

Type I allergic reactions to plant-derived food: A consequence of primary sensitization to pollen allergens

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Patients with pollen allergy also frequently experience allergic symptoms on ingestion of plant-derived foods (fruits, vegetables, and spices).¹⁻³ The association of certain pollen allergies with food intolerance has led to the definition of clinical syndromes such as the celery-mugwort-birch pollen syndrome, the apple-birch pollen syndrome, and similar phenomena. More than 10 years ago, it was suggested that IgE antibodies that cross-react with pollen and food proteins could be responsible for the observed clinical phenomena.⁴⁻⁸ New information allows us to attribute pollen-food allergy syndromes to the cross-reactivity of IgE antibodies to conserved plant allergens that are expressed in related and unrelated plant species and different plant tissues. The term *conserved protein* refers to proteins that fulfill important biologic functions and therefore are conserved in their sequence and/or structure. Prominent conserved allergens responsible for pollen-food cross-reactivities are the actin-binding protein profilin, first described in birch pollen (Bet v 2),^{9,10} and the major birch pollen allergen, Bet v 1,¹¹ which is highly homologous to pathogenesis-related plant proteins.

We have developed the hypothesis that sensitization to airborne pollen allergens represents the primary event leading to the induction of IgE antibodies that are then capable of cross-reacting with homologous food allergens. This study summarizes evidence for this hypothesis.

Complementary DNAs coding for a number of

allergens were characterized and expressed as recombinant allergens in heterologous expression systems. Sequence comparison of several of these allergens has revealed significant homology with conserved proteins. The major birch pollen allergen Bet v 1 showed significant sequence homology with proteins (pathogenesis-related proteins) that are expressed in plants on microbial attack,¹¹ whereas another birch pollen allergen, Bet v 2, could be identified as profilin.⁹ Profilins are known as conserved actin-binding proteins,¹² which also participate in the phosphoinositide pathway in eukaryotes.¹³ The availability of the cDNAs coding for Bet v 1 and Bet v 2 and the recombinant allergens has allowed us to demonstrate that homologous proteins in fruits, vegetables, and spices cross-react with IgE antibodies to the birch proteins, leading to pollen-food allergy syndromes. The presence of a Bet v 1 homologous allergen in apples was demonstrated by Northern blotting with the Bet v 1 cDNA by using Bet v 1 specific monoclonal antibodies and serum IgE.¹⁴ By using recombinant Bet v 1 and Bet v 2 for IgE inhibition experiments, as well as specific antibodies, the presence of Bet v 1 and Bet v 2 homologous allergens could be demonstrated in numerous fruits, vegetables, and spices.¹⁵⁻¹⁷

Allergy to hazelnuts was found to be due to IgE antibodies that cross-react with Bet v 1 and Bet v 2.¹⁸ Although recombinant Bet v 1 could be used to absorb IgE binding to the homologous hazelnut allergen, the food allergens were not able to completely block IgE binding to the pollen allergens, indicating that the cross-reactive IgE antibodies originate primarily from a sensitization to pollen proteins. A 60 to 65 kd component present in mugwort pollen, possibly identical to the major mugwort allergen Art v 1, was recently described to cross-react with homologous allergens present in celery, apple, peanut, kiwi, and pollens from monocot and dicot plants.¹⁹

To test the hypothesis that allergy to plant-

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derived food is primarily due to IgE antibodies that cross-react with homologous allergens present in pollen, we induced cross-reactive IgE antibodies in experimental animal models by using recombinant pollen allergens as immunogens. In mice, as well as in rhesus monkeys, immunization of animals with recombinant pollen allergens, Bet v 1 and Bet v 2, induced IgE antibodies that cross-reacted with homologous allergens present in fruits and vegetables.^{20, 21} Moreover, Bet v 2-immunized rhesus monkeys displayed skin reactivity in response to celery extracts, indicating the clinical relevance of the cross-reactive IgE antibodies.²²

Further evidence that allergy to plant-derived food originates from a primary sensitization to homologous pollen allergens comes from the observation that only allergens, such as Bet v 1 and Bet v 2, which are expressed in pollen and in somatic plant tissues,²³ could be identified as cross-reactive allergens in pollen and plant-derived food. The three major grass pollen allergens (groups I, II, and V) are specifically expressed in pollen and not in other plant tissues.^{24, 25} Although more than 95% of patients allergic to grass pollen react to these allergens, so far none of the allergens could be identified as allergenic proteins in plant-derived food.²⁶ Likewise, several other allergens such as Bet v 3, a calcium-binding birch pollen allergen,²⁷ are expressed exclusively in pollen and are not yet described as food allergens.

In contrast, the birch pollen allergens Bet v 1 and Bet v 2 and their homologues, which are responsible for a great proportion of pollen-food cross-reactivities, can be detected in somatic plant tissues. The fact that the expression of Bet v 1 and Bet v 2 is highly upregulated in pollen, particularly during pollen maturation,^{28, 29} whereas only tiny amounts of the proteins could be detected in somatic plant tissues, also argues in favor of the idea that pollen is the primary sensitizing agent in patients with pollen-food allergy.

The knowledge that similar IgE epitopes present in pollen and plant-derived foods are responsible for the cross-reactivity of IgE antibodies in patients with pollen-food allergy syndromes might be useful for diagnostic and therapeutic purposes. Extracts for use in the diagnosis and treatment of food allergies are extremely difficult to prepare because of the rather low protein versus carbohydrate content of fruits and vegetables and because of the instability of allergenic components in such extracts. In fact, experiments performed in a large number of patients allergic to food corroborate that a high proportion of IgE directed against

proteins in plant-derived foods can be absorbed with homologous pollen proteins. It therefore appears reasonable to consider recombinant pollen allergens that cross-react with homologous food allergens for use in diagnosis and perhaps in treatment. It might be that successful treatment of the pollen allergy would result in a significant reduction of the associated food allergy symptoms.

The knowledge that Bet v 1, Bet v 2, or other homologous allergens are present in certain plant-derived foods may additionally help the clinician to interpret the association of certain pollen and food allergies as being due to the presence of cross-reactive determinants in both sources.

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