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Mammalian-derived respiratory allergens – Implications for diagnosis and therapy of individuals allergic to furry animals

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ABSTRACT

Furry animals cause respiratory allergies in a significant proportion of the population. A majority of all mammalian allergens are spread as airborne particles, and several have been detected in environments where furry animals are not normally kept. The repertoire of allergens from each source belongs to a restricted number of allergen families. Classification of allergen families is particularly important for the characterization of allergenicity and cross-reactivity of allergens. In fact, major mammalian allergens are taken from only three protein families, i.e. the secretoglobin, lipocalin and kallikrein families. In particular, the lipocalin superfamily harbours major allergens in all important mammalian allergen sources, and cross-reactivity between lipocalin allergens may explain cross-species sensitization between mammals. The identification of single allergen components is of importance to improve diagnosis and therapy of allergic patients using component-resolved diagnostics and allergen-specific immunotherapy (ASIT) respectively. Major disadvantages with crude allergen extracts for these applications emphasize the benefits of careful characterization of individual allergens. Furthermore, detailed knowledge of the characteristics of an allergen is crucial to formulate attenuated allergy vaccines, e.g. hypoallergens. The diverse repertoires of individual allergens from different mammalian species influence the diagnostic potential and clinical efficacy of ASIT to furry animals. As such, detailed knowledge of individual allergens is essential for adequate clinical evaluation. This review compiles current knowledge of the allergen families of mammalian species, and discusses how this information may be used for improved diagnosis and therapy of individuals allergic to mammals.

1. Introduction

Allergic diseases affect a significant fraction of the entire population in industrialized countries [1,2]. Domestic animals such as dogs, cats and horses are among the most common allergen sources [3,4], and both sensitization and ownership frequencies for cats and dogs have increased over the last decades [5–7]. In addition, exposure to animals such as mice, rats, guinea pigs, rabbits and cows have been shown to induce allergy. Particularly, sensitization to rodents represents a major health hazard to workers in animal facilities, where 20–30% of all animal workers become sensitized to mammalian allergens [8,9].

Mammalian allergens as inducers of airway symptoms have been frequently studied. Prominently, sensitization to the major cat allergen Fel d 1 has been implicated as a major risk factor for the development of asthma [10,11]. IgE-levels to mammalian allergens have been shown to correlate with an increased risk of developing new allergies in later childhood [12,13]. A recent study demonstrated that sensitization to several mammalian allergens was associated with bronchial inflammation in children with severe asthma [14]. This relationship was not observed in children with controlled asthma, indicating the major role of respiratory allergens in the development of severe IgE-mediated asthma.

Most allergens from furry animals are found in dust and on airborne particles in homes, but also in public facilities such as schools or day care centers [15–17]. It remains unclear whether early life exposure to cat or dog allergens increase the risk of developing pet allergy later in life [18,19]. Even though this matter has been addressed by several studies, the results are contradictive, and the outcome of early cat and dog ownership has been implicated as either protective [20], unaffected [21], or increasing the risk of developing asthma [22,23]. These studies are likely affected by a number of confounding factors, and further investigation is required to elucidate the variables responsible for the observed differences.

The common wish to have a cat or a dog among pet sensitized individuals has spurred several dog breeding companies to market

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"hypoallergenic cats" and "hypoallergenic dogs" that are supposed to have reduced allergenicity. Even though some cat and dog breeds may have a less grooming/shedding that could imply a reduced allergenicity, it is questionable whether certain breeds would express lower allergen levels as claimed. In fact, a recent study demonstrated higher expression of Can f 1 in hypoallergenic dog breeds than in "normal" breeds [24]. The diverse allergen panels of cats and dogs comprise to date eight and six allergens respectively and it is unlikely to envision animals with a defined allergen pattern, that would suite allergic patient' sensitization profile in general.

Since cloning of the first allergen from cDNAs in 1988–1989 [25,26], major focus has been towards completing the different panels of various allergen sources. Characterization of recombinant allergens from multiple furry animal species has contributed to improve diagnostics of allergic patients. In addition, single recombinant allergens may be used to formulate allergy vaccines to improve allergen-specific immunotherapy (ASIT) of allergic patients. The identification of single allergen components allows for classification of allergens into distinctive protein families. This might be particularly important when studying the mechanisms of allergenicity, since less than 2% of all protein families constitute known allergens, and proteins from the same family may share similar structural and functional characteristics [27]. Allergens within the same family may also display cross-reactivity, as demonstrated for the mammalian allergen families albumins [28,29], and lipocalins [30,31], discussed below. Cross-reactive allergens harbour similar three-dimensional structures and epitopes that may imply IgE-mediated cross-reactivity, and share similar T cell epitopes, which may translate into T cell mediated cross-reactivity. Clinically, cross-reactivity has implications for the induction of allergic symptoms, since allergic patients may suffer from hypersensitivity to allergen sources they have not encountered previously [32]. Additionally, features of cross-reactivity can be used to simplify diagnostics of related allergies, due to an abundance of shared epitopes between very similar allergens [33,34]. A strong association has been established between allergies to cat, dog and horse in children [3,35], the latter study showing that sensitization to horse alone (mono-sensitization) was uncommon, likely reflecting cross-reactivity between these allergen sources. The role of cross-reactive allergens in cross-sensitization to related mammalian allergen sources is still not fully elucidated. However, recognition of related cross-reactive allergens by antigen presenting cells and T cells is likely to increase the risk of neo-sensitization to that allergen.

Here, we discuss important aspects of allergen families and allergens from mammalian species. Furthermore, we review how recombinant allergens are used to improve diagnostics and treatment of individuals allergic to furry animals. A summary of respiratory allergens characterized to date of various furry animal species is presented in Table 1.

2. Allergen families of furry animals

2.1. Secretoglobin

Fel d 1, is the most important allergen in cat dander and has been extensively studied since its discovery in 1973 [36]. The protein is found in saliva and is transferred to the fur by grooming, and is spread to the environment predominantly via dander [37,38]. The role of Fel d 1 in cat allergy is very dominant, as it has been shown to account for 60–90% of the IgE reactivity to cat dander [39–41], and up to 95% of all cat allergic patients react to Fel d 1 [40,42,43]. It is a tetrameric protein, joined together by two heterodimers consisting of two disulphide linked peptide chains. The molecular weight of natural (n) Fel d 1 is approximately 38 kDa, while the recombinant (r) version has a molecular weight of 30 kDa [44,45]. The observed difference in molecular weight is probably due to 10–20% N-linked glycosylation on nFel d 1. By recombinant techniques, the two chains of Fel d 1 has been covalently fused and expressed as a folded polypeptide [44]. Importantly, the recombinant protein mimics the structure of the natural protein, which is the basis for maintained allergenicity. The T cell epitope repertoire of Fel d 1 has been studied [46,47], and surface epitopes have been identified with monoclonal antibodies [48–50].

Fel d 1 is special compared to other mammalian allergens by its very dominant role in cat allergy. A human homologue to Fel d 1, Clara cell protein CC16 has been described [51], but the biological role of Fel d 1 is unknown. In 2007, a paper was published describing a potential dog homologue of approximately 20 kDa detected in dander [52]. In several dog sensitized subjects, competitive inhibition with rFel d 1 adsorbed more than 50% of all dog-reactive IgE antibodies, indicating that a majority of all IgE antibodies to dog detected in those individuals could be directed towards a homologue. However, no sequence of the allergen was identified, and replication of this finding should be performed to ascertain the relevance of the described allergen. Recently, a novel secretoglobin protein was identified as a major allergens in rabbit, the lipophilin Ory c 3 [53]. The allergen was identified in rabbit hair by IgE-immunoblotting followed by mass-spectometry and N-terminal sequencing. Similarly as Fel d 1, Ory c 3 consists of two chains forming a heterodimeric allergen, and predictions indicated a similar structure as Fel d 1. The allergen bound IgE in 77% of rabbit allergic patients, and is reported as a major allergen. Despite the shared structural similarity, no cross-reactivity was detected between the allergens, possibly due to low sequence identity (~24%). As such, there is still little evidence to support a role for Fel d 1 in cross-reactivity with other mammalian sources.

2.2. Lipocalin

More than 50% of all allergens from all furry animals belong to the lipocalin superfamily. At least one major lipocalin allergen has been identified in every species, Table 1. Virtually all persons who are in contact with household pets, work in animal facilities or practise horse riding will be exposed to lipocalins. Allergen levels have been detected in facilities where pets are not normally kept [15]. As such, lipocalins hold a dominant position amongst mammalian allergens, and in most cases, the major allergens are lipocalins. As an example, the major allergen found in cow dander is the lipocalin Bos d 2 and is recognized by 80–90% of sensitized patients [54]. By its dominant role in cow dander allergy, it has been thoroughly characterized. The three-dimensional structure of Bos d 2 has been determined [55], and like other lipocalins, it contains a hydrophobic calyx for binding of small hydrophobic molecules. In the following sections, we discuss important lipocalin allergens of different furry animals and their implications for cross-reactivity and allergenicity.

2.2.1. Dog lipocalin allergens

Among dog sensitized patients we have identified a broad population that are sensitized to lipocalin allergens. Four out of six currently identified dog allergens, the major allergen Can f 1 (45–70% dog allergic patients sensitized), Can f 2 (~25%), Can f 4 (15–30%) and Can f 6 (~40%) are lipocalins, and the latter two were identified during recent years [31,56,57]. Can f 1 and Can f 2 is found mainly in saliva, but also in dander [58,59]. Both allergens were originally detected in dog dander extracts [56], and have been extensively investigated among dog allergens.