

Crossreactions Involving Plant Allergens

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Introduction

The allergen sources from plants may be classified as pollinic and nonpollinic. The more important sources are the pollens from grasses, weeds, and trees, which are all responsible for the greatest part of seasonal clinical allergic manifestations such as hay fever and birch and ragweed pollinoses. The nonpollinic plant allergen sources are mainly represented by foods such as fruits, vegetables, and spices, but there are also air-borne allergens such as the allergenic dust from *Ficus benjamina*, *Hevea brasiliensis*, or soja hulls. In this respect, allergies to plants are chiefly respiratory, but food and occupational allergies to plants also exist.

In its broadest definition, crossreactions correspond to allergic symptoms provoked in a patient by various offending agents containing common allergenic structures at the molecular (allergen molecules) or submolecular (epitope) levels. It should be borne in mind that a crossreaction may be limited to the presence of crossreacting IgE antibodies in the serum without any clinical translation (1). The reason for such a dissociation will be discussed later in this review.

Crossreactivity of grass-sensitized patients toward a large number of related grass species has been recognized for a long time. This has produced practical applications both in diagnosis (i.e., through skin testing and detection of grass-specific IgE antibodies), and in the therapeutic management of these patients. On the other hand, crossreactivity against apparently botanically unrelated or distantly related allergenic plants is a well-established but more puzzling phenomenon. In these

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cases, the nature of allergenic sources (i.e., pollen grain vs food) and the route of sensitization (respiratory airways vs digestive tract) are different, as is the taxonomic position (i.e., gramineae vs ombelliferae). For a long time, shared structures were postulated to explain the clinical cross-sensitizations. However, it was not until the mid-1980s that some structures were characterized and, more recently, identified. Not surprisingly, such progress coincided with the application of recombinant technology to the field of allergen study.

We successively reviewed crossreactions between closely related plant allergen sources, mainly pollens, and crossreactions between apparently unrelated allergen sources. This review aims to emphasize the structural bases of crossreactions and their main clinical consequences.

Crossreactions Between Taxonomically Closely Related Plant Allergen Sources

Pollens from Grasses

These pollens are responsible for common hay fever that represents a major form of allergy in several countries. Allergens characterized in one species are found in most of the other species of gramineae (2). This is especially the case for the most closely related species such as those from the festuceae (i.e., rye-grass, timothy, and cockfoot) and the hordeae (i.e., wheat, rye, and so forth) tribes, which both belong to the festuciforme group. This group is also structurally related to the phragmites group and the panicoideae subfamily (i.e., Bermuda grass and Johnson grass). Since the early 1980s, there have been numerous studies on allergens from different species of grass pollens. The well-characterized homologous allergens have been combined to form several groups (2).

The extensive crossreactivity among grass pollens renders skin testing and research of IgE antibodies for many individual grass extracts unnecessary in the great majority of cases. Similarly, specific desensitization of grass pollen-allergic patients should routinely use grass mixture extracts.

Pollens from Weeds

Although some crossreactivity has been described among members of the compositae family, such as ragweed, sunflower, and mugwort, the major allergens seem to be specific to each genus (3).

Pollens from Trees

A great extent of crossreactivity is observed among the families belonging to the order of Fagales such as Betulaceae (birch, alder), Corylaceae (hazel), and Fagaceae (beech, oak). This is owing to a family

of structurally related major allergens. The first known member (4) is the unique major allergen of birch, Bet v 1. Other members in this family are Aln g 1 from alder, Car b 1 from hornbeam, and Cor a 1 from hazel (5). This family of allergens displays sequence similarities with a family of pathogen-induced proteins found in several plants (4).

In the oleaceae family, Ole e 1 is the common allergen shared by olive tree, ash, privet, lilac, and golden bells (6).

Among the conifers, crossreactivity exists between the cupressaceae (cypress, juniper, Arbor-vitae), the podocarpaceae (*Podocarpus gracilior*), and the taxodiaceae (Japanese cedar) families (7,8).

Crossreactions Between Taxonomically Distantly Related Plant Allergenic Agents

Crossreactions Among Pollens from Grasses, Weeds, and Trees

Surprisingly, although the pollen grain, the same functional agent, is implicated in many allergies, major allergens of grass, weed, and tree pollens seem to be specific for each class of pollen. An exception to this rule is the crossreaction observed between the major allergens Cry j 1 and Amb a 1 of *Cryptomeria japonica*, and Amb a 2 from *Ambrosia elatior*. These allergens are structurally related to LAT 56 and LAT 59, two proteins in tomato that possess pectase lyase enzymatic activity (9).

In a recent work, Pham and Baldo (10) reported sera from patients allergic to birch, rye grass, or cypress pollens, with very similar immunoblot patterns obtained with pollens from trees, weeds or grasses. This seems to indicate that no matter what the initial sensitizing allergen, the patient developed specific IgE antibodies directed against multiple crossreacting structures present in all the pollens. Profilin (11) is an example of such a crossreacting minor allergen. Other crossreactivity has been described between grass pollen and the pollen from trees of the oleaceae (12) and between allergens from plantago and groups IV and V grass pollen allergens (13).

In clinical practice, patients often have positive skin tests to several pollens, although they may not have clinical pollinosis for all the pollens to which they are sensitized.

Crossreactions Between Pollinic Plant Allergens and Foods

The first observation suggesting cross-sensitization to fruits and pollens was reported by Tuft and Blumstein in 1942 (14). Other clinical reports extended this observation to many plant-derived foods, including melon and banana, in ragweed pollinosis (15); nut and apple in birch pollinosis (16,17); and celery in mugwort pollinosis (18–22). The most common symptoms reported by patients suffering from fruit and vegetable intolerance are oral pruritus, edema, and itching of the lips

or of the epithelium of the mouth and throat; nevertheless, more severe symptoms may occur, such as angioedema, generalized urticaria, and anaphylactic shock. Several *in vitro* studies clearly demonstrated by ELISA or immunoblot inhibitions that these associations were supported by crossreacting IgE antibodies, strongly suggesting crossreactive allergens in foods and pollens. Recently, several crossreactive allergens have been characterized (23) and identified (24,25). The more defined clusters of cross-sensitization involve weed and tree pollens with fruits from rosaceae and betulaceae families and with vegetables from ombelliferae, solaneae, and cucurbitaceae families.

The cluster birch-apple-celery-mugwort syndrome is based on three crossreactive structures in birch pollen: Bet v 1, the major birch allergen; Bet v 2, a member of the panallergen profilin family (11); and Art v 1, a major allergen in mugwort (26). Two of them are present in apple, Mal d 1 (homologous to Bet v 1) (27), and profilin. Three of them are present in celery: Api g 1 (homologous to Bet v 1) (28), profilin, and Art v 1. Two of them are found in mugwort pollen: Art v 1 and profilin.

Cross-Sensitizations to Food in Birch Allergic Patients

Up to 70% of birch-allergic patients demonstrate intolerance to fruit, most complaints being related to the ingestion of crude apple (16,17). The existence of a crossreactive structure representing a major birch allergen to which more than 95% of birch-allergic patients are sensitized explains such a high frequency. However, all birch-allergic patients do not experience allergic symptoms to apple. Those combining both allergies usually have high levels of anti-birch and anti-Bet v 1 antibodies (17,29,30). These high levels may compensate for the lower affinity of IgE antibodies for Mal d 1 than for Bet v 1 (31,32). It has also been shown that Bet v 1 contains some specific epitopes not present in Mal d 1, which displays 64.5% amino acid identity with Bet v 1 (27). Under these conditions, patients having a response only to these epitopes would not develop allergic reactions to apple.

Variations in the allergenicity of different varieties of apples and variations according to ripening and maturation have been associated with increases in an 18-kDa allergen that is probably Mal d 1 (33,34). This is in accord with some patients, who reported having symptoms only after eating ripe apples. Alternatively, Hsieh et al. (35) correlate the increase in 18-kDa allergens with microbial attack intensity. In addition, the fact that Mal d 1, like Bet v 1 is a thermolabile allergen explains why patients usually tolerate cooked apples.

Because of the predominant role of Bet v 1, other crossreactive structures, such as profilin, seem rarely deeply involved in the birch-apple association. The predominant role of Bet v 1-related allergens can be extended to allergies to members of the Prunoideae family (peach,

cherry, apricot, and plum). In all these fruits, 20-kDa allergens homologous to Bet v 1, have been recently characterized (36).

The major allergen Cor a 1, a member of the Bet v 1 family that is present both in hazel pollen and in hazelnuts, is responsible for food allergies to hazelnut in birch-allergic patients. Profilin also has to be involved to explain cross-sensitization to hazel pollen and hazelnut (37).

A new association has recently developed between birch and kiwi fruit that is attributed to a recent increasing fancy for this exotic fruit (38). Half of the 22 patients investigated had severe systemic reactions. Results of inhibition of ELISA reaction strongly suggest crossreactive antigens between kiwi fruit and birch pollen. In another study, immunoblot inhibitions with birch pollen are in favor of crossreactive polypeptides of 32 and 30 kDa (39).

In birch-allergic patients, allergy to celery is about five times less frequent than allergy to apples (17,40). A possible explanation for this difference could rely on a lesser identity between Api g 1 and Bet v 1 (28), than between Mal d 1 and Bet v 1.

Cross-Sensitizations to Food in Weed Allergic Patients

Surprisingly, despite the absence of allergens homologous to Bet v 1 and Api g 1 in mugwort, allergy to celery is more frequently associated (up to 55%) with mugwort pollinosis than with birch pollinosis (18,20). Sensitization to celery sometimes includes sensitization to carrot and to spices belonging to the umbelliferae family. The syndrome has been called "Celery-carrot-mugwort-spice syndrome" (41). In contrast to fruits that mainly cause the so-called "oral allergy syndrome," celery used raw, cooked, or as a spice is responsible for attacks of urticaria, angioedema and systemic anaphylaxis (42). Two important crossreactive allergens for this association appear to be profilin (43) and a homolog of Art v 1 (46–60 kDa) (25), which is present in celery root.

Patients with ragweed pollinosis often have banana and melon food allergies (15). Enberg et al. (44) demonstrated that 28–50% of patients with ragweed pollinosis have specific IgE for at least one member of the Cucurbitaceae family (i.e., melon, watermelon, cantaloupe). Cross-sensitization to Cucurbitaceae was also reported in 25% of patients suffering from pollinosis to Plantago, a common weed in Spain (45). In both associations, crossreacting IgE against weed pollens and gourds were detected by ELISA inhibition (44,45).

Associated respiratory allergy to mugwort and food allergy to compositeae have been reported: anaphylaxis after ingestion of chamomile tea (*Matriarca chamomilla*) (46), and anaphylaxis consecutive to sunflower oil ingestion (47).

Cross-Sensitizations to Food in Grass-Allergic Patients

It is a common experience that food allergy is much more infrequent in patients monosensitized to grass pollens than in patients monosensitized to birch or weed pollens. In particular, grass allergy is not often concomitant with apple allergy. This is related to the absence of allergens of the Bet v 1 family in grass pollen. However, some associations have been observed in specific areas, probably reflecting dietary habits of the population. In Spain, profilin has been implicated as a crossreactive allergen to explain allergies to rosaceae family fruit in patients allergic to grass pollen (48). Also, 12% of Spanish grass-allergic patients are allergic to melon (45). In Italy, de Martino et al. (49) observed that grass pollen allergies have a tendency to cluster with sensitization to tomato and peanut, and they gave proof of cross-sensitivity by ELISA inhibition. Pastorello et al. (39) found crossreactions proven by immunoblot inhibition between Timothy grass extracts and kiwi allergens of 41, 38, 24, 22, and 14 kDa.

The cross-sensitization to ryegrass pollens and to endosperm proteins from wheat grains has been demonstrated by immunoblot inhibition experiments (50). Jones et al. (51) confirm this result but fail to demonstrate any clinical importance of these crossreactive allergens in food allergy to wheat flour.

Crossreactions Between Nonpollinic Plant Allergens and Foods

Only cross-sensitizations toward different species are considered in this section.

Recently, dust from *Ficus benjamina* was recognized as a new aero-allergen in the domestic environment (52,53). Marginally, anaphylactic shock after fresh fig ingestion was reported in a patient sensitized to *Ficus benjamina* (54). IgE antibodies reacting with Ficus and fig, which both belong to the same genus, have been detected by ELISA inhibition (54).

Logically, in this section, cross-sensitizations between latex aero-allergen and several fruits should normally be described too. However, a review in this issue is integrally devoted to this important topic.

Concluding Remarks

From the numerous observations of associated respiratory allergy and food hypersensitivity, the question arises concerning which allergen is the initial inducer of the crossreactive antibody response. The current opinion is that the pollen allergen is, in most cases, the primary sensitizing allergen (55). However, in some patients, symptoms of food allergy are for several years the only manifestations of the biological cross-sensitization.

The observations of cross-sensitizations in the field of allergies to plants have recently acquired a structural basis. Several crossreactive

allergens have been identified, and some of them are expressed as recombinant proteins. However, the transposition of biological findings (presence of crossreacting IgE antibodies) to the clinical field has to be examined in each particular situation with caution.

In fact, on a large ground of potential crossreactivity, clinical expression is dependent on several factors. It is obvious that, based on the dietary habits and on predominant pollens in each region, certain associations may or may not appear. The status of minor (i.e., profilin) or major allergens (i.e., Bet v 1) responsible for crossreactivity clearly determines the prevalence of the associated food allergy. The relative IgE antibodies levels directed toward cross- and noncrossreactive structures may influence the efficient sensitization of allergic reaction effector cells by crossreactive IgE (56). Considering the inefficiency of several food allergen extracts for diagnostic and therapeutic purposes, recombinant crossreactive allergens may be of value in the future for testing and desensitizing patients suffering from pollen-food allergy syndrome (30).

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