IMMUNOTHERAPY

It takes two to tango

Much of the recent work on the development of active, specific immunotherapy of cancer has focused on the induction of $CD8^+$ cytotoxic T-lymphocyte (CTL) responses, and several studies have shown that it is possible to stimulate tumour-specific CTLs using dendritic cells (DCs) that are loaded with tumour antigens. But $CD4^+$ T-helper type 1 (T_H1) cells are also important components of effective immune responses. In this study, Schuler–Thurner and colleagues provide the first evidence that DCs that are loaded with tumour-specific peptides can rapidly induce T_H1 responses in cancer patients that are readily detectable *ex vivo*.

The DCs that were used for vaccination in this study were derived from blood monocytes that were matured *ex vivo* using a defined cocktail (consisting of interleukin (IL)-1β, IL-6, tumour-necrosis factor and prostaglandin E_2) and cryopreserved before use. Aliquots of cells were thawed on the day of vaccination and loaded with various MHC class-I- and -II-restricted peptides. Patients with incurable melanoma were treated with five biweekly vaccinations of DCs, followed by assessment one month after the final vaccination.

The results showed that the vaccination protocol induced a rapid T_H1 response in patients, both to a control immunizing antigen and also to defined MHC class-II-restricted tumour antigens. Immune responses were assessed on the basis of interferon-γ production using ELISPOT assays and antigen-specific proliferative responses.

So, the results from this Phase I trial provide convincing evidence that cryopreserved DCs can induce T_H1 responses against tumour antigens without significant toxicity, and it also encourages further development of DC-based vaccination technology.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Schuler–Thurner, B. *et al*. Rapid induction of tumor-specific type 1 T helper cells in metastatic melanoma patients by vaccination with mature, cryopreserved, peptide-loaded monocyte-derived dendritic cells. *J. Exp. Med.* **195**, 1279–1288 (2002)

FURTHER READING Wolchok, J. D. & Livingston, P. O. Vaccines for melanoma: translating basic immunology into new therapies. *Lancet Oncol.* **2**, 205–211 (2001)

AUTOIMMUNITY

Sometimes it's hard to be a woman

It is a well-known fact that the incidence of autoimmune diseases is higher in females than in males — systemic lupus erythematosus, for example, occurs at a female-to-male ratio of about 10 to 1. The female sex hormone oestrogen is thought to be important for the pathogenesis of autoimmune diseases, but the molecular basis for this has never been defined. In this study, Betty Diamond's group shows that oestrogen can modulate the survival of immature B cells, leading to a more autoreactive B-cell repertoire.

Earlier work from this group in a mouse model system established that the treatment of non-autoimmune mice that were transgenic for the heavy chain of an anti-DNA antibody with oestradiol (E_2) led to the rescue of autoreactive B cells that would normally have been deleted. The current study looked at changes in gene expression in B cells that were treated with E_2 to determine how this can result in a skewed B-cell repertoire. Several E_2-upregulated genes were identified in B cells, and four of the genes — encoding the CD22 receptor and the intracellular tyrosine phosphatase SHP1 (both of which can regulate the threshold for B-cell activation), the anti-apoptotic molecule Bcl-2 and the adhesion molecule VCAM1 — were chosen for further study.

Flow cytometry showed that receptors for E_2 are expressed on B cells. Furthermore, the ectopic expression of constitutively active E_2 receptors on B cells resulted in the increased expression of CD22, SHP1 and Bcl-2. But, is there a functional consequence of increased expression of these molecules? To assess this, the team overexpressed CD22 or SHP1 in a B-lymphoma cell line to mimic the increased expression of these receptors in E_2-treated B cells. Compared with mock-transfected cells, the CD22- or SHP1-transfected cells had decreased calcium-signalling responses after stimulation with mock antigen. This indicates that moderate changes in the level of expression of these molecules can alter B-cell signalling and, so, might affect the tolerization of autoreactive B cells.

Taken together, these results show that E_2 can enhance the survival and activation of autoreactive B cells, which might contribute to the development of autoimmune disease.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Grimaldi, C. M., Cleary, J., Dagtas, A. S., Moussai, D. & Diamond, B. Estrogen alters thresholds for B-cell apoptosis and activation. *J. Clin. Invest.* **109**, 1625–1633 (2002)