

Molecular mechanisms in allergy and clinical immunology

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Thymic stromal lymphopoietin and OX40 ligand pathway in the initiation of dendritic cell-mediated allergic inflammation

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It was demonstrated 5 years ago that thymic stromal lymphopoietin (TSLP), a IL-7-like cytokine produced by epithelial cells, could strongly activate human myeloid dendritic cells to induce an inflammatory T_H2 response characterized by high TNF- α and little IL-10 production, distinct from the regulatory T_H2 responses characterized by low TNF- α and high IL-10 production. TSLP was found highly expressed by keratinocytes of skin lesions of atopic dermatitis and associated with dendritic cell activation *in situ*. This suggests for the first time that TSLP represents a master switch of allergic inflammation at the epithelial cell and dendritic cell interface. During the last several years, the evidence for the association of TSLP with human asthma was revealed. The direct link between TSLP expression with the pathogenesis of atopic dermatitis and asthma *in vivo* was demonstrated. In addition, OX40 ligand was found to be the TSLP-induced molecule on dendritic cells that triggers inflammatory T_H2 differentiation in the absence of IL-12. TSLP was also demonstrated to direct the innate phase of allergic immune responses through activating mast cells. Therefore, TSLP and OX40 ligand may represent important targets for intervention of the initiation of allergic inflammatory responses. (*J Allergy Clin Immunol* 2007;120:238-44.)

Key words: TSLP, dendritic cells, T_H2 , allergy, asthma, atopic dermatitis, OX40

Allergic inflammation is the result of a complex immunologic cascade leading to the dysregulated production of T_H2 -derived cytokines such as IL-4, IL-5, and IL-13. Allergic inflammation in turn triggers IgE

Abbreviations used

CD40L:	CD40 ligand
DC:	Dendritic cell
IL-7R:	IL-7 receptor
mDC:	Myeloid dendritic cell
OX40L:	OX40 ligand
RXR:	Retinoid X receptor
TLR:	Toll-like receptor
TSLP:	Thymic stroma lymphopoietin
TSLPR:	Thymic stroma lymphopoietin receptor

production, eosinophilia, and mucus production.¹⁻³ Recent studies have shown that dendritic cells (DCs) play a critical role in directing the types of T-cell responses, including T_H1 , T_H2 , and T_H17 . The ability of DCs to induce either T_H1 or T_H2 responses appears to be dictated by the type of signals that the DC received at an immature stage.⁴⁻⁶ The link between DCs and T_H1 immune responses is well defined. Specifically, microbe-derived molecules activate immature DCs through the pattern-recognition receptors, such as the Toll-like receptors (TLRs), to produce IL-12 or type 1 IFNs, which prime naive CD4⁺ T cells to undergo T_H1 differentiation.⁴⁻⁶ In contrast, how DCs instruct T_H2 responses is less clear. This article reviews the information supporting an important role of thymic stromal lymphopoietin (TSLP), an epithelial cell-derived IL-7-like cytokine, in regulating DCs to induce T_H2 cells that are typical of atopic diseases. The important role of OX40 ligand (OX40L) expression on DCs is discussed.

TSLP AND TSLP RECEPTOR

Thymic stromal lymphopoietin is a 140-amino acid IL-7-like 4-helix bundle cytokine that was first isolated from a murine thymic stromal cell line and shown to support B-cell development in the absence of IL-7.^{7,8} Mouse and

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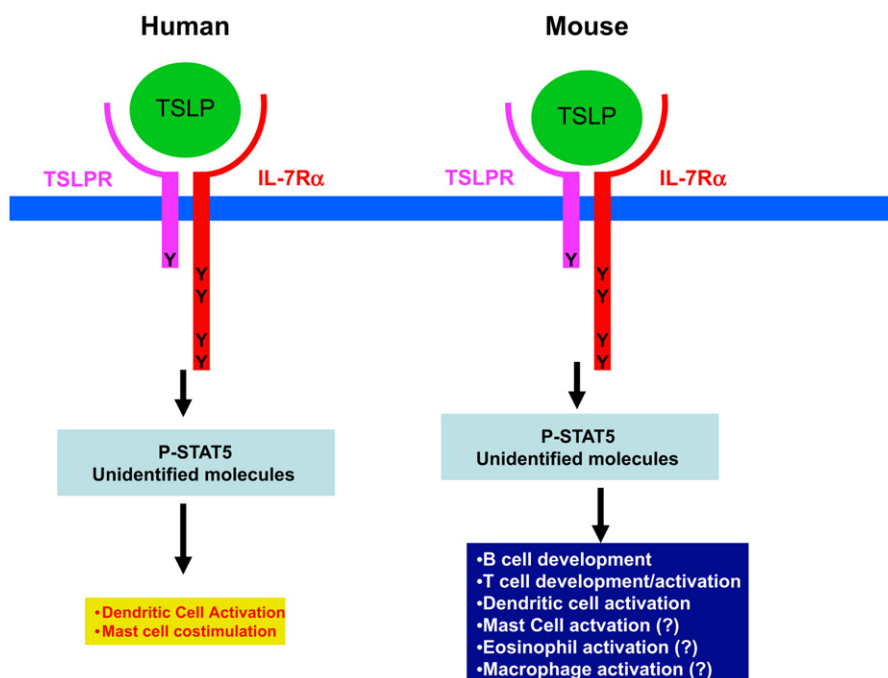


FIG 1. Structure of the TSLP receptor complex. Heterodimer of TSLPR and IL-7R α . TSLP stimulation induces activation and phosphorylation of STAT5 (P-STAT5), as well as activation of other as yet unidentified pathways. TSLP function: in human beings, TSLP directly activates DCs by upregulating MHC class I and II molecules and costimulatory molecules, promotes cell survival, and induces secretion of chemokine. TSLP also directly costimulates mast cells to produce proinflammatory T_H2 cytokines in the presence of TNF- α and IL-1. In mice, TSLP has additional functions, including promoting B-cell and T-cell development and promoting activation of T cells, mast cells, eosinophils, and macrophages.

human TSLP share a poor homology of 43% amino acid identity.⁷⁻¹⁰ The human TSLP gene is localized in chromosome 5q22, not far from the gene cluster encoding for all the T_H2-related cytokines: IL-4, IL-5, IL-9, and IL-13.^{9,10} Epithelial cells appear to be the major potential producer of TSLP in both mice and human beings.^{9,11} In addition, studies in the human system suggest that fibroblasts, smooth muscle cells, and mast cells all have the potential to produce TSLP.¹¹

The TSLP receptor complex consists of a TSLP-binding chain (referred to as TSLPR) and the IL-7R α chain^{9,12,13} (Fig 1). Like TSLP, human and mouse TSLPR share approximately 40% amino acid identity. By interacting with the heterodimeric receptor IL-7R α /TSLPR, TSLP appears to initiate signal transducer and activator of transcription (STAT)-3 and STAT5 phosphorylation.^{9,12,13} Although TSLPR was shown to be expressed by many lymphoid and nonlymphoid tissues, the exact cell types that expressed TSLPR have not been clearly defined. Functional studies suggest that early B-cell and T-cell progenitors, peripheral CD4⁺ T cells, and myeloid cells may express TSLPR^{7-10,12,13} (Fig 1). In the human system, extensive analyses of TSLPR mRNA in highly purified primary cells, including all human immune cell types and cell lines, show that cultured myeloid DCs (mDCs), plasmacytoid DCs after activation, and cultured mast cells have the potential to express TSLPR¹¹

(Hanabuchi et al, unpublished data, February 2007). In addition, human CD4⁺ T cells express low levels of TSLPR after activation by anti-CD3 and anti-CD28 antibodies.^{14,15}

TSLP ACTIVATES mDCs TO CREATE A T_H2-PERMISSIVE MICROENVIRONMENT

Human *ex vivo*-derived mDCs rapidly express TSLPR after culture in medium or with different stimuli, and undergo maturation in response to TSLP.¹¹ Like all stimuli that activate mDCs, including CD40 ligand (CD40L) and TLR ligands, such as bacterial LPS, polyinosinic-polycytidylic, and R848 (a TLR8 ligand), TSLP strongly upregulates the expression of MHC class II, CD54, CD80, CD83, CD86, and DC-lamp on human mDCs. However, unlike CD40L and TLR ligands, TSLP does not stimulate mDCs to produce the T_H1-polarizing cytokine IL-12 or the proinflammatory cytokines TNF- α , IL-1 β , and IL-6 (Table I). Our recent gene expression analyses of TSLP-activated DCs confirm and extend this finding by showing that TSLP does not induce the expression of mRNA that encodes the IL-12 family members IL-12, IL-23, and IL-27, nor the expression of mRNA that encodes the type I IFNs—all cytokines that induce T_H1 differentiation.¹⁶ Interestingly, TSLP treatment causes mDCs to produce large amounts of the chemokines

TABLE I. The unique features of TSLP-DC

	TSLP-DC	CD40L-DC	TLRL-DC
CD80/CD86	Up	Up	Up
MHC II	Up	Up	Up
Survival	Up	Up	Up
IL-1 α / β	—	++	++
IL-6	—	++	++
IL-12	—	++	++
IFNs	—	++	++
IP-10	—	++	++
Eotaxin-2	++	—	—
IL-8	++	++	++
TARC (T _H 2)	++	—	+
MDC (T _H 2)	++	+	+

TLRL, Toll-like receptor ligand; IP-10, IFN-induced protein 10.

IL-8 and eotaxin-2, which attract neutrophils and eosinophils, as well as thymus and activation regulated chemokine (TARC) and macrophage-derived chemokine (MDC), which attract T_H2 cells (Table I).¹⁷ We suggest that the inability of TSLP to induce the production of T_H1-polarizing cytokines by mDCs is one of the most important features of TSLP-activated DCs and helps these cells create a T_H2-permissive microenvironment. The molecular mechanisms underlying TSLP's ability to promote mDC maturation without inducing the production of T_H1-polarizing cytokines are unknown.

TSLP-DCs INDUCE INFLAMMATORY T_H2 CELLS

In most immunology textbooks and literature, T_H2 cells are defined as CD4⁺ T cells that produce IL-4, IL-5, IL-13, and IL-10, and T_H1 cells are defined as CD4⁺ T cells that produce IFN- γ and sometimes TNF- α . When TSLP-DCs are used to stimulate naive allogeneic CD4⁺ T cells *in vitro*, they induce a unique type of T_H2 cell that produces the classic T_H2 cytokines IL-4, IL-5, and IL-13 and large amounts of TNF- α , but little or no IL-10.¹¹ Although not typically considered a T_H2 cytokine, TNF- α is prominent in asthmatic airways, and genotypes that correlate with increased TNF- α secretion are associated with an increased risk of asthma,¹⁸ suggesting that TNF- α plays an important role in the development of asthma and allergic inflammation.

In addition to inducing the production of T_H2 cytokines and TNF- α , CD4⁺ T cells activated by TSLP-DCs produce decreased levels of IL-10 and IFN- γ , 2 cytokines known to downregulate T_H2 inflammation.¹⁹ IL-10, although initially classified as a T_H2 cytokine, counteracts inflammation and is produced at decreased levels in bronchoalveolar lavage fluid from atopic patients compared with normal subjects.²⁰ In addition, recent studies show that DC-cell-derived or T-cell-derived IL-10 prevents airway hypersensitivity after allergen exposure.^{21,22}

Because of their unique profile of cytokine production, we propose that T_H2 cells induced by TSLP-activated DCs be called *inflammatory T_H2 cells*, in contrast with

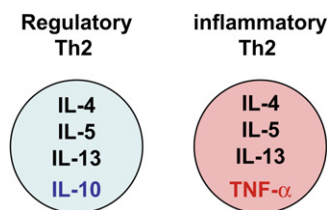


FIG 2. Two types of T_H2 cells defined by their IL-10 and TNF- α production. Regulatory T_H2 cells produce IL-4, IL-5, IL-13, and IL-10. Inflammatory T_H2 cells produce IL-4, IL-5, IL-13, and TNF- α . We propose that only the inflammatory T_H2 cells are associated with allergic diseases.

the *regulatory T_H2 cells* (Fig 2). The pathogenic T cells involved in allergic diseases such as atopic dermatitis and asthma are likely to be inflammatory T_H2 cells. Regulatory T_H2 cells that produce IL-4, IL-5, IL-13, and IL-10, but little TNF- α , may not be involved in promoting allergic diseases but are induced in many circumstances, including when antigen-presenting cells or T cells are treated with immunosuppressive drugs and when T cells are triggered by low-affinity TCR ligands.^{3,23,24} The classification of T_H2 cells into inflammatory T_H2 versus the regulatory T_H2 cells may offer an explanation for why T_H2-inducing parasite infection, such as Helminths infection, does not increase but instead decreases the incidence of atopy. This is because helminth infections induce the IL-10-producing regulatory T_H2 cells, but not the TNF- α -producing inflammatory T_H2 cells, and IL-10 may dampen adaptive immune responses to allergens.²⁵ Therefore, the classification of T_H2 cells into inflammatory T_H2 versus regulatory T_H2 cells may also provide the experimental support for the counterregulatory model used to explain Helminths and the T_H2 paradox.²⁶

OX40L REPRESENTS THE ORIGINAL T_H2 TRIGGER FROM TSLP-DCs

In an attempt to identify the molecular mechanism by which TSLP-DCs induce naive CD4⁺ T cells to differentiate into TNF- α -producing inflammatory T_H2 cells, our group performed gene expression analysis on immature human mDCs that were either resting or activated by TSLP, poly I:C, or CD40L. This analysis showed that only TSLP induces human mDCs to express the TNF superfamily protein OX40L at both the mRNA and protein levels.¹⁶

The expression of OX40L by TSLP-DCs was important for the induction of inflammatory T_H2 cells, because blocking OX40L with a neutralizing antibody inhibited the production of T_H2 cytokines and TNF- α and enhanced the production of IL-10 by the CD4⁺ T cells. Consistent with these results, we found that treating naive T cells with recombinant OX40L promoted the production of TNF- α but inhibited the production of IL-10. In other words, signals triggered by OX40L induced the generation of inflammatory T_H2 cells. A recent study demonstrated that OX40 signaling directly induces T_H2 lineage commitment by inducing nuclear factor of activated T

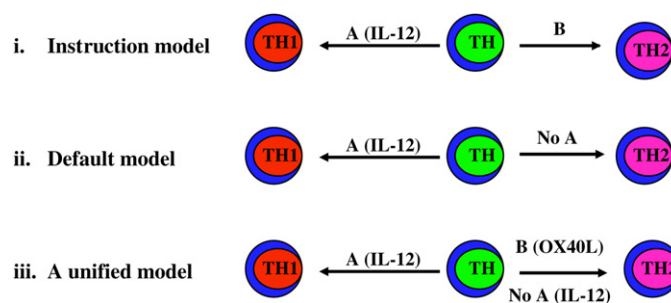


FIG 3. Three models for the regulation of T_H1 and T_H2 differentiation. **A**, Instruction model: T_H1 differentiation requires a T_H1-polarizing signal, and T_H2 differentiation requires a T_H2-polarizing signal. **B**, Default model: T_H1 differentiation requires a T_H1-polarizing signal, and T_H2 differentiation occurs spontaneously in the absence of the T_H1-polarizing signal. **C**, A unified model: T_H1 differentiation requires a T_H1-polarizing signal, and T_H2 differentiation requires a T_H2-polarizing signal. However, the T_H1-polarizing signal is dominant over the T_H2-polarizing signals. The T_H2 signal can induce a T_H2 response only in the absence of a T_H1-polarizing signal.

cell c1, which triggers IL-4 production and then IL-4—dependent GATA-3 transcription.²⁷

THE ABILITY OF OX40L TO INDUCE T_H2 DEPENDS ON A DEFAULT MECHANISM OF IL-12 ABSENCE

OX40 ligand-induced inflammatory T_H2 cell differentiation depends on the absence of IL-12, because OX40L loses the ability to trigger inflammatory T_H2 cell differentiation in the presence of IL-12. The ability of OX40L to trigger T_H2 development is independent of IL-4, although the IL-4 that is produced by the developing T_H2 cells synergizes with the OX40L-derived signals to further promote T_H2 cell development.¹⁶ We thus conclude that TSLP-activated DCs create a T_H2-permissive microenvironment by upregulating OX40L without inducing the production of T_H1-polarizing cytokines. The dominance of IL-12 over OX40L may provide a molecular explanation for the hygiene theory, which proposes that microbial infections that trigger T_H1 responses may decrease the subsequent development of T_H2-driven atopy. Historically, 2 models have been proposed to explain how T_H2 development is initiated: T_H2 differentiation requires a positive T_H2-polarizing signal (Fig 3, A), or T_H2 development is initiated by a default mechanism in the absence of IL-12²⁸⁻³² (Fig 3, B). Our findings suggest that the 2 previously proposed models are not mutually exclusive and that T_H2 differentiation requires a positive polarizing signal such as OX40L as well as a default mechanism (the absence of IL-12).

OX40 LIGAND INDUCES INFLAMMATORY T_H2 CELLS AND IL-4 INDUCES REGULATORY T_H2 CELLS

To investigate the function of IL-4 in the generation of inflammatory TNF- α^{++} IL-10⁻ T_H2 cells induced by TSLP-DCs, we added neutralizing anti-IL-4 mAb in

the beginning of coculture of naive CD4⁺ T cells and allogeneic TSLP-DCs. We found that, similar to anti-OX40L mAb, anti-IL-4 mAb significantly decreased the frequency of T_H2 cells producing IL-4, IL-5, and IL-13 while concomitantly increasing the frequency of cells producing T_H1 cytokine IFN- γ . However, unlike anti-OX40L, anti-IL-4 has little effect on TNF- α or IL-10 production by T cells cultured with TSLP-DCs. These data suggest that IL-4 has the ability to prime naive T cells to differentiate into T_H2 cells without the TNF- α^{++} IL-10⁻ inflammatory property. By contrast, OX40L has the ability not only to prime naive T cells to differentiate into T_H2 cells but also to confer the T_H2 cells with a TNF- α^{++} IL-10⁻ inflammatory property (Fig 4).

Previous studies demonstrated that *Schistosoma mansoni* was found to induce human mDCs to promote T_H2-immune responses through OX40L,³³ and OX40L was important for the *in vivo* development of T_H2 responses to a nematode in mice. These studies suggest that chronic parasite infection may trigger additional mechanisms that may negatively regulate the ability of OX40L to induce the inflammatory responses, sparing the ability of OX40L to induce the T_H2 immune responses.

OX40L AND IL-4 WORK SEQUENTIALLY AND SYNERGISTICALLY IN DRIVING T_H2 RESPONSES

Because anti-OX40L alone or with anti-IL-4 only partially blocks the generation of T_H2 cells that produce IL-4, IL-5, and IL-13, we further investigated whether the combination of anti-OX40L and anti-IL-4 antibodies would completely block the generation of T_H2 cells induced by TSLP-DCs. Indeed, we found the synergistic effect of anti-OX40L and anti-IL-4 and the combination of both almost completely switched a T_H2 response to a T_H1 response. Because TSLP-DCs do not produce IL-4, this experiment suggests that whereas OX40L represents the original T_H2-polarizing signal from TSLP-DCs, IL-4 represents a critical autocrine stabilizer and enhancer of the developing T_H2 cells. Thus, OX40L and IL-4 work

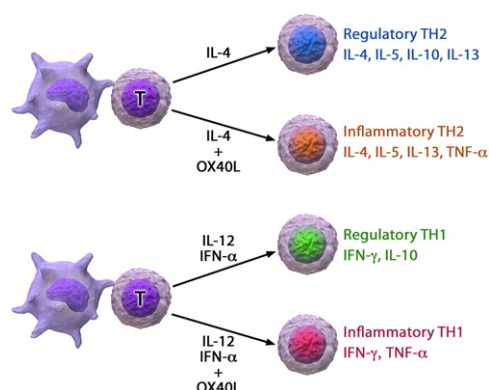


FIG 4. Schematic illustration of T_H1 and T_H2 cell responses classified into inflammatory versus conventional subtypes according to IL-10 and TNF- α^{++} expression. The figure depicts the hypothesis from our study. IL-4 and IL-12 are classic T_H2 cell-polarizing and T_H1 cell-polarizing factors, respectively. IL-4 and IL-12/IFN- α/β induce conventional T_H2 and T_H1 cells, respectively, which produce IL-10. In contrast, OX40L from DCs promotes TNF- α^{++} but inhibits IL-10 production by the developing T_H2 cells induced by IL-4 or T_H1 cells induced by IL-12. These inflammatory T_H2 and T_H1 cells may contribute to the induction of allergic and autoimmune diseases, respectively.

synergistically and sequentially in driving T_H2 responses in T cells¹⁶ (Fig 5).

THE ASSOCIATION OF TSLP WITH ATOPIC DERMATITIS AND ASTHMA

Early studies showed that TSLP mRNA is highly expressed by human primary skin keratinocytes, bronchial epithelial cells, smooth muscle cells, and lung fibroblasts but not by most hematopoietic cells, including B cells, T cells, natural killer cells, granulocytes, macrophages, monocytes, or DCs.¹¹ Interestingly, mast cells activated by IgE receptor cross-linking expressed high levels of TSLP, suggesting an additional cell type that may help trigger allergic inflammation. TSLP protein, examined by immunohistology on cryopreserved tissue sections, is undetectable in normal skin or nonlesional skin in patients with atopic dermatitis but is highly expressed in acute and chronic atopic dermatitis lesions.¹¹ TSLP is expressed mainly in keratinocytes of the apical layers of the epidermis, suggesting that TSLP production is a feature of fully differentiated keratinocytes. TSLP is not found in skin lesions from patients with nickel-induced contact dermatitis or disseminated lupus erythematosus. Interestingly, TSLP expression in patients with atopic dermatitis is associated with Langerhans cell migration and activation *in situ*, suggesting that TSLP may contribute directly to the activation of these cells, which could then migrate into the draining lymph nodes and prime allergen-specific T_H2 responses.¹¹ A more recent study showed by *in situ* hybridization that TSLP expression is increased in asthmatic airways and correlates with both the expression of T_H2 -attracting



FIG 5. OX40L and IL-4 work sequentially and synergistically in driving a T_H2 response. OX40L represents a DC-derived original trigger for T_H2 differentiation, and IL-4 produced by the developing T_H2 cells further amplifies and enhances T_H2 polarization in an autocrine fashion. IL-12 dominantly and negatively regulates function of OX40L and IL-4 in T_H2 differentiation.

chemokines and with disease severity,³² providing the first link between TSLP and human asthma.

A critical role of TSLP in the development of allergic diseases has been shown *in vivo* by many groups. Yoo et al³⁴ demonstrated that mice engineered to overexpress TSLP in the skin develop atopic dermatitis characterized by eczematous skin lesions containing inflammatory cell infiltrates, a dramatic increase in circulating T_H2 cells, and elevated serum IgE. This study also suggested that TSLP may directly activate DCs in mice. In another study, Li et al³⁵ reported the surprising finding that selective ablation of retinoid X receptors (RXRs) in epidermal keratinocytes trigger atopic dermatitis in mice. The authors of that study noted that TSLP expression is rapidly induced in skin keratinocytes that lack RXRs, likely contributing to the development of disease. This group confirmed the finding that transgenic mice overexpressing TSLP in the skin develop atopic dermatitis, thus solidifying the link between TSLP and the development of atopic dermatitis. Two recent studies also formally establish a critical role of TSLP in the initiation of asthma *in vivo*. Zhou et al³⁶ showed that lung-specific expression of a TSLP transgene-induced allergic airway inflammation (asthma) is characterized by a massive infiltration of leukocytes (including T_H2 cells), goblet cell hyperplasia, and subepithelial fibrosis, as well as by increased serum IgE levels. By contrast, mice lacking TSLPR failed to develop asthma in response to inhaled antigen.^{36,37}

TSLP COSTIMULATES MAST CELLS TO PRODUCE INFLAMMATORY AND T_H2 CYTOKINES

Recent studies showed that overexpression of TSLP in mice lacking T cells (T-cell receptor $\beta^{-/-}$ or recombination activating gene [RAG] $^{-/-}$) triggered moderate bronchial or cutaneous allergic inflammation, suggesting that TSLP may directly activate effector cells of the innate immune system.^{34,36,38} More recently, Allakhverdi et al³⁹ demonstrated that human TSLP, synergistically with IL-1 and TNF- α , stimulates mast cells to produce high levels of the T_H2 cytokines IL-5 and IL-13, as well as proinflammatory cytokines GM-CSF and IL-6. This study suggests that TSLP directly activates mast cells and DCs to initiate the innate phase of allergic immune responses, followed by TSLP-activated DCs to initiate the T-cell-mediated adaptive phase of allergic immune responses (Fig 6).

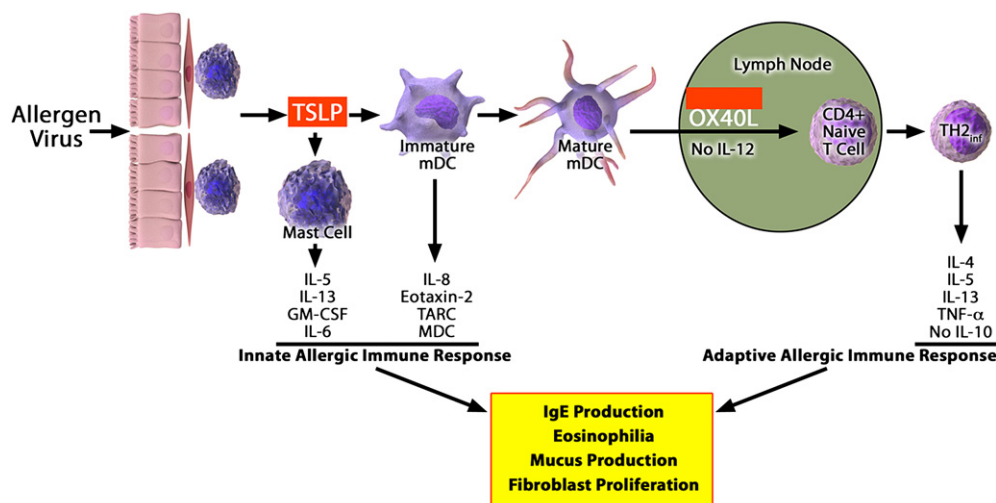


FIG 6. Pathophysiology of TSLP in allergic inflammation. Insults from allergens or viruses trigger mucosal epithelial cells or skin cells (keratinocytes, fibroblasts, and mast cells) to produce TSLP. TSLP initiates the innate phase of allergic immune responses by activating immature DCs to produce the chemokines IL-8, eotaxin-2, and the T_H2 attracting chemokine TARC and MDC and by costimulating mast cells to produce IL-5 and IL-13, as well as GM-CSF and IL-6. TSLP-activated mDCs mature and migrate into the draining lymph nodes to initiate the adaptive phase of allergic immune responses. TSLP-activated DCs express OX40L, which triggers the differentiation of allergen-specific naive $CD4^+$ T cells to inflammatory T_H2 cells that produce IL-4, IL-5, IL-13, and TNF but not IL-10. Inflammatory T_H2 cells then migrate back to the site of inflammation because of the local production of TARC and MDC. The T_H2 cytokines IL-4, IL-5, IL-13, and TNF- α , produced by the inflammatory T_H2 cells, initiate allergic inflammation by triggering IgE production, eosinophilia, and mucus production.

SUMMARY AND FUTURE PERSPECTIVES

We now know that TSLP is highly expressed by skin keratinocytes and airway epithelial cells during allergic inflammation, but how TSLP expression is triggered in these cells—by allergen exposure or virus infection—remains unclear. Because the expression of RXR in skin keratinocytes may actively suppress TSLP production under normal physiological conditions, further studies on the regulation of these receptors may provide important clues about how allergen or viral infection triggers TSLP production.

Thymic stroma lymphopoietin activates mast cells and mDCs to initiate the innate phase of allergic inflammatory responses. TSLP also instructs mDCs to initiate the adaptive inflammatory T_H2 responses (Fig 6). TSLP activates mDCs in 2 unique ways. First, TSLP induces DC maturation without driving the production of the T_H1 -polarizing cytokine IL-12, thus creating a T_H2 -permissive microenvironment. Second, TSLP induces the expression of OX40L on DCs, which directly triggers the differentiation of inflammatory T_H2 cells (Fig 6). The signaling pathway that is triggered by TSLP and leads to this unique T_H2 phenotype is unknown, but it appears to involve STAT5 activation, independent of the classic NF- κ B and MyD88 signaling pathways.

OX40 ligand signaling has several important features. It triggers T_H2 polarization independent of IL-4, promotes TNF- α production, and inhibits IL-10 production by the developing T_H2 cells, but only in the absence of IL-12. In the presence of IL-12, OX40L signaling instead promotes the development of T_H1 cells that, like

inflammatory T_H2 cells, produce TNF- α but not IL-10. This finding may help explain why blocking OX40/OX40L interactions reduces the severity of T_H1 -mediated autoimmune diseases⁴⁰—the reason some immunologists are reluctant to accept OX40L as a T_H2 -polarizing factor. We now believe that this inhibition of T_H1 -induced pathology is a result of the increased production of the immunosuppressive cytokine IL-10 and the decreased production of the inflammation-promoting cytokine TNF- α that results from blocking OX40/OX40L interactions. On the basis of these recent studies, we propose the subdivision of T_H2 cells into inflammatory T_H2 cells that produce high levels of TNF- α but little IL-10, and conventional T_H2 cells that produce little TNF- α but high levels of IL-10. Inflammatory T_H2 cells, but not conventional T_H2 cells, may be involved in allergic inflammatory diseases. Our initial finding that epithelial cell-derived TSLP triggers DC-mediated inflammatory T_H2 responses through OX40L in human beings together with the exciting *in vivo* studies suggests that TSLP represents a master switch of allergic inflammation at the epithelial cell–DC interface. TSLP and OX40L should, therefore, be considered key targets for immunologic intervention in the treatment of allergic diseases (Fig 6).

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