

The Potential of Peptide Immunotherapy in Allergy and Asthma

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Allergic conditions contribute significantly to the burden of chronic disease in the industrialized world. Current treatments offer varying degrees of palliation. The sole proven disease-modifying strategy, specific or whole-allergen immunotherapy, is limited because of the associated risk of systemic adverse effects, such as anaphylaxis. Short, linear allergen-derived peptides, corresponding to T cell epitopes, offer the possibility of a safer approach as they are capable of inducing allergen-specific hyporesponsiveness without cross-linking mast cell-bound IgE. This review evaluates the scientific basis of peptide immunotherapy and clinical experience in allergy up to the present time.

Introduction

Allergic diseases such as asthma, rhinoconjunctivitis, and eczema are a common cause of chronic morbidity in industrialized nations and are rising in prevalence. Direct and indirect consequences include a greater financial burden on health care systems and wide-ranging socioeconomic effects, including absence from employment and education. A number of pharmacologic approaches to alleviate symptoms are available, including antihistamines, topical corticosteroids, and inhaled bronchodilators. However, many patients with moderate to severe disease experience only partial to poor symptom control. Furthermore, they often are unable to adopt standard allergen avoidance techniques, as the aeroallergens responsible for disease are widespread in the environment.

At present, the only alternative approach for patients refractory to conventional treatment is specific immunotherapy (SIT), also known as whole-allergen immunotherapy. This has proven efficacy and involves the

administration, usually by subcutaneous injection, of increasing doses of allergen extracts [1–3]. However, SIT is associated with a significant risk of IgE-mediated adverse effects, including systemic anaphylaxis, and is only obtainable on a restricted basis in the United Kingdom. North America and continental Europe continue to retain asthma as an indication for this form of therapy [4,5]. Other difficulties encountered with SIT include the poor standardization of allergen extracts and the lengthy duration of treatment. Thus, efforts are being focused on the development of other strategies to treat pharmacologically resistant disease.

The role of T lymphocytes in allergic responses has been studied extensively. CD4⁺ T helper-2 (T_H2)-type cells are increased at tissue sites in allergic diseases and asthma [6–8], accumulate at sites of allergen challenge [9–11], and correlate with symptoms [12]. T_H2 cells are capable of orchestrating the allergic response as cytokines made by these cells, including interleukin-4 (IL-4) and IL-5, are relevant in promoting immunoglobulin class switching to IgE and can initiate and stimulate the differentiation, survival, and chemotaxis of eosinophils and other effector cells that release mediators in target tissues [13]. Therefore, the ability to down-regulate T_H2-type cell function represents an important therapeutic strategy. Peptide immunotherapy is an approach that targets CD4⁺ T cells by using allergen-derived peptides containing short, linear T cell epitopes to induce tolerance. The principle has been established in animal models, and the reduced ability of short, peptide epitopes to cross-link surface-bound IgE may provide an attractive alternative to SIT in humans. Initial approaches in man have targeted allergic disorders, but analogous efforts in autoimmune conditions, such as multiple sclerosis, have also been initiated [14,15]. This review focuses on the rationale behind peptide immunotherapy targeting CD4⁺ T lymphocytes and current clinical experience in allergy.

T Cell Activation in vitro

Activation of T cells depends on two stages. The initial step is transient ligation of the T cell receptor (TCR) by an antigen-derived peptide bound in the peptide-binding groove of a major histocompatibility complex (MHC)

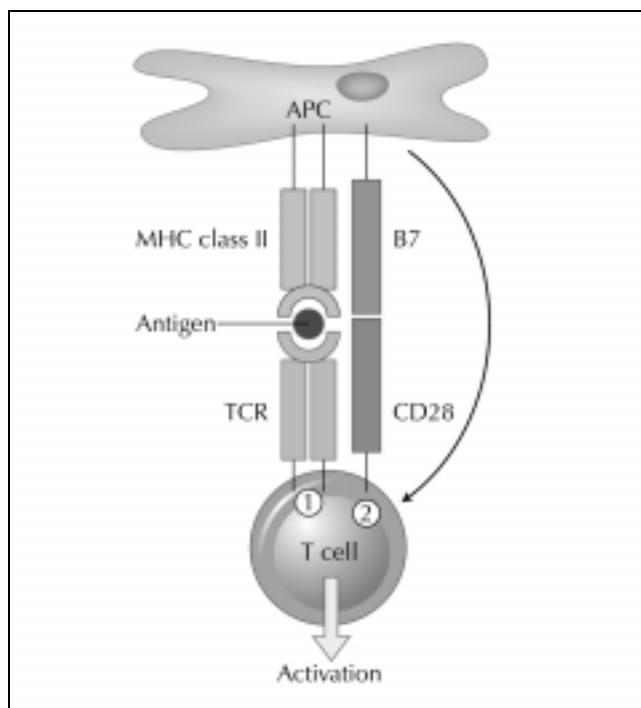


Figure 1. The two-signal model of T cell activation. APC—antigen-presenting cell; MHC—major histocompatibility complex; TCR—T cell receptor.

molecule on the surface of an antigen-presenting cell (APC). The second step is a costimulatory signal provided by triggering of cell surface molecules on the APC, such as the B7 (CD80 and CD86) family, which are ligands for the CD28 or CTLA-4 molecules on the T cell (Fig. 1). Subtle alterations to the complex series of events that gives rise to T cell activation have been shown to affect the outcome of T cell recognition of their cognate ligand.

In vitro experiments have demonstrated that different concentrations of peptides can induce activation or hyporesponsiveness, depending on the dose. Lamb *et al.* [16] employed high doses (50 µg) of peptide to render human T cells nonresponsive in vitro. Influenza virus hemagglutinin-specific human T_H0 T cell clones were exposed to supra-optimal doses of peptide in the absence of APCs. Subsequent whole-antigen challenge was characterized by antigen-specific T cell hyporesponsiveness (anergy), which could be prevented or reversed by the addition of IL-2 [17]. The phenomenon of hyporesponsiveness was accompanied by concomitant changes in the T cell phenotype characterized by down-regulation of the TCR/CD3 receptor complex and enhanced expression of CD2 and CD25 in common with productive T cell activation events [18,19]. Further studies using supraoptimal doses of peptides in human $CD4^+$ T cell clones reactive to house dust mite reproduced clonal anergy and showed that this state was accompanied by down-regulation of IL-2 and IL-4 and maintenance of interferon- γ (IFN- γ) secretion [20].

Investigation of T Cell Responses in vivo: Animal Models

The principle that T cell peptide epitopes may be employed to induce antigen-specific hyporesponsiveness has been extensively investigated in rodent models of autoimmune disease and, more recently, in models of allergic sensitization.

Briner *et al.* [21] established a murine model of cat allergy in which two peptides (IPC-1 and IPC-2), derived from chain 1 of Fel d 1, the major cat allergen, were administered. Soluble IPC-2 was administered subcutaneously to naïve animals prior to challenge with peptide in adjuvant. The peptide-specific T cell response was assessed 10 days after challenge by the culture of mononuclear cells from draining lymph nodes. Decreased IPC-2-specific production of IL-2, IL-4, and IFN- γ was demonstrated. In addition, antigen-specific T cell proliferation was reduced. The effects of subcutaneous IPC-2 administration on animals already primed with Fel d 1 was also examined. Inhibition of T cell function was demonstrated by a reduction in IL-2 production and accompanied by reduced levels of IgG antibodies directed against IPC-2. Furthermore, combined administration of IPC-1 and IPC-2 resulted in a decrease in the T cell response (IL-2 production) to stimulation with the whole chain 1 protein.

Using the mucosal route, Hoyne *et al.* [22] performed peptide challenge and demonstrated the induction of T cell tolerance. Intranasal administration of peptides derived from the house dust mite allergen Der p 1 was not only able to prevent sensitization but could also inhibit T cell responses in previously sensitized mice. In related studies, transient T cell activation was shown to precede the induction of hyporesponsiveness [23]. Rapid activation of MHC class II-restricted $CD4^+$ T cells from lymph node or splenic tissue was observed, peaking 4 days after peptide treatment. However, at day 14, IL-2 and IFN- γ secretion, together with proliferative responses, was down-regulated. Hyporesponsiveness was short lived since rechallenge at day 21 was able to elicit a further transient T cell response that was subsequently down-regulated over time.

The tolerogenic capacity of peptide immunotherapy via the mucosal route has been further evaluated in a murine model of bee venom allergy. An admixture of three long peptides covering the whole sequence of phospholipase A_2 (PLA $_2$), the major bee venom allergen, was employed. Prophylactic administration led to a suppression of subsequent specific IgE response, whereas a therapeutic approach in presensitized mice induced a greater than 60% decrease in PLA $_2$ -specific IgE, together with a decline in the IL-4:IFN- γ ratio [24].

Clinical Studies

Early clinical studies in peptide immunotherapy addressed both perennial and seasonal allergic sensitization, specifi-

cally cat and ragweed allergy. Approximately 95% of individuals with a clinical history of cat allergy are sensitive to one protein, Fel d 1 (*Felis domesticus*), found in cat dander and saliva. This allergen is ubiquitous in the environment, present not only in the homes of cat owners but also in public places, and is transported on clothing [25]. Cloning, sequencing, epitope mapping, and preclinical studies resulted in the selection of two 27-amino acid sequences, IPC-1 and IPC-2, for evaluation in clinical trials [26].

Norman *et al.* [27] evaluated the efficacy of Allervax CAT (IPC-1/IPC-2) (ImmuLogic Pharmaceutical Corp., Waltham, MA) through a double-blind, placebo-controlled trial involving 95 cat-sensitive individuals. Following four weekly subcutaneous injections of either placebo, 7.5- μ g, 75- μ g, or 750- μ g peptides, clinical efficacy was observed only for the highest dose group, 6 weeks after the end of treatment. Clinical outcomes included nasal and lung symptoms during a 60-minute exposure in a room inhabited by live cats. Peptide injections were associated with a significant number of early and late adverse events, including chest tightness, nasal congestion, and flushing. These occurred a few minutes to several hours after administration of the peptides. Interestingly, in the 750- μ g group, the incidence and severity of symptoms decreased progressively with each subsequent dose, implying the induction of tolerance to the peptides. In an associated study, a decrease in IL-4 production by IPC-1/IPC-2-specific T cell lines from subjects in the 750- μ g group was demonstrated, although there was no alteration in cytokine production by whole cat dander-specific lines. Furthermore, the proliferative responses to either peptide or whole allergen remained unchanged [28].

In a related study, peptide immunotherapy was evaluated in cat allergic asthmatic subjects using inhaled allergen challenge. Pène *et al.* [29] performed allergen PD₂₀ before and after a variable cumulative dose of Allervax CAT. Subjects received between two and six injections of placebo or peptides (7.5, 75, or 750 μ g per injection). Six weeks after ending therapy, post-treatment PD₂₀FEV₁ was not significantly different between the treated and placebo groups. However, in the 75- μ g and 750- μ g groups, there was significant improvement between baseline and post-treatment days. In addition, IL-4 release was significantly reduced in the high-dose group. No change was observed in IFN- γ production.

In a randomized, double-blind, parallel-group study [30], 40 cat-allergic subjects received subcutaneous injections of 250- μ g peptides or placebo weekly for 4 consecutive weeks. Peptide treatment did not result in reduced early- or late-phase skin reactivity to whole cat extract up to 24 weeks after the last injection. Furthermore, in vitro cell culture assays showed no significant change in cat antigen-specific cytokine production. Frequent adverse effects, including symptoms of asthma, rhinitis, and pruritus, were reported.

To further investigate the safety and efficacy of IPC-1 and IPC-2, Maguire *et al.* [31] undertook a multicenter, randomized, double-blind, placebo-controlled study of 133 cat-allergic patients who were chronically exposed to cats or had failed previous conventional SIT. Subjects received subcutaneous injections of either 75- μ g or 750- μ g peptides or placebo twice weekly for 2 weeks in two treatment phases, 4 months apart (a total of eight injections). Pulmonary function was improved in the 750- μ g group, but only in those subjects with reduced baseline FEV₁, at a single time point 3 weeks post initial treatment phase. A large number of adverse events were recorded, including the requirement for systemic epinephrine in three peptide-treated patients. The majority of adverse events were associated with respiratory symptoms, occurred a few hours after injection, and declined with successive doses.

Adverse Events in Peptide Immunotherapy

Clinical application of Allervax CAT peptides was associated with frequent adverse effects occurring immediately and up to several hours after peptide injection. Early events may have been due to the length of IPC-1 and IPC-2. Each peptide was 27 residues in length and may have contained conformational determinants (B cell epitopes) capable of triggering IgE-mediated reactions through the cross-linking of surface-bound IgE on mast cells and basophils. Late reactions diminished with successive injections and may have been the correlate of the transient T cell activation and subsequent hyporesponsiveness seen in murine models. The high frequency of adverse events, together with only modest improvement in symptom scores, led to the withdrawal of Allervax CAT and a related product (Allervax RAGWEED; ImmuLogic Pharmaceutical Corp.) from clinical studies.

Peptide Therapy for Bee Venom Allergy

In bee venom-sensitized individuals, PLA₂ represents the major allergen. Müller *et al.* [32•] used an equimolar mixture of three T cell epitopes of PLA₂ (each between 11 and 18 residues long) to treat five patients who had experienced IgE-mediated systemic allergic reactions to bee stings. Ten patients allergic to bee venom receiving SIT served as control subjects. Peptides were administered in an induction phase consisting of an incremental dosing schedule starting at 0.1 μ g and leading to three maintenance injections of 100 μ g each. The total dose received was 397.1 μ g over 2 months. This corresponded to an amount of PLA₂ 40 times higher than that which is normally applied in bee venom SIT. Patients were then challenged with subcutaneous PLA₂ (approximately corresponding to the PLA₂ content of a bee sting) followed 1 week later by a live bee sting. No allergic side effects were reported by the peptide-treated group, and all subjects tolerated the PLA₂ challenge without systemic

symptoms. Two peptide-treated patients developed mild systemic allergic symptoms after the bee sting challenge. After peptide immunotherapy, specific proliferative responses by peripheral blood mononuclear cells (PBMCs) to PLA₂ and the peptides were decreased in the three successfully treated patients. The production of T_H1 (IL-2, IFN- γ) and T_H2 (IL-4, -5, -13) cytokines also was inhibited, and B cells were unaffected in their capacity to produce specific IgE and IgG4 antibodies. Levels increased after allergen challenge in favor of IgG4, as expected with conventional SIT. Further experiments revealed an increase in allergen-specific IL-10 production in these individuals (Akdis and Blaser, personal communication), findings that support earlier data from whole bee venom-treated patients [33••].

Induction of Isolated Late Asthmatic Reactions With Peptides

To more clearly define the role of the CD4⁺ T cell in the induction and maintenance of the late asthmatic reaction, Haselden *et al.* [34••] synthesized three overlapping peptides (designated FC1P) spanning the central region of chain 1 of Fel d 1 and challenged cat-allergic, asthmatic subjects by intradermal injection. Importantly, each peptide was only 16 or 17 residues in length, reducing the ability to cross-link IgE. In vitro histamine release assays supported the reduced allergenicity of the FC1P preparation. A dose of 80 μ g FC1P was administered as a single injection to 40 cat-allergic asthmatics. No reaction was observed at the injection site. However, nine out of the 40 subjects experienced an isolated late asthmatic reaction (LAR), defined as a fall in FEV₁ of 20% or more, 2 to 3 hours after challenge and reaching a plateau at 6 hours. The induction of an isolated LAR without the preceding early phase suggested that peptides bound to MHC molecules could directly activate T cells in the absence of mast cell activation. Rechallenge of subjects with the same dose of FC1P demonstrated the induction of peptide-specific hyporesponsiveness in the lung, suggesting the induction of antigen-specific T cell “tolerance” following transient T cell activation (Fig. 2).

The Major Histocompatibility Complex in Peptide Therapy

Only 25% of subjects demonstrated LARs following administration of FC1P. HLA haplotyping identified DR molecules that appeared to be present at high frequency in the group of subjects developing LARs. Using cat allergen-specific T cell lines and a panel of fibroblasts transfected with human HLA-DR molecules, strong support was provided for MHC restriction of two of the three FC1P peptides. Four out of nine “reactors” were found to express HLA-DR13 as opposed to one out of 31 “nonreactors.” DR13-transfected L cells presented the third of the FC1P peptides to autologous T cell lines. Similarly, DR1 and DR4

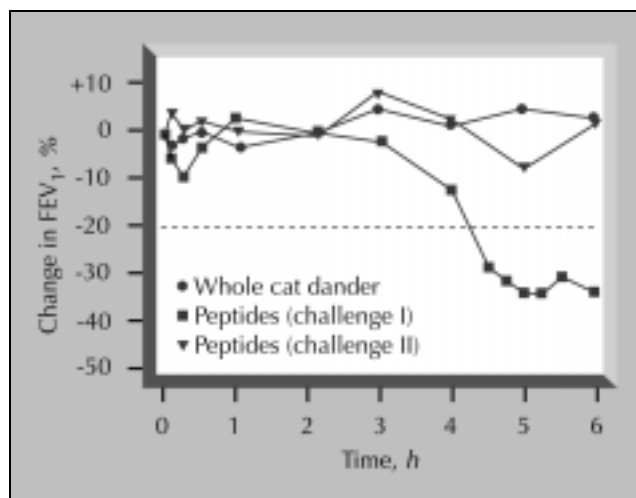


Figure 2. Induction of isolated late asthmatic reaction by intradermal injection of 5 μ g Fel d 1–derived peptides and demonstration of attenuation of the reaction at repeat challenge. FEV₁—forced expiratory volume in 1 second.

bound and presented FC1P peptides. Furthermore, “promiscuous” binding of two peptides was demonstrated, with binding to more than one MHC molecule.

Taken together, these findings imply that successful immunotherapy must take into account the differing HLA haplotypes present in an outbred population. Thus, the number of peptides required to treat all allergic individuals must necessarily be larger than the small number used in studies with inbred animal strains. This may account for the limited clinical benefit seen in the early peptide immunotherapy trials discussed, in which MHC restriction was not considered and fewer peptides were administered.

Major Histocompatibility Complex–based Peptide Vaccines

In further studies, 12 overlapping peptides (each 16 to 17 residues long) spanning the majority of chains 1 and 2 of Fel d 1 were synthesized, increasing the number of HLA haplotypes able to bind and present peptide [35•]. Using this preparation of peptides, termed “multiple overlapping peptides” (MOP), it was demonstrated that the magnitude, as well as the frequency, of isolated LARs in cat-allergic, asthmatic subjects was dose dependent, with 50% of individuals developing an LAR when challenged with a single 5- μ g dose of peptides. A second injection of peptides was associated with a marked reduction or absence of the LAR, with a return to baseline values over up to 40 weeks. Maximal attenuation occurred 2 to 4 weeks after the initial peptide challenge, suggesting an active immunologic process.

More recently, an open study employing an up-dosing protocol with peptides (0.1, 1.0, 5, 10, and 25 μ g) injected at 2-week intervals demonstrated the ability to induce T cell hyporesponsiveness in the absence of LARs. These results

indicate that incremental dosing protocols, starting at a dose that is too low to induce LARs, may allow peptide immunotherapy to be used safely, without adverse effects [36].

Following a single peptide injection, cutaneous late-phase reactions (LPRs) to intradermal challenge with whole cat dander extract were significantly reduced [35•]. To confirm these observations in a blinded study, 24 cat-allergic subjects were recruited into a double-blind, placebo-controlled study, with 16 subjects randomized to peptides via an incremental dosing protocol, to a total dose of 90 µg [37]. Following peptide treatment, a significant reduction in both the early and late cutaneous reactions to Fel d 1 and also to whole cat dander was observed, indicating peptide-induced modulation of both B cell (early-phase reaction) and T cell function (LPR), respectively. Changes in late cutaneous reactions were observed within 3 weeks of completing treatment and persisted for several months. Changes in early cutaneous reactions were only apparent at long-term follow-up (4 to 12 months). No significant differences were demonstrated in bronchial responsiveness to either methacholine or whole cat dander, although actively treated subjects were better able to tolerate exposure to cats.

In vitro T cell responses before and after peptide treatment demonstrated a significant decrease in peptide- and whole allergen-induced proliferation of PBMCs and the production of IL-4, IL-13, and IFN-γ in cultures. Similar inhibitory responses to four additional Fel d 1-derived peptides that did not form constituents of the mixture injected were demonstrated, suggesting the induction of linked suppression [35•]. Furthermore, peptide treatment was not only associated with decreases in whole cat dander-induced proinflammatory cytokines by PBMCs but also with increased IL-10 production (unpublished data). Thus, induction of T cell hyporesponsiveness in man may be associated with the induction/expansion of a population of regulatory/suppressor T cells.

Potential Mechanisms of Peptide Immunotherapy

The nature of T cell hyporesponsiveness induced by allergen-derived peptides remains incompletely understood. Peripheral T cells may be inactivated by a number of mechanisms, including induction of T cell anergy (unresponsiveness without a decrease in cell numbers), clonal deletion (activation-induced cell death), the induction of active suppression via a regulatory T cell population, or immune deviation (a shift in phenotype from T_H2 to T_H1).

T cell anergy

T cell anergy has been well described in murine studies using allergen-derived peptides [21–23] and also in human CD4⁺ cells in vitro [16–19]. The mechanism of inhibition of T cell responses remains enigmatic. Lack of appropriate costimulation has been proposed, although transient

CD4⁺ T cell activation has been observed in certain studies and is thus difficult to reconcile with suboptimal cell signaling [23,34••,35•]. It now appears that many previous descriptions of T cell anergy as a functional outcome may have been models in which immunoregulatory, antigen-specific T cells were induced.

Regulatory T cells

The role of regulatory T cells has been the focus of much recent interest. Elevated IL-10 levels secondary to peptide treatment support a mechanism of active suppression (Fig. 3). Animal models of autoimmune disease have shown that regulatory T cell populations and cytokines, including IL-10 and transforming growth factor-β (TGF-β), appear to be important factors in the modulation of T_H1 and T_H2 responses [38,39]. Akdis *et al.* [33••], employing either whole bee venom or peptides from PLA₂, demonstrated that successful immunotherapy in bee venom-sensitive subjects was associated with the production of IL-10. However, T cell hyporesponsiveness in this model was partially reversed in vitro by the addition of exogenous IL-2 or IL-15 [40], suggesting that further clarification is required to either unify or dissociate the classic anergy model and active suppression by regulatory T cells. Recently, Levings *et al.* [41•] demonstrated the ability to expand cultured regulatory T cells in vitro by the addition of exogenous IL-2. Thus, in vitro hyporesponsiveness after venom immunotherapy may have been due to the induction of regulatory T cells. The presence of elevated levels of IL-10 production post-therapy in this model adds further support.

Intra- and intermolecular suppression

A number of studies have described the ability of antigen-specific T cells, induced by peptide or whole antigen, to modulate the response of distinct populations of T cells specific for other epitopes located within the same or different molecules. These studies include descriptions of regulatory CD4⁺ T cells that can confer nonresponsiveness either to other epitopes within the whole molecule (linked or intramolecular epitope suppression) [42], adjacent molecules (bystander tolerance or intermolecular suppression), or the next generation of regulatory T cells (infectious tolerance) [43]. Studies using overlapping Fel d 1-derived peptides have shown that T cell responses to noninjected peptides and to whole allergen were down-regulated at the same time as those to injected epitopes [35•]. Taken together, these findings provide evidence of linked suppression in human studies and suggest that in the future, peptide immunotherapy may be successfully based on only a limited number of peptides.

Cell contact-dependent regulation

Regulatory T cells may induce suppressive effects via cell-to-cell contact. Using a mouse model, Hoyne *et al.* [44••,45] showed a role for cognate interaction between

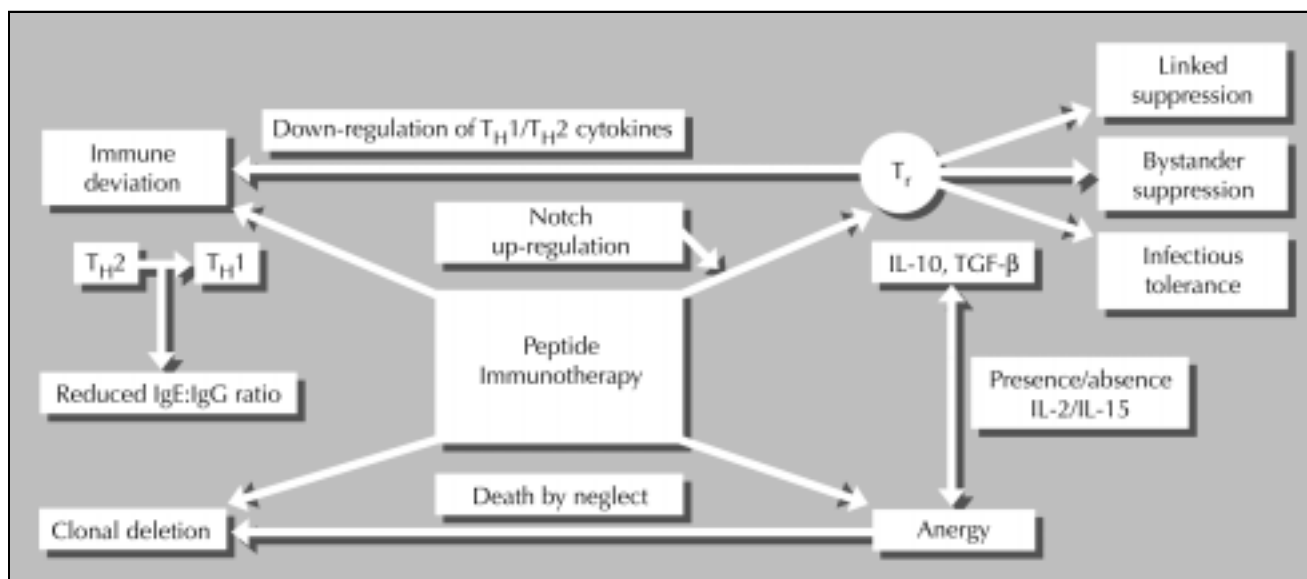


Figure 3. Potential mechanisms of tolerance induced by peptide immunotherapy. Peripheral T cells may be inactivated by a number of routes, including induction of T cell anergy, clonal deletion, immune deviation (T_H2 to T_H1/T_H0), or the induction of active suppression via a regulatory T cell population (T_r), acting via the production of immunosuppressive cytokines, such as IL-10 and TGF- β , or up-regulation of Notch receptor.

T cells mediated by Notch/Delta signaling to induce and maintain peripheral T cell tolerance to Der p 1. Intranasal peptide administered at high dose was found to produce transient expression of Delta1 on inhibitory $CD4^+$ T cells. Ligation of the Notch 1 receptor on adjacent T cells by Delta1 $^+$ regulatory cells prevented clonal expansion.

Clonal deletion

Clonal deletion is known to play a major role in central tolerance during thymic maturation. In an experimental model of mucosal tolerance employing transgenic mice overexpressing the ovalbumin-specific TCR gene, high-dose treatment with antigen induced clonal deletion via apoptosis. Interestingly, low-dose ovalbumin produced TGF- β - and IL-10-secreting regulatory cells, which inhibited specific T cell responses [46]. However, from the studies available, it appears unlikely that this mechanism plays a major role in the hyporesponsiveness induced by peptides.

Immune deviation

Immune deviation from a T_H2 to a T_H1/T_H0 profile has been demonstrated in a large number of studies using conventional SIT and has been associated with a change in the IFN- γ :IL-4 ratio in favor of the former [47]. Two studies investigating IPC-1 and IPC-2 in humans found a reduction in Fel d 1-specific IL-4 production by PBMCs or T cell lines in the high-dose treatment group, without a change in IFN- γ [28,29]. Immunosuppressive cytokines, such as IL-10 and TGF- β , were not measured in these studies. Results from our group [35•] and also from Müller *et al.* [32•] demonstrated a generalized reduction in proliferative and T_H1/T_H2 cytokine responses, together with an increase in IL-10 production, following peptide treatment.

It may be, therefore, that as a result of the way in which soluble peptides are presented to the immune system (perhaps by immature, nonactivated or nonprofessional APCs), a form of immune deviation is induced. In contrast to that induced by conventional whole-allergen immunotherapy, peptide therapy may result in the induction of regulatory T cells that suppress both T_H1 and T_H2 responses (Fig. 4). As a result, peptide immunotherapy may also be of particular interest in autoimmune diseases in which peptide epitopes have been identified.

Conclusions

An increasing number of studies in both murine and human models suggest that peptide immunotherapy may offer a safe and effective approach for the management of allergic disease. While further work is undertaken to determine the exact mechanism of induction of tolerance, the contributory role of regulatory T cells appears to be a common feature of many studies. The use of short peptides to eliminate the likelihood of IgE-mediated side effects may be a prerequisite for success in allergic disease. For maximal efficacy, with the minimum number of peptides, the identification of T cell epitopes that have a broad MHC-binding ability may be considered when designing peptide vaccines. Dose and dose interval selection may also prove critical for the development of optimal hyporesponsiveness in the absence of adverse events. Peptide immunotherapy may be broadly applicable in all areas in which immunopathology is controlled by T lymphocytes. With regard to allergic conditions, the ability to deliver safe and effective vaccines that do not require extensive time and resource commitments from

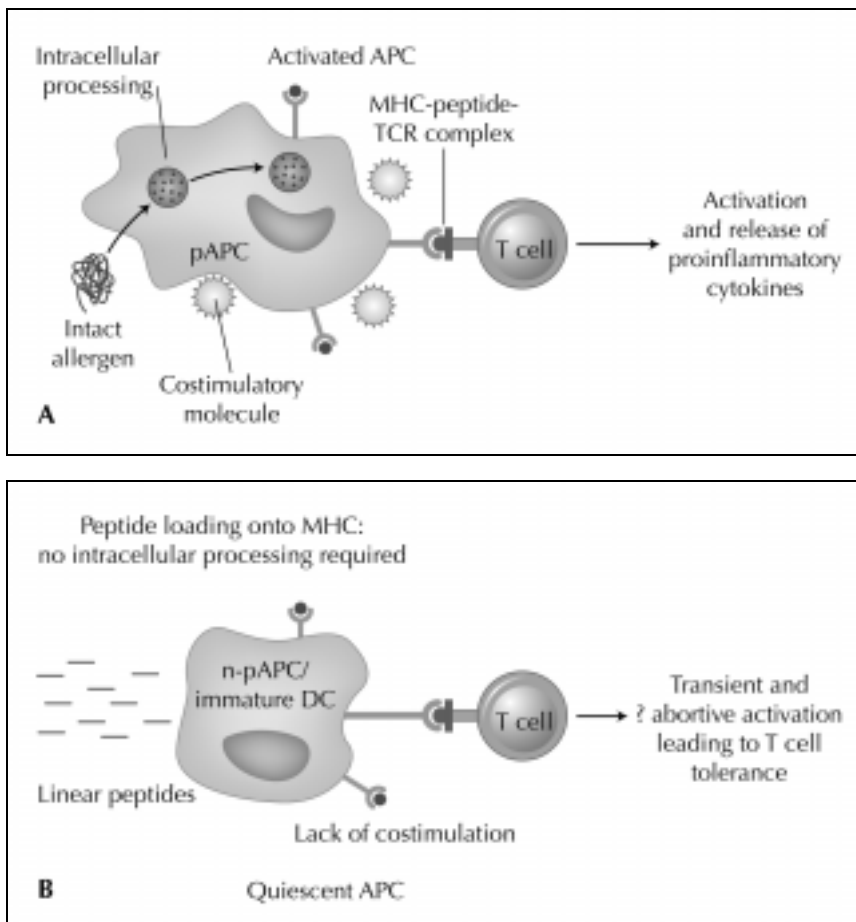


Figure 4. Differing antigen-presenting cell (APC) responses to intact allergen and short allergen-derived peptides may contribute to differences in T cell reactivity. **A**, Activation of professional APCs (pAPC) can be induced by uptake of whole allergen, resulting in up-regulation of costimulatory molecules on the APC cell surface. Intact allergen is intracellularly processed before peptide loading onto major histocompatibility complex (MHC) molecules. Subsequent activation of naïve T cells occurs by recognition of a peptide-MHC accompanied by costimulation, leading to proinflammatory cytokine production. TCR—T cell receptor. **B**, Short allergen-derived peptides are loaded onto the MHC molecule of immature dendritic cells (DCs) and nonprofessional APCs (n-pAPC) without the requirement for intracellular processing. Peptide recognition in the absence of APC activation and costimulation leads to transient and possibly abortive activation, resulting in T cell tolerance.

patient and physician may substantially expand the market for disease-modifying therapy.

Acknowledgments

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- Of major importance

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