

EDITORIAL

Systemic immune response to specific immunotherapy

Introduction

Specific immunotherapy (SIT) of IgE-mediated allergy can be described as the administration of increasing doses of allergen extract to sensitized subjects [1]. The efficacy of SIT has been proven in numerous controlled clinical studies [2,3]. The therapy form has been known and practiced for almost a century [4], however, for a long time the mechanisms underlying successful immunotherapy have not been identified, and the treatment was used on an empirical basis. As a consequence of desensitization treatment, a reduction of number and activity of allergic effector cells could be demonstrated [5]. Moreover, SIT leads to a rise of allergen-specific IgG [6]. This observation had previously been interpreted as the formation of blocking antibodies, which capture and 'neutralize' the allergen before it interacts with mast cell-bound IgE. Furthermore, a feed-back inhibition of IgE by allergen-specific IgG has been discussed. Today, the production of specific IgG is considered as an epiphenomenon, because identical IgG-rises can be observed in non-responders to SIT [7]. Follow-up studies of hyposensitized patients indicated that the therapy success still persists while the levels of allergen-specific IgG have returned to the starting point [8].

Research of the last decade elucidated crucial pathogenetic events in the development of Type-I allergy. It became clear that the production of IgE antibodies is regulated by cytokines produced by a special subpopulation of T helper cells (TH), so called TH₂ cells, which are characterized by the secretion of large amounts of IL-4, the strongest inducer of IgE synthesis, and IL-5, a differentiation and activation factor for eosinophil granulocytes. TH₂ lymphocytes represent one extreme in a broad range of CD4⁺ TH cells with overlapping functions. These functions are mediated by the composition of the cocktail of cytokines produced by the cells [9]. On the other extreme end of this spectrum a cell designated TH₁-lymphocyte can be defined. Also this cell type is associated with inflammatory pathologies. The respective diseases, like delayed-type hypersensitivity and some autoimmune diseases, are typically caused by activated inflammatory cells. The cytokine profile of TH₁ lymphocytes is characterized by the

production of large amounts of interferon gamma (IFN γ) and tumour necrosis factors (TNF). One effect of the TH₁-cytokines is the inhibition of TH₂-activities [9,10].

Immunological changes induced by specific immunotherapy

The understanding of the pathogenetic mechanisms leading to atopic allergy opened new aspects to study mechanisms operative in successful SIT and to develop novel forms of allergy treatment. It was tempting to speculate that SIT would act by modulating the allergic immune response at the level of allergen-specific TH cells, and thereby lead to an improvement in allergy symptoms. Indeed, Secrist *et al.* first reported a decrease of IL-4 production in CD4⁺ Th cells from allergic individuals after SIT [11]. SIT with bee venom resulted in a decrease of IL-4 and IL-5 and an increase of IFN γ in allergen stimulated T cell cultures [12,13]. Moreover, the influence of SIT on the cellular infiltration in mucosa and skin was analysed, and signs for TH₁ activation (increased IFN γ production) could be detected [14]. In a follow-up study, we evaluated the immunological changes induced by conventional injection immunotherapy with grass pollen extract [15]. Already after the initial dose increase phase (10 injections in weekly interval) a significant reduction in lymphoproliferative response to the allergen could be measured *in vitro*, indicating the induction of tolerance to the injected antigen. Before SIT, the majority of allergen-specific TH clones established by special cell culture methods from the peripheral blood of allergic patients, revealed a TH₂-like pattern of cytokine production in response to allergen stimulation. TH cultures produced during and after SIT displayed an altered IL4/IFN γ ratio, i.e. a shift to a phenotype more similar to TH₁ cells could be observed. In conclusion, recently published data indicate a modulation of the allergen-specific immune response at the level of TH by SIT (immune deviation). However, the clear association of these changes with clinical success of SIT remains to be demonstrated. In this issue of *Clinical and Experimental Allergy* Hakansson *et al.* describe effects of SIT on the activation of B-lymphocytes. They obviously lack stimuli for IgE-production and the expression of activation markers (CD23, CD40, HLA-DR), during the pollen season [16]. Again, the authors come to the conclusion that a shift from TH₂ to TH₁ might be the mechanism behind the absence of the signs of B-cell activation.

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In 1980, Rocklin *et al.* described the generation of antigen-specific suppressor cells during allergen desensitization [17]. As TH₁ lymphocytes can be considered as suppressor cells for TH₂ activities, this concept can be regarded as the first correct description of the mechanism operative in SIT.

Consequences for the development of novel forms of specific immunotherapy

As pointed out above, the therapeutic success of SIT depends on the recognition by and the subsequent modulation of specific TH cells. In contrast to antibodies (which characteristically recognize three-dimensional structures of an antigen), T cells react with peptide fragments which are presented to them in association with molecules of the major histocompatibility complex. Thus, for the T-cell recognition, the primary structure (sequence) of the molecule is crucial. It is well established that the cytokine production patterns of specific T cells depend on the ligation density of T-cell receptors — which correlates with antigen concentration. It has been shown that high doses of one antigen preferentially induced a TH₁ response in CD4⁺ lymphocytes, whereas low concentrations of the same antigen led to a TH₂-like cytokine profile [18,19]. One problem with the administration of high allergen doses during SIT consists in the elicitation of allergic side-effects. Hypoallergens (recombinant allergens with low IgE-binding capacity, but displaying high T cell antigenicity) could represent tools for SIT in the future [20,21]. The use of epitope peptides for silencing allergen-reactive TH is under investigation [22]. However, this approach might be hampered by the diversity of the T-cell recognition of allergens (for review see [23]).

It is known that proteins derived from intracellular bacteria (e.g. mycobacterial antigens) induce TH₁ immune responses, thereby creating an environment which is obviously more 'resistant' to allergy development [24,25]. Following this concept it can be hypothesized that coinjection of allergens with adjuvants preferentially inducing TH₁ immune responses would further improve the efficacy of the treatment. In this respect bacterial proteins, inducing IL-12-production in antigen-presenting cells could represent promising substances for immunotherapy-vaccines [26,27].

In conclusion, the concepts for future treatment of IgE-mediated allergies should be based on the experiences obtained from existing forms of immunotherapy of Type-I allergy. SIT is an efficient treatment and, SIT can be improved. Three different factors of SIT could be progressed: the allergen preparation (T cell targeting, recombinant, non-anaphylactogenic), the adjuvant (adjuvants inducing a TH₁ bias), and the route of administration (oral, sublingual). Treatment approaches aimed in an alteration of the allergic immune response by substances influencing

cytokine interactions or the regulation of IgE, should only be taken into consideration when the respective networks are understood (physiological and pathophysiological aspects) in detail. This point has not yet been reached and it is unlikely to be reached within the near future.

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