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Minireview Article

Venom allergens in the venom of venomous animals

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ABSTRACT

Today allergens are known as molecules that induce an IgE-mediated reaction (allergy) in human beings. Protein is one of the most important molecules that could be the allergen. Allergens sources are varied from plants, animals, and fungi to microbial and even viral sources. Melittin, phospholipase A2, hyaluronidase and venom allergen-5 are most important venom allergens in hymenoptera family. The various components are identified as the venom allergens in scorpions and snakes venoms. VAH (Vespid allergen antigen homolog) and ASP (Aspergillus allergen) are two venom allergens group detected in nematode parasites. Recognition of venom allergens and their immune responses is the first step to avoid the animal-related allergic diseases and prevent anaphylactic shock.

***Keywords*:** Venom allergens, venom of toxic animals, anaphylactic death

INTRODUCTION

In recent years, significant progress is made on molecular characterization of allergen. Their sequences are determined by molecular and biochemical methods. Isoallergens are allergen from a species that have similarity in following molecular features: molecular size, biologic function, and more than 67 % identity in their amino acid sequences.

Allergens can belong to the wide set of sources. Plants, animals, fungi, microbial and viral elements are some example of allergen sources [1]. Allergen sources could be

categorized in some groups such as foods, environmental elements, and toxins (venoms). Protein is one of the most important molecules that could be the allergen. Up to now, hundreds of allergens features are characterized. Results show that five percent of 3012 of proteins families contained allergens. Main biochemical functions of allergens include: 1) hydrolysis of all type of molecules include: proteins, polysaccharides, and lipids; 2) binding to some ligands such as metal ions or lipids; 3) storage; and 4) cytoskeleton association [2].

Arthropods and their products could lead to allergy in humans as an allergen. This allergic reactions range could be from a medium annoyance to an anaphylactic shock and death [3]. Venomous animals also can cause death. Hornets, wasps, and bees are responsible for 28.2 % of all deaths in the USA. For Examples snakes, spiders and scorpions are the most venomous animals in the USA [4]. Pet, house dust mites or their feces could be other sources of allergen [5].

Historical evidence from early Greek describes the ill effects of Lepidoptera larvae or caterpillar extract. Ways that an arthropod and its products can be introduced to the victim body includeing (a) direct contact or inhalation of airborne material (b) bite, (c) sting and (d) ejection of its secretions [3]. Many hymenopteras could be able to sting. However, three species of Apidae (bees), Formicidae (ants) or Vespidae (wasps) sting more. One of the smallest bee venom allergens is melittin which has 26-residue and is responsible for one-third of bee-allergies [6]. There is much venom allergen in the venom of Hymenoptera species. The sequences and structures of nearly all of them have been determined. In honey bee (*Apis melifera)* venom, there are five allergens called Api m (Api m 1-5). Api m1 is a phospholipase A2, Api m 2 is a hyaluronidase, Api m 3 is an acid phosphatase and Api m 4 is melittin. Hyaluronidases and phospholipase A2 known as major allergens. Bumble bee (*Bombus pennsylvanicus)* has two venom allergens. Bom p 1 is a phospholipase A and Bom p 4 is a protease. Many allergens detected in white-faced hornet (*Dolichovespula maculate)* venom. For example, Dol m 1 is a phospholipase A1, Dol m 2 is a hyaluronidase or Dol m 5 is an Antigen 5. Two allergens are detected in European hornet (*Vespa crabo)* venom. First one is Vesp c 1 which is a phospholipase A1 and second is Vesp c 5 that is an antigen 5. There are three venom allergens in the venom of *Vespa tropica.* VesT1s is a phospholipase A1 and known as major allergens. Paper wasp (*Polistes annularis)* has five allergens.

Pol a 1 is a phospholipase A1, Pol a 2 is a hyaluronidase and Pol a 5 is an antigen 5. Pol d 3 is a dipeptidyl peptidase IV that found in *Polistes dominula* venom and is a major allergen. Three known allergens of yellow (*Vespula vulgaris*) are Ves v 1 that is a phospholipase A1, Ves v 2 that is a hyaluronidase and Ves v 5 that is an antigen 5. These three venom allergens have cross-reactivity with their homologs allergen in hornet and wasp. In fire ant (*Solenopsis invicta)* venom, five allergens were found. Sol i 1 is a phospholipase A1 and Sol i 3 is an antigen 5. *Myremcia pilosula* has one allergen named Myr p 1in its venom [6-10]. Blank et al. in 2010 identified that Api m 5 from *Apis mellifera* is homologues with Ves v 3 from *Vespula vulgaris* and both are DPPIV (dipeptidyl peptidase IV). Api m 5 and Ves v 3 are major allergens and both are to identity to human DPPIV or CD26 [11]. Till recent years just rApi m1 (recombinant Api m) as a major allergen was available on the ImmunoCAP system for treatment and diagnosis of bee venom (BV) allergy. However, nowadays five novel new recombinants components (rApi m 1, 2, 3, 5, and 10) whit high sensitivity and specificity are reachable for BV- allergic patients [12]. Ts4 (also named TsTX-VI, Tityustoxin-6, Tityustoxin VI, Toxin VI, and TsNTxP) is one of the *Tityus serrulatus* venom toxins. TsTX-VI can induce an IgE-mediated allergic reaction [13,14]. A comprehensively study on Australian scorpions (*Urodacus yaschenkoi*) venom gland transcriptome performed by Ramírez et al. in 2015. Two percent of its coding transcriptome was venom allergens. Two venom allergen sequences (comp4029_c0_seq1 and comp4170_c0_seq1) were found that had similarities with CAP-Uro-1 and CAP-Uro-2 of *U. manicatus* scorpion [15].

Thirteen venom allergen sequences were detected in the venom gland transcriptome of the Enigmatic Scorpion, *Superstitionia donensis*. Component sdc13900_g1_i1 encoding seven putative CAP peptides include allergens. Two components had about 25 % identity with the venom allergen-5 of the *Stegodyphus mimosaroum,* and one component had 55% similarity with putative scp tpx 1 ag5 pr1 of *Ixodes ricinus* venom allergens [16]. *Centruroides limpidus* is one of the most dangerous scorpions in Mexico. Jimena Isaias et al. in 2016 made a comparative proteomic analysis on female and male *C. limpidus* venom. Results validate present of a venom allergen, B2D0J4 belongs to serine protease family in both sex venom samples [17]. Kazemi et al. made a whole transcriptome study on *Hemiscorpius lepturus* in 2017. Results showed that seven sequences of *H. lepturus* transcriptome were

related to allergens (HLAllergen1-7). They showed similarity with other scorpion allergens. For example, HLAllergen1 had 34 % identity to venom allergen-5 of *T. serrulatus* (Brazilian scorpion) [18]. Yujing Hu et al. in 2017 identified nine potential allergens in *Protobothrops mucrosquamatus* venom. Six venom allergen sequences showed similarity to snake serine proteinases and other three allergens had similarity to snake metalloproteinase [19]. Expression of venom allergens were reported in many nematode parasites and depend on species called venom allergen antigen homologue (VAH) or *Ancylostoma* secreted protein (ASP). VAH/ASP family involves two major groups in *Ancylostoma caninum*: *Ac*-ASP-1 and *Ac*-ASP-2. VAH/ASP gene family detected in many other nematode species. In *Haemonchus contortus*, two component, Hc40 and Hc24 as allergens were identified. In *Brugia malayi* VAL-1, is a homolog of VAH/ASP [20] (Table1).

CONCLUSION

Allergens are molecules that could be induced sensitization of the host by induction of type 2 immune responses (Th2 immune responses that cause to the secretion of venom-specific Immunoglobulin E (IgE) [29]. Allergens sources are varied from plants, animals, and fungi to microbial and even viral sources [1]. Allergen source type also can be categorized in some groups like foods, environmental elements, and venoms. Protein is one of the most important molecules that could be the allergen [2]. Many allergens components were identified in the venom of toxic animals like arthropods, snakes, and nematodes [3,4,20]. Melittin, phospholipase A2, hyaluronidase and venom allergen-5 are most important venom allergens in hymenoptera family [6]. Various components were identified as the venom allergens in scorpions [15-18] and snakes venoms [19]. VAH (Vespid allergen antigen homolog) and ASP (Aspergillus allergen) are two venom allergens group detected in nematode parasites [29]. Given to importance of animals on the health of over 7 billion people around the world make the necessity of recognition of venom allergens and their immune responses as the first step, to avoid the animal-related allergic diseases and prevent anaphylactic death.

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Table 1. Venom allergens and its sources, functions, and biological allergic effects

Allergen Familly	Immiono Risponse	Sources Animal	Allergen Molecule
Phospholipase A1	Inducing of platelet aggregation, smooth muscle contraction, and stimulation of cell proliferation. platelet activation [21]. hydrolysis of the plasma membrane phospholipids, formation of edema [22].	*Vespa crabo* *Vespa tropica* *Dolichovespula maculate* *Polistes annularis* *Vespula vulgaris* *Solenopsis invicta*	Vesp c1 Ves T1 Dol m1 Pol a1 Ves v1 Sol i1
Phospholipase A2	IgE-mediated allergic reaction: enhanced mucus secretion, bronchoconstriction, and increased vascular permeability. systemic anaphylactic symptoms [23]. hydrolysis of the plasma membrane phospholipids, formation of edema [22].	*Apis melifera* *Bombus pennsylvanicus*	Api m1 Bom p1
Hyaluronidase	IgE-mediated allergic reaction: increased vascular permeability [24] . hydrolyzes hyaluronic acid, facilitating the penetration of the venom components into the cells [22].	*Apis melifera* *Dolichovespula maculate* *Polistes annularis* *Vespula vulgaris*	Api m2 Dol m 2 Pol a2 Ves v2
Acid phosphatase	Releaser the histamine from basophils. immediate-type wheal and flare in the skin [25]	*Apis melifera*	Api m3
Melittin	Lytic agent for cells. function as an ion channel. effects on intracellular calcium and interacts with calmodulin [26]	*Apis melifera*	Api m4
Dipeptidyl peptidase 4	IgE-mediated allergic reaction: activation of human basophils [11].	*Apis melifera* *Polistes dominula*	Api m5 Pol d 3
Serin Protease	Fibrin(ogen)olytic activity that functions as a prothrombin activator [27].	*Bombus pennsylvanicus* *Centruroides limpidus* *Protobothrops mucrosquamatus*	Bom p4 B2D0J4 --
CAP peptides	Unknown biological function .may be associated with hypersensitivity responses [22]. specific to IgE and IgG [28] .	*Stegodyphus mimosaroum*	sdc13900_g1_i1
Antigen 5	Belongs to CAP superfamily. unknown biological function .may be associated with hypersensitivity responses [22]. specific to IgE and IgG [28] .	*Dolichovespula maculate* *Vespa crabo* *Polistes annularis* *Vespula vulgaris* *Solenopsis invicta*	Dol m5 Vesp c5 Pol a5 Ves v5 Sol i3
VAH/ASP	Producing high levels of IgG3 and IgG4. IL-4 and IFN-γ [20].	*Brugia malayi* *Haemonchus contortus* *Ancylostoma caninum*	VAL-1 Hc24,40 Ac ASP1-2
Other unclassified molecules	Uncompleated data	*Hemiscorpius lepturus* *Ixodes ricinus* *Urodacus yaschenkoi* *Urodacus yaschenkoi* *Stegodyphus mimosaroum* *Myremcia pilosula* *Tityus serrulatus*	HL Allergen1 tpx 1 ag5 pr1 comp4029_c0 comp4170_c0 Venom allergen5 Myr p1 Ts4

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REFERENCES

[1]. King TP, Hoffman D, Lowenstein H, Marsh DG, Platts-Mills TA,Thomas W. Allergen nomenclature. *Allergy*, 1995; 50(9): 765-74.

[2]. Radauer C, Bublin M, Wagner S, Mari A,Breiteneder H. Allergens are distributed into few protein families and possess a restricted number of biochemical functions. *J Allergy Clin Immunol*, 2008; 121(4): 847-52.

[3]. Wirtz R. Allergic and toxic reactions to non-stinging arthropods. *Annu Rev Entomol*, 1984; 29(1): 47-69.

[4]. Scanes CG. Animals and human disease: zoonosis, vectors, food-borne diseases, and allergies, in animals and human society, *Elsevier*; 2018:331-54.

[5]. Nadchatram M. House dust mites, our intimate associates. *Trop Biomed*, 2005; 22(1): 23-37.

[6]. Spangfort MD. Structure and biology of stinging insect venom allergens. *Int Arch Allergy Immunol*, 2000; 123(2): 99-106.

[7]. Marković-Housley Z, Miglierini G, Soldatova L, Rizkallah PJ, Müller U,Schirmer T. Crystal structure of hyaluronidase, a major allergen of bee venom. *Structure*, 2000; 8(10): 1025-35.

[8]. Schiener M, Hilger C, Eberlein B, Pascal M, Kuehn A, Revets D, Planchon S, Pietsch G, Serrano P,Moreno-Aguilar C. The high molecular weight dipeptidyl peptidase IV Pol d 3 is a major allergen of Polistes dominula venom. *Sci Rep*, 2018; 8(1): 1318.

[9]. Müller U. Recombinant hymenoptera venom allergens. *Allergy*, 2002; 57(7): 570-76.

[10]. Lu G, Gonzalez M, Qian N,Soldatova L. Yellow jacket venom allergens, hyaluronidase and phospholipase: sequence similarity and antigenic cross-reactivity with their hornet and wasp homologs and possible implications for clinical allergy. *J Allergy Clin Immunol*, 1996; 98(3): 588-600.

[11]. Blank S, Seismann H, Bockisch B, Braren I, Cifuentes L, McIntyre M, Rühl D, Ring J, Bredehorst R,Ollert MW. Identification, recombinant expression, and characterization of the 100 kDa high molecular weight Hymenoptera venom allergens Api m 5 and Ves v 3. *The*

Journal of Immunology, 2010; 184(9): 5403-13.

[12]. Arzt L, Bokanovic D, Schrautzer C, Schwarz I, Laipold K, Aberer W,Sturm G. Questionable diagnostic benefit of the commercially available panel of bee venom components. *Allergy*, 2017; 72(9): 1419-1422.

[13]. Marangoni S, Ghiso J, Sampaio SV, Arantes EC, Giglio JR, Oliveira B,Frangione B. The complete amino acid sequence of toxin TsTX-VI isolated from the venom of the scorpionTityus serrulatus. *J Protein Chem*, 1990; 9(5): 595-601.

[14]. Pucca MB, Cerni FA, Peigneur S, Bordon KC, Tytgat J,Arantes EC. Revealing the function and the structural model of Ts4: insights into the "non-toxic" toxin from Tityus serrulatus venom. *Toxins (Basel)*, 2015; 7(7): 2534-50.

[15]. Luna-Ramírez K, Quintero-Hernández V, Juárez-González VR,Possani LD. Whole transcriptome of the venom gland from Urodacus yaschenkoi scorpion. *PLoS One*, 2015; 10(5): 1-33.

[16]. Santibáñez-López CE, Cid-Uribe JI, Batista CV, Ortiz E,Possani LD. Venom gland transcriptomic and proteomic analyses of the enigmatic scorpion Superstitionia donensis (Scorpiones: Superstitioniidae), with insights on the evolution of its venom components. *Toxins (Basel)*, 2016; 8(12): 367.

[17]. Uribe JIC, Vargas JMJ, Batista CVF, Zuñiga FZ,Possani LD. Comparative proteomic analysis of female and male venoms from the Mexican scorpion Centruroides limpidus: Novel components found. *Toxicon*, 2017; 125: 91-98.

[18]. Kazemi-Lomedasht F, Khalaj V, Bagheri KP, Behdani M,Shahbazzadeh D. The first report on transcriptome analysis of the venom gland of Iranian scorpion, Hemiscorpius lepturus. *Toxicon*, 2017; 125: 123-30.

[19]. Hu Y, Yang L, Yang H, He S,Wei J-F. Identification of snake venom allergens by two-dimensional electrophoresis followed by immunoblotting. *Toxicon*, 2017; 125: 13-18.

[20]. Murray J, Gregory WF, Gomez-Escobar N, Atmadja AK,Maizels RM. Expression and immune recognition of Brugia malayi VAL-1, a homologue of vespid venom allergens and Ancylostoma secreted proteins. *Mol Biochem Parasitol*, 2001; 118(1): 89-96.

[21]. Yang H, Xu X, Ma D, Zhang K,Lai R. A phospholipase A1 platelet activator from the wasp venom of Vespa magnifica (Smith). *Toxicon*, 2008; 51(2): 289-96.

[22]. Bazon M, Silveira L, Simioni P,Brochetto-Braga M. Current advances in immunological studies on the vespidae venom antigen 5: therapeutic and prophylaxis to hypersensitivity responses. *Toxins (Basel)*, 2018; 10(8): 305-18.

[23]. Mustafa F, Ng F, Nguyen T,Lim L. Honeybee venom secretory phospholipase A2 induces leukotriene production but not histamine release from human basophils. *Clin Exp Immunol*, 2008; 151(1): 94-100.

[24]. Sakamoto K, Nagai H,Koda A. Role of hyaluronidase in immediate hypersensitivity reaction. *Immunopharmacology*, 1980; 2(2): 139-46.

[25]. Barboni E, Kemeny D, Campos S,Vernon C. The purification of acid phosphatase from honey bee venom (Apis mellifica). *Toxicon*, 1987; 25(10): 1097-1103.

[26]. Hoffman DR. Hymenoptera venom proteins, in Natural Toxins 2, *Springer*; 1996: 169-186.

[27]. Qiu Y, Choo YM, Yoon HJ, Jia J, Cui Z, Wang D, Kim DH, Sohn HD,Jin BR. Fibrin (ogen) olytic activity of bumblebee venom serine protease. *Toxicol Appl Pharmacol*, 2011; 255(2): 207-13.

[28]. Santos-Pinto JRA, dos Santos LD, Andrade Arcuri H, Castro FbM, Kalil JE, Palma MS. Using proteomic strategies for sequencing and post-translational modifications assignment of antigen-5, a major allergen from the venom of the social wasp Polybia paulista. *J Proteome Res*, 2013; 13(2): 855-65.

[29]. Tsai M, Starkl P, Marichal T,Galli SJ. Testing the 'toxin hypothesis of allergy': mast cells, IgE, and innate and acquired immune responses to venoms. *Curr Opin Immunol*, 2015; 36: 80-87.