Snake Venom Phospholipase A₂ and Its Antibacterial Potential

Pablo Olvera and Ying Jia*

Biology Department, College of Sciences, The University of Texas Rio Grande Valley, Brownsville, TX 78520, USA

*Corresponding author: Ying Jia, Biology Department, College of Sciences, The University of Texas Rio Grande Valley, Brownsville, TX 78520, USA, Tel: 956-882-7320; E-mail: ying.jia@utrgv.edu

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Phospholipases are a class of ubiquitous enzymes that have the common substrate, phospholipid, and they all hydrolyze the different ester linkages of phospholipid. Depending on which ester linkage hydrolyzed, phospholipases are grouped into four major categories-A, B, C and D. Phospholipase A, originally termed as lecithinase A by Contardi and Ercoli [1], was found for the first time in the venoms of cobra viper family at the end of 19th century, and was further divided into Phospholipase A₁ (cleaves the sn-1 acyl ester of the glycerol backbone) and phospholipase A₂ (cleaves the sn-2 acyl ester of the glycerol backbone). Phospholipase B cleaves either sn-1 or sn-2 acyl ester of the glycerol backbone. Both phospholipase A and B enzyme are also known as a lysophospholipase. Phospholipase C and D are the phosphodiesterases, and they cleave before and after the phosphate, respectively [2]. Snake venom phospholipase hydrolyze the 2-acyl groups in sn-3-phosphoglycerides, thus belong to phospholipase A₂ (PLA₂). In 1994, Dennis for the first time established the systematic group numbering system for PLA₂ enzymes; afterwards, PLA₂ family has grown continuously, and now the superfamily of PLA₂ enzymes currently consists of 16 Groups [3] [4,5]. The major five types of PLA₂ in this 16 groups are Ca²⁺-dependent secretory PLA₂ (sPLA₂), Ca²⁺-dependent cytosolic PLA₂ (cPLA₂), Ca²⁺-independent intracellular PLA₂ (iPLA₂), platelet activation factor acetyl hydrolases (PAF-AH), and lysosomal PLA₂s [6]. Snake venom PLA₂s, part of secretory PLA₂ (sPLA₂), from old world snakes (Elapidae family) including Kraits (Bungarus species), the Indian cobra species (Naja species), tiger snake (Hemachatus haemachatus) and the Australian tiger snake (Notechis scutatus scutatus) belong to group IA, while from new world snakes (Crotalidae family) including Japanese water moccasin, rattlesnakes and vipers belong to group IIA, as well from Viperidae family including Gaboon adder, Bitis gabonica belong to IIB [7,8]. Compared with Group I snake venom PLA₂s, the most distinguishing characteristic of Group II snake venom PLA₂ enzymes is the presence of a negative charged COOH-terminal extension of 6-7 residues [7]. Based on the amino acid composition surrounding the active site, Group II snake venom PLA₂s can be divided into, at least, two isoforms: (a) the Asp49 enzymes, having an aspartic acid residue at position 49, show catalytic activity, and (b) the Lys49 proteins, possessing a lysine residue at position 49, are catalytically inactive [9]. According to the primary structure and pl, the catalytically-active isoforms can be further subdivided into acidic and basic sub-isoforms, and the catalytically-inactive isoforms (Lys49) into only basic sub-isoforms [10]. In addition, two S49 PLA₂ (Serine residue at position 49) proteins [11,12], and one R49 PLA₂ (Arginine residue at positon 49) from snake (Protobothrops mucrosquamatus) [13] have been reported, suggesting the existence of more PLA₂ isoforms in the snake venoms.

Proteins and peptides (commonly referred to as toxins) constitute 90-95% of the dry weight of snake venom, and belong to relatively small stable protein families [14,15]. PLA₂s are the major component of snake venom proteomes, especially in the venoms of Agkistrodon contortrix contortrix [16], Micrurus lemniscatus [17], Agkistrodon piscivorus leucostoma [18-20], and Bungarus multicinctus [14]. Due to the pharmacological and physiopathological effects of snake venom PLA₂ in living organisms, snake venom PLA₂s have been extensively studied. Since two proteins with phospholipase A activity were purified from venom of Eastern diamondback rattlesnake (Crotus adamanteus) [21] and crystallized [22], and one phospholipase A₂ with MW of 14.5 purified from the venom of snake (Crotalus atrox) [23], more than 500 PLA₂s isolated from snake venoms (based on NCBI and UniProt databases). The amino acid sequences of many snake venom PLA₂s have already determined, and some of their structures have been resolved by X-ray crystallography. The secreted PLA₂s including snake venom PLA₂s are characterized by a low molecular weight (13-15 kDa), and containing histidine in the catalytic site, Ca²⁺ bond in the active site, six conserved disulfide bonds with one or two variable disulfide bonds [24], and more than 50% α-helix and 10% β-sheet [25].

Antibacterial Potential of Snake Venom PLA₂

Snake venoms contain numerous medically importantly proteins and peptides with varied physiological activities [26,27]. Since Glaser [28] experimentally observed, for the first time, the bactericidal activity of venom from Crotalus snakes, a considerable body of work has been reported the antibacterial effects of the crude venoms as well as venom components
from different snake species. The major components reported
possessing antibacterial activity in snake venom to date
include PLA₂ [29], L-amino acid oxidase [30],
m metalloproteinase [31] and lectin [32]. Among these venom
molecules, PLA₂ is well documented possessing antibacterial
activity. Forst et al. [33] demonstrated that PLA₂ from the
venoms of snakes (Agkistrodon halys blomhoffii) and
(Agkistrodon halys palas) actively hydrolyzed the phospholipids
of the bactericidal/permeability-increasing
protein (BPI)-treated E. coli. Since then, many researchers
claimed that snake venom PLA₂ exert antibacterial effects
[13,29,34-46]. However, it is interesting that Resende et al.
[47] and Jia et al. [48] reported that PLA₂ isolated from
cottonmouth snake venoms display no antibacterial effects,
implying that not all snake venom PLA₂ possesses antibacterial
effects. The precise bactericidal mechanisms of Group IIA PLA₂
such as hnpsPLA₂ isolated from human tissues and cells were
clarified, and the authors demonstrated that the antibacterial
activity of hnpsPLA₂ is due to a large excess of cationic
residues on its surface [49]. However, it seems that the
molecular mechanisms underpinning antibacterial activity of
snake venom PLA₂ are varied [29,39,41] or need to be
determined.

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