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The Role of Thymic Stromal Lymphopoietin (TSLP) in Allergic Disorders

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Summary

The importance of the epithelium in initiating and controlling immune responses is becoming more appreciated. For example, allergens contact first occurs at mucosal sites in exposed to the external environment such as the skin, airways and gastrointestinal tract. This exposure leads to the production of a variety of cytokines and chemokines that are involved in driving allergic inflammatory responses. One such product is thymic stromal lymphopoietin (TSLP). Recent studies, in both humans and mouse models, have implicated TSLP in the development and progression of atopy and atopic diseases. This review will discuss this work and place TSLP in the inflammatory cascade that leads to allergic disease.

Introduction

The atopic diseases consist of the triad of asthma, allergic rhinitis, and atopic dermatitis. These diseases share a common pathogenesis, involving inflammatory Th2-type cytokines and elevated IgE. Interestingly, they frequently present together in the same individual and family, suggesting common factors and mechanisms are involved in these diseases. Recent evidence has been accumulated to suggest that Th2-type CD4+ T cells play a triggering role in the activation and/or recruitment of IgE antibody-producing B cells, mast cells and eosinophils, i.e. the cellular triad involved in the allergic inflammation. However, the mechanisms underlying the preferential activation by environmental allergens of Th2 cells in atopic individuals still remain obscure.

One possible candidate for a factor involved in the initiation of allergic inflammatory responses is the cytokine thymic stromal lymphopoietin (TSLP). TSLP is expressed by epithelial cells, with the highest levels seen in lung and skin-derived epithelial cells[1]. Studies using human $CD11c^+$ dendritic cells showed that these cells produced CCL17 and CCL22 following exposure to TSLP, chemokines capable of attracting Th2-type $CD4^+$ T cells[1;2]. In addition, when $CD4^+$ T cells are primed on TSLP-treated DCs they take on an inflammatory Th2 phenotype, producing IL-4, IL-5, IL-13, and TNF-α upon restimulation[2]. Notably, lesional, but not unaffected, skin from patients with atopic dermatitis express high levels of TSLP. The DCs in the affected skin have left the epidermis and have acquired an activated phenotype.

TSLP Biology

Thymic stromal lymphopoietin (TSLP) is a member of the cytokine family, most closely related to IL-7. Identified in the culture supernatant of a mouse thymic stromal cell line, it was initially studied as a B cell growth factor [3;4]. In addition, several groups identified a TSLP-binding protein in the mouse, referred to as TSLPR, with sequence analysis showing that TSLPR was similar to the common cytokine receptor γ chain (γ_c) [5]. TSLPR was capable of binding TSLP with low affinity, and further analysis of the TSLP receptor complex showed that the high affinity, functional receptor included the IL-7Rα chain, further linking these cytokines. Subsequently, analysis of sequence databases was used to isolate clones of human TSLP and TSLPR[1;6]. The human and mouse proteins were found to be quite divergent at the sequence level, but, as will be discussed below, they are functionally similar.

Expression of the cytokine and receptor complex is similar between humans and mice. Epithelial cells at barrier surfaces were found to be the principle source of TSLP[23], although additional cell populations are capable of expressing the cytokine. The receptor is expressed broadly on a wide variety of hematopoietic lineage cell populations, including dendritic cells, monocyte/macrophages, B cells, T cells, basophils, and eosinophils[1;7]. However, expression is not limited to hematopoietic cells as structural cells have been shown to respond to TSLP *in vitro*[8].

Little is known as to the signaling pathways that are activated following engagement of the TSLP receptor complex. Initial studies in the mouse showed that Stat5 was activated, but in the absence of detectable Jak activation[4], making TSLPR unique among members of the hematopoietic receptor family. While several pathways and signaling molecules have been implicated in signaling downstream of the mouse TSLPR, including Src kinases and PI 3-K, direct evidence is lacking[9]. In the human, recent studies have shown that, in addition to STAT5, TSLP stimulation activated STAT 1,3,4,5, and 6, as well as JAKs 1 and 2[10]. One possible explanation for the discrepancy in the data between species is that the mouse signaling work used a pre-B cell line, while the human studies were in primary dendritic cells. Clearly, additional studies are required to reconcile these data.

TSLP and Allergic Disease

As described above, TSLP is a strong candidate to be a factor that mechanistically links allergic inflammatory diseases. As summarized below, much of the recent work on TSLP supports this role.

1. Atopic dermatitis

The association of TSLP with allergic disease first became apparent when Soumelis et al. [2] examined TSLP expression in the lesional skin of individuals with inflammatory skin disorders. They found that TSLP expression was significantly elevated in the epidermis of lesional skin from individuals with acute and chronic atopic dermatitis, but not in uninvolved skin or skin from patients with cutaneous lupus erythematous or nickel-induced dermatitis. Interestingly, cytokines that are found at high levels in lesional skin in these patients (IL-1β, TNFα, IL-4 and IL-13) can also synergize to induce TSLP expression by keratinocytes[11], suggesting a feed-forward inflammatory cascade. In addition, in mouse models, mutations that alter skin barrier function also induce TSLP expression, leading to the development of an AD-like skin disease[12].

More recently, it was shown that patients with Netherton syndrome (NS), a severe icthyosis in which affected individuals experience a significant predisposition for atopic disease[13],

have elevated levels of TSLP in their skin[14]. NS is caused by mutations in the serine protease inhibitior Kazal-type 5 (*SPINK5*) gene, which encodes the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI)[15]. LEKTI deficiency leads to dysregulation of the protease kallekrein 5, which in turn activates protease-activated receptor-2 (PAR-2). Activated PAR-2 has been shown to induce the expression of TSLP from either keratinocytes or airway epithelial cells[14;16]. Thus, a mutation that increases TSLP expression in the skin has direct consequences on the development of a severe atopic disease.

TSLP has also been associated with Th2-type skin inflammation in mouse models. Inducible expression of TSLP in the skin lead to the development of a spontaneous skin inflammatory disease with the hallmark features of AD[17]. In an antigen driven model of dermatitis that also uses barrier disruption via tape-stripping He et al.[18] found that TSLP signaling was required for development of skin inflammation. These studies used mice lacking TSLPR, and it was lack of TSLP signaling in CD4 T cells as they infiltrate the skin that appeared to be responsible for the lack of a response.

The role of TSLP in FITC-mediated contact hypersensitivity, a Th2-mediated model of human allergic contact dermatitis, has recently been elucidated. TSLP expression is induced following priming with FITC. The induction of TSLP gene expression is mediated by a component of the solvent used to dissolve the FITC, dibutyl phthalate[19–21]. TSLPR-deficient mice failed to mount a response following challenge, as did mice where TSLP was neutralized during both priming and challenge[19]. Blockade of TSLP during challenge alone partially reduced the response, suggesting that TSLP is required at both priming and challenge to generate a complete response[21]. Unlike the tape-stripping model, in this system a defect was found in skin resident dendritic cells in TSLPR-deficient mice. Antigen-bearing dendritic cells from $TSLPR^{-/-}$ mice displayed a migration defect as well as a reduced capacity to drive CD4 T cell proliferation[19]. TSLPR-deficient CD4 T cells were indistinguishable from their wild-type counterparts in their ability to proliferate and infiltrate the skin following FITC priming, suggesting that these cells do require direct TSLP responses to drive pathology in this model (SFZ and RP Larson, manuscript in preparation).

In addition to these transgenic and antigen-driven models of skin inflammation, TSLP has also been shown to be involved in 2 models using gene targeted mice. Mice that lack expression of the steroid receptors RXRα and RXRβ specifically in keratinocytes were shown to develop a TSLP-dependent AD-like disease[22]. In the second model, epidermal-specific ablation of the Notch1 and 2, or the Notch binding partner RBP-j, resulted in loss of skin barrier function and TSLP-driven skin inflammation[12;23]. While the mechanism by which TSLP was induced by loss of the Notch pathway is not known, these studies show that TSLP induction is a component of the cellular response to skin damage.

2. Asthma

The first association of TSLP with inflammation of the airways was demonstrated using mice expressing a TSLP transgene in the airway epithelium. These mice develop a spontaneous, progressive inflammatory disease with all the characteristics of human asthma[24]. The disease in these mice develops slowly over a three month period, based on adaptive responses to environmental antigens, and challenge at an early age with antigen leads to immediate onset of disease[24;25]. These data suggest that TSLP is functioning to condition the local environment to respond to aero-antigens. Consistent with the mouse data, several studies have now shown that human asthmatics have increased concentrations of TSLP in their lungs[26–28].

The most compelling evidence for the importance of TSLP in the development of airway inflammation comes from genetic studies using mice. TSLPR-deficient mice are resistant to the development of inflammation in the classical OVA plus Alum priming model in mice[24;29]. 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 restored aspects of the inflammatory disease [29]. Taken together with the data from TSLP overexpression in the lung, these data show that TSLP is both necessary and sufficient for the development of asthma-like airway inflammatory disease in mice.

Consistent with the 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 by airway epithelial cells. These factors include inflammatory cytokines present in asthmatic lungs (IL-1β, TNFα, IL-4, IL-13 and IL-25), fungal proteases[16], and respiratory viruses (MB Headley, H-C Lee, and SFZ, manuscript in preparation and [30–32]). The finding that respiratory syncytial virus infection can induce TSLP expression is especially interesting as it has been linked to both development of wheezing, and subsequent asthma, in infants and asthma exacerbations in affected individuals[33–36]. There is also genetic evidence of a link between TSLP and asthma as several genome wide studies have found polymorphisms in the TSLP gene associated with aspects of asthma in human populations[37–41].

3. TSLP and other allergic diseases

In addition to AD and asthma, elevated TSLP expression has been seen in a variety of other allergic inflammatory conditions. These include allergic rhinitis[42;43], food allergy[44], allergic conjunctivitis[45;46], and the response to a wide variety of allergens[47–50]. In addition, TSLP has been associated genetically with eosinophilic esophagitis, a Th2-type inflammatory disease of the esophagus[51;52].

4. TSLP and the atopic march

It has been well documented that atopic diseases present sequentially in humans, a phenomenon referred to as the atopic march[53]. Based on its role in allergic diseases in both skin and lung, TSLP is a prime candidate for a factor involved in this process. Two groups have recently published mouse models examining the possible role of skin-derived TSLP in airway inflammatory responses ([54;55]. Both studies showed that mice with TSLP-mediated AD-like disease showed exaggerated responses when challenged with allergen in the airways. Our group has similar data using the epidermal-specific inducible TSLP transgenic mice ([17] and H Han and SFZ, in preparation). However, a significant caveat in these animal models is the very high concentrations of circulating TSLP, which is not seen in individuals with AD. Thus, while an attractive hypothesis, it is not yet clear what role, if any, TSLP plays in the atopic march.

Conclusions

The role of TSLP in allergic inflammation is an area of intense investigation now. The data, as reviewed above, strongly suggests that TSLP plays a critical role in the induction of allergic disease. However, its potential role in disease progression is still somewhat unclear and will need to be elucidated. Equally important, what role TSLP plays in normal immune homeostasis remains to be determined. This point is critical in that it may determine whether TSLP blockade for the treatment of allergic diseases will be tolerated. Finally, it is now becoming clear that TSLP acts in concert with two other cytokines, IL-17E/IL-25 and IL-33, to drive Th2-type inflammation. Deciphering how these cytokines “talk” to each other, and how they are individually and collectively regulated, is critical.

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