

Epidermal TSLP: a trigger factor for pathogenesis of atopic dermatitis

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“It is possible that the higher expression of thymic stromal lymphopoietin observed in the skin lesions of atopic dermatitis patients could be causally related to atopic dermatitis pathogenesis.”

Atopic dermatitis (AD) is a common allergic inflammatory skin disease that affects 10–20% of infants, besides 3–5% of adults, and is often linked with family history of allergic disease [1]. It is characterized by strongly itchy and inflamed skin and chronic lichenified, more scaly plaques. Atopic dermatitis, asthma and allergic rhinitis form an ‘atopic triad’ and share a common pathogenesis, involving a Th2 cell-mediated allergic inflammation. This inflammation is characterized by secretion of cytokines (IL-4, IL-5, IL-13, and TNF- α) by CD4⁺ T cells, which trigger increased IgE antibody production by B cells; IgE binding to mast cells facilitates initiation of allergic reactions and drives infiltration of leucocytes into the skin dermis (see [2], and the references therein). Homing dendritic cells (DCs) control polarization of naive CD4⁺ T cells to differentiate into Th2 lymphocytes. However, the initiating factor(s) that influences these important antigen-presenting cells to instruct T-helper cell polarization toward this inflammatory phenotype, and the mechanisms underlying the preferential activation of Th2 cells in atopic individuals by external allergens is poorly understood.

Thymic stromal lymphopoietin–thymic stromal lymphopoietin receptor signaling

Thymic stromal lymphopoietin (TSLP) is a cytokine and a candidate protein engaged

in the initiation, development and progression of atopy and related diseases both in mice and in humans. TSLP is a member of the cytokine family, most closely related to IL-7. It was discovered in the supernatants of a mouse thymic stromal cell line, and it was originally characterized by its ability to promote the activation of B lymphocytes and myeloid DCs [3,4]. A TSLP-binding protein identified in mouse, referred to as ‘TSLP receptor’ (TSLPR), has a sequence similarity to the common cytokine receptor γ chain [5]. Thymic stromal lymphopoietin receptor binds to TSLP with low affinity, and the functional, high-affinity TSLPR complex is a heterodimer of TSLPR and IL-7 receptor- α (IL-7R α) [5,6]. Subsequently, bioinformatics analysis led to the isolation of human TSLP and TSLPR [7,8]. Although the human and mouse proteins are quite divergent at the sequence level (~40% homology), they are functionally similar. In mouse, receptor-mediated activation of the STAT5 transcription factor occurs without involvement and activation of the JAKs by the intact receptor complex [4]. By contrast, in humans, TSLP stimulation activates STAT 1, 3, 4, 5 and 6, as well as JAKs 1 and 2 [9]. Additional studies are necessary to resolve the discrepancy between the studies in mice and humans.

Human CD11c⁺ DCs produced CCL17 and CCL22 following exposure to TSLP, which are capable of attracting Th2-type CD4⁺ T cells [8,10]. In addition, when naive

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CD4⁺ T cells were exposed to TSLP-treated DCs, they underwent extensive proliferation and differentiation into Th2 lymphocytes and acquired an inflammatory Th2 phenotype, producing IL-4, IL-5, IL-13 and TNF- α upon restimulation [10]. Besides influencing the differentiation of CD4⁺ Th2 cells potentially via DCs and/or basophils, TSLP can directly promote Th2 cell differentiation of naive T cells. It can also co-stimulate the activation of both mast cells and natural killer T cells, thereby increasing cytokine production. Overall, TSLP can promote Th2 cell differentiation and Th2 cell-mediated inflammation noted in inflammatory disorders (AD, asthma and allergic rhinitis) through DCs, granulocytes, natural killer T cells or directly acting on CD4⁺ T cells.

TSLP & atopic dermatitis

TSLP is expressed by epithelial cells at barrier surfaces of the skin, lung and gut in both mice and humans [8]. By contrast, the receptor complex is expressed in wide variety of hematopoietic cells such as CD11c⁺ DCs, monocyte/macrophages, B cells, T cells, basophils and eosinophils, with highest expression of TSLPR and IL-7R α in DCs [8].

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TSLP expression is higher in the epidermis of the lesional skin in AD patients compared to those of the uninvolved skin, skin from nonallergic dermatitis patients or from cutaneous lupus erythematosus patients [10]. The DCs in the affected skin acquire an activated phenotype, leave the epidermis and migrate toward the draining lymph node, consistent with a role for TSLP in the regulation of tissue-resident DC responses. Proinflammatory (TNF- α or IL-1 α) and Th2 (IL-4 or IL-13) cytokines that are also expressed in the AD skin lesions are known to induce production of TSLP expression by human keratinocytes synergistically [11]. Results suggest the existence of a positive feed-forward loop of inflammatory cascade toward AD pathogenesis. In addition, mutations causing impaired epidermal permeability barrier formation and altered skin barrier functions in mice models can induce TSLP expression in skin epidermis. That has been associated with onset of Th2-type skin inflammation and AD-like skin disease [12,13].

Patients with Netherton syndrome, a genetic skin disease with massive atopic manifestations (recurrent AD, higher IgE levels, asthma and multiple food allergies [14]), have elevated levels of TSLP in their skin [15]. Mutations in the serine protease inhibitor Kazal-type 5 gene encoding the protease inhibitor lymphoepithelial Kazal-type-related inhibitor is the principal cause of NS [16]. Lymphoepithelial Kazal-type-related inhibitor deficiency leads to the deregulation of the protease kallikrein-5 and further activates protease-activated receptor-2. Activated protease-activated receptor-2 induces expression of TSLP from keratinocytes [15]. Thus, induction of TSLP expression in skin due to specific genetic mutation(s) can lead to the development of chronic AD.

Transgenic mice driving inducible expression of TSLP in the epidermis of skin exhibit spontaneous development of a skin inflammation with characteristic features of human AD [17]. These include dermal infiltrates containing lymphocytes, mast cells and eosinophils, an increase in Th2 cytokines in the affected skin and elevated circulating levels of IgE. Barrier disruption by tape-stripping followed by antigen sensitization with ovalbumin resulted in abrogated Th2 cytokine expression by the infiltrating CD4⁺ T cells and impaired allergic skin inflammation in TSLPR-null mice [18]. Also, antibody-mediated neutralization of TSLP blocked the development of allergic skin inflammation after antigen challenge of ovalbumin immunization of wild-type mice [18]. Similarly, TSLPR-null mice demonstrated significantly reduced Th2-type contact hypersensitivity after challenge with hapten (FITC) in combination with dibutyl phthalate as a sensitizing agent [19]. These mice exhibited defects in maturation and migration of DCs and reduced capacity of DCs to drive CD4⁺ T-cell proliferation. Cutaneous infiltration of eosinophils, Th2 cytokine production and serum IgE levels were all reduced in the TSLP-null mice after hapten sensitization and challenge [19].

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In addition, TSLP's role in skin inflammation has been shown in different genetically engineered animal models. First, mice lacking steroid hormone receptors *RXR α* and *RXR β* selectively in keratinocytes develop a TSLP-dependent AD-like skin disease [20]. Second, epidermal specific deletion of the Notch 1 and 2 or the Notch binding partner RBP-j compromised epidermal permeability barrier functions and induced TSLP-driven skin inflammation (see [12], and references therein). Although the mechanisms underlying TSLP induction following loss of the Notch signaling pathway is unknown, studies indicate that TSLP induction is an integral part of the cellular response to skin damage. Recently, selective ablation of transcription regulator CTIP2 (also known as BCL11b) in the epidermal keratinocytes triggered a human-AD-like skin inflammatory phenotype characterized by high-level expression of Th2-type cytokines/chemokines (IL-4, IL-13, CCL17 and TSLP) and elevated plasma concentration of IgE [13]. In the epidermis of *Ctip2*-mutant mice, TSLP was induced approximately 30-fold at postnatal day 1 and remained significantly higher at all later time points after birth. Furthermore, CTIP2 was recruited on the proximal promoter of TSLP, suggesting a possible direct regulation of TSLP by CTIP2. The above results underscore the role of epidermal TSLP in inducing Th2 cytokine-associated inflammation and AD pathogenesis. It is possible that the higher expression of TSLP observed in the skin lesions of AD patients could be causally related to AD-pathogenesis.

Conclusion

Studies in mice and humans have clearly established TSLP secreted by epidermal keratinocytes as a key cytokine to trigger the Th2 cytokine-associated inflammation in atopic diseases consisting of the triad of AD, asthma and allergic rhinitis. Polymorphisms in TSLP have been associated with atopic disease including asthma and allergic rhinitis. The mechanisms underlying the regulation of TSLP expression in skin is poorly understood and need to be further investigated. Similarly, it is important to establish the role of TSLP in other proliferative skin diseases and skin cancer. Therefore, targeting the TSLP–TSLPR signaling axis via pharmacological inhibition or by antibody-mediated neutralization of TSLP could be a beneficial tool to prevent and possibly treat specific AD subtypes with elevated TSLP and associated allergic inflammation.

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