IN THE NEWS

Gene therapy for HIV

A new therapy that has been described as "probably the most exciting of the anti-HIV strategies around at the moment" (Alan Kingsman, Oxford Biomedica; *BBC News*) is producing encouraging results in Phase I safety trials, according to a report in *New Scientist* (15 May 2004).

VRX496 uses anti-sense technology to prevent HIV replication. T cells are isolated from patients and infected with a modified form of HIV containing an anti-sense gene. T cells containing the integrated viral genome are re-infused into patients so that when HIV tries to infect the modified T cells *in vivo*, the anti-sense mRNA is produced and binds to the sense viral mRNA, thereby preventing translation of viral proteins.

So far, three patients who had failed two regimens of anti-retroviral drug therapy have been treated with VRX496. Boro Dropulic, Founder and Chief Scientific Officer of VIRxSYS Corporation, which is developing VRX496, says that no adverse events have been observed in these patients and they are encouraged by the finding that "viral load results are not above pre-dose levels and CD4 counts have remained stable" (*VIRxSYS*). On the basis of these results, the Data Safety Monitoring Board, USA, recommended in April that a further two patients should be enrolled in the trial without delay.

Assuming that no safety concerns arise, the therapy could soon enter Phase II trials to determine efficacy. However, not everyone is convinced. This is the first time that a lentiviral vector has been used in a clinical trial in humans, and concerns about recombination and other safety issues have led many researchers to abandon research into gene therapy, according to Richard Sutton of Baylor College of Medicine (*New Scientist*).

Kirsty Minton

AUTOIMMUNITY

The more the merrier

In a surprising new study published in *Cell*, Nora Sarvetnick and colleagues have shown that autoimmunity can be caused by insufficient numbers of T cells. This indicates that having a crowded immune system can actually be good for you and provides a possible explanation for the beneficial effects of a 'less-than-hygienic' environment.

They showed that female autoimmune-prone non-obese diabetic (NOD) mice have fewer peripheral $CD4^+$ T cells than control strains that do not develop autoimmunity. This lymphopaenia was associated with disease development, as increasing the number of T cells in NOD mice by injection of complete Freund's adjuvant (CFA; which contains T-cell stimulatory mycobacterial cell-wall components) protected the mice from developing diabetes. Furthermore, the effect was due to T-cell number rather than phenotype as the transfer of T cells from NOD littermates also prevented diabetes.

The artificial induction of lymphopaenia — for example, by irradiation — results in proliferation of the remaining T cells to fill the 'space' that is left. To see if this homeostatic expansion occurs in NOD mice, the authors monitored labelled NOD T cells expressing a T-cell receptor (TCR) specific for pancreatic β-cells after transfer to various hosts. These TCR-transgenic T cells only proliferated in lymphopenic NOD mice and not in NOD mice treated with CFA. Analysis of cell-surface markers such as CD62L to distinguish between classically activated and homeostatically expanding T cells was also used to show that a far greater percentage of the natural T-cell populations of NOD mice is undergoing homeostatic expansion compared with non-lymphopenic, non-autoimmune-prone mice. Importantly, NOD mice with the most proliferating T cells had the most severe pancreatic insulitis, which indicates that there is a direct link between homeostatic expansion and disease.

Part of the explanation for the lymphopenia of NOD mice might lie in the observation that they have increased levels of interleukin-21 (IL-21) production, leading to upregulation of IL-21 receptor (IL-21R) expression by T cells, and clear

HIV

Pulling out the stops

In the absence of an effective vaccine, blocking infection and transmission of HIV at mucosal surfaces might be our best chance of stemming the spread of HIV infection. Reporting in *The Journal of Experimental Medicine*, Qinxue Hu *et al.* explore the potential of HIV-1-specific antibodies and compounds that target HIV-1-binding cell-surface receptors to inhibit HIV-1 infection of and dissemination from human cervical tissue.

To infect cells, HIV-1 must interact with two receptors, CD4 and a co-receptor — CC-chemokine receptor 5 (CCR5) for R5 viruses and CXC-chemokine receptor 4 (CXCR4) for X4 viruses. Using a CD4-specific antibody or small molecule inhibitors of CCR5 and CXCR4, the authors could inhibit localized infection of mucosal tissue by R5 and X4 viruses, respectively. Although *in vitro* studies have identified viruses that can use other co-receptors, here, they show that infection of human cervical tissue using co-receptors other than CXCR4 or CCR5 is unlikely.

In addition to direct infection of mucosal tissue, HIV-1 can become attached to migratory cells, facilitating viral transmission and infection in lymphoid organs. Dendritic cells (DCs) that express the mannose-binding C-type lectin DC-SIGN are thought to be involved in this process. So, the authors collected migratory cells (which included both $DC\text{-}SIGN^-$ and $DC\text{-}SIGN^+$ DCs) emigrating from cervical explants after HIV-1 inoculation in the presence or absence of inhibitors, and assayed for infection of indicator cells in co-cultures. In contrast to infection of cervical tissue, uptake of HIV-1 by migratory cells was not inhibited by a combination of CXCR4 and CCR5 inhibitors, but was inhibited when CD4-specific antibodies and mannan were present. Presence of DC-SIGN-specific antibody also inhibited the capture of infectious virus by migratory cells, albeit to a lesser extent, indicating an important but not exclusive role for this receptor in virus capture and transmission.

evidence of increased responsiveness to this cytokine. IL-21 is a recently identified member of the γc cytokine family, other members of which (such as IL-7) mediate T-cell proliferation and survival. However, in contrast to IL-7, IL-21 did not support the survival of T cells *in vitro*. The IL-21R$^+$ T cells of NOD mice proliferate rapidly but do not survive, leading to low numbers of long-lived memory T cells. The observation that stimulated T cells have a short life was supported by their failure to upregulate expression of the anti-apoptotic molecules Bcl-2 or Bcl-X_L. The important role of IL-21 in autoimmune susceptibility in this model ties in with the fact that the gene encoding IL-21 lies in a known NOD susceptibility locus on chromosome 3.

Sarvetnick and colleagues suggest that a lymphopenic environment favours the proliferation of those T cells specific for readily available antigens. In most cases, this will be autoreactive T cells that have escaped deletion in the thymus. Being 'too clean', particularly during childhood, could create such a lymphopenic environment in humans by reducing the constant stimulation of our immune systems by bacteria and viruses in the environment. This could explain the increasing prevalence of autoimmune diseases in modern 'hygienic' societies.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER King, C. *et al.* Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. *Cell* **117**, 265–277 (2004)

Finally, by targeting HIV-1 directly with neutralizing gp120-specific antibodies and a CD4–immunoglobulin fusion protein, both localized infection of cervical tissue and transfer of infectious virus by migratory cells were inhibited.

The design of novel microbicides that provide effective protection from sexual transmission of HIV relies on a detailed understanding of viral attachment and infection. This report indicates the main receptors involved in these processes in human cervical tissue and so might help towards the development of highly specific microbicides.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Hu, Q. *et al.* Blockade of attachment and fusion receptors inhibits HIV-1 infection of human cervical tissue. *J. Exp. Med.* **199**, 1065–1075 (2004)

FURTHER READING Davis, C. W. & Doms, R. W. HIV transmission: closing all the doors. *J. Exp. Med.* **199**, 1037–1040 (2004)

IN BRIEF

STRUCTURE

Supine orientation of a murine MHC class I molecule on the membrane bilayer.

Mitra, A. K. *et al. Curr. Biol.* **14**, 718–724 (2004)

Previous studies looking at the structure of MHC molecules have used recombinant forms consisting of only the extracellular domains. However, these structures do not take into account interactions with specific lipid microdomains of the plasma membrane. To address this, Luc Teyton and colleagues used electron microscopy to analyse the extracellular domains of the MHC class I molecule H–2K^b tethered to a lipid bilayer by a histidine tag. Surprisingly, the MHC molecule was shown to lie on its side parallel to the membrane, rather than standing up perpendicular to the membrane as is usually depicted. This orientation was maintained by ionic interactions between lipid head groups in the membrane and the length of the MHC protein. As the supine orientation was shown to be optimal for binding of the co-receptor CD8, changes in MHC orientation might be another way to regulate T-cell-receptor signalling.

SIGNALLING

The cell-surface receptor SLAM controls T cell and macrophage functions.

Wang, N. *et al. J. Exp. Med.* **199**, 1255–1264 (2004)

In this study, mice deficient for signalling lymphocyte activation molecule (SLAM, also known as CD150) were generated and used to analyse the specific contribution of SLAM to immune responses. SLAM-mediated signalling occurs through SLAM-associated protein (SAP), and SAP-deficient mice have a severe X-linked immunodeficiency. As SAP also mediates signalling through five other SLAM-related receptors, the precise contribution of SLAM to the immunodeficiency was unknown. The SLAM-deficient mice had impaired macrophage responses to lipopolysaccharide and increased susceptibility to infection with *Leishmania major*, as well as defective T_H2-cell responses. This indicates that SLAM functions as a co-receptor for signalling through Toll-like receptor 4 and the T-cell receptor.

INNATE IMMUNITY

Nucleic acid is a novel ligand for innate immune pattern recognition collectins surfactant proteins A and D and mannose-binding lectin.

Palaniyar, N. *et al. J. Biol. Chem.* 15 May 2004 (doi:10.1074/jbc.M403763200)

Collectins, including surfactant protein D (SP-D), are extracellular innate immune proteins known to bind microbial carbohydrate patterns. In this study, SP-D was shown to bind linear plasmid DNA directly, as well as synthetic oligonucleotides, even at high salt concentrations. Whereas this strong interaction was mediated largely by the collagen-like region of SP-D, electron microscopy indicated that the globular regions of the molecule also associated with DNA. Furthermore, because SP-D co-localized with the DNA of apoptotic cells, the authors suggest that SP-D functions as an opsonin, binding the DNA of apoptotic cells to enhance their clearance.