

Allergic cross-reactions between cat and pig serum albumin

Study at the protein and DNA levels

Hilger C, Kohnen M, Grigioni F, Lehnert C, Hentges F. Allergic cross-reactions between cat and pig serum albumin. Study at the protein and DNA levels.

Allergy 1997; 52: 179–187. © Munksgaard 1997.

After observing a patient allergic to cat dander and pork but devoid of other allergies, we prospectively screened patients known to be allergic to cat for a second sensitization to pork. After collecting the sera of 10 young patients found to contain specific IgE to cat dander and pork, we undertook this study to detect the possible cross-reactive allergen, define its molecular characteristics, and evaluate its clinical relevance. Through immunoblotting techniques, cat and porcine serum albumin were found to be jointly recognized molecules. These findings were further analyzed by specific anti-albumin IgE titrations and cross-inhibition experiments. Cat serum albumin cDNA was obtained from cat liver, and the corresponding amino acid sequence was deduced and compared to the known porcine and human serum albumin sequences. Inhibition experiments showed that the spectrum of IgE reactivity to cat serum albumin completely contained IgE reactivity to porcine serum albumin, suggesting that sensitization to cat was the primary event. In two cohorts of cat-allergic persons, the frequency of sensitization to cat serum albumin was found to lie between 14% and 23%. Sensitization to porcine albumin was found to lie between 3% and 10%. About 1/3 of these persons are likely to experience allergic symptoms in relation to pork consumption. Sensitization to cat serum albumin should be considered a useful marker of possible cross-sensitization not only to porcine serum albumin but also to other mammalian serum albumins.

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Key words: allergy; CAP inhibition; cat; cDNA;
IgE; IgE cross-reactivity; immunoblot; pig.

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Accepted for publication 27 September 1996

The phenomenon of cross-sensitization between inhalent and food allergens is gaining increasing importance in clinical allergy as well as in fundamental immunology. Allergic cross-reactions between pollen allergens and food allergens of plant origin are well known. This is especially true of the birch pollen-hazelnut-apple and the mugwort-celery allergic clusters (1–4). In recent years, much insight has been gained into the nature of the cross-reactive molecules and allergic epitopes (5–7). Another example of cross-sensitization is the bird feather-hen's egg allergy syndrome (8–11). Recently, cross-reactivity between house-dust mite and vineyard snail has been reported (12, 13). Here we present results indicating a possible cross-reactivity between cat dander and pork. After observing a patient showing anaphylactic reactions after eating ham and sensitized to cat dander (14), we detected

several patients who had specific IgE to cat dander and pork. This paper presents evidence from the protein and DNA level that cat serum albumin (SA) and porcine SA are the cross-reactive allergens. Results will be discussed in the light of recent publications showing the importance of dog SA as a cross-reactive inhalent allergen (15, 16) and the role of bovine SA in causing severe anaphylactic reactions (17).

Material and methods

Patients and patient sera

The sera of 10 patients found to contain IgE antibodies to cat dander and pork were used for extensive characterization. All the patients had respiratory symptoms: asthma or rhinitis due to cat

dander exposure. Of these, three had immediate-type allergic reactions provoked by pork.

To investigate the overall sensitization to cat SA and porcine SA, we tested two groups of cat-allergic patients for specific IgE against cat SA and porcine SA. The first group comprised 37 consecutive patients seen for allergy work-up who were found to have positive skin prick tests and specific IgE to cat dander (group A). The second group comprised 39 patients strongly sensitized to cat dander whose sera had therefore been kept frozen (group B).

Skin tests

Skin prick tests were performed with routine inhalent allergens including mite, pollen, mold extracts, and animal epithelia, as well as food allergens including pork and a mixture of pork, beef, and mutton (Bencard and Allerbio). Histamine was used as positive control and glycerol as negative control. The results of skin testing were evaluated at 20 min, and the positive results were graded as follows: (+) when the diameter of the wheal was 3–5 mm, (++) for 5–10 mm, and (+++) for 10–15 mm.

IgE determination

Total and specific IgE were determined by the ImmunoCAP method (Pharmacia CAP-System, Uppsala, Sweden) according to the manufacturer's recommendations. The CAP results were expressed in kU/l. Concentrations of less than 0.35 kU/l represent a negative result. For the purpose of this study, specific ImmunoCAPs were produced for cat SA, dog SA, and porcine SA (Pharmacia, Uppsala, Sweden).

SDS-PAGE and immunoblotting

To determine and evaluate the allergen specificity of the patient IgE, allergen extracts were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) followed by immunoblotting with patient sera. Cat, porcine, dog, and bovine SA were purchased from Sigma. Cat dander and grass pollen extracts were obtained from HAL (Haarlem, The Netherlands). Meat extract was prepared by homogenizing pork in single detergent lysis buffer (50 mM Tris Cl, pH 8, 150 mM NaCl, 1% Triton X-100, 100 µg/ml PMSF). The mixture was incubated at 4°C for 30 min and centrifuged at 17 500 g for 10 min to remove insoluble particles. The protein concentration of the supernatant was determined by the method of Bradford (Bio-Rad Laboratories, Hertfordshire, UK), and the super-

natant was stored at –20°C. Samples were separated by 12% SDS polyacrylamide gels according to molecular weight. Several gels were run in parallel. One of the gels was stained with silver nitrate (Pharmacia, Sweden) to visualize the proteins; the others were used for immunoblotting. Blotting was performed by electrical transfer (Novablot, Pharmacia, Sweden) of the proteins onto nitrocellulose membranes, according to Towbin et al. (18). Membranes were saturated with 2% cold water fish skin gelatin in PBS/0.1% Tween-20 (blocking buffer) before being incubated overnight with the patient sera diluted 1/20 in blocking buffer. The membranes were incubated for 1 h with ¹²⁵I-labeled antihuman IgE antibodies (Pharmacia, Sweden) at 10 000 cpm/cm². Autoradiography was performed at –80°C for 48–72 h with intensifying screens.

Immunoblot-inhibition and CAP-inhibition experiments

In immunoblot-inhibition experiments, patient sera were incubated with equal volumes of cat SA or porcine SA so as to obtain final concentrations of 1, 0.5, 0.25, 0.125, and 0.0625 mg SA/ml. The mixture was kept at 4°C for 2 h before incubation overnight with blots of cat SA, porcine SA, dog SA, and bovine SA.

For CAP-inhibition with cat SA, patient sera were mixed at equal volumes with serial dilutions of cat SA so as to give final concentrations of 0.5, 0.05, 0.005, 0.0005, and 0.00005 mg cat SA. For inhibition with porcine SA, 9 volumes of patient sera were added to 1 volume of porcine SA solution so as to obtain final serial mixtures of 0.5, 0.05, 0.005, 0.0005, and 0.00005 mg porcine SA per ml. Sera were incubated overnight at 4°C before proceeding to routine CAP assay. Control CAP-inhibition experiments were performed at the same conditions with human SA and a grass pollen extract at final concentrations of 0.5 mg/ml.

Isolation of the cDNA coding for cat SA

cDNA was obtained from cat liver RNA as described previously (19). Briefly, total cellular RNA was extracted from cat liver by acid guanidium thiocyanate-phenol-chloroform extraction (20). Reverse transcription was performed with 5 µg of total cellular RNA, 500 ng of reverse primer, 0.4 mM of each dNTP, 40 U RNasin (Promega), 200 U M-MLV reverse transcriptase (BRL), and reverse transcriptase buffer in a total volume of 50 µl. RNA was reverse transcribed for 2 h at 37°C. The reaction was terminated by heating at 65° for 5 min. Polymerase chain reaction (PCR) (21) was performed with 5 µl of the cDNA in a 100-µl

reaction volume containing PCR-buffer (Promega), 200 ng forward primer, 200 ng reverse primer, 200 μ M of each dNTP, and 2.5 U Taq DNA polymerase. Samples were subjected to PCR for 25 cycles. The amplified DNA was cloned into the SalI site of pBluescript (Stratagene, Heidelberg, Germany) and sequenced by the dideoxy chain termination method (22). The nucleotide sequences of two clones obtained from independent reverse transcriptions, and PCRs were determined for both DNA strands. The nucleotide sequences of the PCR primers were derived from highly homologous regions found at the 5' and 3' ends of different SA nucleotide sequences. A SalI restric-

tion site was incorporated at the 5' end (underlined), as follows: forward primer: 5'-GAC AGAGTCGACTTTGGCACAATGAAGTGGGT; reverse primer: 5'-TGTATGGTCGACTCTCAG-GGTAGGCTGAGATG.

Results

Clinical and serologic profile of patients allergic to cat dander and pork

All the patients were young adults 17–37 years of age (Tables 1A and B). At the time of testing, all were regularly exposed to cat dander. All the

Table 1. Patient characteristics

A

Patient no.	Sex (age in years)	Animal exposure	Respiratory symptoms	Skin test cat dander	IgE cat*	Other respiratory sensitizations**
1	F (17)	Cat	A, R	Cat + + +	>100	Dog 7 Grasses 2
2	F (37)	Cat	R	Cat + + +	>100	Rabbit + + Dog + +
3	M (17)	Cat	A, R	Cat + + +	>100	Dog >100
4	M (23)	Cat	A, C	Cat + + +	>100	Dog 31 Mite 3
5	M (34)	Cat	R, C, A	Cat + +	>100	Dog 50
6	M (26)	Cat	A	Cat + +	61	Dog 19 Grasses 4
7	F (29)	Cat	R, A	Cat + +	92	Horse >100 Dog 67
8	M (36)	Cat	A, R	Cat + +	11	Grasses 5 Dog 12
9	F (23)	Cat	R, C	Cat + + +	>100	Grasses 43 Horse 8
10	M (27)	Cat	R, A	Cat + + +	>100	Grasses 1 Horse 40 Dog 60 Grasses 12

B

Patient no.	Responsible food	Symptoms	Skin test pork or meat mix	IgE pork*	Other food sensitizations**	Total IgE
1	Ham	Q, U, E, A, R	Pork + +	22	—	506
2	Sausage	U, C	Pork + +	32	Rabbit + +	133
3	Pork	Neg.	nd	14	Milk 9	6620
4	Cooking	Neg.	nd	15	—	1952
5	—	E	Meat mix +	5	Casein 13	1584
6	—	Neg.	Pork +	3	—	181
7	—	E	Meat mix + + +	24	Milk 5	1055
8	—	Neg.	nd	5	—	366
9	—	Itching palate	Meat mix + +	22	Beef 2	1075
10	Pork	U, E	Pork + +	4	—	614

A=asthma, C=conjunctivitis, R=rhinitis, U=urticaria, Q=angioedema, E=eczema, neg.=no symptoms, —=no food suspected, / =no food definitely identified, nd=not done. * IgE values are given in KU/l; ** allergy scores are given as IgE units when available or as skin test results according to scoring index given.

patients had respiratory symptoms (rhinitis and/or asthma) due to their exposure to cat dander. Only three patients had symptoms that were unequivocally provoked by pork, although all had IgE reacting with pork and porcine SA. Patient 1 experienced anaphylactic reactions on two occasions when the only food consumed was pork. The first time, she suffered from angioedema, rhinitis, and asthma within half an hour after eating a slice of ham. The second time she had urticaria and asthma shortly after eating sausage. On several occasions, this patient also had exercise-induced asthma and urticaria after a meal containing pork. She had also had episodes of atopic eczema. Patient 2 suffered repeatedly from conjunctivitis and urticaria of the face while preparing or cooking pork. Patient 10 repeatedly experienced urticaria while eating pork; he also had had episodes of atopic eczema. These three patients had positive prick tests to pork extract. Patients 5 and 7 had atopic eczema and positive skin tests with meat (mixture); the worsening of their cutaneous symptoms was related to pork consumption. Patient 9 experienced itching of the palate during certain meals containing pork. Patients 3, 4, 6, and 8 had no symptoms that seemed to be provoked by pork.

Cross-reactivity of the patient sera with cat and porcine SA

Immunoblot analysis showed that cat SA and porcine SA are allergens recognized by sera of patients sensitized to cat and pork. This is demonstrated in Fig. 1 in lanes 2–5 of the immunoblots at the height of the 66-kDa marker. The higher,

fainter bands seen in lanes 2, 3, and 4 were due to aggregated SA. These bands are also found with purified albumin and are weak or absent in freshly prepared albumin solutions (23).

Titration of the patient anti-SA IgE antibodies

Table 2 shows the IgE levels against cat SA, porcine SA, dog SA, and bovine SA of eight patients. For patients 9 and 10, there was no serum available for titration. In Table 3, anti-SA IgE titers are shown for the nine patients of group B who were positive for anticat SA. It should be noted that in both groups the anticat SA titers were highest, followed by the antidog SA (even in those patients who did not have a dog) and the antiporcine SA titers. Some patients also had a low titer of antibovine SA IgE.

Table 2. Anti-SA IgE titers of index patients characterized in Table 1

Patient no.	Anti-SA IgE (kU/l)			
	Cat	Pig	Dog	Bovine
1	165	22	37	2.5
2	75	27	38	2.3
3	89	5	73	1.2
4	22	2	10	0
5	11	4	17	0
6	38	4	42	0
7	70	25	nd	nd
8	8	8	12	0
9	nd	nd	nd	nd
10	nd	nd	nd	nd

nd = not done.

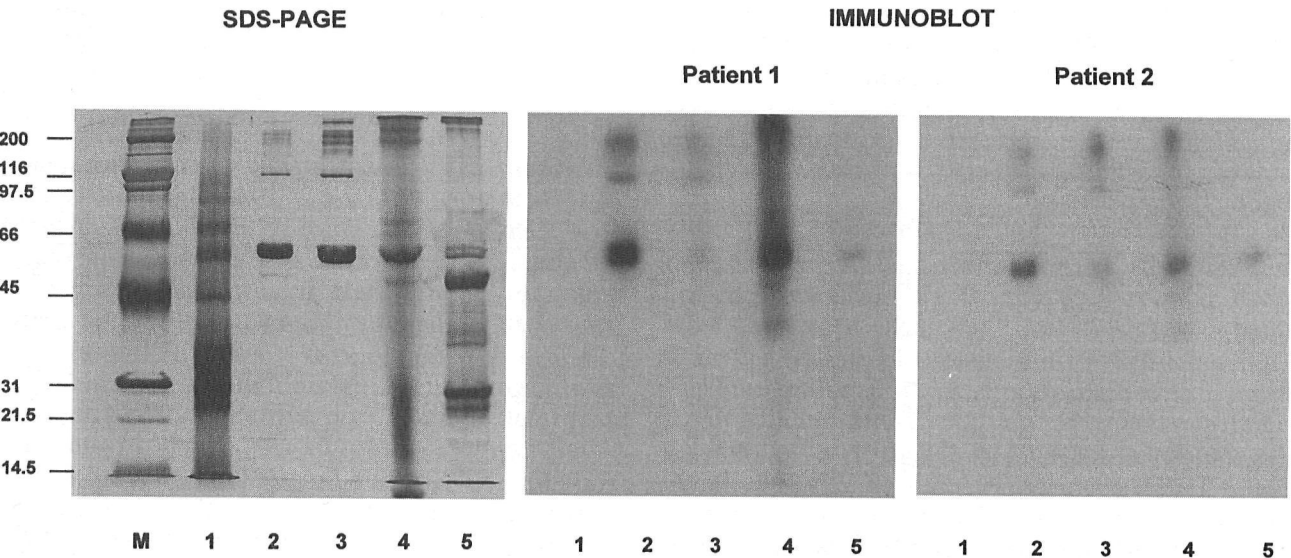


Fig. 1. SDS-PAGE of different allergen extracts and corresponding IgE immunoblots with sera of patients 1 and 2. SDS-PAGE: lane M) molecular weight markers in kDa; lane 1) grass pollen extract; lane 2) cat SA; lane 3) porcine SA; lane 4) cat dander extract; lane 5) pork extract. Lanes 1–5 of immunoblots correspond to lanes 1–5 of SDS-PAGE stained with silver nitrate.

Overall frequency of IgE against cat SA and against porcine SA

In group A, 5/37 consecutively seen cat-sensitized patients (14%) had specific IgE to cat SA (range 0.5–19 kU/l), and one patient had IgE against porcine SA. In group B, 9/39 highly cat-sensitized patients (23%) had specific IgE to cat, and four of these nine had significant amounts of IgE to porcine SA (Table 3).

IgE immunoblot-inhibition and CAP-inhibition experiments

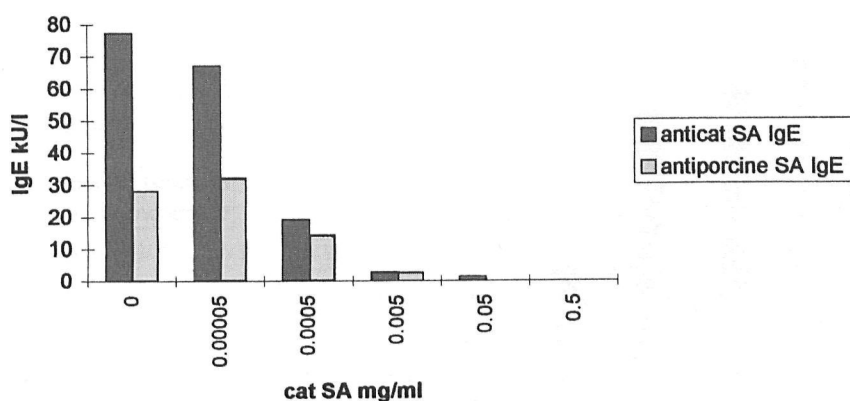
Sera of patients 2, 3, and 4 were incubated with increasing doses of porcine SA, or cat SA, and the progressively decreasing IgE reactivity was deter-

mined by immunoblotting (data not shown). Incubation with porcine SA eliminated the antipig IgE

Table 3. IgE titers of anticat SA-positive patients in group B (39 patients)

Patient no.	Anti-SA IgE (kU/l)			
	Cat	Pig	Dog	Bovine
B6	9	0.5	12	0
B10	15	7	8	0
B17	55	8	22	0
B18	67	1	43	0
B20	29	1	13	1.1
B23	>100	5	41	0.4
B32	32	6	12	0
B33	26	0.9	31	0
B38	17	0.8	7	0

Patient 2 serum inhibition with cat SA



Patient 2 serum inhibition with porcine SA

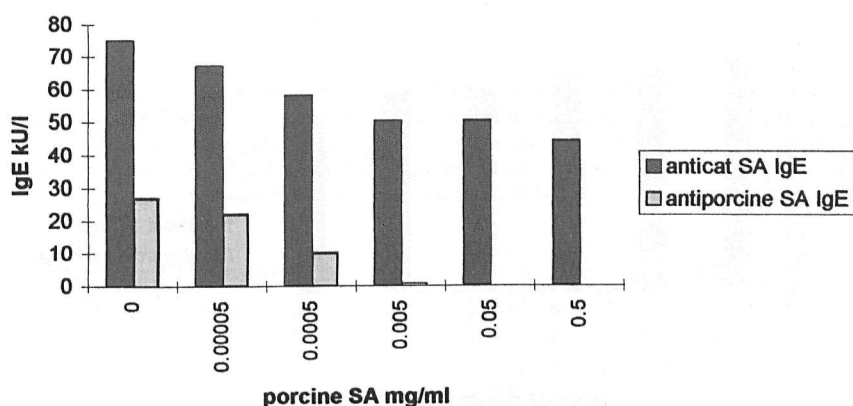


Fig. 2. Serum inhibition experiments with cat and porcine SA. Patient sera were incubated with increasing doses of cat SA (top) or porcine SA (bottom), and anticat SA IgE and antiporcine SA IgE were determined by CAP assay. IgE concentrations are given in kU/l; SA concentrations are in mg per ml final concentration.

reactivity of all three sera. It partly inhibited IgE against dog SA in the sera of patients 2 and 4. IgE against cat SA was not markedly changed. Incubation with cat SA eliminated IgE reactivity against cat SA, porcine SA, and dog SA for patients 2 and 4, and against cat SA, porcine SA, and partly dog SA for patient 3 (who had a dog).

Fig. 2 (patient 2) and Fig. 3 (patient 1) show the CAP-inhibition data. Sera were incubated with increasing amounts of cat SA and porcine SA. With increasing doses of cat SA, IgE reactivity against porcine SA and, at higher concentrations, IgE reactivity against cat SA were no longer detectable. During incubation with porcine SA, IgE reactivity against porcine SA was already completely removed at a dose where only part of the reactivity against cat SA was affected. Neither anticat SA nor

antiporcine SA IgE reactivity was affected in control experiments using human SA or grass pollen extract (data not shown).

Determination of cat SA sequence and comparison with porcine SA and human SA sequence

The nucleotide sequence of cat SA cDNA obtained from cat liver RNA was determined (19). The deduced cat SA amino acid sequence and the porcine SA amino acid sequence (24) were compared to the human SA amino acid sequence (25) (Fig. 4). Mature cat SA is composed of 584 amino acids (aa 25–608), human SA of 585 amino acids, and porcine SA of 583 amino acids. Comparison of the three protein sequences shows that cat SA and human SA differ by 106 amino acids, and porcine

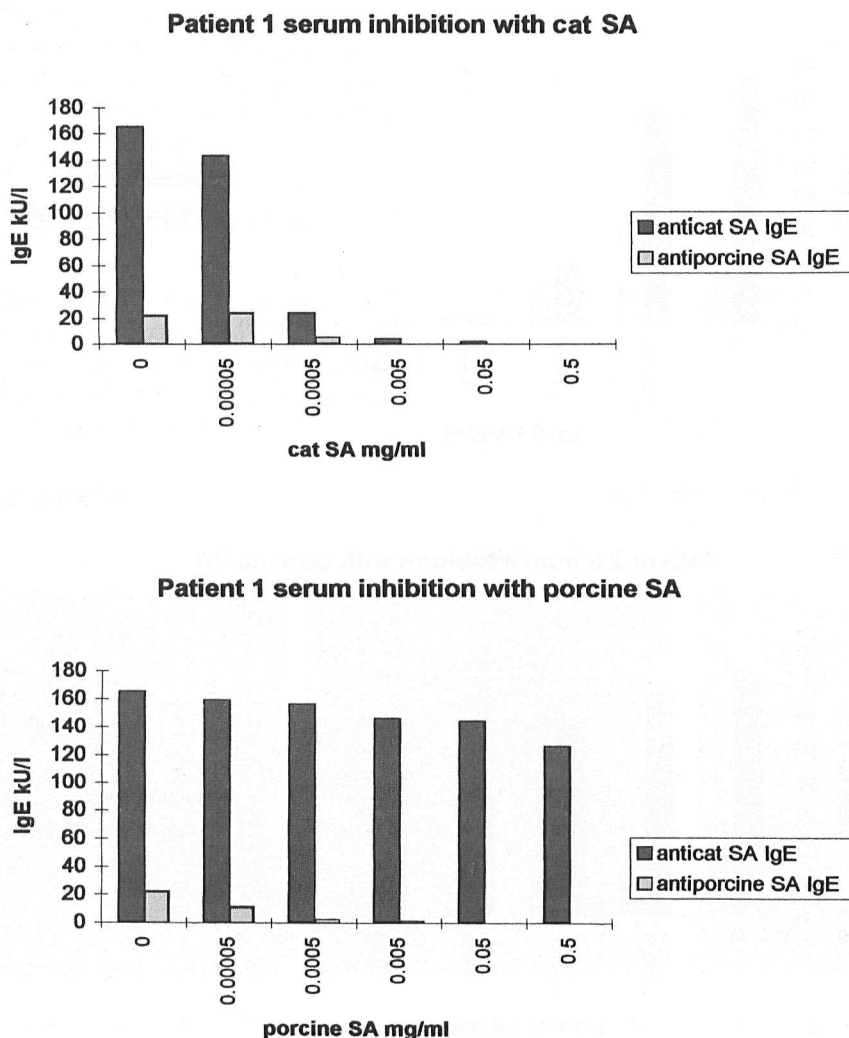


Fig. 3. Serum inhibition experiments with cat and porcine SA. Patient sera were incubated with increasing doses of cat SA (top) or porcine SA (bottom), and anticat SA IgE and antiporcine SA IgE were determined by CAP assay. IgE concentrations are given in kU/l; SA concentrations are in mg per ml final concentration.

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Fig. 4. Comparison of cat SA, porcine SA, and human SA protein sequences. Human SA amino acid sequence is given as reference sequence. Only cat and pig SA amino acids that differ from human sequence are given. Positions identical for cat SA and porcine SA but different from human SA are underlined. Swissprot accession numbers for human SA and porcine SA are P02768 and P08835, respectively. Minor variants from this human SA sequence have been described. Nucleotide sequence of cDNA coding for cat SA has been deposited in EMBL database under accession no. X84842.

SA and human SA differ by 142 amino acids. The respective homologies are 82% and 76%.

Discussion

The first data on the role of cat SA in cat allergy were presented in the 1970s (26, 27). Recently, in dog-allergic persons, dog SA has been shown to be

an allergen of intermediate importance (15). The stimulus of our study was the observation of a patient having at the same time allergic reactions to an inhalent allergen, cat dander, and to a food allergen, pork. After immunoblotting techniques had shown that the serum of this patient and the sera of other patients recognized both cat and porcine SA, immunoinhibition experiments demonstrated

that IgE reactivity against porcine SA was included within the reactivity to cat SA.

To investigate in more detail the similarity of the two allergens, we cloned the cDNA coding for cat SA and determined the nucleotide sequence. Our results agree with the data of Dandeu et al., who sequenced the 30-residue N-terminal peptide of cat albumin (28). Comparison of cat SA and porcine SA amino acid sequences with human SA showed that 50 of the 106 amino acids by which cat SA differs from human SA are common to cat SA and porcine SA. This means that about half the amino acids of cat SA that may be recognized as allergenic epitopes by the human immune system are also present on porcine SA. The three-dimensional structure of human SA has been determined by crystallography (29). It has three homologous domains that assemble to form a heart-shaped molecule. A total of 17 disulfide bridges determine the overall structure of human SA. These Cys-Cys pairs are conserved among the different animal SA sequenced so far. Human IgE that are cross-reactive for cat and porcine SA probably recognize epitopes at the surface of these SA molecules that contain amino acid motifs present on cat and porcine SA but absent from human SA. Of course, such critical amino acids could be expected to form continuous as well as discontinuous epitopes. Recent work studying cross-reactivity among horse, dog, and cat SA by means of proteolytic peptides has yielded the first data suggesting that structural epitopes might cause the cross-reactivity observed (30).

Basically, three ways can be imagined to explain how this cat-pork cross-sensitization can develop. The direction can be a cat to pig cross-sensitization or a pig to cat cross-sensitization. Coexisting but independent sensitizations to cat and pig can also be conceived of. A pig to cat sensitization cannot explain the situation because the IgE reactivity to cat SA is the broadest and embraces the reactivity to porcine SA. Indeed, the fact that the spectrum of anticat SA IgE reactivity completely contains the antiporcine reactivity argues for a primary respiratory sensitization to cat SA. This sequence of events, starting with sensitization to an aero-allergen and leading to cross-sensitization to a food allergen, also appears in the pollen-fruit-vegetable and the feather-egg syndrome found in young atopic patients. Coexisting, overlapping, but independent sensitizations to cat SA as an inhalant allergen and porcine SA as a food allergen may occur in young atopic children, in whom primary digestive sensitizations are frequent due to an easily permeable digestive mucosa. This was not the situation in the age group we studied. The chronology of events was also that of regular

exposure to cat dander, followed by clinical symptoms of cat allergy and then elicitation of allergic reactions to pork. However, not all the patients experienced clinical allergic reactions to pork. For some, this was related to the physical condition of the allergen. Fresh meat or dried and smoked pork were most likely to provoke allergic reactions. However, well-cooked meat, in which SA is likely to be heat-denatured, hardly elicited clinical symptoms. Of course, the quality of the digestive process in the different patients and the existence of food-protective antibodies – for instance, that of secretory IgA – are also possible explanations of the difference in clinical manifestation. In addition, the titer of specific IgE to porcine SA seems to be related to the presence or absence of allergic symptoms.

In the two additional patient groups studied, the overall frequency of sensitization to cat SA lay between 14% and 23%. Anticat SA IgE were of greater frequency and overall of higher titer in the patients strongly sensitized to cat dander. In terms of cross-sensitization to inhalant allergens, it is important to note that all the patients allergic to cat SA also had high IgE titers to dog SA even if they had no contact with dogs. As for the food allergens concerned, one patient in group A and four patients in group B had significant titers of IgE to porcine SA. Two patients also had low titers of IgE to bovine SA. It has previously been shown (15) that about 35% of patients allergic to dog dander are sensitized to dog SA. The role of bovine SA in certain anaphylactic reactions during medical procedures has been reported (31–34). A recent paper (17) has shown that a patient who experienced an anaphylactic reaction to bovine SA, and who kept cats at home (thought to be the source of sensitization), had IgE to cat SA but also to pig, dog, and other mammalian SA. Taking into consideration our findings and those of previous authors (26, 27, 35), we can say that, as an inhalant allergen, cat SA is of intermediate importance, clearly ranking behind *Fel d 1*. But as a molecule prone to induce allergic cross-reactions to other mammalian SA (15, 17), it is an important inhalant and food allergen. Indeed, all the persons analyzed who were sensitized to cat SA had IgE to dog SA. Of cat SA-sensitized subjects, 20–44% had cross-reacting IgE to porcine SA. About one in three of these were likely to experience allergic reactions to porcine SA. This represents about 6–14% of cat SA-allergic patients and 1–3% of cat-allergic patients. Sensitization to cat SA is a marker that allows us to predict inhalent cross-reactions to other mammalian SA, to foresee possible allergic reactions to meat, and eventually to recognize the rare anaphylactic reactions that may be induced by administration of nonhuman SA to sensitized patients.

Acknowledgments

This work was supported by grant 94/05 of the CRP-Santé and grant 94/04 of the Fondation Recherche Cancer et Sang, Luxembourg. We thank Dr André Steinmetz for critically reading the manuscript, and Birgitta Grell of Pharmacia AB, Diagnostics, Uppsala, Sweden, for preparing and standardizing the serum albumin CAP.

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