IN THE NEWS

The how and when of HIV-2

Research published in the *Proceedings of the National Academy of Sciences* investigating the history of the HIV-2 epidemic has been in the news this month. Unlike HIV-1, which has spread globally, HIV-2 is predominant only in West Africa, where it infects ~1% of the population. Although both of these viruses are thought to have spread from monkeys to humans, how and when this occurred are questions of considerable debate.

HIV-2 closely resembles the strain of simian immunodeficiency virus (SIV) found in sooty mangabey monkeys. As explained in a report in the *New Scientist*, to investigate when this virus spread to humans, Dr. Ann-Mieke Vandamme and colleagues from the Katholieke Universiteit Leuven, Belgium, analysed the mutations present in HIV-2 and mangabey SIV and estimated the rate at which these would have accumulated. From this analysis, they concluded that HIV-2 probably crossed to humans as early as the 1940s.

AIDS caused by HIV-2 first occurred in Guinea-Bissau, and levels of infection remained low until the 1960s. As Vandamme told the *Associated Press*, the sharp increase in disease incidence coincided with the war to gain independence from Portugal between 1963 and 1974, and she speculated that the use of non-sterile injections and increased sexual activity during this time might have been important.

Not all of the coverage of this study has been positive, as reported by *HealthScoutNews*. Ernest Drucker, a professor of epidemiology at the Montefiore Medical Center and Albert Einstein College of Medicine in New York, has his doubts as to whether HIV-2 really spread to humans this early, and when asked about this work he said, 'The dates are very iffy'.

Jenny Buckland

LYMPHOPOIESIS

Partners in crime

Bcl11a and *Bcl11b,* which encode zinc-finger transcription factors, are both associated with malignancies of the immune system. Gene-targeting studies, now published in *Nature Immunology*, indicate interesting differences between the roles of these paralogues in lymphocyte development.

Liu *et al.* first became interested in *Bcl11a* when they discovered that activation of this proto-oncogene by retroviral integration is associated with the development of myeloid leukaemia in mice. To investigate further the function of this gene, they generated *Bcl11a*$^{-/-}$ mice, which died a few hours after birth. B cells were absent in the fetal livers of these mice, and fetal liver cells did not express genes that are normally expressed by B cells, including early B-cell factor 1 (*Ebf1*), paired box gene 5 (*Pax5*) and the interleukin-7 receptor (*Il7r*). Also, *Bcl11a*$^{-/-}$ fetal liver cells failed to develop into B cells after transplantation into lethally irradiated wild-type recipients. This indicates that Bcl11a is required for normal B-cell development and that it functions upstream of Ebf1 and Pax5.

In addition, T-cell development was disrupted in these mice, and when *Bcl11a*$^{-/-}$ fetal liver cells were transferred into irradiated recipients, they failed to contribute normally to T-cell development. With age, most of the mice that had received *Bcl11a*$^{-/-}$ cells developed leukaemia and died. Further experiments showed that the leukaemia cells were mainly of host origin, indicating that transplantation of *Bcl11a*$^{-/-}$ cells resulted in tumorigenesis of host T cells, by some as-yet-unknown mechanism. This implies that normally, this tumour-suppressor gene functions in a non-cell-autonomous manner — in other words, haematopoietic cells that express *Bcl11a* protect other cells from tumorigenesis. This paper confirms that, in addition to its roles in normal B- and T-cell development, *Bcl11a* can function as a tumour suppressor.

IMMUNE EVASION

Germ warfare

Imagine the scene. You are planning an invasion into enemy territory but know that the army waiting to defend against any attack is far bigger than your own small-scale operation. What you really need is a weapon that will wipe out a large number of the enemy in one go, without having to get involved in hand-to-hand combat. *Staphylococcus aureus* seems to have come up with an ideal solution. It secretes a protein that knocks out a large percentage of the B-cell repertoire in a supraclonal manner.

S. aureus **protein A (SpA) is a B-cell superantigen that forms a complex with lymphocytes expressing B-cell receptors (BCRs) with clan-VHIII-encoded variable regions. These BCRs are displayed by 5–10% of mature mouse B cells, including marginal-zone and follicular B cells, and B1 cells with a BCR antigen-binding region of the T15 idiotype. Now, Goodyear and Silverman have characterized the deletion of B cells in response to this toxin in a study published in *The Journal of Experimental Medicine*.**

T15i immunoglobulin knock-in (T15i$^{+/+}$) mice, in which almost all B cells express an S107 (clan VHIII) V_H transgene, were exposed to SpA and analysed after various time points. The initial response of B cells to SpA was shown to be similar to the normal response to antigen exposure. After 2 hours, levels of the targeted cell-surface BCR were decreased; after 16 hours, the BCR co-receptors CD19 and CD21 were downregulated, and the activation markers CD69 and CD86 were upregulated; and after further *in vitro* culture, levels of MHC class II molecules and other markers were increased.

Next, the authors looked at whether the decrease in the number of T15i$^{+/+}$ B cells that follows this initial activation in response to SpA is owing to effects on trafficking or apoptosis. The adoptive transfer of labelled T15i$^{+/+}$ splenocytes to C57BL/6 recipients treated with SpA showed that after 48 hours of *in vivo* exposure, despite certain B cells having undergone 2–3 rounds of proliferation, the number of T15i B cells was decreased by ~36%. This indicates that splenic T15i$^{+/+}$ B cells exposed to SpA undergo an increased rate of apoptosis, and this was also seen at other anatomical locations. After *in vivo* exposure to SpA, levels of caspase-3 were increased in parallel with the induction of DNA fragmentation. The inclusion of Z-VAD, a potent pan-caspase inhibitor, delayed the 'assisted suicide' of SpA-targeted T15i$^{+/+}$ B cells. Bcl-2 overexpression, but not Fas (CD95) deficiency, was shown to rescue B cells of SpA-treated T15i$^{+/+}$ mice from apoptosis. The authors suggest that apoptosis in response to SpA is similar to the activation-induced cell death of B cells in response to antigen. The authors are now hoping to put this microbial battle plan to therapeutic use. Up to 50% of human B cells express clan-VHIII-encoded BCRs and are therefore susceptible to SpA. Silverman and colleagues are engineering variants of SpA with higher binding affinities, and also with specificities for different framework variable regions, which will be evaluated for

Wakabayashi *et al.* showed previously that mutations in *Bcl11b* could result in thymic lymphoma in mice. Here, they generated *Bcl11b*$^{-/-}$ mice, which also died soon after birth, and examined lymphocyte development in embryos lacking this protein. Thymic cellularity was reduced in the absence of Bcl11b, and αβ T-cell development was severely, although not entirely, blocked in the double-negative compartment at the CD25^{+}CD44^{-} to CD25^{-}CD44^{-} transition.

Reconstitution of irradiated recipient mice with *Bcl11b*$^{-/-}$ fetal liver cells resulted in normal development of γδ T cells and B cells, but αβ T-cell development, as in the knockout mice, was blocked at an early stage. In addition, further experiments indicated that *Bcl11b*$^{-/-}$ thymocytes were highly susceptible to apoptosis, although the downstream targets in this pathway remain unknown. Taken together, these results show that Bcl11b has an important role in regulating the differentiation and survival of thymocytes.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPERS Liu, P. *et al.* Bcl11a is essential for normal lymphoid development. *Nature Immunol*. 28 April 2003 (DOI: 10.1038/nri925) | Wakabayashi, Y. *et al.* Bcl11b is required for differentiation and survival of αβ T lymphocytes. *Nature Immunol.* 28 April 2003 (DOI: 10.1038/nri927)

FURTHER READING Satterwhite, E. *et al.* The BCL11 gene family: involvement of BCL11A in lymphoid malignancies. *Blood* **98**, 3413–3420 (2001) | Wakabayashi, Y. *et al.* Homozygous deletions and point mutations of the *Rit1/Bcl11b* gene in γ-ray induced mouse thymic lymphomas. *Biochem. Biophys. Res. Commun.* **301**, 598–603 (2003)

the selective destruction of malignant B-cell populations in autoimmune diseases, such as systemic lupus erythematosus, and cancers, such as lymphoma and leukaemia.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Goodyear, C. S. & Silverman, G. J. Death by a B-cell superantigen: *in vivo* V_H-targeted apoptotic supraclonal B-cell deletion by a Staphylococcal toxin. *J. Exp. Med*. **197**, 1125–1139 (2003)

WEB SITE

Gregg Silverman's homepage: http://medicine.ucsd.du/rdcc/silverman.shtml

IN BRIEF

HIV

Perturbations in B cell responses to CD4^{+} T cell help in HIV-infected individuals.

Moir, S. *et al. Proc. Natl Acad. Sci. USA* **100**, 6057–6062 (2003)

Infection with HIV results in defective B-cell responses, which have been investigated previously using *in vitro* surrogates of antigen stimulation. In this study, Moir *et al.* used a more physiological system to investigate the effects of HIV infection on B-cell responses to T-cell help. Co-culture of B cells and CD4^{+} T cells from HIV-infected individuals resulted in poor B-cell proliferation despite normal expression of CD154 by the activated T cells. Further experiments showed that this was due to reduced B-cell expression of CD25 (the IL-2 receptor), resulting in a reduced ability of the B cells to proliferate in response to IL-2. This study helps to explain why humoral responses against HIV are ineffective.

B-CELL RESPONSE

E-proteins directly regulate expression of activation-induced deaminase in mature B cells.

Sayegh, C. E. *et al. Nature Immunol.* 28 April 2003 (DOI: 10.1038/ni923)

Previous work indicated that the E-protein transcription factors might have a role in B-cell activation and class-switch recombination (CSR) and this new study provides a molecular mechanism to explain how. The authors show that expression of *Aicda* — the gene that encodes activation-induced cytidine deaminase, the only B-cell-specific factor that is crucial for CSR — can be induced by overexpression of the E-protein E47, whereas overexpression of the E-protein inhibitor Id3 can suppress *Aicda* expression. By comparison of mouse and human *AICDA* loci, they identified a highly conserved regulatory sequence that contains two E-box sites. E-protein binding to these sites was shown to activate transcription of the *Aicda* locus.

IMMUNE EVASION

Steroid hormone synthesis by vaccinia virus suppresses the inflammatory response to infection.

Reading, P. C. *et al. J. Exp. Med.* **197**, 1269–1278 (2003)

The mammalian enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD) is central to the synthesis of all steroid hormones, including anti-inflammatory glucocorticoids. Vaccinia virus (the smallpox vaccine virus) seems to exploit the immunosuppressive properties of steriods by encoding its own 3β-HSD, known as the A44L protein. *A44L* has been shown previously to contribute to virulence in a mouse-infection model; this study investigates the potential immune mechanisms behind this observation. Early in infection, *A44L*-mutant virus induced lower levels of the glucocorticoid corticosterone than the wild-type virus. Although the initial inflammatory responses induced by both viruses were similar, the recruitment and activity of CD4^{+} and CD8^{+} T cells was greater with the mutant virus. This indicates that *A44L* promotion of corticosterone synthesis leads to the suppression of the host response to vaccinia.