DOI:
10.1038/nri2029

TOLERANCE

Inducing T-cell tolerance in the gut

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Tolerance to intestinal self-antigens in the gut is thought to be mediated by professional antigen-presenting cells that obtain membrane proteins from tissue cells and process and cross-present these proteins to naive T cells in nearby lymph nodes. But now, a study published in *Nature Immunology* reports a new mechanism for T-cell tolerance in the gut whereby stromal cells in lymph nodes present endogenously expressed peripheral tissue antigens to T cells and elicit deletional tolerance.

How can dendritic cells (DCs) induce tolerance to intestinal antigens when they are surrounded by microbial stimuli that promote inflammatory responses? To address this question, the authors used the iFABP-tOVA mouse model in which a truncated, cytosolic form of ovalbumin (tOVA) is expressed

as an endogenous antigen in mature intestinal epithelial cells under the control of the promoter for intestinal fatty-acid binding protein (iFABP). To identify where self-reactive CD8⁺ T cells encounter antigen, OVA-specific T-cell receptor transgenic CD8⁺ T cells (OT-I T cells) were transferred into iFABP-tOVA mice and their proliferation was measured using the fluorescent dye 5,6-carboxyfluorescein diacetate succinimidyl diester. Surprisingly, in addition to detecting OT-I T-cell proliferation in mesenteric lymph nodes (MLNs) and Peyer's patches in iFABP-tOVA mice, the authors also detected OT-I T-cell proliferation in extra-intestinal lymph nodes.

Treatment with FTY720, the sphingosine-1-phosphate receptor agonist, to prevent egress of OT-I T cells from MLNs, had no effect on the proliferation of OT-I T cells in extra-intestinal lymph nodes, ruling out the possibility that OT-I T cells were encountering antigen in MLNs and that proliferating T cells were then migrating to other lymph nodes. An alternative possibility was that professional antigen-presenting cells were carrying intestinal-epithelial-cell-associated self-antigens to lymph nodes and presenting antigen to T cells there. To test this possibility, DCs, B cells and macrophages isolated from lymph nodes in iFABP-tOVA mice were cultured with OT-I T cells. The OT-I T cells were found to proliferate in response to DCs from MLNs but not from peripheral lymph nodes.

So, which are the cells in the peripheral lymph nodes that present OVA to the OT-I T cells that were transferred into iFABP-tOVA mice? OVA mRNA was detected by RT-PCR (PCR after reverse transcription of RNA) in CD45-negative stromal cells of lymph nodes in iFABP-tOVA mice. To determine whether these stromal cells can stimulate OT-I T cells, the authors generated chimeric mice by injecting bone marrow from MHC-class-I-deficient mice into lethally irradiated iFABP-tOVA mice. In these mice, only the stromal cells, and not DCs, could present OVA to transferred OT-I T cells. Proliferation of OT-I T cells was comparable in chimeric versus non-chimeric iFABP-tOVA mice, and resulted in the deletion of the OT-I T cells. Further experiments revealed that several other peripheral tissue antigens are expressed in lymph nodes and that lymph node stromal cells express AIRE (autoimmune regulator), a molecule implicated in tolerance induction by medullary thymic epithelial cells.

This study identifies a new mechanism for the induction of peripheral tolerance in CD8⁺ T cells and reveals that lymph-node stromal cells seem to act similarly to medullary thymic epithelial cells in inducing deletional tolerance.

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ORIGINAL RESEARCH PAPER Lee, J.-W. *et al.* Peripheral antigen display by lymph node stroma promotes T cell tolerance to intestinal self. *Nature Immunol.* 31 December 2006 (doi:10.1038/nri1427)