV-1 transmembrane (gp41) glycoprotein with the CD4 receptor of the host cell.

In the 20 May issue of the *New England Journal of Medicine*, Lalezari *et al.* and Lazzarin *et al.* present data on the efficacy of the drug in a total of 661 patients whose regimens were not adequately suppressing viral replication. Patients were treated with enfuvirtide in a background regimen of four or five other drugs and evaluated after 24 weeks. The amount of HIV-1 in the blood of the enfuvirtide-treated patients decreased by about tenfold compared with a group of 334 control patients. The drug also boosted $CD4^+$ cell counts.

The new drug does not come without costs, both in terms of side effects and money. Bacterial pneumonia and eosinophilia (an abnormal buildup of eosinophils in the blood) occurred more frequently in enfuvirtide-treated patients than in the control groups. Previous studies have also suggested that resistance to the drug can evolve rapidly.

Enfuvirtide, a 36-amino-acid peptide, will cost about $20,000 a year. Its manufacturer, Roche and Trimeris, estimates it can only produce enough to treat 12,000 to 15,000 patients by December 2003, and 39,000 patients by 2005.

Enfuvirtide represents the first new class of antiretrovirals approved for prescription use since 1996; other fusion inhibitors are under development. Enfuvirtide (formerly known as T-20) was described in 1993 by Wild *et al.* and received accelerated approval from the US Food and Drug Administration this March.

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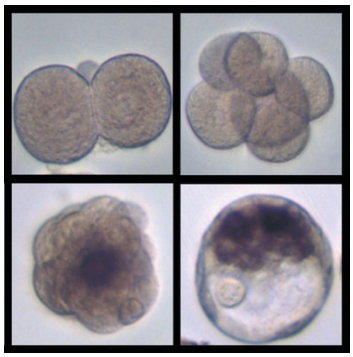
Eternal self-renewal



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What is the secret to the youthfulness of embryonic cells? Two studies in the 30 May *Cell* provide part of the answer: a divergent homeodomain protein dubbed 'Nanog' after the mythological Celtic land of the ever-young, 'Tir na Nog'. Mitsui *et al.* and Chambers *et al.* found that Nanog is expressed very early in embryogenesis independent of another known early factor, Oct4 (Nanog in blue). Nanog fades as cells acquire identity, after which it persists in the primordial germ cells. In embryonic stem cells in culture, Nanog deletion triggered differentiation whereas overexpression held it back—without addition of LIF, a factor normally added to cultured embryonic stem cells.

Vector trouble

A new study calls into question the safety of a gene therapy vector currently in clinical trials for hemophilia and cystic fibrosis. In the July *Nature Genetics* Nakai *et al.* report that adeno-associated virus (AAV) seems to have a predilection for actively transcribed genes. The investigators analyzed integration sites in the liver and found that 21 of 29 occurred in genes (all expressed in the liver). The study follows an earlier report that HIV-1 prefers to integrate into active genes. But compared with HIV-1 and the recently troubled retroviral vector used to treat severe combined immunodeficiency disease (SCID), AAV integrates into the genome only rarely. In an accompanying News and Views in *Nature Genetics*, David Russell notes that the greatest danger of integration may be activation of a gene such as an oncogene—as appears to have occurred in the SCID trials. The preference of AAV for actively transcribed genes reduces this risk. Gene inactivation would normally leave the second allele intact. The careful choice of promoters and insulator elements could help reduce the risks.

Deconstructing long-term depression

Research into molecular events in Purkinje cells brings neuroscientists closer to understanding how the cerebellum controls memory storage processes necessary for motor learning. In the 13 June *Science*, Chung *et al.* examine a process thought to be crucial for such learning: long-term depression (LTD), long-term synaptic changes that reduce synaptic sensitivity. LTD occurs through internalization of an excitatory glutamate receptor, AMPA, and requires protein kinase C (PKC). But what events link these two molecules? The investigators found that in isolated mouse Purkinje neurons, PKC phosphorylated the AMPA receptor at a site in the GluR2 subunit. Purkinje neurons lacking the subunit did not undergo LTD, and transfection with GluR2 restored LTD. But transfection of neurons with GluR2 mutated at a PKC binding site failed to rescue LTD. The investigators are eager to create a transgenic mouse with constitutively phosphorylated GluR2, which should enable the first direct *in vivo* test of whether cerebellar LTD contributes to motor learning.