

R.J.J. van Neerven

The role of allergen-specific T cells in the allergic immune response: relevance to allergy vaccination

Authors' affiliations:

van Neerven R.J.J., ALK-Abelló, Hørsholm, Denmark

Current address: Tanox Pharma BV, Amsterdam, The Netherlands

Correspondence to:

R.J.J. van Neerven

Tanox Pharma BV

Paasheuvelweg 15

1105 BE

Amsterdam

The Netherlands

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Recent research has elucidated many of the immunologic mechanisms that underlie atopic allergies. In particular, it has become clear that the role of CD4⁺ allergen-specific T cells is crucial for the induction of IgE and eosinophilia, factors that mediate the immediate hypersensitivity reaction and late-phase responses, respectively. Therefore, the reactivity patterns and activation requirements of allergen-specific T cells are important parameters for understanding and manipulating the allergic immune response. This review addresses these issues and discusses their relevance to the further development of allergy vaccines.

The allergic immune response

The immediate hypersensitivity reaction

Type I allergy is now recognized as a disease that is at least in part based on immune deviation (Table 1). Allergic patients respond strongly to innocuous proteins, which they should tolerate, as they pose no threat to the organism. In immediate allergic responses, an allergen enters the body and binds to allergen-specific IgE, which in turn binds to the high-affinity IgE receptor present on mast cells and basophils. Upon cross-linking of the high-affinity IgE receptors as a result of allergen binding, these cells release inflammatory mediators such as histamine, leukotrienes, and prostaglandins, resulting in an immediate hypersensitivity reaction.

The late-phase response

Some patients develop a late-phase reaction approximately 8–24 h after the immediate reaction. This late-phase reaction is dominated by an influx of activated eosinophilic

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Table 1. Immunologic factors associated with atopic allergy

Factor		Cell type	Function
IL-4	↑	CD4 ⁺ (and CD8 ⁺) T cells	IgE induction, Th2 induction
IL-5	↑	CD4 ⁺ (and CD8 ⁺) T cells	Eosinophil recruitment and survival, late-phase response
IFN- γ	↓	CD4 ⁺ (and CD8 ⁺) T cells	antagonizes IL-4, Th1 induction
Mucus	↑	Th2 cells	Role in airway obstruction
IL-12	↓	M ϕ /DC	Th1 induction
IgE	↑	B cells	Immediate hypersensitivity, role in late-phase response
MBP/ECP	↑	Eosinophil	Late-phase response
CD23	↑	B cell/M ϕ	IgE-mediated antigen presentation, late-phase response
Fc ϵ R1	↑	DC, LC	IgE-mediated antigen presentation
Eotaxin	↑	Bronchial epithelium and endothelium, BAL, M ϕ , T, EO	Recruitment of eosinophils (and Th2 cells)
Eosinophil recruitment after s.c. injection of RANTES	↑		Recruitment of several cell types

granulocytes and CD4⁺ T cells, and contributes to the chronic inflammation that is especially noticeable in allergic asthma. Late-phase responses have been shown to be dependent on the presence and activation of CD4⁺ T cells (1–7), eosinophils (3, 4), factors involved in eosinophil differentiation such as IL-5 (8–10), and molecules that play a role in the *in vivo* presentation of allergens to T cells such as CD23, the low-affinity IgE receptor (11), and IgE (8).

The influx of eosinophils and allergen-specific T cells into target tissues is under the control of chemokines such as RANTES, MIP-1 α , MCP-1, and eotaxin (12–16). These chemokines are locally expressed and bind to the CC chemokine receptor CCR3, which is selectively expressed on TH2 cells and eosinophils (15, 17–21). The chemokine receptor CCR8, which is preferentially expressed on Th2, but not Th1 cells, binds the human CC chemokine I-308, and may also prove to play an important role in the influx of allergen-specific T cells into target tissues (22). In addition to these chemoattractants, an enhanced expression of VCAM-1 and ICAM-1 on the vascular endothelium mediated by T-cell-derived cytokines appears to be necessary for the influx of eosinophils (16).

The late-phase reaction and the allergic inflammation seen in chronic disease are therefore primarily dependent on the costimulation-dependent activation of tissue-residing allergen-specific T cells, followed by an influx of activated eosinophils and CD4⁺ T cells that induce local tissue damage. This leukocyte trafficking critically depends on the chemoattractant activity of chemokines and the presence of adhesion molecules on the vascular endothelium (16, 23).

The role of allergen-specific T cells in the allergic immune response

T cells have been shown to be a key player in the induction of both the immediate allergic response and the late-phase reaction (Fig. 1, Table 1). Allergen-specific T cells of allergic patients, but not control donors, display a Th2-like pattern of cytokine production upon activation (24–26). This Th2-like cytokine production profile includes cytokines such as IL-4 and IL-5, cytokines that play an important role in the induction of class switching of B cells toward the production of IgE, and differentiation and survival of eosinophilic granulocytes, respectively. This suggests that allergen-specific Th2-like T cells are directly involved in orchestrating the immediate hypersensitivity reaction and the late-phase reaction.

Activated allergen-specific Th2-like CD4⁺ T cells have been identified in the lungs of asthma patients (27, 28), the eyes of allergic conjunctivitis patients (29), the lesional skin

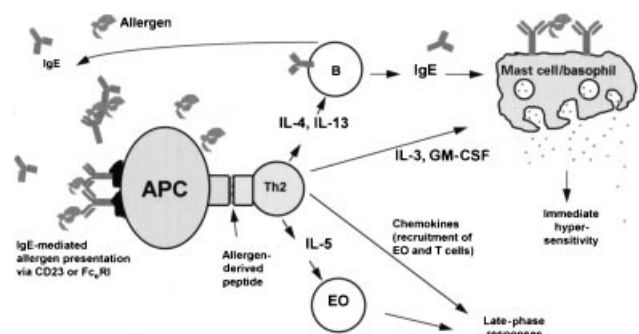


Figure 1. Schematic representation of allergic immune response.

in atopic dermatitis (30, 31), and the nasal washes of rhinitis patients (27), and have been shown to play a direct role in the mucus production in affected airways (32), further demonstrating the clinical relevance of these cells. The production of Th2-type cytokines appears to be more biased in chronic disease manifestations to perennial allergens (e.g., mite- or cat-allergic asthma) than in recent onset allergies to seasonal allergens (e.g., rhinitis from pollen allergens). Interestingly, recent reports indicate that CD8⁺ T cells from allergic patients may also be biased toward the production of type-2 cytokines (33).

Role of antigen-presenting cell (APC)-derived factors

In addition to this aberrant T-cell cytokine secretion profile, allergic patients have been shown to have a decreased ability to produce IL-12 (34), the most important Th1-inducing factor, and an increased production of PGE₂ (35), a factor that inhibits IL-12 production and thereby promotes Th2 development (36, 37). Allergic patients, but not control donors, express the high-affinity IgE receptor, Fc_εRI, on peripheral blood monocytes (38, 39), and have an increased expression of CD23, the low-affinity IgE receptor on B cells (40, 41). Both these IgE receptors expressed on APC play an active role in capturing and presenting allergens to T cells (42–45); as a result, allergic patients' T cells become activated at much lower allergen doses *in vivo* than those of nonallergics.

T-cell responses to allergens

As allergen-specific CD4⁺ T cells play a crucial role in the allergic immune response, specific inactivation of these Th2 cells, or the selective induction of T helper 1 (Th1)-type cytokines, might directly interfere with the disease process (Fig. 2). Therefore, allergen-specific T cells are obvious targets for intervention in atopic disease, and a detailed characterization of the allergens recognized and the epitopes present on major allergens is required for evaluating the feasibility of novel allergen preparations such as synthetic peptides or recombinant allergens for therapeutic allergy vaccination.

CD4⁺ T cells need two signals in order to become fully activated (46, 47). The first signal is generated when the T-cell receptor engages an antigen-derived peptide of 12–25 amino acids that is presented by the correct HLA class II molecule on the surface of an APC. A second, costimulatory signal is provided by interaction of CD28 on the T cells with CD86 or CD80 on the APC (47). Allergen-specific CD4⁺ T cells from allergic patients as well as nonallergic controls have been shown to be equally dependent on

costimulation via CD28/CD86 interaction (6). In addition, the role of costimulation for the development of airway hyperresponsiveness has been documented in several animal models, stressing the importance of complete T-cell activation for late-phase responses *in vivo* (1, 2, 5, 7).

HLA restriction and TCR usage of allergen-specific CD4⁺ T cells

MHC restriction patterns of allergen-specific human T cells appear to be very diverse, as is T-cell epitope recognition. HLA-DR, HLA-DRB3, HLA-DP, and HLA-DQ restriction has been demonstrated for several allergens (48–56). Such diverse restriction patterns suggest that there is only a weak or no correlation between HLA alleles and IgE responsiveness. In addition, because allergenic extracts are generally complex mixtures of many allergens, a correlation between HLA and one of these allergens does not strongly affect IgE responsiveness to an allergen extract.

As expected from the HLA restriction and epitope-diversity, human allergen-specific T-cell clones utilize a diverse set of T-cell receptor V β and V α segments (49, 57–62). Although only a small number of T-cell clones have been tested in these studies, no biased TCR V gene product usage could be demonstrated. In addition, populations of T cells expressing almost the full range of TCR V α and TCR V β segments are present in BAL fluid and in peripheral blood of allergic asthma patients (63). After exposure to allergens, however, an oligoclonal T-cell expansion could be observed in BAL fluid, but not in the peripheral blood, suggesting that allergen-specific T cells are expanded or recruited in lung tissue after allergen exposure (63). This is in line with a recent study of Borgonovo et al. that showed a depletion of allergen-specific T cells from the peripheral blood after allergen challenge (64).

TCR usage has also given a good insight into the longevity of allergen-specific T cells. Wedderburn et al. have reported that

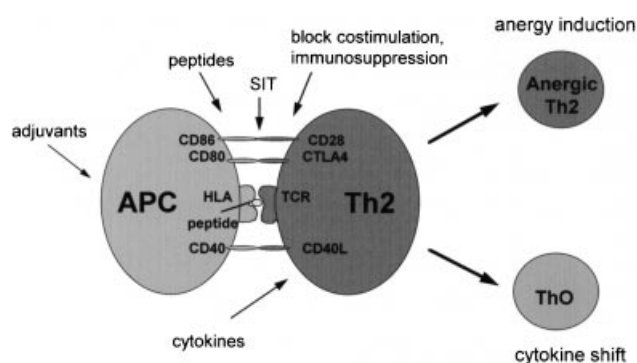


Figure 2. Therapeutic intervention pathways directed at allergen-specific Th2 cells.

T-cell clones with identical TCR V and J regions can be isolated from the same patients after a time interval of 6 years (65). This has recently been confirmed by Bohle et al., who could demonstrate the presence of an identical TCR clonotype expressing allergen-specific T cells in allergic patients over a period of several years (66), clearly illustrating the presence of memory in allergen-specific Th2 responses.

Multiple T-cell epitopes are present in major allergens

A large fraction of allergen-specific T cells are specific for major allergens (reviewed in ref. 67), i.e., proteins that are recognized by serum IgE of more than 50% of allergic patients, and T-cell epitope-mapping studies have focused on these molecules because their amino-acid sequences have been identified. In epitope-mapping studies using long-term T-cell clones and lines, all allergens studied to date have been found to contain multiple T-cell epitopes. They are present throughout the molecule (49, 52, 54–57, 60, 68–91), and a single patient can recognize up to eight or more epitopes of a single major allergen. There is no difference between the epitopes that nonallergic donors recognize (70, 75) and the epitopes recognized by allergic patients, and specific immunotherapy does not change the epitope specificity (92).

The effect of isoallergenic variation on the activation of allergen-specific T cells

Isoallergenic variation of aeroallergens, i.e., the presence of multiple sequence variants of a given allergen within a single species, has been noted by analyzing purified major allergens in 2-D gel electrophoresis systems (93, 94). The appearance of several spots on such 2-D gels indicated that these major allergens probably exist as several closely related entities. Indeed, cDNA cloning of allergens has clearly shown that isoallergenic variation occurs frequently (77, 95–101). To illustrate this, it can be mentioned that more than 40 different isoallergen sequences have been described for Bet v 1 alone.

The effect of isoallergenic variation on the activation of allergen-specific T cells has been addressed in only a few studies to date (99, 102). This is an important issue, because to replace allergenic extracts for vaccination with recombinant allergens, one needs to make sure that the recombinant allergen used (i.e., the single isoform of the allergen) is recognized by the patient's T cells. In addition, diagnosis of allergy may have to be defined on the major allergen level (103), as treatment of a patient who primarily reacts to group

1 grass allergens with a recombinant group 5 allergen will not be efficacious.

A few studies have shown that allergen-specific T cells that are specific for native purified major allergens do not all react with all recombinant versions of the same protein (81, 99). In the case of the major birch allergen, Bet v 1, it was clearly shown that high as well as low IgE-binding isoforms were equally effective in activating Bet v 1-specific T cells (99). However, not all T-cell clones reacted with all recombinant isoallergens tested, which has also been noted in our laboratory (R.J.J. van Neerven, personal observation).

The situation appears to be more complex for the grass allergen Phl p 5 (P.A. Würtzen, personal communication). This major allergen can be subdivided into at least two distinct groups of recombinant allergens, namely, Phl p 5a and Phl p 5b. The members of these isoallergen groups have only a few amino-acid substitutions, whereas there are relatively large differences between the two groups. T-cell clones that were derived with native purified Phl p 5 could be subdivided into three different groups. The first group (about 50% of all T-cell clones) did not recognize any of the recombinant Phl p 5a or Phl p 5b isoforms used, the second group recognized native allergen as well as all isoforms tested, and the third group exclusively recognized either Phl p 5a or Phl p 5b isoforms. A differential isoallergen recognition was found for individual patients, as polyclonal Phl p 5-specific T-cell lines also showed an isoallergen group-specific reactivity pattern.

These results with recombinant grass- and tree-pollen allergens indicate that the selection of the recombinant isoform used for vaccination may be very important for ensuring the optimal effect. If single recombinant proteins are used, there is a theoretic possibility that some patients may not be treated optimally, because their T cells, which are currently regarded as the target cells for allergy vaccination, may simply not recognize them. Therefore, in some cases, such as Phl p 5, it may be desirable to consider mixtures of several recombinant isoallergens for treatment, rather than single recombinant allergens.

Interspecies cross-reactivity of allergen-specific T cells

In natural allergen exposure, one is continuously exposed to allergens from many different, taxonomically related species. For example, grasses belonging to the Poaceae family have a worldwide distribution, and many of these species are closely related to each other. Major allergens cloned from the different Poaceae grasses have sequence identities of 70–95%. This means that large stretches of these molecules

may be identical throughout all Poaceae grasses. Similar homologies have been noted for tree-pollen allergens, mite allergens, and cat allergens. As a result of structural homology, major-allergen-specific T cells may cross-react with allergens from different species within the same genus, as shown for house-dust mite Der f-specific T-cell clones and lines that cross-react with house-dust mite Der p (51, 104), as well as for Eur m 1 and Der p 1 (83). A similar phenomenon can be observed among grass-pollen group 1 allergen-specific T cells (60), and tree-pollen group 1 allergen-specific T cells (81) that cross-react with group 1 allergens from different genera of grasses and trees. At least a part of these cross-reactivities must result from isoallergenic variation, because some natural Bet v 1- or Phl p 1-specific T-cell clones were shown to cross-react with group 1 allergens from other families, but did not react with recombinant Bet v 1 or Phl p 1, which represent single isoforms.

If T-cell epitopes are located in such homologous regions, a single T cell may be activated by allergenic extracts of all these species. As a result of this, a *Phleum pratense*-specific T cell may be activated when a patient is exposed to *Lolium perenne*, and help a *Lolium*-specific B cell to produce IgE. Studies with allergen-specific T-cell lines and clones have confirmed these cross-reactivity patterns between related grass (60, 105, 106), tree (81, 98, 107), and mite species (104), as had previously been described on the level of IgE binding.

The effect of allergy vaccination on T cells and other effector mechanisms in allergic disease

Specific allergen immunotherapy with allergen extracts, recently termed “therapeutic allergy vaccines” in the WHO position paper on allergen immunotherapy (108), has been practiced ever since its introduction by Noon in 1911 (109). However, even though the clinical efficacy of allergen vaccination is well documented (reviewed in ref. 108), the mechanisms of this treatment are only now emerging from studies using unmodified allergen extracts for vaccination (110).

Effect on specific antibody production

The first reports on the effects of vaccination on the immune system date back to the early 1980s, when it was noted that this treatment does not really influence allergen-specific serum IgE levels, but that there is a large increase in

allergen specific IgG, most notably IgG4, an observation which gave rise to the “blocking antibody” theory (111, 112). However, the rises in specific IgG4 occur in all patients undergoing allergen vaccination, irrespective of their clinical response (113, 114). This implies that, even though allergen-specific Ig antibodies may play a not yet described role in allergen vaccination, their mere presence does not correlate with the effect of the treatment.

Effects on allergen-specific T cells

Since the identification of the role of Th2-like cells in allergy, several studies have described the effects of allergen vaccination on the level of the allergen-specific T cells. Varney et al. were the first to show that there is an apparent shift from the production of Th2-like cytokines to a more desirable, Th1-like cytokine production profile (115). This was soon followed by several other papers with similar results (92, 116–119). Interestingly, such Th0 cells are potent inducers of IgG production, thereby possibly linking the cytokine shift theory to the blocking antibody theory. This effect may be primarily mediated by the enhanced IL-10 production that has recently been noted after allergy vaccination, both in T cells and APC (120).

However, the influence of allergen vaccination on allergen-specific T cells does vary considerably between the different studies. A study based on *in situ* cytokine production after allergen challenge, probably the most relevant study because *in vitro* artifacts may be minimal here, showed an unchanged production of IL-4, and an induction of IFN- γ -producing T cells (115). *In vitro* studies can be subdivided into those that see a general decrease in T-cell activation and production of most cytokines (121), with the exception of IL-10 (120), and those that have noted a qualitative shift in cytokine production, in some cases accompanied by decreased specific T-cell proliferation (92, 116–119). However, in some of these studies, IFN- γ production was increased with unchanged IL-4 production (115, 118, 119), and, in others, IL-4 and IL-5 production was decreased with decreased or unchanged IFN- γ production (92, 116, 117). Interestingly, the same epitopes appear to be recognized before and after allergen vaccination (92). Yet another study could not show a difference in IL-5 production of peripheral blood T cells after specific allergy vaccination (122). When all these results are combined, it is clear that there is an influence on the cytokine production profile of allergen-specific T cells. However, it is not clear at present whether these changes can completely explain the clinical improvement of patients undergoing allergen

vaccination, as it is not yet clear whether these changes correlate with the efficacy of treatment.

Effect on homing of T cells and eosinophils

Significant decreases of the migration of CD4⁺ T cells and eosinophils into the target tissues after allergen challenge have been described in patients receiving allergen vaccination (115, 123). In addition, pollen-season-related eosinophil counts are decreased (124). These studies show that the presence in and recruitment of late-phase reaction effector cells to target tissues are decreased, an effect which may explain the decrease in late-phase reactions in treated patients.

Effect on APC-derived factors

A recent study has shown an increase in *in situ* allergen-induced IL-12 production (125). However, IL-12-producing dendritic cells and macrophages do not have a specific antigen receptor, a fact which indicates that this effect may be vaccination-specific, rather than allergen-specific. An interesting explanation is that the adjuvants used in this study may induce IL-12 production by APC, resulting in the cytokine shift in allergen-specific T cells noted in other studies. Production of the immunosuppressive cytokine IL-10 by APC is also increased, and this has been shown to have a promoting effect on the production of IgG4 by B cells (120, 126).

Effects on basophilic granulocytes

A decreased releasability of basophilic granulocytes has also been described after specific allergy vaccination (127). However, this appeared to be the result of a decrease in the numbers of circulating basophils in the peripheral blood, rather than the result of a decreased release of mediators by basophils on a single-cell basis. However, it is not clear whether this depletion of basophils from the peripheral blood represents a decrease in total basophil numbers in allergic patients, or whether it is a result of the selective influx of basophils into target tissues, as has been described for T cells after allergen challenge (64).

Conclusion

Many studies in recent years have shown that specific allergen vaccination with unmodified allergen extracts clearly has an effect on patients' immune system. T-cell

cytokine production and proliferation changes, and serum levels of allergen-specific IgG4 increase sharply while IgE levels remain largely unchanged; IL-12 and IL-10 production by APC increases; the influx of eosinophils and T cells into target tissues decreases, as do peripheral basophil numbers; and even general inflammatory markers decrease (128). In addition, it will be of great interest to see whether production of chemokines that play an important role in the recruitment of T cells and eosinophils is also affected by allergen-specific vaccination.

Novel therapeutic strategies for the specific treatment of allergy

Due to the nature of the therapy, allergy vaccination may give rise to local allergic reactions at the injection site, and even systemic reactions and anaphylaxis may occur occasionally. In addition, the standardization of allergenic extracts is a complicated procedure, and extracts may vary from supplier to supplier. The increasing knowledge of the role of allergen-specific T cells in the disease process has enabled the design of several T-cell-directed therapies which are currently being considered (Fig. 2).

In addition, with regard to patient compliance, alternative administration routes to s.c. injection, or treatment with fewer injections may be favorable. Therefore, much attention has recently focused on the development of alternative approaches to allergy vaccination, most of which await clinical testing in the near future.

Synthetic peptides and recombinant allergens with reduced IgE binding (99, 129) have been proposed as safe alternatives to injection allergy vaccination. However, peptide immunotherapy has not been shown to have major advantages over specific allergy vaccination (130–132), and recombinant allergens, whether low or high IgE binders, have not yet been tested in clinical trials.

The use of alternative adjuvants that strongly induce Th1 responses has been suggested to achieve an even better effect of specific allergy vaccination, probably resulting in fewer injections (133, 134). Once again, this has not yet been documented in clinical trials. Several studies have shown the efficacy of alternative local administration routes for allergy vaccination such as sublingual and intranasal vaccination, but additional documentation is needed (108).

Conclusions

The last decade has shown a tremendous increase in our knowledge of the allergic reaction and the role of both the immune system and our environment in the development of atopic allergies. This knowledge is currently being applied in new strategies for the specific treatment of atopic allergies.

The use of promising new adjuvants, and new administration routes and delivery systems, as well as the possibility of combining more general approaches, such as anticytokine or anti-IgE treatment, with the specific treatment of atopic allergies may result in even more effective and safe ways of treatment, thereby enhancing patient compliance and the efficacy of specific allergy vaccination.

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