JOURNAL OF PROTEOMICS 75 (2012) 3829–3841

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/jprot

Review

Interactome: Smart hematophagous triatomine salivary gland molecules counteract human hemostasis during meal acquisition

*Carla Nunes de Araújo, Ana Carolina Bussacos, Alessandro O. Sousa, Mariana M. Hecht, Antonio R.L. Teixeira**

Chagas Disease Multidisciplinary Research Laboratory, Faculty of Medicine of the University of Brasilia, 70.910.900, Brasília Federal District, Brazil

ARTICLE INFO

Article history:
Received 3 January 2012
Accepted 1 May 2012
Available online 9 May 2012

Keywords:
Triatomine bug
Hematophagy
Salivary gland proteins
Sialome
Interactome

ABSTRACT

Human populations are constantly plagued by hematophagous insects' bites, in particular the triatomine insects that are vectors of the *Trypanosoma cruzi* agent in Chagas disease. The pharmacologically-active molecules present in the salivary glands of hematophagous insects are injected into the human skin to initiate acquisition of blood meals. Sets of vasodilators, anti-platelet aggregators, anti-coagulants, immunogenic polypeptides, anesthetics, odorants, antibiotics, and detoxifying molecules have been disclosed with the aid of proteomics and recombinant cDNA techniques. These molecules can provide insights about the insect–pathogen–host interactions essential for understanding the physiopathology of the insect bite. The data and information presented in this review aim for the development of new drugs to prevent insect bites and the insect-transmitted endemic of Chagas disease.

Contents

* *Corresponding author at:* Chagas Disease Multidisciplinary Research Laboratory, Faculty of Medicine, University of Brasília, P.O. Box 04536, 70.910-900, Brasília-DF, Brazil. Tel.: +55 61 33494987; fax: +55 61 32734645.
E-mail addresses: cnunes@unb.br (C.N. de Araújo), acbussacos@gmail.com (A.C. Bussacos), alessandro.oof@gmail.com (A.O. Sousa), marianahecht@gmail.com (M.M. Hecht), ateixeir@unb.br (A.RL. Teixeira).

1874-3919/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.jprot.2012.05.001

1. Introduction

The nuisance resulting from the sting of an insect that injects a poisonous moiety into the skin of a human prey can be life-threatening. Insects capable of attacking out of a defensive instinct are not necessarily predators. However, true predators posing severe harm are hematophagous insects that need to prey upon a warm-blooded host in order to fulfill its growth and replication. Unfortunately, this requirement has made some families of blood-feeding insects excellent transmitters of harmful pathogens to humans. Among these there are the mosquitoes belonging to the families Phlebotominae, Culicidae, Anophelinae, which are transmitters of leishmaniasis, dengue virus and filariasis, and malaria, respectively [1].

Among the Reduviid insects is the Triatominae sub-family that are strictly hematophagous disease transmitters of *Trypanosoma cruzi* [2]. The insect classification is based on morphological, physiological, and genetic differences. Additionally, a readily visible variance related to the color and structure of salivary glands is observed; pinkish in the tribe Rhodniini, whereas those in the tribe Triatomini have translucent saliva [3,4]. A molecular clock phylogeny study suggests that *Rhodnius* and *Triatoma* diverged 40 million years ago (Mya) [4], but there are indications that the triatomines originated on the South American continent 95 Mya [5]. Regardless of the evolutionary pathway in the sub-family Triatominae, prominent tools are found in mouthparts of these insects adapted for blood-feeding. The segmented triatomine mouthparts have pairs of mandibles, maxillae, and a proboscis to pierce the skin. The maxilla contains salivary and alimentary canals suitable for saliva injection and blood intake. In the insect's head there is a cibarial pump connected to muscles for contractile suction of blood [6].

The triatomines are classified as hemimetabolous with five nymphal stages and male and female imagos that need to ingest blood meals in order to fulfill their life-cycle and/or reproduce [2,7]. It has been shown that ionized iron (Fe^{++}) bonded to globin is essential for the insect's fertility and reproduction [8]. Over 140 triatomine species are considered potential transmitters of *T. cruzi*, now widespread on the American Continent. At least 40 wild-life species of triatomines named "assassin bugs" or "cone-nosed bugs" are considered of primary importance to public health because they harbor this protozoan parasite [8]. *Triatoma infestans*, *Panstrongylus megistus*, *Rhodnius prolixus*, *Triatoma pseudomaculata*, *Triatoma brasiliensis* and *Triatoma sordida* [9] are the main vectors of *T. cruzi* infections to humans. Interestingly, the infective *T. cruzi* parasitic forms are not delivered with saliva, but instead they are passed through the elimination of wastes, which contaminate a bite wound usually after a successful blood meal [10].

During blood-feeding, upon detection of a suitable host, the triatomine starts to probe the skin surface with its mouthparts [6]. This is followed by a piercing or penetration phase when it directly introduces its proboscis into the skin, injecting saliva into the host tissue and local blood vessel. In this phase, saliva is pumped continuously into the host tissue [11]. The cibarial pump muscle contracts the insect's head simultaneously to suck in the blood while feeding upon its prey. The quick-feeding is intensified by the pump contractile frequency regulated by electrical muscle signals. *T. infestans* salivation occurs during the entire feeding process that can last up to 15 min before ceasing, when a critical abdominal volume is reached [12,13]. The cibarial pump regulates the quantity of saliva injected in the vessel and skin surroundings, which achieves analgesia and counteracting the host's hemostasis and immediate immune response [11].

The success in feeding relies heavily on the pharmacological properties of their saliva. To facilitate the blood intake, saliva contains potent pharmacologically active proteins that counteract hemostatic (vasoconstriction, platelet aggregation, and blood coagulation), inflammatory and immune system reactions [14]. Although it is conceivable that the host's hemostatic systems should evoke increasingly tight barriers against hematophagous insects, we have shown that the triatomine probes and withdraws blood faster from hosts immunized with saliva gland allergens than from naïve hosts, and that nymphs feeding upon immune hosts reach adult life usually earlier than those feeding upon non-immune hosts [15]. It has been suggested that the triatomine bug takes advantage of immunomodulatory properties of salivary proteins in order to enhance its feeding upon the vertebrate host [15]. Also, it has been shown that humans exposed to triatomine bites in endemic areas of Latin America have high levels of IgG1- and IgG4-specific antibodies against saliva allergens [16]. IgG1, among other functions, is involved in Fc