VIROLOGY

Turning off class switch

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 IgG and IgA.

B cells generate IgG and IgA by a process known as immunoglobulin class switch recombination (CSR), which is initiated when activated $CD4^+$ T cells bind to IgD^+ B cells. Signalling through the T-cell CD40 ligand (CD40L), together with secretion of the T-cell cytokines interleukin (IL)-10 and IL-4, induces the transcription of IgG, IgA or IgE heavy-chain genes. In addition, activated B cells differentiate into plasma cells that secrete large amounts of IgG, IgA or IgE. Compared with IgM, these class-switched immunoglobulins acquire novel effector functions, including the ability to neutralize invading pathogens at sites of entry. In HIV-1 infection, T-cell-dependent IgG and IgA antibody 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 doesn't explain all the features of humoral immune dysfunction in HIV-1.

HIV-1 does not infect B cells, and 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

Links:

HIV-1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome&cmd=Retrieve&dopt=Overview&list_uids=12171

Nef
http://ca.expasy.org/uniprot/P04324

CD40L
http://ca.expasy.org/uniprot/P29965

(IL)-10
http://ca.expasy.org/uniprot/P22301

IL-4
http://ca.expasy.org/uniprot/P05112

IκBα
http://ca.expasy.org/uniprot/P25963

SOCS1
http://ca.expasy.org/uniprot/O15524

SOCS3
http://ca.expasy.org/uniprot/O14543

molecular markers of CSR revealed that exogenous Nef protein inhibits the induction of CSR in B cells that had been activated by CD40L, IL-4 and IL-10. Nef blocks the CD40 signalling pathway by increasing the amounts of the regulatory protein IκBα. Increased IκBα prevents 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 SOCS1 and SOCS3, which inhibit the Jak–STAT 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 progression in the early stages of infection when the pool of $CD4^+$ T cells is replete.

Shannon Amoils

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)
WEBSITE
Andrea Cerutti's website: http://www.med.cornell.edu/research/acerutti/index.html