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TSLP
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ASTHMA AND ALLERGY

TSLP: key role in allergic responses confirmed

The cytokine thymic stromal lymphopoietin (TSLP) has previously been linked to allergic inflammatory diseases in humans. Now, three recent studies have confirmed that TSLP is a key initiator of allergic diseases — that is, asthma and atopic dermatitis — by analysing mouse models, and this will help to advance our understanding of these diseases in humans.

In the first study, Steven Ziegler and colleagues set out to characterize the role of TSLP in the allergic skin disease atopic dermatitis by generating mice that express an inducible *Tslp* transgene in the skin. Skin-specific TSLP expression could be switched on by including doxycycline in the diet. *Tslp*-transgenic mice given doxycycline developed eczematous skin lesions that were similar to atopic dermatitis lesions in humans and involved epidermal hypertrophy and inflammatory-cell infiltration of the dermis. Consistent with an important role for T helper 2 (T_H2) cells in allergic diseases, the *Tslp*-transgenic mice had increased numbers of interleukin-4-producing $CD4^+$ T cells in skin-draining lymph nodes but not in intestinal mesenteric lymph nodes. The expression of skin-homing molecules by the T_H2 cells, such as ligands for platelet selectin (P-selectin) and endothelial-cell selectin (E-selectin), probably contributed to this tissue specificity. Despite this, however, skin disease also occurred when the *Tslp*-transgenic mice lacked T cells, indicating that TSLP might act directly on cells other than T cells; dendritic cells (DCs) are the most likely candidate, as has been suggested by studies of human TSLP.

This aspect was further explored by the same group, in the second study. In this study, the authors generated mice that specifically expressed the *Tslp* transgene in epithelial cells of the lungs. Lung-specific expression of TSLP induced airway inflammation, which was characterized by infiltration of eosinophils and T_H2 cells that expressed the lung-homing receptor CC-chemokine receptor 4 (CCR4). TSLP overexpression in the lungs also led to spontaneous airway hyper-responsiveness after inhalation of methacholine. The allergic responses were thought to be initiated by DCs responding to TSLP, because bone-marrow-derived DCs that were cultured in TSLP had upregulated expression of co-stimulatory molecules and the T_H2-cell-attracting chemokine CC-chemokine ligand 17 (CCL17).

Consistent with this, the third study, by Warren Leonard and colleagues, showed that TSLP could act on DCs to promote T_H2-cell differentiation and recruitment, but the authors also showed that TSLP could act directly on naive $CD4^+$ T cells to promote proliferation in response to antigen. To study the role of TSLP in allergic responses, these authors studied mice lacking the receptor for TSLP (TSLPR). TSLPR-deficient mice were protected from allergic airway inflammation induced by methacholine or following sensitization and intranasal challenge with ovalbumin. Bronchoalveolar-lavage fluid from TSLPR-deficient mice contained fewer T_H2 cells and had lower levels of CCL11 and CCL17 than bronchoalveolar-lavage fluid from wild-type mice. Airway inflammation did occur in these mice, however, if they received wild-type $CD4^+$ T cells, indicating that, in this model, TSLP is mainly involved in the activation of $CD4^+$ T cells.

Therefore, although the exact mechanism remains to be determined, these studies clearly show a crucial role for TSLP in allergic responses.

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References and links

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