

Editorial

Lipid transfer protein as a potential panallergen?

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Accepted for publication 6 May 2002

In central and northern Europe, allergy (1) to food of plant origin is mediated, in most instances, by sensitization to birch pollen, and up to 80% of birch pollen allergic patients suffer from an associated food allergy. Patients sensitized to birch pollen are mainly affected by allergic reactions to foods of the Rosaceae family (such as apple, pear, cherry, peach and nectarine) and to various vegetables.

The immunological basis of this phenomenon is IgE crossreactivity due to highly homologous amino-acid sequences resulting in homologous structures of pollen and food allergens of plant origin (2). The major allergen of birch pollen, Bet v 1, and its homologous proteins in food of plant origin (Mal d 1 in apples, Pru av 1 in cherries, and Cor a 1 in hazelnuts), were identified as the most important mediators of crossreactivity (3–5). Profilin, first identified as the birch pollen allergen Bet v 2 (6), was recognized as another important crossreacting structure. In addition, the recently identified birch pollen allergens Bet v 6, a phenyl coumaran benzylic ether reductase, and Bet v 8, a pectin esterase, may also be involved in similar cross-reactivity (7, 8).

Identification of these potentially cross-reactive structures provides a molecular basis for clinical observations of fruits-and-nut allergy often being related to birch pollinosis. This was first reported in the early half of the last century.

The general view that allergy to fruits (especially Rosaceae) and to nuts, is mainly birch pollen-mediated, was heavily challenged by the first publications from the Mediterranean area. These mentioned a small 9–10 kDa allergen as a major allergen for patients sensitized to members of the subfamily of Prunoideae. Leonart et al. (9) reported in 1992 that an 8–10 kDa allergen was the most important allergen for peach-allergic patients in Spain. In 1994, Pastorello et al. (10) described a low molecular weight IgE-binding component as the most important major allergen of all Prunoideae, which was

not shared with grass or birch pollen. In that study, 12 of 19 patients with a positive open challenge to peach were not sensitized to birch pollen, and their IgE-reactivity was exclusively directed against this low molecular weight allergen—identified a few years later as a lipid transfer protein (LTP). LTPs were the only allergens recognized by IgE from patients allergic to peach (11, 12), apple (12, 13), apricot (14) and plum (15), but not to birch pollen.

LTPs isolated from the different Prunoideae fruits depict high amino-acid sequence identities with each other, accounting for the frequent clinical cross-reactivity between Prunoideae fruits as reported by patient histories. LTPs are ubiquitous plant proteins involved in defence against pathogens and environmental stress, with low molecular weights (9–10 kDa), and isoelectric point > 9 (16–18). They are highly concentrated in the peel of fruits (19). Members of the LTP family comprise 91–95 amino acids, including eight conserved cysteines forming four disulfide bridges (15). LTPs are very stable allergens, as shown by their extreme resistance to pepsin digestion and heat treatment (20–23).

The wide distribution of LTPs among plant foods suggests a potential role of these proteins as plant panallergens. Several studies have attempted to elucidate the cross-reactivity between foods and pollen-LTP from different sources (21, 23, 24). Díaz-Perales et al. (22) reported on partial cross-reactivity between Rosaceae LTPs (peach, apple, apricot) and those from different plant sources (mugwort, chestnut) due to common epitopes shared by LTPs from these foods and pollens. Also, the major allergen of *Parietaria* pollen has been found to show homology to LTP, but no cross-reactivity to grass pollen and birch pollen was identified (10, 23–25). Even though mugwort LTP binds IgE antibodies from sera of Rosaceae fruit-allergic patients, substantially lower values of IgE-antibody binding and

maximum ELISA inhibition percentages are obtained for mugwort LTPs when compared to those from apple and peach. These results, and the observation that allergy to Rosaceae fruits in the Mediterranean area may be acquired independently from any pollen sensitization, suggest that sensitization to LTP may occur by the oral route.

Most interestingly, we have to face as yet unexplained geographic differences in LTP sensitization. Very recently we performed skin prick tests with three recombinant cherry allergens (Bet v 1-related allergen: rPru av 1, profilin: rPru av 4 and LTP: rPru av 3) in 24 Swiss patients with cherry allergy confirmed by positive double-blind placebo-controlled food challenge (DBPCFC), and in 9 Spanish patients recruited on the basis of a positive case history. Only 1 patient from the Swiss group, but 8 from the Spanish group, were sensitized to cherry LTP rPru av 3 (26).

Similar results were obtained by Scheurer et al. (27) *in vitro*. Just 3% of 101 cherry-allergic German patients (selected by positive case histories), but 100% (7/7) of cherry-allergic Italian patients were sensitized to cherry LTP.

Additionally, in a multicenter study performed in Copenhagen, Zurich and Milan, in 65 patients with hazelnut allergy (DBPCFC-positive), sensitization to a 9 kDa allergen was recognized in 2 people from Milan, but in no Swiss or Danish (28). Thus, LTP sensitization seems to be a special hallmark of the Mediterranean area.

More importantly, sensitization to LTP may be accompanied by higher prevalence of systemic symptoms (29). Thus, 7 Italian patients with severe anaphylactic reaction to hazelnut showed reactivity of IgE antibody to hazelnut LTP (28); and 86% of 22 patients with systemic symptoms after ingesting maize were sensitized to maize LTP (22).

Our own data in cherry-allergic Swiss and Spanish patients strengthen the view of LTP as potentially "severe" fruit allergens. In general, clinical features of patients sensitized to cherry LTP were more severe than for patients sensitized to the Bet v 1-related rPru av 1, and six of eight patients exclusively sensitized to cherry LTP had urticaria and/or angioedema—symptoms not observed in any of the patients monosensitized to rPru av 1 (26).

The study of Asero et al. in this issue of *Allergy* (Immunological crossreactivity between lipid transfer proteins from botanically unrelated plant-derived foods: a clinical study) considers whether LTPs are clinically relevant panallergens, i.e. whether sensitization to Rosaceae LTP is associated with allergic reaction to non-Rosaceae foods. This study selected patients sensitized to LTP, but not to Bet v 1 or Bet v 2. Interestingly, the patients reported allergic reactions to a wide range of non-Rosaceae foods, especially different nuts like walnut, hazelnut and peanut. Unfortunately, no challenges were performed in these patients to prove the clinical relevance of cross-sensitization to LTPs from different, phylogenetically unrelated food families. However, food challenges (particularly DBPCFC) are regarded as the gold standard for diagnosing food allergy, and they cannot be regarded as unethical as stated by the authors of that paper (30). Sampson et al. (31) reported confirmation of food allergy by case history in less than 50% of their highly atopic (mostly pediatric) patients; our own data (32–34) show that up to 30% of history-positive adult patients do not suffer from any symptoms during DBPCFC. Taking both these reports into account shows that challenge procedures are most important for proving clinically relevant sensitization.

Unfortunately, until now no DBPCFCs have been performed in any of the clinical studies performed in LTP-sensitized food-allergic patients. In spite of these drawbacks, the study by Asero et al. is very interesting regarding the putative role of LTP as a panallergen in plant-derived foods, at least in Mediterranean countries, but it lacks the final proof of clinical relevance of the observed cross-reactivities.

Why are food-allergic patients from Central and Northern Europe not prone to acquiring LTP sensitization? This remains unanswered. Is it because of regional differences in eating habits? Probably not—for instance, in Switzerland the so-called Mediterranean diet, rich in fresh fruits and vegetables, is increasingly common. Nevertheless, sensitization to LTPs in Swiss food-allergic patients is very unusual. Or is it perhaps because of genetic differences between populations in the north and south of Europe? Certainly more work is to be needed in this highly interesting field to resolve these issues satisfactorily.

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