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Clinical risk assessment of GM foods

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Abstract

The main concerns about adverse effects of genetically modified (GM) foods on health are the transfer of antibiotic resistance, toxicity and allergenicity. There are two issues from an allergic standpoint. First, the transfer of a known allergen may occur from a crop into a non-allergenic target crop. The second scenario is the creation of a neo-allergen where de novo sensitisation occurs in the population. The first scenario occurred in 1996 when the 2S albumen protein from Brazil nut was transferred into soy bean (N. Engl. J. Med. 334 (1996) 688). 2S albumen was found to be a major Brazil nut allergen and the newly expressed protein in transgenic soy retained its allergenicity. Patients allergic to Brazil nuts and not to soy bean now showed an IgE mediated response towards GM soy bean. We argue that it is possible to prevent such occurrences by doing IgE-binding studies and taking into account physico-chemical characteristics of proteins and referring to known allergen databases. The second possible scenario of de novo sensitisation does not easily lend itself to risk assessment. We compare GM technology to traditional plant breeding and food processing methods. There is no evidence that the technology used for the production of GM foods poses an allergic threat per se compared to other methodologies widely accepted in the food industry. We need to proceed cautiously in the future, assessing individual GM foods on the basis of their individual merits and risks prior to introducing them into the market. © 2002 Published by Elsevier Science Ireland Ltd.

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1. Introduction

The application of genetic manipulation (genetic 'engineering') to crop breeding and food production is an extension of traditional agricultural technology. Analysis of plant genomes and gene cloning techniques advance the practice of crop breeding by permitting the incorporation of a desired trait through the insertion of a specific gene into a plant.

There are four main approaches by which plants are manipulated by genetic 'engineering'. These are: (i) gene insertion using a bacterial vector; (ii) microballistic impregnation; (iii) poration and (iv) gene neutralisation by means of antisense technology, homologous recombination (gene knock out) and gene replacement.

Despite potential benefits of such techniques, serious concerns have been raised concerning the potential environmental and medical consequences of GMOs. In May 1999, the British Medical Association published a statement on GMO addressing three areas over potential health effects of genetically modified (GM) foods (BMA Science

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Department, 1999). It focussed on the transfer of antibiotic resistance, toxicity, and allergenicity. The Committee highlighted the importance of further research on the potential allergenicity of GM products.

2. Allergenicity of GMOs

An allergic reaction must be distinguished from allergic sensitisation. Sensitisation is the process whereby the immune system of an individual becomes reactive to an allergen. This requires exposure to an allergen over a period of time, resulting in allergen specific CD4 T-cell responses and the production of allergen specific IgE by B cells. The distinction between allergic sensitisation and allergic reactions is critical and raises important considerations relevant to the allergenicity of GMOs. Thus, one must consider not only whether GM products can cause allergic reactions in sensitised individuals but whether a newly expressed transgene may lead to de novo allergic sensitisation in the population.

Thus the genetic manipulation of crops could potentially cause allergic problems in one of two ways. First, there is the potential to transfer a known allergen into a target crop. The second possibility is to create a new allergy to a neoallergen. The latter could occur when a transgenic protein is newly introduced into the food chain and de novo sensitisation occurs in the population. The first scenario has already occurred and was described 4 years ago (Nordlee et al., 1996). In order to improve the nutritional content of soy bean for cattle feed, the 2S albumen from Brazil nut (rich in cystein and methionine) was transferred into soy. As Brazil nuts are known allergens, it was decided to determine the allergenicity of the transgenic soy bean. The results of detailed experiments showed that 2S albumen from Brazil nut was a major Brazil nut allergen and that the newly expressed protein in transgenic soy retained its allergenicity and therefore its potential ability to provoke clinical reactivity in patients with allergy to Brazil nut. Patients allergic to Brazil nuts and not to soy bean now showed an IgE mediated immune response towards GM soy bean. On this basis, the soy bean was not marketed.

The second question as to whether a new transgene could express a neoallergen and lead to de novo allergic sensitisation is more difficult to predict as it is not clear, in the first place, why allergic sensitisation occurs to some proteins and not to others.

3. The safety of GM food

An argument favouring the safety of GM foods is that this represents a far more precise and safe manner of genetic alteration in plants compared to traditional plant breeding methods. Traditional plant breeding, which has been practised for millennia, involves the transfer of hundreds of genes and potentially new proteins to create a crop with certain desirable characteristics. Such large-scale genetic changes in the plants have significant implications for protein expression. Many changes in protein expression are likely to occur with these traditional methods, which we ignore. Conversely, GM foods allow the precise transfer of a single gene into a host species. There is precise information on the protein transferred, its sequence and therefore the ability to test for allergenicity in the new product.

It has been argued that traditional plant breeding does not cross species barriers and in GM foods there is the potential to introduce a far greater diversity of genes into the host species. However, there are examples in traditional plant breeding where genetic material is exchanged between different species.

4. Food allergens

If it were possible to define the properties of allergens and the rules of allergenicity, we would be able to identify whether novel proteins could induce allergic sensitisation in a population. This has prompted a variety of approaches to define allergenicity. Investigators have characterised physico-chemical properties of food allergens. Thus the majority of food allergens are glycoproteins, with a molecular weight greater than 10 000. Stability to digestion, proteolysis, hydroly-

sis, heat and changes in pH have been found to distinguish food allergens from other plant proteins (Taylor and Lehrer, 1996). However, there are important exceptions to this, notably in the families of fruit allergens, and lack of these characteristics does not allow one to confidently predict that a protein is not allergenic.

The use of amino acid sequence technology is useful in certain circumstances in predicting cross-reactivity between crustaceans. It is not helpful in other cases. Thus high sequence homology between shrimp and beef tropomyosin does not allow prediction of cross-reactivity. Inability to predict cross-reactivity based on amino acid sequence homology is usually due to the occurrence of conformational epitopes comprised of a discontinuous (non-linear) amino acid sequence along a folded protein. Analysis of the 3D structures of diverse allergens reveals that allergens have no structurally defining features (Aalberse, 2000). In vivo rodent models do not allow the prediction of allergenicity of novel proteins. In summary, there are no reliable rules of allergenicity.

5. Predicting allergenicity

One approach to predicting allergenicity was published from a Joint FAO/WHO Expert Consultation which met in 1995 (Food and Agriculture Organisation at the United Nations, 1995) and has more recently been revised. The consensus report recommended a stepwise assessment of foods taking into account the source from which a gene was obtained, amino acid sequence comparisons with known allergens, immunological analyses (in vitro and in vivo) and physico-chemical properties of the gene product. The report stressed that there was no single diagnostic test to assess the probability of a GM food being allergenic, but that the totality of these assessments needs to be taken into account.

The stepwise approach varied, depending on the source of the gene. The most stringent assessment was required in the case of commonly allergenic foods. The report recommended that if a food contains protein from a gene derived from a commonly allergenic food it be subjected to a series of solid phase immunoassays (RAST or RAST inhibition or ELISA). Each food should be tested against immune sera from at least 14 sensitised individuals with positive clinical histories. This should ensure a $>99.9\%$ probability of detecting the presence of a major food allergen and $>95\%$ probability of detecting a minor allergen to which more than 20% of the population reacts. If the in vitro assay is positive, there is the potential for that protein to be allergenic and it was recommended that unless this possibility is dismissed by in vivo testing, food labelling on the GM product should include the source of the donor gene. It was recommended in the event of negative or equivocal results with solid phase assays skin prick testing should be undertaken using a minimum of 14 allergic individuals and that safety of the food be confirmed by double blind food challenges.

It should be noted that GM technology offers a possibility of preventing and treating allergy.

There is a possibility of using recombinant technology to change known allergens into hypoallergens. This has indeed been done for major allergens in rice and soy and such work is under way for peanut allergies.

Hypoallergens have a potentially important role in allergic desensitisation. Recently, single amino acid substitution in the major house dust mite allergen has been shown to reduce IgE binding by more than ten fold. Similar approaches using recombinant peanut allergens offer possibilities to desensitize individuals with peanut allergy.

6. Conclusions

In summary, GM technology could cause the transfer of a known allergen into new crops. This is both foreseeable and preventable. While GM technology could theoretically result in neoallergens there is no greater risk for this occurring compared to other technologies in traditional plant and animal breeding.

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