Published in final edited form as:

Curr Opin Pharmacol. 2008 June ; 8(3): 249–254.

Thymic stromal lymphopoietin: a new cytokine in asthma

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Abstract

Airway epithelial cells provide mechanical and immune protection against pathogens and allergens. Following activation, these cells produce a wide range of cytokines including thymic stromal lymphopoietin (TSLP). Recently it was established that a high level of TSLP is associated with asthma in mice and in humans. These findings suggest that interfering with the ability of cells to respond to TSLP might prevent the development of airway inflammation. Our review presents current knowledge on mediators that induce TSLP production and on the actions of TSLP on different populations of cells that are related to airway inflammation. TSLP affects dendritic cells, T cells, NKT cells, and mast cells, indicative of the broad role of TSLP in the regulation of inflammatory/allergic processes.

Introduction

Asthma is a disease characterized by chronic airway inflammation that is mediated by T-helper 2 (T_H2) cells [1,2]. T_H2 cells release interleukin-4 (IL-4), IL-5, IL-9, and IL-13, driving IgE production by B cells, stimulating basophils and eosinophils, enhancing mast cell differentiation, and increasing mucus production [1,2]. Allergens trigger the cross-linking of IgE on mast cells, leading to the activation and degranulation of these cells. The inflammatory mediators released by mast cells cause bronchial smooth muscle contraction, vascular permeability, inflammatory cell infiltrate, increased mucus in airways, epithelial cell loss, and goblet cell hyperplasia [1,3].

Airway epithelial cells provide the initial barrier against pathogens (allergens) invading the lung. In addition to mechanical protection, epithelial cells provide immune defense against harmful materials. Following their activation, these cells produce an array of cytokines and chemokines, including IL-1, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferons- α and β , tumor necrosis factor- α (TNF- α), and RANTES (regulated upon activation, normal T cell expressed and secreted), eotaxin and others, which promote the recruitment and activation of immune and inflammatory cells [4–6]. Among the mediators produced by epithelial cells is thymic stromal lymphopoietin (TSLP) [7]. Recent studies have established that high levels of TSLP are associated with airway inflammatory disease in humans and mice [8*,9*]. Strikingly, mice lacking TSLPR fail to develop inflammatory allergic response in the lung [10**]. Conversely, the over-expression of TSLP in transgenic mice induces spontaneous airway inflammation and atopic dermatitis, consistent with an important role for this cytokine in allergy/inflammation [11**,12].

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TSLP/TSLPR signaling

TSLP was originally identified as a growth factor in the supernatant of Z210R.1 thymic stromal cells that support proliferation and survival of the NAG8/7 pre-B cell line [13]. TSLP is a short-chain four α -helical bundle type I cytokine that is closely related to interleukin-7 (IL-7), another stromal factor [14,15]. IL-7 signals via IL-7R α and the common cytokine receptor γ chain (γ_c), a protein that is also a critical component of the receptors for IL-2, IL-4, IL-9, IL-15, and IL-21 [16]. TSLP also signals via IL-7R α , but instead of γ_c , uses a specific TSLPR subunit that is highly related to γ_c [17,18] (see Figure 1). TSLPR contains a Box 1 region that is common to all type I cytokine receptor family proteins and is important for the binding of Janus family tyrosine kinases (JAKs). Although it has been suggested that TSLP failed to activate any JAK [19], TSLP mediates Stat5 activation [19,20], and this activation requires the Box1 region of both TSLPR and IL-7R α [20]. In addition to its activation of Stat5, TSLP presumably might activate other pathways as well, including perhaps those often activated by other cytokines such as PI 3-K/Akt, MAPK and/or Src family kinase pathways [9*]. A better comprehension of the signaling pathways activated by this cytokine will be useful to the understanding of the mechanisms by which TSLP exerts its effects, and may lead to additional ways of regulating its actions.

Induction of TSLP in allergic disorders

Studies on TSLP have indicated that epithelial cells, keratinocytes, and stromal cells are major producers of TSLP [7]. Recently, it was demonstrated that allergen-activated basophils also produce TSLP and thus also may be important in the initiation of T_H2 responses [21]. TSLP is implicated in allergic inflammation, and a number of mediators have been defined, with the potential to promote TSLP expression that might be associated with airway inflammation and atopic dermatitis (Figure 2) [22–25].

A key molecular mechanism that links mediators and TSLP production is the NF- κ B signaling pathway, which is activated by many pro-inflammatory cytokines and Toll-like receptor (TLR) ligands [23*,26]. Recent findings reveal that pro-inflammatory cytokines, such as TNF α and IL-1, synergize with T_H2 cytokines (IL-4 and IL-13) in increasing TSLP production by human airway epithelial cells and human keratinocytes [23*,24]. Similarly, engagement of TLR3 by viral double-strand RNA (dsRNA) of rhinoviruses or by synthetic dsRNA can augment production of TSLP by epithelial cells [25,27*]. Although it has not been proven that respiratory viruses induce asthma, they are known to induce airway hyper-responsiveness (AHR) and amplify the response to allergen exposure [28]. Therefore, TSLP may at least in part explain this observation. Similarly, a role of TLR2, TLR8, and TLR9 in the release of TSLP has been suggested [23*,27*]. Although it was proposed that the activation of airway epithelial cells via TLR4 does not affect TSLP expression, it was found that LPS-stimulated intestinal epithelial cells up-regulate TSLP mRNA expression [26]. Together these findings suggest that TSLP may be important in a range of inflammatory processes.

The role of TSLP in the development of immune cells

TSLP, like IL-7, has effects in T- and B-cell lymphopoiesis [9*,29,30,33]. In mice, disruption of IL-7R α signaling leads to T- and B-cell lymphopenia and an absence of $\gamma\delta$ T cells [31]. In humans, mutation of the *IL7R* gene results in a form of severe combined immunodeficiency in which T cells are profoundly diminished in number while other lineages are intact [31,32]. It is reasonable to predict that TSLP might partially replace the role of IL-7 in T cell development because IL-7R α is also shared by TSLP. Indeed, although the lack of TSLP signaling does not affect hematopoiesis, TSLPR/ γ_c double knockout mice have more impaired T-cell development than do γ_c -deficient mice, and recovery of T cells is defective in sub-lethally irradiated TSLPR knockout mice [33]. Similarly, transgenic overexpression of TSLP

in *Il7*^{-/-} lymphopenic mice promotes generation of functional B- and T-cells, consistent with the ability of TSLP to compensate for IL-7 deficiency [30].

Whereas lymphoid and myeloid progenitors are the major targets for TSLP in the development of the immune system, relatively limited information is available regarding the cells that respond to TSLP in the periphery.

TSLP exerts actions on multiple lineages

TSLP has effects on a range of immune cells, including dendritic cells (DCs), T cells, natural killer T (NKT) cells, and mast cells. These effects will be summarized, focusing on the relationship to asthma (Figure 2).

Dendritic cells

DCs are professional antigen presenting cells (APCs) that bridge between innate and adaptive immunity. DCs can be activated directly by pathogens via Toll-like receptors or by mediators produced by epithelial cells. Activated DCs up-regulate co-stimulatory molecules including MHC class II antigens, and release cytokines and chemokines that together induce recruitment, activation, and differentiation of T cells. Human DCs express TSLP receptors [34] and rapidly respond to TSLP, as evaluated by the up-regulation of MHC class II, CD40, CD80, CD86, OX40L, TARC, and MDC molecules (Figure 2) [9*]. Following TSLP stimulation, DCs mediate homeostasis and differentiation of human CD4⁺ T cells to inflammatory T_H2 cells [9*] and CD8⁺ T cells to pro-allergic cytotoxic cells with IL-13 production [35]. In mice, TSLP also is able to induce the maturation of DCs, and TSLP-activated DCs regulate the differentiation of naive CD4⁺ T cells to T_H2 cells [10**,11**]. These results suggest that in both humans and mice, TSLP-activated DCs promote the differentiation of T cells to pro-allergic cells.

T cells

Much discussion has focused on possible species-specific actions of TSLP on T cells. TSLP was reported to have certain specific T cell-related actions in mice, whereas human TSLP was shown to activate DCs, with only an indirect effect on T cells [9*]. However, when we investigated the action of TSLP on human and mouse T cells, we found that CD4⁺ T cells in both species can directly respond to this cytokine [33,36**], indicating that there is not a significant species-specific variation in the actions of this cytokine in humans and mice.

Careful analysis of human CD4⁺ T cells showed that pre-activated but not naïve CD4⁺ T cells express TSLPR and that TSLP can rapidly activate Stat5 and induce expression of Stat5 target genes, indicating the presence of functional TSLP receptors on activated human T cells. Consistent with this, TSLP augments the proliferation rate of T cell receptor (TCR)-activated human CD4⁺ T cells [36**], analogous to the effect previously observed in mice [33]. In addition, TSLP also increases IL-2R α expression, thus increasing the sensitivity of CD4⁺ T cells to low doses of IL-2; this indicates a possible mechanism for regulating the proliferation of these cells following TCR engagement [36**].

In mice, TSLPR deficiency has been associated with defective development of an inflammatory allergic response to ovalbumin in the lung, but this can be reversed by the addition of wild type (WT) CD4⁺ T cells [10**]. Interestingly, a comparison of the four possible combinations of DCs and CD4⁺ T cells from WT versus TSLPR KO mice in a proliferative assay revealed that the absence of TSLPR on CD4⁺ T cells appeared to be even more deleterious than the loss of TSLPR on DCs [10**]. Moreover, it was shown that TSLP can regulate differentiation of pre-activated mouse CD4⁺ T cells towards the T_H2 phenotype in a DC-independent fashion [37].

Together these data demonstrate a unique role of TSLP in the regulation of CD4⁺ T cell action (Figure 2).

Natural Killer T cells

NKT cells represent a unique sub-population of T cells that have properties of both conventional T cells and NK cells. Like T cells, NKT cells develop from thymocyte progenitors, migrate to the same organs as T cells, and rapidly produce IL-4 and IFN- γ upon TCR stimulation. NKT cells play an important role in the rejection of malignant tumors and in the regulation of infections and autoimmune diseases [38]. The percent of NKT cells appears to be enriched in bronchoalveolar lavage fluid, as compared with whole peripheral blood in asthmatic patients [39]. Recent evidence has established a role for NKT cells in the development of allergen-induced AHR by producing IL-4 and IL-13 [40]. Although NKT cells are not required for the development of T_H2 cells, the lack of NKT cells or inability of NKT cells to release IL-4 and/or IL-13 could potentially prevent development of AHR [40]. In this regard, TSLP was proposed to increase production of IL-13 by TCR-activated NKT cells based on studies using TSLP transgenic mice [41]. Interestingly, the percent of eosinophils in the lung and level of serum IgE are much higher in TSLP transgenic mice than in wild type animals [11**,41]. Thus, further studies on the effect of TSLP on the differentiation of eosinophils and maturation of B cells may provide a better understanding of the mechanism(s) of increased airway inflammation in asthma.

Mast cells

The infiltration of mast cells to mucosal gland stroma and airway smooth muscle in asthma subsequently leads to mucous gland hypertrophy, mucus hypersecretion, and smooth muscle dysfunction, which are hallmarks of asthma [3,42]. Mast cells release numerous mediators, including histamine, enzymes, TNF- α , pro-inflammatory T_H2 cytokines and chemokines in response to different stimuli including IgE, cytokines, Toll-like receptor ligands and complement. It also has been established that mast cells not only express high levels of TSLP mRNA [7,8*], but also they can respond to TSLP [27*]. Immunostaining of a bronchial biopsy of an asthmatic patient has revealed TSLP receptor expression on infiltrating mast cells. Furthermore, stimulation of human mast cells *in vitro* with IL-1 β and TNF- α in the presence of TSLP strongly augments production of pro-inflammatory T_H2 cytokines, including IL-5, IL-6, IL-10, and IL-13, as well as chemokines that are involved in allergic diseases. Consistent with this, blocking endogenous TSLP that is released by primary activated human epithelial cells completely inhibits production of IL-13 by mast cells [27*]. This suggests that TSLP may facilitate crosstalk between epithelial cells and mast cells.

Old and new therapeutic strategies

The general approach in the treatment of asthma is to diminish symptoms by using bronchodilators and corticosteroids that can prevent and reduce airway swelling and decrease the amount of mucus in the lungs [1]. However, these medications can have side effects, and tolerance can arise during long-term treatment. Moreover, because each case of asthma is different, treatment needs to be modified for each person. A novel approach for asthma is to develop immunological therapies to prevent its development instead of solely treating symptoms of the disease [1,43,44]. Anti-IgE (Omalizumab) is one such treatment [44,45]. However, whereas IgE binding to Fc ϵ RI activates mast cells, anti-IgE treatment alone is not enough to prevent AHR [46]. Another innovative approach is to block T_H2 cytokines or their receptors [43]. For example, treatment using humanized monoclonal antibodies to IL-5 reduces eosinophil levels in asthmatic patients [47]. Moreover, inhalation of soluble forms of IL-4 receptor α chain (sIL4-4R α) in humans and chemically modified IL-4R α antisense oligonucleotide (IL-4R α ASO) in mice can diminish asthma symptoms and AHR [48,49].

Importantly, administration of TSLPR-Fc fusion protein can prevent lung allergic inflammation in a mouse model [10**]. This beneficial response in such models of asthma has suggested that inhibiting TSLP may have potential as a therapeutic approach to asthma in humans.

Conclusion

TSLP is a cytokine of tremendous interest that is implicated as playing a pathophysiologic role in allergic inflammatory disease, including asthma and atopic skin disease. As such, it is a potential target for the modulation of inflammation/allergy. Although highly related to IL-7, including the sharing of a receptor component, TSLP is distinctive in having a greater role in inflammation whereas IL-7 appears to be more important for lymphoid development and survival. Additional data on the biology and signaling pathways of TSLP should provide a more comprehensive understanding of its function in the immune system. More information about the mechanisms controlling TSLP production and the actions of this cytokine will hopefully also allow the design of new therapeutic approaches for the control of pathological immune responses.

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Figure 1. Schematic showing TSLP and IL-7 receptors sharing IL-7R α and IL-7, IL-2, IL-15, IL-9, IL-21, and IL-4 receptors sharing γ_c
 The receptors are grouped to show TSLP on the far left, IL-7 complexes adjacent in both groups and IL-4 at the far right, as it activates Stat6. For each γ_c family cytokine receptor, Jak1 associates with the more “distinctive” type I cytokine receptor chain, whereas Jak3 associates with γ_c . TSLP, IL-2, IL-7, IL-9, and IL-15 primarily activate Stat5a and Stat5b, IL-4 primarily activates Stat6, and IL-21 primarily activates Stat3 and Stat1.

Figure 2. Schematic showing production of TSLP by epithelial cells in response to a range of stimuli These include viruses, bacterial components such as peptidoglycan, lipoproteins, lipoteichoic acid, LPS and bacterial DNA, biochemical compounds like vitamin D and low-calcemic analogs [22], and pro-inflammatory cytokines TNF α and IL-1 β . In turn, TSLP can act on cells of multiple lineages, inducing the production of cytokines and also having effects on proliferation and differentiation.