VIRAL IMMUNITY

Therapeutic HIV vaccines

An effective immune response to simian immunodeficiency virus (SIV) can be elicited *in vivo* by a new therapeutic dendritic-cell (DC) vaccine, as reported by Lu and colleagues in *Nature Medicine*.

Chronic infection with HIV or SIV results in progressive immunodeficiency and ineffective antiviral immune responses. Although highly active antiretroviral therapy (HAART) can reduce the viral load and improve $CD4^+$ T-cell counts, these drugs do not restore immune functions completely, and a therapeutic vaccine is highly sought after. Previous studies have shown that DCs that have been pulsed with chemically (aldrithiol-2, AT-2)-inactivated HIV or SIV can stimulate the activity of antiviral cytotoxic T lymphocytes (CTLs) *in vitro*. Here, Lu and colleagues test the activity of an AT-2-inactivated SIV-pulsed DC vaccine *in vivo* in SIV-infected rhesus monkeys.

Fourteen SIV-infected monkeys were split into two groups of vaccinated (ten) and control (four) animals. Vaccinated monkeys received immunizations and boosters of AT-2-inactivated SIV-loaded DCs, whereas control monkeys received comparable injections of unloaded autologous DCs. Levels of SIV cellular DNA and plasma RNA decreased rapidly in the vaccinated animals, and the levels remained low and stable for the remainder of the study. In addition, vaccination led to higher numbers of $CD4^+$ T cells and increased titres of neutralizing antibodies. In the control animals, the levels of viraemia, $CD4^+$ T cells and antibodies remained unchanged throughout the study.

Next, the authors assessed SIV-specific immunity. Higher numbers of SIV-specific memory T cells could be detected after vaccination, the cytolytic activity of SIV-specific CTLs was increased and the inhibitory effect of $CD8^+$ T cells on replication of SIV was enhanced.

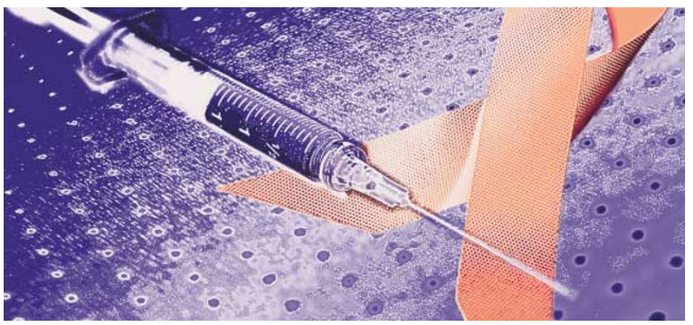
Secondary lymph nodes are important sites for the replication of SIV and HIV, and for the development of antiviral responses. Lymph-node biopsies carried out in the last week of the study showed that the lymphoid follicular DC network was destroyed in half of the control monkeys, whereas it was intact in all of the vaccinated monkeys. Also, the levels of cellular SIV DNA and SIV RNA were considerably lower in the vaccinated monkeys than in the control monkeys. Most importantly, high levels of lymph-node SIV-specific CTLs were associated with low levels of local cellular SIV burden, illustrating the effective control of viral spread by cell-mediated immunity *in situ*.

This study shows that inactivated SIV-pulsed DC-based vaccines can elicit effective cellular and humoral immune responses against SIV *in vivo*, resulting in the control of SIV replication in secondary lymphoid tissues and reduced levels of viraemia in vaccinated monkeys. If this approach could be adapted for use in humans, then inactivated whole-virus DC vaccines could be promising therapies for controlling chronic infection with HIV.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Lu, W. *et al.* Therapeutic dendritic-cell vaccine for simian AIDS. *Nature Med.* **9**, 27–32 (2002)



IN BRIEF

DENDRITIC CELLS

Activation of influenza virus-specific $CD4^+$ and $CD8^+$ T cells: a new role for plasmacytoid dendritic cells in adaptive immunity.

Fontaneu, J. *et al. Blood* 2 January 2003 (DOI: 10.1182/blood-2002-10-3063)

Plasmacytoid dendritic cells (pDCs) contribute to innate immune responses to viral infections by producing type I interferons, but their ability to process and present antigens to T cells has not been demonstrated. In this study, Nina Bhardwaj's lab assessed the ability of pDCs to activate influenza-specific T cells. The results show that pDCs can process and present antigens from influenza virus to $CD4^+$ and $CD8^+$ T cells, and they provide the first direct evidence that pDCs contribute to the adaptive immune response to this virus. Whether such responses are protective at the level of T cells during chronic viral infection remains to be determined.

DEVELOPMENT

Regulation of blood and lymphatic vascular separation by signaling proteins SLP-76 and Syk.

Abtahian, F. *et al. Science* **299**, 247–251 (2003)

Lymphatic vessels are derived from pre-existing blood vessels, but it is not clear which factors control the separation of emerging lymphatics from blood vessels. Mice lacking SLP76 or Syk show a failure to separate these vessels, resulting in embryonic haemorrhage and arteriovenous shunting. The transfer of bone-marrow cells derived from SLP76- or Syk-deficient animals was sufficient to recreate the abnormal vascular phenotype, which indicates that haematopoietic cells and not lymphatic endothelial cells are responsible for the defect. Further work is necessary to determine how defects in circulating cells can influence the growth of lymphatic vessels.

INFECTIOUS DISEASE

Mycobacteria target DC-SIGN to suppress dendritic-cell function.

Geijtenbeek, T. B. H. *et al. J. Exp. Med.* **197**, 7–17 (2003)

DC-SIGN is the major *Mycobacterium tuberculosis* receptor on human dendritic cells.

Tailleux, L. *et al. J. Exp. Med.* **197**, 121–127 (2003)

Although macrophages are the main cellular target of *Mycobacterium tuberculosis*, dendritic cells (DCs) are important mediators of immune responses against *M. tuberculosis*. These studies show that *M. tuberculosis* infects DCs using the C-type lectin receptor DC-SIGN. This interaction prevents the maturation of DCs induced by mycobacteria or lipopolysaccharide through Toll-like receptors. Interaction of mycobacteria with DC-SIGN also results in production of the anti-inflammatory cytokine IL-10, which can modify the immune response, and might promote survival of mycobacteria. These results indicate that *M. tuberculosis* infects DCs and interferes with DC-mediated immune responses by targeting DC-SIGN. So, DC-SIGN is a Trojan horse for *M. tuberculosis* as has been shown previously for HIV-1.