GENE THERAPY

It's all in the timing

Everyone knows that time is of the essence when you have a train to catch. Recent work by Cohen and colleagues in the journal *Blood* shows that timing is also essential when it comes to the application of suicide gene therapy of graft-versus-host disease (GVHD), a life-threatening complication of allogeneic haematopoietic stem-cell transplantation (HSCT).

Mature donor T cells present in an allograft after HSCT improve engraftment and T-cell reconstitution, and provide a graft-versus-leukaemia (GVL) effect. In addition to these beneficial effects, activation of donor T cells that are specific for recipient alloantigens (termed alloreactive) result in GVHD.

Is it possible to selectively eliminate the alloreactive donor T cells, but spare the T cells which mediate immune reconstitution and the GVL effect? A strategy has been developed to eliminate donor T cells. Before transplantation, donor T cells are transduced with the herpes simplex type I thymidine kinase (*TK*) suicide gene. Treatment with gancyclovir (GCV; a thymidine analogue that is toxic to dividing cells expressing TK) allows these donor T cells to be eliminated. However, as the TK–GCV system is based on the cell-cycle status of donor TK-expressing T cells, and not on their alloreactivity, its therapeutic usefulness was thought to be limited.

Cohen *et al.* assessed the kinetics of T-cell expansion after semiallogeneic bone marrow transplantation (BMT) (when both alloreactive and homeostatic T-cell expansion occur) and syngeneic BMT (when only homeostatic expansion occurs). T cells from double-transgenic mice expressing TK in $CD4^+$ and $CD8^+$ T cells and a marker (human CD4) were stained with carboxyfluorescein diacetate succinimide ester (CFSE) and infused with wild-type BM into lethally irradiated recipients. Spleen cells were then collected from the recipient mice at different time points after BMT, and donor T-cell division was assessed on the basis of CFSE fluorescence. In semiallogenic hosts, the donor T cells proliferated rapidly, and after 88 hours most donor T cells had divided at least once. In syngeneic hosts, T-cell divisions were significantly delayed. These results indicate that alloreactive T cells divide earlier than non-alloreactive T cells.

The authors then investigated the persistence and expansion of donor T cells in the semiallogeneic BMT setting after GCV treatment. This treatment resulted in the death of most donor T cells, with surviving T cells being those that had not divided. After a 7-day GCV course, a pool of donor T cells persist, which significantly expands after GCV treatment is stopped. Finally, the authors show that the surviving T cells contribute to the replenishment of the T-cell compartment and provide a diversified T-cell receptor repertoire.

This study has identified a therapeutic window when GCV treatment can be administered to specifically kill alloreactive donor T cells (and so control GVHD), but spare non-dividing, non-alloreative T cells, which enables T-cell reconstitution to be maintained.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Cohen, J.L., Boyer, O. & Klatzmann, D. Suicide gene therapy of graft-versus-host disease: immune reconstitution with transplanted mature T cells. *Blood* **98**, 2071–2076 (2001)

FURTHER READING Cohen, J. L., Boyer, O. & Klatzmann, D. Would suicide gene therapy solve the 'T-cell dilemma' of allogeneic bone marrow transplantation? *Immunol. Today* **20**, 172–176 (1999)

IN BRIEF

AUTOIMMUNITY

Granulocyte macrophage colony-stimulating factor: a new putative therapeutic target in multiple sclerosis.

McQualter, J.L. *et al. J. Exp. Med.* **194**, 873–882 (2001)

The chronic autoimmune demyelinating disease mutliple sclerosis (MS) is characterized by an inflammatory infiltration of immune cells into the central nervous system (CNS). Immunization of mice with myelin proteins results in a similar disease, experimental autoimmune encephalomyelytis (EAE), and provides a useful animal model. The cytokine granulocyte macrophage colony-stimulating factor is implicated in chronic inflammation, leading the authors to investigate whether this might be a therapeutic target in MS. *GM-CSF*$^{-/-}$ mice were found to be resistant to the induction of EAE and, importantly, immune cells failed to infiltrate the CNS.

T-CELL SIGNALLING

Single-cell analysis of signal transduction in CD4 T cells stimulated by antigen *in vivo*.

Zell, T. *et al. Proc. Natl Acad. Sci. USA* **98**, 10805–10810 (2001)

Lymphocyte signal transduction is commonly analysed *in vitro*, in bulk populations of transformed cells. However, results are often contradictory. Here, the early signalling events following activation of naive $CD4^+$ T cells was studied in a more physiological *ex vivo* system. Traceable numbers of naive $CD4^+$ T-cell receptor transgenic T cells were transferred into normal mice, which were then challenged with specific antigen. At various time points, lymphoid tissues were removed, fixed immediately and then phosphorylation of key signalling molecules was measured by flow cytometry. In contrast with previous *in vitro* studies, this analysis indicates that phosphorylation of c-jun and p38 mitogen-activated protein kinase does not depend on co-stimulatory signals from CD28.

ALLERGY

Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors.

Jutel, M. *et al. Nature* **413**, 420–425 (2001)

Specialized subsets of T helper cells (T_H1 and T_H2) are present at sites of inflammation where effector cells, including mast cells and basophils, produce mediators such as histamine. In this study, Cezmi Akdis' group show that histamine can regulate inflammatory reactions by enhancing T_H1-type responses through the histamine receptor type 1 (H1R). Conversely, T_H1- and T_H2-type responses are both negatively regulated through the H2R. Secretion of interferon-γ was suppressed in *H1R* knockout mice, and T_H2 cytokines (IL-4 and IL-13) were predominantly expressed. T_H1 and T_H2 cytokine expression was upregulated in *H2R* knockout mice. Interestingly, mice lacking the H1R display increased antibody responses, expressing higher levels of immunoglobulin E (IgE), IgG1, IgG2b and IgG3 in comparison with the H2R-deficient mice. These results show a new immunoregulatory role for the effector mediator histamine.