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The immunotherapy of allergic diseases was conceived under the false premise of immunizing against a – nonexistent – pollen toxin; nevertheless, it proved to be effective. The immunologic changes that are induced are probably heterogeneous in nature and, despite a wealth of new information, are still largely unknown. “Blocking antibodies” have previously dominated explanations of the mechanisms of immunotherapy, but, currently, changes within the T-cell compartment seem to be considered to be more central and of greater importance. Obviously, real immunotolerance cannot be achieved. Most of the available data can be interpreted as indicating a switch of the Th₂/Th₁ ratio toward normalization. This could also explain certain early effects of immunotherapy. The many open questions represent an important obstacle to all activities aimed at improving this kind of therapy on a scientific basis. The term “allergen vaccine” coined in the WHO position paper should not hide this problem.

Attempts to improve immunotherapy tend toward minimizing side-effects and/or increasing efficacy. They can be divided into

- 1) further improvement of conventional immunotherapy
- 2) new developments which often lead away from the native allergen.

A special approach – often combined with both trends – is to use adequate adjuvants.

Further improvement of conventional approaches

As a consequence of the activities of the WHO/IUIS, several allergen extracts have been standardized. However, a

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generally accepted standardization is still lacking. During the last 15 years, the structures of many allergens have been analysed, and some of them can be produced homogeneously. Both developments will extend the indication for specific immunotherapy. This seems to be especially important for allergens which cannot be avoided and/or induce severe systemic reactions (e.g., peanut, celery, latex). Another trend within this conventional approach is to improve the means of application (e.g., liposomes or other kinds of encapsulation). Finally, it can be expected that individual regimens can be established, based on better immunologic insight. At present, the tendency is to maximize the doses administered, these being limited only by side-effects. However, these may not be the optimal dosages.

Development of modified allergens with decreased binding of IgE antibodies and increased efficacy

The aim is to reduce IgE binding without changes in T-cell epitopes. However, this is useful only if the preparation can induce either T-cell anergy or a switch to Th₁ activities. Both effects have been confirmed experimentally. The first step in this direction by enzymatic cleavage did not yield convincing results. It has been followed up by the use of defined genetic manipulation techniques to achieve adequate changes in recombinant molecules. Another approach is to use peptides. Long-chain peptides should be superior as they offer possibilities of individual presentation by means of MHC molecules. The transition to the use of recombinant modified allergens represents a logical step. A special modification of the therapy concept is the application of plasmid DNA. This has been proved to be successful in microbiological vaccinations. The first investigations in animals using DNA coding for major allergens have

provided evidence that this kind of application promotes a Th₁ response. However, at present, it seems to be too early to speculate on the possible clinical application.

Application of adjuvants

Adjuvants are compounds which may intensify the immune response. They are already in use both in classical vaccination and immunotherapy, especially as depots which prolong the availability of antigens. Selective effects can be expected from compounds which interfere with sensitization and the production of IgE antibodies, respectively, in a defined and desired manner. Such effects can be expected from substances which interfere with IL-4 (anti-IL-4, sIL-4r), which develop antagonistic activities (IL-12, IFN γ), or which block important costimulatory cell-cell interactions (anti-CD86). All these approaches have been proved to be successful in experimental situations. Especially interesting may be fusion proteins containing the allergen or a modified form (conferring specificity) and the modulating compound (conferring adjuvant activity).

At present, it is difficult to predict which approach will be the most successful. The improvement of conventional immunotherapy is a realistic aim. The application of scientifically based modifications of allergens will be a realistic step in selected allergies (one or only a few dominant major allergens). The transfer of the other approaches from the experimental phase into the clinical will need more time.

There is every reason to believe that immunotherapy or allergen vaccination will be improved and the indications will expand. The decisive advantage is its high selectivity – all other immune reactivities remain intact. However, this specificity is the drawback of this therapy, as it can be successful only when all relevant allergens are incorporated.