Tweaking of Memory T Helper 2 Cells by TSLP

Thymic stromal lymphopoietin conditions dendritic cells to support homeostatic proliferation of central memory T cells. In this issue of *Immunity*, Wang et al. (2006) show that these dendritic cells are critical in maintaining T helper 2 central memory cells and impart them with expression of unique proallergic molecules.

Immune responses are initiated upon presentation of pathogen-derived antigens by activated dendritic cells (DCs) to lymph node resident naïve T cells. Depending on the nature of the pathogen, DCs promote the development of effector T helper (T_H) cells that migrate to infected tissues where they produce specialized sets of cytokines upon restimulation by local DCs Protective T_H cells developing in response to intracellular pathogens express interferon-γ (IFN-γ) and are termed T_H1 cells, whereas T_H2 cells develop in response to parasites, in particular helminths, and express the protective cytokines interleukin-4 (IL-4), IL-5, and IL-13. A well-established concept is that DCs orchestrate protective primary T cell responses by sensing the class of pathogens they encounter and transferring this information to naïve T cells via the expression of T cell-polarizing molecules. In line with this concept, DCs activated upon recognition of helminthic compounds constitutively express a specific set of molecules, including OX40L (de Jong et al., 2002) and Notch-ligand Jagged (Amsen et al., 2004), that promote the development of naïve T cells into T_H2 cells.

In addition to direct activation via pathogens, DCs can also be activated and conditioned by factors produced by tissue cells. An example of such a tissue factor is thymic stromal lymphopoietin (TSLP), which is produced under homeostatic conditions in the thymus, as well as in epithelium of mucosal tissues (Watanabe et al., 2004; Rimoldi et al., 2005) and found at high amounts in skin affected by atopic dermatitis (Soumelis et al., 2002), and in bronchial epithelium and submucosa in allergic asthma (Ying et al., 2005). Liu and colleagues (Soumelis et al., 2002; Ito et al., 2005) were the first to discover that TSLP is a strong activator of DCs that drive naïve T_H cells to develop into an 'inflammatory type' of effector T_H2 cell expressing classical T_H2 cytokines and large amounts of pro-inflammatory tumor necrosis factor-α (TNF-α) but no anti-inflammatory IL-10. As for helminthic compounds, TSLP drives the development of T_H2 cells via its intrinsic ability to imprint DCs for the expression of OX40L (Ito et al., 2005). As allergy is causally related to the activity of allergen-specific T_H2 cells, this finding has prompted the hypothesis that TSLP is critical in the development and maintenance of atopic allergic disease, a concept that was recently validated in TSLP-deficient and TSLP-transgenic mouse models.

TSLP may not only be associated with immunity. When testing epithelial cell line supernatants, Rescigno and colleagues (Rimoldi et al., 2005) found that TSLP is a critical component in conditioning DCs to induce "noninflammatory" effector T_H2 cells producing the classical T_H2 cytokines in combination with anti-inflammatory IL-10. They propose that, as such, homeostatic expression of intestinal epithelial TSLP contributes to local tolerance, counteracting the T_H1-inducing properties of gut commensals. Their data further reveal that Crohn's disease is associated with a loss of TSLP-mediated homeostatic control.

Apart from DC-driven activation of naïve T_H cells resulting in immunity mediated by "inflammatory" effector T_H2 cells or in tolerance mediated by "noninflammatory" effector T_H2 cells, TSLP also affects established memory T cells. T_H2 cells producing high amounts of cytokines in peripheral tissues represent short-lived effector memory T_H (T_{EM}) cells. However, long-term protection is supported by a separate subset of long-lived central memory T (T_{CM}) cells that home to lymphoid tissue, and may become effector T cells upon secondary stimulation (Lanzavecchia and Sallusto, 2005). T_{CM} cells maintain their numbers by continuously dividing, which in humans is driven by the cytokines IL-7 and IL-15, and this response can be enhanced by DCs. An important step in understanding how DCs contribute to homeostatic proliferation of memory T cells is offered by the previous finding by Liu and colleagues (Watanabe et al., 2004) that TSLP-primed DCs (TSLP-DCs), and not DCs that have been primed differently, are capable of stimulating long-term proliferation of both naïve T and T_{CM} cells in the absence of antigen. Although the expression of OX40L is critical in the induction of this homeostatic proliferation, OX40L in the absence of antigen does not additionally skew naïve T cells toward a T_H2 phenotype.

In this issue of *Immunity*, Wang et al. (2006) extend these findings by reporting that TSLP-DCs, in particular, support homeostatic proliferation of central memory T_H2 cells (T_H2 T_{CM}), the CRTH2$^+$ cells in blood, thereby exceeding the potential of the classical combination of the homeostatic cytokines IL-7 and IL-15 to enhance their proliferation. Strikingly, even after multiple rounds of TSLP-DC-driven proliferation, CRTH2$^+$ T_H2 T_{CM} cells maintain their central memory phenotype and their strictly T_H2-biased cytokine profile. In contrast, CRTH2$^+$ T_{CM} cells that proliferate less vigorously in response to homeostatic cytokines or to other DCs tend to lose their central memory phenotype, and many acquire expression of the T_H1 cytokine IFN-γ. In addition, TSLP-DC-induced T_H2 T_{CM} cells were found to transcribe genes coding for cystatin A, Charcot-Leydon crystal protein, and prostaglandin D_2 synthetase, which are molecules known to be uniquely expressed by eosinophils and basophils, and further contribute to allergic inflammation. Thus, TSLP-DCs not only maintain the central memory phenotype, but also further strengthen the allergy-inducing T_H2 properties of the CDTH2$^+$ T_H2 T_{CM}.

As T_H cell expression of these additional proallergic genes has not been shown before, this interesting finding needs to be confirmed at the level of protein
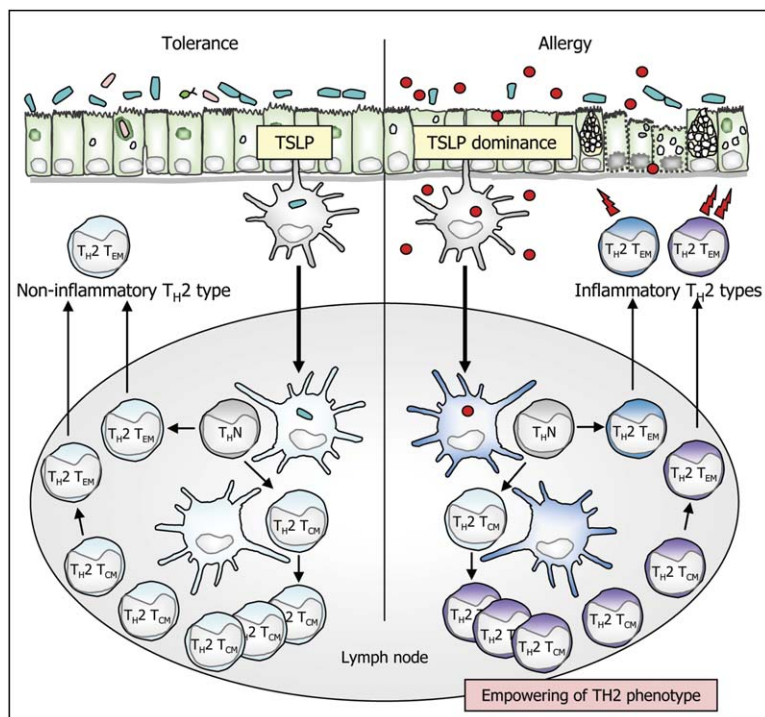
Figure 1. TSLP in Homeostatic Maintenance and Further Tuning of Central Memory T_H2 Cells

Homeostatic amounts of intestinal epithelial cell-derived TSLP (left panel) prime DCs that promote naïve T_H cells (T_HN) to develop into "noninflammatory"-type of effector memory T_H2 (T_H2 T_{EM}, light blue) cells. These cells prevent inflammation to commensal bacteria that potentially induce T_H1 responses. In allergic conditions, high amounts of airway or skin epithelium-derived TSLP primes DCs that induce "inflammatory" type effector memory T_H2 (T_H2 T_{EM}, dark blue) cells. These T_H2 T_{EM} cells initiate allergic inflammation to harmless environmental proteins (red dots). During any immune response, a pool of central memory T_H2 (T_H2 T_{CM}) cells additionally develops, which keeps its size by homeostatic proliferation in response to TSLP-primed DCs in the absence of allergen, and that may become T_H2 T_{EM} upon antigen challenge. The study by Liu and colleagues (Wang et al., 2006) in this issue of *Immunity* shows that TSLP-primed DCs are superior in promoting homeostatic proliferation of T_H2 T_{CM} cells in the absence of antigen, and further empower these cells (T_H2 T_{CM}, purple) by inducing the expression of allergy-associated genes that have been detected only in eosinophils and basophils, thus far.

expression. In addition, establishing a role for these cells in vivo is of paramount importance. According to the present study, these genes are not expressed in circulating T_H2 cells of healthy individuals. However, it is reasonable to assume that they may appear during, or after, acute disease associated with enhanced TLSP expression, such as allergy. Unfortunately, whereas the authors provide details on the physical association between CRTH2^{+} cells and DCs in atopic dermatitis skin, they do not report to what extent these skin-homing T cells are T_H2 cells expressing the additional proallergic genes documented in the vitro experiments, nor did they report on the phenotype of the CRTH2^{+} T_H2 T_{CM} counterparts in the circulation of these patients. It will be interesting to fully establish the physiological significance of the empowered T_H2 T_{CM} phenotype generated in vitro.

Obviously, whereas atopic allergy represents T_H2-mediated pathology, T_H2-associated immunity has evolved to provide protection against helminth infection. Helminths are complex organisms which effectively evade immunity in many ways, resulting in chronic infection. It is tempting to speculate that the proposed TSLP-DC-induced enhancement of the T_H2 phenotype has evolved to arm T_H2 T_{CM} cells with additional molecules effective in the defense against parasites in the chronic phase of disease. Analysis of the presence of these empowered cells in acute and chronic helminthic infection may further elucidate their physiological role in order to exclude the possibility that these cells merely represent pathological misfits associated with allergic disease.

Altogether, the data discussed above lead to the attractive concept that extra-thymic TSLP controls T_H cells at different stages of differentiation (Figure 1). According to the study of Rescigno and colleagues (Rimoldi et al., 2005), homeostatic amounts of TSLP produced by mucosal epithelial cells, in the context of other mediators, condition DCs to induce the development of "noninflammatory" T_H2 T_{EM} cells specific to commensals, which counteracts the potential of these microorganisms to induce T_H1-responses evoked by these organisms. The earlier studies of Liu et al. (Watanabe et al., 2004) further suggest that, at the same time, a pool of T_H2 T_{CM} T_H cells is generated, which is maintained by TSLP-conditioned DCs carrying irrelevant antigens. Furthermore, in conditions of high amounts of TSLP, TSLP-conditioned DCs induce "inflammatory" T_H2 T_{EM} cells (Ito et al., 2005) that are pathological in allergic reactions to harmless environmental proteins, while they may be effective in protection against helminths. The present study represents an important step forward by expanding the concept of TSLP control of immune cells, indicating for the first time that such TSLP-conditioned DCs are critical in the maintenance of T_H2 T_{CM} homeostasis. Importantly, the study furthermore shows that during TSLP-driven homeostatic proliferation, T_H2 T_{CM} cells acquire the expression of additional proallergic molecules, which would render them more powerful in T_H2-type inflammation.

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