VIRAL IMMUNITY

Turning off class switching

Although impairment of humoral immunity is a well-recognized feature of HIV infection, the mechanisms behind this B-cell dysfunction are not well understood. Now, a study just published in *Nature Immunology* describes a novel mechanism by which HIV-1 directly inhibits B-cell function. Andrea Cerutti and colleagues report that the HIV-1 negative factor (Nef) protein crosses into bystander B cells and blocks the production of class-switched immunoglobulins such as IgA and IgG.

B cells generate IgA and IgG by a process known as class-switch recombination (CSR), which is initiated when activated $CD4^+$ T cells interact with IgD^+ B cells. Signalling mediated by CD40 ligand (CD40L) interaction with CD40, together with secretion of the T-cell cytokines interleukin-10 (IL-10) and IL-4, induces the transcription of IgA, IgE or IgG heavy-chain genes. Compared to IgM, these class-switched immunoglobulins have different effector functions, including the ability to neutralize invading pathogens at sites of entry. In HIV-1 infection, T-cell-dependent IgA and IgG responses to specific antigens are suboptimal, which indicates an impairment of the class-switch programme. Although viral destruction of $CD4^+$ T cells clearly has a role in impaired B-cell function, this does not explain all the features of humoral immune dysfunction in individuals infected with HIV-1.

HIV-1 does not infect B cells, so the authors looked for a soluble factor that might disrupt B-cell function. They focused on the immunosuppressive early HIV-1 protein Nef, which is released into the extracellular milieu from infected cells.

The authors first showed that Nef enters IgD^+ B cells from the extracellular environment. Assays that detect molecular markers of CSR showed that exogenous Nef inhibits the induction of CSR in B cells that have been activated by CD40L, IL-4 and IL-10. Nef blocks the CD40 signalling pathway by increasing the amount of the regulatory protein IκBα (inhibitor of nuclear factor-κB (NF-κB) α. Increased IκBα concentrations prevent translocation of cytoplasmic NF-κB dimers into the B-cell nucleus, a step that is required for induction of the transcriptional programme that initiates CSR. Nef also upregulates the negative-feedback proteins suppressor of cytokine signalling 1 (SOCS1) and SOCS3, which inhibit the JAK (Janus kinase)–STAT (signal transducer and activator of transcription) pathways that are induced by IL-4 and IL-10. Inhibition of JAK–STAT signalling impairs CSR and blocks the differentiation of class-switched B cells into antibody-producing cells.

The inhibition of immunoglobulin class switching by HIV-1 Nef prevents the production of antibody classes that are most adept at neutralizing and clearing the virus. This is especially important for viral defence in the early stages of infection when the pool of $CD4^+$ T cells is replete.

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ORIGINAL RESEARCH PAPER Qiao, X. *et al.* Human immunodeficiency virus 1 Nef suppresses CD40-dependent immunoglobulin class switching in bystander B cells. *Nature Immunol.* **7**, 302–310 (2006)
FURTHER READING Peterlin, B. M. Nef: out and in? *Nature Immunol.* **7**, 229–230 (2006)
WEB SITE
Andrea Cerutti's website: http://www.med.cornell.edu/research/acerutti/index.html

IN BRIEF

ASTHMA AND ALLERGY

Glycolipid activation of invariant T cell receptor$^+$ NK T cells is sufficient to induce airway hyperreactivity independent of conventional $CD4^+$ T cells.

Meyer, E. H. *et al. Proc. Natl Acad. Sci. USA* **103**, 2782–2787 (2006)

Conventional $CD4^+$ T cells are thought to have an essential role in the pathogenesis of asthma. However, natural killer T (NKT) cells expressing a semi-invariant T-cell receptor (denoted *i*NKT cells) have been shown to be involved in the development of allergen-induced airway hyper-responsiveness (AHR). Meyer *et al.* set out to characterize the role of *i*NKT cells in the development of AHR and found that intranasal administration of an *i*NKT-cell ligand (either α-galactosylceramide (α-GalCer) or a synthetic version of a glycolipid from some *Sphingomonas* spp.) induced severe AHR in mice. Induction of AHR required both interleukin-4 (IL-4) and IL-13 but not the presence of conventional $CD4^+$ T cells. The authors therefore suggest that *i*NKT cells might synergize with conventional $CD4^+$ T cells in the induction of asthma.

LYMPHOID ORGANS

Evidence for a functional second thymus in mice.

Terszowski, G. *et al. Science* 2 March 2006 (doi:10.1126/science.1123497)

While analysing lymphoid tissues in the neck, Terszowski *et al.* identified structures with lymphoid characteristics that were not lymph nodes. Instead, these tissues had characteristics of the thymus, including a cortico-medullary architecture, the presence of $CD4^+CD8^+$ double-positive thymocytes and the expression of genes associated with thymopoiesis (such as recombination-activating gene 1). Transplantation of these cervical thymi into mice lacking a thymus showed that these structures could be colonized by recipient progenitors, could mediate positive and negative selection and could produce a diverse repertoire of T cells able to provide T-cell help in a T-cell-dependent antibody response. Cervical thymi were found in 90% of BALB/c mice analysed and ~40% of C57BL/6 mice. Therefore, as the authors point out, this study might complicate the interpretation of a large number of previous studies of T-cell function in which the thoracic thymus was removed to eliminate *de novo* T-cell production.

TECHNIQUE

Rapid analysis of T-cell selection *in vivo* using T cell-receptor retrogenic mice.

Holst, J. *et al. Nature Methods* **3**, 191–197 (2006)

Vignali and colleagues have developed a way of bypassing the endless rounds of breeding required to generate T-cell receptor (TCR)-transgenic mice, in which all (or most) T cells express the same TCRαβ. By adapting a method previously developed by this group, they made retroviral constructs expressing both TCR chains from a single composite open reading frame. These constructs were then transduced into mouse haematopoietic stem cells before being adoptively transferred to immunodeficient mice. Using this technique, the authors generated several so-called retrogenic mice that expressed previously characterized TCRs. Importantly, T-cell development and function in these retrogenic mice were similar to the corresponding TCR-transgenic strain. This method therefore offers new practical options to researchers studying T-cell development and function.