

REVIEW

The role of thymic stromal lymphopoietin in the immunopathogenesis of atopic dermatitis

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Summary

Atopic dermatitis (AD), a skin disease characterized by pruritus and chronic inflammation, results from a complex interplay between environmental and genetic factors. Thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine, is believed to propagate AD lesions through T helper 2 (Th2) polarization. This paper describes the immunologic mechanisms involving TSLP in the generation of allergic disease. Specifically in AD, TSLP has been shown to be an inducer of myeloid dendritic cells, Th2 responses, mast cells, and natural killer T cells, thereby leading to cytokine secretion and the development of AD. We hope that further understanding of the TSLP pathway and its role in the pathogenesis of AD will lead to improved clinical management of AD in the future.

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Introduction

The prevalence of atopic dermatitis (AD), otherwise known as eczema, has increased in Western and industrialized countries over the last 30 years while even afflicting up to 10–20% of young children [1]. AD is characterized by a pruritic rash occurring on distinct regions of the body (e.g. cheeks, scalp, flexural surfaces, and neck) with involvement usually determined by age of onset. Chronic itching can result in lichenification and hyper/hypopigmentation of the skin. An inflammatory skin disorder that is driven by T helper 2 (Th2) cell polarization, AD has been linked to genetic, environmental, and lifestyle factors [2].

Proposed mechanisms for the development of AD have focused upon epithelial barrier dysfunction and immune dysregulation. An altered skin barrier allows for increased transepidermal uptake of environmental allergens and water loss, leading to dry skin and local inflammation [3, 4]. Alterations in certain epithelial barrier genes have been connected to AD. The filaggrin (FLG) gene, which encodes a major protein involved in epidermal differentiation, contributes to keratin scaffolding. FLG's products are even-

tually degraded to aid in the water-binding capacity of the stratum corneum [5]. Mutations in FLG have been identified in Japanese and European patients with AD and ichthyosis vulgaris. Both conditions are similarly characterized by scaly and dry skin [6]. Furthermore, a model of FLG deficiency in human keratinocytes demonstrated increased thymic stromal lymphopoietin (TSLP) expression [7].

Another hypothesis regarding AD pathogenesis suggests that specific immunologic disturbances result in IgE-mediated sensitization [8, 9]. Patients with severe AD have been found to have IgE antibodies not only against food and aeroallergens, but also to proteins from keratinocytes and endothelial cells [10]. It has been proposed by Bieber [1] that AD occurs in three phases, each with distinct immunologic sequelae. The initial phase occurs in infancy and is usually characterized by non-atopic, or non-IgE-associated, dermatitis, even though auto-IgE antibodies have been detected in AD patients as young as 1-year old. This stage is then followed by the induction of IgE-mediated sensitization to allergens, and is mediated by genetic factors. This second phase occurs in 60–80% of the original patients who developed non-atopic dermatitis and represents the transition to true AD. The third phase consists of IgE autoantibody induction, which is

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triggered by the release of autoantigens from keratinocytes due to scratching. In general, the serum level of IgE autoantibodies often correlates with disease severity [11]. A quarter of adults who have AD demonstrate IgE autoantibodies, elevated serum IgE levels, increased pruritus, and susceptibility to bacterial skin infections [12].

Dendritic cells (DCs) are key players in the immunologic cascade that contributes to AD lesions. In AD, both Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) bear IgE and express high levels of the corresponding receptor, Fc epsilon receptor I (FcεRI) [13, 14]. By penetrating the dysfunctional epidermal barrier that characterizes AD, environmental, food, and microbial allergens facilitate DC-mediated activation of distinct Th-associated pathways. DCs uptake and collectively present allergens to Th1 and Th2 cells [15]. In the acute phase of AD, allergens stimulate LCs through FcεRI binding, and activated LCs then play a key role in Th2 polarization with an associated predominance of IL-4, IL-5, and IL-13. LCs also stimulate the production of monocyte chemoattractant protein 1 and IL-16, which recruit CD4⁺ T cells to the skin [16, 17]. Recruited monocytes undergo differentiation and become IDECs, which produce the pro-inflammatory Th1-related cytokines IL-12 and IL-18 [18]. The chronic phase of AD is characterized by the switch from Th2 to Th1 or Th0 cells (i.e. Th0 cells can differentiate into Th1 or Th2 cells) through which there is a subsequent increase in the production of IFN-γ, IL-5, IL-12, and granulocyte-macrophage colony-stimulating factor [19]. IFN-γ plays a role in the activation of keratinocyte apoptosis [20].

TSLP is recognized as the master switch for AD and other atopic diseases, such as asthma, as it has been shown to induce Th2-type allergic inflammation via activation of DCs and mast cells [21]. This key role of TSLP serves as a potential target for the treatment of AD. This paper reviews: the immunologic roles of TSLP in allergic diseases, particularly AD; key areas of research that may further elucidate TSLP-related pathways; and potential immunologic targets in the treatment of AD.

Immunologic roles of thymic stromal lymphopoietin

TSLP participates in the allergic cascade via activation of DCs, natural killer T (NKT) cells, and mast cells and by stimulation of downstream Th2-related cytokine production [22] (Fig. 1). Originally cloned from a murine thymic stromal cell line in 2001, TSLP is an IL-7-like cytokine, and binds to a heterodimeric receptor comprised of the IL-7 receptor α-chain (IL-7Rα) and the TSLP receptor (TSLPR) chain [23]. Mainly expressed by skin keratinocytes and epithelial cells, TSLP activates myeloid DCs, which subsequently induce the proliferation of naïve CD4⁺ T cells. These CD4⁺ T cells then differentiate into Th2 cells that produce the Th2 cytokines IL-4, IL-5, and IL-13 in addition

to TNF-α, but minimal or absent IL-10 production [24, 25]. TSLP expression in keratinocytes may be induced by several factors including mechanical injury and ligands (e.g. flagellin, *Staphylococcus aureus* membrane, and diacylated lipoproteins) through distinct Toll-like receptor (TLR)-mediated pathways [26–28]. In a murine model, He et al. [23] demonstrated that TSLP can trigger the Th2 differentiation pathway by direct action on CD4⁺ T cells. Thus, TSLP can either directly or indirectly activate T cells through DC stimulation.

The mechanism underlying TSLP activation of DCs is currently unclear, although TSLP may activate a pathway that is independent of nuclear factor κB and TLR adaptor protein MyD88, which are both necessary for Th1 differentiation [29]. When TSLP binds with its receptor complex consisting of IL-7Rα and TSLPR, phosphorylation of signal transducer and activator of transcription (STAT) 3 and STAT 5 occurs. TSLP fails to activate Janus kinase (JAK) 1 and JAK 3, but may interact with JAK 2 [21, 30, 31]. Interestingly, TSLPR deficiency has been associated with attenuated IL-13-induced skin inflammation in AD patients. Furthermore, peroxisome proliferator-activated receptor γ negatively regulates TSLP-stimulated DCs, and prevents AD onset in murine models [32]. These findings illustrate the allergy-inducing properties of TSLP, although much remains to be elucidated regarding additional TSLP-associated receptors, specific transcription factors, kinases, and cytokines involved.

TSLP is further involved in the immunologic cascade since the differentiation of CD4⁺ T cells into inflammatory Th2 cells is partly driven by the expression of OX40 ligand (OX40L) on TSLP-activated DCs (TSLP-DCs). As demonstrated by Liu [33], neutralizing antibodies against OX40L decreased the secretion of Th2 cytokines and TNF and increased the CD4⁺T cell-mediated production of IL-10. Moreover, anti-OX40L strongly inhibits the production of IL-4, IL-5, and IL-13, and may promote a Th1 response [34]. The OX40L facilitation of Th2 cell differentiation is dependent upon the absence of IL-12; therefore, a relative lack of IL-12 production may be one of the basic underlying mechanisms in atopy [35]. The regulatory control of IL-12 over OX40L may help explain the hygiene hypothesis, which states that early exposure to infections that trigger Th1 responses may induce autoimmunity and prevent the development of Th2-driven atopy [33].

Thymic stromal lymphopoietin and allergic diseases

Along with its proposed role in AD, TSLP has been implicated in asthma and allergic rhinitis (AR). TSLP is highly expressed by bronchial epithelial cells in asthma patients [36–38]. Al-Shami et al. [39] suggested that TSLPR knockout mice fail to mount a Th2-mediated inflammatory lung response to inhaled antigen. Instead, these mice exhibit strong Th1 responses, with high levels of IL-12, IFN-γ, and

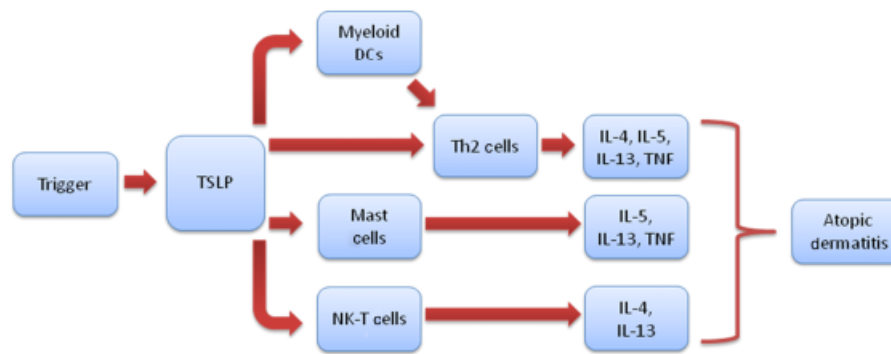


Fig. 1. Thymic stromal lymphopoietin (TSLP)-associated allergic cascade [45, 53, 54]. DCs, dendritic cells; NK, natural killer.

Table 1. Studies connecting thymic stromal lymphopoietin (TSLP) and atopic dermatitis

Study	Conclusion
Human studies	
Soumelis et al. [25]	TSLP is highly expressed in keratinocytes and activated dendritic cells leading to production of proallergic cytokines
Lee et al. [50]	Serum TSLP levels higher in children with AD than in controls
Wu et al. [45]	TSLP in severe lesional AD skin stimulates NKT cells to secrete Th2 cytokines
Gao et al. [52]	Association between TSLP markers/receptors and risk of AD
Le et al. [26]	Flagellin, a major protein of gram-negative bacteria, induces TSLP expression in keratinocytes leading to Th2-type skin inflammation
Vu et al. [28]	<i>Staphylococcus aureus</i> stimulates Th2 inflammation in keratinocytes via TSLP
Alysandratos et al. [51]	TSLP gene expression increased in AD skin lesions than in controls
Murine studies	
Yoo et al. [44]	Overexpression of TSLP in a murine model resulted in the development of AD
Li et al. [46]	Selective ablation of retinoid X receptors (RXRs) in epidermal keratinocytes triggered AD in mice. These keratinocytes had a rapid induction of TSLP expression
Seshasayee et al. [34]	Anti-OX40L slows the production of IL-4, IL-5, and IL-13, and may promote a Th1 response
He et al. [23]	Anti-TSLP prevented the development of allergic inflammation following antigen challenge
Zheng et al. [48]	IL-13 induces TSLP expression in the skin and both are increased in AD-like inflammatory skin lesions
Oyoshi et al. [27]	Mechanical damage upregulates TSLP leading to Th2 response
Jung et al. [32]	PPAR γ can be provided as an inhibitory regulator of TSLP-stimulated DCs in a murine model of AD

AD, atopic dermatitis; DCs, dendritic cells; NK, natural killer; PPAR, peroxisome proliferator-activated receptor.

IgG2a, with corresponding decreases of IL-4, IL-5, IL-10, IL-13, and IgE [39]. TSLP has also been shown to stimulate human bronchial epithelial cell proliferation and injury repair through IL-13-dependent mechanisms [40]. Interestingly, distinct single nucleotide polymorphisms in the TSLP gene have been linked to a decreased risk for asthma in a gender-specific manner [41].

In support of the hypothesis that TSLP plays a significant role in the development of AR, Mou et al. [42] demonstrated that the mRNA and protein expression of TSLP are increased significantly in AR-affected human nasal mucosa compared with unaffected controls. Miyata et al. [43] have postulated that mast cells may regulate epithelial TSLP expression in AR, and mice treated with anti-TSLP neutralizing antibody have significantly reduced nasal submucosal leucocyte infiltration and goblet cells. These findings highlight the key role of TSLP in allergic inflammatory responses.

TSLP is a key player in the innate and adaptive immune mechanisms underlying the development of atopic diseases such as AD, asthma, and AR. *In vivo*, TSLP has been associated with LC migration and activation, which suggests that TSLP is an early trigger of DC-mediated allergic inflammation [33] (Table 1). Yoo et al. [44] demonstrated that overexpression of TSLP in a murine model resulted in the development of AD characterized by inflammatory cell infiltrates within eczematous lesions, an increase in serum Th2 CD4⁺ T cells, and elevated serum IgE. It has been similarly shown that TSLP in severe lesional AD skin stimulates NKT cells to secrete Th2 cytokines [45]. An additional study demonstrated that skin keratinocytes that lack retinoid X receptors (RXRs) experience a rapid induction of TSLP expression, and selective ablation of RXRs in epidermal keratinocytes has been associated with AD in mice [46]. Similarly, topical application of the vitamin D receptor ligand calcitriol or the analogous calcipotriol has been shown to induce TSLP expression in epidermal keratinocytes, thereby resulting in an AD-like condition in mice [47].

Several ILs have been linked to mechanisms surrounding TSLP and AD. As suggested by Zheng et al. [48], IL-13 induces TSLP expression in the skin and both IL-13 and TSLP are increased in AD-like inflammatory skin lesions. IL-25 levels are similarly increased in AD skin lesions, and IL-25 stimulates the expansion of TSLP-DC-activated Th2 memory cells [49]. Furthermore, serum TSLP levels are increased in children with AD, whereby lesional AD skin demonstrates increased TSLP gene expression [50, 51].

Summary and future directions

The link between TSLP and atopic diseases has been validated by a growing body of evidence, although details of this connection are still unclear. The types of triggers leading to TSLP expression remain to be elucidated, along with the possible roles played by allergen, pollutant, and viral exposures in TSLP expression. As Gao et al. [52] recently suggested, distinct TSLP polymorphisms may predispose towards the development of AD or eczema herpeticum, which is a potential complication of AD. Because TSLP contributes to the development of a Th2-polarized environment, further studies should be per-

formed to determine whether TSLP plays a role in chronic AD, which may be characterized by a Th1/Th0 environment. Perhaps there is an on/off functionality of TSLP expression in acute chronic AD, and more studies are necessary to determine whether targeted therapies could help prevent the progression of disease. Additional analysis will also help to elucidate the role of TSLP in other allergic skin diseases (e.g. chronic urticaria, contact hypersensitivity), as well as gender-specific associations between TSLP polymorphisms and atopic manifestations.

To date, the mainstay of therapy for AD includes moisturization, topical and systemic corticosteroids, and topical calcineurin inhibitors. Relatively few data exist for immunologic therapies such as chemokine receptor antagonists, IgE monoclonal antibodies, or recombinant IFN- γ . Promising findings include the utilization of a blocking antibody targeted against OX40L and consequent inhibition of TSLP expression and TSLP-mediated inflammation [34]. As additional cytokines and inflammatory response elements are linked to the TSLP-mediated cascade related to AD, there will be an increased number of targets upon which immunologic therapies will be able to act and treat AD.

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