

Peptide-Mediated Immune Responses in Specific Immunotherapy

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Key Words

Peptide · Epitope · Immunotherapy · MHC · Tolerance

Abstract

Conventional immunotherapy using whole allergen extracts has been shown to be an effective, disease-modifying treatment in carefully selected patients with allergic conjunctivo-rhinitis, asthma and bee and wasp venom hypersensitivity. However, this form of therapy is associated with the risk of systemic anaphylaxis, which, when severe, can be life threatening. A potentially significant reduction in the incidence of IgE-mediated events during immunotherapy may be achieved by the use of short peptides corresponding to T cell epitopes which, by virtue of their size, are incapable of cross-linking allergen-specific IgE bound to the surface of mast cells and basophils. Initial clinical studies have demonstrated degrees of efficacy which have, in some cases, been associated with adverse events occurring immediately or several hours after peptide administration. Preliminary data from studies employing shorter peptides (20 amino acids or less) suggest that improved efficacy may be achieved by using peptides of defined major histocompatibility complex-binding specificity administered in an incremental dose fashion comparable to conventional immunotherapy. This review will discuss the concept of peptide immunotherapy and the implications of recent studies.

Introduction

Specific immunotherapy with purified and partly purified allergen extracts is an effective treatment of allergic diseases such as seasonal and perennial rhinitis and allergic asthma. Specific immunotherapy has been shown to modify the course of disease, even after discontinuation of therapy [1]. However, specific immunotherapy may be associated with potentially life-threatening complications of systemic anaphylaxis [2] following cross-linking of allergen-specific IgE on the surface of mast cells and basophils. There is considerable evidence to suggest that allergen-specific Th2-type lymphocytes play an important role in the pathophysiology of atopic disease, including rhinitis [3, 4], asthma [5–7] and dermatitis [8]. Several studies in animal models have demonstrated the induction of tolerance with high doses of peptides containing T cell epitopes. The reduced ability of short peptide epitopes to cross-link surface-bound IgE indicates that an alternative, safer form of immunotherapy may be possible. Synthetic peptides have the additional advantage of being defined chemical substances that do not require the cumbersome standardization required of crude extracts currently used in immunotherapy.

The concept of peptide immunotherapy has emerged from studies on inbred strains of mice whose T cell epitope specificities have been defined. In such models, T cell responses to allergens have been inhibited by the intranasal or subcutaneous administration of allergen-

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derived synthetic peptides [9, 10]. Murine models, together with in vitro studies on human T cell clones, have provided useful information relating to the mechanisms involved in the induction of T cell tolerance by allergen-derived peptides. Early studies attempting to extend these findings to humans were complicated by the variability of major histocompatibility complex (MHC) haplotypes expressed in the human population. Proof of concept was achieved in these studies, although in some circumstances, adverse reactions following peptide administration were unacceptably high.

The development of peptide-mediated allergen-specific immunotherapy and associated mechanisms of T cell hyporesponsiveness will be discussed in this review.

Peptide Recognition by CD4+ T Cells

CD4+ T lymphocytes recognize antigen by means of specific cell surface receptors (T cell receptors; TCRs). TCRs are incapable of recognizing whole allergen proteins but rather, engage peptide fragments of the antigen bound to the protein products of the MHC [11]. Initially, allergen proteins are internalized and proteolytically degraded by antigen-presenting cells (monocytes, B cells, macrophages, dendritic cells). Peptides generated during processing complex with MHC modules in intracellular compartments and are subsequently displayed on the cell surface [12]. Allergens (together with other extracellular sources of antigen) are usually processed into peptide fragments that associate with class II MHC molecules [13]. Class II molecules generally bind peptides of approximately 11–20 amino acids, but as a result of an open-ended structure can also bind longer peptides [14].

Thus, whether a peptide can be presented by the antigen-presenting cell to T cells is dependent on its intrinsic ability to bind to the MHC molecules expressed by the individual. For subsequent activation of a T cell to occur, costimulation through CD28-CD80/CD86 and CD40-CD40 ligand is usually required [15, 16]. Whether the activated CD4 cell develops a Th1 or Th2 cytokine profile is dependent on the genetic background of the host [17] and a variety of local factors. These include the affinity of the TcR-peptide-MHC trimeric complex [18–20], interaction of accessory molecules (costimulation and adhesion), dose of antigen [21, 22] and the microenvironment for antigen presentation of hormones and cytokines [23].

HLA Linkage

A number of studies have investigated linkage of particular MHC genes to the atopic phenotype. Allergen-specific CD4 lymphocytes have been shown to have diverse class II MHC restrictions, including HLA-DR, HLA-DQ, HLA-DP, and HLA-DRw52 and HLA-DRw53 [24]. Young et al. [25] have demonstrated a possible excess of DR1 in Fel d 1-allergic subjects, together with an association of DR4 with individuals mounting an IgE response to Alt a 1. However, at present, the only robust associations are of Amb a 5 (ragweed allergen) and DRB1*15 [26]. The small size of this protein may result in the generation of a limited number of T cell epitopes, allowing clear linkage to a single MHC molecule.

Selection of Peptide Epitopes for Immunotherapy

The selection of peptides for allergen-specific immunotherapy should be based on a detailed knowledge of the T cell epitopes present within the allergen, as well as an understanding of their potential to bind to MHC class II molecules. Many of the important major allergens have now been cloned [27], and important B [28] and T cell epitopes identified [24]. The small size and linear conformation of synthetic peptides tend to restrict the number of B cell epitopes that are present. The T cell-stimulatory capacity of peptides has been assessed by either short-term cultures of peripheral blood mononuclear cells from atopic patients [29–33], or by growing T cell lines and/or T cell clones to identify specific epitopes [34–37]. Polyclonal T cell responses may reflect more clearly the diversity of T cell responses to allergens than T cell clones, as epitopes generating strong proliferative responses may introduce a selection bias during the in vitro cloning procedure.

Studies comparing proliferative and cytokine responses of T cells from atopic and normal individuals have indicated regions within allergens that may be allergenic. For example, Parronchi et al. [38] defined two peptides of the Par o 1 allergen of *Parietaria officinalis*. Both peptides induced IL-4 and IL-5 secretion from Par o 1-specific T cell clones derived from atopic donors, but differed in their ability to induce Th2-type cytokine secretion from clones from non-atopic donors [38]. Peptides inducing high levels of IL-4, supporting IgE production and secretion of IL-5, may be particularly important to target in immunotherapy.

As recognition of allergen-derived peptides by T cells is dependent on presentation in the context of appropriate MHC molecules, the limited clinical benefit previously observed with peptide immunotherapy may be in part explained by the fact that MHC restriction was not accounted for in the original peptide design [39, 40]. However, the complexity of providing an exhaustive analysis of T cell epitope binding is illustrated by the description of more than 200 molecules expressed by the HLA-DRB 1 locus (the most abundant class II molecules at the surface of antigen-presenting cells) [41].

Peptide-Induced Activation of T Cells in vivo

In a recent study of cat-allergic asthmatics, the intradermal administration of short overlapping peptides derived from chain 1 of the cat allergen Fel d 1 induced IgE-independent, MHC-restricted isolated late asthmatic reactions. MHC restriction of the biological response to peptide administration was demonstrated, as the development of late asthmatic reactions in response to chain 1 of Fel d 1 was dependent upon HLA type. Restriction specificity of peptide responses was confirmed using fibroblast cell lines transfected with HLA-DR molecules, which were used to present peptides of chain 1 of Fel d 1 to autologous allergen-specific T cell lines. The study employed three short peptide epitopes spanning approximately 25% of the sequence of the major cat allergen Fel d 1. All subjects developing an asthmatic reaction expressed HLA-DR1, -4 or -13, each of which was demonstrated to restrict T cell responses to one of the three peptides. Interestingly, promiscuous binding of peptides to MHC was demonstrated in this study with one of the peptides recognized in the context of both DR13 alleles (DRB1*1301, 1302) and DR1 (DRB1*0101).

The ability of one peptide to bind to more than one MHC molecule (promiscuous binding) was also demonstrated in a recent study by Texier et al. [42]. Binding assays were used to test a number of peptides derived from the major bee venom allergen against a panel of most commonly expressed HLA class II molecules. These included DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1301 and DRB1*1501, and cover approximately 60% of the HLA-DRB1 frequency in Caucasian populations. Several peptides were identified that were either allele specific, or could bind to more than one HLA molecule.

Clinical Trials of Allergen-Specific Peptide Immunotherapy

Recently, clinical trials have been performed on peptides derived from cat and bee venom allergens. Fel d 1, the major cat allergen, is recognized by the majority of cat-allergic subjects [43], and thus is a suitable target for synthetic peptide immunotherapy. Two overlapping peptides (termed IPC 1 and IPC 2) 27 amino acids long and spanning the majority of chain 1 of Fel d 1 were designed on the basis of proliferation assays mapping T cell epitopes. Following encouraging results in mouse models, demonstrating the induction of tolerance to both the peptide and whole allergen following peptide treatment [10], a number of dose-finding and therapeutic clinical studies have been performed.

In a randomized double-blind placebo-controlled study, Maguire et al. [40] investigated the effect of IPC 1 and IPC 2 peptides (derived from the sequence of the major cat allergen Fel d 1) in 133 cat-allergic patients chronically exposed to cats or who had previously failed conventional cat immunotherapy. Eight subcutaneous injections of IPC 1 and IPC 2 were administered at two doses (75 and 750 µg), and the efficacy of therapy was assessed 3 and 8 weeks following the onset of treatment. A significant increase in baseline FEV₁ in the high-dose group compared with the placebo group was observed, but only in those subjects with reduced baseline FEV₁ at the beginning of the study. Moreover, the improvement in baseline FEV₁ was only demonstrated 3 weeks after treatment and not at 16 or 21 weeks. An increased overall ability to tolerate exposure to cats by diary symptom scores was also observed. However, cutaneous challenge with a standardized cat hair extract did not change significantly for any of the groups through the course of this study.

Norman et al. [39] detected an improvement in symptom scores of patients receiving high-dose (750 µg) therapy. In a related study [44], *in vitro* proliferative and cytokine (IL-4 and IFN-γ) responses in T cell lines from subjects receiving IPC 1 and IPC 2 were evaluated. In whole cat dander-specific T cell lines, no changes in proliferation or IL-4 or IFN-γ production were observed. In contrast, peptide-specific lines from patients receiving 750 µg of IPC 1 and IPC 2 showed significantly reduced IL-4 production following peptide therapy when compared to both patients receiving placebo and the 75-µg dose. Proliferative responses and IFN-γ production remained unchanged [44].

No significant differences from placebo were demonstrated in immediate- and late-phase skin sensitivity to a

cat hair preparation containing Fel d 1 in studies performed by Simons et al. [45]. Furthermore, no changes in cytokine production were observed in vitro. In another study, the effect of peptide treatment on the response to bronchial provocation tests (PD₂₀FEV₁) with a standardized Fel d 1 extract [46] was evaluated following peptide immunotherapy with IPC 1 and 2. Subjects were treated with between 2 and 6 injections of placebo or peptides (7.5, 75 or 750 µg). Six weeks after treatment, PD₂₀FEV₁ was not significantly different between the placebo and treatment groups. However, when PD₂₀FEV₁ values were compared within groups (pre-treatment versus post-treatment), significant increases were observed in the higher-dose groups (75 and 750 µg). When peripheral blood mononuclear cells from study subjects were analysed for IL-4 production before and 6 weeks after treatment, significantly reduced levels of IL-4 production were observed.

Although a preliminary safety study of increasing doses of IPC 1 and 2 peptides up to 1,500 µg showed no immediate effects [39], subsequent studies reported occasional immediate reactions requiring adrenaline therapy [39, 40]. The majority of adverse events reported following administration of IPC 1 and IPC 2 were recorded in diary cards and occurred from 35 min to 6 h after injection. Adverse events were common and were frequently recorded in the placebo group, as well as in the active treatment groups. For example, Maguire et al. [40] recorded the incidence of chest symptoms as 67.9 and 56.6% in subjects receiving 75 and 750 µg of the IPC peptide preparation, respectively, with 40.7% of the placebo group also reporting the same events.

Thus, studies performed with IPC 1 and IPC 2 have produced conflicting data on both efficacy and mechanism of action. Moreover, in all studies, a high frequency of allergic symptoms has been reported, which may have been due to both IgE cross-linking by the relatively long IPC 1 and IPC 2 peptides, and direct activation of T cells leading to late asthmatic reactions.

Using T cell peptide epitopes of phospholipase A₂ (PLA₂; the major allergen and immunogen recognized by bee venom-sensitized individuals) of only 11, 12 and 18 amino acids in size, Muller et al. [47] treated five patients who had experienced IgE-mediated systemic allergic reactions to bee stings. Peptide therapy in these subjects was compared with 10 patients receiving conventional venom immunotherapy [47]. No placebo group was evaluated in this study. Patients were treated for 2 months to a total of 397.1 µg. An incremental dosing schedule was employed, starting at 0.1 µg and increasing to three 'maintenance'

doses of 100 µg. Subsequently, patients were challenged with PLA₂ and a live bee sting 1 week later. No adverse events were reported during peptide immunotherapy, and all patients tolerated the PLA₂ challenge without systemic allergic symptoms. Two patients, however, developed mild systemic allergic symptoms after the bee sting challenge. These results are promising and support the need for larger, placebo-controlled, double-blind studies in this area.

More recently, smaller peptides spanning most of both chain 1 and chain 2 of Fel d 1 were administered to cat-allergic asthmatic subjects in an open study [48]. The peptides were shorter (16 or 17 amino acids), and were shown to be recognized by the majority of cat-allergic subjects. In a proportion of subjects, a single intradermal administration of the peptides was associated with the development of isolated late asthmatic reactions. Following rechallenge with peptides, abrogation of the asthmatic reaction was observed. In addition, the response to intradermal skin challenge with whole cat dander was markedly reduced.

Mechanisms of Peptide Immunotherapy

T cells can be functionally inactivated by a number of different mechanisms, including clonal deletion, the induction of anergy (where cells do not decrease in number but no longer proliferate) or the induction of active suppression. In addition, or as part of the above, a shift in phenotype, or 'immune deviation', may be induced, for example from Th2- to Th1-type cells. Although the mechanisms involved in allergen-specific peptide immunotherapy are currently unclear, extensive studies in animal models and initial results from early trials suggest that the latter three mechanisms may all be involved.

Anergy or Antigen-Specific Non-Responsiveness

The induction of anergy was first demonstrated in human T cells in vitro by Lamb et al. [49]. Purified Th0 cell clones specific for influenza virus haemagglutinin were treated with high (supra-immunogenic) doses of specific peptides. Treatment resulted in an inability to respond to rechallenge with antigen 24 h later. Subsequent studies of human allergen-specific Th2 cells with synthetic peptides showed that when clones of T cells from an allergic patient were exposed in vitro to high concentrations of specific peptide in the absence of antigen-presenting cells and then rechallenged, there was reduced production of IL-4 and IL-5, but IFN-γ was still released [50].

In vivo studies in mouse strains have shown that T cell responses to allergens can be inhibited by the subcutaneous, intranasal or oral administration of allergen-derived synthetic peptides [9, 10]. In these models, there was a reduction in both cytokine production and proliferation, consistent with the in vitro demonstration of anergy described above. For example, Hoyne et al. [9] administered intranasal peptide derived from Der p 1 to H-2b mice. Splenic and cervical lymph node CD4⁺ cells from the mice underwent a rapid but transient activation of MHC class II-restricted CD4 T cells that peaked 4 days after peptide treatment. However, T cells obtained 14 days after treatment showed a reduction in both proliferation and cytokine production (IL-2 and IFN- γ) in response to the peptides [9].

In murine studies with the Fel d 1 peptides IPC 1 and IPC 2, mice were pre-treated subcutaneously with high-dose IPC 2 prior to challenge with IPC 2 in Freund's complete adjuvant. This resulted in tolerization of T cells, as evidenced by decreased IL-2, IL-4 and IFN- γ production when lymph node and spleen cells were subsequently cultured with IPC 2. In addition, T cell proliferation was decreased in the peptide-tolerized animals. In the same model, mice were primed with Fel d 1 and 4 months later treated by subcutaneous injection of IPC 2 in PBS. Subsequently, IL-2 production in response to the challenge of lymph node cells with IPC 2 was shown to be reduced compared to mice treated with PBS. Additionally, IgG antibodies directed against IPC 2 peptide were also decreased when peptide-treated sera were compared to those from mice treated with PBS [10].

The modulation of proliferative and cytokine responses has recently been demonstrated following peptide immunotherapy in bee venom-allergic subjects [47]. Peripheral blood mononuclear cells isolated following successful bee venom peptide immunotherapy revealed suppression of both proliferative and cytokine responses, compared with baseline assays. The production of both Th1 and Th2 cytokines was inhibited. Immediately following treatment, B cells were not affected in their ability to produce IgE and IgG4 antibodies, although following whole-allergen challenge, IgG4 increased and there was a change in the PLA₂-specific IgE:IgG4 ratio in favour of IgG4. However, these experiments were performed in only five subjects in an open fashion, and comparison with a placebo group was not made.

Akdis et al. [51] investigated ultra rush bee venom immunotherapy with whole allergen. They demonstrated down-regulation of T cell proliferative responses to allergen following immunotherapy, but showed that responses

could be recovered by the addition of exogenous IL-2 or IL-15, suggesting the induction of a state of anergy. Once proliferation was restored, IL-2 and IFN- γ were produced in preference to IL-4, IL-13 and IL-5. Thus, anergy induced by high levels of allergen exposure may in itself result in a more Th1-like phenotype. More recently, the same group has shown that the induction of anergy by bee venom-specific immunotherapy is associated with increased IL-10 production [52], providing a mechanism by which the observed reduction in both proliferative and cytokine responses may be explained.

The precise mechanisms underlying the induction of anergy remain incompletely understood. However, peptide-mediated anergy is associated with compound changes in the T cell phenotype characterized by the down-regulation of the TCR/CD3 receptor complex and enhanced expression of CD2 and CD25 [53, 54]. Restoration of TCR expression without recovery of function suggests that differential signalling through the TCR, and not receptor down-regulation, accounts for the altered responsiveness observed. Anergic cells have been shown to be defective in their ability to release intracellular calcium upon restimulation, and altered signalling pathways may be utilized by anergic T cells [55, 56]. Studies of peptide-anergized PLA₂-specific cloned CD4⁺ T cells have identified abrogation of the activity of p56lck and ZAP-70 tyrosine kinases [57].

The induction of anergy does not appear to be dependent on the expression of costimulatory molecules, as no changes in the expression of cell surface CD80 or CD86 were observed on Th0 or Th2 cells that had become unresponsive after peptide modulation. In addition, in the absence of antigen-presenting cells, stimulation with peptide induces anergy in allergen-specific human Th2 cells, irrespective of cell surface expression of CD80 and CD86 [54]. CD28, however, may be down-regulated [58]. The characteristic down-regulation of cytokine production, in particular IL-2 secretion, is accompanied by an initial transient rise in cytokine-specific mRNA, in keeping with activation preceding the development of anergy [59]. Transient activation preceding the development of hyporesponsiveness has been demonstrated in humans administered intradermal peptides derived from Fel d 1. Initial challenge with peptides was associated with the development of a T cell-dependent isolated late asthmatic reaction, whereas upon rechallenge, no reaction was obtained [5]. Recent studies have suggested that the transient T cell activation eventually gives rise to a population of regulatory T cells whose function is to modulate, rather than promote antigen-specific immune responses [60].

Clonal Deletion and Immune Regulation

Clonal deletion is an important mechanism in thymic education [61] and may be induced by a variety of mechanisms. An experimental model of mucosal tolerance, however, in mice transgenic for ovalbumin-specific TCR genes, demonstrated that high-dose antigen treatment induced clonal deletion by apoptosis. Low-dose antigen induced antigen-specific cells that produced TGF- β and IL-10, termed Th3, which were able to negatively regulate T cell responses to antigen [62].

Hoyne et al. [63] provided evidence that regulatory cells are involved in the induction of tolerance by inhalation of a dominant peptide of Der p 1, a major house dust mite allergen, in a mouse model of allergy. In this study, lymph node cells from mice tolerized to the Der p 1 peptide completely inhibited specific antibody production by immune spleen cells when the two were mixed together. In addition, treatment with the immunodominant peptide abrogated T cell responses to the whole Der p 1 molecule, although responsiveness could be reversed by subsequent immunization with a minor epitope and adjuvant. In a separate study, mice fed recombinant fusion peptides were not only less responsive to the whole allergen, as measured by the *in vitro* production of IL-2 and GM-CSF/IL-3 release on stimulation with protein or peptides, but also became less responsive to epitopes other than those in the fusion peptides used for feeding [64].

Thus, regulatory T cells have the potential to mediate linked suppression *in vivo*, enabling T cell responses directed at a multi-determinant protein to be effectively controlled. The concept of linked suppression has significant implications for peptide-based immunotherapy. The mechanisms by which regulatory T cells exert this modulatory effect are not yet clear, but could involve either the activity of immunosuppressive cytokines or direct cell contact [60]. However, inhibitory cytokines in the above models have not been detected as yet. An alternative mechanism which has been proposed is cognate interaction between T cells mediated by Notch/Delta signalling to induce and maintain peripheral T cell tolerance. Using *in situ* hybridization and virus-mediated gene transfer, the expression and function of Delta1 were investigated in a murine model of T cell tolerance to Der p 1 *in vivo* [65]. High-dose peptide delivered intranasally induced transient expression of Delta1 on inhibitory CD4⁺ T cells. Ligation of the Notch1 receptor on neighbouring T cells by Delta1⁺ regulatory T cells inhibited clonal expansion and may therefore be an important factor in underlying mechanisms of linked suppression.

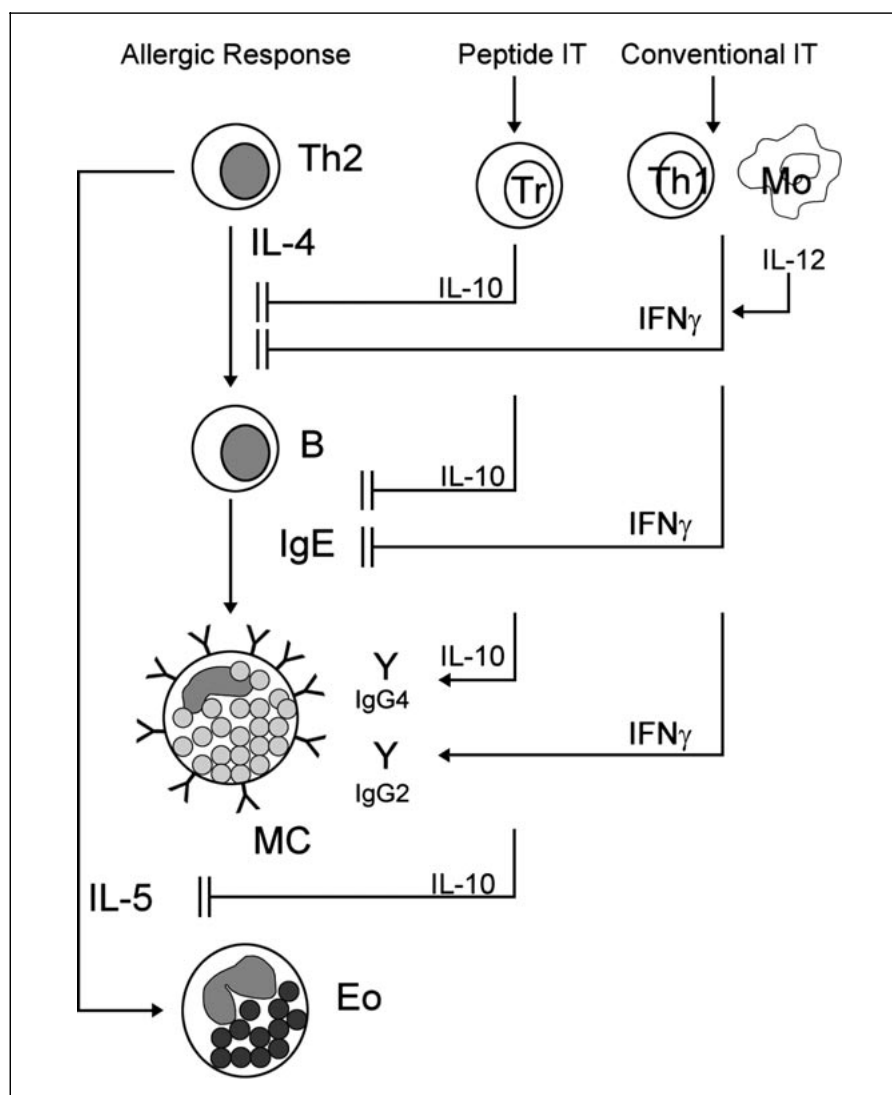
Immune Deviation

Conventional whole-allergen immunotherapy has been shown to induce immune deviation from a Th2 to a Th1 or Th0 profile in several studies (fig. 1) [66–68]. However, the mechanisms underlying the observed alteration of T cell phenotype still remain to be elucidated. Specifically, studies addressing the issue of whether cytokine phenotype is switched at the level of the individual cell, or whether there is an expansion of a Th0/Th1 subset of specific cells, are urgently required. Hamid et al. [69] showed increases in the numbers of nasal and skin tissue cells (predominantly CD68⁺) expressing IL-12 after immunotherapy, suggesting that T cells may be driven towards the Th1 phenotype by macrophages. A shift in polarization away from predominantly Th2-type T cells was demonstrated in some, but not all of the early clinical trials investigating peptide immunotherapy with IPC 1 and 2. The discrepancies observed reflect the variable clinical efficacy of the studies. Pene et al. [46] and Marcotte et al. [44], but not Simons et al. [45], demonstrated a reduction in IL-4 production by peripheral blood mononuclear cells and T cell lines, respectively, in response to Fel d 1 in high-dose treatment groups after peptide immunotherapy. Norman et al. [39] demonstrated a symptomatic improvement following peptide therapy which was not associated with a change in proliferative responses to the peptides or recombinant chain 1 and chain 2 of Fel d 1. Cytokine profiles were not evaluated in this study [39]. Recent studies with PLA₂ (both peptide and whole allergen) have demonstrated a generalized reduction in proliferative and cytokine responses through the induction of IL-10 (fig. 1) [47, 52]. Thus, it appears that the mechanisms of whole-allergen immunotherapy and peptide desensitization may differ at the level of the T cell, with either immune deviation or active regulation in evidence.

Conclusion

Initial studies have revealed that peptide immunotherapy shows limited, but significant, clinical benefit in allergic patients. The potential for lower frequencies of IgE-mediated side effects than observed with whole-allergen immunotherapy means that a wider range of patients, including individuals with asthma, may benefit from this approach. However, the issue of peptide-induced late asthmatic reactions must be addressed by employing up-dosing protocols similar to those used in conventional whole-allergen immunotherapy. The administration of allergen-derived peptides to sensitized subjects results in

Fig. 1. Allergic sensitization is characterized by the presence of Th2 cells which secrete IL-4 and IL-5. The production of IL-4 supports B cell isotype switching to epsilon heavy chain and IgE secretion. IgE binds to cell surface receptors on mast cells (MC) and basophils, sensitizing these cell types for allergen encounter. Elaboration of IL-5 leads to the release of bone marrow eosinophils (Eo) and enhances the survival and maturation of these cells. A potential mechanism of action of successful peptide immunotherapy is through the induction of IL-10-producing T cells (T regulatory cells; Tr), which exert their function by down-regulating IL-4 and IL-5 production and by favouring production of allergen-specific IgG4 over IgE. Conventional immunotherapy may differ mechanistically, in that evidence from several studies supports an overall shift from Th2-type cytokine production by T cells to a Th1 phenotype. The production of IFN- γ antagonizes the effects of IL-4 and leads to IgG2 secretion rather than IgE.



transient activation and subsequent tolerance of allergen-specific T cells, probably by the induction of clonal anergy or populations of regulatory T cells. Recognition of peptide epitopes by T cells is dependent on the presentation of peptides by appropriate MHC molecules, and for maximal efficacy of therapy, peptides should be both short and selected on the basis of their ability to bind to MHC molecules commonly expressed in the target population. Some allergen-derived peptides are capable of binding to more than one type of MHC molecule and are, therefore, promiscuous in this regard [5, 42]. Since recognition of a major epitope may be associated with the down-regulation of responses to neighbouring epitopes, the identification of allergen epitopes with broad MHC-binding ability may be advantageous in peptide vaccine design.

By considering issues of peptide selection, MHC restriction, dose and dose interval, it is likely that the efficacy of peptide immunotherapy will be increased significantly in future studies. As with conventional immunotherapy studies, careful patient selection remains an important issue. Long-term prospective studies will be required to determine whether peptide immunotherapy, like whole-allergen immunotherapy, is capable of modifying the clinical course of asthma and rhinitis.

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