HIV

A step ahead of drug resistance

A promising new target for the development of antiretroviral therapies to treat HIV-1 has been identified, according to a recent study published in *The Journal of Clinical Investigation*.

At present, patients are treated with various combinations of drugs that inhibit the HIV-1 life cycle by targeting the viral proteins HIV-1 reverse transcriptase, HIV-1 protease and gp41. These drug combinations have markedly reduced death rates caused by HIV-1 infection during the past few years. However, HIV-1 can acquire resistance to all existing drugs, and the number of patients who are infected with multidrug-resistant strains is rising, limiting future treatment options. So, there is a pressing need for novel anti-HIV drugs, particularly those that have a novel mechanism of action, as these might be less likely to show cross-resistance with current therapies.

Hauber and colleagues now report that blocking a host-cell factor — human deoxyhypusine synthase (DHS) — provides a successful means of preventing the replication of HIV-1, including strains that are resistant to highly active antiretroviral therapy (HAART). CNI-1493, a small molecule that is currently undergoing Phase II trials for Crohn's disease, was found to be a potent inhibitor of DHS. Inhibition of DHS by RNAi also effectively inhibited DHS in cell culture and in primary cells. These authors then cultured T-cell-tropic and macrophage-tropic laboratory strains, peripheral blood mononuclear cells from patients infected with HIV-1 and a series of antiretroviral-resistant viruses in the presence of CNI-1493, which effectively prevented viral replication. This indicated that this compound would make an ideal inhibitor of drug-resistant viruses.

Normally, DHS activates eukaryotic initiation factor 5A (eIF-5A) by initiating the first of two reactions that convert inactive eIF-5A to its active hypusine-containing form. eIF-5A is involved in the metabolism of specific cellular RNAs, and is a cellular cofactor of the HIV-1 viral regulatory protein Rev, which is essential for the replication of HIV-1. Blocking DHS therefore suppresses viral replication by interfering with eIF-5A activity. Nevertheless, the precise mechanism of action of the anti-DHS activity of CNI-1493 remains to be determined.

Importantly, it seems that the action of CNI-1493 was restricted to inhibition of DHS, because there were no detrimental effects on apoptosis, cell-cycle progression and cytotoxicity, as seen in some other studies of inhibitors of eIF-5A activity, at concentrations that successfully prevented viral replication. This new work therefore supports the idea that small-molecule inhibitors of DHS could be developed as successful antiviral therapies to combat strains of HIV that are resistant to currently available therapies.

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References and links

ORIGINAL RESEARCH PAPER Hauber, I. *et al.* Identification of cellular deoxyhypusine synthase as a novel target for antiretroviral therapy. *J. Clin. Invest.* **115**, 76–85 (2005)

FURTHER READING De Clercq, E. Antivirals and antiviral strategies. *Nature Rev. Microbiol.* **2**, 704–720 (2004)