

Molecular and structural dissection of pro-inflammatory complexes pivotal to widespread chronic allergic disorders

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Thymic stromal lymphopoietin (TSLP), a cytokine produced by epithelial cells at barrier surfaces, is pivotal for the development of widespread chronic inflammatory disorders such as asthma and atopic dermatitis. We are pursuing structural and mechanistic studies to dissect the assembly principles leading to signalling assemblies mediated by TSLP. The structure of the TSLP-mediated signaling complex reveals how TSLP establishes extensive interfaces with its cognate receptor (TSLPR) and the shared interleukin 7 receptor α -chain (IL-7Ra) to evoke membrane-proximal receptor-receptor contacts poised for intracellular signaling. Binding of TSLP to TSLPR is a mechanistic prerequisite for recruitment of IL-7Ra to the high-affinity ternary complex, which we propose is coupled to a structural switch in TSLP at the crossroads of the cytokine-receptor interfaces. Functional interrogation of TSLP-receptor interfaces points to putative interaction hotspots that could be exploited for antagonist design. During my presentation I will highlight specific methodological milestones that have enabled progress in this project.