Indian Journal of Allergy, Asthma & Immunology

EDITORIAL
Year : 2016 | **Volume** : 30 | **Issue** : 1 | **Page** : 1--3

Safety assessment of genetically modified crops

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How to cite this article:
Kale SL, Arora N. Safety assessment of genetically modified crops.Indian J Allergy Asthma Immunol 2016;30:1-3

How to cite this URL:
Kale SL, Arora N. Safety assessment of genetically modified crops. Indian J Allergy Asthma Immunol [serial online] 2016 [cited 2016 Sep 20];30:1-3
Available from: http://www.ijaai.in/text.asp?2016/30/1/1/187543

Full Text

Due to rapid increase in the population, especially in developing economies, the demand for food is expected to rise by 70% by 2050 (Food and Agriculture Organization [FAO], 2009). Recent advances in biotechnology and improvements in molecular techniques for plant genetic engineering have led to the genetic modification of plants so that they can express transgenes (protein of a foreign origin). This transgene can confer the added advantage such as herbicide resistance, insect resistance, or abiotic stress tolerance for survival in unfavorable conditions which can further lead to increase the yield of the crops and can help in mitigating the food crisis. Genetic manipulation has been used to produce high yielding variety of crops resistant to pathogen attack and tolerant to environmental imbalances such as drought, cold, and salinity. [1] Flavr Savr tomato was the first genetically modified (GM) crop approved for commercial production in 1994. [2] As of 2014, 181 million hectares of land in 28 countries was under transgenic crop cultivation. Although Bacillus thuringiensis (Bt) cotton happens to be the only GM crop approved for commercial production in India, India ranks 4 th in the world with 11.6 million hectares of Bt cotton (ISAAA, 2015). Many GM crops are in the pipeline of development or are awaiting regulatory permissions for field trials and mass production, a prime example being Bt brinjal and transgenic mustard. [3],[4]

GM crops express a transgene, a protein foreign to the wild type. Before introducing them into the wild-type crops for feed and fodder, these transgenes need to be evaluated for allergenicity. [5] Genetic manipulation can also alter the allergens already present in the wild type crops. Food allergy has become a major health concern worldwide over the past few decades and is associated with a significant impact on the quality of life. The prevalence of food allergy is increasing and affecting as many as 6-8% of children and 3-4% of adults. [6] Hence, before introduction for commercial cultivation, it is absolutely necessary to evaluate the allergenicity and toxicity potential of the transgenes used for GM crop production. To assess the safety of foods derived from GM plants including allergenic potential, a rigorous safety assessment protocol has been developed by a number of international scientific bodies. [7] The International Food Biotechnology Council (IFBC), in collaboration with the Allergy and Immunology Institute of the International Life Sciences Institute (ILSI), was the first one to release its guidelines in 1996 and was followed by the FAO/World Health Organization (WHO) consultation in 2001 and

Codex Alimentarius Commission guidelines in 2003. [8] In India, the safety assessment is regulated by the Indian Council of Medical Research Guidelines for allergenicity assessment of GM crops. [9] These safety guidelines involve an integrated case by case approach to be used in allergenicity assessment. The IFBC-ILSI and FAO/WHO guidelines both used a decision tree approach to evaluate the risk of allergenicity. This involves the assessment of the allergenicity of transgene source, followed by in silico sequence homology studies using allergen databases, immunoreactivity with allergic patient's sera, physiochemical stability, and animal studies. The Codex Alimentarius Commission uses a weight of evidence approach that takes into account several parameters for safety assessment such as gene source, amino acid sequence homology to known allergens and in vitro stability to pepsin digestion, and specific IgE binding studies such as skin prick test. Codex abandoned the risk assessment methods based on a decision tree and emphasized on the need to use scientifically validated testing, specifically removing the animal tests due to the lack of a validated animal model that can predict the risk of sensitization in humans.

SOURCE OF THE GENE

The assessment begins with the evaluation of the source of the transgene which can be classified as allergenic, moderately allergenic, or of unknown allergenic potential. If the source of transgene happens to be allergenic or moderately allergenic, then a rigorous assessment is warranted to conclude that the transgene does not code for an allergen. Most of the time, the gene selected for producing the GM crops is obtained from the sources that have unknown allergenic potential.

SEQUENCE HOMOLOGY STUDIES

Sequence homology studies include comparison of the transgene protein sequences with that of the known allergens. The basis was that if two proteins share a linear sequence, they tend to share three-dimensional structural motifs and might share allergenic cross-reactive epitopes. The IFBC-ILSI guideline suggests eight amino acid matches to indicate a risk of cross reactivity with known allergens, whereas the FAO/WHO guideline changed it to six amino acid matches. According to the FAO/WHO, 2001, and Codex, 2003, if the sequence similarity between a transgene and a known allergen is >30% in an 80 amino acid sliding window, then the transgene is considered as an allergen and warrants further safety assessment with IgE serum screening. The potential drawbacks of this approach are that very few food allergens are known and have been included in allergen databases and that a short stretch of amino acid matches can give a high rate of false positives.

PHYSIOCHEMICAL STABILITY

A specific set of characteristics that confers allergenicity to certain proteins is still unknown. Food allergens are mostly resistant to heat treatment and are resistant to pepsin digestion. Heat treatment is the most important step in food processing, which includes cooking, roasting, baking, sterilization, or pasteurization. Several allergens have been shown to be thermal resistant. Optimum temperature for thermal stability studies ranges from 25°C to 95°C for 30 min. Depending on the protein, the heat treatment can reduce or increase its allergenic potential.

Ability of a protein to withstand the peptic and acidic conditions of the digestive tract is considered to be a major risk factor for allergenicity. Codex 2003 has listed pepsin resistance as one of the important parameters for safety assessments. Several food allergens are resistant to degradation in an in vitro pepsin digestion assay carried using simulated digestive fluids, whereas most of the nonallergenic dietary proteins are readily digestible. Main drawback of this assay is that several food allergens that cause oral allergy syndrome are heat labile.

SERUM SCREENING

Serum screening test evaluates IgE binding and cross-reactivity of the transgenes. The FAO/WHO 2001 recommends specific and targeted serum screening. For specific serum screening, sera from the cases that are allergenic to or sensitized to the source or the sequence-matched allergen are used for allergenicity assessment. In targeted screening,

sera from cases sensitive to the allergen sources from the same broad group (taxonomic groups such as monocots and dicots) to the source of the gene are used. Codex guidelines, as a part of weight of evidence approach, recommend use of specific serum screening to identify potential allergens.

ANIMAL MODEL STUDIES

Animal models possess the potential to mimic the human disease condition and hence serve as a useful model to study the onset of disease, disease triggering molecules, and evolving therapeutic measures. [10] The FAO/WHO 2001 guidelines recommend the use of animal models for allergenicity prediction of transgenes. It is proposed that for the assessment of allergenicity of GM crops an animal model should preferentially meet the specified criteria: (1) having similar allergenic response as humans, (2) should not involve the use of an adjuvant which can potentiate antigen-specific immunity and may influence the type of immune response elicited, (3) should be able to elicit response using typical routes of exposure (e.g., oral) for administration, (4) should trigger an IgE response to the protein, as well as other Th2-associated immune responses in the animal, [11] and (5) being reproducible, specific, and sensitive. The guidelines also recommend the use of two different species or two different routes of sensitization in a single species. A number of different factors promote sensitization in humans making food allergy a complex disorder. This along with the complex genetic diversity that predisposes humans to food allergy makes it difficult for a single animal model to predict the allergenic potential of novel food antigens. Codex abandoned the use of animal models for allergenicity prediction due to lack of sufficient reliable animal models.

Growing number of studies have used these guidelines for safety assessment of GM crops and to evaluate the allergenic potential of the transgenes. Mishra et al. used in silico assessment for determination of allergenic cross-reactivity of six transgenes: Bacillus subtilis glycine betaine aldehyde dehydrogenase (gbs A), Triticum aestivum beta-1, 3-glucanase, Medicago sativa beta-1, 3-glucanase, Oryza sativa chitinase, Nicotiana plumbaginifolia mitochondrial manganese superoxide dismutase, and Nicotiana tabacum osmotin, which are routinely used for the development of GM crops. [12] The allergenicity of transgenic mustard expressing bacterial CodA gene was similar to that of the native mustard, demonstrating no enhancement in allergenicity due to genetic manipulation. [13] Safety assessment of bacterial choline oxidase, a protein that provides tolerance against abiotic stress in transgenic crops, showed no significant toxicity and allergenicity in mice. [14] Osmotin, a pathogenesis-related protein used in development of transgenic crops, was identified as a potential allergen as it was resistant to pepsin digestion and heat treatment and showed cross-reactivity with apple and tomato allergens. [15]

In conclusion, these studies highlight the importance of safety assessment of GM crops and the transgenes before introducing them for commercial production and simultaneously highlight the role of the regulatory guidelines in ensuring the safety.

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