ALLERGY

Peaceful death ends pain

Repeated exposure to low doses of a contact allergen is known to prevent allergic sensitization to that particular allergen. This process has been termed 'low-zone tolerance' and, although previous experiments have described a role for suppressor $CD8^+$ T cells in this process, the exact mechanisms that drive low-zone tolerance have been unclear. A recent study in the *Journal of Clinical Investigation* has now suggested that low-zone tolerance is mediated by 'killer' dendritic cells (DCs) that are activated by suppressor $CD8^+$ T cells and induce apoptosis in pro-allergic effector $CD8^+$ T cells.

To explore the immune mechanisms responsible for low-zone tolerance, Luckey *et al.* used a model of hapten-induced contact hypersensitivity, in which mice that are sensitized epicutaneously with a hapten develop an allergic reaction following subsequent cutaneous exposure to the same hapten. However, if the mice are exposed to repeated low doses of the hapten before the sensitization step (the induction phase of low-zone tolerance), they show markedly reduced contact hypersensitivity responses when they are later exposed to the hapten (the effector phase of low-zone tolerance).

The authors found that hapten-restimulated lymph node cells from mice exposed to the low-zone tolerance protocol prior to hapten sensitization produced higher levels of tumour necrosis factor (TNF) than lymph nodes cells from non-tolerized hapten-sensitized mice. Analysis of gene-deficient mice showed that both TNF and TNF receptor 2 (TNFR2), but not TNFR1, were required for the induction of low-zone tolerance. In adoptive transfer experiments, $CD8^+$ T cells from tolerized TNF-deficient mice were able to protect naive recipients from hapten sensitization, but $CD8^+$ T cells from tolerized wild-type mice could not inhibit contact hypersensitivity in TNF-deficient recipients. These data suggest that TNF is essential during the effector phase of low-zone tolerance, rather than during its induction, and that suppressor $CD8^+$ T cells themselves are not a crucial source of the tolerogenic TNF.

Similarly, further adoptive transfer experiments showed that TNFR2 was not required for the development of suppressor $CD8^+$ T cells during low-zone tolerance induction. Instead, the authors found that expression of TNFR2 by allergen-specific effector $CD8^+$ T cells was necessary to mediate the effector phase of low-zone tolerance and protect mice from contact hypersensitivity. When tolerized or control mice were reconstituted with congenic $CD8^+$ T cells from hapten-sensitized mice, significantly fewer transferred $CD8^+$ T cells persisted in the tolerized recipients. This suggested that tolerance may be driven by TNFR2-induced apoptosis in allergen-sensitized effector $CD8^+$ T cells. In further support of this, increased levels of $CD8^+$ T cell apoptosis occurred during contact hypersensitivity responses in mice that had previously been tolerized compared with in control mice.

Intracellular cytokine staining analyses showed that a population of 'killer' $CD11c^+CD8^+$ DCs was the major source of the tolerogenic TNF. Notably, low-zone tolerance could be induced in TNF-deficient mice following the adoptive transfer of wild-type $CD11c^+CD8^+$ DCs. Finally, the authors found that suppressor $CD8^+$ T cells isolated from mice following low-zone tolerance induction could upregulate TNF expression in co-cultured $CD11c^+CD8^+$ DCs. They suggest a model whereby repeated exposure to low doses of a contact allergen promotes the development of suppressor $CD8^+$ T cells. During subsequent exposure to the allergen, these suppressor $CD8^+$ T cells induce TNF expression in $CD11c^+CD8^+$ DCs. The DC-derived TNF induces apoptosis in allergen-specific effector $CD8^+$ T cells via TNFR2, thereby inhibiting the contact hypersensitivity response.

Yvonne Bordon

ORIGINAL RESEARCH PAPER Luckey, U. *et al.* T cell killing by tolerogenic dendritic cells protects mice from allergy. *J. Clin. Invest.* 1 Sep 2011 (doi:10.1172/JCI45963)