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Regulation of chronic inflammation and the development of new strategies for treating airway inflammatory diseases

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Abstract

Many Japanese people suffer from chronic inflammatory diseases of the upper and lower respiratory tracts, such as chronic rhino-sinusitis and chronic bronchial asthma. These diseases are generally resistant to steroids, and no effective treatment has yet been developed. Chronic allergic airway inflammation is thought to be induced and maintained by allergen-specific memory $CD4^+$ helper T (Th) cells (Th1, Th2, and Th17 cells), although the precise roles of these Th subsets in chronic inflammatory diseases remain unknown. With relevance to these issues, we have recently identified several key mechanisms regulating Th-cell mediated inflammation as described below.

Firstly, we identified pathogenic memory Th2 cells in the $CD62L^{lo}CXCR3^{lo}$ population of memory Th2 cells. The pathogenic population selectively produces IL-5 and induces memory Th2-dependent allergic airway inflammation. Furthermore, in memory Th2 cells, IL-5 is uniquely regulated by two distinct mechanisms: (i) chromatin conformation at the IL-5 locus, and (ii) the expression of Eomesodermin that prevents GATA3-dependent transcriptional activity (Endo et al. Immunity 35:733, 2011). Secondly, although TGFβ is known as an immune-suppressor in diseases including allergic asthma, the precise mechanisms regulating this function had remained unknown. We found that Sox4, a member of the Sry-related high-mobility group box (Sox) family, plays a key role in the regulation of transcription during developmental processes. Our data show that Sox4 negatively regulates GATA3, the master regulator of Th2 cell function. By inhibiting GATA3, Sox4 blocks Th2 cell differentiation both *in vitro* and *in vivo*, resulting in the amelioration of Th2 cell-driven airway inflammation in mice expressing transgenic Sox4 (Kuwahara et al. Nature Immunology 13:778, 2012).

In this project, we will clarify the cellular and molecular bases for induction and maintenance of chronic airway inflammation further, and propose therapeutic strategies that may be used for chronic airway inflammatory diseases.