Cockroach, Tick, Storage Mite, and Other Arthropod Allergies: Molecular Aspects

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23.1 Introduction

Arthropods form an extensive phylum of the animal kingdom, comprising widely varying members such as insects, arachnids, chitin-exoskeleton animals (e.g., crabs, shrimp, and lobsters), and centipedes (◉ Fig. 23.1). The molecular-based diagnoses of the common house dust mite allergy and the hymenoptera venom allergy are discussed in ▶ Chaps. 16 and 19. The present chapter deals with rarer allergies to specific members of the arthropod kingdom. The extracts available for diagnostic purposes, as well as the currently known individual allergens, are presented, and their potential application in allergy diagnostics is discussed.

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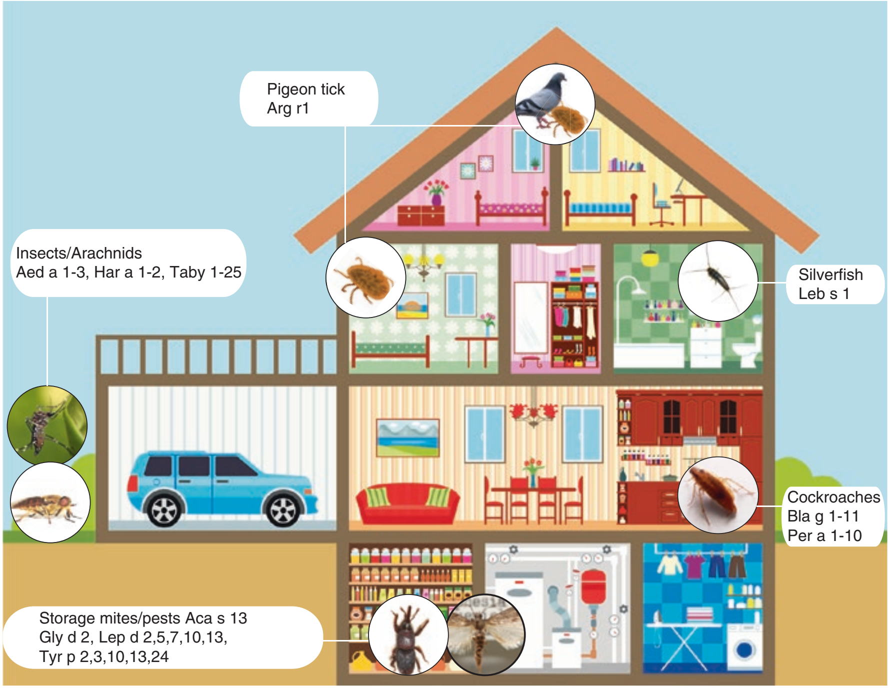

Fig. 23.1 Preferred habitats of various allergy-triggering arthropods in the house and garden, as well as their characterized allergens (© [M] mylisa/fotolia.com)

23.2 Cockroach Allergy

23.2.1 Exposure and Distribution

The cockroach order (Blattodea) comprises more than 4,600 species distributed worldwide. Most cockroaches are nocturnal and indigenous primarily to the tropics and subtropics. The domestic cockroaches best investigated as allergen sources include the German cockroach (*Blattella germanica*), which dominates in the USA in terms of numbers, as well as the American cockroach (*Periplaneta americana*) and the oriental cockroach (*Blatta orientalis*), which are common in South American and Asian countries. By infesting containers transported either by ship or air, the *Periplaneta fuliginosa* cockroach, which was originally indigenous only to Japan, Southeast Asia, and the Southern United States, has spread worldwide.

The frequency of cockroach allergies depends to a great extent on the level of exposure to cockroach allergens (Pomés and Arruda 2013). Allergen exposure in urban areas is as a whole significantly higher than in suburban areas, where, nevertheless, these allergens are found in up to 30 % of US households (Cohn et al. 2006; Matsui et al. 2003).

23.2.2 Allergen Identification

The official allergen database from the World Health Organization and International Union of Immunological Societies (WHO/IUIS) (www.allergen.org) includes German and American cockroach allergens from up to 12 different groups according to their molecular features and physiological functions (Pomés and Arruda 2013) (◉ Table 23.1). These allergens have been identified in feces, eggs, and exoskeletons. Homologous, possibly cross-reactive allergens have been described in other cockroach species.

Table 23.1 Single allergens of the German and American cockroaches identified according to the WHO/IUIS Allergen Nomenclature Sub-committee

Allergen	Name	Molecular weight (kDa)
Blattella germanica[a, c–f] (German cockroach)		
Bla g 1[b]	Midgut microvilli protein homolog	25–90
Bla g 2[b]	Aspartic protease	36
Bla g 3	Hemocyanin	78.9
Bla g 4	Calycin	21
Bla g 5[b]	Glutathione S-transferase	23
Bla g 6	Troponin C	17
Bla g 7[b]	Tropomyosin	33
Bla g 8	Myosin light chain	_
Bla g 11	α-Amylase	57
Periplaneta americana[a, c, d] (American cockroach)		
Per a 1	Midgut microvilli protein homolog	25–45
Per a 2	Aspartic protease-like	42
Per a 3	Arylphorin/hemocyanin	46–79
Per a 6	Troponin C	17
Per a 7	Tropomyosin	33
Per a 9	Arginine kinase	43
Per a 10	Serine protease	28

(continued)

Table 23.1 (continued)

Allergen	Name	Molecular weight (kDa)
Per a 11	α-Amylase	55
Per a 12	Chitinase	45

[a]ImmunoCAP®, Phadia/ThermoScientific and Siemens Healthcare, Freiburg, Germany
[b]ImmunoCAP® ISAC, Phadia/ThermoScientific and Siemens Healthcare, Freiburg, Germany
[c]3gAllergy™/Immulite, Siemens Healthcare, Eschborn, Germany
[d]ALLERG-O-LIQ®, Dr Fooke Laboratorien GmbH, Neuss, Germany
[e]Allergozyme®, Omega Diagnostics, Reinbek, Germany
[f]Allercoat™, EuroImmun, Lübeck, Germany

23.2.3 Function and Structure

Some cockroach allergens are proteins associated with the digestive tract and presumably contribute to digestion, e.g., Bla g 1/Per a 1 (midgut proteins), Per a 9 (arginine kinase), Per a 10 (serine protease), and Bla g 11 (α-amylase) (Pomés et al 1998; Jeong et al. 2013; Suazo et al. 2009: Sudha et al. 2008; Yu et al. 2003). The basic structural unit of Bla g 1 has been determined and forms a spherical capsule with a large cavity that contains lipids (Mueller et al. 2013). This structure facilitated the standardization of assays in absolute units for the assessment of environmental allergen exposure.

Other cockroach allergens are involved in muscle contraction. These include Bla g 6/Per a 6 (troponin C), Bla g 7/Per a 7 (tropomyosin), and Bla g 8 (myosin light chain) (Hindley et al. 2006; Jeong et al. 2004). Bla g 6 and Per a 6 belong to the family of EF-hand proteins. They bind calcium ions via α-helices made up of 12 amino acids. Bla g 7 and Per a 7 are tropomyosins, consisting of two intertwined helical molecules. Myosin light chains are small, calcium-binding subunits of the high-molecular-weight myosin complex, which are associated with the heavy chains in a helical configuration (Messer and Kendrick-Jones 1988).

The biological function of the cockroach allergen Bla g 2 has not yet been elucidated. Analysis of the crystal structure demonstrated that the molecule is an inactive aspartic protease that preserves the typical fold of this group of enzymes (Wünschmann et al. 2005). Five disulfide bridges, as well as a binding site for the cofactor zinc, contribute to the stability of this allergen (Gustchina et al. 2005; Li et al. 2008).

The allergens Bla g 3 and Per a 3 are hemocyanins, the arthropod homolog of hemoglobins, responsible for oxygen transport (Mindykowski et al. 2010). Oxygen binding in hexameric cockroach proteins is coordinated via one copper ion per monomer.

The cockroach-specific protein, Bla g 4, belongs to the lipocalin family, which includes important inhalant allergens from dog (Can f 1, Can f 2), cat (Fel d 4), horse (Equ c 1, Equ c 2), and cow (Bos d 2, Bos d 5) (Hilger et al. 2012). Bla g 4 appears to be involved in reproduction as a transport molecule for low-molecular-weight hydrophobic compounds (Fan et al. 2005). Analysis of the crystal structure showed that it has a fold typical for lipocalins: a funnel-shaped structure that is closed off with a lid-like molecule following ligand binding (Tan et al. 2009).

As a glutathione S-transferase, the allergen Bla g 5 is biologically active and thought to be involved in metabolic detoxification processes (Arruda et al. 1997). IgE cross-reactivity was found between Bla g 5 and a GST homolog from glutathione S-transferase of *Wuchereria bancrofti*, a major lymphatic filarial pathogen of humans, despite a low amino acid identity between both proteins (30 %). This low degree of cross-reactivity was attributed to a similar N-terminal linear epitope (Santiago et al. 2012). Recently, the structures of Bla g 5, the homologs Der p 8 and Blo t 8 from mites, and the Ascaris allergen Asc s 13 were determined and compared. A low similarity at the level of the molecular surface explains the low cross-reactivity observed among these allergens in patients from temperate areas (Mueller et al. 2015).

23.2.4 Relevance and Sensitization Frequency

Cockroach allergen sensitization is one of the greatest risk factors for high asthma-related morbidity among the low-income population in the USA, with the greatest prevalence in densely populated inner city housing (Gruchalla et al. 2005). Sensitization rates in Europe are generally far lower (Raulf et al. 2014). A study by Hirsch et al. (2000) found that only 4.2 % of approximately 3000 children studied in Dresden, Germany, had specific IgE (>0.7 kU/l) to the German cockroach (*Blattella germanica*), although the prevalence of sensitization among asthmatic children was 6.1 %. Most cockroach-sensitized children in this study were also sensitized to other allergens. Also, in a study carried out at several European centers, where skin tests were performed using various indoor and outdoor allergens in over 3,000 patients, an overall prevalence of sensitization of 8.9 % was found to *Blattella germanica*; the rate was 12 % in German patients (Heinzerling et al. 2009).

The prevalence of specific IgE antibodies to single cockroach allergens varies significantly, a phenomenon that appears to depend on regional exposure (Barbosa et al. 2013; Sohn and Kim 2012). The major allergens are found in the protein groups 1–5 (Bla g 1–5). Since group-1 and group-2 cockroach allergens (Bla g 1 and Bla g 2) are released into the environment, they serve well as markers for the assessment of cockroach allergen exposure (Pomés and Arruda 2013).

23.2.5 Cross-Reactive Allergens

Homologous allergens from different cockroach species, e.g., Bla g 1 and Per a 1, exhibit high but variable cross-reactivity. The tropomyosins, Bla g 7 and Per a 7, as well as arginine kinase (Per a 9), are quite similar to the homologous allergens of other arthropods (>80 % identity). The clinical significance of IgE cross-reactivity between tropomyosins and arginine kinases of cockroaches, chitin-skeleton arthropods, and house dust mites has not yet been fully elucidated (Binder et al. 2001; Wang et al. 2011).

23.3 Storage Mite Allergy

23.3.1 Exposure and Distribution

Storage mites, microscopic arachnids, which feed on plant and animal matter, are typical storage (pertaining to their feeding on stored foodstuffs) pests. Depending on the species, they are found in grain and animal feed, including hay, as well as in straw. The storage mites most commonly found in Europe include *Lepidoglyphus destructor*, the flour mite *Acarus siro*, *Glycyphagus domesticus*, and the mold mite *Tyrophagus putrescentiae*. The latter has a predilection for foods containing protein and fat, such as ham or cheese. All species thrive at temperatures of 20–30 °C and at a relative humidity of >65 % (Fernández-Caldas et al. 2007; Franz et al. 1997; vanHage-Hamsten and Johansson 1998).

23.3.2 Allergen Identification

The groups of allergens listed in the allergen database are shown in ◉ Table 23.2 and include the panallergen tropomyosin (Lep d 10, Try p 10). However, with an IgE prevalence around 13 %, tropomyosin is a minor allergen. Allergens have been identified in carcasses as well as in feces. The major allergen belongs to group 2 (Lep d 2, Tyr p 2, and Gly d 2) and has been found in mite intestine; its function, however, is unknown.

23.3.3 Relevance

Airborne storage mite allergies frequently affect mainly farmers and individuals working in the animal-feed industry. Symptoms include allergic rhinitis and, eventually, bronchial asthma. Isolated cases of oral dust mite allergy have been described. Severe allergic symptoms occurred following the ingestion of flour-based foods baked using contaminated ingredients (Sánchez-Borges et al. 2013). These reports related to contamination with storage mites as well as with house dust mites.

23.3.4 Cross-Reactive Allergens

Although there is strong serological cross-reactivity between extracts from different species of storage mites (flour, stored food, mold), there is little IgE cross-reactivity between house dust and storage mites.

Table 23.2 Single allergens of storage mites identified according to the WHO/IUIS Allergen Nomenclature Sub-committee

Allergen	Name	Molecular weight (kDa)
Acarus siro[a, c–f] (Flour mite)		
Aca s 13	Fatty acid-binding protein	15
Glycophagus domesticus[a, c–f] (House mite)		
Gly d 2		15
Lepidoglyphus destructor[a, c–f] (Storage mite)		
Lep d 2[b]	NPC2 family	16
Lep d 5		
Lep d 7		
Lep d 10	Tropomyosin	
Lep d 13	Fatty acid-binding protein	
Tyrophagus putrescentiae[a, c–f] (Mold mite)		
Tyr p 2	NPC2 family	16
Tyr p 3	Trypsin	26
Tyr p 10	Tropomyosin	
Tyr p 13	Fatty acid-binding protein	15
Tyr p 34	Troponin C	18

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Diagnostic assays providing (molecular) allergens from the indicated source:
[a]ImmunoCAP®, Phadia/ThermoScientific and Siemens Healthcare, Freiburg, Germany
[b]ImmunoCAP® ISAC, Phadia/ThermoScientific and Siemens Healthcare, Freiburg, Germany
[c]3gAllergy™/Immulite, Siemens Healthcare, Eschborn, Germany
[d]ALLERG-O-LIQ®, Dr Fooke Laboratorien GmbH, Neuss, Germany
[e]Allergozyme®, Omega Diagnostics, Reinbek, Germany
[f]Allercoat™, EuroImmun, Lübeck, Germany

Co-sensitizations appear to be common. Group-2 allergens, in particular (Lep d 2 and Gly d 2), exhibit high sequence identity. The tropomyosin from storage mites (Lep d 10) has a high degree of identity with Der f 10 and Der p 10 in house dust mites, supporting the known cross-reactivity.

23.4 Tick Allergy

23.4.1 Exposure and Distribution

Cases of anaphylactic reactions to pigeon ticks have been consistently reported in recent years, most notably in France, Poland, and Italy but also in Germany

(Hilger et al. 2005; Kleine-Tebbe et al. 2006). The pigeon tick (*Argas reflexus*), which belongs to the soft tick family, is a temporary ectoparasite of wild pigeons in Southern and Central Europe. It feeds primarily nocturnally on blood from its host and seeks refuge in wall crevices and wood cracks during the day. If the pigeon does not return to its nest, the tick will seek new hosts by invading homes, where it infests humans. Adult ticks can be dormant for several years without food and are extremely challenging to combat. In addition to the severe anaphylactic reactions described in the literature, there are also many instances of mild local reactions. A study carried out in Leipzig found an 8 % rate of severe systemic reactions and a 99 % rate of local reactions in subjects with pigeon tick bites (Kleine-Tebbe et al. 2006).

In addition to pigeon ticks, isolated cases of classic immediate-type reactions have been described following bites from the common wood tick (*Ixodes ricinus*), the Australian paralysis tick (*Ixodes holocyclus*), and the brown dog tick (*Rhipicephalus sanguineus*), which is found primarily in Southern Europe. Such cases involve an IgE-mediated reaction to protein in tick saliva.

A specific form of allergy, the delayed red meat allergy, is also associated with tick bites. This allergy involves IgE sensitization to a sugar epitope, galactose-α-1.3-galactose, which is believed to be triggered by tick bites (Commins et al. 2011). While in the USA the American Lone Star tick (*Amblyomma americanum*) and in Australia the Australian paralysis tick (*Ixodes holocyclus*) are discussed as allergy triggers, the wood tick (*Ixodes ricinus*) and Dermacentor ticks (*Dermacentor*) are associated with sensitization to galactose-α-1.3-galactose in Europe (Steinke et al. 2015).

23.4.2 Allergen Identification

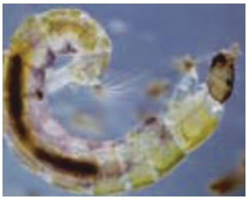
Like the cockroach allergen Bla g 4, the major allergen Arg r 1 from the pigeon tick belongs to the lipocalin family. Arg r 1 is a histamine-binding salivary protein. The crystal structure has been determined in complex with its ligand histamine (PDB code 2X45). The overall structure is that of a lipocalin. However, cross-reactivity within this group of proteins is most likely low or absent, since the structure (as well as the amino acid sequence) of the tick protein differs significantly from other allergenic lipocalins.

Galactose-α-1.3-galactose, the tick allergen epitope relevant in delayed red meat allergy, is a significant component of bovine thyroglobulin. Galactose-α-1.3-galactose in bovine thyroglobulin is available for the diagnosis of galactose-α-1.3-galactose sensitization in the ImmunoCAP system.

23.5 Allergies to Other Arthropods

Rarely, a variety of other arachnids and insects can cause allergies (Raulf et al. 2015) (◉ Table 23.3). Individuals who work in barns or stables, where spiders are found in abundance, can experience allergic reactions to the spiders themselves as well as to their cobwebs. Salivary proteins from mosquitoes and horseflies cause

Table 23.3 Single allergens from other arthropods identified according to the IUIS Allergen Nomenclature Sub-committee

Allergen	Name	Molecular weight (kDa)
Aedes aegypti (yellow fever mosquito), *Aedes* spp., *Culex pipiens* (common house mosquito)[a, c–f]		
Aed a 1	Apyrase	68
Aed a 2	Salivary D7 protein	37
Aed a 3	Undefined 30 kDa salivary protein	30
Aed a 4	α-Glucosidase	67
Aed a 5	Sarcoplasmic Ca+(EF-hand)-binding protein	
Aed a 6	Porin 3	
Aed a 7		
Aed a 8	Heat shock cognate protein-70	
Aed a 10	Tropomyosin	32
Aed a 11	Lysosomal aspartic protease	
Argas reflexus[e] (Pigeon tick)		
Arg r 1	Lipocalin	17
Chironomus thummi thummi[a, c–f] (Red chironomid larvae)		
Chi t 1	Hemoglobin component III/IV	16
Chi t 2	Hemoglobin component I/IA	16
Chi t 3	Hemoglobin component II-β, VI, VIII, IX	16
Chi t 4	Hemoglobin component IIIA	16
Chi t 9	Hemoglobin component X	16

(continued)

Table 23.3 (continued)

Allergen	Name	Molecular weight (kDa)
Harmonia axyridis (Ladybug)		
Har a 1		10
Har a 2	Aldehyde dehydrogenase	55
Lepisma saccharina (Silverfish)		
Lep s 1	Tropomyosin	36
Tabanus yao, *Tabanus* spp.[a, c–f] (Horsefly)		
Tab y 1	Apyrase	70
Tab y 2	Hyaluronidase	35
Tab y 5	Antigen 5-related protein	26

[a]ImmunoCAP®, Phadia/ThermoScientific and Siemens Healthcare, Freiburg, Germany
[b]ImmunoCAP® ISAC, Phadia/ThermoScientific and Siemens Healthcare, Freiburg, Germany
[c]3gAllergy™/Immulite, Siemens Healthcare, Eschborn, Germany
[d]ALLERG-O-LIQ®, Dr Fooke Laboratorien GmbH, Neuss, Germany
[e]Allergozyme®, Omega Diagnostics, Reinbek, Germany
[f]Allercoat™, EuroImmun, Lübeck, Germany

strong local allergic reactions of varying severity and, more rarely, systemic reactions (Ma et al. 2011; Simons and Peng 2001). Other insects can cause allergies in areas of the world that they infest (silkworm, pharaoh ant, Indian meal moth, pine processionary, caddisflies, etc.) (Pomés 2014).

To date, ten allergens from the *Aedes aegypti* mosquito are listed in the WHO/IUIS Allergen Database, including Aed a 1, an apyrase (68 kDa), Aed a 2 (37 kDa), and Aed a 3 (30 kDa), of as yet unknown function, tropomyosin Aed a 10 (32 kDa), and lysosomal aspartic protease (Aed a 11) (Simons and Peng 2001) (◉ Table 23.3).

Three major allergens have been identified to date from the horsefly (*Tabanus spp.*): Tab y 1, an apyrase; Tab y 2, a hyaluronidase; and Tab y 5, an antigen-5 protein (Ma et al. 2011). The last two show cross-reactivity with hyaluronidase and antigen 5 of the Vespidae family (An et al. 2012) and offer an explanation for presumed cross-reactions between wasp venom and horsefly saliva.

Table 23.4 Available storage pest extracts

Species name	Common English name
Ephestia kuehniella[a, c, e] 	Mediterranean flour moth
Sitophilus granarius[a, e] 	Wheat weevil
Tenebrio molitor[a] 	Mealworm beetle
Tribolium confusum[a, d–f] 	Confused flour beetle
Trogoderma angustum[a, e, f] 	Berlin beetle

[a]ImmunoCAP®, Phadia/ThermoScientific and Siemens Healthcare, Freiburg, Germany
[b]ImmunoCAP® ISAC, Phadia/ThermoScientific and Siemens Healthcare, Freiburg, Germany
[c]3gAllergy™/Immulite, Siemens Healthcare, Eschborn, Germany
[d]ALLERG-O-LIQ®, Dr Fooke Laboratorien GmbH, Neuss, Germany
[e]Allergozyme®, Omega Diagnostics, Reinbek, Germany
[f]Allercoat™, EuroImmun, Lübeck, Germany

The red chironomid midge larvae (*Chironomus thummi thummi*) are popular as fishing bait and are known to trigger allergic respiratory symptoms in individuals working in fish food manufacture and in hobby-related aquarists (Baur and Liebers 1992). Their various hemoglobin components are recorded in the WHO/IUIS database as allergens Chi t 1–9.

The silverfish (*Lepisma saccharina*) is found primarily in kitchens, bathrooms, and cellars. In the case of high levels of infestation, allergens may be present in house dust. The tropomyosin Lep s 1 is the only known allergen to date. It exhibits cross-reactivity with tropomyosin of other arthropods, such as the house dust mite, the cockroach, and the shrimp (Barletta et al. 2005).

The multicolored Asian ladybug (*Harmonia axyridis*) was introduced in the USA between 1916 and 1990 to control aphids. Since then, ladybugs produce infestations, as they swarm out and invade houses and other buildings in their hundreds in order to hibernate. They have become a new and significant source of seasonal indoor allergens in the USA (Nakazawa et al. 2007). Extract-based diagnosis of ladybug allergy showed high cross-reactivity with cockroach extract (Nakazawa et al. 2007). Two major allergens have been identified to date: Har a 1 (10 kDa), a protein believed to be specific for ladybug sensitization, and Har a 2 (55 kDa), a protein related to the aldehyde dehydrogenase of the red flour beetle (Nakazawa et al. 2007).

Storage pests, such as the wheat weevil (*Sitophilus granarius*), the rice weevil (Kleine-Tebbe et al. 1992), the mealworm beetle (*Tenebrio molitor*), the confused flour beetle (*Tribolium confusum*), the Berlin beetle (*Trogoderma angustum*) (Kleine-Tebbe et al. 1983), and the Mediterranean flour moth (*Ephestia kuehniella*), have also been described as allergen sources (◉ Table 23.4). Since these storage pests are found primarily in stored grain, occupational groups such as farmers, bakers, millers, and grain storage workers are particularly affected and, depending on the duration of exposure, can develop allergic rhinitis and, eventually, bronchial asthma (Raulf et al. 2014). It has not been possible as yet to include any IgE-binding proteins from these sources in the WHO/IUIS allergen database.

23.6 Diagnostics and the Added Benefit of Molecular-Based Diagnosis

Routine diagnosis of the rarer allergies to arthropods is accomplished by means of skin testing or specific IgE antibody detection using extracts. At present, extracts from three cockroach species (*Periplaneta americana*, *Blatella germanica*, and *Blatta orientalis*), four storage mite species (*Lepidoglyphus destructor*, *Acarus siro*, *Glycyphagus domesticus*, and *Tyrophagus putrescentiae*), and a number of storage pests (*Sitophilus granarius*, *Tribolium confusum*, *Trogoderma angustum*, and *Ephestia kuehniella*) are available from a variety of manufacturers for in vitro diagnostic purposes. *Argas reflexus* extract from the pigeon tick is available only from Omega Diagnostics, Reinbeck, Germany. However, a clinical history can provide a strong indication of pigeon tick allergy: nighttime tick bite, typically during the warm months and in the vicinity of pigeon breeding sites. Allergen components

(Lep d 2, Bla g 1, Bla g 2, Bla g 5, and Bla g 7) are only available as yet in the ISAC test system (Thermo Scientific), but not in the ImmunoCAP system.

One advantage of molecular-based diagnostics (Matricardi et al. 2016) is that it employs standardized reagents, because both the protein and allergen content in commercial extracts vary, as previously demonstrated for cockroach extracts (Patterson and Slater 2002). The use of extracts also bears the risk of cross-reactivity with related arthropod species (Raulf et al. 2014). Since the IgE-binding profiles of patients vary not only on an individual but also on a geographic basis, the goal should be to make as complete a range of standardized allergens as possible available for diagnostic purposes (Barbosa et al. 2013; Matricardi et al. 2016).

23.7 Treatment and Diagnostic Outlook

Preparations for specific immunotherapy are currently available for storage mite allergy only in Germany. Studies on subcutaneous and sublingual immunotherapy of cockroach allergy are currently underway in the USA (Wood et al. 2014), and the results are promising.

Given that a variety of arthropod allergens (e.g., cockroach, tick, and storage mite) are already well characterized and for the most part available as recombinant molecules, the way has been paved for the development of IgE-based diagnostic tests using individual allergen components.

Conclusions

Although not well standardized, the available extracts permit IgE-based diagnosis of allergies to cockroaches, storage mites, and storage pests. A future broadening of IgE-based diagnostics with individual allergens would be beneficial.

An important goal for further developments in molecular testing systems should be the use of marker allergens for the unequivocal detection of sensitization and differentiation from cross-reactions. Marker allergens for tick sensitization, such as Arg r 1 from the pigeon tick, could be used to exclude pigeon tick allergy in cases of unexplained anaphylaxis.

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