was not a consequence of the transcription of a downstream effector, as a point mutant of Tat without transcriptional activity could still function as an SRS. Instead, Tat was shown *in vitro* to target the host RNAi mechanism upstream of vsiRNA generation, at the level of Dicer.

Another Tat mutant was transcriptionally proficient but lacked SRS activity; recombinant HIV containing this mutated form of Tat replicated less efficiently than HIV containing wild-type Tat. However, the difference was only slight, indicating that HIV infection is controlled by a range of host factors, one of which is the balance between host-exploited RNAi and viral SRS. When this balance was disrupted by the addition of oligonucleotides that inhibit vsiRNA to HIV-1-transfected cells, there was a dose-dependent increase in viral replication.

The authors suggest that the finding of only one duplex sequence in the HIV-1 genome indicates that there is a strong selective pressure exerted by host RNAi against such sequences and that the remaining sequence must have a crucial non-mutatable function for HIV-1, requiring the maintenance of a viral SRS.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Bennasser, Y., Le, S.-Y., Benkirane, M. & Jeang, K.-T. Evidence that HIV-1 encodes an siRNA and a suppressor of RNA silencing. *Immunity* **22**, 607–619 (2005)

an individual with type 2 diabetes did not recognize any pro-insulin peptide.

Knowing which autoantigens trigger autoimmunity is still out of reach for many researchers studying autoimmune disease, but the evidence from both of these papers that insulin has a crucial role will no doubt increase our chances of developing antigen-specific tolerization therapy for diabetic patients.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPERS Nakayama, M. *et al*. Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. *Nature* **435**, 220–223 (2005) | Kent, S. C. *et al*. Expanded T cells from pancreatic lymph nodes of type 1 diabetic subjects recognize an insulin epitope. *Nature* **435**, 224–228 (2005)

TUMOUR IMMUNOLOGY

B cells lead the way in tumour progression

Many studies have reported a link between chronic inflammatory diseases and cancer development. However, it has not been clear how the recruitment of inflammatory innate immune cells is initiated or sustained at sites of tumour development. Lisa Coussens and colleagues now report an important role for B cells in promoting innate-immune-cell inflammation in a mouse model of epithelial carcinogenesis, which is in contrast to the view that adaptive immune cells are involved in 'surveillance' against developing neoplasms.

K14-HPV16 **mice express oncogenes from human papillomavirus type 16 under the control of the human keratin 14 promoter/enhancer, leading to multi-stage epithelial carcinogenesis. The pre-malignant stage is characterized by infiltration of innate immune cells such as granulocytes and mast cells into the skin. However, when *K14-HPV16* mice were crossed with recombination-activating-gene-1-deficient mice (*K14-HPV16/Rag1*$^{-/-}$ mice), which lack T and B cells, this infiltration was significantly reduced. Decreased infiltration of the skin was associated with decreased activity of matrix metalloproteinase 9 (MMP9) compared with *K14-HPV16* mice. MMP9 is secreted by leukocytes and has a role in cancer development through its effects on tissue remodelling and release of the angiogenic growth factor vascular endothelial growth factor (VEGF) from the extracellular matrix. Correspondingly, *K14-HPV16/Rag1*$^{-/-}$ mice had reduced levels of VEGF in skin lysates compared with *K14-HPV16* mice, as well as decreased markers of angiogenesis.**

The lack of typical pre-malignant inflammatory characteristics in *K14-HPV16/Rag1*$^{-/-}$ mice was associated with decreased progression to epithelial carcinoma. Only 6.4% of *K14-HPV16/Rag1*$^{-/-}$ mice developed full-blown carcinomas compared with 47% of *K14-HPV16* mice. Therefore, the lack of T and B cells of the adaptive immune system inhibits pre-malignant inflammation and tumour progression in this model.

To examine the specific role of B cells in this process, the authors looked at antibody deposition. B cells do not infiltrate pre-malignant skin, but they might exert their effects through the systemic production of antibodies specific for antigens in the skin. Deposits of IgG and IgM could be detected in the skin of *K14-HPV16* mice by 1 month of age, and these increased up to 6 months of age in association with the development of chronic inflammation. The adoptive transfer of B cells from *K14-HPV16* mice, which would contain primed and/or memory B cells of the desired specificity, to *K14-HPV16/Rag1*$^{-/-}$ mice confirmed the important role of B cells by restoring leukocyte infiltration of the skin and other downstream characteristics such as angiogenesis. The transfer of serum from *K14-HPV16* mice had a similar effect, which is in line with the postulated systemic actions of B cells through the production of antibodies and/or soluble mediators such as cytokines.

The authors conclude that B cells are a crucial part of tumour progression in this model through the promotion of chronic inflammation in the pre-malignant state. Therefore, therapies that aim to stimulate B-cell responses, such as vaccination, should be used with caution in cancer-prone patients or patients with pre-malignant disease.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER de Visser, K. E., Korets, L. V. & Coussens, L. M. *De novo* carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. *Cancer Cell* **7**, 411–423 (2005)