Editorial

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Journal of Molecular Sciences

2018
Vol.2 No.2:9

Snake Venom Phospholipase A_2 and Its Antibacterial Potential

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Received date: July 15, 2018; **Accepted date:** July 18, 2018; **Published date:** July 23, 2018

Citation: Olvera P, Jia Y (2018) Snake Venom Phospholipase A_2 and Its Antibacterial Potential. J Mol Sci. Vol. 2 No. 2: 9.

Snake Venom Phospholipase A_2

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 A_1 (cleaves the sn-1 acyl ester of the glycerol backbone) and phospholipase A_2 (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 A_2 (PLA_2). In 1994, Dennis for the first time established the systematic group numbering system for PLA_2 enzymes; afterwards, PLA_2 family has grown continuously, and now the superfamily of PLA_2 enzymes currently consists of 16 Groups [3] [4,5]. The major five types of PLA_2s in this 16 groups are Ca^{+2}-dependent secretory PLA_2s ($sPLA_2$), Ca^{+2}-dependent cytosolic PLA_2s ($cPLA_2$), Ca^{2+}-independent intracellular PLA_2s ($iPLA_2$), platelet activation factor acetyl hydrolases (PAF-AH), and lysosomal PLA2s [6]. Snake venom PLA_2s, part of secretory PLA_2 ($sPLA_2$), from old world snakes (*Elapidae* family) including Kraits (*Bungarus* species), the Indian cobra species (*Naja* species), tiger snake (*Hemachatus haemuchatus*) and the Australian tiger snake (*Notechis scututus 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 as from Viperidae family including Gaboon adder, *Bitis gabonica* belong to IIB [7,8]. Compared with Group I snake venom PLA_2s, the most distinguishing characteristic of Group II snake venom PLA_2 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 PLA_2s 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 pI, 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 PLA_2 (Serine residue at position 49) proteins [11,12], and one R49 PLA_2 (Arginine residue at positon 49) from snake (*Protobothrops mucrosquamatus*) [13] have been reported, suggesting the existence of more PLA_2 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]. PLA_2s 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 PLA_2 in living organisms, snake venom PLA_2s have been extensively studied. Since two proteins with phospholipase A activity were purified from venom of Eastern diamondback rattlesnake (*Crotus*. *adamanteus*) [21] and crystalized [22], and one phospholipase A_2 with MW of 14.5 purified from the venom of snake (*Crotalus atrox*) [23], more than 500 PLA_2s isolated from snake venoms (based on NCBI and UniProt databases). The amino acid sequences of many snake venom PLA_2s have already determined, and some of their structures have been resolved by X-ray crystallography. The secreted PLA_2s including snake venom PLA_2s are characterized by a low molecular weight (13-15 kDa), and containing histidine in the catalytic site, Ca^{2+} 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 PLA_2

Snake venoms contain numerous medically important 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 PLA_2 [29], L-amino acid oxidase [30], metalloproteinase [31] and lectin [32]. Among these venom molecules, PLA_2 is well documented possessing antibacterial activity. Forst et al. [33] demonstrated that PLA_2s 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 PLA_2s exert antibacterial effects [13,29,34-46]. However, it is interesting that Resende et al. [47] and Jia et al. [48] reported that PLA_2s isolated from cottonmouth snake venoms display no antibacterial effects, implying that not all snake venom PLA_2 possesses antibacterial effects. The precise bactericidal mechanisms of Group IIA PLA_2 such as hnpsPLA$_2$ isolated from human tissues and cells were clarified, and the authors demonstrated that the antibacterial activity of hnpsPLA$_2$ 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 PLA_2 are varied [29,39,41] or need to be determined.

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