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Viewpoint

A potential vaccine strategy for asthma and allied atopic diseases during early childhood

Patrick G Holt

The human T-cell system searches for environmental antigens throughout life, but the nature of the responding T cell determines whether individuals become atopic or remain normal. The selection of the appropriate T-cell population is an antigen-driven process that occurs during the early stages of the immune response in the naive host. If T-cell selection favours the growth of T helper 1 (Th1) cells, which secrete interleukin (IL)-2 and interferon (IFN)- γ , low-grade non-pathogenic IgA and IgG responses follow. However the emergence of T helper 2 (Th2) cells, secreting IL-4 and IL-5, can lead to IgE production, eosinophilia, and atopic disease.

Additionally, Th1 cytokines suppress Th2 cell expansion, and a dominant stable Th1 response may protect against the development of Th2-dependent allergic disease. Early childhood has been pinpointed as the period when specific T-cell responses to environmental antigens are initiated, and the ensuing T-cell selection process may take several years to complete. My view is that we already know how this process operates and should contemplate controlling it in humans by deliberate administration of allergens to stimulate the development of Th1 immunity.

Regulation of IgE production

IgE responses are regulated by competing signals from CD4 T-cell subsets, particularly Th2 cells which promote IgE production, and Th1 cells, which inhibit Th2 cells.^{1,2} Various data suggest an identical mechanism exists in man.^{3,4} Both atopic and IgE-negative normal adults have T cells in the peripheral blood which react with major inhalant allergens. In atopic individuals, these cells are predominantly Th2, whereas in non-atopic subjects they are mainly Th1.^{5,6}

Therefore, in normal adults, each exposure to an environmental allergen will elicit a burst of Th1-like cytokines. This cytokine release should protect against

potential pathogenetic Th2 reactivity and each additional exposure should consolidate host-protective Th1 memory.

Induction and suppression of IgE responses to food and inhalant allergens

Earlier this century⁷ it was found that feeding animals antigens they had not previously encountered gave rise to transient symptoms of immediate hypersensitivity, which, after continued antigen exposure, were replaced by a state of antigen-specific unresponsiveness. The phenomenon is now known as oral tolerance, and is preferentially directed against IgE and delayed-type hypersensitivity (DTH) responses.⁸ This form of tolerance can be transferred to other animals by transplanting a specific subset of T-cells that secrete Th1 cytokines.⁹⁻¹¹ These allergen-specific Th1 cells develop rapidly in the mesenteric lymph nodes during allergen-feeding.^{10,12}

We have studied the same immune response in the respiratory tract. The essential elements are identical: repeated antigen aerosol inhalation elicits an immune response that includes a Th2 component. The Th2 response eventually wanes with repeated antigenic challenge, leaving only the vestiges of specific IgG and IgA production.^{11,13,14} Animals passively exposed to antigen aerosols are unable to mount subsequent IgE responses to the same antigen for the remainder of their lives, irrespective of the route or intensity of challenge.^{13,14} As with antigen feeding,⁸ tolerance resulting from antigen inhalation inhibits the IgE response,^{13,14} and is mediated by CD4 and CD8 T-cells which secrete Th1 cytokines.¹¹ The immune system is susceptible to this type of tolerance induction only at the time of initial allergen exposure—presensitised animals with stable on-going IgE responses are not desensitised by aerosol exposure.¹³

Two further features are also seen in animals. First, sensitivity to tolerance induction is genetically determined and high sensitivity is co-inherited with low-IgE-responder-phenotype. This manifests itself as a requirement for up to 10³-fold to 10⁴-fold more intense allergen exposure to tolerate high IgE responders.^{15,16} Both high and low responders can ultimately become tolerant by

Division of Cell Biology, Institute for Child health Research,
PO Box 855, West Perth, Western Australia, Australia 6872
(P G Holt psc)

Correspondence to: Dr Patrick G Holt

either route, and the inherent sluggishness of these mechanisms in the high-IgE responders can be overcome by applying intense allergen stimulation.^{15,16}

Second, tolerance functions poorly in the pre-weaning period¹⁷⁻²⁰ so allergen exposure in the very early phase of infancy primes for subsequent T-cell reactivity.^{19,20} This phenomenon is consistent with the existence of an early window of high risk for allergic sensitisation, presumably due to delayed postnatal maturation of one or more key elements of mucosal immune function that are rate-limiting in inducing tolerance.¹⁷

It is not clear to what extent mucosal allergen exposure via the gastrointestinal tract can suppress continuing Th2 responses in IgE-positive high-responder animals, but work with intranasally administered allergen peptides²¹ is encouraging.

Primary allergy sensitisation

Humans are initially exposed to environmental allergens during infancy or early childhood and there is a growing consensus that high-level allergen exposure during the first few months of life predisposes to allergic sensitisation,¹⁷ which manifests in later childhood as Th2 reactivity.

Normal children and those with atopic family history usually develop serum IgE antibody responses against common food allergens during the first year of life, the magnitude and duration of the response reflecting IgE-responder phenotype.^{22,23} A similar pattern is seen for IgE responses to inhalant allergens.²³ However, the latter commence later in infancy and take much longer to switch off (tolerise) in non-atopic children. Furthermore, a much higher proportion of potential atopic subjects maintain their serum IgE reactivity to inhalant allergens into later childhood than for food allergens.²³

These differences in the kinetics and overall efficiency of tolerance induction to inhalant versus dietary antigens may be because of the different levels of antigen exposure in the lung and gastrointestinal tract. Because T-cell subset selection is antigen driven, the less intense stimulation provided via low-level respiratory tract exposure may result in a slower and ultimately less efficient process.

Prophylaxis of atopy

My view is that the natural mechanism for prevention of allergic sensitisation in humans is a cognate immunological process. During early childhood, there is active immunological recognition of the major environmental allergens and the maturing immune system responds by mounting low-grade, initially heterogeneous T-cell responses, comprising cross-competing Th1-like and Th2-like allergen-specific clones.

During repeated rounds of normal environmental restimulation one of the competing T-cell phenotypes eventually becomes dominant in the response, leading to a store of memory T cells that direct immune responses to the allergen throughout later life.

The competition between co-existing antagonistic Th1 and Th2 T-cell populations continues for several years during childhood, as these allergen-specific IgE responses often do not stop in non-atopics until age 5–7 years.^{22,23} It seems that responses to inhalant allergens are plastic during childhood and can be influenced toward either direction by exogenous factors. The known environmental risk factors for primary allergic sensitisation¹⁷ must ultimately promote

selection for Th2-like reactivity. Additionally, cytokines such as IL-12, IFN- α , and IFN- γ may push the equilibrium towards host protective Th1-like anti-allergen responses. The plasticity of these early allergen-specific T-cell responses provides potential opportunities for intervention.

A future vaccine strategy

Early childhood, which has long been designated as the time for sensitisation to environmental allergens, may also be considered as an opportunity to regulate the development of normal anti-allergen immunity in unsensitised children. In principle, we should contemplate active intervention in the continuing allergen-specific T-cell selection process that occurs during early childhood, to optimise selection for allergen-specific host-protective Th1 immunity. The slow overall kinetics of the natural immune response to inhalant allergens provides the most obvious initial target for such an approach.

There appear to be two options. It may be feasible to accelerate and control the natural selection process by feeding or intranasal administration of allergen (or associated peptides) during childhood. This approach derives from the finding that even in atopic individuals the success with which nature tolerises emerging IgE responses to food allergens during infancy is much higher than that achieved with inhalant allergens. Thus, enhanced allergen stimulation via the right route at the right time may increase the overall efficiency of Th1 selection.

While this approach may appear similar to many desensitisation strategies, it is precisely the opposite: desensitisation strategies are based on silencing pathogenetic Th2 cells in the sensitised host with pre-established Th2 memory, whereas this approach is based on prevention of their emergence as a stable memory population in the first place.

A more direct strategy is suggested by developments in vaccine technology, which hold the promise of being able to induce Th1 responses to nominal antigens appropriate parenteral immunisation, with minimal danger of stimulating parallel Th2 pathways. Thus, deliberate parenteral vaccination with a cocktail of the major inhalant allergens at the appropriate time in childhood, especially in combination with an appropriate Th1-selective adjuvant, may provide a safe and reliable method to bolster populations of appropriate Th1 cells. A high serum IgE concentration in most atopic subjects can be accounted for by a relatively small number of major environmental allergen specificities²⁵ and encourages the view that the relevant allergen (vaccine) cocktails may not have to be highly complex. Studies with atopic adults indicate that repeated parenteral challenge with tolerising doses of grass pollen allergen selectively stimulates allergen-specific Th1-like T-cell reactivity as opposed to Th2,²⁶ and this may be more effective in children who do not have an established stable T-cell memory.

Ethical considerations

The justification for paediatric vaccines is based on their perceived need in the community and on the premise that their potential benefits should greatly outweigh the risks associated with their use. Respiratory illness is a major cause of morbidity in children and adults, and allergy is recognised as one of the most important contributing factors. However, further research is required in several

areas. For example, while oronasal allergen administration during childhood may improve the overall efficiency of tolerance induction to inhalants, it may increase transient anti-inhalant IgE responses up to levels which produce temporary clinical responsiveness, as with food allergens.²⁷ The possibility that deliberate administration of allergen may trigger DTH reactivity should be explored in detail, although the failure of DTH to emerge in atopic adults undergoing desensitisation via repeated parenteral allergen injection suggests that this possibility is unlikely. The issue of whether such a vaccination strategy can be justified in the absence of clear evidence of genetic “risk” for atopy also needs detailed consideration, but this question is likely to be resolved in the near future as better screening procedures become available.

My approach is based on principles that form the basis of all modern vaccination programmes: identify the antigens in or the agent causing disease; find the successful defence mechanisms(s) employed by the human immune system against the antigen; and devise a method to deliver the antigen (or an appropriate analogue) to the immune system in a form which optimally primes the appropriate defence mechanism(s) to stimulate the development of protective immunological memory.

In the context of allergic diseases such as atopic asthma, the potential benefits of successful prophylaxis, both in human and economic terms, vastly outweigh those of therapy.

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