
Evaluation of patatin as a major cross-reactive allergen in latex-induced potato allergy

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Background: Potential cross-reactions between natural rubber latex and fruit/vegetable specific immunoglobulin (Ig)E antibodies have been reported for many years. This study was designed to investigate the molecular basis of acquired food sensitization focusing on the storage protein patatin and the patatin-like latex protein Hev b 7.

Objective: The amount of potato-specific IgE in the serum of latex-allergic health care workers and children with atopic dermatitis was determined to evaluate cross-reactivity between Hev b 7 and patatin. Additionally, the stability of potato patatin to digestion was investigated.

Methods: Human serum was tested on its reactivity to latex and potato proteins by IgE immunoblotting after one-dimensional (1-D) and 2-D electrophoresis. Latex- and potato-specific IgE concentrations were measured in fluorescence enzyme immunoassays (CAP, Pharmacia, Uppsala, Sweden). Further, potato patatin was chromatographically isolated to perform auto-inhibition tests. Stability of patatin to degradation was determined by digestion *in vitro*.

Results: Patatin was identified as major cross-reactive potato allergen by N-terminal sequencing. Seventy-five percent of the potato-sensitized people reacted with patatin in 1-D immunoblots, and 25% of the positive reactions to Hev b 7 could be blocked by preincubation of the patients' sera with purified potato patatin. Examination of children with atopic dermatitis showed that most sera contained patatin-specific IgE, whereas no Hev b 7-specific IgE was detected. Finally, patatin has been found partially stable to digestion *in vitro*.

Conclusions: Patatin was identified as a major cross-reactive protein in latex-associated potato allergy and appears to be relevant for atopic dermatitis. Therefore, patatin could be a suitable marker for the determination of potato sensitization, and it may also constitute an important food allergen. Cross-reactivity between Hev b 7 and patatin was restricted to primarily latex-sensitized adults, suggesting a different mechanism of sensitization in children with atopic dermatitis.

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INTRODUCTION

Latex allergy is developed by people who are frequently exposed to natural rubber latex (NRL) products such as health care workers (HCWs) and persons undergoing repeated surgical operations. Up to 18% of surgeons and nurses^{1,2} and up to 72% of children suffering from spina bifida (SB)³ become sensitized to the protein components of NRL. Affected persons may also develop a food allergy and become sensitized to certain fruits and vegetables.^{4,5}

Cross-reactions between NRL and avocado, potato, banana, tomato, chestnut, sweet pepper, and kiwi have previously been described. The effect is caused by similar epitopes in NRL and food, recognized by immunoglobulin (Ig)E antibodies originally targeted at latex proteins.⁶ The aim of this study was to determine the extent of cross-reactivity between potato patatin and the patatin-like NRL protein Hev b 7.^{7–10} These proteins are approximately 60% homologous. Posch et al^{11–13} found Hev b 7 to be recognized by antibodies from 23% of people with a sensitization to latex. By using bio-

chemical methods, this study intends to examine the amount of cross-reaction between these two proteins and to investigate how their similarity influences the sensitization of latex-allergic persons to potato.

MATERIAL AND METHODS

Study Population

Twenty HCWs aged 17 to 51 years (median age 29.5 years) with measurable amounts of latex- and potato-specific IgE participated in this study. Ten donors with high anti-latex IgE levels but no detectable potato-specific IgE (median age 32.8 years) and eight donors with low IgE levels (median age 39.3 years) served as negative controls. Additionally, nine children with atopic dermatitis (AD) aged 4 to 9 years (median age 6.3 years) were included in this study. Nine sera with low IgE levels (median age 6.8 years) were used as negative controls. None of the subjects had a history of clinical reactivity to the ingestion of potato. Table 1 provides a complete description of the examination groups.

Informed consent was obtained either from the patients or from their parents if patients were younger than 18 years. Blood samples were taken and skin prick tests to latex only were performed voluntarily on adult HCWs but not on children with AD. A questionnaire completed by the patients or their parents evaluated clinical symptoms on contact with latex products in the daily environment and with medical

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Table 1: Characterization of the Study Population Consisting of 20 Latex-Allergic HCWs and 9 Children with atopic dermatitis (AD).

Patient no.	Age (y)	Sex	SPT result	Total IgE (kU/L)	Latex specific IgE (kU/L)	Latex CAP class	Potato specific IgE (kU/L)	Potato CAP class	IgE patatin *	IgE to Hev b7*
Latex-allergic HCWs										
1	42	M	+	2000	27.6	4	71	5	+	+
2	24	M	+	867	71.7	5	24.8	4	+	+
3	33	F	+	467	9.8	3	14.6	3	+	+
4	18	M	+	294	19.1	4	11.7	3	+	+
5	28	F	+	468	17.3	3	10.2	3	+	+
6	51	F	+	707	2.4	2	6	3	+	+
7	43	M	+	932	19.3	4	3.8	3	+	+
8	22	F	+	143	19.3	4	3.8	3	+	+
9	19	F	+	603	11.9	3	3.4	2	+	+
10	37	F	+	243	4.5	3	3.2	2	+	+
11	30	M	+	307	94.9	5	2.2	2	+	+
12	20	F	+	777	25.6	4	1.5	2	+	+
13	17	M	+	131	7.7	3	1.4	2	+	+
14	41	M	+	413	1	2	1.2	2	+	+
15	32	M	+	452	5	3	1	1	+	+
16	28	F	+	267	35.8	4	1	1	+	+
17	24	M	+	835	2.1	2	0.6	1	+	+
18	25	F	+	876	0.6	1	0.5	1	+	+
19	36	M	+	187	3.7	3	0.5	1	-	-
20	20	F	+	193	1.7	2	0.4	1	-	-
Children with AD										
1	4	F	n.d.	334	< 0.35	0	77.7	5	+	-
2	8	F	n.d.	563	< 0.35	0	11.4	3	+	-
3	6	M	n.d.	967	< 0.35	0	10.1	3	+	-
4	4	F	n.d.	1243	0.9	2	36.8	4	+	-
5	5	M	n.d.	1055	9.1	3	22.5	4	-	-
6	7	M	n.d.	769	4.1	3	5.5	3	+	-
7	9	F	n.d.	238	3.2	2	5.1	3	+	-
8	8	M	n.d.	424	10.4	3	4.3	3	-	-
9	6	M	n.d.	395	41.5	4	2.1	2	+	-

AD: Atopic dermatitis; HCW: Health care worker; SPT: Skin prick test with natural rubber latex.

*As determined by immunoblot, n.d.: not determined.

equipment. Questions about clinical symptoms after consumption of avocado, banana, and kiwi, but not potato, were part of the questionnaire. Total IgE as well as latex- and potato-specific IgE were determined from patients' sera using the Pharmacia CAP system fluorescence enzyme immunoassay (Pharmacia, Uppsala, Sweden). Skin prick tests were performed with low ammoniated raw and unfinished NRL milk. A solution of 0.1% histamine dihydrochloride served as a positive control and a physiologic sodium chloride solution as a negative control. Skin test responses with maximum wheal diameters of 3 mm or greater and without reaction to the negative controls, together with skin indices >0.6, were evaluated as positive. The skin index was calculated as the ratio of the diameter of the allergen wheal to the histamine wheal.

Protein Isolation

Total protein was isolated from *Solanum tuberosum* tuber and *Hevea brasiliensis* C-serum [clone RRIM 600]¹⁴ by acetone

precipitation (10% trichloroacetic acid and 0.25% dithiothreitol in ice-cold acetone) after homogenization with an Ultra-Turrax dispenser (Ika, Staufen, Germany). Pure patatin was isolated with a combination of standard chromatographic methods as described below. Total glycosylated protein was bound to a Sepharose-conjugated concanavalin A column. Attached proteins were eluted with 0.5 M methyl- α -D-mannopyranoside. As a second step, patatin was isolated by anion-exchange chromatography in a salt gradient of 0 to 1 M sodium chloride. Remaining contaminations were removed by gel filtration over a Superdex 75 column (Pharmacia). Purity of the isolated patatin was controlled by one-dimensional (1-D) and 2-D electrophoresis followed by silver staining.

1-D and 2-D Electrophoresis, Immunoblotting

Standard sodium dodecyl sulfate-polyacrylamide gel electrophoresis was performed according to Laemmli¹⁵ and Schagger and von Jagow.¹⁶ Isoelectric focusing for 2-D electro-

phoresis was performed in immobilized pH gradient gels with a linear pH gradient from 4 to 8 (25,300 Vh, 3,500 V) followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (1,600 Vh, 25 mA). Proteins were transferred to a polyvinylidene difluoride (PVDF) membrane, blocked overnight (1% bovine serum albumin [BSA], 1% polyvinylpyrrolidone-40 in Tris-buffered saline [TBS]) and were subsequently incubated with undiluted patient serum for 8 hours. Attached IgE was detected with the alkaline phosphatase conjugated goat anti-human antibody A-3525 from Sigma (Deisenhofen, Germany) and visualized with 5-bromo-4-chloro-2-indolyl phosphate/nitroblue tetrazolium salt solution (Roche, Mannheim, Germany) as a chromogen. If enough serum was available to perform a verification experiment, 1 mL was preincubated with 5 μ g/mL purified patatin overnight before immunoblotting, to remove patatin-specific IgE from the patient's serum. For N-terminal sequencing proteins were transferred to a PVDF membrane after 2-D electrophoresis, stained with Coomassie brilliant blue (0.1% CBB in water containing 40% ethanol and 10% acetic acid), cut out with a razor blade, and analyzed by Edman degradation (Department of Chemistry, Ruhr-University of Bochum, Germany).

Determination of Latex- and Potato-Specific IgE (CAP Assay)

IgE concentrations in human serum were measured with the CAP system fluorescence enzyme immunoassay (Pharmacia) according to the manufacturer's guidelines. CAP inhibition assays were performed by incubation of 40 μ L serum with 10 μ L pure chromatographic isolated patatin (final concentration 0.72 μ g/mL) as a competitive inhibitor, if enough serum remained after immunoblotting and auto-inhibition blots.

Digestion in Vitro

Digestion was simulated with Enzynorm Forte (Nordmark, Uetersen, Germany). This preparation contains pepsin, gastrin, and aminohydrochloride from dried pork stomach. Enzynorm Forte solution was created by dissolving one tablet in 87.5 mL 0.9% NaCl; 12.5 μ L of this solution were combined with 12.5 μ L of 0.1 M HCl and 25 μ L of a protein stock solution (0.5 mg/mL of pure isolated patatin, ovalbumin [OVA] or BSA) and incubated at 37° C for different time periods.

RESULTS

Potato protein lysates were separated by 2-D electrophoresis followed by immunoblotting with the pooled sera of five HCWs containing latex- and potato-specific IgE (Fig 1). A cluster of proteins with an approximate molecular weight of 45 kDa and an isoelectric point approximately 5.5 showed a strong reactivity with serum IgE. N-terminal Edman degradation of those proteins identified them as patatin isoforms (Fig 1B).

To determine the frequency of the presence of patatin-specific IgE in potato sensitized people with latex allergy, we examined 20 sera with measurable amounts of latex- and potato-specific IgE. Ten donors with high anti-latex IgE levels but no anti-potato IgE and eight donors with low IgE

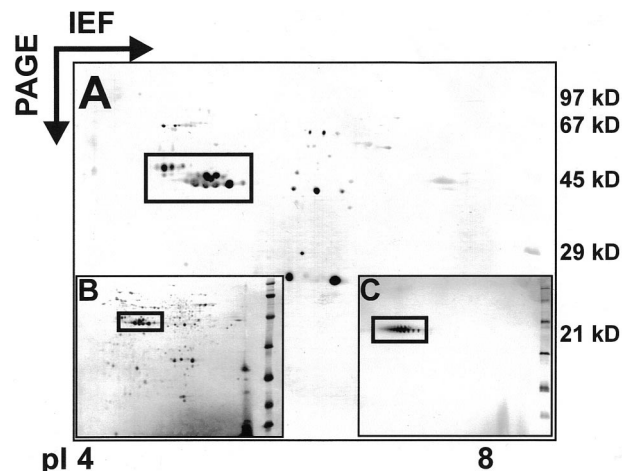


Figure 1. (A) 2-D electrophoresis of isolated potato proteins subsequently immunoblotted with the pooled sera of five latex- and potato-sensitized HCWs. The spots within the box were identified as patatin isoforms by N-terminal sequencing. (B) shows the preceding 2-D blot stained with CBB. (C) The purity of the chromatographically isolated patatin used in this work was checked by 2-D analysis and subsequent silver staining.

levels served as negative controls. Potato proteins were blotted and incubated with patients' sera as previously described. Seventy-five percent of the sera examined contained IgE specific to a protein with a molecular weight of 45 kDa, whereas no similar reaction could be observed in the control groups. Auto-inhibition blots were performed with the 13 remaining sera and were incubated with chromatographically isolated patatin (purity shown in Fig 1C; 5 μ g/mL serum in inhibition blots, Fig 2A). Reactivity to the 45-kDa protein was reduced in all cases, therefore identifying this protein as patatin. Additional bands at 15 to 25 kDa were also seen. These were most likely degradation products, as they were also observed when leaving purified patatin at room temperature (not shown). In seven cases, enough serum was available to quantify the amount of inhibition by CAP inhibition tests (Fig 2B). The solid phase of the assay consisted of potato proteins, whereas pure patatin was used as an inhibitor (0.72 μ g/mL). The results of the CAP assays confirmed the blotting observations.

Similar examinations were performed with latex proteins. In 25% of the Hev b 7 positive sera, reactivity to this 46-kDa protein could be weakened by preincubation with potato patatin (5 μ g/mL, Fig 3A). Hev b 7 positive sera of latex sensitized persons without potato-specific IgE remained unaffected (data not shown). CAP inhibition tests with latex proteins as a solid phase and potato patatin as an inhibitor (5 μ g/mL, Fig 3B) confirmed the results.

Further, we determined the amount of patatin-specific IgE within the sera of children with AD and sensitization to latex and/or potato. Unlike in adults, some of the children were exclusively sensitized to potato. IgE immunoblots of potato proteins were performed as previously described (Fig 4). In

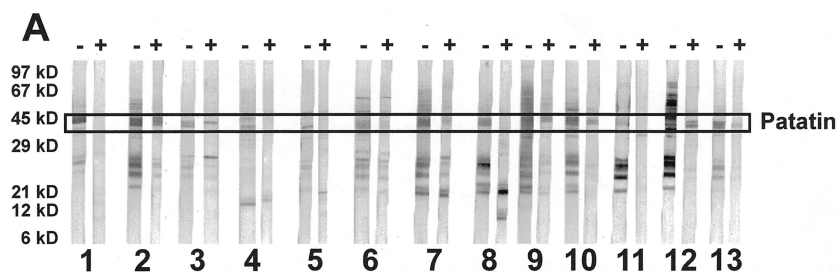
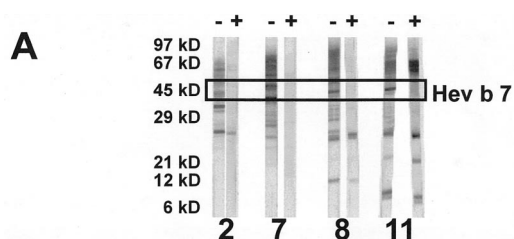


Figure 2. Prevalence of patatin-specific IgE antibodies within the sera of latex- and potato-sensitized persons. (A) Fifteen of 20 latex-sensitized people showed a reaction to the 45-kDa protein (marked by a box) in immunoblots with potato proteins. Thirteen sera underwent an inhibition assay with purified patatin (shown above). The reaction to patatin was weakened in all 13 cases. (B) In seven cases, enough serum was available to quantify the amount of inhibition in CAP confrontation assays. —, Unmodified serum; +, serum incubated overnight with 5 µg/mL purified patatin before immunoblotting.

B

Serum	CAP value (kU/L)	CAP inhibition value (kU/L)	Inhibition
1	1.91	<0.35	100%
4	0.75	<0.35	100%
6	6.65	2.39	64%
7	6.29	3.14	50%
8	3.25	1.80	45%
10	7.56	5.56	26%
12	1.27	0.98	23%



B

Nr.	CAP value (kU/L)	CAP inhibition value (kU/L)	Inhibition
2	1.91	<0.35	>80%
7	2.75	<0.35	>85%
8	6.44	4.78	26%
11	4.40	3.64	17%

Figure 3. Prevalence of patatin-like protein Hev b 7 specific IgE antibodies within the sera of latex- and potato-sensitized persons. (A) Sixteen of 20 latex-sensitized persons showed a reaction to the patatin-like protein in standard immunoblotting with latex proteins. In the four cases shown, the reaction to Hev b 7 (marked by a box) was inhibited by preincubation with purified potato patatin. (B) The amount of inhibition was quantified in CAP confrontation assays. —, Unmodified serum; +, serum incubated overnight with 5 µg/mL purified patatin before immunoblotting.

summary, all three potato positive sera and 4 of 6 latex- and potato-positive sera contained patatin-specific IgE. Surprisingly, no reaction to the patatin-like protein Hev b 7 could be detected (blots not shown). None of the control sera (not sensitized or latex-sensitized only) showed any reaction to patatin.

Finally, the disposition of patatin as a food allergen was investigated by digestion in vitro (Fig 5). Pure isolated patatin was digested for various times with Enzynorm Forte, and subsequently immunoblotted with the pooled sera of five latex- and potato-sensitized HCWs (Fig 5A). After 1 hour of incubation, a significant amount of intact protein as well as several IgE reactive fragments were detected. As controls, OVA and BSA were used (data not shown). The food aller-

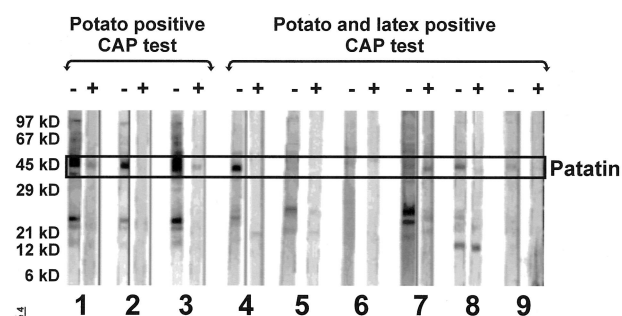


Figure 4. Prevalence of patatin-specific IgE antibodies within the sera of children with AD. All three sera containing potato-specific IgE only showed a strong reaction to patatin (marked by a box). Four of the 6 sera containing latex- and potato-specific IgE showed a positive reaction to patatin as well,^{4,7,8,9} whereas two did not.^{5,6} —, Unmodified serum; +, serum incubated overnight with 5 µg/mL purified patatin before immunoblotting.

gen OVA remained stable in this assay, whereas BSA was completely digested after 5 minutes. Because the stability of patatin ranges between both albumins, we conclude that patatin might be a potential food allergen. The assay was quantified by CAP confrontation assays with potato proteins as solid phase and digested patatin (0.72 µg/mL; Fig 5B). Sera of latex- and potato-sensitized adults as well as potato-sensitized children with AD were examined. Comparing the results of undigested to digested patatin, the CAP values remained almost unchanged in adults, whereas the values decreased in children. In the latter case, patatin-specific IgE appeared to recognize a different epitope. This may indicate an alternative way of primary sensitization to potato.

DISCUSSION

This study identified patatin as a major cross-reactive protein in latex associated potato allergy. 75% of the sera derived from potato-sensitized, latex-allergic HCWs showed a positive reaction to patatin. The real value may be higher, as all

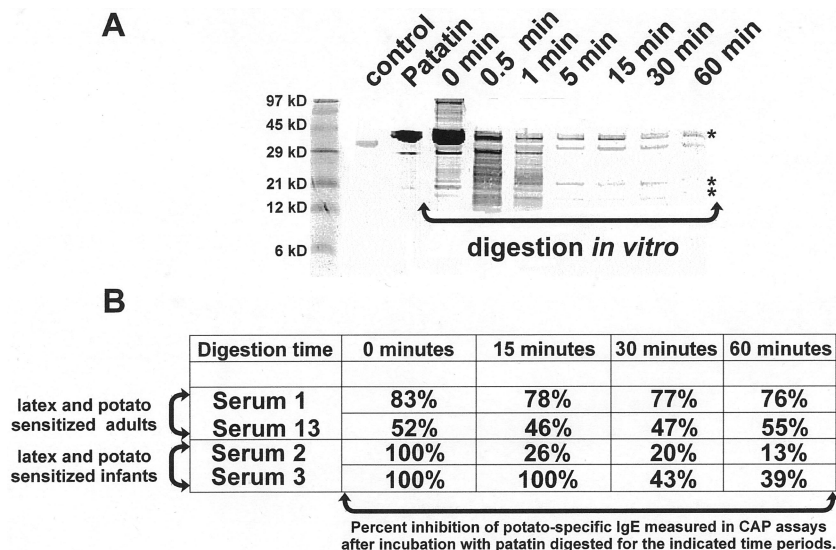


Figure 5. Identification of patatin as a potential food allergen by ingestion of purified protein *in vitro*. (A) Patatin was digested for the indicated time periods. After standard immunoblotting, proteins were incubated with the pooled sera of five latex- and potato-sensitized HCWs. Even after 1 hour of ingestion, a significant amount of patatin together with several fragments remained IgE-reactive (*). (B) CAP confrontation assays revealed that in adults the IgE reactivity toward patatin was not affected by digestion. In contrast, the antigen determinant rapidly disappeared in children with AD.

negative sera contained a low concentration of patatin-specific IgE (<1 kU/L), which may have been undetectable by standard immunoblotting. This also applies to the Hev b 7-negative sera. Additionally, 25% of the sera that tested positive for Hev b 7 contained antibodies that could be inhibited by purified potato patatin. The inhibition effect of potato patatin toward Hev b 7-specific IgE compared with patatin-specific IgE was lower, probably because these proteins are only approximately 60% homologous. Some of the IgE idiotypes originally directed against Hev b 7 showed a cross-reaction with potato patatin, whereas others did not. It has to be mentioned that the high amount of Hev b 7 positive sera (80% compared with 23% found by Posch et al¹¹⁻¹³ in latex-allergic HCWs) is caused by the composition of the group of patients studied, which were selected on the basis of reaction to latex. Our results support the hypothesis that homologous proteins induce cross-reactions between different allergens. Our results correspond well to those obtained by Seppala et al¹⁷ using enzyme-linked immunoadsorbent assay. They found that 74% of children's sera with a positive skin prick test to potato contained patatin-specific IgE. This value is close to our findings in adult HCWs (75%).

In a second study,¹⁸ they found that 43% of NRL-allergic adults and 83% of NRL-allergic children had patatin-specific IgE, which supports our suggestion that patatin is a major cross-reactive protein in latex-fruit syndrome. We suggest that latex-induced potato allergy is mediated by patatin-specific antibodies. Additionally, we propose that the initial sensitization occurs by the exposure to latex. Accordingly, the majority of patatin positive sera would test positive for Hev b 7 because the patatin-like protein is necessary for the initial production of patatin-specific antibodies. This contention is supported by our data (Table 1).

Our results also agree with the data obtained by Wagner et al.¹⁹ They reported that 13% of children with SB developed

Hev b 7-specific antibodies and therefore identified the patatin-like protein as the third major SB-associated latex allergen. Supporting evidence for the role of patatin in latex-fruit syndrome was also found by Reche et al,²⁰ who reported cross-reactivity between potato patatin and the patatin-like proteins in latex and tomato.

An interesting finding was the high amount of patatin-specific IgE in children with AD. A similar observation was made by Majamaa et al.²¹ However, no Hev b 7-specific antibodies were detected in our sera. Therefore, the data suggest that the sensitization of children with AD to potato occurs in a different manner to that in adults. It is probably not latex-associated, but could be caused by patatin epitopes that do not appear in Hev b 7. We conclude that the molecular basis of AD and acquired latex fruit syndrome are different and should be carefully compared.

Finally, we present evidence that patatin is a potential food allergen by digestion in an environment similar to the stomach. This model was described by Astwood et al²² and has shown its usefulness in case of the food allergen Ara h 1 derived from peanut.²³ Patatin was partially indigestible in this model, indicating its stability in the intestine. Further, patatin has been shown to refold after heat denaturation, especially in its α -helical areas.²⁴ This is consistent with our observation that the major patatin epitopes remain unaffected by cooking (data not shown). Indeed, all inhibition assays as well as the *in vitro* digestion assay have been performed with chromatographically purified patatin, isolated before purification from potato tubers by acetone precipitation (containing 10% trichloroacetic acid). As a result this pure patatin was denatured and therefore comparable with cooked patatin. In conclusion, our model is closer to a food allergy than it is to a contact urticaria that is caused by native patatin in raw potatoes. We conclude that patatin has the potential to create the symptoms of a food allergy.

CONCLUSION

Taken together, we propose that, in adults, initial sensitization to potato occurs by exposure to latex. Thereafter, Hev b 7-specific antibodies detect homologous regions in potato patatin to mediate potato allergy. Although clinical food allergy to potato is rare, there have been reports about anaphylactic symptoms²⁵ and oral allergy syndrome²⁶ induced by this vegetable. Additionally, patatins derived from other plants (eg, tomato²⁰) have been reported to induce similar reactions as potato patatin. We conclude that patatin could be a useful marker for the determination of potato sensitivity in blood serum, and it is a good example for the molecular development of a latex-associated food allergy.

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