ILC2 induce innate IgE secretion by B1 cells via IL-4 production

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Group 2 innate lymphoid cells (ILC2s), a new type of innate lymphocyte that we originally reported as natural helper cells in 2010, are known to regulate type 2 immune responses in an antigen-independent manner. In contrast to Th2 cells, ILC2s lack rearranged antigen receptors and are directly stimulated by epithelial cell-derived cytokines such as IL-33 and IL-25. Activated ILC2s are capable of producing a variety of cytokines, chemokines, and peptides including IL-5, IL-6, IL-9, IL-13, GM-CSF, amphiregulin, eotaxin, and methionine-enkephalin. ILC2s play a vital role in protection against parasite infections and induction of eosinophilic inflammation, which is involved in asthma, atopic dermatitis, eosinophilic esophagitis, allergic rhinitis, and chronic rhinosinusitis with nasal polyps. ILC2s are now considered to be associated with a wide range of diseases including allergic diseases, infection, obesity, cancer, and fibrosis.

IL-4, a key type 2 cytokine, is involved in multiple immune reactions including Th2 cell development, IgG1 and IgE production by B cells and M2 macrophage differentiation. While Th2 cells produce IL-4 together with IL-5 and IL-13 under antigen-induced TCR stimulation, ILC2s fail to produce IL-4 under IL-33 stimulation, which induces a large amount of IL-5 and IL-13. Based on this fact, ILC2s are not thought to contribute to IL-4-mediated immune responses, even though they express high levels of the IL-4 gene.

Recently, we identified the physiological condition that induces IL-4 production from ILC2. The mechanisms for IL-4 production from ILC2 were more intricate than that in Th2 cells and differ widely from those in IL-5 and IL-13 production. Furthermore, IL-4 from ILC2s elevates polyclonal IgE levels in steady state, helminth infection and allergy, and supports survival and expansion of Fc ϵ R⁺ cells such as basophils and mast cells. These findings provide evidence for factors involved in susceptibility to allergic diseases, which is still not understood, but is an important issue in the treatment or prevention of allergic disorders.