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TSLP and asthma: fellow travelers

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Abstract

The incidence of asthma, a heterogeneous inflammatory disease affecting over 300 million people worldwide, continues to increase in developed countries. Human epithelial cells (ECs) express the alarmin-type cytokine thymic stromal lymphopoietin (TSLP) following tissue injury triggered by several environmental insults, which include allergens, smoke, pollutants, or other irritants. Furthermore, TSLP has an emerging but well-documented pathogenic role in asthma. TSLP has been called a "master switch" of allergic inflammation at the epithelial-dendritic cell (DC) interface, where it supports T helper 2 (Th2) inflammatory polarization and promotes the maintenance of Th2 memory responses. Therefore, targeting TSLP/TSLP-mediated signaling may represent an attractive therapeutic strategy for asthma. Several studies of anti-TSLP drugs are ongoing; the first-in-class anti-TSLP monoclonal antibody (mAb) tezepelumab, the immunoglobulin G1 antibody fragment CSJ117, or TSLP-traps [a combination of anti-interleukin-13 (anti-IL-13) and anti-TSLP mAbs] all represent promising new treatment approaches. This article reviews the characteristics of TSLP and discusses the treatment of severe asthma through TSLP-associated mechanisms.

Keywords

Asthma, thymic stromal lymphopoietin (TSLP), alarmin

Introduction

Allergic diseases are considered an increasing global health problem [1]. Atopic dermatitis (AD), which suffers high prevalence in infants and children, is an allergic skin inflammatory disease being one of the most common reasons for consultation. There is a strong association between AD and other allergic disorders. It has been described approximately half of AD patients will develop asthma (especially those with severe AD), while two-thirds will develop allergic rhinitis (AR) [2]. Asthma describes a variety of diseases with different phenotypes and endotypes and variable responses to management approaches. The miscellaneous inflammation in asthma correlates with varied profiles of upregulated immune cells and biomarkers; however, several inflammatory phenotypes of asthma can be designated from these

profiles. Eosinophilic (including allergic) type 2 (T2) inflammation asthma phenotype seems to be the most common one [3].

Several innate immune cells and molecules critical for the T2 and allergic immune profile response have been described, with thymic stromal lymphopoietin (TSLP) emerging as an important potential contributor to allergic inflammation [4]. TSLP, a cytokine first identified and characterized in mice thymus cell secretions in the 1990s [5], is a member of the alarmin class of cytokines [which also includes interleukin-25 (IL-25) and IL-33] and is considered an IL-7-like cytokine. TSLP was first identified as a factor capable of supporting the proliferation and development of immature B cells [6]. In humans, TSLP is mainly produced by epithelial cells (ECs) of the skin (keratinocytes), lung (small airway ECs), and intestine (intestinal ECs). It is secreted after an environmental insult, stimuli such as allergens, pollution agents, pathogens, and physical injury, to initiate downstream inflammatory processes [7].

TSLP has recently been described as a trigger of allergic immune responses, as it is the first cytokine primarily produced and released by ECs at barrier surfaces [8]. Tezepelumab is a fully human immunoglobulin G2 (IgG2) monoclonal antibody (mAb) that binds human TSLP and prevents interaction with its receptor and subsequent recruitment of IL-7 receptor α chain (IL-7Rα) to the signaling complex. The heterodimeric TSLP receptor (TSLPR) complex comprises the IL-7R and the specific TSLPR subunit, which is expressed in many tissues, including the liver, brain, testis, bone marrow, spleen, and thymus [9].

Reports have linked TSLP to the pathogenesis of human asthma [10], AD [11], and eosinophilic esophagitis [12]; indeed, TSLP blockade in murine models of AD reduced both disease severity and the risk of developing asthma [13, 14]. TSLP expression becomes elevated in cases of severe asthma, despite high-dose corticosteroid therapy, and correlates with the expression of T2 cytokines. The nasal mucosa of patients with AR or nasal polyps and the conjunctiva of patients with allergic keratoconjunctivitis also overexpress TSLP [15].

In atopic asthma, viruses, bacteria, and allergens have a potential role as triggers of TSLP-dependent inflammatory response, pointing the way to the inappropriate activation of the innate and adaptive immune systems [16].

Airway epithelium activation provokes chemokines and cytokines secretion that attract monocytes and immature dendritic cell (DC) to the inflamed location and prime immune responses. The airway epithelium represents a pivotal regulator of innate and T helper 2 (Th2)-mediated immunity, which has a central role in asthma pathogenesis. Zhou et al. [17] demonstrated TSLP as a necessary and sufficient factor for the initiation of allergic airway inflammation via the direct induction of T2 inflammation or through DC, the amplification of basophil and eosinophil production, and the inhibition of antigen-specific regulatory T cells. TSLP plays a critical role in the genesis of Th2-type inflammation in the asthmatic airway mucosa by directly activating T2 innate lymphoid cells and inducing Th2-type T cell differentiation [18]. Moreover, TSLP inhibits the production of IgA by memory B cells, which may negatively impact the immunity of mucosal surfaces, especially in asthma [19].

Several reasons support TSLP as a likely candidate for perpetuating the atopic state. First, TSLP expression occurs at elevated levels in the skin of AD patients and the lungs of asthma patients; second, TSLP is an EC-derived cytokine, with both AD and asthma developing at EC surfaces; and third, a role for TSLP in allergic inflammation has been previously described in humans and mice [14].

Previous studies have suggested that targeting TSLP may only be efficacious in a subset of asthma patients characterized by increased Th2 inflammation [20]. TSLP prompts the differentiation of naive $CD4^+$ T lymphocytes into T2 cells, the production of IL-4, IL-5, and IL-13, and reduces the expression of interferon-γ, which is related to T1 cells [21]. Allergen exposure markedly increases the expression of all three alarmins (TSLP, IL-33, and IL-25), which play pivotal roles in late-phase airflow obstruction in the airways [22]. The ability of healthy control pulmonary T regulatory cells to produce IL-10 can be suppressed by TSLP from bronchoalveolar lavage of asthmatic patients and exert their suppressive activity [23]; overall, this mechanism may suppress the development of allergen tolerance in the lungs while enhancing pro-inflammatory Th2 responses [24]. The IgE dependence of these phenomena remains unclear.

For example, there is no correlation between the concentrations of alarmins, and the concentration of specific IgE in shrimp-allergic patients [25].

Komai et al. [26] reported Th2 response as the main pathogenic via the development of airway remodeling. As TSLP-induced airway remodeling in asthma requires cellular senescence, inhibiting cellular senescence by TSLP-targeted therapies could block airway remodeling [27]. Chen et al. [28] studied the effect of repeated respiratory exposure in a house dust mite (HDM) allergic murine model and observed significant airway eosinophilic inflammation, peribronchial collagen deposition, goblet cell hyperplasia, airway hyperreactivity (AHR) to methacholine, and the upregulation of Th2-type cytokines (IL-4 and IL-13) and the GATA binding protein 3 (GATA-3) transcription factor. Moreover, local TSLP neutralization with an mAb significantly reversed airway eosinophilic inflammation, reduced peribronchial collagen deposition, goblet cell hyperplasia, and mucus overproduction, and decreased both AHR and transforming growth factor-beta1 (TGF-β1) levels in chronic HDM-exposed mice. In another study, Chen and Chiang [29] reported that the lentiviral expression of an anti-TSLP short-hairpin RNA construct significantly decreased TSLP secretion, which prompted a particular decrease in CC chemokine ligand 17 (CCL17) expression in the bronchial epithelium.

A study that examined associations between variants in multiple TSLP-related genes [*OX40L*, *IL-7R*, and retinoid X receptor alpha (*RXRα*)] and AR detected an inverse male-specific association between the T allele of the rs1837253 single nucleotide polymorphism in TSLP and AR in three independent cohorts of children with asthma from Costa Rica, North America, and Sweden [30]. This finding corroborated previous *in vitro* and murine studies and supports our current understanding of TSLP-driven allergic inflammation.

Therefore, targeting TSLP and TSLP-mediated signaling may represent an attractive therapeutic strategy for asthma. Below, we review the critical role of TSLP-targeted drugs in asthma treatment.

TSLP-targeted therapies

Regardless of standard-of-care treatments (including currently available biologic drugs), uncontrolled severe asthma affects many patients associated with an important risk of hospitalization and elevated healthcare costs. Current available biologics for severe asthma include anti-IgE (omalizumab), anti-IL-5 (mepolizumab, reslizumab), anti-IL-5Rα (benralizumab), and anti-IL-4Rα (dupilumab which blocks both IL-4 and IL-13 cytokine actions) mAbs. These drugs are generally prescribed to patients with eosinophilic or allergic asthma phenotypes (high-T2 asthma); however, there is a lack of authorized biologic treatments for low-T2 asthma patients [2].

Tezepelumab (AMG 157) is a fully human IgG2 mAb that binds human TSLP, blocks interaction with the TSLPR, and, consequently, inhibits potentially high-T2 and low-T2 inflammatory pathways. A phase IIb, double-blind, placebo-controlled trial included asthma patients treated with medium-to-high doses of inhaled corticosteroids/long-acting β2-agonists, which were randomized for being treated with three dose levels of subcutaneous tezepelumab (70 mg every four weeks, 210 mg every four weeks, or 280 mg every two weeks) or placebo over 52 weeks [31]. Tezepelumab decreased blood eosinophil count and fractional exhaled nitric oxide (FeNO) levels and reduced levels of IL-5, IL-13, periostin, thymus- and activation-regulated chemokine (TARC), and IgE [32]. Furthermore, tezepelumab treatment reduced the frequency of hospitalizations and emergency department visits and decreased the number of days in the hospital or intensive care unit [33]. Remarkably, blood eosinophils or other T2 biomarkers did not influence the efficacy of tezepelumab on exacerbations and FeNO reduction [34]. Tezepelumab is currently in phase III trials [NAVIGATOR (NCT03347279), SOURCE (NCT03406078), and DESTINATION (NCT03706079)] in severe asthmatics, with 210 mg every four weeks provided as the optimal dose [35]. In addition, a phase II study is evaluating the effect of tezepelumab on airway inflammation and remodeling in patients with T2 inflammation. Interestingly, in the phase III NAVIGATOR trial, tezepelumab resulted in reductions in the asthma exacerbation rate, compared with placebo of 41% for low-T2, and 39% for non-T2 asthma patients.

CSJ117, an antibody fragment belonging to the immunoglobulin G1/λ isotype subclass, binds to TSLP after delivery by inhalation. Phase I studies to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of CSJ117 in adult subjects with mild atopic asthma have been completed, although the results have yet to be posted (ClinicalTrials.gov Identifier: NCT03138811). Meanwhile, phase II studies on the efficacy and safety of CSJ117 in patients with severe uncontrolled asthma are ongoing (ClinicalTrials.gov Identifier: NCT04410523, ClinicalTrials.gov Identifier: NCT04946318).

In December 2021, tezepelumab was approved by the Food and Drug Administration (FDA) with the indication for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. In September 2022, tezepelumab was approved by the European Medicines Agency with the same indication. In fact, tezepelumab has been added to the last Global Initiative for Asthma (GINA) guideline 2022 in step 5 for consideration in patients older than 12 years who have no evidence of T2 inflammation on repeated testing [36].

Several TSLP inhibitors are also under investigation, including scFvs, Zweimab, and baicalein. In addition, TSLP-traps combine an anti-IL-13 mAb with an anti-TSLP mAb by fusing ectodomains of TSLPR and IL-7Rα that extend into the extracellular space with fragments capable of disrupting TSLP [5].

Conclusions

TSLP, in the context of persistent allergic asthma, plays a pivotal role in the initiation and persistence of airway inflammation and remodeling. TSLP expression becomes elevated in severe asthma and correlates with the expression of T2 cytokines. Blood eosinophils or other T2 biomarkers do not influence the effect of TSLP blockade, a fact that opens the door for anti-TSLP therapeutics as highly utile treatments for high-T2 and presumably low-T2 asthma. We must also consider the possibility that viral infection-induced exacerbations are particularly amenable to treatment with anti-TSLP drugs. Phase III clinical trials of tezepelumab will assess the safety of TSLP blockade and the possible risk of infections and cancer development.

Abbreviations

AD: atopic dermatitis

AR: allergic rhinitis

ECs: epithelial cells

IgG2: immunoglobulin G2

IL-13: interleukin-13

IL-7Rα: interleukin-7 receptor chain α

mAb: monoclonal antibody

T2: type 2

Th2: T helper 2

TSLP: thymic stromal lymphopoietin

TSLPR: thymic stromal lymphopoietin receptor

Declarations

Author contributions

DEQ and AL equally contributed to: Writing—original draft, Writing—review & editing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

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