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TSLP: A Key Regulator of Asthma Pathogenesis

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Abstract

Asthma is a complex disorder of the airways that is characterized by T helper type 2 (Th2) inflammation. The pleiotropic cytokine TSLP has emerged as an important player involved in orchestrating the inflammation seen in asthma and other atopic diseases. Early research elucidated the role of TSLP on CD4⁺ T cells, and recent work has revealed the impact of TSLP on multiple cell types. Furthermore, TSLP plays an important role in the sequential progression of atopic dermatitis to asthma, clarifying the key role of TSLP in the pathogenesis of asthma, a finding with therapeutic implications.

Introduction

Asthma is a disorder of the airways that affects over 300 million people worldwide and is increasing in prevalence in developed countries [1]. Asthma is characterized by airway obstruction, excessive mucus production, and airway hyperresponsiveness (AHR). In allergic asthma, inflammation of the airways is a key component resulting in airway remodeling and damage [1]. Th2 immunity and Th2 cytokines, including IL-3, IL-4, IL-5, IL-9, IL-13, and GM-CSF, have been shown to play a major role in this disease, resulting in mast cell and eosinophil differentiation and maturation, basophil recruitment, and B cell isotype switching to IgE synthesis [1]. Recently, the cytokine thymic stromal lymphopoietin (TSLP) has emerged as an important factor in the pathogenesis of asthma, with higher concentrations of TSLP found in the lungs of asthmatics, correlating with increased Th2 responses and disease severity [2,3]. Further, multiple genome-wide association studies have identified TSLP as a susceptibility locus [4,5], and TSLP polymorphisms and single-nucleotide polymorphisms in the TSLP promoter in humans are associated with a higher risk of developing asthma [6-10], further strengthening data indicating a key role for TSLP the pathogenesis of this disease.

TSLP: Sources, Inducing Factors, and Mechanism of Signaling

TSLP is a short-chain four α -helical bundle type I cytokine that was initially isolated from a thymic stromal cell line supernatant and was determined to be a factor that supported the maturation of B cells [11]. Initially, TSLP primarily was thought to be a survival and maturation factor for B and T cells, but it has now been shown to act on a broad range of cell types including those implicated in the development of lung inflammation and asthma, such

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as dendritic cells (DCs), CD4⁺ T cells, eosinophils, basophils, mast cells, innate type II cells (Figure 1), as well as on CD8⁺ T cells, B cells, natural killer T cells and smooth muscle cells [11-13]. TSLP is most highly produced by epithelial and stromal cells lining the barrier surfaces of the skin, gut, and lungs; however, it has recently also been shown to be produced by other cell types implicated in asthma, including dendritic cells, mast cells, and basophils (Figure 1), and there are reports of its expression by smooth muscle cells as well [13,14]. Although TSLP is a member of the IL-2 family of cytokines and shares homology with IL-7, its receptor does not contain the common cytokine receptor γ cytokine chain that is common to the IL-2 family of cytokines, but instead the high affinity TSLP receptor is composed of the IL-7R α chain paired with a TSLP-specific receptor component, TSLPR. Unlike IL-7 signaling which utilizes JAK1 and JAK3 to activate STAT proteins, upon TSLP binding to its high affinity receptor, TSLPR recruits JAK2 and IL-7R α recruits JAK1, resulting in the activation of primarily STAT5A and STAT5B, as well as STAT1, STAT3, and other STAT proteins to a lesser extent, depending on the cell type [15,16].

Interestingly, TSLP can be induced by a variety of factors including the proinflammatory cytokines IL-1 and TNF- α in combination with other Th2 cytokines, commensals in the gut, bacterial and viral infections, Toll-like receptor or Nod2 signaling, and allergens [17]. NF- κ B has been shown to be an important mechanism of TSLP activation, and there are NF- κ B binding sites in the promoters of both the mouse and human TSLP gene [11]. In the context of lung responses TSLP has been shown to be induced by proteases that react with PAR-2 (including those found in common airborne fungal allergens) and by dsRNA produced by infections with viruses, such as Respiratory syncytial virus (RSV) and rhinovirus infection [1,11,18]. Further, recent studies have highlighted the fact that lung epithelial cells from asthmatics respond more strongly to dsRNA and produce more TSLP than cells from non-asthmatic patients [19,20]. This may help to explain why asthmatics tend to be more sensitive to lung viral infections than non-asthmatics [21]. In addition, uric acid is released in mouse lungs upon primary challenge with a common allergen, house dust mites, and is also found in the bronchoalveolar lavage fluid of asthmatic patients upon allergen challenge, resulting in an increase in TSLP and other Th2 cytokines in the lung. Thus, uric acid can also increase TSLP expression [22].

Recent studies have focused on not only understanding how TSLP influences CD4⁺ T cell Th2 immunity and disease progression but also have examined the broader role of TSLP in asthma pathogenesis by studying the action of TSLP on other cell types, including regulatory T cells and innate immune cells. Overall, these studies have elucidated the mechanism of TSLP action on asthma development and progression, by examining the interplay of multiple cell types. Moreover, they have provided a better understanding of the role of TSLP in the sequential progression of atopic diseases, a process termed the atopic march.

TSLP and Asthma

Early studies clearly established the importance of TSLP and Th2 cytokines in the development of asthma and other atopic diseases, such as the chronic inflammatory skin disease atopic dermatitis (AD). TSLP is highly expressed in human AD lesions [23], and overexpression of TSLP in mouse skin results in a spontaneous atopic dermatitis-like disease [24], whereas overexpression of TSLP in the lung, results in the development of severe airway inflammation and AHR [25]. Initially TSLP was shown to play a major role in pro-allergic responses by acting on dendritic cells (DCs). TSLP results in DC maturation and increased costimulatory expression, including upregulation of OX-40 ligand, thus allowing these DC to prime naïve CD4⁺ T cells to differentiate into proinflammatory Th2 cells expressing IL-4, IL-5, IL-13, and TNF- α [23,26]. The initial dogma was that TSLP

worked indirectly on CD4⁺ T cells through TSLP-induced DC maturation and subsequent T cell priming; however, subsequently the direct actions of TSLP on CD4⁺ T cells were appreciated. Using the well-established ovalbumin (OVA) model of inhaled antigen-induced allergic inflammation of the lung, it has been shown that mice lacking TSLPR expression, or mice given a neutralizing Fc-TSLPR fusion protein, fail to develop allergic inflammation, in contrast to wildtype (TSLPR sufficient) mice [25,27]. Additionally, transfer of wildtype CD4 T cells into these TSLPR-deficient mice re-establishes OVA-induced inflammation, emphasizing the importance of the direct actions of TSLP on CD4⁺ T cells [27]. Recently, however, the direct action of TSLP on DCs has re-emerged as even more intriguing in light of a recent report showing that DCs themselves can produce TSLP upon TLR stimulation, suggesting that TSLP may be able to act in an autocrine manner on DCs to further amplify the Th2 response [14•].

Recent studies have increased our understanding of the broad impact of TSLP, highlighting the role of TSLP on multiple cell types including regulatory T (Treg) cells, innate immune cells such as basophils, eosinophils, mast cells, and the newly identified innate type 2 cells [11,28]. TSLP has been shown to induce natural Treg cell development in the thymus, likely in a manner redundant with IL-7 [29,30]. However, less is understood about the effect of TSLP on antigen-induced pulmonary Treg cell development and function. The depletion of Treg cells during the sensitization phase of allergen-induced lung inflammation results in an exacerbation of inflammation, indicating that Treg cells may decrease asthma pathogenesis [31]. Recent studies have clarified the interplay of TSLP and Treg cells, illustrating that TSLP from the BAL of asthmatic patients can suppress the ability of healthy control pulmonary Tregs to make IL-10 and exert their suppressive activity [32]. Moreover, even low amounts of TSLP can suppress the development of *in vivo* allergen-specific Treg cells in mouse lungs and in *in vitro* human CD4 T cell cultures [32,33]. Thus, TSLP may suppress the development of tolerance to allergens in the lungs, while enhancing pro-inflammatory Th2 responses.

In addition to its effects on adaptive immune cells and dendritic cells, TSLP can act on multiple innate immune cells that play a role in Th2 immunity and asthma pathogenesis [11]. Asthma is characterized by increased innate immune cells responses, as the prototypical Th2-type cytokines influence basophil recruitment (GM-CSF and IL-3), eosinophil maturation, and survival (GM-CSF, IL-3 and IL-5), and mast cell differentiation and maturation (IL-3, IL-9 and IL-13) [1]. In the last few years, it has also been shown that TSLP can promote basophil responses [34], and that during an allergen-induced Th2 response, basophils can function as antigen-presenting cells [34-36]. Furthermore, TSLP can act directly on bone marrow progenitors to induce basophil hematopoiesis in an IL-3 independent manner [37•]. Therefore, TSLP plays an important role in basophil responses and may aid in Th2 responses by recruiting basophils that can act as APCs upon allergen challenge; however, these effects have yet to be determined in the context of asthma. In addition, TSLP can act on eosinophil and mast cells to increase their Th2-type cytokine production [38,39]. Recent data indicate that TSLP may also enhance the formation of bactericidal extracellular traps consisting of cytotoxic granule proteins and DNA, termed eosinophil extracellular traps, however, the function of these traps in asthma is not yet well understood [40]. Together, these data show that TSLP can affect innate immune cells, which may play a role in amplifying Th2 inflammation.

In addition to adaptive and traditional innate immune cell responses, the newly characterized innate type 2 cells have been implicated in playing a role in Th2-like response in lung inflammation [28]. In the last few years, multiple non-T non-B cells have been identified in mice that participate in allergic conditions and have been generally characterized as innate type 2 cells. There appear to be several human counterparts to these cells, so these cells may

play a role in human allergic diseases as well [28]. Although relatively little is known about the role of these cells in asthma, it is clear that one innate type 2 cell population, the nuocyte, is present during allergic lung inflammation and can induce airway hyper-responsiveness [41]; however, it is not yet known if TSLP plays a role in this process. Furthermore, another innate lymphocyte population called lung natural helper cells (LNH), can respond to IL-33 in combination with TSLP, IL-2, or IL-7 to produce IL-5 and IL-13, and LNH play a crucial role in protease allergen-induced inflammation [42•]. These data indicate that innate type 2 cells play a role in lung inflammation and that TSLP may be involved; therefore, it is important to determine the role of TSLP on these cells and their role in asthma.

TSLP and the Atopic March

Persons with one atopic disease have an increased probability of acquiring other atopic diseases, and often this progression follows a sequential path from atopic dermatitis to asthma or rhinitis, with approximately half or two-thirds of all AD patients progressing to develop asthma or allergic rhinitis, respectively [43,44]. TSLP has been shown to be involved in both AD and asthma, and recent studies have focused on understanding the role of TSLP in the atopic march. Previous studies have shown that overexpression of TSLP in the skin, achieved either by topical application of a vitamin D analog (MC903) or by targeting Notch signaling in the skin in genetically altered mice, coupled to antigen sensitization results in airway hyper-responsiveness upon allergen challenge in the lung [18,45]. These data suggest that TSLP may play a role in the atopic march (see Figure 2). In these earlier studies the methods used resulted in high systemic levels of TSLP, which are not normally present in patients with atopic dermatitis, but after intradermal injection of TSLP and OVA antigen, which resulted in AD-like symptoms but no detectable systemic TSLP, intranasal challenge with OVA induced lung inflammation and AHR, confirming a role for TSLP in the atopic march [46•]. Memory CD4⁺ T cells derived from the skin sensitization phase were the key mediators of this TSLP-induced response [46•], consistent with the key role previously shown for CD4⁺ T cells in the development of OVA-induced allergic lung inflammation [27] and the identification of functional TSLP receptors on mouse and human CD4⁺ T cells [47]. Interestingly, allergic asthma was blocked by oral antigen exposure as long as the oral exposure preceded skin sensitization. These data indicate that allergic asthma can result even without TSLP being expressed in the lung or systemically, and that once sensitization to the antigen occurs in the presence of TSLP, oral tolerance to the antigen can no longer be achieved [46•]. Whereas previous studies commonly used OVA as an allergen, a recent study has proven that TSLP plays a role in atopic march to a common natural aeroallergen, the house dust mite [48]. A more physiological model of atopic dermatitis, tape-stripping, was also used to recreate the reduced barrier function of the skin caused by dermal abrasion, which is often seen with AD patients upon scratching. Tape-stripping combined with OVA antigen administration on the skin resulted in increased TSLP production by keratinocytes and these mice developed asthma-like symptoms upon intranasal challenge with OVA [49]. Finally, when IL-13 was overexpressed in the skin of mice to induce AD, upon allergen sensitization and challenge, these animals develop asthma-like manifestations characterized by increased mucus production, Th2 responses, and AHR via a TSLP dependent mechanism [50]. Together, these data show that TSLP plays an integral role in the atopic march.

Conclusion

TSLP is a pleiotropic cytokine that is expressed at barrier surfaces, such as the lung, and plays an important role in allergic inflammation and asthma. Recent studies have increased our understanding of what stimuli induce TSLP production and have helped elucidate how

TSLP contributes to the development and progression of atopic diseases, such as asthma. Through its actions on both adaptive and innate immune cells, TSLP promotes and amplifies Th2 immunity, which can help shift the immune response to antigens/allergens away from tolerance towards that of a proinflammatory response. Furthermore, TSLP in the skin can drive atopic dermatitis upon allergen exposure and can promote asthma-like characteristics in mice upon inhaled (intranasal) allergen challenge, even without systemic levels of TSLP. These data highlight the important role of TSLP in atopic diseases and the atopic march. The recent appreciation of the importance of TSLP and other epithelial-derived cytokines, such as IL-33 and IL-25, in Th2 type responses have expanded the field by highlighting not only the role of adaptive immune cells, but also the contribution of stromal/epithelial cells and innate immune cells to Th2 responses in atopic diseases. Moreover, it appears that some of these epithelial-derived cytokines can cooperate and act on multiple cell types, as it is known that IL-25 can enhance the Th2 memory cell response initiated by TSLP-primed DCs, and that IL-33 and TSLP can act cooperatively on a subset of innate type 2 cells, lung natural helper (LNH) cells [42,51]. Thus, a better understanding of how these cytokines interact to help orchestrate allergic diseases is important. In addition, whereas innate type 2 cells have been shown to play an important role in Th2 responses to helminth infections, it is unknown how these cells contribute to asthma and other atopic diseases and whether TSLP may play a role, an area that warrants more research. Lastly, the role of microbes and viruses in lung inflammation and asthma is now better appreciated. Initially the lung was thought to be a relatively sterile environment, but over 2,000 bacterial genomes are found per square centimeter and there is evidence that there are differences in the microbial colonies of the airways of asthmatic patients compared to non-asthmatic patients [52]. This along with recent evidence that antibiotic treatment can exacerbate Th2 lung inflammation to house dust mite challenge [53•], indicate that commensal bacteria may play an important role in the lungs. In addition to bacterial stimuli, TSLP can also be induced by viral infection, such as rhinovirus infection, and rhinovirus infection early in life has been associated with increased risk of asthma later in life [1]. Elucidating whether there is a link between TSLP, rhinovirus, and asthma risk is important to better understand the initiation of asthma. Overall, while there are still many questions to answer, TSLP has proven to play an important role in the development of atopic diseases and in the atopic march, and provides a rational target for the therapy of allergic diseases and asthma.

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Cellular sources of TSLP	Cellular targets of TSLP	Actions
Epithelial Cells	Dendritic Cells	↑ Co-stimulatory molecules, Th2 priming
Fibroblasts	CD4 ⁺ T Cells	↑ Proliferation, Th2 differentiation
Dendritic Cells	Mast Cells	↑ Cytokine production
Basophils	Eosinophils	↑ Extracellular trap formation, cytokine production
	Basophils	↑ Expansion, cytokine production
	Treg Cells	↓ Suppressive activity
Mast Cells	Lung natural helper innate type 2 cells	↑ Th2 cytokine production (with IL-33)

Figure 1.

Sources and targets (direct and indirect) of TSLP in asthma/lung inflammation, including the actions of TSLP on these targets.

Figure 2.

The role of TSLP in the progression of atopic dermatitis to asthma. TSLP is induced in keratinocytes by dermal abrasion (tape-stripping), application of a vitamin D analog, inhibition of Notch signaling, or by TSLP overexpression. Primary exposure of antigen to the skin results in Th2 inflammation, antigen-specific CD4⁺ T cell activation and atopic dermatitis. Upon secondary exposure to antigen in the lung (right side of panel), CD4⁺ T cells previously primed in the skin induce Th2 inflammation, resulting in airway hyperresponsiveness. Other inflammatory cells, including DCs, basophils, mast cells, and fibroblasts are shown (see symbol scheme shown in Figure 1).