

Allergy or Tolerance, That's the Question

Beatrice Jahn-Schmid

Department of Pathophysiology, Medical University of Vienna, Vienna, Austria

CD4⁺ T helper cells have been recognized as major players in the development and maintenance of type I allergy. Originally the Th1/Th2 paradigm explained that allergy is due to an overwhelming allergen-specific Th2 response and insufficient counter-regulation by the Th1-arm of the cellular response [1]. During the last decade, T cell-mediated regulatory mechanisms that control immune responses became overt. This had long been missed by the scientific community due to the relative anergic behaviour of the respective cell subsets, which hardly proliferate or produce inflammatory cytokines like known T effector cell populations. Tolerance to self antigens, but also to exogenous antigens including allergens, is maintained by strong active suppression executed by certain regulatory cells mainly of the CD4⁺ T cell subset. This quite heterogeneous subset is collectively called 'regulatory T cells' (Treg) and comprises thymus-derived natural (n)Treg with a CD4⁺CD25⁺ phenotype constitutively expressing the transcription factor Forkhead box 3 (FoxP3), as well as adaptive or inducible (i)Treg that are induced in the periphery upon repetitive antigenic stimulation. While nTreg suppress their target cells in a contact and granzyme B-dependent manner, iTreg suppress through inhibitory cytokines such as IL-10 or TGF- β . Treg apparently express rather heterogeneous phenotypes, and there are no conclusive panels of markers for the identification of Tregs are CD4, CD25 (high levels), FoxP3 and CD127 (low levels) [2].

In allergy, the first observations of suppressive mechanisms operating through IL-10 and CD4⁺ T cells were made in allergic patients after specific immunotherapy

(SIT) with bee venom or different inhalant allergens (ref. in [3]). In principle, successful SIT results in a drastic suppression of allergen-specific T cell responses mediated by Treg through IL-10 and TGF- β and a shift from Th2 towards Th1/0. Non-allergic individuals do not principally ignore allergens, but show weaker Th1/0-biased allergen-specific T effector cell responses. In line, a lower frequency of allergen-specific CD4⁺ T cells in the peripheral blood of non-allergic subjects could recently be demonstrated by the use of HLA-class II/peptide tetramers specific for allergens from cat or pollen [4–7]. Increased IL-10-production was observed in non-allergic subjects with high dose exposure [8–10]. Comparing IFN- γ -, IL-4-, IL-10-producing T cells from allergic and non-allergic subjects, Akdis et al. [11] found that Tr1-like cells represented the dominant allergen-specific subset in healthy individuals which were CD4⁺CD25⁺ and used multiple suppressive mechanisms: IL-10 and TGF- β as secreted cytokines, and cytotoxic T lymphocyte antigen 4 and programmed death 1 as surface molecules [11]. Thus, tolerance to allergens in healthy individuals seems also to be mediated by regulatory mechanisms.

In the current issue of *International Archives of Allergy and Immunology* Domdey et al. [10] examine the role of Treg and IL-10 and TGF- β in timothy grass pollen-allergic and non-allergic individuals. The authors stimulated PBMC of both groups with natural, purified Phl p 1 or Phl p 5 and observed higher proliferation and Th2 cytokines but no difference in IL-10-production in allergic subjects. Interestingly, blocking of IL-10 and TGF- β led to an increase of IL-10 in allergic but not in non-allergic subjects.

Under these blocking conditions, an increase of proliferation and especially IFN- γ production in the allergic group was also found. In healthy individuals, blocking of suppressive cytokines had no influence on cytokine production or proliferation in PBMC. These results are striking, since increased IL-10 levels had been reported in non-atopic individuals in previous studies and one would rather expect a defect in suppression of at least Th2 responses in allergy. The regulatory effect described was apparently allergen-specific, since parallel experiments with a control antigen did not show differences between both groups.

To investigate the mechanism underlying the observed differential regulation, the authors compared Treg cells, which were characterized as CD4⁺CD25^{hi} cells, as possible source of the suppressive cytokines in PBMC of both groups. The frequency of CD4⁺CD25^{hi} was found to be similar. To detect potential differences within this Treg population, Domdey et al. compared expression of CCR4 (a chemokine receptor involved in trafficking to secondary lymphoid organs and sites of inflammation and found on skin/lung homing T cells) and CLA (a skin homing molecule). Interestingly, differential expression of CCR4 and CLA was observed: atopic donors had a higher frequency of CLA⁺, but a lower frequency of CCR4⁺

Treg cells. Recently, Nguyen et al. [12] have found no difference in CCR4-expression between allergic and non-allergic subjects. This divergence may be due to the additional marker used to define their Treg population (CD4⁺CD25^{hi}CD127^{lo}). Ahern et al. [13] also found no differences in the expression of several chemokine receptors including CCR4 on CD4⁺CD25^{hi} Treg which were characterized as mainly Foxp3⁺ and CD127^{lo/-}. These controversial findings concerning the Treg phenotype or function are possibly due to different experimental setups. Obviously, in this field of research it is difficult to compare and interpret data from different laboratories. The type of allergy, definition of cell subsets or even time of blood sampling relative to pollen season may influence the results.

In conclusion, the study by Domdey et al. reporting differences between allergic and non-allergic individuals with respect to regulatory mechanisms and molecules involved in trafficking provides an interesting contribution to the question of what distinguishes allergy from tolerance. The cellular background of this disparity certainly needs more research for clarification. The presented data may instigate interest in the cellular origin of allergen-specific suppression and tissues or microenvironments relevant for priming/sensitization or homing of iTreg.

References

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