

Review

The role of thymic stromal lymphopoietin on mast cell-mediated allergic inflammatory reactions

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ABSTRACT

Thymic stromal lymphopoietin (TSLP) is a novel interleukin (IL)-7-like cytokine and was originally discovered in the supernatant of a murine thymic stromal cell line. TSLP signal initiates via complex of the TSLP receptor and the IL-7 receptor α chain. TSLP expression is closely connected with many diseases such as atopic dermatitis, allergic rhinitis, asthma, inflammatory arthritis, eosinophilic esophagitis, rheumatoid arthritis, inflammatory bowel diseases, and cancer. In this review, I discussed biological roles of TSLP on mast cell-mediated allergic responses. In addition, this review summarizes the effective drugs in allergic-inflammatory reactions induced by TSLP on mast cells.

Keywords thymic stromal lymphopoietin, atopic dermatitis, allergic rhinitis, mast cells

INTRODUCTION

1. Mast cells

Mast cells play a critical role in the initiation and propagation of allergic inflammatory processes such as, allergic asthma, life-threatening anaphylaxis, inflammatory response, atopic dermatitis (AD), and allergic rhinitis (AR) (El-Agamy, 2012; Galli and Tsai, 2012). The cross-linking of IgE triggers mast cell de-granulation and the synthesis of a variety of mediators including biogenic amines, serglycin proteoglycans, serine proteases, cytokines, and growth factors (Plaut et al., 1989). Histamine released by mast cells evoked vascular permeabilization and hence enhances the migration of eosinophils, macrophages, and neutrophils into inflamed tissues (Oskeritzian et al., 2015). Thus, mast cell degranulation and activations intensifies and extends TH2-dependent inflammatory response (Galli and Tsai, 2012). Furthermore, interleukin (IL)-3, IL-5, IL-9, IL-6, tumor necrosis factor (TNF)- α , macrophage inflammatory protein-2, intercellular adhesion molecule-1, and thymic stromal lymphopoietin (TSLP) induce the recruitment of inflammatory cells leading to the late allergic response expressed by nasal congestion, chronic wheeze, and nasobronchial hyper-reactivity (Mandhane, 2011; Moon and Kim, 2011; Perlman, 1999; Xu et al., 1995). Intracellular signaling pathways such as mitogen-activated kinases and caspase-1 regulate the production of these pro-inflammatory cytokines (Oh et al., 2012). The mRNA expressions of IL-1, IL-6, IL-8, TNF- α , and TSLP are induced by activation of a transcription factor, nuclear factor (NF)- κ B. NF- κ B bound to a specific consensus DNA element of promoter region increases the transcription of inflammatory cytokine genes (Jeong et al., 2002).

Mast cells are also multifunctional immune cells involved

in the pathogenesis of various chronic inflammatory disorders, autoimmune diseases, and cancers (Galli and Tsai, 2012). Increased number of mast cells has been found in AD, AR, asthma, rheumatoid arthritis, tumor, and mast cell leukemia (El-Agamy, 2012; Galli and Tsai, 2012; Jeong et al., 2013). Mastocytosis is disorders determined by abnormal proliferation and accumulation of mast cells in various tissues, including liver, skin, gastrointestinal tract, bone marrow, spleen, and lymph nodes (Horny et al., 2008). The number of mast cells is increased by migration, proliferation, and survival (Kneilling and Röcken, 2009). Proliferation of mast cells was mainly induced by stem cell factor and IL-3 (da Silva et al., 2014). Recently, we have been demonstrated that TSLP also increased the proliferation of mast cells (Han et al., 2014a). Proliferation of mast cells exaggerates the several inflammatory diseases. Thus, inhibition of mast cell proliferation is regarded as an attractive therapeutic strategy for various inflammatory diseases.

2. TSLP

TSLP is a novel interleukin (IL)-7-like cytokine and was originally discovered in the supernatant of a murine thymic stromal cell line (Friend et al., 1994; Sims et al., 2000). TSLP has been known to promote Th2 cell-associated inflammation. TSLP is mostly expressed by epithelial cells of barrier surfaces in response to inflammatory cytokines, microbial products, or physical injury (Allakhverdi et al., 2007). The TSLP receptor (TSLPR) complex consists of a heterodimer of the IL-7 receptor α chain (IL-7R α) and TSLPR (Pandey et al., 2000; Park et al., 2000). TSLP signaling is initiated by heterodimerization of the IL-7R α and TSLPR (Pandey et al., 2000; Park et al., 2000). TSLP affects immune responses of nonhematopoietic and hematopoietic cell lineages, including mast cells, dendritic cells, natural killer, CD4⁺, and CD8⁺ T cells, basophils, eosinophils, epithelial cells, and B cells (Ziegler et al., 2013). TSLP is involved in the initiation and progression of numerous disorders including skin disorders, respiratory diseases, intestine inflammation, cancer, and autoimmune diseases (Ziegler et al., 2013). Mast cell activation via the TSLP produced by epithelial cells has a central function in allergic responses and it exacerbates infection and

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Table 1. An inhibitory effect of drugs on TSLP production

Cell/Animal models	Drugs	Reference
HMC-1 cell	2-(4-{2-[(phenylthio)acetyl]carbonohydrzonoyl}phenoxy)acetamide	Moon et al., 2016
DNFB-induced atopic dermatitis animal model(BALB/c mice)	Resveratrol	Caglayan et al., 2016
HMC-1 cell	Alumium-doped zinc oxide nanoparticle	Kim et al., 2016
HMC-1 cell	Hydrogen sulfide	Han et al., 2016a
HMC-1 cell	Cordycepin	Yoou et al., 2016a
DNFB-induced atopic dermatitis animal model(NC/Nga mice)	<i>Acer tegmentosum</i> , <i>Salidroside</i>	Yang et al., 2016
DNFB-induced atopic dermatitis animal model(NC/Nga mice), HMC-1 cell	Niram (natural dye)	Han et al., 2014b
DNFB-induced atopic dermatitis animal model(NC/Nga mice), HMC-1 cell	Beta-sitosterol	Han et al., 2014c
HMC-1 cell	Hyperoside	Han et al., 2014d
DNFB-induced atopic dermatitis animal model(NC/Nga mice), HMC-1 cell, Splenocyte	Tryptanthrin	Han et al., 2014e
DNFB-induced atopic dermatitis animal model(NC/Nga mice), HMC-1 cell, Splenocyte, Allergic rhinitis animal model	Naju jjok	Han et al., 2014f Jeong et al., 2014
THP-1 (human monocyte)	Bamboo salt	Nam et al., 2014
Allergic rhinitis animal model, Eo-1 (eosinophil cell line)	Kaempferol	Oh et al., 2013a
Allergic rhinitis animal model, HMC-1	Ginsenoside Rg1	Oh et al., 2013b
DNFB-induced atopic dermatitis animal model(NC/Nga mice)	<i>Catalpa ovata</i>	Yang et al., 2013
HMC-1 cell	Curcumin	Moon et al., 2013
THP-1 (human monocyte)	BaekJeol-Tang, Chondroitin sulfate	Jeong et al., 2012
HMC-1 cell	Schizandrin	Moon et al., 2012a
HMC-1 cell	BAPTA-AM (calcium chelator)	Han et al., 2012
HMC-1 cell	Selenium	Moon et al., 2012b
HMC-1 cell	Epigallocatechin-3-O-gallate (EGCG)	Moon et al., 2012c
HMC-1 cell	Berberine	Moon et al., 2011a
HMC-1 cell	Naringenin	Moon et al., 2011b

inflammation (Allakhverdi et al., 2007). TSLP is expressed and released by NF- κ B and caspase-1 in activated mast cells (Moon and Kim, 2011). In addition, TSLP stimulation of mast cells leads to signal transducers and activators of transcription (STAT6) phosphorylation, murine double minute 2 (MDM2) expression, and IL-13 production and then increased mast cell-mediated allergic inflammatory reaction (Han et al., 2014a).

TSLP plays a pivotal role as a chief regulator of allergic inflammation in mice and human and is a new target for anti-allergic inflammatory therapy. In this review, we will focus on TSLP and describe how TSLP plays a role in development of allergic inflammation, and discuss TSLP as an attractive therapeutic target for allergic diseases.

2.1. TSLP in AD

TSLP was highly overexpressed by keratinocytes in the skin lesions of AD patients and mice (Soumelis et al., 2002; Corrigan et al., 2009). It causes the initiation of allergic inflammation by stimulating activation and infiltration of Langerhans cells into skin-draining lymph nodes (Soumelis et al., 2002; Zhang and Zhou, 2012). TSLP was also important for local antigen-induced Th2 cytokine production by directly acting on skin-infiltrating antigen-specific CD4⁺ T cells (He et al., 2008; Zhang and Zhou, 2012). Consistent with a requirement for TSLP in AD, challenged TSLPR deficient mice showed significantly decreased allergic skin inflammation, decreased eosinophils infiltration, and decreased Th2 cytokines expression compared with wild type mice in the skin (He et al., 2008). TSLP-deficient mice failed to generate AD development

through the down-regulation of STAT6 and MDM2 (Han et al., 2014a).

2.2. TSLP in AR

TSLP is also critical factor for the pathophysiology of AR. In nasal epithelial cells, expression of TSLP was significantly higher in AR patients than in normal controls (Mou et al., 2008; Zhu et al., 2009; Kimura et al., 2011). TSLP level in nasal tissue biopsies was closely associated with IL-4 levels and AR severity (Mou et al., 2008). Highly TSLP levels were detected in nasal polyps of AR patients (Kimura et al., 2011; Liu et al., 2011).

3. Anti-allergic inflammatory effects of drugs via blockade of TSLP function

TSLP as a developmental factor of AD and AR was released and expressed by the intracellular calcium/caspase-1/ receptor-interacting protein 2/NF- κ B pathways on mast cells (Han et al., 2012; Moon and Kim, 2011). Overexpressed-TSLP deteriorates the pathogenesis of AD and AR via the beginning of allergic inflammatory reactions (Han et al., 2014a; Oh et al., 2013a). TSLP stimulation of mast cells leads to STAT6 phosphorylation, murine double minute 2 expression, and IL-13 production and then increased mast cell-mediated allergic inflammatory reaction (Han et al., 2014a). Therefore, TSLP may be a useful therapeutic target for mast cell-mediated allergic diseases. Based on the inhibitory effect of TSLP production reported, drugs were shown in Table 1. Anti-proliferative effects of drugs on TSLP-induced the mast cell proliferation were also shown in

Table 2. An inhibitory effect of drugs on TSLP-induced mast cell proliferation

Cell/Animal models	Drugs	Reference
HMC-1 cells	Tryptanthrin	Han et al., 2016b
HMC-1 cell (mast cell), HaCa T cell (keratinocyte), pollen-induced allergic conjunctivitis mouse model.	Rosmarinic acid	Yoou et al., 2016b
HMC-1 cells	Beta-sitosterol	Han et al., 2015
HMC-1 cells	Acteoside	Yoou et al., 2015
HMC-1 cells	Zinc oxide nanoparticle	Kim and Jeong 2016

Table 2.

CONCLUSION

The role of cytokines towards inflammation and modulation of various allergic diseases is a hot topic today. TSLP is an important factor in the pathogenesis of various allergic diseases and involved in the initiation and progression of allergic response. TSLP also induces the expression of a cascade of various potent inflammatory cytokines. Therefore, I suggested that TSLP is an attractive therapeutic target for allergic inflammatory diseases.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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