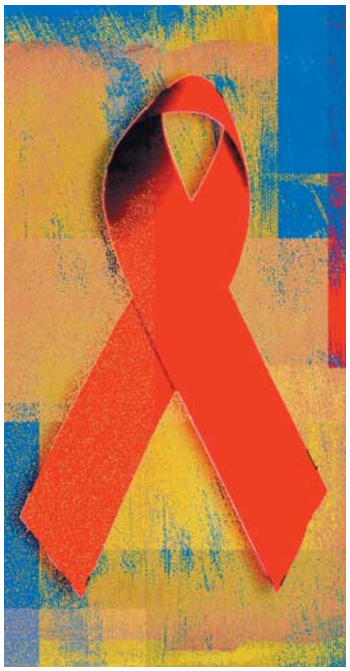
HIV

Driving HIV out of hiding

HIV-1 can hide in latently infected cells, and elimination of these viral reservoirs is a key obstacle to eradicating infection. Little is known about the mechanisms that maintain latency of HIV. A new study has identified genes that are differentially expressed in latently infected cells and has shown that targeting such genes can drive lytic replication, which might make the virus susceptible to antiretroviral drugs.

The authors used DNA microarrays to study gene expression in cell lines that were chronically infected with HIV, both before and during activation of lytic infection with phorbol myristate acetate, and they compared these cells with uninfected control cells. Activation of the lytic cycle and production of virus was confirmed by measuring the expression of the late HIV protein p24 by flow cytometry. Several differences in gene expression were observed between chronically infected cells and uninfected cells, and these genes could have a role in the maintenance of latency. Several genes that encode proteasome subunits and histone deacetylases were upregulated before lytic induction, and other genes were downregulated, including EGR1 (which is involved in cell-cycle regulation), CDC42 (a RHO-family GTPase) and the tyrosine kinase LYN.

The authors reasoned that by targeting genes that are both differentially expressed and possibly important for latency, they could drive the virus out of latency into the lytic cycle. To test this, they targeted the proteasome subunits and EGR1 because specific agents were available to target these molecules. Treating latently infected cells with a proteasome inhibitor or an EGR1 activator induced dose-dependent increases in p24 expression, showing that viral reactivation had occurred — although the exact mechanisms by which these molecules end latency needs further study. The authors also identified several cellular genes that were



differentially expressed during active viral replication — targeting these genes might therefore inhibit viral replication.

The identification of genes that are differentially regulated in latent infection provides useful information for further studies of the mechanisms of latency and the cellular functions involved in lytic replication. This study also indicates possible new therapeutic approaches for promoting or inhibiting HIV replication. The ability to drive HIV out of latency into lytic replication means that the virus could be susceptible to antiretroviral drugs, indicating that it might be possible to considerably reduce viral reservoirs.

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References and links

ORIGINAL RESEARCH PAPER Krishnan, V. & Zeichner, S. L. Host cell gene expression during human immunodeficiency virus type 1 latency and reactivation and effects of targeting genes that are differentially expressed in viral latency. *J. Virol.* **78**, 9458–9473 (2004).

FURTHER READING Hamer, D. H. Can HIV be cured? Mechanisms of HIV persistence and strategies to combat it. *Curr. HIV Res.* **2**, 99–111 (2004).

WEB SITE

Steven Zeichner's homepage: http://ccr.cancer.gov/Staff/staff.asp?profileid=5571

IN BRIEF

TOLERANCE

The site of primary T-cell activation is a determinant of the balance between intrahepatic tolerance and immunity.

Bowen, D. G. *et al*. *J. Clin. Invest*. **114**, 701–712 (2004).

This study by Bertolino and colleagues provides an explanation for the fact that the liver can be both tolerogenic and immunogenic. Liver allografts can often be accepted across a complete MHC mismatch, and the liver is thought to have a role in oral tolerance. By contrast, immune responses to pathogens such as the hepatitis B and C viruses can occur in the liver. Recent studies have shown that the liver can be a site of primary $CD8^+$ T-cell activation. These authors showed that hepatic versus lymph-node activation of naive $CD8^+$ T cells determines whether tolerance or immunity develops to an antigen expressed in the liver. T-cell activation in the lymph nodes resulted in acute hepatitis, whereas activation in the liver led to inefficient function and reduced half-life of T cells.

T-CELL RESPONSES

Upregulation of the CLIP self peptide on mature dendritic cells antagonizes T helper type 1 polarization.

Rohn, T. A. *et al*. *Nature Immunol*. **5**, 909–918 (2004).

Many studies have indicated that recognition of self-peptide–MHC complexes is involved in T-cell development, function and survival in both the thymus and the periphery. This study looked specifically at the role of class-II-associated invariant-chain peptide (CLIP)–MHC class II complexes, and it provides the first example of a self-peptide that regulates the activation of T cells specific for foreign antigen. The authors show that mature dendritic cells can upregulate expression of cell-surface CLIP–MHC class II complexes as a result of downregulation of HLA-DM activity (which would normally exchange CLIP for an exogenous antigen). The CLIP–MHC class II complexes are localized to immunological synapses with $CD4^+$ T cells — together with MHC class II molecules carrying exogenous peptide — where they influence the type of T helper (T_H)-cell response to the exogenous peptide by favouring T_H2-cell polarization.

STRUCTURE

Crystal structure of a shark single-domain antibody V region in complex with lysozyme.

Stanfield, R. L. *et al*. *Science* **305**, 1770–1773 (2004).

Cartilaginous fish such as the nurse shark are the oldest living organisms to have components of the adaptive immune system, but the relationship of these components to human antigen receptors is unclear. This paper reports the crystal structure of the nurse-shark immunoglobulin IgNAR bound to hen-egg lysozyme. Similar to camelid antibodies, IgNAR is a heavy-chain homodimer, with each IgNAR heavy chain consisting of one variable (V) domain and five constant (C) domains. However, the V domain of the IgNAR heavy chain clusters phylogenetically with the V regions of the T-cell receptor or immunoglobulin light chains, and this new structure will help to further our knowledge of the origins and evolution of the antigen receptors of the adaptive immune system.