IN THE NEWS

Revisiting HIV therapy

The publication of a study in the *New England Journal of Medicine* has led to a war of words for and against the use of structured treatment interruptions (STIs) for HIV$^+$ patients. Advocates have suggested that STIs give patients a break from the side effects of drugs and allow the virus to mutate back to a form that is more susceptible to therapy. Drug resistance is one of the main challenges to therapy. The new study, which is the largest so far to test this theory, indicates that in some patients, the 'drug holiday' could actually be detrimental, causing more frequent progression of disease and speeding up the attack on the immune system.

Jody Lawrence of the University of California, who led the study, claims that the results were "disappointing" and that STI "did not work and should be avoided" by drug-resistant HIV$^+$ patients (*BBC News Online*; *HealthDay*). This claim was supported by Bernard Hirschel of Cantonal University Hospital, Geneva, who said, "it is hard to see what could be achieved by interrupting treatment for a few weeks" (*Reuters*).

However, Anthony Fauci (NIAID Director) warned against over-generalizations, as this study only included patients in whom HIV was detectable in the blood and the virus had already become resistant to drugs, and did not apply to "individuals who are being successfully treated with anti-HIV medications" (*Reuters*).

Hirschel suggests that as this new study is larger than a previous study that favoured STIs and includes clinical end-points, doctors "must go with the results of the large study" (*Associated Press*). A spokesperson for the Terrence Higgins Trust agreed that for anyone taking a drug holiday, it is important that they are "more closely monitored during that time" (*BBC News Online*).

Kirsty Minton

IMMUNE REGULATION

Signalling death

The decision whether or not to mount a productive immune response to an antigen is determined largely by environmental factors such as the presence or absence of microbial products. These molecules provide signals to alert the immune system to the presence of potentially dangerous antigens and many are thought to function by stimulating dendritic cells (DCs) to mature. Dying cells, when co-injected into mice with antigen, have the same immunostimulatory properties, inducing strong cytolytic CD8$^+$ T-lymphocyte (CTL) responses to the antigen.

The factor present in dying cells that facilitates this CTL priming to antigen has been shown to reside in the cytosol, and now using chromatography and mass spectrometry, Shi *et al.* have identified uric acid as one of the main agents responsible for this effect. This was confirmed by showing that purified uric acid could induce a similar CTL response to co-injected antigen as the active cytosolic fractions obtained by chromatography, and that treatment of either these fractions or the immunized mice with uricase — a highly specific enzyme that mediates the degradation of uric acid — markedly reduced their ability to promote a measurable CTL response.

Increased uric-acid production was observed to be a general characteristic of cells undergoing death, and as the CTL response generated in animals depleted of uric acid was substantially less than that detected in control mice, it is probably a key immunoactivating signal produced by dying cells.

Soluble uric acid was unable to support DC maturation *in vitro*, however, monosodium urate (MSU) crystals increased the expression of co-stimulatory molecules by bone-marrow-derived DCs in culture and facilitated CTL priming to antigen *in vivo*. By contrast, MSU crystals did not affect the uptake of antigen by DCs. Uric acid has been reported to

ANTIGEN PRESENTATION

Revealing hidden peptides

The peptides presented by MHC class I molecules are traditionally thought to be derived from full-length endogenous proteins. Now, unexpectedly, functional translation from a non-AUG initiation codon, and MHC class I presentation of a peptide encoded by the 3′ untranslated region (3′ UTR) has been described in a recent paper published in *Science*.

Schwab *et al.* generated mice that ubiquitously express a bi-cistronic transgene, encoding a peptide derived from the *Uty* gene and a peptide derived from the *H60* histocompatibility gene (LYL8). The first peptide was initiated by a conventional AUG codon, whereas the second peptide, which was downstream of a stop codon in the 3′ UTR, had CUG as its initiation codon. Cells derived from transgenic mice could present both peptides to peptide-specific T-cell hybridomas, and were lysed by LYL8-specific cytotoxic T lymphocytes (CTLs). Further evidence for the presence of LYL8–MHC class I complexes was provided by the observation that transgenic splenocytes elicited LYL8-specific CTL responses after immunization of non-transgenic animals, but that transgenic mice expressing the cryptic LYL8 peptide were tolerant to the peptide.

Given that LYL8 is encoded downstream of a stop codon in the 3′ UTR, and has a non-AUG start codon, the authors investigated the mechanisms that regulate translation of this cryptic peptide. Analysis of peptide extracts from transgenic splenocytes by chromatography confirmed that the LYL8 initiation codon (CUG) was decoded as leucine, and was not misread as methionine. Interestingly, translation initiation was specific to the leucine-encoding codon CUG, indicating that ribosome read-through of the upstream stop codon was not responsible for LYL8 translation. This was confirmed by the observation that increasing the number of stop codons between the two peptides and shifting the peptides out of frame with the initial AUG codon did not affect MHC class I presentation of LYL8.

These studies identify two mechanisms — translation of 3′ UTR-encoded peptides and translation of non-AUG initiated peptides — that could markedly increase the number of peptides surveyed by the immune system, making the prospect of defining the peptides resulting in CD8$^+$ T-cell-mediated tumour immunity and autoimmunity that much harder.

Karen Honey

References and links

ORIGINAL RESEARCH PAPER Schwab, S. *et al.* Constitutive display of cryptic translation products by MHC class I molecules. *Science* **301**, 1367–1371 (2003)

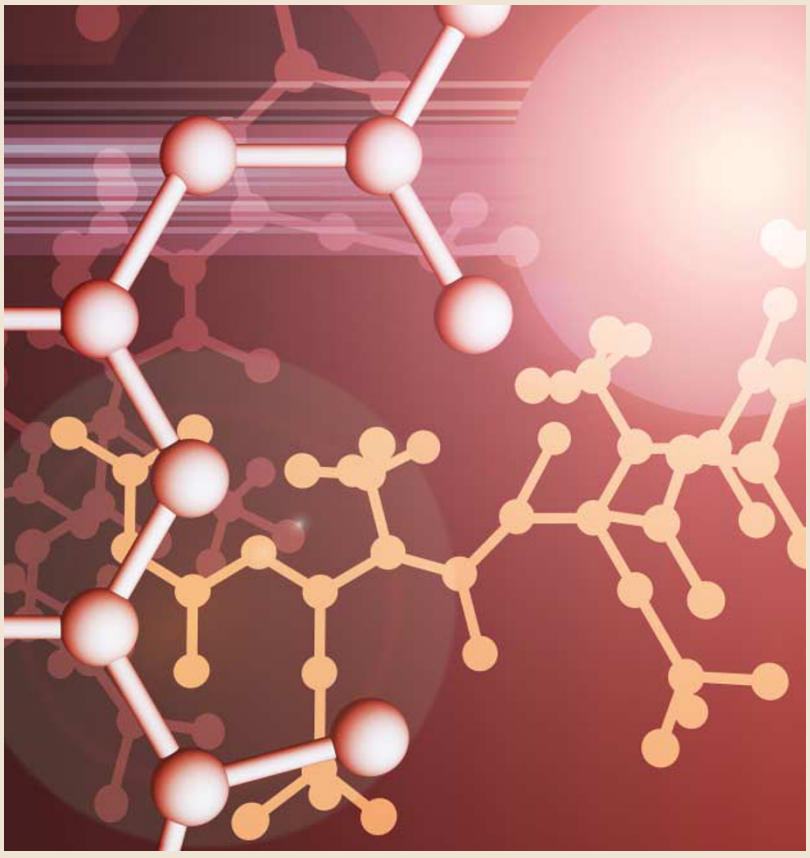
precipitate *in vivo* at the concentrations used in these studies and so the authors suggest, during cell death, the levels of uric acid produced locally could increase sufficiently to cause this endogenous metabolite to precipitate and promote DC maturation and activation. If the dying cell contained antigen to which the host was not tolerant then such DC activation would lead to the induction of a productive immune response to these antigens.

This study identifies uric acid as an endogenous mediator of immune activation, implicating it as crucial for surveillance by the adaptive immune system. As such, it is possible that uric acid could act as a type of adjuvant, stimulating an immune response to antigens to which the immune system was previously non-responsive, such as virus infections and tumours. Furthermore, these studies are also important to our understanding of the pathogenesis of gout — an inflammatory disease initiated by the precipitation of MSU in the joints — and raise the possibility that uric acid has a central role in the inflammatory response to tissue damage.

Karen Honey

References and links

ORIGINAL RESEARCH PAPER Shi, Y. *et al*. Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature* 7 September 2003 (DOI:10.1038/nature019991)
FURTHER READING Gallucci, S. & Matzinger, P. Danger signals: SOS to the immune system. *Curr. Opin. Immunol.* **13**, 114–119 (2001)



IN BRIEF

PSYCHONEUROIMMUNOLOGY

Affective style and *in vivo* immune response: neurobehavioral mechanisms.

Rosenkranz, M. A. *et al*. *Proc. Natl Acad. Sci.* USA 5 September 2003 (DOI: 10.1073/pnas.1534743100)

This study looked at the correlation between physiological measures of negative emotion and the immune response to an influenza vaccine. Individuals with high comparative levels of activation of the right-hand side of the prefrontal cortex of the brain (at baseline and in response to a negative-emotion-inducing task) experience more intense negative emotions and are more likely to suffer from depression. These individuals produce lower antibody titres in response to vaccination. Antibody titres were also correlated with the eye-blink response to a task that induced negative emotions. Individuals with a larger eye-blink response (which indicates stronger negative emotion) produced lower antibody titres in response to vaccination. These studies help to clarify the link between depression and suppressed immune function.

LYMPHOCYTE MIGRATION

The strategy of T cell–antigen-presenting cell encounter in antigen-draining lymph nodes revealed by imaging of initial T cell activation.

Bajénoff, M. *et al*. *J. Exp. Med.* **198**, 715–724 (2003)

Activated, antigen-loaded dendritic cells (DCs) migrate to the draining lymph node (LN), but how are they located by antigen-specific $CD4^+$ T cells? Bajénoff *et al.* show that DCs that acquire antigen in the periphery preferentially accumulate in the paracortical region of the LN. More specifically, the DCs were close to the high endothelial venules (HEVs), where the initial stages of T-cell activation can be observed. The authors then showed that only antigen-specific T cells are retained in the proximity of the HEVs, indicating that DCs position themselves at the site of T-cell entry into the LN to maximize the chance of an immunogenic $CD4^+$ T cell–DC interaction occurring.

VIRAL IMMUNITY

Self-inhibition of synthesis and antigen presentation by Epstein–Barr virus-encoded EBNA1.

Yin *et al*. *Science* **301**, 1371–1374 (2003)

The glycine–alanine repeat domain (GAr) of the Epstein–Barr virus-encoded protein nuclear antigen 1 (EBNA1) has been thought to prevent MHC class I presentation of EBNA1 peptides by inhibiting its proteasomal degradation. However, Yin *et al.* show that the GAr inhibits mRNA translation in cis, both *in vitro* and *in vivo*. The GAr sequence was most efficient at inhibiting translation when present at the amino-terminus of the protein, but its position did not influence its ability to inhibit proteasomal degradation, enabling the authors to show that GAr-mediated inhibition of translation and not proteasomal degradation is the mechanism by which EBNA1 evades MHC class I presentation. This is likely to prevent peptide production from defective ribosomal products (DRiPs) of EBNA1 translation — a key source of MHC class I presented peptides.