

Editorial

Thymic Stromal Lymphopoietin: A Promising Target in the Treatment of Asthma?



Linfopoyetina del estroma tímico: ¿un objetivo prometedor para el tratamiento del asma?

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Thymic stromal lymphopoietin (TSLP)

In the last decade, it has become clear that asthma is a heterogeneous disease composed of several phenotypes. The identification of those phenotypes has been associated with the development of biological therapies targeting antibodies, cytokines and their receptors such as immunoglobulin E, interleukin (IL)-5 and IL-5 receptor, or IL-13 in the treatment of severe asthma.

Thymic stromal lymphopoietin (TSLP) is an epithelial derived cytokine that belongs to the type I cytokine group, which is part of the IL-2 cytokine family (IL-2, IL-4, IL-7, IL-9, IL-13, IL-21).¹ TSLP was first discovered in 1994 in the supernatants of a murine thymic stromal cell line that supported the growth of a pre-B cell line. In the year 2000, a TSLP human homolog was isolated. The human TSLP gene is located on chromosome 5q22.1 next to the atopic cytokine cluster (IL-4 IL-5, IL-9, IL-13) of the chromosome 5q31. Its important role in allergic airway inflammation has become evident over the past few years.¹ Polymorphisms of the TSLP gene have been shown to be associated with allergic asthma. There is a wide spectrum of stimuli that are able to trigger TSLP activation; for example, viral infections, bacterial peptidoglycan, air pollutants, and allergens.² TSLP acts by binding to its receptor (TSLP-R), which consists of a TSLP-binding α chain and an IL-7R α chain.³ TSLP is expressed through injured epithelial cells of the skin, abdomen, and lungs. It exerts its main biological actions on dendritic cells (DCs) and mast cells.⁴ TSLP is also involved in the Th2 differentiation of T lymphocytes.⁵ There is evidence that basophils, eosinophils, and airway smooth muscle cells express TSLP-Rs and thus, TSLP could enable them to release Th2 cytokines.⁶

Role of TSLP in the Type 2 response

The principal role of TSLP is to induce a Th2 adaptive response by means of diverse cells. Dendritic cells play an important role in the process of inducing this Th2 response. When DCs are stimulated by TSLP, an upregulation of the ligand OX40L expressed on DCs occurs, which promotes the transformation of CD4⁺ cells into activated Th2 cells.³ TSLP also stimulates mast cells to release Th2 inflammatory cytokines such as IL-4, IL-5, IL-6, and IL-13. Under resting conditions, CD4⁺ and CD8⁺ T-cells are insensitive to TSLP. However, the number of TSLP receptors increases on the surface of CD4⁺ and CD8⁺ T cells after their activation. Following a T-cell receptor stimulation, TSLP can promote CD4⁺ and CD8⁺ T-cell proliferation through the induction of the IL-4 gene transcription.³ The role of TSLP in B-cells during an allergic inflammatory reaction has not been described.

TSLP can also activate innate lymphoid cells (ILCs) in an allergen-independent manner. Activated ILCs produce high amounts of IL-5 and IL-13, and can induce eosinophilic airway inflammation independently of T-cells.³ Insults to the airway epithelium such as oxidants (ozone and other irritants) may lead to activation of these cells, contributing to airway hyperresponsiveness that is independent of adaptive immunity.⁷

Role of TSLP in asthma

There is evidence that TSLP plays an important role in inducing an allergic asthmatic response in not only transgenic asthmatic mice models, but also in humans. Several studies have demonstrated a relationship between the expression of TSLP, airway hyperresponsiveness, and airflow limitation.⁸ In 2014, Gauvreau et al.⁹ conducted a double-blind, placebo-controlled study, in which 31 patients with mild allergic asthma were randomized to receive three monthly doses of an intravenous anti-TSLP monoclonal immunoglobulin or placebo. Allergen challenges were conducted on day 42 and day 84 to assess the effect of the anti-TSLP on FEV₁ during the asthmatic reaction. The maximum percentage

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fall in FEV₁ observed during the late response was 34% smaller in the treated group compared to the placebo group on day 42 and 46% smaller on day 84. Patients treated with the anti-TSLP monoclonal immunoglobulin had significant decreases in their levels of blood and sputum eosinophils and in the fraction of exhaled nitric oxide, before and after the allergen challenge. In 2014, Gauvreau et al.¹⁰ also developed a double-blind, randomized, placebo-controlled, parallel-group trial, which aimed to compare an anti-OX40L monoclonal antibody to placebo in a sample of 28 mild & atopic asthmatic subjects. Allergen inhalation challenges were completed 56 and 113 days after the initial dose of the study drug. However, no difference was observed in allergen-induced airway responses, although the total serum IgE and airway eosinophils decreased by week 16 after the initial dose with the anti-OX40L monoclonal antibody. These results differed substantially from the data obtained in murine models of asthma where the absence or the blockade of OX40L induced a decrease in Th-2 cytokines, eosinophilia and airway responsiveness (10). The lack of effect in humans may be related to an insufficient duration or dose of treatment. It is also possible that anti-OX40L maybe more effective when administered prior to the onset of an established allergic sensitization. Whether anti-OX40L may have an effect on asthma exacerbations remains to be demonstrated.

Relevance of anti-TSLP therapies and future challenges

There is no doubt that the introduction of biological therapies constitutes an important step in the modern treatment of severe asthma. Although inhaled corticosteroids are still the cornerstone of asthma treatment, it has become obvious that a deeper understanding of asthma's pathophysiology provides the opportunity to customize asthma treatment according to each patient's phenotype. The blockade of the inflammatory cascade at a high level is likely to have a profound effect on airway inflammation. Interrupting the Th2 inflammatory pathway through a blockade of the TSLP seems a promising alternative for patients suffering from severe asthma. Although questions regarding TSLPs actions and targets still remain,¹⁰ the impact of TSLP on Th2 inflammation has already been clearly established.

Current biologic therapies such as monoclonal anti-IgE or anti-IL-5 antibodies target patients with specific phenotypes such as allergic or eosinophilic asthma. Anti-TSLP monoclonal antibodies might be promising in a greater variety of asthma phenotypes than

these previous therapies. TSLP is a key player in the differentiation of CD4+ cells into activated Th-2 cells. Since this pathway is involved in the majority of patients showing a Th2-high asthma phenotype, the blockage of TSLP is likely to affect a larger number of individuals than anti-IgE, anti-IL5 or anti-IL13/IL4 treatments. The efficacy and safety of anti-TSLP monoclonal antibodies in a wide spectrum of patients with Th2-mediated airway inflammation remain to be demonstrated in large clinical trials.

Conflict of interests

Dr. Lemiere has received research funding and personal fees from GlaxoSmithKline, AstraZeneca, and TEVA outside the submitted work.

Acknowledgements

IO is a researcher supported by "ERS and SEPAR, LTRF 2016" and the *Societat Catalana de Pneumologia* (SOCAP).

References

1. Leonard WJ. TSLP: finally in the limelight. *Nat Immunol.* 2002;3:605–7.
2. Cianferoni A, Spergel J. The importance of TSLP in allergic disease and its role as a potential therapeutic target. *Expert Rev Clin Immunol.* 2014;10:1463–74.
3. Watson B, Gauvreau GM. Thymic stromal lymphopoietin: a central regulator of allergic asthma. *Expert Opin Ther Targets.* 2014;18:771–85.
4. Allakhverdi Z, Comeau MR, Jessup HK, Yoon B-RP, Brewer A, Chartier S, et al. Thymic stromal lymphopoietin is released by human epithelial cells in response to microbes, trauma, or inflammation and potently activates mast cells. *J Exp Med.* 2007;204:253–8.
5. Rochman I, Watanabe N, Arima K, Liu Y-J, Leonard WJ. Cutting edge: direct action of thymic stromal lymphopoietin on activated human CD4+ T cells. *J Immunol.* 2007;178:6720–4.
6. Giacomini PR, Siracusa MC, Walsh KP, Grecis RK, Kubo M, Comeau MR, et al. Thymic stromal lymphopoietin-dependent basophils promote Th2 cytokine responses following intestinal helminth infection. *J Immunol.* 2012;189:4371–8.
7. Yu S, Kim HY, Chang Y-J, DeKruyff RH, Umetsu DT. Innate lymphoid cells and asthma. *J Allergy Clin Immunol.* 2014;133:943–50.
8. Shikotra A, Choy DF, Ohri CM, Doran E, Butler C, Hargadon B, et al. Increased expression of immunoreactive thymic stromal lymphopoietin in patients with severe asthma. *J Allergy Clin Immunol.* 2012;129, 104–11–19.
9. Gauvreau GM, O'Byrne PM, Boulet L-P, Wang Y, Cockcroft D, Bigler J, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med.* 2014;370:2102–10.
10. Gauvreau GM, Boulet L-P, Cockcroft DW, FitzGerald JM, Mayers I, Carlsten C, et al. OX40L blockade and allergen-induced airway responses in subjects with mild asthma. *Clin Exp Allergy.* 2014;44:29–37.