Published in final edited form as:
Expert Rev Proteomics. 2013 August ; 10(4): 309–311. doi:10.1586/14789450.2013.814881.

Epidermal TSLP: A trigger factor for pathogenesis of Atopic Dermatitis (AD)

Arup K. Indra[1,2,3]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, Oregon State University, Corvallis, Oregon 97331, USA

[2]Molecular and Cellular Biology Program, Oregon State University, Corvallis, Oregon 97331, USA

[3]Dermatology Research Division, Oregon Health and Science University, Portland, Oregon 97239, USA

Introduction

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 strong itchy and inflamed skin and chronic lichenified, more scaly plaques. AD, asthma and allergic rhinitis forms an “atopic triad” and share a common pathogenesis, involving a T helper type 2 (Th2) cell–mediated allergic inflammation. This inflammation is characterized by secretion of cytokines (IL-4, IL-5, IL-13, and TNFα) 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 {[2], and refs therein}. Homing dendritic cells (DCs) control polarization of naive CD4+ T-cells to differentiate into Th2 lymphocytes. However, the initiating factor(s) that influence 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.

TSLP-TSLPR signaling

Cytokine thymic stromal lymphopoietin (TSLP) is a possible candidate protein involved in the initiation, development and progression of atopy and atopic diseases both in mice and in humans. TSLP is a member of the cytokine family, most closely related to interleukin 7 (IL-7). Identified in the cultured supernatant 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 (γc) [5]. TSLPR binds to TSLP with low affinity, and the functional, high affinity TSLPR complex is a heterodimer of TSLPR and interleukin 7 receptor-α (IL-7Rα) [5,6]. Subsequently, bioinformatics analysis was used to isolate 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 engagement activated the STAT5 transcription factor; however, no JAK kinases are activated by the intact receptor

complex [4]. In contrast in humans, TSLP stimulation activated 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 naïve CD4+ T cells are 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 is capable of directly promoting Th2 cell differentiation of naive T-cells. TSLP can also co-stimulate the activation of both mast cells and natural killer T (NKT) cells, which results in increased cytokine production. Altogether, these data suggest that TSLP, through DCs, granulocytes, NKT cells or directly on $CD4^+$ T-cells, can promote Th2 cell differentiation and Th2 cytokine–associated inflammation, observed in many inflammatory diseases including AD, asthma and allergic rhinitis.

TSLP and Atopic dermatitis

TSLP is expressed by epithelial cells at barrier surfaces of the skin, lung and gut [8]. Expression of the cytokine and receptor complex is similar between humans and mice. The receptor is expressed broadly on a wide variety of hematopoietic lineage cell populations, including CD11c+ DCs, monocyte/macrophages, B-cells, T-cells, basophils, and eosinophils. The cell populations with the highest known coexpression of TSLPR and IL-7Rα are DCs [8].

The epidermis of lesional skin in patients with allergic forms of dermatitis e.g. AD has higher TSLP expression than that of epidermis in uninvolved skin or skin from patients with nonallergic dermatitis or cutaneous lupus erythematous [10] The DCs in the affected skin acquires 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. 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 loop of inflammatory wave. In addition, in mouse models, mutations that disrupt skin barrier functions also induce TSLP expression, leading to the development of an AD-like skin disease[12,13].

Patients with Netherton syndrome (NS), 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]. NS is caused by mutations in the serine protease inhibitor Kazal-type 5 (*SPINK5*) gene, which encodes the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI) [16]. Dysregulation of the protease Kallikrein-5 due to LEKTI deficiency further activates protease-activated receptor-2 (PAR-2). Activated PAR-2 induces expression of TSLP from keratinocytes [15]. 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 epidermis drives development of a spontaneous skin inflammatory disease with the hallmark/characteristics 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. In an antigen-sensitized model of dermatitis that also uses barrier disruption via tape stripping, TSLP signaling was required for development of skin inflammation [18]. These studies used mice lacking TSLPR, and it was failure to express Th2 cytokines locally by CD4+ T-cells as they infiltrate the skin, appeared to be responsible for impaired allergic skin inflammation. TSLPR-null mice failed to demonstrate a response following hapten challenge, as did mice where TSLP was neutralized during both priming and challenge [19]. Antigen bearing DCs from TSLPR-null mice manifested defects in maturation, migration and reduced capacity to drive CD4+ T cell proliferation [19].

In addition, TSLP role in skin inflammation has been shown in different genetically engineered animal models. First, mice lacking steroid hormone receptors RXRα and RXRβ selectively in keratinocytes develop a TSLP-dependent AD-like skin disease [20]. Second, epidermal specific deletion of the Notch1 and 2, or the Notch binding partner RBP-j, compromised epidermal permeability barrier functions and induced TSLP-driven skin inflammation {[12]; and refs. 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 COUP-TF-interacting protein 2 (CTIP2; also known as BCL11b) in the epidermal keratinocytes, triggered an human-AD like skin inflammatory phenotype characterized by high levels 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 ~30-fold at postnatal day 1 (P1) 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. Altogether, these models demonstrate that increasing TSLP concentrations in the epidermis induces the onset of Th2 cytokine–associated inflammation, which suggests that the higher expression of TSLP in the lesional skin of AD patients could be causally related to disease pathogenesis and is not a consequence of the disease.

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. They share a common pathogenesis and, frequently present together in the same person and family, indicating involvement of common factors and mechanisms. Higher expression of TSLP in the inflamed tissue is another common feature of these diseases [10]. Genetic analysis has also linked polymorphisms in *TSLP* with different aspects of atopic allergic disease, including asthma and airway hypersensitivity. Therefore, targeting 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.

Acknowledgments

We sincerely thank Dr. Gitali Ganguli-Indra for critical reading of the manuscript. The studies on Ctip2/Bcl11b were supported by grant AR056008 from NIAMS, a NIEHS Center grant (ES00210) to OSU Environmental Health Sciences Center, and the OHSU Knight Cancer Institute Research Core Services Grant P30CA69533. We thank Drs. Mark Zabriskie Gary DeLander and Mark Leid of the OSU/OHSU College of Pharmacy for continuous support and encouragement.

References

1. Simon D, Kernland Lang K. Atopic dermatitis: from new pathogenic insights toward a barrier-restoring and anti-inflammatory therapy. Current opinion in pediatrics. 2011; 23(6):647–652. [PubMed: 21970829]
2. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. The Journal of clinical investigation. 2004; 113(5):651–657. [PubMed: 14991059]
3. Friend SL, Hosier S, Nelson A, Foxworthe D, Williams DE, Farr A. A thymic stromal cell line supports in vitro development of surface IgM+ B cells and produces a novel growth factor affecting B and T lineage cells. Experimental hematology. 1994; 22(3):321–328. [PubMed: 8112430]
4. Levin SD, Koelling RM, Friend SL, et al. Thymic stromal lymphopoietin: a cytokine that promotes the development of IgM+ B cells in vitro and signals via a novel mechanism. Journal of immunology. 1999; 162(2):677–683.
5. Pandey A, Ozaki K, Baumann H, et al. Cloning of a receptor subunit required for signaling by thymic stromal lymphopoietin. Nature immunology. 2000; 1(1):59–64. [PubMed: 10881176]
6. Park LS, Martin U, Garka K, et al. Cloning of the murine thymic stromal lymphopoietin (TSLP) receptor: Formation of a functional heteromeric complex requires interleukin 7 receptor. The Journal of experimental medicine. 2000; 192(5):659–670. [PubMed: 10974032]
7. Quentmeier H, Drexler HG, Fleckenstein D, et al. Cloning of human thymic stromal lymphopoietin (TSLP) and signaling mechanisms leading to proliferation. Leukemia. 2001; 15(8):1286–1292. [PubMed: 11480573]
8. Reche PA, Soumelis V, Gorman DM, et al. Human thymic stromal lymphopoietin preferentially stimulates myeloid cells. Journal of immunology. 2001; 167(1):336–343.
9. Arima K, Watanabe N, Hanabuchi S, Chang M, Sun SC, Liu YJ. Distinct signal codes generate dendritic cell functional plasticity. Science signaling. 2010; 3(105):ra4. [PubMed: 20086239]
10. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. Nature immunology. 2002; 3(7):673–680. [PubMed: 12055625]
11. Bogiatzi SI, Fernandez I, Bichet JC, et al. Cutting Edge: Proinflammatory and Th2 cytokines synergize to induce thymic stromal lymphopoietin production by human skin keratinocytes. Journal of immunology. 2007; 178(6):3373–3377.
12. Dumortier A, Durham AD, Di Piazza M, et al. Atopic dermatitis-like disease and associated lethal myeloproliferative disorder arise from loss of Notch signaling in the murine skin. PloS one. 2010; 5(2):e9258. [PubMed: 20174635]
13. Wang Z, Zhang LJ, Guha G, et al. Selective ablation of Ctip2/Bcl11b in epidermal keratinocytes triggers atopic dermatitis-like skin inflammatory responses in adult mice. PloS one. 2012; 7(12):e51262. [PubMed: 23284675]
14. Judge MR, Morgan G, Harper JI. A clinical and immunological study of Netherton's syndrome. The British journal of dermatology. 1994; 131(5):615–621. [PubMed: 7999590]
15. Briot A, Deraison C, Lacroix M, et al. Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. The Journal of experimental medicine. 2009; 206(5):1135–1147. [PubMed: 19414552]

16. Chavanas S, Bodemer C, Rochat A, et al. Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. Nature genetics. 2000; 25(2):141–142. [PubMed: 10835624]

17. Yoo J, Omori M, Gyarmati D, et al. Spontaneous atopic dermatitis in mice expressing an inducible thymic stromal lymphopoietin transgene specifically in the skin. The Journal of experimental medicine. 2005; 202(4):541–549. [PubMed: 16103410]

18. He R, Oyoshi MK, Garibyan L, Kumar L, Ziegler SF, Geha RS. TSLP acts on infiltrating effector T cells to drive allergic skin inflammation. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105(33):11875–11880. [PubMed: 18711124]

19. Larson RP, Zimmerli SC, Comeau MR, et al. Dibutyl phthalate-induced thymic stromal lymphopoietin is required for Th2 contact hypersensitivity responses. Journal of immunology. 2010; 184(6):2974–2984.

20. Li M, Messaddeq N, Teletin M, Pasquali JL, Metzger D, Chambon P. Retinoid X receptor ablation in adult mouse keratinocytes generates an atopic dermatitis triggered by thymic stromal lymphopoietin. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102(41):14795–14800. [PubMed: 16199515]