Role of Thymic Stromal Lymphopoietin (TSLP) in Allergic Responses

Atsushi Kato, PhD

Allergy-Immunology Division, Northwestern University Feinberg School of Medicine

TSLP (thymic stromal lymphopoietin) is an IL-7-like cytokine that was first isolated from a murine thymic stromal cell line and was shown to support B cell development. TSLP is now recognized as an important regulator of Th2 inflammation. TSLP is produced mainly by epithelial cells, and is also known to be produced by skin keratinocytes, stromal cells, smooth muscle cells and fibroblasts. The TSLP receptor is a heterodimeric receptor consisting of the IL-7 receptor α chain (IL7RA) and a common γ-like TSLP specific receptor (TSLPR). TSLPR is known to be expressed on dendritic cells (DC), T cells, B cells, NKT cells, basophils, eosinophils, mast cells and type 2 innate lymphoid cells (ILC2), but in humans expression is mainly restricted to DC, mast cells and ILC2. TSLP stimulates DC to induce naive CD4+ T cell differentiation into Th2 cells. TSLP also strongly induces the production of chemokines, TARC and MDC (known to recruit Th2 cells) and eotaxin (for eosinophils) in DC. TSLP can directly activate ILC2 to produce Th2 cytokines, including IL-5 and IL-13. Although TSLP alone isn't sufficient to stimulate mast cells, TSLP synergizes with the inflammatory cytokines IL-1 and IL-33 to potently activate mast cells to produce Th2 cytokines. Taken together, these data suggest that TSLP may involve the enhancement of innate and adaptive Th2-related inflammation.

These properties of TSLP have increased interest in this molecule, and considerable evidence now implicates TSLP in the pathogenesis of several allergic diseases. TSLP has been found to be increased in the epithelium of patients with atopic dermatitis, bronchial asthma, eosinophilic esophagitis and chronic rhinosinusitis with nasal polyps. In addition, genome wide association studies have shown that TSLP gene variants are associated with asthma and eosinophilic esophagitis. Several animal models clearly showed the importance of TSLP in allergic diseases. Lung-specific overexpression of TSLP in mice induces airway inflammation, whereas TSLPR deficient mice fail to develop an allergic response in the OVA-induced allergic model. Skin-specific overexpression of TSLP in mice is sufficient to induce an atopic dermatitis-like phenotype. TSLP is therefore considered to be an important target for development of new therapeutics in allergic diseases.

Based on the importance of TSLP in Th2-related diseases, our laboratory has extensively studied its regulation in human epithelial cells and its function in airway diseases. TSLP is induced by proinflammatory cytokines, dsRNA (poly (I:C)), and the infection of respiratory virus in epithelial cells. Importantly dsRNA- and virus-dependent production of TSLP is synergistically enhanced by the Th2 cytokines, IL-4 and IL-13, and significantly suppressed by the Th1 cytokine IFN-γ or the Th17 cytokine IL-17A. This suggests that epithelial cells can amplify Th2 inflammation during virus infection via production of TSLP but only when a Th2

microenvironment exists in the airway. This might be one of the mechanisms of asthma exacerbations.

Recently, several groups discovered the accumulation of mast cells in the epithelium of patients with Th2-high asthma. Therefore we hypothesized that interaction of mast cells and epithelial cells induces Th2 cytokine production. We have recently discovered that IL-4 and dsRNA induce Th2 cytokine production from mast cells only when co-cultured with epithelial cells. Interestingly, Th2 cytokine production has not been seen as a result of co-stimulation with IFN-γ and dsRNA in this co-culture. We have identified a mechanism that epithelial cell derived IL-1α and IL-1β act as initiators and TSLP acts as an amplifier of Th2 cytokine production in mast cells. This suggests that epithelial mast cells may contribute to the amplification of Th2 inflammation when respiratory virus infects the epithelial cells of patients with asthma.

Although TSLP is involved in Th2 inflammation and disease in both mice and humans, the mechanism of induction of Th2 inflammation by TSLP might differ between these species. This complicates the study of TSLP in humans. I will also present the role of TSLP in chronic rhinosinusitis with nasal polyps, which is characterized by eosinophilia and Th2-related inflammation, as an example of the potential role of TSLP in Th2-related diseases in humans and of the difficulty of studying human TSLP.