
Leading article

Food allergens and food allergy—complex relationships and responsibilities

(See paper by Palmer et al., pages 76–81)

Scientific and medical perspectives

The gaps in knowledge surrounding development of food allergy in infants have led to clinical practices with a poor level of evidential substantiation. This situation arises because of the significant population of infants affected: up to 3% of infants generally (1) and at least 0.5% of exclusively breastfed infants (2), and because of the need for medical support and advice to address their symptoms. Classical allergy presumes that the immediacy of adverse reactions to foods reflects IgE-mediated inflammatory processes. However, diagnostic tests for IgE-mediated allergy such as skin-prick testing and measurement of antigen-specific levels of circulating IgE are well known for false positive and false negative results depending on the antigen (3). Hence, studies using these biomarkers ideally require confirmation of allergy with double-blind, placebo-controlled food challenge trials. The lack of reliable correlation between antigen-specific IgE and allergy symptoms indicates that non-IgE-mediated pathways are also involved in allergic responses to foods. Non-IgE-mediated inflammatory responses to food antigens that are driven by T cells and other immune cell types have been implicated in delayed hypersensitivity reactions affecting both babies and adults (1,4). The role of the effector T cells in allergy and intolerance is further implicated from the benefits associated with probiotics, which are thought to restore tolerance to an allergenic Th2-skewed system by inducing a counterbalancing Th1-type response (5).

The immunological processes involved in the development and regulation of oral tolerance to foods are currently the subjects of intense scientific scrutiny, but as yet, the mechanisms at a molecular and cellular level remain unresolved. Hence, key biomarkers for respective pathways are not yet established for diagnostic use. In the absence of suitable diagnostic biomarkers to identify all pathways of food hypersensitivity, medical practitioners are severely limited in their ability to diagnose food allergen sensitivities, and to subsequently determine if an intervention strategy, such as maternal dietary restriction, is effective. Hence, there is a need for the development of models to account for the development of food tolerance and aberrant responses such as allergy.

The lack of high quality evidence for benefits of dietary exclusion of major food allergens in breastfeeding mothers in order to avoid development of atopic disease in infants (2), reflects the incomplete understanding of the causal links between diet (infant and maternal) and manifestations of allergic symptoms. The natural recovery from food hypersensitivity in the majority of allergic babies with age suggests that immune-mediated reactions resulting from immature digestion, gut integrity and mucosal immune tolerance are reversible as the infant gut matures. Furthermore, it appears that dietary immune modulators such as components of colostrum (6), whey

and probiotics can reprogram an aberrant immune response to one of tolerance. If the mechanisms of food tolerance can be fully elucidated, then strategies for controlling exposure risk to infants that are not based on maternal dietary exclusion might be envisaged. Models should be developed from establishment of causative relationships between key immune cell and humoral immunological biomarkers and challenge-related symptoms. Physiological factors that should also be systematically considered include the integrity of the gut barrier and digestive function. Such information could assist in the development of improved strategies for intervention that address the complex regulatory framework of food tolerance and not just IgE-mediated reactions.

The supply of antigen to infants via breast milk brings further unknowns to the diagnostic equation (2). In particular, how does the antigen supply in breast milk affect the development of food tolerance in the infant? For example, what role does the host play in modulating the immunogenicity of food proteins? Is the digestive function of the mother and survival of epitopes in her milk important for regulation of tolerance by the infant, analogous to the superior effect of partial versus fully hydrolysed infant formulae for promoting food tolerance (7)? Furthermore, what is the relative importance of co-delivery in breast milk of serum IgA for antigen exclusion and regulatory cytokines for promoting maturation of the infant gut, as opposed to presumption that reactions are related exclusively to the delivery of antigen via breast milk *per se*? A final challenge for researchers of food allergy is to determine the precise effector molecules responsible for respective gut and skin symptoms. The dependence of the dose response and associated thresholds for reactivity represent crucial information required to assist the food industry in addressing and managing risk for allergic members of the public.

Perspectives of allergic individuals and the community

Valuable information has been collated from the EU Framework study 'Protall', which has shown that allergens known to trigger acute reactions following contact and processing along the gastrointestinal tract have structural features in common and belong almost exclusively to the prolamin, cupin and cysteine protease protein families (8). Many of these food proteins are of interest as targets for genetically-modified expression systems incorporating improved production and technological efficiencies. It is also possible that GM technology can silence genes responsible for expression of allergenic epitopes, as has been demonstrated for soy protein (9). However, this strategy is not desirable if technological properties of food proteins are adversely affected (10). Immunotherapies for acute IgE-mediated allergy are based on therapeutic administration of structurally modified antigens, usually produced through genetic

modification, and which induce favourable modulation of immune responses. Hence, recombinant forms of allergenic and hypo-allergenic proteins have been developed for the purpose of their use for immunotherapy, but not as hypo-allergenic food products *per se*. Nevertheless, until a substantiated model for the development and intervention of food allergy is available, it is risky to propose that 'hypo-allergenic' analogues of the major allergenic food proteins will be innocuous for all as the removal or modification of common epitopes may not guarantee hypo-allergenicity of the product for all allergic individuals. This is supported by the admission that factors leading to loss of allergenicity are not understood and that development of hypo-allergenic analogues of potent food allergens was undertaken through trial and error modification of known epitopes (11). Other factors associated with allergenic food proteins in relation to IgE-mediated allergy include resistance to digestion, stability in peptic and gastric fluids and the presence of post-translational modifications (12), which represent additional strategic targets for genetic modification.

From the viewpoint of hypersensitive individuals, undeclared food allergens represent a full spectrum of risk, from mild discomfort to life threatening, depending on the individual and the type of allergen. For the latter category of individuals, this represents an imposition requiring vigilant attention that is typically nutritionally and socially compromising. In the case of breastfeeding mothers, it is desirable that the merits of dietary restriction in relation to treatment of food allergy symptoms be established with sound evidence before recommending dietary modification.

Food industry perspectives

It has been speculated that the apparent rise in the incidence of food allergy may be related to the practices of food processors over the last few decades with the introduction of processing technologies that modify the molecular properties of food allergens (13). While in some cases processing can increase allergenic potency, processing technologies can also help to reduce food allergenicity. Many allergens exhibit reduced allergenicity following standard cooking procedures. One demonstration has been the significant reduction in oral allergy syndrome reported following the treatment of apples with high pressure (14). This offers some evidence that processing may induce structural modification of epitopes that are unlike modifications associated with traditional processes, and may thereby offer alternative strategies for modulating the allergenicity of foods.

In addition to investigating process-based interventions for reducing the allergenicity of foods, the food industry is responding to the increasing concern regarding allergen traceability in processed products, through the new regulations surrounding mandatory labelling. The onus of managing risk for susceptible individuals has thus been transferred to the manufacturer in recent times, which has far-reaching implications for the food processing industry, its suppliers and stakeholders. The implementation of risk management practices is also applicable to the food service industry, with increasing regulation of the information supplied to consumers at the point of purchase and consumption. This development has brought a completely new range of supply chain controls

in an attempt to inform allergic individuals about potential exposure to allergens. The new Australian Food Safety Centre of Excellence, an initiative of the National Food Industry Strategy, has recently established an Allergen Forum in support of the issues affecting the Australian food industry. The aims of the forum are to identify and document allergen issues, provide industry with a means to establish and champion priorities, to develop networks and communicate with regulatory bodies. Currently, the combination of unknowns, including the threshold for reaction of an individual, together with the unknown immunogenicity of processed antigens and unknown residual concentration of a potential allergen in food products on a per serve basis, generates a very large opening for risk management, and requires a practical and reasonable approach that serves the needs of all stakeholders.

A related outcome from the attention of the food industry to the issues which face hypersensitive individuals has been to develop hypo-allergenic food products using strategies such as substitution of non-allergenic for allergenic food proteins, and also in the marketing of products with 'free-from' allergenic protein labelling. These trends are fuelled both by the marketing push and consumer pull for foods with individualised attributes and apparent benefits. On the face of it, this appears to be a win-win situation for the industry and consumers alike. However, in the absence of adequate clinical diagnostic tools, the food industry may have unwittingly released a growing consumer trend towards associating a range of unrelated symptoms with food ingredients, and consumers who modify their diets accordingly. This trend is reflected in the wide discrepancy between individuals with challenge-confirmed versus perceived food allergy (15). By complying with the new labelling regulations, the food industry is addressing the risk management of hypersensitive individuals who are susceptible to acute and life-threatening reactions, and is simultaneously informing others who exercise choices based on perceived allergy-related symptoms. However, in the continuing absence of diagnostic tools relevant to proven biological processes of symptom elicitation, claims by consumers regarding liability of the food industry for their perceived symptoms may be legitimised by the industries' provision of a growing range of alternative food products. In other words, the marketing of hypo-allergenic food products for individuals who do not need them may be lucrative in the short term, but this may backfire in the longer term by apparently validating the link between food components and a plethora of unrelated reactions. Hence, the apparent short-term benefits to the food industry and consumers surrounding the increasing marketing of hypo-allergenic food products without evidential substantiation, may actually reflect poor long-term management of relationships and responsibilities of the industry towards its customers.

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References

1. Hill DJ, Clifford CS, Zhie CY, Leung R, Baratwidjaja K, Iikura Y, et al. The frequency of food allergy in Australia and Asia. *Environ Toxicol Pharmacol* 1997; 4:101-10.
 2. Palmer DJ, Gold MS, Makrides M. Treatment and prevention of food allergies in breastfed infants: practice and evidence. *Nutr Diet* 2004;61:xx-xx.
 3. Norgaard A, Bindslev-Jensen C, Skov PS, Poulsen LK. Specific serum IgE in the diagnosis of egg and milk allergy in adults. *Allergy* 1995 50;8:636-47.
 4. Bischoff SC, Sellge G. Immune mechanisms in food-induced disease. In: Metcalfe DD, Sampson HA, Simon RA, editors. *Food Allergy: Adverse reactions to foods and food additives*. Oxford: Blackwell; 2003. p. 14-37.
 5. Kalliomäki M, Salminen S, Arvilomni H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *The Lancet* 2001;357:1076-9.
 6. Pakkanen R, Aalto J. Growth factors and antimicrobial factors of bovine colostrum. *Int Dairy J* 1997;7:286-97.
 7. Exl BM. A review of recent developments in the use of moderately hydrolyzed whey formulae in infant nutrition. *Nutrition Research* 2001; 21:1-2:355-79.
 8. Mills ENC, Madsen C, Shewry PR, Wichers H J. Food allergens of plant origin—their molecular and evolutionary relationships. *Trends in Food Science & Technology* 2003;14:4,145-56.
 9. Anonymous. *Agricultural Research Magazine*; September 2002;50:9.
 10. Shewry PR, Tatham AS, Halford NG. Genetic modification and plant food allergens: risks and benefits. *J Chromatography, B: Bio-medical Sciences and Applications* 2001; 756(1-2):327-35.
 11. Lorenz A-R, Hausteil D, Vieths S. IgE-binding properties of recombinant food allergens. *Internet Symposium on Food Allergens* 2001;3(1):1-36.
 12. Huby RD J, Dearman RJ, Kimber I. Why are some proteins allergens? *Toxicol Sciences* 2000;55;2:235-46.
 13. Moneret-Vautrin D-A. Food allergies. *Annales Pharmaceutiques Francaises* 1999 57:6,442-5.
 14. Meyer-Pittroff R. High pressure applications in medicine. In: Winter R, editor. *Advances in high pressure bioscience and biotechnology II*, Dortmund 16-19 September, Berlin: Springer Verlag; 2003. p. 295-305.
 15. Altman DR, Chiaramonte LT. Public perception of food allergy. *J All Clin Immunol* 1996 97;6:1247-51.
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