

Peptides as toxins/defensins

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Peptides have important roles in many physiological processes, functioning as neurotransmitters, hormones, toxins, antibiotics, and defensins. Venom peptides target a wide variety of membrane protein receptors and may interact directly with the phospholipids of the plasma/organelle membranes or with cytosolic proteins to regulate their activities. Venomous animals use peptides in their predation strategies, defence against territorial intruders, and prevention against infections by pathogenic microorganisms (Palma 2006; Turillazzi et al. 2006). These peptides are directed against a wide range of pharmacological targets and can induce pain, inflammation, blood pressure changes, heart arrhythmia, and neurotoxicity, among other toxic actions (De Souza and Palma 2009).

Many of the peptides from animal venoms and toxic secretions seem to have evolved convergently with their cellular and molecular targets to optimize their effects, making them highly selective ligands for specific types of receptors. The wide array of molecular structures that induce physiological and pharmacological actions on the victims underscores the high degree of plasticity for these peptide toxins. For each group of venomous organisms, nature adopted a different strategy to create peptide toxins, based on the biology, life history, longevity, and foraging/feeding behaviour, among other factors. The venoms of Hymenoptera insects became a rich source of short linear polycationic peptides with multifunctional activities to cause pain and generalized inflammation (Palma 2006). Scorpions and wandering spiders evolved their venoms to

contain structurally compact peptides due to the presence of disulfide bonds; and, these peptides are characterized by their high affinity for ion channels and/or nervous receptors, causing activation or blockage of the ion flux through the cellular membranes (Escoubas 2006; Sollod et al. 2005). Snake venom has evolved to have linear peptides that act on the receptors localized on the endothelium surface. These peptides form their secondary structure upon interacting with the targeted receptors, and this generally produces a decrease in the blood pressure of the victims (Fry et al. 2003; Fry 2005). The skin secretions of many amphibian groups contain linear polycationic and/or polyanionic peptides that are structurally simple and have antimicrobial activities (Nicolas et al. 2003).

Many organisms produce short charged amphiphilic peptides that have antimicrobial activity at physiological concentrations. They are part of an ancient innate non-specific immune system, and in many cases, their primary function is to kill the invading pathogens. These peptides are known as antimicrobial peptides (AMPs).

AMPs have been isolated from animal venoms, bacterial secretions, and hemolymphs from arthropods, plants, amphibians, birds, fish, and mammals, including humans (Sitaram et al. 2003). Bacterial AMPs contribute to the survival of individual bacterial cells by attacking the bacteria that compete for nutrients in the same medium (Klaenhammer 1988).

In higher organisms, AMPs may be constitutively expressed or induced by a series of infectious/inflammatory stimuli (Hancock 2001). Some AMPs are potent modulators of the innate immune system (Bowdish et al. 2005), promoting phagocytosis and/or prostaglandin release or acting as chemoattractants for different types of immune cells to the site of inflammation (Yang et al. 2002). The main role attributed to these peptides is their direct biocidal

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actions towards bacteria, fungi, and parasites. However, the importance of the host defence activity depends on the site specificity of action within each organism (Jenssen et al. 2006).

Mammalian AMPs generally are chemotactic for human monocytes and T cells but may have adjuvant and polarizing effects in dendritic cell development. These peptides appear to have had an active role in the transition to the adaptive immune response (Chertov et al. 1996). Although AMPs may act directly on microbial cells by damaging or destabilizing the cell membrane, they seem to be involved in the organization of the innate immune and inflammatory responses (Hancock and Diamond 2000). They are also known as host defence peptides or defensins.

Defensins are widely distributed in plants, insects, reptiles, birds, and mammals (Zasloff 2002). Mammalian defensins are generally classified into three structural groups: α -, β -, and θ -defensins. The α -defensins and β -defensins differ from each other by their pattern of disulfide bonds and the number of cationic charges. The θ -defensins are characterized by the splicing and cyclisation of two of the nine amino acids in α -defensins (Ganz 2003). In addition to controlling bacterial growth and development, the β -defensins may act against fungi (Song et al. 2009).

The structure, molecular targets, and mechanisms of action of AMPs/defensins differ with the animal species. Depending on the amino acid sequence, the secondary structures of these peptides may adopt the following four distinct conformations: (1) α -helix, (2) β -strand, (3) β -hairpin, and (4) extended conformation. Most AMPs are unstructured in aqueous solutions; however, due to their amphiphilic nature, they interact with biological membranes and adopt a relatively organized secondary structure. These peptides may utilise a variety of antimicrobial actions, such as membrane perturbation and cell permeabilisation, to interact with its cytoplasmic and organellar targets (Ganz 2003).

The amino acid sequence of classical AMPs determines their general organization into four large groups:

1. *Anionic* rich in aspartic acid and/or glutamic acid residues, such as reported in the maximin H5 peptide from amphibians (Lai et al. 2002).
2. *Linear cationic α -helical peptides* rich in lysine, arginine and/or histidine residues but lacking cysteine residues, as observed in insect peptides, like mellitin and mastoparans (Palma 2006).
3. *Cationic* enriched with some specific amino acid residues (proline, arginine, phenylalanine, glycine and tryptophan), such as reported in the abaecins and apidaecins from honeybee hemolymph (Bulet and Stöcklin 2005).

4. *Anionic and cationic peptides* contain disulfide bond-forming cysteine residues and are found in drosomycins from fruit fly hemolymph (Cohen et al. 2009), human defensins (Schneider et al. 2005), and tachyplesins from horseshoe crabs (Muta et al. 1990).

Antimicrobial peptides act through different mechanisms, such as killing bacteria by membrane disruption, interfering with the metabolism, and interacting with cytoplasmic targets. Most bacterial membranes have anionic surfaces, suggesting that the interaction between the AMPs and microorganisms are initially electrostatic in nature. Depending on the amino acid sequence, AMPs can present different biophysical features (i.e., amphiphilicity, charge, and size) to interact with biological membranes to penetrate into the cell through one of the classical mechanisms (barrel-stave, carpet, and toroidal pores) or novel ones. Upon entry into the cells, the peptides can bind to their cytoplasmic/organellar molecular targets, inhibit the synthesis of the cell wall, interfere in the organization of the cytoplasmic membrane, and inhibit the synthesis of DNA, RNA, and proteins (Hancock and Diamond 2000; Hancock 2001).

The current research on toxic peptides and defensins is continually reporting molecular structures that are similar to the classical peptides and novel molecular structures that have either well-known physiological/pharmacological mechanisms or unidentified functional roles. As we further investigate these natural peptides, we become more aware of their potency, selectivity, and multifunctionality. To provide a broad overview of the current progress in the area of toxic peptides and defensins, we gathered contributions from chemists, biochemists, biophysicists, toxinologists, zoologists, and microbiologists. This issue is intended to present snapshots of the peptides identified as toxins/defensins and to explore the diversity of biological systems, novel structures, and the mechanisms of action. The reviews and original manuscripts in this issue focus on peptides from insects (De Souza et al. 2010; Leite et al. 2010), spiders (Kuhn-Nentwig et al. 2010; Rodríguez et al. 2010; Santos et al. 2010), amphibians (Calderon et al. 2010; Libério et al. 2010; Meneses et al. 2010), and humans (Corrales-Garcia et al. 2010) by using spectroscopic strategies for the detection, structural elucidation (Barbosa et al. 2010; De Souza et al. 2010; Leite et al. 2010), and characterization of the molecular interactions with biological membranes (De Souza et al. 2010; Zhou et al. 2010). Some of the contributions focus on the studies of the structure–activity relationship to achieve a better understanding of the mechanisms of the action (Zhou et al. 2010). A series of novel and classical biological assays is reported to screen peptides for antimicrobial (Kuhn-Nentwig et al. 2010; Rodríguez et al. 2010; Santos et al.

2010; Zhou et al. 2010), insecticidal (Kuhn-Nentwig et al. 2010), inflammatory, algescic (Brigatte et al. 2010), and anticancer/antiproliferative actions (Kuhn-Nentwig et al. 2010; Libério et al. 2010), opening the possibilities to exploit these peptides in drug discovery programs and biotechnological applications (Barbosa et al. 2010; Calderon et al. 2010; Vetter et al. 2010).

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