Food allergies, cross-reactions and agroalimentary biotechnologies

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Abstract

The discrepancy between what the general public and specialist in allergic diseases regard as a true food allergy can in part depend on the frequent evidence of subjects in whom clinical symptoms elicited by a given food allergen are frequently not reproducible: this suggests the existence of allergens variably present in certain foods. In adults and older children common is a form of food allergy associated with inhaled allergens, especially pollens. In this allergic form pollens and various vegetal food often cross react but the underlying scientific rationale is largely unclear. From the study of the "latex-fruits allergic syndrome" and the "oral allergic syndrome" emerged that the cross reactivity depends on epitopes of pollens and vegetables belonging to one of the 14 classes of the "pathogenesis related proteins" (PRPs). Vegetables produce PRPs in response to infection or after plant injury or application of chemicals: long-term conservation and methods used for rapid artificial ripening of vegetables can cause plant to produce PRPs or other allergens. A genetic selection of vegetables "protecting themselves against infection and infestation" by mean of PRPs production is practiced in agroalimentary biotechnology. We deem it urgent that the two realms, Medical Science (Allergology) and Agricultural Biotechnology begin to communicate openly in order to produce food as efficiently as possible but without harming the large part of the population which is predisposed to allergy and react to PRPs.

Key words: food allergy, cross-reactions, biotechnology.
Background: the prevalence of food allergies.

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Introduction

The discrepancy between what the general public, medical practitioners and specialists in allergic diseases regard as a true food allergy is beyond doubt. Whereas a large percentage (from 12 to 20%) of the general population complain of symptoms that they blame on food, double-blind controlled studies using oral challenge tests disclose food allergies or food-related disorders in no more than 1% of the population [1-2].

One reason for this situation is that there are no straightforward diagnostic tests for food allergy-intolerance with sufficient sensitivity [3]. The double-blind placebo-controlled oral challenge is a laborious undertaking (especially in children) [4-6]. It hinges upon the concept that a certain limited quantity of a given food administered in the course of 2 hours is sufficient to trigger the reported symptoms. Yet even in the most clear-cut cases, that is, patients with positive histories and positive prick tests, it actually does so in no more than half the cases [7,8]. In the other 50% of subjects with a clear-cut history and in all those whose history is less clear or who have negative prick tests we doubt whether clinical double-blind testing is sensitive enough to exclude a food allergy. If it is not, then we presume that the prevalence of allergy-intolerance in the general population considerably exceeds 1%.

Clinical types of food allergy and cross-reactions between vegetal allergens

Food allergies can be subdivided into two types. The first type is provoked by cow's milk, hen's egg, legumes and other foods containing allergens resistant to digestion that induce gastrointestinal tract sensitisation. It tends to disappear after the first years of life and is later replaced by other clinical forms of atopy [9]. The second type of food allergy, more commonly seen in older children or adults, is associated with sensitisation

to inhaled allergens (especially pollens) that often cross react with other pollens or various vegetal foods [10,11].

The scientific rationale underlying cross-reactions between vegetables, although extensively discussed in the literature [12--17] remains largely unclear. The chief reason is that natural extracts of plant proteins are extremely labile. Hence diagnostic procedures *in vivo* and *in vitro* often yield irreproducible results.

The history of unexpected allergic cross reactions began in 1970 with a report describing coincident allergies to *Parietaria* and banana [18] followed by reports describing a frequent coupling of allergies to birch and apple [19], mugwort and celery [20], and latex-banana-avocado [21]. Over recent years the list of syndromes involving cross-reactivity between pollens, fruits and vegetables has steadily lengthened.

The most favoured hypothesis to explain cross-reactivity is that an individual produces IgE that can recognise structurally similar epitopes on the proteins of the vegetables in question. Until today these epitopes were regarded as phylogenetically related, probably being conserved throughout the various evolutionary processes.

To illustrate the problem of cross-reactivity as seen in clinical practice we describe here two of the better known, though complex and poorly understood syndromes.

"Latex-Fruits Allergy" and Chitinase type 1

Allergy mediated by IgE specifically directed against latex from natural rubber creates major problems for certain health professionals (2-10%) and for children with congenital anomalies (bifid spine, 28-37%) that are daily exposed to latex products. The prevalence of the syndrome (currently less than 1% in the general population and 3% in children with severe allergic diseases) is high in urban areas where particles from the wear-and-tear of car tyres are continually released into the air [17]. A high frequency (50-70%) of cross-reactions has been shown between latex and food allergens such as banana, avocado, chestnut, as well as kiwi, papaya, peach, apricot, grapes, pineapples, passion fruit, potatoes and tomatoes [22-24].

Another potential allergen is the whitish secretion that exudes from injured parts of *Ficus benjamina* (the commonest houseplant in Europe). When the secretion dries, organic substances it contains are released into the environmental air, and if inhaled can provoke allergic symptoms in people with the "latex-fruits syndrome" [25]. The latex-fruits syndrome [22,26] aroused great interest among allergists because the lack of an apparent taxonomic relationship between the vegetal species involved made it difficult to imagine that they each possessed a structurally similar epitope. Finally attention turned up to an allergen from latex (*Hevea brasiliensis*) denominated "Hevein", which derives from a precursor. Its amino acid sequence with an N-terminal permits to adhere to chitin, one of the structural components in the walls of numerous fungi and the skeleton of many insects. Because Hevein adheres to and hydrolytically degrades chitin, it belongs to the plant defence system: by digesting the outer covering of fungi and insects it increases the plant's defences against numerous vegetal pathogens [24,25,27-29]. As well as the principal chitinase of latex (chitinase 1) other chitinase classes abound in nature (some in latex itself), for example: potatoes, turnips and tomatoes produce chitinase type 2.

Latex also contains many other allergens: some (gluconases and esterases) are recognized by specific IgE from patients allergic to vegetal food [27].

A high percentage of subjects who are allergic to the vegetables in the latex-fruits syndrome are allergic also to pollens [30,31].

It is important to underline that chitinases are produced when (and mostly only if) plants are damaged, infected or chemically treated [14,32,33]. Therefore the correspondence between the allergen content of a vegetable, positive skin tests and the presence of clinical symptoms is a highly complex matter that depends on the environmental conditions under which the vegetal was grown, stored, and processed as a foodstuff.

Many explanations can be put forward to explain why an individual who ingests a certain food in the group, contrary to expectations derived from previous experiences, has no symptoms: aside the possible allergen degradation (qualitative and quantitative) caused by digestion or cooking it is possibly because the vegetal ingested contains no chitinases or other allergens that plants produce in excess only in response to a noxious stimulus.

The oral allergy syndrome (OAS), Bet v 1 and lipid transfer proteins (LTPs)

The oral allergy syndrome [34-36] is a disorder involving the sensitisation to birch pollen allergens and apple, mugwort, hazelnut, walnuts, green beans and various fruits belonging to the *Rosaceae* family (pears, cherries, plums, and apricots) and vegetables belonging to the *Apiaceae* species (parsley, potatoes, carrots, courgettes, lettuce and celery). The number of foods involved in this syndrome is continuously growing.

Patients with OAS manifest a wide range of symptoms, caused by direct contact of plant food with the oral mucosa ranging from swelling and angioedema of the lip, itching and sudden desquamation of the oral mucosa, oedema of the glottis, gastroenteritis and diarrhoea to occasional systemic reactions such as urticaria, asthma and shocking [34]. More than 70% of patients with OAS react to two foods or more, they typically tolerate cooked foods [35,37]. The association between pollen and plant-derived food allergy can be explained by the presence of specific IgE against allergens (panallergens) that share a homologous structure and are thus cross-reactive. Allergy to apple (Mal d 1) and to major birch pollen allergen (Bet v 1) is frequently associated with OAS. Some of patients are also sensitized to minor birch pollen allergen, profilin Bet v 2, but recent studies suggested that profilin sensitization has little or no clinical relevance [35].

Studies conducted in the early 1990s recognised that this association between birch and apple allergens depended on the homology of its antigenic determinants, in particular the Bet v 1 antigen from apple and birch [29]. This antigen, like

chitinase in the latex-fruit syndrome, belongs to one (class 10) of the 14 classes of the pathogenesis-related proteins (PRPs), namely proteins that vegetals produce for defence or functional purposes (for a complete scientific classification of PRPs see references 14 and 38).

Later studies in Southern Europe noted that many subjects sensitised to apple were not sensitised to birch, a relatively rare allergen in the various Mediterranean areas [39-42]. In these subjects, many of whom are sensitive to cherries, peaches, plums and apricots and occasionally to soybean and barley, the common allergen is a protein that transfers phospholipids across the vegetal cell, hence the name lipid transfer protein (LTP). LTPs are located in the skin or hull of vegetables [39]. Their function is to defend the plant from fungi and bacteria [40]. These substances provoke allergic sensitisation through the oral route because they are extremely resistant and readily survive oral and gastrointestinal digestive processes [42-43]. The recent studies indicate that the IgE cross-reactivity patterns and the clinical relevance is still not clear and that only some of patients with confirmed IgE cross allergy to Bet v 1 and Mal d 1 demonstrated clinical symptoms after ingestion of apple [8,39].

Pathogenesis-related proteins (PRPs) and other plant food allergens

Faced with the growing problem of cross-reactivity among pollens-vegetables and fruits that has now extended to encompass taxonomically distant plant derivatives, immunologists and specialists in allergy have devoted their most recent efforts to discovering "panallergens" as ubiquitous substances in the vegetal world, panallergens could underlie the ability of the various vegetables to elicit identical IgE in predisposed subjects [43-48].

The "latex-fruits syndrome" and the "oral allergy syndrome" have probably provided the clearest evidence so far that rather than being constitutively present in a given list of vegetables, many panallergens have precise defence functions in the vegetal world (like chitinase 1 in latex and BET v1 in birch) – innumerable vegetables may produce them when necessary, e.g. in response to infection by pathogens (fungi, bacteria, and virus) or after plant injury or application of chemicals [45,49].

Despite their enormous and emerging complexity, "plant defense-related proteins" or "stress-inducible plant proteins" or "pathogenesis-related proteins" (PRPs) engender new concepts that help to put the problems of cross-reactivity in vegetables, and some of those related to food allergy into perspective [14,38]. PRPs have been classified into 14 classes some of which (classes 2, 3, 4, 5, 9, 10, 14) are richer in substances with allergenic properties – together with other classes of proteins (alpha amylases and proteases inhibitors) they form the "plant defence system". Several basilar papers have described these substances and their clinical meaning [14,50,51].

Vegetables may also contain other substances that are potent allergens and have different biological activities. Foods that are especially rich in these allergens are seeds and tubers [14]. Many of these substances are proteolytic and glycolytic enzyme inhibitors, seeds use them to resist invasion and digestion by microorganisms and insects. These allergens are frequently found in seeds from cereals (including Kunitz-trypsin inhibitor from soybean; alfa-amylases inhibitors in barley rice, grain and rye that cause baker's asthma) and make up a family (alfa-amylase-trypsin inhibitors) with functional and structural homologies [14].

Proteolytic plant enzymes, especially those belonging to the family of thiol-proteases have been frequently found to exert the function of cross-reactive allergens, for example ficin and papain from fig and papaya. Moreover, antibodies reacting papain and ficin cross-reacted with allergens of house dust mites (Der p 1 and Der p 2) which also belong to the family of thiol-proteases. However, no clinical association between house dust mite allergy and allergy to tropical fruits has been reported [14,36].

The profilins (proteins that help to regulate the cyto-skeletal components of vegetables) were for long considered the allergens responsible for the "mugwort-celery-spice" syndrome. Later studies recognised them as relatively common allergens in tree pollens (birch), grass (*Graminaceae*) and mugwort. Antigens cross-reacting with profilins are found in various vegetables including carrots, hazelnuts, peanuts, tomatoes, pumpkins, soybeans and pears [14,52,53].

It must be said that plant food allergens belong to a limited number of protein families: they are in general characterized by a number of biochemical and physiochemical properties like resistance to proteolysis and enhanced ability to bind ligands such as lipids (membranes or other lipid structures) or enhanced stability, for example thermal stability, which is a frequent characteristic of allergens [51].

Tropomyosins are a family of proteins which are heat-stable cross-reactive food allergens (e.g. boiled shrimps contain Pen a 1 and water soluble allergens that are released into boiling water). In this family heat-stability probably derives from the presence in their structure of numerous repeat series (40 or more) of heptads of amino acids – these proteins adopt an helical structure with two molecules wound around each other [54,55].

Also the globulin seed storage proteins share the propensity to become heat resistant (forming large structures, from trimers to dodecamers) depending on salt concentration in the environment and on wet or dry thermal processing; often proteins become more thermostable during thermal processing at low water levels, like roasting (e.g. peanuts and other nuts) but also baking, grilling, frying, etc. This involves sugars reacting with free amino groups of proteins with the consequent production of advanced glycation-glycosylation end products (AGEs). In addition to forming during dry heating procedures these products are also slowly formed over days and months as a consequence of the aging process of foods. However, AGEs ingestion in humans largely depends by the consumption of heat-processed foods (in general degree and time of heat exposure determine AGEs content of different foods) [51]. It must be said that the problem represented by the allergenic properties of AGEs containing foods are far outweighed by their detrimental metabolic effects ranging from multiple gene activation to pro-atherosclerotic and glomerulosclerotic effects involving cytokine and growth factor modulation, lipid oxidation and albuminuria [56].

Other groups of allergenic substances are proteins contained in seeds (seed-storage proteins). These usually exist as dimers, tetramers or hexamers but their subunits, released during the processes of ripening and conservation, have strong allergenic potential and can provoke symptoms when inhaled or ingested. Albumins are water soluble at low salt concentration and, in appropriate environmental conditions, they are cleaved into large and small subunits held together by a disulfide bond (2S albumins). 2S albumins are major allergens in Brazil nut, peanut, yellow mustard. Seed storage globulin is soluble at high salt concentration – to this class belong most of the allergens of soybeans and of peas [14,51].

The seed storage proteins therefore represent example of proteins which can become allergenic when conservation conditions modifies them.

In conclusion, current evidence shows that most of the cross-reacting allergens contained in vegetables are functional substances that vegetables may contain depending on the conditions the vegetal encountered during growth and maturation, conservation and food processing.

Food allergies and biotechnology in the production of fruit and vegetable foodstuffs

Over the past few years, immunologists have laboriously become aware that cross allergies to fruits, vegetables, and pollens depend on substances found widespread in the vegetal world. Plants use them as tools for functioning or to prevent or combat the action of pathogens or environmental stress. No wonder these substances have long been known to those botanists and scientists who strive to seek more efficient ways of producing vegetal foodstuffs. Research conducted some years ago showed that if a transgenic plant is induced to express high concentrations of chitinases it will become far more resistant to chitin-containing pathogens [57-61].

Intense research efforts are of course underway to exploit this field commercially: chitinase-producing microorganisms may in future be disseminated in the soil to create a space into which nematodes and fungi cannot penetrate [57]. Species of cereal, fruits and vegetables acclimatized to be cultivated in cold or glacial temperatures survive thanks to chitinases or LTPs [59-60]. A further promising field of research is that of using transgenic plant technology aimed to induce plant production of inhibitors of the various digestive enzymes present in the intestine of predator insects [61].

Another cause of concern is the widespread use of ethylene gas in controlling the ripening of fruit and vegetable foodstuffs before they go on sale. Ethylene is the final product of a major metabolic amino acid pathway present not only in plants but also in bacteria and fungi. Ethylene is a hormone that has complex actions: it stimulates cell respiratory activity thus enabling cells to mature, and by interacting with other substances (auxines), seems to have a central directive role in plant life. Ethylene applied to batches of fruit and vegetable products (especially apples, bananas, tomatoes and avocado pears) to accelerate ripening induces the production of high chitinase concentrations in the treated vegetables ultimately destined for sale to consumers [45-62].

In this way repeated trauma (imagine for example the periodic bark cutting that rubber trees producing latex suffer), the application of phytohormones or other chemical substances, long-term conservation, methods used for ripening, or even genetic selection of vegetables to make production cheaper can cause a plant to produce allergens. A recent article entitled "Will genetically modified foods be allergenic?" states that only "few" genetically modified vegetables have already been introduced commercially: these few include staples such as potatoes, soybeans and maize [63]. But within years dozens of new vegetables capable of "protecting themselves against infection and infestation" will come onto the market.

Delving more deeply into a highly technical subject is outside the scope of this article. These few data should nonetheless suffice to delineate a possible "conflict of interest" between the Food and Agriculture Industry and the Public Health Service. Their duty is on a planetary level to use scientific knowledge to feed the largest number of people as efficiently as possible and to ensure that commercially available foods are in general healthy and, in particular, non allergenic for the many people who are predisposed.

We deem it urgent that the two realms, Medical Science and Agricultural Biotechnology begin to communicate openly. As so often happens, they may well discover that an ethical and rational approach will identify the problems we need to worry about so that much damage can be avoided with modest expense.

By example, if chitinase is useful in agriculture then we need to be told which foods contain it. Being largely degradable by heat it should pose no danger for those who consume cooked foods. People who have an allergy to chitinases could therefore avoid eating raw vegetables and fruits labelled as containing this enzyme in large amounts. Technology could then certainly use less economically attractive methods aimed at producing "anallergic foods" for persons who are sensitised. Another practical point is that the public needs to know that many of the quoted "panallergens" are contained in the external parts of fruits and vegetables.

In practice, we consider that generic assurances by the food and agricultural industry that their products are harmless are not enough. Industry and experts in allergy must collaborate so as to guarantee food for all yet avoid damaging the vulnerable part of the population.

Concluding remarks

Concern over the steady rise in food allergy-intolerance and vegetal cross reactions over the past ten years prompted us to fill in the gaps in our knowledge of this emerging health problem and hypothesize changes in future practice that might help to solve it.

Evidence that vegetables contain cross-reacting substances in variable amounts provides the scientific rationale for certain clinical observations related to allergy heretofore poorly understood. It might for example explain the ever increasing

prevalence or incidence of intolerance or allergy to foods of plant origin, or the wide variability of symptoms in an individual, even if that person avoids the food that previously caused symptoms and follows a strict, unchanging diet [36].

An important concept to understand is that a vegetable may not be tolerated because it contains one or more of the vegetal "pan allergens" that elicited in that individual the production of specific IgE. Yet because the presence of panallergens depends strongly on the environmental conditions under which the vegetal was grown, manured, treated, harvested and conserved, the specific clinical reactions to an ingested vegetal depend on its origin. Various cross-reacting foods, each containing panallergens in highly variable amounts, can elicit allergic reactions even when the recognized offending food has been removed from the diet. This could also, at least partially, explain the low sensitivity of challenge tests.

To apply these concepts in clinical practice we need ask several questions. Instead of the array of vegetable extracts obtained from each food shall we soon use an allergen panel including the most important PR proteins, the "seed storage proteins", alpha-amylase, or proteases inhibitors? [63] Could this allergen panel also be used to desensitise subjects with food allergies? Will industries learn to produce non-allergic foods eventually diversifying their production so as to offer people who are sensitised (up to 20% of the population) safer products? Could we make foods less allergenic by conserving them better (length of storage, temperature, and humidity)? We certainly would like to stop recommending empiric diets for patients who complain of food-associated disorders and instead, prescribe proper diets based on new diagnostic procedures able to cope with multifaceted reality that is emerging.

Our children along with their families and we ourselves have the right to receive information. To be properly informed means collaborative efforts to improve communication between the general public, scientific institutions, and industrial authorities. Being dogmatic about the matter would do more harm than good. In facing one of the possibly less pleasant aspects of progress we need to keep an open mind. But we need to know more.

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