

TSLP in Asthma — A New Kid on the Block?

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Asthma is a complex inflammatory disease in which the airways narrow too easily, too much, and too often. Despite the availability of bronchodilators to widen the constricted airways and inhaled glucocorticoids, many patients with asthma still have uncontrolled airway obstruction. Lack of adherence to inhaled therapies may explain treatment failures, but it is also clear that there is a need for a better understanding of the pathobiologic mechanisms that could lead to a greater repertoire of treatments for asthma.

Gauvreau et al.¹ now report in the *Journal* the results of a study that introduces a potential new target for such treatment. They found that 5 to 12 weeks of treatment with a humanized monoclonal antibody (AMG 157) against a novel target in human asthma, thymic stromal lymphopoietin (TSLP), blunted asthma attacks evoked by the inhalation of allergens. The magnitude of the effect of this new kid on the asthma-treatment block was sizable — similar to what may be achieved in the same clinical-research model by blocking established asthma mediators such as the cysteinyl leukotrienes.²

TSLP, which was discovered as a growth factor for lymphocyte progenitors, is now recognized as a protein released primarily from epithelial cells in response to irritating stimuli. It initiates signaling pathways leading to inflammation driven by type 2 helper T (Th2) cells. Previous findings have implicated the involvement of TSLP in asthma,³ but this cytokine has not ranked highly among candidates for new treatment targets, with studies in mouse models of asthma showing conflicting results.^{4,5}

In the study by Gauvreau et al., the investigators used the most predictive model for the assessment of drug effects in asthma, allergen bronchoprovocation.⁶ In this test, inhalation of a predetermined dose of allergen leads to an early asthmatic response, a decrease in lung function that occurs within 2 hours after inhalation and that is caused by the release of bronchoconstrictive mast-cell mediators.² In some patients, the early response is followed by a late asthmatic response, a decline in lung function that occurs during the subsequent 24 hours, during which

prolonged swelling of the airway mucosa, including infiltration of inflammatory cells, aggravates the airway obstruction. The late response is thought to be caused by the continued release of mast-cell mediators,² as well as by cytokines and other mediators produced by activated inflammatory cells.

How do we explain that treatment with a highly selective anti-TSLP antibody blocked both the early and late asthmatic responses in this study? It is unlikely that TSLP is released directly in response to the actual allergen challenge, and TSLP does not contract airway smooth muscle.⁷ Previous trials targeting interleukin-4 or interleukin-13, two downstream cytokines induced by TSLP, have been found to be effective in allergen challenge or treatment trials.⁸⁻¹⁰ Thus, it is likely that the anti-TSLP treatment indirectly inhibited such pathways; this likelihood is supported by the observed reduction in the number of eosinophils in induced sputum and the level of nitric oxide in exhaled air. As the authors point out, it is unclear whether the reduced eosinophil numbers are responsible for the inhibition of the allergen-induced responses or whether such a reduction follows another event explaining the protective effect.

Along with previous data, the results of this study indicate that there are two fundamentally different ways to inhibit allergen-induced asthmatic responses. Whereas direct antagonism of mast-cell mediators may block the acute response, long-term inhibition of regulatory networks appears to inhibit allergen responses by reducing the mechanisms that sustain the immunologic and inflammatory processes. These findings raise the question of whether TSLP is a master switch in the signaling between airway epithelium and other inflammatory cascades or whether it is part of a concerted action by several parallel pathways (e.g., those involving interleukin-33, interleukin-25, and interleukin-17).

These data show that AMG 157 can inhibit allergen-induced asthma attacks by blocking TSLP. Although this newcomer has earned our respect, it is an open question as to whether this strategy will be successful in the treatment

of patients with asthma. We will first have to unravel the biologic mechanisms involved in this unexpected effect of AMG 157 and show why TSLP signaling allows airways to narrow too easily, too much, and too often.

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