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ANTIVIRAL DRUGS

Third strike against HIV enzymes

A new type of HIV drug has shown promising results in tests in monkeys. As reported in *Science*, treatment with an inhibitor of HIV-1 integrase — one of three key virally encoded enzymes involved in HIV infection — mediated a sustained suppression of viral levels in rhesus macaques infected with simian/human immunodeficiency virus (SHIV), and preserved their immune system, allowing an effective virus-specific cell-mediated immune response to develop.

Death rates due to infection with HIV have been markedly reduced in the past few years by treatment with combinations of drugs that inhibit the other two key enzymes in the viral life cycle — HIV-1 reverse transcriptase and HIV-1 protease. However, the durability of viral suppression with these combination regimens is often limited by the development of resistance, underscoring the need for new antiretroviral drugs. HIV-1 integrase, which catalyses the insertion of the viral DNA into the host-cell genome, thereby allowing it to be expressed, has been considered an attractive drug target for some time, but numerous previous efforts to develop integrase inhibitors have failed.

In their paper, Hazuda and colleagues at Merck describe the effects of L-870812, a novel integrase inhibitor that shows potent antiviral activity *in vitro* against both HIV-1 and SIV. Their studies were designed to investigate the *in vivo* efficacy of L-870812 in a rhesus-macaque model of both early and late-stage HIV infection, and

to examine the role of viral-specific cellular immunity in its effects.

Rhesus macaques infected with SHIV 89.6P exhibit an accelerated disease that is marked by profound depletion of key immune-system cells — CD4⁺ T cells — concomitant with progression from acute viraemia to a chronic phase about two weeks after infection. To evaluate L-870812 in the context of early infection, it was given to six monkeys ten days after infection. Viral levels in four of the six monkeys were suppressed to undetectable levels, and all six monkeys showed little or no decline in CD4⁺ cell counts, in contrast to six untreated monkeys.

To study the effects of therapy later in disease, L-870812 was given to the previously untreated monkeys 87 days after infection. However, although a therapeutic effect was apparent in all these animals, the subsequent durability of the response was variable.

Why might the nature of the therapeutic response in the two groups differ? Hazuda *et al.* found that differences in the response to therapy were associated with significant differences in viral-specific cellular immunity: L-870812 treatment initiated during early infection preserved CD4⁺ counts and allowed the induction of persistent cellular immune responses against the viral proteins gag and nef, which involved both CD4⁺ T cells and CD8⁺ T cells. However, in the delayed-treatment group, L-870812 did not induce or increase cellular immune responses, and the magnitude and durability of the treatment effect varied

in conjunction with the pre-treatment immune response and viral load.

Overall, these results indicate that integrase inhibitors such as L-870812 could be a valuable addition to the anti-HIV armoury, particularly when used in the early stages of infection. Early-stage clinical trials with related compounds are now in progress.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Hazuda, D. J. *et al.* Integrase inhibitors and cellular immunity suppress retroviral replication in rhesus macaques. *Scienceexpress* 8 Jul 2004 (doi: 10.1126/science.1098632)

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