Toxicon 54 (2009) 938–948

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Studies on the venom proteome of *Bothrops asper*: Perspectives and applications

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ARTICLE INFO

Article history:
Received 21 April 2009
Received in revised form 7 June 2009
Accepted 9 June 2009
Available online 17 June 2009

Keywords:
Snake venom protein families
Proteomics
Viperid toxins
Snake venomics
Antivenoms

ABSTRACT

Bothrops asper is responsible for the vast majority of snakebite accidents in Central America and several studies have demonstrated that specific toxic and enzymatic activities of its venom vary with the geographic origin and age of the specimens. Variability in venom proteins and enzymes between specimens from the Caribbean and the Pacific versants of Costa Rica has been reported since 1964. Recently, we performed a comparative proteomic characterization of the venoms from one population of each versant. Proteins belonging to several families, including disintegrin, phospholipases A_2, serine proteinases, C-type lectins, CRISP, L-amino acid oxidase, and Zn^{2+}-dependent metalloproteinases show a variable degree of relative occurrence in the venoms of both populations. The occurrence of prominent differences in the protein profile between venoms from adults and newborns, and among venom samples from individual specimens of the same region or developmental stage, further demonstrated the existence of geographic, ontogenetic and individual variability in the venom proteome of this species. These findings provide new insights towards understanding the biology of *B. asper*, contribute to a deeper understanding of the pathology induced by its venom and underscore the importance of the use of venoms pooled from specimens from both regions for producing antivenom exhibiting the broadest cross-reactivity. Furthermore, knowledge of the protein composition of *B. asper* venom paves the way for detailed future structure–function studies of individual toxins as well as for the development of new protocols to study the reactivity of therapeutic antivenoms.

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1. Introduction

Snake venoms are secretions produced by specialized exocrine glands, containing a complex mixture of toxic proteins which contribute to subdue, kill and/or digest the prey (Fry et al., 2006; Vonk et al., 2008). Venom toxins likely evolved from a reduced set of proteins with normal physiological functions which were recruited into the venom proteome before the diversification of the advanced snakes (Fry and Wüster, 2004; Fry, 2005). Toxins from Viperidae can be grouped into just a few protein families, including enzymes (serine proteinases, Zn^{2+}-metalloproteinases, L-amino acid oxidase, group II PLA_2) and proteins without enzymatic activity (disintegrins, C-type lectin-like molecules, bradykinin-potentiating peptides, ohanin, myotoxins, cysteine-rich secretory proteins, nerve and vascular endothelium growth factors, cystatin and

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0041-0101/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.toxicon.2009.06.011

Kunitz-type proteinase inhibitors) (Calvete et al., 2007). Each toxin family is usually represented in the same venom by multiple proteins, which often differ in their pharmacological activities, but might share remarkable structural and antigenic similarities (Fry and Wüster, 2004; Fry, 2005). These proteins are encoded by paralogous genes, probably originated by gene duplications and accelerated Darwinian evolution processes (Nakashima et al., 1995; Deshimaru et al., 1996; Ogawa et al., 2005). The specific proteins found in the venoms of different species vary in amino acid sequence and abundance and thereby contribute to the differences in the overall biological activity of individual venoms. Variability in protein composition among snake venoms from individuals of different geographic origins, sex, or age is a well documented phenomenon (Chippaux et al., 1991) and this variability has very important implications for the production and use of therapeutic antivenoms in the treatment of snakebite envenomings.

A deep analysis of the variability in the toxin composition of venom proteomes is now possible using high-throughput approaches. The combination of 2D electrophoresis or RP-HPLC with Edman sequencing, MALDI-TOF/MS and ESI/MS/MS has opened the opportunity to study snake venom proteomes, making possible to identify the complete set of proteins from several viperid venoms and to perform quantitative comparisons of related venoms (Gutiérrez et al., 2009; Calvete et al., 2007, 2009a). The understanding of the protein/peptide content of snake venoms could help in unravelling the evolution of the venom protein families, for the development of novel drugs and also has several potential applications in antivenom preparation (Gutiérrez et al., 2009). In this work we review the studies performed to characterize the venom proteome of *B. asper* and discuss their potential applications in the development of more effective therapeutic antivenoms.

2. *Bothrops asper*: the medically most important pitviper in Central America and Northern South America

The genus *Bothrops* (Subfamily Crotalinae of Viperidae) comprises at least five lineages of pitvipers commonly referred as lanceheads, which inhabit from northeastern Mexico, through Central and South America to Argentina and are also present in some Caribbean islands (Campbell and Lamar, 2004). *Bothrops* snakes are terrestrial or semi-arboreal, nocturnal pitvipers, and in tropical regions activity peaks usually correspond to rainy periods, during which most reproductive activities occur (Campbell and Lamar, 2004). Most species of *Bothrops* feed largely on exothermic prey as juveniles but shift to endothermic prey when they reach a size sufficient to swallow rodents, marsupials, birds, and other bulky prey items (Campbell and Lamar, 2004). *Bothrops* species are included into various groups according to their phylogenetic relationships (da Salomão et al., 1997). The *asper–atrox* group represents a monophyletic clade of medium to large-sized pitvipers widely spread throughout the tropical parts of Central and South America northward of the Amazon Basin, and includes *Bothrops atrox*, *Bothrops isabelae*, *Bothrops leucurus*, *Bothrops marajoensis*, *Bothrops moojeni*, *Bothrops colombiensis* and *B. asper* (da Salomão et al., 1997) (Fig. 1). However, the status and phylogenetic alliances of many of the conventionally recognized species within the *asper–atrox* group are still under debate (Wüster et al., 1999, 2002; Castoe and Parkinson, 2006).

B. asper is widely distributed in humid lowlands. It is the only *Bothrops* species that occurs in Trinidad Island; in Mexico and Central America, it occurs up to 1500 m altitude, whereas in South America it occurs up to 2500 m (Campbell and Lamar, 2004). The Caribbean distribution of *B. asper* extends continuously along the coast of the Gulf of Mexico, the Yucatan Peninsula, Central America, Panama, the Caribbean coast and through the inter-Andean valleys of Colombia, thence eastward across northern and Central Venezuela. The Pacific distribution of *B. asper* includes the region from the Central and South part of Costa Rica, through Panama, continuing along western Colombia, northern Ecuador and the northeastern extreme of Peru.

Specimens assigned to *B. asper* have a long history of taxonomical change. Cope (1887) recognized the species in the synonymy of *B. atrox*, Smith and Taylor (1945) recognized it as a subspecies of *B. atrox* from South America, and therefore the trinomial *B. atrox–asper* was adopted by earlier researchers of its toxins (Jiménez-Porras, 1964a). The binomial name *B. asper* was adopted after Hoge (1966) and is currently the accepted nomenclature. Some of the common names applied to this species are: terciopelo and barba amarilla (Central America), nauyaca (Mexico and Guatemala), mapepire (Trinidad) and equis (South America).

Many people are bitten each year in the New World by *B. asper* because it has a widespread distribution and is capable to adapt to altered environments such as agricultural fields and peridomestic areas (Gutiérrez, 1995; Warrell, 2004). Most cases occur in rural areas and affect

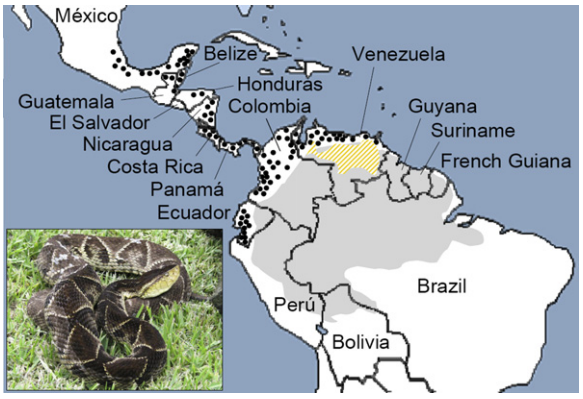

Fig. 1. Distribution of some snake species of the *Bothrops asper–atrox* complex in Central and South America. Physical map of Central and northern South America highlighting the geographic distribution of *B. asper* (closed circles), *B. atrox* (gray), and *B. colombiensis* (white and yellow). *B. asper* is found in the Atlantic lowlands of eastern Mexico and Central America, including Guatemala, Belize, Honduras, Nicaragua, Costa Rica and Panama. In northern South America it is found in the Pacific versant of the Colombian and Ecuadorian Andes and the adjacent coastal lowlands, and in northern Venezuela. The picture shown at the lower left corner corresponds to an adult specimen of Costa Rican *B. asper*.

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