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Sensing the outside world: TSLP regulates barrier immunity

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Abstract

Thymic stromal lymphopoietin (TSLP) is an interleukin 7 (IL-7)-like cytokine originally characterized by its ability to promote the activation of B cells and dendritic cells (DCs). Subsequent studies have shown that TSLP promotes T helper type 2 (T_H2) cell responses associated with immunity to some helminth parasites and the pathogenesis of many inflammatory diseases, including atopic dermatitis and asthma. This review will focus on recent findings indicating that in addition to influencing B cell and DC function, TSLP can promote T_H2 cytokine–associated inflammation by directly promoting the effector functions of CD4+ T_H2 cells, basophils and other granulocyte populations while simultaneously limiting the expression of DC-derived proinflammatory cytokines and promoting regulatory T cell responses in peripheral tissues.

Thymic stromal lymphopoietin (TSLP) is a cytokine with structural and functional similarities to the hematopoietin family of cytokines. As the name suggests, it was originally isolated from a mouse thymic stromal cell line and characterized as a lymphocyte growth factor[1–3]. A TSLP homolog was subsequently identified in humans by *in silico* methods[4,5]. Similarly, several groups isolated a TSLP-binding protein in both humans and mice (referred to as the 'TSLP receptor' (TSLPR)), most closely related to the common γ-chain, which bound TSLP with low affinity[6]. It is now known that the functional, high- affinity TSLPR complex is a heterodimer of TSLPR and interleukin 7 receptor-α (IL-7Rα)[6,7]. Cross-species homology for both the cytokine and its receptor is relatively low (~40% for each), although, as described below, functionally they seem to be quite similar. Finally, it is not clear how the TSLPR complex transmits signals. There are abundant data showing that receptor engagement can activate the STAT5 transcription factor[4,7–9]; however, no Jak kinases are activated by the intact receptor complex[8].

The similarity of TSLP to IL-7 and the homology of TSLPR to the common γ-chain suggested that TSLP may have a role in regulating lymphocyte development and/or function. Indeed, early studies did show that TSLP was able to influence the development and proliferation of both T cells and B cells, both *in vitro* and *in vivo*[2,3,10]. However, the effects were modest, which suggested that the influence of TSLP on lymphocyte development is redundant.

Analysis of the expression profiles of the two receptor subunits in human cell populations provided important insights into the primary biological role of TSLP. The cell populations with the highest known coexpression of TSLPR and IL-7Rα are myeloid dendritic cells (DCs)[4]. In confirmation of the expression data, treatment of human DCs with TSLP induces several

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phenotypic changes, including improved survival, upregulation of major histocompatibility complex class II and costimulatory molecules (CD86 and CD40), and the production of a variety of chemokines, most notably the chemokine receptor CCR4 ligands CCL17 and CCL22 (refs. [4,11]). Mouse bone marrow–derived DCs acquire a similar activated phenotype after TSLP stimulation[12].

Cellular targets and biological properties of TSLP

Several cellular targets of TSLP have been identified, including DCs, lymphocytes and granulocytes (Fig. 1). TSLP-stimulated DCs are able to activate $CD4^+$ T cells. Culture of TSLP-activated DCs together with naive syngeneic $CD4^+$ T cells leads to T cell proliferation but no differentiation, which suggests a role for TSLP in $CD4^+$ T cell homeostasis[13]. However, when TSLP-stimulated DCs prime $CD4^+$ T cells in an antigen-specific manner (for example, in an allogeneic culture), the resulting T cells show characteristic features of T helper type 2 (T_H2)-differentiated cells (production of IL-4, IL-5, IL-13 and tumor necrosis factor), with the exception that IL-10 production is not evident[11]. These data suggest that TSLP-activated DCs prime for inflammatory T_H2 cell differentiation. Interestingly, TSLP, in the absence of IL-12, induces expression of OX40L, the ligand for the cell survival factor OX40, on DCs, and OX40-OX40L interactions are critical for the ability of the DCs to drive T_H2 cell differentiation[14]. Consistent with a role in regulating T_H2 cytokine responses, TSLP-activated DCs are also able to support the maintenance and further polarization of $CRTH2^+$ T_H2 effector-memory cells[15].

In addition to promoting chemokine production and expression of OX40L, TSLP has a potent immunoregulatory effect on human and mouse DCs. For example, TSLP inhibits expression of the IL-12 (and IL-23) p40 subunit in human monocyte-derived DCs[16,17]. In addition, pretreatment of mouse bone marrow–derived DCs with recombinant TSLP inhibits p40 expression induced by Toll-like receptor ligands[18,19] and impairs their ability to promote antigen-specific T_H1 differentiation[19]. DCs isolated from TSLPR-deficient mice have higher expression of the IL-12p40 subunit, which supports the idea of a role for TSLP in limiting the expression of proinflammatory responses[19]. Coupled with the induction of OX40L expression on DCs, the ability of TSLP to limit expression of the p40 subunit suggests that TSLP may indirectly promote a microenvironment permissive for T_H2 cell differentiation by limiting the proinflammatory functions of DCs.

DCs have a critical role in promoting T_H2 cytokine responses[20–23], and the ability of TSLP to limit p40 expression may be essential in this. Basophils also show antigen-presenting-cell functions in the context of helminth- or allergen-induced T_H2 cytokine responses[24–26]. Importantly, TSLP seems to promote basophil responses *in vivo*[24], which suggests that in addition to influencing cytokine expression in DCs, the T_H2-promoting properties of TSLP may be mediated, at least in part, through basophils. It has been shown that bone marrow–derived basophils, but not bone marrow–derived dendritic cells, can induce IL-4 production in antigen-specific $CD4^+$ T cells. In addition, exposure to papain, a protease allergen, induces the activation of major histocompatibility complex class II–positive basophils and their recruitment into the draining lymph nodes. Basophils that have endocytosed fluorescein isothiocyanate–labeled ovalbumin upregulate the expression of major histocompatibility complex class II and costimulatory molecules and form immunologic synapses with ovalbumin- specific T cells[25]. Basophils can also capture immunoglobulin E (IgE) complexes and promote T_H2 cytokine responses in a mouse model of antigen-IgE-mediated inflammation[26]. In the context of helminth infection, exposure to schistosome eggs elicits robust recruitment of major histocompatibility complex class II–positive basophils into the draining lymph nodes, and depletion of basophils impairs T_H2 cytokine–dependent expulsion of the gastrointestinal helminth *Trichuris muris*[24]. Published studies have shown that TSLP-

TSLPR interactions are essential for immunity to *Trichuris*[19,27]. The importance of the TSLP pathway and basophils in protective immunity to *Trichuris*, coupled with the demonstration that delivery of recombinant TSLP can augment basophil numbers in the periphery[24], suggest that coordinated TSLP-dependent regulation of DCs and basophils may have an important role in developing T_H2 cytokine responses. How TSLP promotes basophil responses and whether TSLP-induced T_H2 cytokine responses are dependent on eliciting antigen-presenting functions in basophil populations remains to be examined. In addition, how basophils and DCs interact to promote T_H2 cell differentiation and whether this interaction is regulated by TSLP in the lymph node, as well as its consequences on promoting optimal T_H2 cytokine responses, are unclear at present.

In addition to its effects on the differentiation of $CD4^+$ T_H2 cells potentially via DCs and/or basophils, TSLP is able to directly promote the T_H2 cell differentiation of naive T cells. The combination of TCR stimulation and TSLP treatment can induce IL-4 transcription and further T_H2 differentiation[28]. The induction of IL-4 transcription is accompanied by partial remodeling of the *Il4* locus (M. Omori and S.F.Z., unpublished data).

In addition to DCs, basophils and $CD4^+$ T cells, several other cell types are able to respond to TSLP (Fig. 1). For example, TSLP can costimulate the activation of both mast cells and natural killer T cells, which results in increased cytokine production[29–31]. Eosinophils respond to TSLP by upregulating the common myeloid marker CD11b and the integrin $\alpha_L\beta_2$ ligand ICAM-1, which suggests that TSLP may recruit eosinophils to sites of T_H2 cytokine–associated inflammation[32]. Together, these data suggest a model in which TSLP, acting through DCs, granulocytes, natural killer T cells or directly on $CD4^+$ T cells, can promote T_H2 cell differentiation and T_H2 cytokine–associated inflammation.

TSLP and normal barrier homeostasis

Despite the initial identification of TSLP in the culture supernatant of a thymic stromal cell line, this cytokine is expressed mainly by epithelial cells at barrier surfaces (skin, gut and lung)[4]. There is mounting evidence that epithelial cell–derived factors are critical for the generation and maintenance of noninflammatory, tissue-resident DCs in the gut, an important aspect of gut immune homeostasis[33–36]. TSLP is expressed constitutively in intestinal epithelial cells, with its highest expression in colonic epithelial cells[19]. DCs licensed by those cells can drive the generation of induced $Foxp3^+$ T regulatory cells, commonly secrete less IL-12p40 and generally drive T_H2 cytokine responses[34,37–39]. TSLP produced by the colonic epithelium has a key role in this tonic signal to DCs[18,19,34,40]. One of the signals that induces TSLP expression by these cells may be interactions with commensal bacteria, thus providing a mechanistic rationale for tolerance to commensals[41]. Consistent with that, TSLPR-deficient mice show a more rapid onset and severity of disease in a commensal-dependent mouse model of inflammatory bowel disease[19]. Further evidence for the involvement of TSLP in maintaining gut homeostasis is the finding that colonic epithelial cells from patients with Crohn's disease have lower expression of the *TSLP* gene[40].

TSLP promotes immunity to helminth parasites

In addition to maintaining intestinal immune cell homeostasis in the steady state, TSLP-TSLPR interactions have a profound influence on the function of cells of the immune response, tissue inflammation and/or host protective immunity after exposure to helminth parasites. In the *Trichuris* model, treatment with monoclonal antibody to TSLP or deletion of TSLPR in normally resistant wild-type mice is associated with lower expression of pathogen-specific T_H2 cytokine responses, which results in a failure to control infection. Disruption of the TSLP-TSLPR pathway also increases expression of the IL-12p40 subunit, interferon-γ and IL-17A and the development of severe infection- induced inflammation[19]. Notably, blocking p40 or

interferon-γ in *Trichuris*-infected TSLPR-deficient mice restores expression of T_H2 cytokines and host protective immunity[19,27], which suggests that TSLP-independent T_H2 responses can develop if endogenous proinflammatory responses are blocked. Consistent with that, TSLP-TSLPR interactions are dispensable for immunity to infection with *Nippostrongylus* and *Heligmosomoides*, two other intestinal nematodes. Unlike antigens from *Trichuris*, antigens derived from these pathogens can directly limit expression of the IL-12p40 subunit independently of TSLP[27]. The existence of TSLP-independent T_H2 cytokine responses *in vivo* has been confirmed in the *Schistosoma mansoni* model. Experiments with TSLPR-deficient mice have shown that although the TSLP-TSLPR pathway contributes to the development of *S. mansoni* egg–induced $CD4^+$ T_H2 cell responses, its influence on the development of T_H2 cytokine–dependent inflammation is transient[42]. Specifically, although expression of IL-5 and IL-13 is lower in egg-injected TSLPR-deficient mice, the effect on infection-induced T_H2 cytokine–dependent inflammation is minimal. Although TSLP expression seems to have a critical role in the development of optimal T_H2 cytokine responses, these experimental findings suggest that the requirements for this pathway in the development of type 2 inflammation are dependent on the antigenic stimulus, route of exposure and site of the inflammatory lesion.

TSLP and allergic inflammation

The atopic diseases consist of the triad of asthma, allergic rhinitis and atopic dermatitis[43,44]. These share a common pathogenesis and, importantly, frequently present together in the same person and family, which suggests that common factors and mechanisms could be involved[45]. Although common effectors such as T_H2 cytokines, IgE, mast cells and eosinophils are involved, the mechanisms underlying the 'preferential' activation of T_H2 cells by environmental allergens in atopic patients are still obscure. Higher expression of TSLP in the inflamed tissue is another common feature of these diseases[11,46–48]. Genetic analysis of atopic populations has shown an association of polymorphisms in *TSLP* with aspects of atopic allergic disease, including asthma and airway hyper-responsiveness, IgE concentrations and eosinophilia[49–52].

The first indication of a connection between TSLP and allergic inflammatory responses came from patients with atopic dermatitis. The epidermis of lesional skin in patients with allergic forms of dermatitis has higher TSLP expression than that of epidermis in uninvolved skin or skin from people with nonallergic dermatitis[19]. Interestingly, skin-resident DCs in patients with atopic dermatitis have an activated phenotype and seem to migrate toward the draining lymph node, consistent with a role for TSLP in the regulation of tissue-resident DC responses.

In mouse models, more TSLP in the skin leads to a T_H2 cytokine–dominant inflammatory disease. Inducible epidermal TSLP expression in mice induces a spontaneous atopic dermatitis–like disease[53]. The disease in these mice has all the cardinal features of human atopic dermatitis[53]. Epidermis-specific ablation of the steroid hormone receptors RXRα and RXRβ leads to spontaneous dermatitis[54], which is associated with higher epidermal TSLP expression. Finally, keratinocyte-specific ablation of Notch signaling, through deletion of the Notch transcriptional effector RBP-j, leads to higher TSLP concentrations and dermatitis[55]. These experimental models demonstrate that increasing TSLP concentrations in the epidermis induces the onset of T_H2 cytokine–associated inflammation, which suggests that the higher expression of TSLP in the lesional skin of patients with atopic dermatitis could be causative and is not a consequence of disease.

Perhaps the most direct causal link between higher expression of TSLP in the skin and human disease is Netherton syndrome, a genetic skin disease with severe atopic manifestations (recurrent atopic dermatitis, higher IgE concentrations, asthma and multiple food allergies)

[56]. Netherton syndrome is caused by mutations in *SPINK5*, which encodes the protease inhibitor LEKTI[57]. LEKTI deficiency leads to dysregulation of kallekrein 5, which in turn activates the protease-activated receptor PAR-2. Activated PAR-2 induces the expression of TSLP from either keratinocytes or airway epithelial cells[57,58]. Thus, a mutation that increases TSLP expression in the skin has direct consequences on the development of a severe atopic disease.

Higher TSLP expression in the skin can increase airway inflammatory responses in mouse models, providing a potential link between atopic dermatitis and asthma[58,59] (H. Han and S.F.Z., unpublished data). However, an important caveat for these animal models is the very high concentrations of circulating TSLP, which is not seen in people with atopic dermatitis. Thus, although it is a likely hypothesis, it is not yet clear what role, if any, TSLP has in the 'atopic march', the term used to describe the phenomenon in which people with one atopic disease (such as atopic dermatitis) are more likely to develop a second or third[43–45]. In general, people tend to develop atopic dermatitis first, followed by asthma, then allergic rhinitis[44].

TSLP is both necessary and sufficient for the development of T_H2 cytokine–associated inflammation of the airways in rodents. Mice expressing a TSLP transgene in the airway epithelium develop a spontaneous, progressive inflammatory disease with all the characteristics of human asthma[12], whereas direct intranasal delivery of TSLP (in the presence of antigen) leads to rapid onset of severe disease[60]. The disease in these mice develops slowly over a 3-month period, as determined on the basis of adaptive responses to environmental antigens[60]. Challenge at an early age with antigen leads to the immediate onset of disease, which suggests that TSLP is functioning to condition the local environment to respond to aerosolized antigens[60]. In addition, human asthmatics have higher concentrations of TSLP in their lungs[46,61].

The most compelling evidence for the importance of TSLP in the development of airway inflammation has been provided by genetic studies of mice. TSLPR-deficient mice are resistant to the development of inflammation in the classical ovalbumin-plus-alum priming model in mice[12,62]. It has been suggested that this is due to the inability of $CD4^+$ T cells to respond to TSLP, as reconstitution with TSLPR- sufficient T cells restores aspects of the inflammatory disease[62].

Consistent with the above mentioned link between TSLP and airway inflammation, factors known to be involved in either the development of asthma or the exacerbation of existing disease can induce TSLP expression in airway epithelial cells. These factors include inflammatory cytokines present in asthmatic lungs (IL-1β, tumor necrosis factor, IL-4, IL-13 and IL-25) and respiratory viruses[63,64] (M.B. Headley, H.-C. Lee and S.F.Z., unpublished data). The finding that infection with respiratory syncytial virus can induce TSLP expression is especially interesting, as it has been linked to both the development of wheezing and subsequent asthma in infants and asthma exacerbations in affected people[65–68]. Respiratory syncytial virus can induce both protective T_H1 cytokine responses and nonproductive T_H2 cytokine responses in humans and susceptible mouse strains[65]. The T_H2 cytokine response, which is unique to this virus, is thought to be a form of an immune-evasion process of the virus, involving dampening of the T_H1 response, as well as affecting memory generation[69]. It is also possible that TSLP induced by infection of airway epithelial cells with respiratory syncytial virus is critical for the T_H2 cytokine responses after infection.

Concluding comments

Building on original studies that identified a function for TSLP in activation of B cells and DCs[70], subsequent studies have indicated that TSLP coordinates the effector functions of many

myeloid and lymphoid populations (Fig. 1). These findings suggest a model in which TSLP promotes T_H2 cytokine responses that can be either host protective or pathological. Epithelial cells and other cells, including keratinocytes and granulocytes, produce TSLP as a result of a real insult (Fig. 2a) or a perceived insult (Fig. 2b). TSLP then acts to create an environment that is permissive to the development of T_H2 cytokine responses. This environment can either function to maintain normal barrier homeostasis or lead to the development of type 2 inflammation. In the latter case, TSLP seems to coordinately inhibit p40 expression in DC populations and activate basophils that can then migrate into lymph node that drains the site of infection or insult. DCs conditioned by TSLP at the tissue site may be simultaneously or subsequently recruited to lymph node and participate in T cell activation[11] (R.P. Larson and S.F.Z., unpublished data). In the lymph node, DCs and basophils may act cooperatively to promote optimal T_H2 cell differentiation.

In circumstances in which infection with a helminth parasite may induce epithelial damage, subsequent exposure to Toll-like receptor agonists from the pathogen or resident microbial communities would be expected to elicit a potent T_H1 cytokine response. Microbial products can also elicit TSLP expression[41,71], and the ability of TSLP to modulate or inhibit T_H1 responses may be its chief function in these circumstances (Fig. 2a). However, after exposure to an innocuous allergen, TSLP expression may be induced through the protease-activated receptor pathway[58]. In this scenario, as no T_H1 responses will be induced, TSLP can actively drive a T_H2 cytokine response, potentially through effects on DCs, granulocytes, natural killer cells and $CD4^+$ T cells (Fig. 2b). It is this last aspect of TSLP function that makes it a likely therapeutic target for the treatment of allergic diseases.

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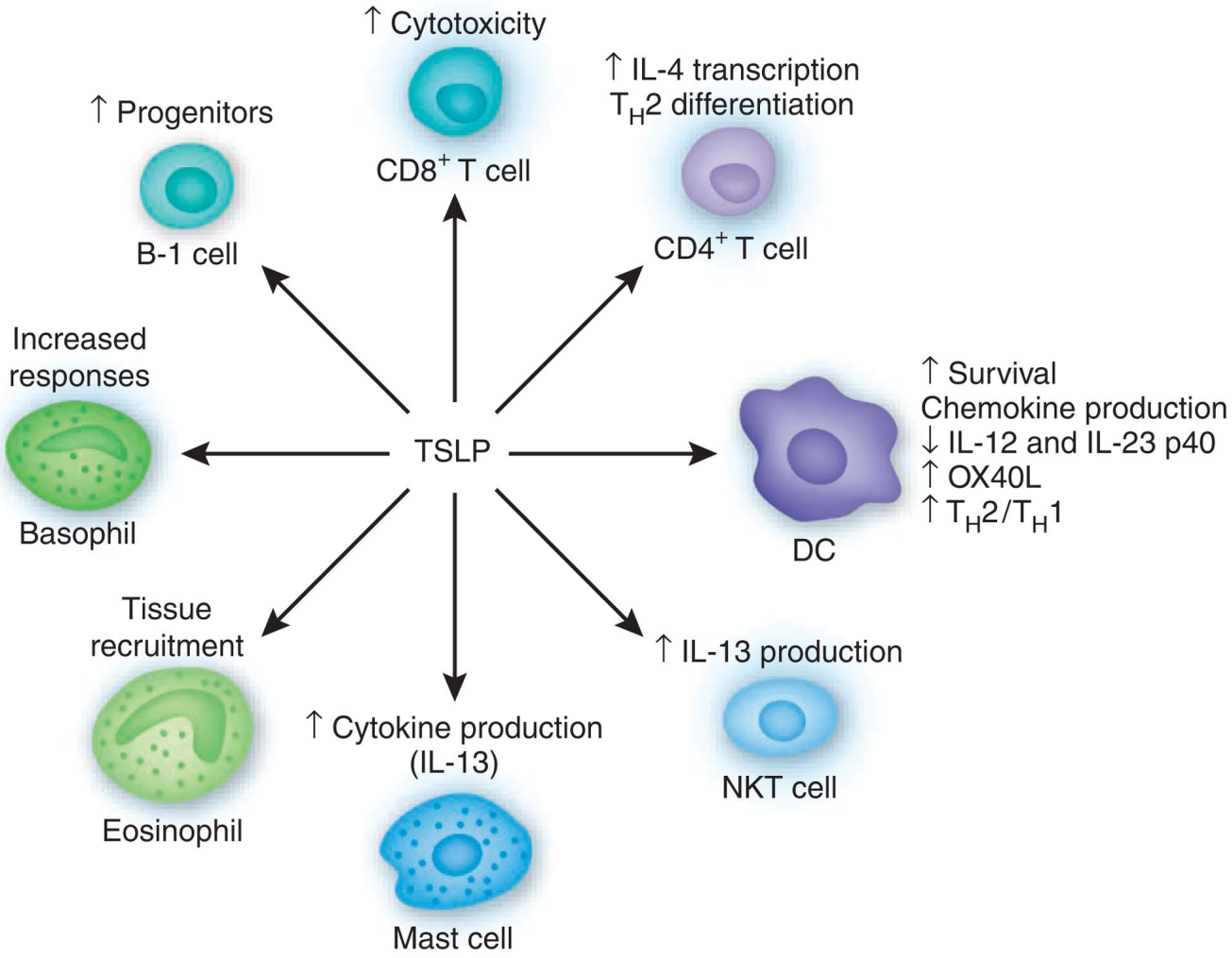

Figure 1.
Pantheon of TSLP-responsive cells. NKT, natural killer T.

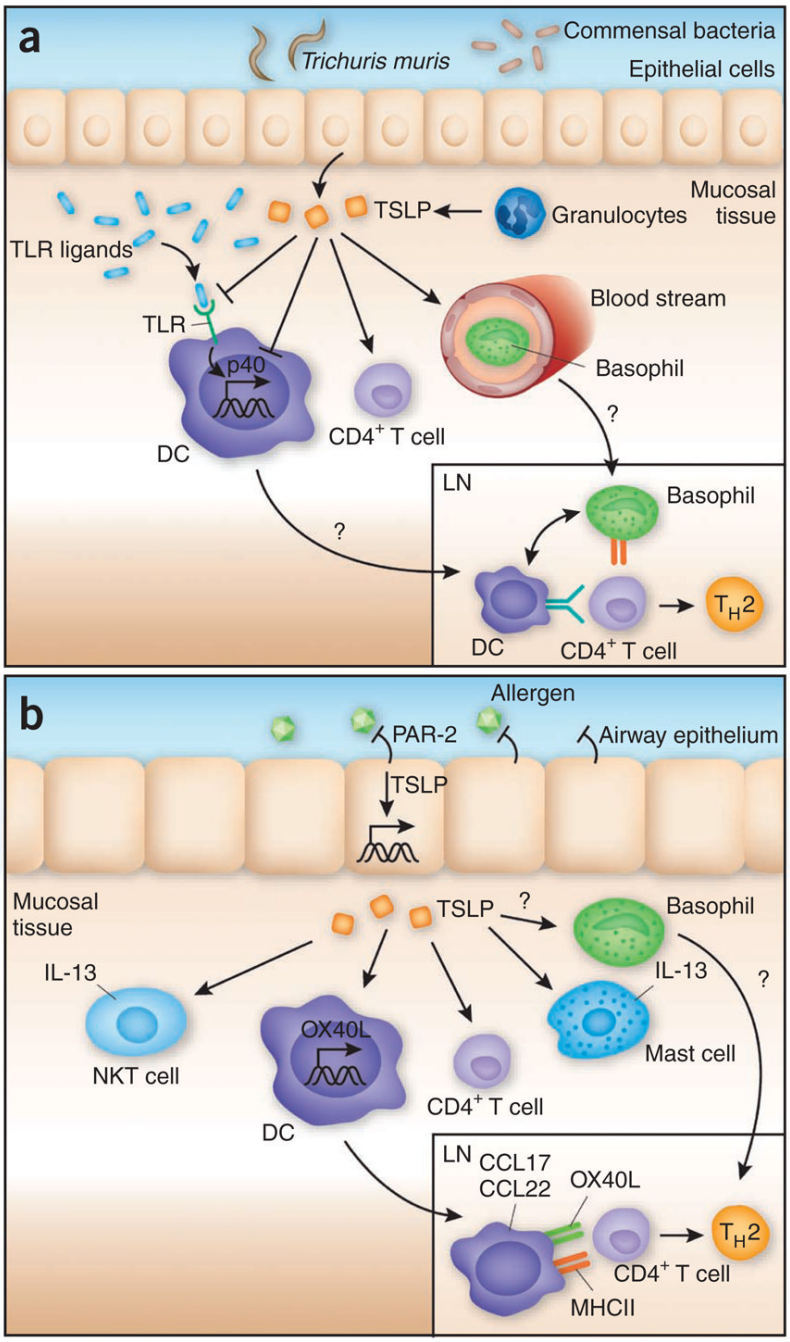

Figure 2.

TSLP regulates T_H2 cytokine responses after helminth infection and exposure to allergens. (**a**) After exposure to helminth parasites, infection and/or disruption of colonic epithelium elicits responses to Toll-like receptor (TLR) and Nod-like receptor agonists that are able to induce IL-12p40 expression and subsequent T_H1 cytokine responses. TSLP, which is also induced during infection, acts to suppress p40 expression by DCs, which inhibits the development of T_H1 responses, while also inducing OX40L to promote T_H2 responses. TSLP may also act to recruit IL-4-producing basophils to draining lymph nodes (LN) that act cooperatively with DCs to prime T_H2 cytokine responses. (**b**) After allergen exposure, proteases present in the allergen complex activate PAR-2, which in turn induces TSLP

expression. TSLP induces resident DCs to upregulate OX40L and to produce chemokines (CCL17 and CCL22) to promote T_H2 responses. TSLP acts on resident mast cells and natural killer T cells to increase cytokine production, which further promotes the T_H2 inflammatory cascade. MHCII, major histocompatibility complex class II.