A Generally Applicable Translational Strategy Identifies S100A4 as a Candidate Gene in Allergy

The identification of diagnostic markers and therapeutic candidate genes in common diseases is complicated by the involvement of thousands of genes. We hypothesized that genes co-regulated with a key gene in allergy, IL13, would form a module that could help to identify candidate genes. We identified a T helper 2 (TH2) cell module by small interfering RNA–mediated knockdown of 25 putative IL13-regulating transcription factors followed by expression profiling. The module contained candidate genes whose diagnostic potential was supported by clinical studies. Functional studies of human TH2 cells as well as mouse models of allergy showed that deletion of one of the genes, S100A4, resulted in decreased signs of allergy including TH2 cell activation, humoral immunity, and infiltration of effector cells. Specifically, dendritic cells required S100A4 for activating T cells. Treatment with an anti-S100A4 antibody resulted in decreased signs of allergy in the mouse model as well as in allergen-challenged T cells from allergic patients. This strategy, which may be generally applicable to complex diseases, identified and validated an important diagnostic and therapeutic candidate gene in allergy.