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Sequence diversity and evolution of antimicrobial peptides in invertebrates

Anchalee Tassanakajon [a,*], Kunlaya Somboonwiwat [a], Piti Amparyup [a,b]

[a] Center of Excellence for Molecular Biology and Genomics of Shrimp, Department of Biochemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand
[b] National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), 113 Paholyothin Road, Klong 1, Klong Luang, Pathumthani 12120, Thailand

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ABSTRACT

Antimicrobial peptides (AMPs) are evolutionarily ancient molecules that act as the key components in the invertebrate innate immunity against invading pathogens. Several AMPs have been identified and characterized in invertebrates, and found to display considerable diversity in their amino acid sequence, structure and biological activity. AMP genes appear to have rapidly evolved, which might have arisen from the co-evolutionary arms race between host and pathogens, and enabled organisms to survive in different microbial environments. Here, the sequence diversity of invertebrate AMPs (defensins, cecropins, crustins and anti-lipopolysaccharide factors) are presented to provide a better understanding of the evolution pattern of these peptides that play a major role in host defense mechanisms.

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1. Introduction

Antimicrobial peptides (AMPs), which are found in all living organisms ranging from bacteria to humans, are an evolutionarily conserved component of the innate immune system (Hancock and Diamond, 2000; Zasloff, 2002). AMPs exhibit a broad spectrum of activity against bacteria, fungi, yeast, protozoa and viruses. Besides their antimicrobial activity, some AMPs are also recognized for their immunomodulatory properties (Bowdish et al., 2005). AMPs are typically less than 100 amino acids in length, display hydrophobic and cationic properties, and adopt an amphipathic structure (Hancock and Sahl, 2006; Zasloff, 2002). Some AMPs have been discovered to originate as the processed form of other larger proteins, such as buforin II from histone 2A (Kim et al., 2000) and astacidin1 from hemocyanin (Lee et al., 2003). AMPs are grouped into four major classes based on their secondary structure: β-sheet, α-helical, loop and extended peptides (Giuliani et al., 2007). Most AMPs disrupt the target cell membrane and exhibit selectivity for prokaryotic cells over eukaryotic cells (Brogden, 2005; Yeaman and Yount, 2003). The mechanism of membrane permeation may vary for different AMPs depending on the amino acid sequence of the peptides as well as the membrane lipid composition of the microorganism.

As of February, 2014, more than 2000 AMPs have been reported in the Antimicrobial Peptide Database (http://aps.unmc.edu/AP/main.php), and they exhibit tremendous sequence diversity. It has been found that AMPs have retained their antimicrobial activity during evolution since they have been used for hundreds of millions of years and yet they have remained effective against microbial targets. Thus, the sequence diversity of AMPs likely indicates the adaptation of organisms to survive in different microbial (pathogen) containing environments (Peschel and Sahl, 2006; Zasloff, 2002).

Invertebrates, which lack an adaptive immune system, rely on an effective innate immunity to protect themselves against microbial infections. Insects, in particular, possess various types of AMPs, including defensins and cecropins, which appear to be major defense molecules. Insect AMPs are predominantly produced by the fat body and are released into the hemolymph (Bulet and Stöcklin, 2005). Upon microbial infection, a single insect might produce up to 10–15 AMPs that can effectively kill the microbial invaders. In the fruit fly *Drosophila*, distinct inducible AMPs have been found to exhibit activity against Gram-positive (defensins) and Gram-negative (cecropins, diptericin, drosocin, attacins and mature prodomain of attacin (MPAC)) bacteria, as well as against filamentous fungi (drosomycin and metchnikowin) (Imler and Bulet, 2005). The simultaneous release of multiple AMPs during an immune response might be a key factor that constrains the evolution of the pathogens (Dobson et al., 2013). AMPs are among the insect immune proteins that evolve more rapidly than non-immune proteins and even more so in the social insects, such as ants and honey bees (Bulmer et al., 2010; Patil et al., 2004; Viljakainen et al., 2009), since they are attributed to a sustained

* Corresponding author. Tel.: +66 2 218 5419.
E-mail address: anchalee.k@chula.ac.th (A. Tassanakajon).

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arms race between the host and pathogens and to rapid environmental changes that expose the insects to new pathogens.

In crustaceans, especially shrimps, different AMP families have been reported and characterized (Rosa and Barracco, 2010; Tassanakajon et al., 2010). Shrimp AMPs are primarily produced by circulating hemocytes and are released upon pathogen infection. To overcome the fairly diverse variety of harmful microbes that they are exposed to, shrimps have evolved and use a diverse array of AMPs as an important part of their host defense system. Shrimp AMPs, such as penaeidins, crustins, anti-lipopolysaccharide (LPS) factors (ALFs), lysozymes and stylicins, are comprised of multiple classes or isoforms (Rolland et al., 2010; Tassanakajon et al., 2010).

In this review, we restrict our focus on the evolution of the major AMPs in insects (defensins and cecropins) and crustaceans (crustins and ALFs). Analysis of the sequence diversity found in these invertebrate AMPs should provide an improved understanding of the evolutionary dynamics of the peptides and how the host immune system uses them to counteract different pathogens.

2. Invertebrate defensins

Defensins are an evolutionarily ancient family of cationic AMPs that are commonly characterized by the presence of six or eight cysteine residues that form three or four intramolecular disulfide bonds, respectively, in a complex folded arrangement of two or three antiparallel β-sheets with or without an α-helix structure (Bulet et al., 2004; Froy, 2005). Defensin and defensin-like genes have been discovered in diverse species of fungi, plants, vertebrates and invertebrates (Bulet et al., 2004; Froy, 2005; Hughes, 1999; Mygind et al., 2005; Semple and Dorin, 2012; Zhu, 2008). Generally, the primary structure of defensins can differ considerably between different isoforms according to the spacing patterns between the conserved cysteine residues (Bulet et al., 2004; Froy, 2005; Hazlett and Wu, 2011). In vertebrates, it is well known that defensins are key components of the host innate immune system. Vertebrate defensins can be classified into the three sub-families of α-defensins (three disulfide bonds are formed by the linkage of C1–C6, C2–C4 and C3–C5), β-defensins (C1–C5, C2–C4 and C3–C6), and θ-defensins (a cyclic peptide containing three disulfide bonds), based on the spacing pattern of the six cysteine residues. The α- and β-defensins of vertebrates adopt a three-stranded antiparallel β-sheet structure. The diversification between these three families of vertebrate defensins indicated a likely common evolutionary origin and suggested that the origin of the vertebrate defensin family comes from β-defensins (Dimarcq et al., 1998; Hughes, 1999; Hazlett and Wu, 2011).

Although the evolutionary relationship between invertebrate and vertebrate defensins remains obscure, phylogenetic and three-dimensional structure analyses revealed that there is a closer relationship between invertebrate defensins and vertebrate β-defensins than between vertebrate α- and β-defensins. This then suggests that defensins are ancient molecules that are conserved across the eukaryotic kingdom (Zhu and Gao, 2013). In fungi, defensin-like peptides with a high degree of sequence and structural similarity to invertebrate defensins have been discovered, supporting that invertebrate defensins and fungal defensin-like peptides share a common evolutionary and genetic origin (Mygind et al., 2005; Zhu, 2008). Recently, the likely ancestor of defensins in invertebrates and fungi was traced to a bacterial defensin-like peptide of myxobacterium (Gao et al., 2009), suggesting that myxobacterial defensins are the potential origin of eukaryotic defensins (Zhu, 2007).

In invertebrates, defensins have also been identified in a different phylogenetic group composed of arthropods, mollusks and nematodes, in which they act as key effectors of the innate immune system (Bulet et al., 2004; Dimarcq et al., 1998; Froy, 2005). The evolutionary history of invertebrate defensins has already been reviewed elsewhere (Froy, 2005; Froy and Gurevitz, 2003, 2004; Zhu and Gao, 2013). Invertebrate defensins are secreted AMPs that exhibit similarity in their amino acid sequences, mode of action and three-dimensional structure to each other and are expressed ubiquitously. The defensins are synthesized as prepropeptides, which are then processed through various events to different extents before being released as the active peptides. Several insect defensins have been isolated from the hemolymph of infected animals and also found in the granular hemocytes of non-infected mollusks, termites and scorpions (Bulet et al., 2004; Dimarcq et al., 1998; Froy, 2005). Several defensins have been reported to be active against the membrane of invading microbes. Mammalian α- and β-defensins disrupt the microbial membrane integrity (Froy and Gurevitz, 2003; Risso, 2000), whereas invertebrate defensins (defensin A and sapecin) devastate the bacterial membrane by interacting with the membrane phospholipids and forming complexes that are not miscible in the lipid phase (Bulet et al., 2004; Froy and Gurevitz, 2003; Maget-Dana and Ptak, 1997; Matsuyama and Natori, 1990). Additionally, defensins from lepidopteran insects not only function as membrane-disrupting agents, but also interact with the fungal glucosylceramides (Thevissen et al., 2004). Moreover, mammalian, invertebrates (non-lepidopteran insects and mollusks like oysters), and fungal defensins can act as specific inhibitors of the bacterial peptidoglycan biosynthesis pathway (de Leeuw et al., 2010; Sass et al., 2010; Schneider et al., 2010).

Two major types of invertebrate defensins have been classified. The first type is the largest group and is comprised of peptides that contain six cysteine residues (C1–C4, C2–C5 and C3–C6), and includes the arthropod, insect and mollusk defensins (oyster and abalone). Members of the second type are characterized by having eight cysteine residues (C1–C5, C2–C6, C3–C7 and C4–C8) and contain the mollusk (mussel and oyster) and nematode (worms) defensins (Bulet et al., 2004; Froy, 2005).

In this review, based on the sequence analysis of the conserved cysteine spacing pattern within the defensin motif, invertebrate defensins can be further classified into the five major groups (Fig. 1) of: (I) arthropod and mollusk-type 6-cysteine defensins (known as arthropod defensins), (II) mollusk-type 8-cysteine defensins, (III) nematode-type 8-cysteine defensins, (IV) invertebrate big defensins and (V) invertebrate (putative) β-defensin-like peptides. Alignment of all known invertebrate defensins revealed the consensus defensin motif of each group (Fig. 2) as follows. (I) Arthropod and mollusk-type 6-cysteine defensins: C–X_{5-16}–C–X_3–C–X_{9-10}–C–X_{4-7}–C–X–C; (II) mollusk-type 8-cysteine defensins: C–X_{5-6}–C–X_3–C–X_{4-6}–C–X_{3-4}–C–X_{7-8}–C–X–C–X_2–C; (III) nematode-type 8-cysteine defensins: C–X_{6-15}–C–X_3–C–X_4–C–X_4–C–X_{4-8}–C–X–C–X_2–C; (IV) invertebrate big-defensins: C–X_6–C–X_3–C–X_{13-14}–C–X_4–C–C; and (V) invertebrate β-defensin-like peptides: C–X_6–C–X_4–C–X_{7-9}–C–X_5–C–C, which is similar to the β defensins: C–X_{4-8}–C–X_{3-5}–C–X_{9-13}–C–X_{4-7}–C–C, Bulet et al., 2004).

2.1. Arthropod and mollusk-type 6-cysteine defensins

This defensin family is the major group of invertebrate defensins and contains insect and mollusk defensins (Bulet et al., 2004; Dimarcq et al., 1998; Froy, 2005; Froy and Gurevitz, 2003). Along with plant and fungal defensins, they contain six cysteine residues that form the three disulfide linkages of C1–C4, C2–C5 and C3–C6 and are composed of an α-helix linked to an antiparallel two-stranded β-sheet by these disulfide bridges, referred to as the cysteine-stabilized α-helix/β-sheet (CSαβ) motif (Bulet et al., 2004). This leads to a tertiary structure that is completely different

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