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T CELLS

A tissue checkpoint for T_H2s

> ILC2s and effector T_H2 cells complete their differentiation in affected tissues

Numerous diverse signals promote type 2 immune responses, which are characterized by interleukin-4 (IL-4), IL-5 and IL-13 production. However, the mechanisms that drive the production of these effector cytokines remain unclear. Reporting in *Nature Immunology*, Locksley and colleagues show that the production of effector cytokines by type 2 innate lymphoid cells (ILC2s) and T helper 2 (T_H2) cells reflects the integration of a combination of tissue-derived cytokines.

Previous studies suggested a model for the induction of type 2 immunity in which ILC2s (which are tissue resident) sense the epithelial cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) that are released in response to tissue damage and then instruct primed T_H2 cells to become effector cells. To investigate the regulation of type 2 cytokines *in vivo*, the authors challenged mice carrying an *Il4*-reporter allele (termed 4get mice) with various type 2 immune stimuli. Epigenetic analysis of T cells from 4get mice that were infected with the migratory nematode *Nippostrongylus brasiliensis* (which induces a type 2 immune response in the lungs) showed that IL-4$^+$ (primed) T cells that had exited the lymph node and entered the inflamed lungs exhibited chromatin accessibility at the *Il5* and *Il13* loci and thus are effector T_H2 cells. Furthermore, lung IL-4$^+$ T cells more closely resembled lung ILC2s than lymph node IL-4$^+$ T cells at the transcriptional and epigenetic levels, suggesting that ILC2s and effector T_H2 cells complete their differentiation in affected tissues.

N. brasiliensis infection induces the expression of the epithelial cytokines IL-25, IL-33 and TSLP, which was shown to be coincident with the increase in ILC2 and effector T_H2 cell numbers in the lungs. Mice deficient for TSLP receptor, IL-33 receptor and IL-25 (triple knockout (TKO) mice) had greatly reduced eosinophil numbers, fewer lung ILC2s and defective worm clearance compared with controls. However, the number of primed T cells that had entered the lungs was only partially diminished. Further analysis using additional models of allergic inflammation confirmed the observation that epithelial cytokines were not required for T_H2 cell priming in the lymph nodes or for their accumulation in tissue, but they were crucial for the acquisition of effector functions of T_H2 cells in locally inflamed tissue.

The authors showed that ILC2s and T_H2 cells from the lungs of helminth-infected wild-type recipient mice secreted IL-5 and IL-13 *in vitro*, whereas the corresponding cells from the lungs of TKO mice (whose cells cannot intrinsically sense the epithelial cytokines) did not produce these effector cytokines. Adoptive transfer of naive wild-type CD4$^+$ T cells, which express receptors for epithelial cytokines, into TKO mice, however, led to their differentiation into effector T_H2 cells and the restoration of worm clearance. Thus, T cells that can intrinsically sense tissue cytokines can develop into effector T_H2 cells, even in a microenvironment where other resident cells, including ILC2s and dendritic cells, cannot sense the local cytokines. Of note, these and other data presented in this study indicate that ILC2s are not required for T_H2 cell priming in lymph nodes or for T_H2 cell effector functions in tissues.

Together, these data show that the expression of effector cytokines by both ILC2s and T_H2 cells depends on the cell-intrinsic sensing of tissue-derived IL-25, IL-33 and TSLP at sites of tissue damage, revealing a shared tissue checkpoint that regulates allergic immunity.

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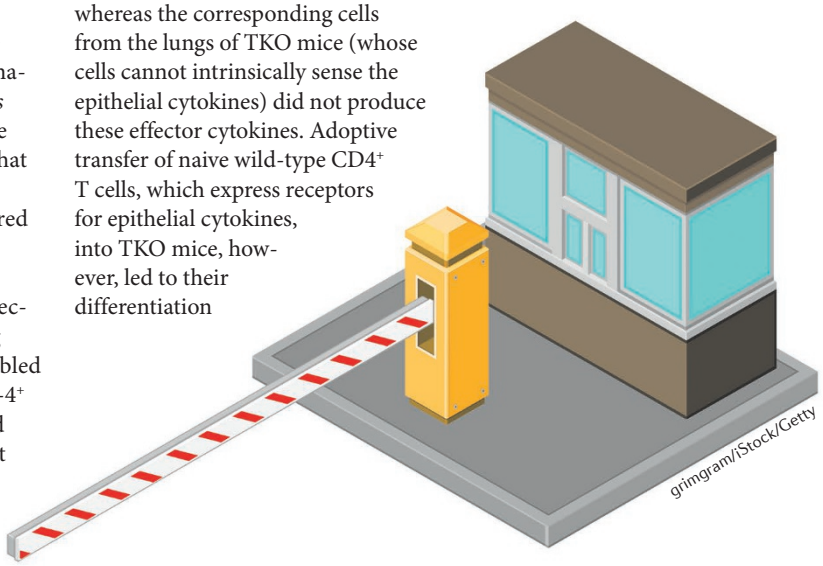
FURTHER READING Wynn, T. A. Type 2 cytokines: mechanisms and therapeutic strategies. *Nat. Rev. Immunol.* **15**, 271–282 (2015)



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