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Current approaches in allergen immunotherapy

Postępy w immunoterapii swoistej

INTRODUCTION

The beginning of immunotherapy may be traced to the end of 19th century [38] but only recently immunotherapy suitable for the treatment of allergic diseases seems to have gained its reputation.

Allergen vaccines belong to methods of complex therapy of allergic IgE-dependent diseases, such as allergic rhinitis, bronchial asthma, or allergy to insect venoms [8, 9]. Attention paid recently to the possibility of wider application of specific immunotherapy (SIT) is due to some disappointment about the fact that no expected decrease in the frequency of allergic diseases is observed, despite better understanding of the pathomechanism of immune processes in allergic reactions and wider knowledge of allergen prevention and new anti-inflammatory drugs.

Current therapy for allergic diseases and bronchial asthma is aimed at neutralizing inflammatory mediators such as histamine and leukotrienes or at inhibiting the function of inflammatory cells such as eosinophils and Th_2 lymphocytes by the administration of anti-histamine and anti-leukotrien drugs, and corticosteroids. In addition, potential therapies of the future with anti-IgE antibodies, cyclosporin / FK506 [4], soluble fragments of IL-4 receptors (Borish 1999), anti-IL-5 antibodies [19], or soluble fragments of IL-13 receptors [49], focus on neutralization of cytokines, chemokines, or adhesion molecules important in the allergic inflammatory process. This type of pharmacotherapy, especially the use of corticosteroids, is effective in controlling allergic inflammation and relieving the clinical symptoms of allergic diseases, however discontinuation of therapy results in the recurrence of symptoms on exposure to the sensitizing allergens. Therefore this therapy has a limited effect on the natural course of the disease and does not correct immunological processes underlying allergic diseases.

Specific immunotherapy (SIT) is a term used to describe the injection of allergen vaccine to an allergic individual in doses increased gradually to a maximally tolerated level, generally 10^5 times the initial dose, an equivalent to 2 to 100 μg of the major allergen. SIT in desensitized patients effectively relieves the symptoms due to the previous exposure to a specific allergen [8], and clinical benefit is observed after several months of therapy with a growing tendency towards reduction of symptoms over 3–4 years of immunotherapy. Effective SIT in patients with allergic rhinitis and asthma enables good tolerance of inhaled offending allergen and reducing clinical symptoms [9, 13, 15, 18]. The effect of clinical improvement is maintained for 3–6 years after the cessation of immunotherapy in the majority of desensitized patients [14, 16, 46]. Thus, in contrast to pharmacologic therapy, specific immunotherapy in some specific atopic patients seems to induce allergen-specific immune response responsible for the development of local allergic inflammation and for inducing permanent protective response, similar to that observed in non-atopic individuals.

However, despite numerous recent studies that were possible due to the development of new techniques of obtaining biological material and immunological techniques of marking cell phenotype, determining their activation and capacity to release inflammatory mediators, SIT mechanisms are still incompletely understood [8, 31, 36].

MECHANISMS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

Effect on serum IgE and IgG concentration

It has been demonstrated that in the course of specific immunotherapy the inhibition of IgE-dependent allergic response with the gradual decrease in the allergen-specific serum concentration IgE (asIgE) ([12] and Table I) accompanied by the increase in allergen-specific IgG and IgG_4 and a diminution of immediate and delayed skin reactivity to allergen is observed [21, 22, 33]. Initially, SIT process was explained using the theory of "blocking antibodies" [34–36], according to which exogenous allergens induced the production of antibodies of subclass IgG_4 that bind to the allergen and prevent combining allergen with IgE antibodies on the surface of mast cells or basophils. Taking into consideration the fact that it is difficult to demonstrate definitely a causative relationship between IgG_4 concentration and the effectiveness of SIT using inhaled allergens [10, 11, 40], the presence of elevated concentrations of these antibodies was determined as the indicator of persistent allergen immunity [32]. Results of recent studies suggest another possible mechanism of the above processes. It has been demonstrated that IgG induced by immunotherapy may inhibit antigen presentation to T lymphocytes, that is, in order to activate allergen-specific lymphocytes a significantly higher allergen dose is required [47].

Modulation in the activation and anergy of Th2 lymphocytes

In atopic diseases both IgE synthesis and the activation of mast cells as well as tissue eosinophils are affected by cytokines released by activated T lymphocytes of

Table I. Immunological effects of allergen-specific immunotherapy (Campbell D. et al., 2000, with author's modifications)

PRE-IMMUNOTHERAPY	POST-IMMUNOTHERAPY
Positive immediate and late skin test reaction	↓Immediate and late skin test reaction
↑Allergen-specific IgE	↓Allergen-specific IgE
↓Allergen-specific IgG	↑Allergen-specific IgG
↓Allergen-specific IgG_4	↑Allergen-specific IgG_4
↑Allergen-specific IL-4, ↑IL-5, ↓IFN-γ	↓Allergen-specific IL-4, ↓IL-5, ↑IFN-γ
↓Allergen-specific IL-10, ↓TGF-β	↑Allergen-specific IL-10, ↑TGF-β
↑Allergen-specific T cell proliferation to allergen	↓Allergen-specific T cell proliferation to allergen

Th_2 type. Many studies suggest that the basic mechanism of SIT is to modulate lymphocyte T response activated by natural exposure to allergen [8], therefore the effective SIT results in reorientation of the type of activity of specific T lymphocytes from the Th_2 domination releasing mainly interlukine 4 (IL-4) and IL-13 to protective Th_1, releasing also substantial amounts of interferon γ [30, 31].

The increase in the number of CD4+ cells revealing the expression for IFN-γ was observed in mucous membrane of patients with allergic rhinitis desensitized to grass pollen [17]. However, the failure of specific immunotherapy may be associated with the failure to reduce allergen-specific IL-4 production by T lymphocytes [2]. This change in the function of T lymphocytes seems to result in restoring normal allergic response in atopic patients, because the differentiation of B lymphocytes and IgG_4 synthesis and inhibition of IgE synthesis are associated with the effect of IFN-γ) [29, 31].

Recent studies suggest that the modulation in the functional phenotype of T lymphocytes concerns the inhibition of proliferation and activation and inducing anergy of specific T2 lymphocytes. The explanation for the above phenomena may be the change in the expression markers in mononucleated cells CD28 — a molecule co-stimulating the transmission of activation signal from TCR receptor to the inside of T lymphocyte. In this process of inducing anergy from T lymphocytes, IL-10 plays an important role by the indirect inhibition of tirosine phosphorylation and binding phosphatidiloinositol kinaze to CD28 molecule and thus blocking the transfer of the activation signal by CD28 [27].

Interleukine 10 — a cytokin with potent anti-inflammatory properties, is released mainly by the activated T2 lymphocytes, and also by B lymphocytes, monocytes and macrophages. Studies on the presence of intracellular cytokines demonstrate that at the initial stage of SIT mainly specific T lymphocytes reveal the increased IL-10 production, while B lymphocytes and monocytes producing IL-10 are involved at the stage of maintaining anergy of T cells [3]. Some authors suggest the formation of a separate population of lymphocytes Th as a result of SIT, called regulatory Tr1 [20, 28], releasing IL-10 and the growth factor β (TGF-β) — cytokines inhibiting bronchial hyperactivity and eosinophilia in the respiratory tract in experimental animals. IL-10 demonstrates the ability to inhibit the proliferation of lymphocytes stimulated by

antigen and to produce cytokines by Th_1 and Th_2 cells, and also by monocytes and macrophages. In relation to the latter, IL-10 reduces also the ability to present antigen by the inhibition of MHC molecules of class II and co-stimulating ligands, that is CD80 and CD86 molecules [27].

It has been also found that in the presence of IL-10 the inhibition of IgE production occurs and the increased synthesis of IgG_4 by B lymphocytes [26], and also the inhibition of maturation and activation of basophiles is observed [3, 29].

Summing up current approaches to the mechanism of specific immunotherapy it seems that SIT results in the increased production of IL-10 and TGF-β, that, due to autocrine mechanism, induce the anergy of specific Th_2 lymphocytes and participate in the regulation of activity of the inflammatory cells in the local allergic process and in the regulation of IgE and IgG_4 synthesis (Fig. 1).

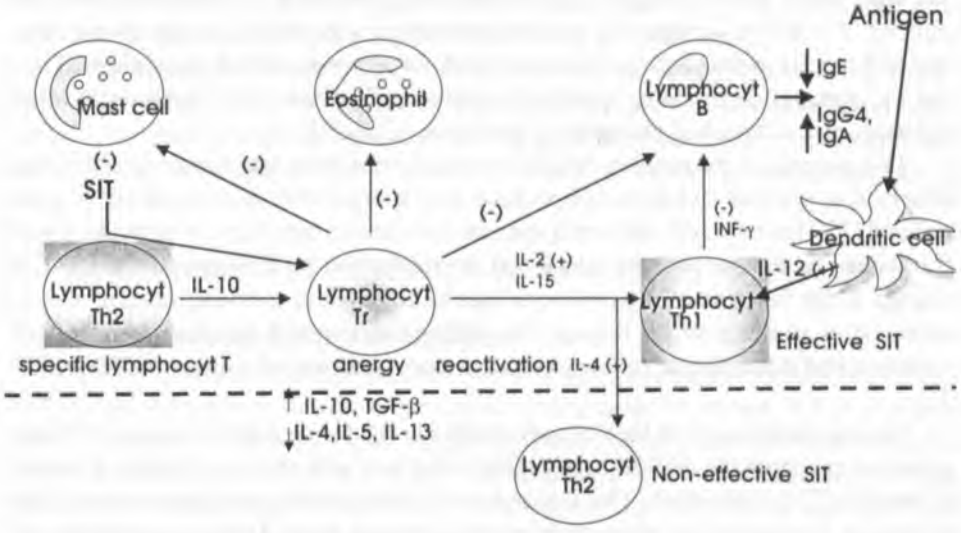

Fig.1. Mechanisms of specific immunotherapy — current view

Microenvironment as a crucial element in the SIT mechanism?

The analysis of possible mechanisms of allergen immunotherapy suggests the possible regulatory function of not only T lymphocytes but also CD8+ cells and lymphocytes $\gamma\delta$, and cells representing antigen, that form a cytokine profile of microenvironment in tissues [1, 29] and stimulate areactive T lymphocytes [6].

An important factor inducing Th_1 response is IL-12, produced mainly by cells representing antigen, and also by mast cells and granulocytes, whose local production may maintain or enhance this response [8]. The main source of IL-12 are dendritic cells, that constitute the most important population of cells representing antigen in skin and mucous membrane, where they induce lymphocyte T response [41, 45]. There is a relationship between increased mRNA expression for IL-12 and the inhibition of

Table II. Novel approaches to immunotherapy (Campbell D. et al., 2000, with author's modifications)

Type of immunotherapy	Observed effect	Possible mechanisms of action	Potential advantages	Potential disadvantages	Human use
Sublingual immunotherapy (SLIT)	Clinical improvement ↓IgE Th2→Th1 responses	Antigen-specific T cell deletion/ apoptosis IL-10/TGF-β induction ?Oral tolerance	No injections Anaphylaxis and broncho-spasm	Large allergen doses requires	Yes
Modified allergen	↓IgE Th2→Th1 responses	Reduced allergenicity ↓Mast cell degranulation	Safer Larger allergen doses possible	Difficulty with stability and manufacture	Human trials
ISS+allergen ISS-allergen	Clinical improvement Reversal of airway hyperactivity (murine)	Induction of Th1 responses Allergen-specific CD8 cells	↑Immuno-genicity	Allergen-nonspecific responses Toxic Th1 side effects	Human trials
Adjuvants+allergen, e.g.,heat-killed *Listeria, M.tuberculosis*	Prevention/reversal of airway hyperactivity(murine) Th2→Th1 responses ↓IgE	Induction of regulatory cells (IL-10/TGF-β) CD8 cells IL-12/IL-18	Very potent effects Regulatory cells limit Th1 effects		No
DNA vaccination	Reversal of airway hyperactivity(murine)	Induction of Th1 responses Antigen-specific CD8 cells		?Route of administration	No

the following skin response to the allergen as a result of effective SIT [25]. These findings may confirm the hypothesis of the Th_1 response by IL-12, and indicate the important role of dendrite cells in SIT mechanisms.

Dendritic cells are not a uniform population and they display a range of flexibility according to the site of origin (that is marrow or lymphoid progenitor cell) [48], or, in a considerable degree, to a type of activating stimulus [23, 42]. Some authors suggest that the type of induced T lymphocyte response depends on the degree of activation of dendritic cells, because it has been demonstrated that the considerable increase in the release of IL-12 and stimulation of naive T lymphocytes to type Th1 cells is observed only in a definite time following the activation of dendritic cells [23]. Other considered suggested factors that may affect the type of immunological response are: the way of transmission of co-stimulating signal by CD28 molecules and CD80 and CD86 ligands on dendritic cells, duration of contact between APC cell and T lymphocyte, and also the dose of allergen and its chemical affinity to the receptor of T lymphocytes (TCR) and MHC molecules [23]. These latter processes were a scientific basis for the improvement of the effectiveness of SIT and its safety due to the use of allergoids, that is chemically modified allergens or recombined allergens. Modifications in the conformation of epitopes that bind antibodies obtained in these specimens resulted in reducing the reaction with IgE antibodies, preserving the capacity to present synthetically prepared allergens by dendritic cells to T lymphocytes and inducing Th1 type response [43, 44]. Table II presents other suggested methods of cur-

rent specific immunotherapy that may prove to be more effective in the process of inducing tolerance and/or immune modulation in patients with allergic diseases.

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STRESZCZENIE

Mechanizmy swoistej immunoterapii (SIT) alergenami nadal nie są dokładnie poznane. Wiele jednak danych wskazuje, że zmiany odpowiedzi humoralnej są wtórne do wpływu SIT na elementy komórkowe alergicznego procesu zapalnego. Omówiono oddziaływanie SIT na komórki efektorowe reakcji alergicznej, a także wpływ na reorientację aktywności swoistych limfocytów T od dominacji typu Th_2 w kierunku Th_1. Podkreślono rolę IL-10 w indukowaniu anergii limfocytów Th_2 oraz znaczenie mikrośrodowiska, a zwłaszcza komórek dendrytycznych i IL-12, w podtrzymywaniu lub wzmacnianiu odpowiedzi typu Th_1.