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Review

Serum albumins—Unusual allergens ☆

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ABSTRACT

Background: Albumins are multifunctional proteins present in the blood serum of animals. They can bind and transport a wide variety of ligands which they accommodate due to their conformational flexibility. Serum albumins are highly conserved both in amino acid sequence and three-dimensional structure. Several mammalian and avian serum albumins (SAs) are also allergens. Sensitization to one of the SAs coupled with the high degree of conservation between SAs may result in cross-reactive antibodies in allergic individuals. Sensitivity to SA generally begins with exposure to an aeroallergen, which can then lead to cross-sensitization to serum albumins present in food.
Scope of review: This review focuses on the allergenicity of SAs presented in a structural context.
Major conclusions: SA allergenicity is unusual taking into account the high sequence identity and similarity between SA from different species and human serum albumin. Cross-reactivity of human antibodies towards different SAs is one of the most important characteristics of these allergens.
General significance: Establishing a relationship between sequence and structure of different SAs and their interactions with antibodies is crucial for understanding the mechanisms of cross-sensitization of atopic individuals. Structural information can also lead to better design and production of recombinant SAs to replace natural proteins in allergy testing and desensitization. Therefore, structural analyses are important for diagnostic and treatment purposes. This article is part of a Special Issue entitled Serum Albumin.

1. Introduction

Serum albumins (SAs) are multifunctional proteins which are highly conserved in both sequence and structure. SAs are α-helical proteins with several disulfide bridges that stabilize the structure [1]. The molecule, which has three domains, is very flexible and may change its conformation easily in order to bind many diverse ligands [2,3]. SAs are also thermolabile and undergo denaturation with relative ease in milk or beef extracts, leading to the formation of water-insoluble aggregates [4].

SAs are used in many medical laboratory applications; most likely very few, if any, molecular biologists have never worked with bovine serum albumin (BSA) at least once. SAs are also present in animal products that are a major component of the human diet. While most people tolerate exposure to foreign serum albumins well, a small fraction of people develop allergic reactions to mammalian and/or avian SAs [5]. Serum albumins are also present in animal dander and it is highly likely that contact with this dander is the major source of health problems associated with SAs in humans. Up to approximately 30% of patients allergic to animal dander exhibited IgE reactive toward serum albumins [6]. Moreover, people do not have to be exposed directly to mammalian or avian sources of SA to become sensitized, as some allergens, such as Fel d 1, are transferred on the clothes of animal owners in public places [7,8]. The amount of allergen transferred, in many cases, is sufficient to sensitize people without direct exposure to the allergen source.

This review presents information on serum albumin allergenicity in relation to sequence and structure conservation of these proteins. Although the Allergome database (www.allergome.org) currently identifies 26 different SAs as potential allergens, this review focuses on the 18 SAs (14 mammalian and 4 avian) to which humans are most often exposed (see Supplementary Materials for the list and sequence alignment). Six of the analyzed albumins are registered as allergens by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee (Table 1).

Abbreviations: BSA, bovine serum albumin; FSA, feline serum albumin; HSA, human serum albumin; IgG, immunoglobulin G; IgE, immunoglobulin E; MMR, measles–mumps–rubella; MMRV, measles–mumps–rubella–varicella; PSA, porcine serum albumin; SA, serum albumin

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Although SAs are not a major cause of allergic sensitization, they compose a very interesting and unusual group of allergens. Foremost, they have sequences that are similar to the sequence of human serum albumin (HSA) and surprisingly they are able to sensitize atopic individuals. As shown previously, there are relatively few allergens with sequence identities to human homologs greater than 50–60% [9,10]. Moreover, due to the high similarities of their sequences, SAs are often cross-reactive, which can cause additional health risks to allergic individuals.

2. Sequence and structure conservation

Mammalian SAs have high sequence identities (72–82%) and similarities (83–88%) relative to HSA (Table 2 and also Supplemental Fig. 2). Cat and dog SAs are the most similar to HSA, while rodent SAs are the least similar among the mammalian species described in this review. Avian serum albumins display a relatively high similarity to the human protein (61–63%) and moderate sequence identity (46–49%). High sequence similarity between different SAs also results in similar structures (Fig. 1). There are currently four mammalian serum albumins with experimentally-determined structures: BSA, horse SA, HSA and rabbit SA [2,3,11].

High sequence identity increases the likelihood of cross-reactivity between serum albumin allergens due to their structural similarity. Table 2 indicates that sequence identity between all mammalian serum albumins is higher than 70%, the threshold typically required for cross-reactivity [13]. However, the mean 50% sequence identity shared between mammalian and avian SAs is well below the typical limit for cross-reactivity.

3. Bovine SA

BSA is one of the most well known proteins because of its widespread availability, similarity to HSA, use in medical formulations, and incorporation into many medical and biochemical assays. It is present in beef [14] and cow's milk [15]. BSA is used as a component of many vaccines [16,17], such as MMR, MMRV, Varicella, and Zoster, and is an important part of the culture medium used in artificial insemination. It is also studied because of its allergenicity; BSA has been identified as a minor allergen in bovine dander and serum [18].

Cow's milk allergy is one of the most common food allergies, together with allergies to eggs, fish, and peanuts. In most cases childhood allergy to cow's milk does not persist into adulthood; only 10–15% of young children diagnosed with the allergy remain so over five years of age [19,20]. A majority of patients with persistent milk allergy are also allergic to bovine serum albumin [21]; IgE from the affected patients was shown to be reactive toward several mammalian danders and meats. These patients have a greatly increased risk of developing rhinoconjunctivitis or asthma due to animal epithelia.

Very rarely, contact with BSA may cause an anaphylactic reaction. It was reported to be responsible for anaphylaxis in an artificial insemination patient [22]. The patient was previously diagnosed with asthma and shown to have subclinical allergy to mammalian serum and thus cross-reactivity with BSA was suggested to be the origin of the anaphylactic reaction. Another patient with respiratory allergic reactions to feline epithelium had episodes of anaphylaxis after contact with BSA [23]; in this case the patient could tolerate well-cooked beef. More recently, it was reported that inhalation of BSA during work in a laboratory induced asthma in a patient [24].

The observation that thorough cooking of food improves tolerance is quite common in reports describing allergic reactions to SAs. Heat treatment has been shown to modify the allergenicity of beef and BSA and reduce, but not eliminate, their capacity to bind IgE from patients [21,25,26]. However, heat treatment in the presence of reducing agents was able to eliminate IgE binding, suggesting that disulfide bridges were preserving the structure [26,27].

BSA is important in our understanding of SA allergenicity and the cross-reactivity of BSA with SAs from other animals has been studied extensively. The binding of IgG and IgA antibodies was studied by Hilger et al. [28], who found significantly higher anti-BSA titers in individuals suffering insulin-dependent diabetes mellitus. Furthermore, the N-terminal region of BSA degraded first in simulated gastrointestinal fluid. This agreed with the result that the IgG to IgA ratio was altered for this region because the epitope was destroyed before reaching the gut-associated lymphoid tissue. Other studies identified residues 524–598 of BSA as forming the IgE epitope [29], of which residues 524–542 were the most critical for antibody binding. Several previous studies also suggested that this fragment of the BSA sequence was immunogenic [18,30–32]. Fergusson et al. and Wahn et al. also showed that the N-terminal part of the protein is immunogenic, identifying residues 115–184 and 1–306 specifically. In addition, the so-called ABBOS epitope (residues 126–144) was suggested to be responsible for an autoimmune reaction against pancreatic islet cells, which leads to islet cell dysfunction [33]. For a more detailed summary of epitopes relevant to bovine, horse and rabbit albumins see Majorek et al. [2] as well as references therein.

4. Cat and dog SA

Initial reports on the role of cat SA as an allergen were published four decades ago using extracts from cat pelts [34]. Cat and dog SA, which have 81.7% and 79.7% sequence identity (88.4% and 88.0% sequence similarity) to HSA respectively (Table 2), are the two major causes of sensitization of SA allergic individuals. Sensitization to feline and canine epithelia is highly correlated with sensitization to epithelia of other mammals like rabbit, cow, or horse [35]. It was shown that 85% of patients allergic to SAs had IgE reactivity to cat and dog SA [6]. Cross-reactivity between these two SA proteins, which have 87% sequence identity and almost 93% sequence similarity to one another, was demonstrated by Boutin et al. using monoclonal antibodies [36]. In that study, anti-cat SA monoclonal antibody was equally reactive to cat and dog SAs, as was an anti-dog SA monoclonal antibody. Furthermore, the murine monoclonal antibodies used were able to significantly inhibit human IgE binding. It was also shown that three tryptic peptides derived from horse (equine) SA (Equ c 1), composed of residues 21–113, 188–275 and 503–560 respectively, were not only

Table 1
A list of serum albumins that are registered as allergens by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee (www.allergen.org).

Albumin source common name	Albumin source Latin name	Allergen name	Route of exposure	Structures in Protein Data Bank
Bovine	*Bos domesticus*	Bos d 6	Iatrogenic/ingestion/inhalation	3v03, 4f5t
Dog	*Canis familiaris*	Can f 3	Inhalation	–
Horse	*Equus caballus*	Equ c 3	Inhalation	3v08, 4f5s, 4f5u
Cat	*Felis domesticus*	Fel d 2	Inhalation	–
Chicken	*Gallus domesticus*	Gal d 5	Ingestion/inhalation	–
Guinea pig	*Cavia porcellus*	Cav p 4	Inhalation	–