Anaphylaxis to plant-foods and pollen allergens in patients with lipid transfer protein syndrome

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Purpose of review
Nonspecific lipid transfer protein (LTP) is the main cause of primary food allergy in adults living in the Mediterranean area. The way allergic patients get sensitized to this protein is all but established, and the clinical expression of sensitization is extremely variable, ranging from long-lasting symptomless sensitization to severe anaphylaxis. Such variability is seemingly due to the presence/absence of a number of cofactors.

Recent findings
The possibility that LTP sensitization occurs via the inhalation of LTP-containing pollen particles seems unlikely; in contrast, peach particles containing the protein seem able to sensitize both via the airways and the skin. Cosensitization to pollen allergens as well as to labile plant food allergens makes LTP allergy syndrome less severe. In some LTP sensitized subjects clinical food allergy occurs only in the presence of cofactors such as exercise, NSAIDs, or chronic urticaria.

Summary
Lipid transfer protein allergy syndrome shows some peculiarities that are unique in the primary food allergy panorama: geographical distribution, frequent asymptomatic sensitization, frequent need for cofactors, and reduced severity when pollen allergy is present. Future studies will have to address these points as the results may have favorable effects on other, more severe, types of food allergy.

Keywords
cofactors, food allergy, lipid transfer protein, pollen allergy, sensitization

INTRODUCTION

Nonspecific lipid transfer protein (LTP), a heat-resistant and pepsin-resistant plant pan-allergen, is unquestionably the most frequent cause of primary food allergy in adults living in the Mediterranean area [1,2], and the most frequent cause of food-induced anaphylaxis as well [3]. In view of the widespread distribution of this phylogenetically highly conserved protein in the plant kingdom, which often leads LTP hypersensitive patients to corecognize a variable array of plant-derived foods and some pollen species also, the term 'Lipid transfer proteins syndrome' has been suggested [4]. The functional role of nonspecific LTP in plant is thought to be a defensive role against phytopathogens (bacteria and fungi) [5,6]. The present article will review some controversial aspects of the LTP sensitization process and of the clinical expression of the syndrome.

HOW DOES LIPID TRANSFER PROTEIN SENSITIZATION OCCUR?

Peach is unquestionably the most frequently offending food in LTP-allergic patients. The researchers who believe that sensitization to LTP occurs via the gastrointestinal tract strongly support the idea that this fruit is responsible for the primary sensitization to this protein. In effect, in reviewing the clinical studies published so far, LTP-sensitized patients seem almost always characterized by the presence of IgE to peach LTP (Pru p 3) even when they tolerate the fruit, whereas this is not the case for a number of other fruits and vegetables which contain LTPs showing variable degrees of homology with peach LTP. Recent studies have shown that the peach LTP dominates the immunological response to this proteins [7▪] as if Pru p 3 contained all existing IgE-binding LTP epitopes, whereas the

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KEY POINTS

- The way LTP sensitization occurs is unclear; along with the gastrointestinal tract, sensitization through the skin and the airways cannot be ruled out.
- LTP sensitization is often symptomless and needs cofactors to express clinically.
- In LTP hypersensitive patients the clinical expression of food allergy is strongly influenced by cosensitization to pollen allergens and/or labile plant-food allergens.

homologous proteins from other allergenic sources (e.g. maize, mustard, tomato, broccoli, etc.) don't [8]. The only notable exception to this rule has been a cohort of hazelnut-allergic children living in northern Europe who showed IgE reactivity to Cor a 8, the hazelnut LTP, but not to Pru p 3 [9], which demonstrates the extent to which the environment where the patient lives may play a role in the different types of sensitization. As said before, due to the conserved structure and amino acid sequence of the protein, LTP allergic patients frequently develop cross-reactivity to a number of botanically unrelated plant-derived foods [10,11], a phenomenon that appears to be strictly related to the level of peach-specific IgE [12,13].

One unclear aspect of the lipid transfer protein syndrome is its peculiar geographical distribution, as this type of food allergy seems virtually absent in Northern Europe, as shown by the fact that nearly all of the reports about it come from Spain, Italy, and Greece. This has led some to hypothesize the possibility that primary sensitization to this allergen is linked to environmental factors that are specifically present in these areas. Among 'local factors' pollen has received much attention. Lipid transfer proteins have been detected in pollens from several anemophylous plants [14] and this fact has led to investigating the possible cross-reactivity between pollen and plant-food LTPs, as well as the possibility that the primary sensitization to this allergen may occur through the airways.

Apart from Par j 2, the major Parietaria pollen allergen, that is also a LTP but shows a low degree of homology to peach LTP in comparison with other pollen LTPs, which does not present any relationship with nonspecific plant food LTPs, Art v 3, Ole e 7, and Pla a 3, the lipid transfer proteins in mugwort, olive, and plane pollen, respectively, have received some attention.

Art v 3 shows about 50% identity with Pru p 3 and some cross-reactivity as well [15], although Pru p 3 shows a significantly higher degree of specific IgE binding [16]. Nonetheless, on the basis of both clinical studies showing that patients who corecognize Pru p 3 and Art v 3 seem to recognize a wider range of plant-foods and of in-vitro cross-inhibition experiments, it has been suggested that, at least in some patients, Art v 3 might represent the primary sensitizing agent to LTPs [17,18]. Further, patients allergic to Cas s 8 (the chestnut LTP) are frequently sensitized to Artemisia pollen [16], and it has been suggested that the cabbage LTP (Bra o 3) may play a relevant role in food-pollen cross-reactivity and that Art v 3 hypersensitivity might identify Artemisia pollen-allergic patients who are more likely to experience severe food allergy reactions [19]. These conclusions have been tackled by studies carried out by Pastorello *et al.* [20] that led them to conclude that in peach-allergic patients Art v 3 reactivity is the result of a corecognition in patients primarily sensitized to Pru p 3 (i.e. an epiphenomenon of peach LTP sensitization) as demonstrated by cross-inhibition experiment showing that a large amount of mugwort LTP is necessary to inhibit the peach LTP, but not vice versa. Moreover, no inhibition of IgE binding to peach LTP was observed after preincubation with other pollen extracts (grass, olive, ragweed and wall pellitory), thus confirming the hypothesis of a primary sensitization to peach LTP.

Ole e 7 also displays a sequence identity with plant food LTPs of about 50% [14], and it has been reported that in patients with both olive pollen allergy and plant food-induced reactions a strict association between severe food allergy and Ole e 7 sensitization exists [21]. However, recently Barber *et al.* [22] did not observe any correlation between sensitization to peach and olive pollen sources across LTP sensitization, and Tordesillas *et al.* [23] finally ruled out any relationship between foods and olive pollen LTPs.

Plane pollen sensitization has been frequently observed in Spanish patients with food allergy [4], and cross-reactivity between *Platanus acerifolia* pollen and plant-derived foods has been found as well [24]. Further, lettuce LTP (Lac s 1)-allergic patients frequently corecognize Pla a 3 [25]. Thus, Pla a 3, the plane pollen lipid transfer protein, seems to behave as a major allergen in patients with both plane pollen allergy and peach allergy living in the Mediterranean basin, although its variable allergenic potency does not allow drawing any general conclusion about the primary sensitizer agent [26].

Recently, cypress (*Cupressus arizonica*) pollen has been included in the list of candidates for a possible role as primary sensitizer to LTP in patients with plant-food allergy [27]. However, as the prevalence of cypress pollen sensitization in another study [4] of LTP allergy from the same area was low,

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the role of such pollen as a primary sensitizer remains unproven.

A recent clinical study [28] carried out in a cohort of Italian LTP-allergic patients looking simultaneously at four allergen sources (peach and three pollens) found Artemisia, Platanus, and Olea pollen hypersensitivity in 24, 15, and 15% patients, respectively, arguably too small a measure to conclude that pollen acts as the primary sensitizer. In keeping with previous observations [13], peach-specific IgE levels were higher than the levels of IgE to each of the three pollens in all cases, with a strong correlation between peach-specific IgE levels and the levels of IgE specific for both mugwort and plane. It was concluded that, at least in Northern Italy, olive, plane, and mugwort pollen are an unlikely source of primary sensitization to LTP and the most likely primary sensitizer to this protein remains the peach [8,28]. This was also demonstrated in other Italian studies [29–34] about LTP where many patients showed IgE binding exclusively to food LTP, without any positivity to pollen allergens.

In conclusion, the relationships between plant food LTPs and pollen LTPs remain poorly defined and sensitization to LTPs from different pollen sources probably have to be considered more as a marker than an inducer [35▪]. The identity of amino-acid sequence on Pru p 3 and homologous LTPs in different pollen sources are shown in Table 1.

The surprising geographical distribution of LTP allergy syndrome has also led to the hypothesis that sensitization to peach (the most likely primary sensitizer to this protein) may occur via the skin or the airways. LTP is particularly concentrated in peels and cutin layers of fresh fruits [36] and peach LTP is probably the most relevant cause of contact urticaria among food-allergic patients [37]; the relevance of peach fuzz, which is particularly rich in LTP [38] in inducing contact urticaria is clearly shown by the absence of any skin reactivity after contact with nectarines in the same patients [37]. Further, cases of airborne sensitization to peach LTP preceding the onset of food allergy have been reported [39] and LTP found in peach leaves may act as a respiratory allergen causing occupational rhinoconjunctivitis and asthma [40], suggesting that peach is able to release LTP in the environment as inhalable particles.

Only in tomato fruit has LTP been demonstrated to be present not only in peel, but also in pulp and seeds, with three different allergenic isoforms, with consequent allergic symptoms following ingestion of industrial products [32,41].

FOOD-INDUCED ANAPHYLAXIS IN LIPID TRANSFER PROTEIN HYPERSENSITIVE PATIENTS

A large number of LTPs have been characterized as allergens since the discovery of these proteins about 30 years ago (lipid transfer proteins of plant foods and pollens currently registered in the International Union of Immunological Societies or reported by Allergome are listed in Table 2), 46 of which are plant foods [8,42]; thus, it is not surprising that an extremely long list of foods have been reported to cause anaphylaxis in LTP-sensitized patients, including Rosaceae (peach, apple, pear, cherry, plum, almond, loquat), tree nuts (walnut, hazelnut, chestnut), peanut, tomato, cereals (wheat, maize, rice, barley), beer, grapes, and wine, legumes (string beans, pea, lentil), citrus fruits, fennel, broccoli, lettuce, asparagus, saffron, mustard, and different berries [3,8,29–34,43–60].

Nonetheless, the prevalence of anaphylactic episodes in patients sensitized to LTP is much lower than the one observed among patients allergic to other food plant allergens such as the seed storage proteins [3,10,11] and in the study by Gonzalez-Mancebo *et al.* [61▪] a large proportion (at least

Table 1. Identity of amino-acidic sequence of peach lipid transfer protein (Pru p 3) with pollen lipid transfer proteins, by sequence alignment in UniProt Knowledgebase (UniProtKB)

		Pru p 3 versus other pollen LTPs		
Pollen		% Identity	Identical position	Similar position
Plane	Pla or 3	46.61%	55	20
Plane	Pla a 3	45.76%	54	21
Mugwort	Art v 3	40.52%	47	25
Ragweed	Amb a 6	26.67%	32	25
Wall pellitory	Par j 2	18.80%	25	35
Wall pellitory	Par j 1	14.77%	26	29
Olive	Ole e 7	4.35%	4	7

LTP, lipid transfer protein.

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Table 2. Lipid transfer proteins in vegetable foods (a) and plants (b) whose amino-acid sequence is registered in IUIS (‡) or in Allergome (§)

	Allergen	Order	Species	LTP type	Accession number (UniProt)
Plant food a					
Asparagus	Asp o 1	Asparagales	Asparagus officinalis	nsLTP1	‡
Onion	All c 3	Asparagales	Allium cepa	nsLTP1	A6N9I7§
Shallot	All a 3	Asparagales	Allium ascalonicum	nsLTP4	A6N9J0§
Saffron	Cro s 3	Asparagales	Crocus sativus	nsLTP1	D2T0A6§
Banana	Mus a 3	Zingiberales	Musa acuminata	nsLTP	P86333‡
Wheat	Tri a 14	Poales	Triticum aestivum	nsLTP1	P24296‡
Maize	Zea m 14	Poales	Zea mays	nsLTP	P19656‡
Barley	Hor v 14	Poales	Hordeum vulgare	LTP	P07597§
Wheat	Tri a LTP2	Poales	Triticum aestivum	nsLTP2	P82900§
Rice	Ory s 14	Poales	Oryza sativa	nsLTP2	A2ZAT0, Q0IQK9§
Gold kiwi	Act c 10	Ericales	Actinidia chinensis	nsLTP1	P85204‡
Kiwi fruit	Act d 10	Ericales	Actinidia deliciosa	nsLTP1	P85205, P85206‡
Bilberry	Vac m 3	Ericales	Vaccinium myrtillus	nsLTP	———§
Redcurrant	Rib r 3	Saxifragales	Ribes rubrum	LTP	———§
Pomegranate	Pun g 3	Myrtales	Punica granatum	LTP	———§
Sunflower	Hel a 3	Asterales	Helianthus annuus	LTP	Q7X9Q5‡
Lettuce	Lac s 1	Asterales	Lactuca sativa	LTP	A1E2H4, A1E2H5‡
Celery	Api g 2	Apiales	Apium graveolens	nsLTP1	E6Y8S8‡
Celery	Api g 6	Apiales	Apium graveolens	nsLTP2	P86809‡
Parsley	Pet c 3	Apiales	Petroselinum crispum	nsLTP	——§
Carrot	Dau c 3	Apiales	Daucus carota	nsLTP	P27631§
Fennel	Foe v 3	Apiales	Foeniculum vulgare	nsLTP	B3EWP9§
Peanut	Ara h 9	Fabales	Arachis hypogaea	nsLTP1	B6CEX8, B6CG41‡
Lentil	Len c 3	Fabales	Lens culinaris	nsLTP1	A0AT29‡
Green bean	Pha v 3	Fabales	Phaseolus vulgaris	nsLTP1	D3W146, D3W147‡
Chestnut	Cas s 8	Fagales	Castanea sativa	nsLTP1	F1AHA2‡
Hazelnut	Cor a 8	Fagales	Corylus avellana	nsLTP1	Q9ATH2‡
Walnut	Jug r 3	Fagales	Juglans regia	nsLTP1	C5H617‡
Cabbage	Bra o 3	Brassicales	Brassica orelacea	LTP	Q39382‡
White mustard	Sin a 3	Brassicales	Sinapis alba	nsLTP1	E6Y2L9‡
Turnip	Bra r 3	Brassicales	Brassica rapa	nsLTP1	Q42614§
Lemon	Cit l 3	Sapindales	Citrus limon	nsLTP1	P84160‡
Mandarine	Cit r 3	Sapindales	Citrus reticulata	nsLTP1	——‡
Orange	Cit s 3	Sapindales	Citrus sinensis	nsLTP1	Q6EV47‡
Strawberry	Fra a 3	Rosales	Fragaria ananassa	nsLTP1	Q8VX12‡
Apple	Mal d 3	Rosales	Malus domestica	nsLTP1	Q9M5X7, Q9LED0‡
Pear	Pyr c 3	Rosales	Pyrus communis	nsLTP1	Q9M5X6‡
Black mulberry	Mor n 3	Rosales	Morus nigra	nsLTP1	P85894‡
Red raspberry	Rub i 3	Rosales	Rubus idaeus	nsLTP1	Q0Z8V0‡
Apricot	Pru ar 3	Rosales	Prunus armeniaca	nsLTP1	P81651‡
Cherry	Pru av 3	Rosales	Prunus avium	nsLTP1	Q9M5X8‡
Plum	Pru d 3	Rosales	Prunus domestica	nsLTP1	P82534‡
Almond	Pru du 3	Rosales	Prunus dulcis	nsLTP1	C0L0I5‡
Peach	Pru p 3	Rosales	Prunus persica	nsLTP1	P81402‡
Grape	Vit v 1	Vitales	Vitis vinifera	nsLTP1	P80274‡
Tomato	Lyc e 3	Solanales	Lycopersicon esculentum	nsLTP2	P93224‡

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Table 2 (*Continued*)

	Allergen	Order	Species	LTP type	Accession number (UniProt)
Plant B					
Ragweed	Amb a 6	Asterales	Ambrosia artemisiifolia	LTP	O04004‡
Mugwort	Art v 3	Asterales	Artemisia vulgaris	nsLTP1	P0C088, C4MGG9, C4MGH0, C4MGH1‡
Wall pellitory	Par o 1	Rosales	Parietaria officinalis	LTP	——‡
Wall pellitory	Par j 1	Rosales	Parietaria judaica	Probable nsLTP1	O04404‡
Wall pellitory	Par j 2	Rosales	Parietaria judaica	Probable nsLTP 2	O04403‡
Olive	Ole e 7	Lamiales	Olea europea	putative nsLTP	P81430‡
Plane	Pla a 3	Proteales	Platanus acerifolia	nsLTP1	Q14K71‡
Plane	Pla or 3	Proteales	Platanus orientalis	nsLTP1	A9YUH6‡

LTP, lipid transfer protein.

50%) of LTP-hypersensitive patients had an asymptomatic sensitization; thus, in this sense, LTP might be considered as a 'benign' stable allergen. On the contrary, by analyzing the studies of LTP hypersensitivity it clearly emerges that the majority of patients presenting the most severe symptoms were sensitized exclusively to food LTPs, without any pollen cosensitization, and that patients suffering from both pollinosis and LTP allergy experienced oral allergy syndrome of grade I or II [62].

The influence of different cofactors in modulating the severity of allergic reactions to LTP-containing food plants in patients suffering from a concomitant pollen allergy is of great interest.

Cosensitization to labile plant-food allergens, namely allergens from the PR-10 family and profilin, reduces the severity of LTP allergy as if the partial occupancy of FcεRI by IgE specific for other allergens reduces histamine release from mast cells. This has recently been demonstrated in a large population of peach allergic patients with and without concomitant pollen allergy [63▪]: the simultaneous reactivity to rPru p 3 and rPru p 1 and/or Pru p 4 represented an antibody pattern at lower risk for the occurrence of severe symptoms. Thus, the existence of different forms of cosensitization can determine significantly different clinical situations in comparison to monosensitized patients. The same study [63▪] established for the first time a cutoff level of specific serum IgE to rPru p 3 (2.69 kUA/L) as a better discriminating value in patients at risk for peach-induced symptoms. The management of patients sensitized to Pru p 3 but clinically tolerating LTP-containing foods is still ill-defined, as no study clearly investigated so far the odds ratio of the appearance of clinical symptoms when assuming or avoiding LTP positive foods.

Among amplifying cofactors, exercise seems to play a relevant role in patients sensitized to this protein [64▪], and also the way the offending food is ingested (whether alone or associated with other foods) seems to influence the clinical outcome of exposure [65]. Also the association with alcoholic drinks and with nonsteroidal anti-inflammatory drugs seems to accelerate the absorption of the protein from the gut, thus, inducing more severe clinical symptoms [66]. Finally, an association between LTP hypersensitivity and chronic urticaria [67] as well as with intolerance to nonsteroidal anti-inflammatory drugs has been observed; it is possible that both chronic urticaria and NSAID-intolerance make mast cells more easily excitable by these food allergens.

CONCLUSION

Lipid transfer protein allergy syndrome shows some peculiarities that are unique in the primary food allergy panorama. These include the geographical distribution, the frequent asymptomatic sensitization, the frequent need for cofactors for clinical allergy to appear, and the reduced severity when LTP sensitization is associated with pollen allergy. Future studies will have to address these points as the results may have favorable effects on other, more severe, types of food allergy.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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