Published in final edited form as:

Nature. 2010 January 28; 463(7280): 434–435. doi:10.1038/463434a.

Immunology: The expanding TH2 universe

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TH2 growth factors, which are involved in allergy and in defence against parasites, are produced by many different cell types, including a newly identified population found in fat-associated lymph clusters in the abdomen.

It is almost 25 years since the publication of Mosmann and Coffman's seminal work¹ that defined two main subtypes of helper T lymphocyte: TH1 cells and TH2 cells. The TH2 cells of this dichotomy were shown to produce a collection of growth factors (cytokines) and cell-attractant molecules (chemokines) that are involved in mediating allergic responses and host defence against parasitic infection. But the properties of the original TH2 T lymphocyte are now known to be shared by several different cell types. For instance, a recently reported subpopulation of T cells, TH9 T cells², produce IL-9 and IL-10 — TH2-type cytokines that exacerbate allergic inflammation. In addition, cells that produce IL-25 (macrophages, epithelial cells and mast cells) induce others to secrete the TH2-type cytokines IL-5 and IL-13, and chemoattractants of eosinophils — inflammatory cells that contribute to allergic diseases and TH2-type host defences³. Thus, we currently think of 'TH2' not so much in the context of a cell, but rather as a function or, in business parlance, a 'franchise'. On page 540 of this issue, another cell contributing to the TH2 franchise is reported by Moro and colleagues⁴.

The authors detected the new cell population in previously overlooked fat-associated lymphoid clusters (FALCs), which are scattered along the blood vessels in the peritoneal mesentery (a vascular membrane that surrounds part of the intestine in the abdomen). The researchers show that these cells do produce TH2 cytokines, but that they are not T cells because they lack the typical T-cell surface receptor and do not respond to antigens. They do, however, respond to IL-2, in line with their expression of the common γ -chain receptor, which functions as the signalling component of the IL-2 receptor. Moro and colleagues⁴ name these cells 'natural helper cells' and, on the basis of similar activation properties⁵, draw analogies with the natural killer cell (NK cell) — a type of lymphocyte that forms part of the innate immune defence against viruses and tumour cells, and that responds to cytokine stimulation and/or cell-surface components rather than specific antigens. However, natural helper cells lack NK-cell-lineage markers and, unlike NK cells, bear receptors commonly found on progenitor (rather than differentiated) cells, such as the IL-7 receptor and stem-cell-factor receptor (c-Kit). In view of these characteristics, it might be more accurate to call these cells 'natural TH2 cells'.

The abundance of these cells is limited by the small size and number of FALCs. Nevertheless, their strategic location and the particular cytokines that they secrete endow them with considerable functional impact. Indeed, Moro et al.⁴ show that, in mice, these cells help to combat infection with the hookworm-like helminth parasite *Nippostrongylus brasiliensis* by inducing proliferation of B cells in Peyer's patches (lymph-node-like

structures in the gut wall) and mucus formation, which helps to expel worms from the gut (Fig. 1).

Moro and colleagues identify a population of cells producing TH2-type cytokines in tiny accumulations of lymphoid cells, termed fat-associated lymphoid clusters (FALCs), in the mesentery. b, These cells can be stimulated by the cytokines IL-25 and IL-2 and by the atypical cytokine IL-33, which signals the cell through the ST2 receptor. Natural helper cells produce TH2 cytokines, including IL-13, inducing proliferation of B lymphocytes in Peyer's patches and the production of mucus, factors that counter infection with helminth worms. The cytokines produced by natural helper cells also support B1-lymphocyte maintenance and production of antibodies by B cells in the spleen. High resolution image and legend (38K)

The natural helper cells produce IL-5 and IL-13 in response to IL-25 (and IL-2), and also in response to IL-33, an atypical cytokine that activates the cell through the ST2 receptor⁶ (Fig. 1). IL-33 is secreted largely by non-lymphoid cells such as endothelial cells that line blood vessels, epithelial cells, fibroblasts and, notably in the present context, adipose cells. IL-33 then stimulates cells to produce TH2-type cytokines such as IL-5 and IL-13 (but not IL-4, the archetypal TH2 cytokine). It also stimulates certain types of progenitor cell to produce the blood-cell growth factor GM-CSF.

Rather than being secreted, most IL-33 is targeted to the nucleus of the cell that it is produced by, where it has ill-defined functions that relate to chromatin structure⁷. Because of this intra-nuclear accumulation, IL-33 is released to function as a cytokine only when the cell dies. In this situation, IL-33 may act as an 'alarmin' — a substance that signals to the immune system that cell death is occurring and that the organism may be in danger⁷. It is therefore possible that the induction of natural-helper-cell functions by IL-33 is a form of immune response to danger signals that are released when the gut mucosa is attacked by parasites such as helminth worms.

The location of natural helper cells potentially allows them to contact a special population of self-renewing B lymphocytes called B1 cells, which reside in the peritoneal cavity⁸. B1 cells make antibodies that are specific for components of commonly encountered microorganisms or self-antigens, including those generated by programmed cell death (apoptosis) ⁹. It is of considerable interest, therefore, that Moro et al.⁴ show that natural helper cells support proliferation of B1 cells, and induce production of antibodies by splenic B cells, particularly IgA antibodies that operate on the mucosal surface. These findings provide a potential answer to the question of how B1 cells are maintained and how they participate in mucosal responses. Last, the stimulation of natural helper cells by IL-33, and their subsequent activation of B cells that neutralize self-antigens arising from cell destruction, may represent a newly discovered but evolutionarily old mechanism for the prevention of autoimmunity.

Acknowledgments

This research was supported [in part] by the Intramural Research Program of the NIH, NIAID DIR, LHD.

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Figure 1.
Newly discovered 'natural helper cells'.