Editorial

CD27 expression on allergen-specific T cells: A new surrogate for successful allergen-specific immunotherapy?

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To date, allergen-specific immunotherapy (ASIT) is the only causal treatment for allergic diseases. The principle of ASIT is to administer gradually increasing doses of allergen, either as allergen extracts or as recombinant allergen. The aim is to reprogram the allergen-specific immune response from a T_H2-driven IgE-dominated response toward a tolerant state. By inducing immune tolerance to an allergen, diseases such as allergic rhinitis might even be prevented in progressing toward a severe chronic disorder, such as asthma. Although the concept of specific immunotherapy is more than 100 years old,[1] our knowledge about the underlying immunologic mechanisms is limited (for overview, see Fig 1[2,3]). Moreover, some patients are clinically unresponsive to ASIT, and the identification of solid predictors for successful ASIT remains an unmet clinical need.

In this issue of the *Journal*, Wambre et al[2] demonstrate that ASIT leads to selective elimination of terminally differentiated allergen-specific T_H2 cells in the peripheral blood of patients with alder pollen allergy. Allergen-specific effector cells were characterized by lack of expression of CD27, the TNF receptor superfamily member of costimulatory molecules. This important study implies that the differentiation state determines the pathogenic relevance of allergen-specific T cells and that elimination of terminally differentiated allergen-specific T_H2 cells might be a prerequisite for the induction of specific tolerance. Importantly, the results of this study could lead to the development of predictive markers for the clinical success of ASIT.

The first transient effect of ASIT is an early increase in allergen-specific IgE levels but also in specific IgG_1 and IgG_4 antibody levels. The biologic relevance of increases in immunoreactive serum IgG and IgG_4 levels after ASIT has been questioned because of the poor correlation with improvement in clinical symptoms. As levels of specific IgG, especially IgG_4, continue to increase, specific IgE levels gradually decrease in the course of ASIT, accompanied by blunting of seasonal increases in IgE.[3] This can most likely be explained by the differentiation of increasing numbers of regulatory T cells, shifting the cytokine profile from a T_H2 toward a regulatory cytokine pattern.[4,5] In addition to regulatory T cells, allergen-specific T_H1 cells seem to contribute to the counterbalancing of T_H2 cells.[6,7] The emerging regulatory T cell/T_H1-like cytokine profile presumably induces B cells to undergo isotype switching. After discontinuation of immunotherapy, as allergen-specific IgG_4 levels eventually return to near-baseline levels, allergen-specific IgE levels gradually recover. In spite of this, the clinical benefits of ASIT prevail as long as 2 years after discontinuation of treatment. This seemingly paradoxical finding was only recently explained by the persistence of a few highly bioactive IgG antibodies that competitively inhibit the binding of IgE-allergen complexes to the surface of immune effector cells.[8] How this selective persistence of inhibitory antibodies is achieved is not known.

With respect to predictors of successful immunotherapy, a high ratio of serum specific to serum total IgE was found to correlate with the effectiveness of ASIT.[9] However, given the fact that specific IgE levels to seasonal allergens, such as pollen, can vary considerably depending on seasonal changes in exposure, it remains to be determined how solid this relationship is in predicting the outcome of ASIT. Conclusively, many questions remain in explaining how and why immunotherapy does or does not work. To address these questions, we have to better understand the early immunologic steps that ultimately result in a protective antibody response. In fact, a key might be to learn more about the T-cell responses to allergens in healthy subjects, allergic patients, and patients undergoing immunotherapy.

When attempting to analyze allergen-specific T-cell responses *ex vivo*, one inevitably encounters the problem of low precursor frequencies. The seminal work by Wambre et al[2] deals with this problem in an elegant way by using allergen peptide-specific MHC class II tetramers. The tetramer technique, formerly restricted to MHC class I–restricted peptides, now allows *ex vivo* monitoring of allergen-specific T_H cells without the requirement of prolonged *in vitro* expansion.[10] The present work of Wambre et al[2] focuses on the comparison of allergen-specific $CD4^+$ T cells of alder pollen–tolerant subjects, patients with alder pollen allergy, and patients with alder pollen allergy who successfully completed ASIT. The authors show that $CD4^+$ T cells specific for the major allergen Aln g 1 are present in both tolerant and allergic subjects reacting to the same immunodominant epitope; however, they are present at different frequencies. These cells predominantly display a memory phenotype and are functionally active during natural pollen exposure in nonallergic and allergic subjects. The key finding is that Aln g 1–specific $CD4^+$ T cells from alder pollen–tolerant subjects and patients with alder pollen allergy differ in their differentiation state: Aln g 1–specific $CD4^+$ T cells from alder pollen–tolerant subjects express CD27,

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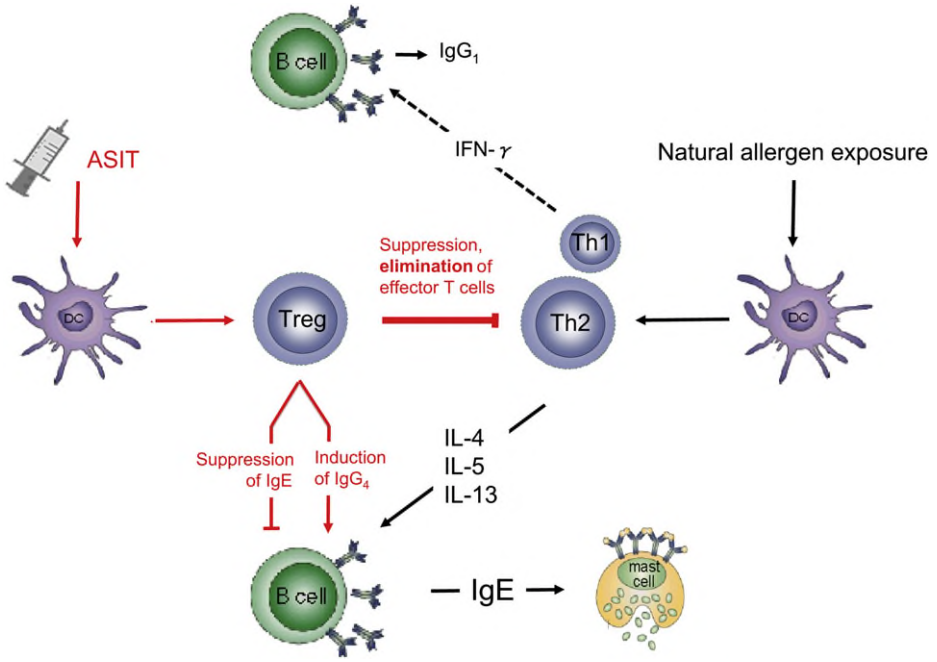

FIG 1. Changes in T-cell and antigen responses during ASIT. In susceptible subjects naturally exposed to an allergen, dendritic cell *(DC)*–derived signals lead to the differentiation of T_H2 cells, which induce specific IgE production in B cells. During ASIT, increasing doses of allergen are administered. Through mechanisms that are incompletely understood to date, this licenses DCs to induce the differentiation of regulatory T *(Treg)* cells, which functionally inhibit the allergen-specific effector cells and promote the production of specific inhibiting IgG_4 antibodies by B cells. Wambre et al[2] now provide evidence that in patients who successfully completed ASIT, allergen-specific effector (T_H2) cells are selectively deleted while allergen-specific T_H1-like cells prevail. Modified with permission from Akdis and Akdis.[3]

which is concordant with a central memory phenotype. In contrast, Aln g 1–specific $CD4^+$ T cells from patients with alder pollen allergy fall into 2 subsets, with the smaller subset expressing and the larger subset lacking CD27, marking them as terminally differentiated effector cells. Cytokine and chemokine profiles of the 2 subsets are highly divergent: the $CD27^+$ subset expresses CCR7 and T_H1-associated markers, such as CXCR3 and IFN-γ, whereas the $CD27^-$ cells are $CCR7^-CCR4^+CRT_H2^+$ and express the T_H2 cytokines IL-4, IL-5, and IL-13. Most interestingly, this $CD27^-$ population of Aln g 1–specific T_H2 cells was preferentially deleted in patients after successfully completed immunotherapy, whereas their T_H1-like $CD27^+$ counterparts prevailed.

The finding that allergen-specific T_H2 cells are highly differentiated effector cells characterized by loss of CD27 expression is in good agreement with recent data on the heterogeneity of T_H2 cells either analyzed *ex vivo* or differentiated by *in vitro* differentiation protocols. This work showed that $IL\text{-}4^+IL\text{-}13^+$ T_H2 cells coexpressing IL-5 are $CD27^-$ are generated after recurrent antigenic exposure and represent a subset of highly differentiated T cells.[11] Interaction of the costimulatory molecule CD27 on the T cell with its ligand, CD70, on dendritic cells has recently been implicated in supporting the differentiation of T_H1 cells.[12,13] On the T-cell side, CD70 expression is restricted to T_H1 cells and might serve to amplify T_H1-instructing signals in T/T-cell interactions through a positive feedback mechanism.[12] This raises the question of whether loss of CD27 expression on allergen-specific $CD4^+$ T cells is *per se* sufficient and necessary for the progression of differentiation into pathogenic T_H2 cells. It would certainly be interesting to compare CD27 expression on allergen-specific memory T cells of nonsensitized subjects, subjects who are sensitized but asymptomatic, and sensitized subjects with clinical allergic symptoms.

Another important issue to be addressed in future studies is to examine the role of $CD27^-$ allergen-specific $CD4^+$ T cells in patients who have completed specific immunotherapy but are clinically nonresponsive. It is to be expected that a deletion of the $CD27^-$ allergen-specific $CD4^+$ T-cell subset will not be observed in these patients. Future prospective studies that monitor CD27 expression on allergen-specific T cells during the course of ASIT will reveal whether CD27 is a suitable early marker distinguishing between responders and nonresponders of immunotherapy.

The findings of Wambre et al,[2] originally linked to the allergy immunotherapy field, might even reflect a general principle in immune responses to vaccination. Of note, a recent report assessed the T-cell response to different vaccinia virus strains. Here a strongly replicating vaccinia virus strain that promoted the generation of high numbers of protective memory $CD8^+$ T cells engaged the TNF receptor family costimulatory receptors OX40 and CD27, whereas a weakly replicating strain, which was a poor inducer of a protective $CD8^+$ T cell response, did not engage OX40 or CD27.[14] Engagement of CD27 might therefore turn out not only to be a surrogate for successful immunotherapy but also a novel tool to enhance the power of allergen vaccines.

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