

IMMUNE MEMORY

ILC2s drive allergen recall

“allergen-induced IL-13 signals from ILC2s license lung DCs to produce CCL17”

Innate lymphoid cells (ILCs) are best known for their role in initiating immune responses at barrier sites, with group 2 ILCs (ILC2s) being an early source of cytokines that promote the development of T helper 2 (T_H2) cell responses. Now, findings described in *Nature Immunology* extend the role of ILC2s to promoting memory T_H2 cell responses to secondary exposure to antigen.

The mechanism of memory T_H2 cell recall responses was studied in mice that were primed and then rechallenged intranasally with the

protease allergen papain. Priming with papain induced acute eosinophilia and an increase in the number of ILC2s in the lungs, which resolved by day 15. Upon rechallenge, eosinophilic inflammation was greatly amplified and was associated with a rapid influx of memory T_H2 cells to the lungs. The recall response required enzymatically active papain, which has previously been shown to activate ILC2s.

So, to assess the role of ILC2s in memory T_H2 cell responses, the authors used mice in which ILC2s were temporarily ablated before antigen rechallenge, leaving their function in T_H2 cell priming unaffected. T_H2 cell numbers in the lungs were substantially lower in these ILC2-depleted mice than in ILC2-replete mice after allergen rechallenge. Lower concentrations of T_H2 cell-derived interleukin-4 (IL-4) were also noted in bronchoalveolar lavage (BAL) fluid in the ILC2-depleted mice after papain rechallenge. So how are the ILC2s involved? The authors showed that ILC2s (rather than T_H2 cells) were the major producers of IL-13 before and immediately after allergen rechallenge and that increased IL-13 concentrations in the BAL fluid coincided with increased levels of CC-chemokine ligand 17 (CCL17), which is known to be produced by dendritic cells (DCs) and to attract memory T_H2 cells. Indeed, blockade of either IL-13 or CCL17 using

specific antibodies significantly limited the memory T_H2 cell recall response, which suggests that these factors both contribute to memory T_H2 cell induction.

Further analysis revealed that a population of CCL17-producing type 2-associated CD11b⁺CD103⁻ DCs expanded following papain challenge. These cells also expressed high levels of the receptor for IL-13, suggesting that they might be responding to ILC2-derived IL-13. Indeed, using several types of ILC2-deficient mice, the authors showed that ILC2s are crucial for driving the allergen-induced increase in CD11b⁺CD103⁻ lung DCs and in CCL17 concentrations. Depletion of lung DCs during papain rechallenge markedly impaired T_H2 cell recruitment. A similar defect in T_H2 cell recruitment was observed in chimeric mice in which the IL-13 receptor was absent specifically on DCs, together suggesting that allergen-induced IL-13 signals from ILC2s license lung DCs to produce CCL17 that recruits memory T_H2 cells. Finally, the authors show that this mechanism of ILC2-mediated expansion of CCL17⁺ DCs also seems to be important for memory T_H2 cell recruitment in the skin and peritoneum.

Lucy Bird

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S. Bradbrook/NPG