REGULATORY LYMPHOCYTES

Direct DC hit activates T_{Reg} cells

Delivering antigen directly to immature dendritic cells (DCs) in lymphoid tissues might be an effective way of activating regulatory T (T_{Reg}) cells according to a recent study published in *Blood*.

The idea that steady-state antigen presentation by immature or resting DCs leads to immune tolerance is an attractive hypothesis, but it is difficult to test. Evidence in support of this model has come from studies showing that antibodies specific for the lymphoid DC marker CD205 (also known as DEC205) can target antigens specifically to DCs *in vivo*. CD205, a C-type lectin, is involved in the uptake of antigen into the MHC class II antigen-processing/presentation pathway. Previously, Ralph Steinman, Michel Nussenzweig and colleagues had shown that injection of a modified CD205-specific monoclonal antibody containing an ovalbumin (OVA) peptide resulted in antigen presentation by DCs and OVA-specific T-cell tolerance. But, the mechanism of tolerance was not clear.

In this new study, Karsten Mahnke and co-workers conjugated a CD205-specific antibody to OVA protein and injected it into mice containing OVA-specific T-cell-receptor-transgenic $CD4^+$ T cells. Eight days later, OVA-specific T cells were stimulated *in vitro* with OVA-pulsed DCs, but they failed to proliferate or secrete interleukin-2 (IL-2). Approximately 20% of these T cells had an increased level of expression of the T_{Reg}-cell-associated markers CD25 and cytotoxic T-lymphocyte antigen 4 (CTLA4).

So, does this minor $CD25^+CTLA4^+$ population suppress the function of the other T cells? When the OVA-specific T cells recovered from mice injected with the OVA–CD205-specific antibody were depleted of $CD25^+$ cells, IL-2 production and proliferation *in vitro* were restored. Moreover, these $CD25^+$ cells were capable of suppressing the proliferation of T cells in a mixed leukocyte reaction, whereas OVA-specific $CD25^+$ T cells from control mice had no effect. This indicates that the T_{Reg} cells are induced *in vivo* and that their effects are antigen nonspecific.

The authors conclude that antigen presentation by immature DCs *in vivo* can lead to the activation of T_{Reg} cells. But, the importance of these cells to the tolerance that is induced by CD205-targeted antigen *in vivo* remains to be investigated.

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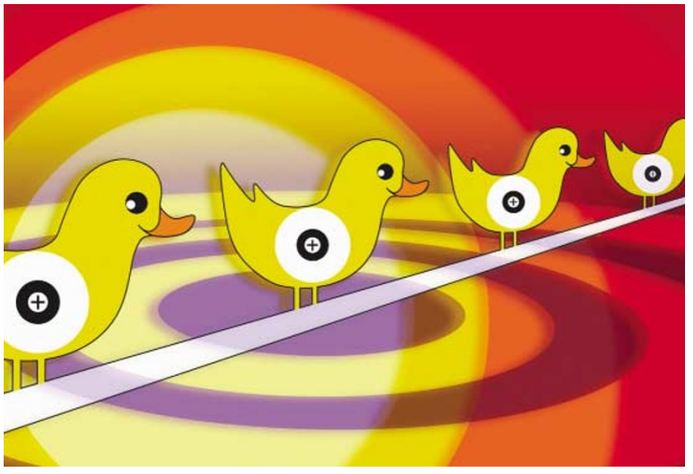
References and links

ORIGINAL RESEARCH PAPER Mahnke, K. *et al.* Induction of $CD4^+/CD25^+$ regulatory T cells by targeting of antigens to immature dendritic cells. *Blood* 23 January 2003 (DOI: 10.1182/blood-2002-10-3229)

FURTHER READING Hawiger, D. *et al*. Dendritic cells induce peripheral T-cell unresponsiveness under steady-state conditions *in vivo*. *J. Exp. Med.* **194**, 769–779 (2001) | Steinman, R. M. & Nussenzweig, M. C. Avoiding horror autotoxicus: the importance of dendritic cells in peripheral T-cell tolerance. *Proc. Natl Acad. Sci. USA* **99**, 351–358 (2002)



TRIAL WATCH

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Two recent reports in the *New England Journal of Medicine* support the idea that blocking the entry of aggressive leukocytes into inflamed tissues could be an effective strategy for the treatment of autoimmune disorders. A 'humanized' monoclonal antibody specific for α_4 integrin — known as natalizumab — was tested in Phase II clinical trials, in patients with Crohn disease and multiple sclerosis.

α_4 integrin pairs with β_1 integrin or β_7 integrin to form dimers that are expressed by activated lymphocytes and monocytes and that are involved in the migration of these cells from the circulation into tissues. $\alpha_4\beta_1$ integrin, also known as very late antigen 4 (VLA4), recognizes vascular cell-adhesion molecule 1 (VCAM1), an adhesion molecule that is upregulated on inflamed endothelium. $\alpha_4\beta_7$ integrin binds mucosal vascular addressin cell-adhesion molecule 1 (MADCAM1) and facilitates the entry of leukocytes into the intestines.

Previous studies in humans with Crohn disease or ulcerative colitis, which are forms of inflammatory bowel disease, had shown that monoclonal antibodies specific for α_4 integrin had beneficial effects. In this placebo-controlled double-blind trial, 248 patients with moderate to severe Crohn disease received two antibody infusions, four weeks apart, of placebo or natalizumab, and were assessed over a 12-week period. The groups that received the drug had a significantly higher (by approximately twofold) clinical response and rate of remission than the placebo groups.

The anti-inflammatory effects of natalizumab were only partial, but the authors concluded that for the treatment of Crohn disease, natalizumab seems to be at least as effective as the approved drug infliximab, which is a tumour-necrosis factor inhibitor.

Multiple sclerosis is characterized by the appearance of inflammatory and demyelinating lesions in the central nervous system, in which expression of VCAM1 is upregulated. In the multiple sclerosis trial, 213 patients with relapsing multiple sclerosis received either placebo or natalizumab once a month for six months. Whereas the placebo groups had an average of 9.6 new lesions per patient during the treatment period (as assessed by magnetic resonance imaging), groups that received natalizumab had approximately ten times fewer lesions. Moreover, significantly fewer relapses were reported in the groups that received the drug. The downside is that the effect is lost when the treatment stops.

In both trials, no adverse effects were associated with natalizumab and only a small percentage of patients developed antibody responses to the drug. However, in the multiple sclerosis trial, there was a trend towards increased susceptibility to infections. Further studies will be required to determine the consequences of long-term treatment with natalizumab on immunity to infection.

Together, these studies show that blocking the access of leukocytes to inflammatory regions produces beneficial effects, in at least two inflammatory disorders. However, larger Phase III trials (which are now underway) will be necessary to establish longer-term safety and efficacy compared with existing treatments.

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References and links

ORIGINAL RESEARCH PAPERS Miller, D. H. *et al.* A controlled trial of natalizumab for relapsing multiple sclerosis. *N. Engl. J. Med.* **348**, 15–23 (2003) | Ghosh, S. *et al.* Natalizumab for active Crohn's disease. *N. Engl. J. Med.* **348**, 24–32 (2003)