

CD27 Effector Cell Depletion during Allergen-Specific Immunotherapy.

Erik Wambre, PhD

Currently, allergen-specific immunotherapy (ASIT) is the only known disease-modifying treatment of allergic diseases. The principle of ASIT is to administer gradually increasing doses of allergen, either as allergen extracts or as recombinant allergen. While evidence to date has revealed that ASIT is clinically efficacious, a long period of time may elapse before achievement of clinical benefit and some patients are clinically unresponsive to ASIT. In the absence of information about primary clinical endpoints, biomarkers can provide critical insights that allow investigators to guide the clinical development of the candidate vaccine. However, assumptions about a correlation between immunological end-points and clinical outcomes of allergy vaccine are not supported by current monitoring strategies. Understanding the mechanism associated with the breakdown and restoration of tolerance after ASIT is dependent upon definition of the heterogeneity and complexity of the cellular immune response toward allergens in individuals with and without allergy. Given their pivotal role in both the induction and control of allergic inflammation, molecular changes at the level of CD4⁺ T cells could represent a clinically meaningful signature that will reflect and quantify an underlying allergic disease process. This, in turn, would facilitate the design and evaluation of allergy vaccines, as well as enable our understanding of mechanisms of action associated with successful immunotherapy. The main obstacle to elucidating the role of CD4⁺ T cells in ASIT has been the absence of an adequately sensitive approach to directly characterize rare allergen-specific CD4⁺ T cells without introducing substantial phenotypic modifications by *in vitro* amplification. However, recent progress in peptide-MHC class II (pMHCII) tetramer staining has allowed reliable direct *ex vivo* visualization of antigen-specific CD4⁺ T cells, enabling quantification and characterization of these cells in a setting closer to their natural physiological state. The recent use of this technology in the allergy context demonstrated that the degree of differentiation of pollen allergen-specific CD4⁺ memory T cells is correlated with their functional activities and sensitivity to ASIT. These data have several important implications for understanding the basic immunologic mechanisms involved in the amelioration of allergic symptoms during allergen-SIT. First, it demonstrate that allergic and non-allergic individuals have functionally and phenotypically distinct circulating allergen-specific CD4⁺ T cells which can be clearly differentiated based on their differentiation stage. Both of these subsets actively respond to natural allergen exposure, but they appear to play markedly different roles in allergic disease. While CD27⁺ allergen-specific memory CD4⁺ T cells are detected in both allergic and non-allergic subjects, CD27⁻ allergen-specific memory CD4⁺ T cells were exclusively observed in allergic subjects. CD27⁻ allergen-specific CD4⁺ T cells were associated with T_H2 cytokine production, providing a clear functional connection with allergic disease. In contrast, CD27⁺ allergen-specific CD4⁺ T cells were associated with IFN- γ and IL-10 production and represent the only subset observed in non-allergic individuals, implying that these cells were protective and play a role in tolerance to allergens. Finally, the *ex vivo* tetramer staining approach revealed that successful ASIT leads to selective elimination of CD27⁻ allergen-specific T cells (allergic disease related T cells) in the peripheral blood without significant changes in the CD27⁺ counterpart. These data suggest a novel mechanism in which the depletion of allergen-specific T_H2 cells might be a prerequisite for the induction of specific tolerance. Importantly, this could lead to the development of predictive markers for the clinical success of ASIT but also to new vaccine strategies to enhance the power of allergen-specific Immunotherapy.