

HIV

Complex regulation of immune responses to HIV and SIV

The function of regulatory T cells in infectious diseases is a hot topic at present. In retroviral infection, it is not clear whether regulatory T cells suppress appropriate immune responses, in which case the elimination of these cells might be beneficial, or whether they can have a protective role, in which case impaired generation of regulatory T cells would contribute to the aberrant T-cell activation that is a hallmark of HIV infection. Two recent studies emphasize the complexity of this issue in retroviral infections.

Reporting in *The Journal of Immunology*, Andersson and colleagues show that chronic infection with HIV can influence the tissue distribution of endogenous regulatory T (T_{Reg}) cells. The authors analysed the role of T_{Reg} cells in HIV infection by quantifying the lymphoid-tissue expression of three T_{Reg} -cell markers: CTLA4 (cytotoxic T-lymphocyte antigen 4), GITR (glucocorticoid-induced tumour-necrosis factor (TNF)-receptor-related protein) and the transcription factor FOXP3 (forkhead box P3). They found that, compared with patients who were treated with highly active antiretroviral therapy (HAART), patients in whom HIV was actively replicating had higher levels of these three T_{Reg} -cell markers in their lymphoid tissues. The authors suggest that T_{Reg} cells are recruited to lymphoid organs in which HIV is actively replicating and that these T_{Reg} cells could hamper the development of appropriate anti-HIV responses at these sites. This model indicates that elimination of T_{Reg} cells should be beneficial for the development of protective immune responses.

In another study, which was reported in *The Journal of Clinical Investigation*, Kornfeld and colleagues assessed the correlates of protection against simian immunodeficiency virus (SIV) infection of African green monkeys (using the isolate SIV_{AGM}). This SIV infection of a natural African host is non-pathogenic;

only SIV infections of African primate species result in non-pathogenic infections, which is in contrast to infection of Asian macaques with SIV_{MAC}, even though the viral loads are similar in these systems. In this study, the authors focused on assessing the early stages of SIV_{AGM} infection in African green monkeys. They examined patterns of T-cell activation and cytokine profiles in various tissues during primary SIV_{AGM} infection. A transient increase in T-cell activation was detected but returned to a baseline level at ~3 weeks after infection. In contrast to infection with HIV, there were no significant increases in the levels of the chemokines CC-chemokine ligand 3 (CCL3) and CCL4 or of the cytokine TNF. An early and strong induction of expression of transforming growth factor- β and FOXP3 was detected, and this correlated with an increase in the numbers of CD4⁺CD25⁺ and CD8⁺CD25⁺ T cells. Although functional studies are required to confirm the regulatory nature of these cells, the authors suggest that these results favour a protective role for regulatory T cells in controlling abnormal T-cell activation, which then leads to non-pathogenic infection. On the basis of this model, it might be possible to develop novel intervention strategies for the treatment of HIV infection.

Taken together, these studies, which investigated two different phases of retroviral infection, show the difficulties in identifying the correlates of protection against retroviral infection and in determining the role of regulatory T cells. It will be crucial to gain a better understanding of regulatory T-cell function at different stages of infection for the design of appropriate therapeutics.

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References and links

ORIGINAL RESEARCH PAPERS Andersson, J. *et al.* The prevalence of regulatory T cells in lymphoid tissue is correlated with viral load in HIV-infected patients. *J. Immunol.* **174**, 3143–3147 (2005) | Kornfeld, C. *et al.* Antiinflammatory profiles during primary SIV infection in African green monkeys are associated with protection against AIDS. *J. Clin. Invest.* **115**, 1082–1091 (2005)

IN BRIEF

TUMOUR IMMUNITY

DC–NK cell cross-talk as a novel CD4⁺ T cell-independent pathway for antitumour CTL induction.

Adam, C. *et al.* *Blood* 15 Mar 2005 (doi:10.1182/blood-2004-09-3775)

While assessing the ability of peptide-pulsed dendritic cells (DCs) to protect against tumour-cell challenge, Adam *et al.* observed that non-pulsed, syngeneic, bone-marrow-derived DCs protected mice against challenge with A20 B-cell lymphoma cells. Protection was natural killer (NK)-cell dependent, and surprisingly, protected mice showed A20-specific CD8⁺ T-cell-dependent immunological memory. Such memory was also observed after immunization with CD40-deficient DCs, indicating that CD8⁺ T-cell activation occurred independently of CD4⁺ T-cell help. Because NK cells secrete interferon- γ (IFN- γ) in response to CD40-deficient DCs and because this was required for CD8⁺ T-cell activation, the authors suggest that immunization with DCs can activate NK cells to produce IFN- γ , which then activates endogenous DCs to activate CD8⁺ T cells independently of CD4⁺ T-cell help.

INFLAMMATION

The N-terminal domain of thrombomodulin sequesters high-mobility group-B1 protein, a novel antiinflammatory mechanism.

Abeyama, K. *et al.* *J. Clin. Invest.* 14 Apr 2005 (doi:1172/JCI200522782)

Abeyama *et al.* set out to investigate whether thrombomodulin (TM) — an endothelial-cell-specific membrane receptor that is an anticoagulant co-factor — also inhibits inflammation by sequestering pro-inflammatory mediators such as high-mobility group box 1 protein (HMGB1). They found that TM associates with HMGB1 through its amino (N)-terminal lectin-like domain (D1), which prevents HMGB1 from binding its receptor RAGE (receptor for advanced glycation end-products). Functional evidence to support their hypothesis was provided by the observation that both recombinant soluble human TM and a recombinant polypeptide corresponding to D1 inhibited HMGB1-induced activation of nuclear factor- κ B and generation of reactive-oxygen species *in vitro*, as well as ultraviolet-light-induced cutaneous inflammation and lipopolysaccharide-induced lethality *in vivo*.

T-CELL SIGNALLING

A ligand-induced conformational change in the T cell receptor associated with productive immune synapses.

Risueño, R. M. *et al.* *Blood* 24 Mar 2005 (doi:10.1182/blood-2004-12-4763)

There are two main models for the initiation of T-cell receptor (TCR) signalling: the clustering model, in which TCR signalling is initiated by TCR clustering, a model that is supported by the ability of antibodies to crosslink the TCR and stimulate signalling; and the conformational-change model. So far, structural studies have not provided much evidence to support a role for conformational change. In this study, Risueño *et al.* show that the antibody APA1/1 detects a conformational change in the cytoplasmic tail of the CD3 ϵ chain following TCR ligation. This change was only detectable when the TCR was stimulated with an agonist peptide in the context of MHC and not with a partial agonist peptide, and the change was detectable both *in vitro* and *in vivo*.