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In This Issue

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Profiling T-cell gene expression in anergy and arthritis (See article on pages 519– 528.) T cells that lose their characteristic ability to proliferate and secrete cytokines in response to antigen stimulation are said to be anergic. Anergy occurs under several different circumstances, suggesting that T cells are poised to become anergic - presumably a protective response that helps limit immune reactions and prevent responses to self antigens. Still, as Ali and colleagues point out, T cells in at least one autoimmune condition, rheumatoid arthritis (RA), are resistant to apoptosis and antigen stimulation, features that they share with anergic T cell clones. To explore the idea that anergic cells participate in RA pathogenesis, these authors used differential display to identify genes that are induced or suppressed during the onset of anergy, and they tested RA-associated synovial T cells to determine how well they fit the resulting expression profile. Ali et al. identified six transcripts whose up- or downregulation in RA (as compared with reactive arthritis, a distinct disease, in which T cells remain sensitive to antigen stimulation) parallels the changes in expression seen in anergic cells. Several of these changes are modest or equivocal, but the suppression of calmodulin expression in RA is consistent and dramatic. Ali et al. further show that calmodulin expression is restored in patients receiving treatment for […]

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By John Ashkenas, Science Editor

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HIV population shifts following HAART

(See article on pages 431–438)

Highly active antiretroviral therapy (HAART) involves combinations of protease inhibitors and other drugs to block HIV proliferation. While there is abundant evidence that this approach reduces viremia, far less is known about its qualitative effects on the surviving HIV population. HIV variants, sometimes called quasispecies, can differ in their host cell tropism, their pathological effects, and the structure of their envelope glycoprotein, env. Variation in env sequence determines which of two chemokine receptors, CXCR4 or CCR5, will serve as a coreceptor for viral entry. Typically, CCR5-dependent viruses (R5) are the major population early in the course of an infection, and CXCR4-dependent viruses (X4) overtake them later, leading to a drop in $CD4^+$ T-cell count. By following the relative prevalence of R5 and X4 viruses in a set of women with advanced disease, Philpott et al. now show that R5 viruses can re-emerge as the predominant HIV-1 population following HAART or other combination therapies. Indeed, most of these subjects, even those with little reduction in their overall circulating HIV levels, showed a suppression of X4 strains in preference to R5 strains. The authors suggest that this qualitative effect could provide an additional basis for the benefit of combination therapies, independent of their quantitative effect on viral titer.

The molecular evolution of viral drug resistance

(See article on pages 449–455)

As with HIV, the distribution of variants of hepatitis B virus (HBV) can shift in response to drug therapy. Although viral replication is often controllable using nucleotide analogues that inhibit the viral DNA polymerase, drug-resistant variants often emerge following chronic treatment, as a result of mutations in the nucleotide binding site of this enzyme. Here, Ono and colleagues show that known HBV polymerase point mutants blunt the effect of these drugs but that they do so at the cost of reducing the baseline replication rate of the virus. However, second-site mutations occurring at one specific residue in the polymerase can restore the catalytic efficiency of the enzyme, generating a virus that is both drug-resistant and quick to replicate. Ono and coworkers also describe the effects of a battery of newly developed antiviral agents on viral replication, comparing wild-type HBV with several known polymerase point mutants. They confirm that the efficacy of lamivudine, now the standard drug used for controlling HBV, is greatly diminished in all of the drug-resistant viruses studied, but they show that some of the other agents retain significant activity against these variants. One drug, the purine analogue entecavir, stands out because of its thousand-fold greater potency than lamivudine and its ability to suppress replication of even the most vigorous drug-resistant mutants. For more on the importance of pathogen genotype, see the Perspective series on bacterial polymorphisms, beginning in this issue of the *JCI*.