IN THE NEWS

AIDS initiative

- ITAC: http://www.itacoalition.org/

"Does anyone deserve to be sentenced to death because he or she cannot access care that costs less than $2 a day?", asked Dr Gro Harlem, the World Health Organisation Director General, at the launch of a new alliance to tackle inequality in access to treatment for HIV/AIDS (*BBC News*).

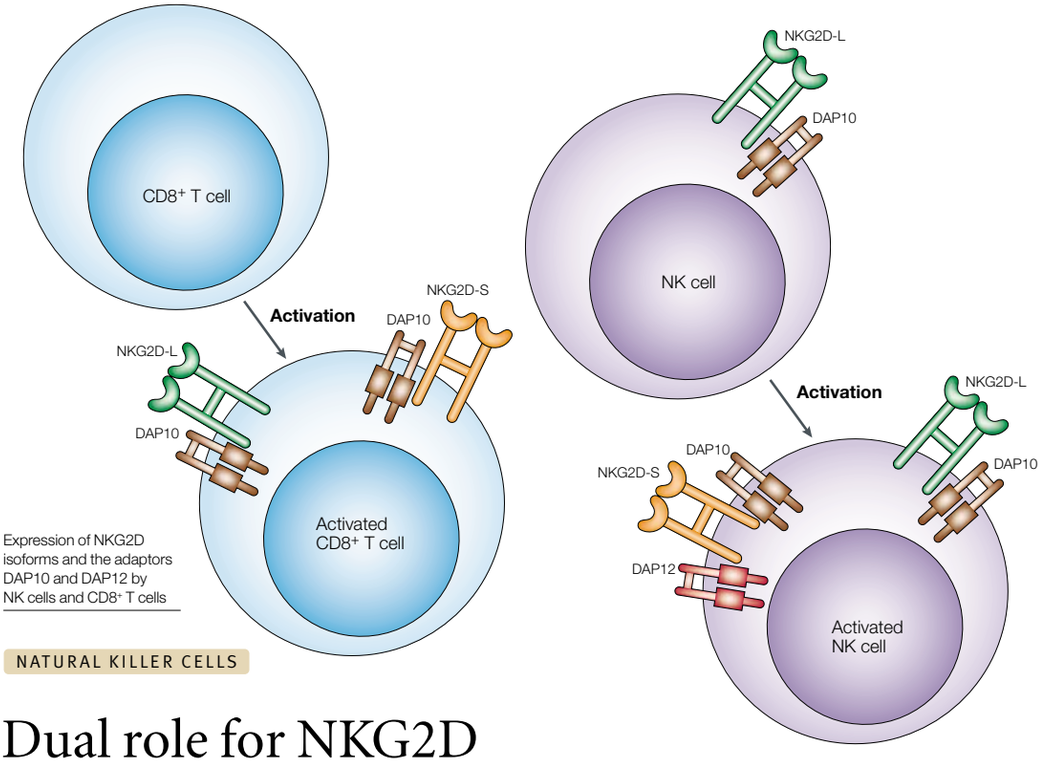
The International HIV Treatment Access Coalition (ITAC) — which brings together more than 50 groups, including United Nations (UN) agencies, governments and health organizations — aims to develop best practices for purchasing drugs and for implementing HIV/AIDS treatments, and, crucially, it will maintain international pressure for cheaper drugs.

The launch of ITAC in December 2002 coincided with publication of the AIDS Epidemic Update 2002, which showed that access to HIV/AIDS treatment continues to divide rich and poor nations. Worldwide, between 5 million and 6 million people are estimated to be in need of HIV treatment. In countries of low-to-middle income, only 5% of individuals with HIV/AIDS have access to treatment, compared with 100% in rich countries.

"Extending access to life-saving antiretroviral treatment is a moral, political and economic imperative," said Dr Peter Piot, executive director of UNAIDS, the UN joint programme on HIV/AIDS.

The UN has set the target of increasing the number of people in the developing world who receive treatment for HIV to 3 million by 2005. The hope is that ITAC will help achieve this goal. "If we continue as we are today, we will never reach the UN target," warned Professor Jope Lange, the co-ordinator of the new coalition (*The New York Times*).

Jennifer Bell



Expression of NKG2D isoforms and the adaptors DAP10 and DAP12 by NK cells and CD8+ T cells

NATURAL KILLER CELLS

Dual role for NKG2D

NKG2D is an activating receptor that is expressed by T cells, as well as by natural killer (NK) cells and macrophages. Previously, it had been found to associate with the adaptor molecule DAP10. When engaged on T cells, NKG2D transmits a co-stimulatory signal, but on NK cells, it can provide a direct stimulatory signal. How can a single receptor transmit such different signals in different cell types? The molecular basis for this ability of NKG2D is now shown in two papers published in the December issue of *Nature Immunology*.

Diefenbach and colleagues identified two splice variants of mouse NKG2D — a long form (NKG2D-L) that has a 13-amino-acid extension at the amino terminus, and a short form (NKG2D-S). Resting NK cells express messenger RNA encoding NKG2D-L, and after activation, mRNA encoding NKG2D-S is upregulated. Neither isoform can be detected in resting macrophages or CD8$^+$ T cells. After T-cell receptor stimulation, the expression of both isoforms is upregulated on CD8$^+$ T cells, whereas stimulation of macrophages with bacterial lipopolysaccharide upregulates the expression of NKG2D-S preferentially. Immunoprecipitation studies showed that the two isoforms associate differentially with the adaptor molecules DAP10 and DAP12 (also known as KARAP) — NKG2D-L associates only with DAP10, whereas NKG2D-S can associate with both DAP10 and DAP12. Because CD8$^+$ T cells do not express DAP12, the two NKG2D isoforms that are expressed by activated T cells can interact only with DAP10, whereas activated NK cells can transmit signals through DAP10 and DAP12. Could the failure of T cells to respond directly to signals through NKG2D in the absence of co-stimulation be due to the absence of DAP12 in these cells? Ectopic expression of DAP12 in CD8$^+$ T cells allowed a direct stimulatory signal to be transmitted through NKG2D-S. NK cells from *Dap12*$^{-/-}$ mice have defective signalling through NKG2D, which would not have been predicted from previous results.

Gilfillan and colleagues generated *Dap10*$^{-/-}$ mice to investigate the function of this adaptor. Although DAP10 was known previously to associate only with NKG2D, expression studies showed that the expression of NKG2D is low, but detectable, on NK cells, but absent on T cells. Activation of NK cells resulted in the upregulation of expression of NKG2D, but this did not occur when T cells were activated. How can NKG2D be expressed by NK cells in the absence of DAP10? The obvious explanation is that NKG2D can associate with another adaptor molecule, possibly DAP12. Immunoprecipitation studies showed that this is indeed the case.

These studies indicate that the differential signalling ability of NKG2D depends both on the cell type and the activation state, which is determined by the differential expression of DAP10 versus DAP12, and on the two different NKG2D isoforms. It makes sense that NKG2D can deliver a direct stimulatory signal to NK cells, but only a co-stimulatory signal to T cells, because the specificity of T-cell signalling would be compromised by direct stimulation of T cells by NKG2D.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPERS Diefenbach, A. *et al.* Selective associations with signaling proteins determine stimulatory versus costimulatory activity of NKG2D. *Nature Immunol.* **3**, 1142–1149 (2002) | Gilfillan, S., Lo, E. L., Cella, M., Yokoyama, W. M. & Colonna, M. NKG2D recruits two distinct adapters to trigger NK-cell activation and costimulation. *Nature Immunol.* **3**, 1150–1155 (2002)