Natural killer T cells are targets for human immunodeficiency virus infection

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HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Acquired immune deficiency syndrome (AIDS) is the result of a prolonged infection by the highly mutable retrovirus HIV. The US Centers for Disease Control and Prevention currently defines AIDS in an adult as the presence of one of 26 conditions indicative of severe immunosuppression associated with HIV infection. These conditions include pneumonia caused by *Pneumocystis carinii* and Kaposi's sarcoma, a tumour probably caused by human herpes virus 8, both of which are rare in people not infected with HIV.

HIV targets $CD4^+$ T cells by binding to the CD4 molecule on the cell surface, as well as a chemokine coreceptor – usually CCR5 or CXCR4. Transmission, and the early phases of infection, are usually dominated by CCR5-tropic variants, which can bind CD4-expressing antigen-presenting cells, such as macrophages, as well as activated $CD4^+$ T cells. In about 50% of infected people, the later stages of infection are characterized by CXCR4-tropic variants, which bind naïve CD4 T cells.

The latter stages of the disease are usually associated with dramatic reductions in the numbers of $CD4^+$ T-cells circulating in the peripheral blood – from the 600–1500/mm^3 seen in healthy adults, to unmeasurably low levels. It has been suggested that the emergence of CXCR4-tropic variants is responsible for much of the depletion of $CD4^+$ T cells, since CXCR4 is expressed on a much broader range of $CD4^+$ T cells than CCR5, and that this depletion is responsible for the immunosuppression associated with HIV. This assumption may need revisiting in light of the recent findings that a powerful subset of immunoregulatory T cells, NKT cells, are also affected by HIV.

NATURAL KILLER T (NKT) CELLS

NKT cells are a unique lineage of T cells characterized by CD1d restriction/recognition and a heavily biased T-cell receptor (TCR) repertoire, such that the majority express the TCR beta chain Vβ11 and greater than 80% express an invariant alpha chain, Vα24JαQ. Both $CD4^+$ and $CD4^-$ subsets of NKT cells exist in similar proportions. The function of CD4 on NKT cells is unknown, but does not appear to be related to interaction of these cells with MHC class II molecules. NKT cells produce very high levels of immunoregulatory cytokines upon stimulation through their TCR, and this activity is associated with a potent ability to influence immune responses in a broad range of diseases, including autoimmunity, cancer and tissue graft-associated responses (see 1–3 for reviews). NKT cells are also known, from work in mouse models, to play a role in protection from a variety of infections including: yeast (*Cryptococcus*), spirochaetes (*Borrelia*), bacteria (*Pseudomonas*), parasites (*Plasmodium*, trypanosomes, *Leishmania*) and viruses (Hep B) (reviewed in 1 and 2). Although of these organisms, only *Cryptococcus* presents a clinical problem associated with HIV, it seems likely that this list is indicative of an involvement of NKT cells in a broad range of infections. It therefore follows that the loss of NKT cells could have a profound negative impact on the normal functions of the immune system.

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HIV TARGETS NKT CELLS

In this issue of *Immunology*, Fleuridor *et al*.[4] provide evidence that NKT cells are likely to be an important target of HIV. This study, along with recent reports from three independent groups[5–7] collectively demonstrate that Vα24/Vβ11 NKT cells are depleted from the peripheral blood of HIV-infected individuals when compared with healthy donors. Most of the depletion appears to occur within the first year of seroconversion, and is out of proportion with the loss of conventional $CD4^+$ T cells over this period.[7] While other possibilities exist as to the fate of NKT cells in HIV-infected patients, several convincing pieces of data support the idea that NKT cells are directly infected by HIV early in the course of the disease and could therefore play a role in establishing HIV infection.

NKT CELLS EXPRESS HIV CORECEPTORS

In light of the requirement for HIV coreceptor expression for cellular entry, Sandberg *et al*.[6] and Motsinger *et al*.[5] found between 25 and 50% of naïve NKT cells from healthy subjects simultaneously expressed CD4 and CCR5, identifying them as candidates for infection with R5-tropic HIV. In this issue, Fleuridor *et al*.[4] confirmed that NKT cells are potential candidates for infection by HIV using three NKT cell lines from a healthy donor.

NKT CELLS ARE INFECTED BY HIV *IN VITRO*

Motsinger *et al*.[5] found that following stimulation with αGalCer, a CD1d-presented superantigen-like ligand for NKT cells, approximately 50% of $CD4^+$ NKT cells could be infected with a green fluorescent protein (GFP)-encoding R5-tropic virus, while only about 4% of NKT cells could be infected with a GFP-encoding X4-tropic virus. Consistent with these findings, Fleuridor *et al*.[4] found that each of the NKT cell lines from a healthy donor were susceptible to infection by both R5 and X4-dependent strains of HIV as well as to infection with a primary isolate. $CD4^-$ NKT cells remained resistant to HIV infection.[5,6] As $CD4^-$ NKT are thought to derive from CD4 expressing precursors in the thymus, it is possible that these could also be depleted in the longer term.[8,9] Differences in the level of infection between NKT and conventional T-cell cultures suggest that NKT cells are preferentially targeted by R5-tropic HIV infection[5], possibly because conventional T cells have relatively low levels of CCR5 expression. Motsinger *et al*.[5] also found that in the absence of prior (αGC-induced) activation, NKT cells were substantially less susceptible to HIV infection, consistent with their finding of increased levels of the HIV coreceptor CCR5, following αGalCer stimulation.[5]

POSSIBLE IMPLICATIONS OF NKT CELL DEPLETION

NKT cells rapidly secrete large amounts of immunoregulatory cytokines, such as interleukin-4 and interferon-γ, upon primary stimulation and thus are thought to act as a bridge between innate and adaptive immune responses. It is not known if NKT cells have significant anti-HIV activity, but it is possible that early depletion of these cells could compromise antiviral immune responses. As NKT cells play important roles in many other responses, including prevention of the development of certain autoimmune diseases, inhibition of tumour development and growth and clearance of some infections, depletion of NKT cells could also play a role in the clinical sequelae of HIV infection. For example, as NKT cells contribute to the prevention of sarcoma in mice[10,11] it is possible that the depletion of NKT cells in AIDS patients is related to the increased susceptibility of these patients to the development of Kaposi's sarcoma. Similarly, the autoimmune phenomena associated with the introduction of highly active antiretroviral therapy in patients with severely depressed $CD4^+$ T-cell numbers may reflect differences between the recovery of NKT cells and that of conventional T cells, resulting in failure of regulation by NKT cells of autoimmune T-cell responses.[12] These papers therefore raise more questions than they answer and only further study will reveal the full significance of the susceptibility of NKT cells to infection by HIV.

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