

Immunology and allergy

ALLERGY FALLS SQUARELY into the class of common disorders caused by interaction between a genetic predisposition and an environmental stimulus. Genetic approaches are revolutionising the treatment of many primary immunodeficiencies, which are caused by single gene defects, but are unlikely to be of therapeutic value in the short term for multifactorial allergic disorders such as asthma, rhinitis and eczema. Nevertheless, advances have been made in our understanding and management of these disorders, which together are among the five most common conditions for which people consult their general practitioners.

Prevention. It is unclear why the incidence of atopic diseases, particularly asthma, is rising so sharply in First World countries. Atopic diseases are associated with the persistence beyond infancy of a strong interleukin-4 (IL-4) dominant response by T cells that favour IgE synthesis and inflammation (T_H2 , or type 2 helper T cells). The "hygiene hypothesis" attributes this persistence to changes in infant diets (such as sterile water), early and increased use of antibiotics within the first year of life with consequent changes in gut bacterial flora, and reduced incidence of bacterial infections because of cleaner homes, smaller families and use of cleaner and more supervised childcare. The data support the view that a less affluent or rural lifestyle is protective.¹ Mechanistically, the hypothesis postulates that a "clean lifestyle" is associated with decreased stimulation of the innate immune system because of less exposure to immunostimulatory DNA sequences (CpG motifs) ubiquitous in environmental bacteria. Vaccine adjuvants and DNA vaccines are under investigation that include these bacterial CpG motifs and drive an immune interferon (IFN- γ) dominant cytokine response by type 1 helper T cells (T_H1), thereby inhibiting the allergic phenotype. These approaches and other forms of novel allergen-specific immunotherapy may play a preventive role in the future.

Diagnosis. Diagnosis of allergy is now more precise, with better standardisation of allergen extracts and increasing use of monoclonal antibodies prepared from recombinant allergen proteins. Commercial diagnostic kits using recombinant antigens should become available within the next five years, particularly for conditions such as latex allergy, for which current tests have low diagnostic sensitivity and specificity.²

The causative mutations have been identified for most of the catastrophic sex-linked and autosomal primary immunodeficiencies, such as adenosine deaminase deficiency and severe combined immunodeficiencies, and prenatal diagnosis of these conditions is now available.

Intervention. Some primary immunological disorders resulting from single gene defects can be corrected by gene therapy, largely because the treatment (which would be hazardous if attempted *in vivo*) can be undertaken *ex vivo* on cells from the patient's marrow or blood.³ This therapy is available in specialist centres only.

Pharmacotherapy for atopic disorders has advanced over the past five years.⁴ Long-acting β -agonists for symptom control have been extremely effective additions to the treatment regimens for moderate and severe asthma, and

exercise-induced asthma. The leukotriene-receptor antagonists are the first new class of asthma drugs for 25 years. Although their role in asthma is still not fully defined, they may be valuable in other allergic and immunological disorders, such as rhinitis, nasal polyposis and urticaria. Once-daily topical corticosteroid preparations are now available for use in rhinitis, asthma and eczema, providing increased topical potency, low systemic bioavailability and improved compliance.

Allergic inflammatory processes involve multiple cytokines, decreasing the usefulness of antagonists to single cytokines, such as IL-4 and IL-5, or the anti- T_H2 cytokine IL-12. IL-10 therapies were initially unsuccessful, but increasing evidence suggests this cytokine is important in effective immunotherapy, possibly by inducing antigen-specific tolerance (anergy) and by promoting a switch from IgE to IgG4 synthesis. Strategies focusing on IL-10 are likely to increase over the next five years.

More recently, a monoclonal antibody directed against IgE has been developed for human use. This agent has potential for treating patients with multiple sensitivities, who benefit little from conventional allergen-specific immunotherapy. Clinical trials demonstrate that it attenuates both early and late asthmatic responses after allergen challenge. However, it is likely to be expensive. Anti-IgE treatments may play an adjunctive role in enhancing safety during rapid up dosing of allergen immunotherapy.

Allergen-specific immunotherapy may modify the natural course of allergic disorders, or even prevent their occurrence, and is attracting a resurgence of interest, particularly for bee-venom, pollen, cat and latex allergy. Research on vaccines containing the allergenic sites that react with T cells, but not IgE-binding sites (to minimise anaphylactic side effects), should result in new specific immunotherapy products within the next five years.⁵

Nevertheless, the strong environmental influence in atopic disorders suggests that public health intervention strategies are needed in addition to pharmacotherapy. The real advances of the next decade should come from creative combinations of molecular biology, immunology, pharmacology, genomics and proteomics, and allow us to manage allergic and immunological disorders more effectively and safely.

Robyn E O'Hehir

Director, Department of Allergy, Asthma and Clinical Immunology, Alfred Hospital, Prahran, VIC 3181; and Professor of Allergy and Clinical Immunology, Monash University Medical School, Melbourne VIC
Robyn.O'Hehir@med.monash.edu.au

Figure: Crosslinking of mast-cell IgE bound by allergens.

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