Journal of Fiber Bioengineering and Informatics 8:1 (2015) 25–36
doi:10.3993/jfbi03201503

Mechanism of Anticancer Effects of Antimicrobial Peptides

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Abstract

Antimicrobial Peptides (AMPs) were first known as a group of innate immune products that mainly targets on the invading pathogens among multiple species. The essential mechanisms of action of AMPs toward microbial cells have been reported as electrostatic attraction and hydrophobic interaction between AMPs (cationic AMPs) and microbial cell membranes. These effects also contribute to the potential mechanism of anticancer activities of AMPs as well. The membrane difference between cancer cells and normal cells are believed to play significant roles in AMPs orienting process. Membrane selective targeting properties make AMPs promising candidates for alternative approach to solve the problems from anticancer drug resistance.

Keywords: Antimicrobial Peptides; Anticancer Activity; Electrostatic Attraction; Hydrophobic Interaction; Anticancer Drug Resistance

1 Introduction

Among the abundant anticancer therapeutic approaches, the main measure, conventional chemotherapy usually accompany with severe side effects. Current anticancer drugs mostly focus on highly proliferated cells, which do not spare healthy cells that grow with similar rate. Meanwhile,

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March 2015

the appearance of Multi Drug Resistant (MDR) cancer cells has greatly hindered the efficiency of drugs. Drug compounds can be transported out of the cells via resistance mechanism from cancerous cells [1, 2]. There are other mechanisms that cancer cells involved to failure anticancer drugs, including repairing damaged DNA, overcoming the stress conditions (ROS) and expression of drug detoxifying enzymes in response.

Antimicrobial Peptides (AMPs), as an innate defense guard, place heavy force on membrane targeting towards invading pathogens. Destruction of membrane structure or indirectly trigger the cascade consequences make the pathogenic microbe less possible to develop resistance. This property of AMPs is believed play significant role in anticancer activity as well. AMPs not only show adverse effect on the expression of receptor of angiogenic endothelial cells, but also associate with immune response. It renders the cancer cells more susceptible to immune system navigation which can be easily escaped under pathological state. This short manuscript tends to review the mode of mechanism of AMPs owing anticancer activity through following points of views.

2 Membrane Differences Contribute to the Selective Targeting of Antimicrobial Peptides

The progression of cancer correlated with alteration and transformation of cell membranes which is vital to neoplasm cells in cellular response to surrounding signals. Biological membranes are composed of phospholipid bilayer which is a fundamental component being amphipathic, having both hydrophobic and hydrophilic domains. It is believed that multiple membrane proteins are represented on the surface of mammalian cells with complex ingredients or modifications, but the portions of proteins which carry net electrons often face to the inner side of the membrane. Healthy plasma membranes usually present a zwitterionic amphiphile distribution. Cancer cell membranes, on the other hand, usually express a vast number of anionic molecules (such as phosphatidylserine (PS) [3-9], sialic acid [10-15], membrane-associated glycoproteins [16, 17], chaperone proteins HSP90 and GRP78 [18-20]) which are contributed to the net negative charge of membrane surface. The membrane structures of normal cells and cancerous cells are shown in Fig. 1.

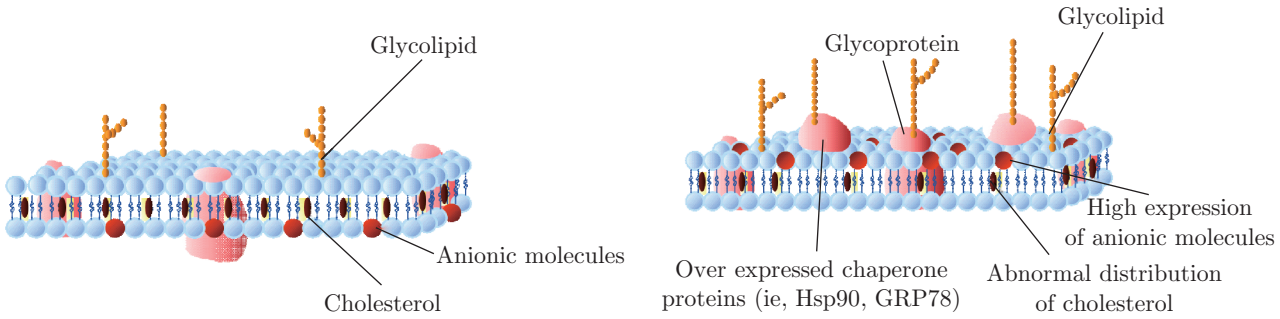

Fig. 1: Schematic diagrams of membrane structure of mammalian cells. Compared to normal cells (left), over expressed anionic molecules or proteins and abnormal distribution of cholesterol may contribute to the negative charged membrane surface in cancerous cells (right)

Among these membrane-associated proteins, the abnormal vitality of post-translational modification of proteins on the cancer cell membrane surface made cancerous cells more susceptible to

AMPs. Glycosylation of membrane-associated glycoproteins and glycolipids are the most typical post-translational modification when a cell becomes cancerous. It can trigger the alteration or translocation of a membrane-associated protein and contribute the net negative charge to cell membranes [21]. The electrical charge of tumor cells at physiological pH can therefore represent the changes that occurred during cancer transformation.

Additionally, mammalian plasma membranes possess the unique component, cholesterol, which can affect the fluidity and stiffness of the membrane [22]. The difference of the cell membrane structure between cancerous and normal cells plays a critical role in the orientation of AMPs. Studies have shown that the cancerous cells showed greater susceptibility to AMPs when the cholesterol content in the membrane is relative less than normal cells [22, 23]. Roughness of cell membrane is also a key factor in cellular response to AMPs. Cancerous cell surface area is greater than that of normal cells may be due to the higher possession of microvilli [24, 25]. Those projections may enhance the attraction of AMPs and a positive loop can be formed to trigger increasing interaction between cancer cells and AMPs molecules.

3 Mode of Mechanisms are Determined by Dynamic Conformation of AMPs

Despite the diversity of size, primary and secondary structures, AMPs share common characteristics in that almost all peptides possess cationic surface charges and a significant proportion of hydrophobic residues to form a membrane-bound amphipathic conformation. The former characteristic is obviously responsible for the reason why there is electrostatic attraction between AMPs and target cells. The latter plays a key role in the mechanism of AMPs actions after the initial attraction between AMPs and cell membrane.

Most common conformations among AMPs with anticancer activities are α-helical AMPs (BMAP-27, 28 [26-28]; Cecropin A, B [29-32]; LL-37 [33-36]; Magainins [37, 38]; Melittin [39, 40]), β-sheet AMPs (Defensins [6, 41, 42], Lactoferricin [43-45], Tachyplesin I [46, 47], SVS-1 [39, 40]) and Extended AMPs (Tritrpticin [48], Indolicidin [49, 50]). The net charge at physiological pH, conformation and mechanisms of anticancer activity were recorded in Table 1. The α-helical structure is believed to be closely correlated with the hydrophobicity of peptides. Hence, hydrophobicity is one of the critical factors for peptide secondary structure when peptides interact with the target cytoplasmic membrane. Self-association ability may help peptide to aggregate with each other to form transmembrane pore or channel and cause the cell death [51]. Studies also demonstrated that β-sheet structure peptide can trigger rapid phospholipid translocation while sparing the membrane integrity at certain concentration [52, 53]. β-hair pin structure of peptides showed greater potent at enhancing the binding affinity between peptides and cancer cell surface [54].

Several mode of AMPs' action of the membrane disruption have been reported in literatures including barrel stave, toroidal, carpet, and detergent pore model [3, 4, 55-59]. Membrane disruption process of barrel stave model can be described as following stages. Followed by the initial binding stage, increasing peptides are attracted to the cell membrane leaflets, conformational changes can be triggered leading to exposure of the hydrophobic amino acid of peptides toward to the hydrophobic core of lipid bilayer. Finally, the trans-membrane pore is formed and causing leakage of cellular material. In order to convert cytoplasmic membrane and causing membrane

Table 1: The original source, net charge at physiological pH, class of conformation and the corresponding mechanism of anticancer activity of AMPs

Antimicrobial peptides (AMPs)	Source	Net Charge	Class of secondary structure	Mechanism of anticancer activity	References
BMAP-27	*Bostaurus*	10.5	α-helical	Membranolytic	[26-30]
BMAP-28	*Bostaurus*	7	α-helical	Membranolytic	[28-30]
Cecropin A	*Hyalophoracecropia*	7	α-helical	Membranolytic	[31-34]
Cecropin B	*Hyalophoracecropia*	7	α-helical	Membranolytic	[31-34]
Defensins	*Homo sapiens*	2-4.5	β-sheet	Membranolytic	[43, 44]
Indolicidin	*Bostaurus*	4	Extended AMP	Organic anion carrier	[51-52]
LfcinB	*Bostaurus*	8	β-sheet	Membranolytic Anti-angiogenic, Apoptosis	[45-47]
LL-37/hCAP-18	*Homo sapiens*	6	α-helical	membranolytic	[35-38]
Magainin 2	*Xenopuslaevis*	3	α-helical	Membranolytic	[39, 40]
Melittin	*Apismellifera*	4	α-helical	Membranolytic Phospholipase A2 and D activator	[41, 42]
Tachyplesin I	*Tachypleustridentatus*	6	β-sheet	Binds hyaluronan and activates complement	[48, 49]
Tritrpticin	*Porcine sp.*	5	Extended AMP	Membrane depolarization Secondary intracellular targeting	[50]

damage, one α-helical peptide needs around twenty two amino acids in length (eight amino acids for a β-sheet peptide) to achieve the alternation of the membrane [3]. The barrel stave model demonstrates the pore formation process which is conducted by sole AMP. Toroidal model describes a process of pore formation very similar to the barrel stave model, except that both peptides and lipids are involved to form the torus-like pores that disintegrate cell membrane. Like the barrel stave model, "toroidal" pore maker peptides can span the membrane to make a channel causing the leakage of cellular material [4, 15]. The Carpet model describes a typical encounter scenario of peptides and membrane. Initially, the hydrophilic residues of AMPs align the phospholipid head groups, then, after certain concentration of peptides is achieved (usually in terms of MIC value), peptides rotate and reorient towards the membrane, causing a curvature strain of membrane or a reduction of phospholipid components. A stable pore formation is not necessary for the carpet model. AMPs may enter the cytoplasmic membrane without causing membrane disintegration, leading to an indirect mechanism of attack [3, 4]. It is proposed in the detergent model that AMPs can destabilize cell membrane by causing micelle-like structures. In this model, though still needing to be proved by more evidence, micelle-like structures represent themselves as membrane blebs and closely relate to rapid cell membrane damage [3, 21]. Upon contact with the negative cell membrane, the peptide acquires α-helical conformation or β sheet

structure to arch and destroy the membrane.

4 Necrosis, Apoptosis and Death Pathways of Cells Triggered by AMPs

As mentioned above, the mechanism of action of AMPs is not limited to membrane disruption but also include intracellular killing pattern. After initial contact with cell membrane, AMPs may gain the access of entering membrane structure and intracellular spaces. Several types of structure of AMPs can be found responsible for affecting intracellular target. For instance, the extended structure of AMPs (e.g. Indolicidin) is usually not membrane active [60, 61], and β-sheet structures (tachyplesin) tend to form toroidal pores causing consequently intracellular translocation [46, 47].

These consequences might lead to two possible outcomes which are necrosis and apoptosis. AMPs can alter the necrosis and apoptosis pathways of cancer cells separately or simultaneously [3]. Necrosis and apoptosis both can lead to cell death which can be observed by different cellular morphological changes such as the cell skeleton shrinkage or swelling, chromatin condensation, cytoplasmic vacuoles or membrane blebbing [3]. It is a general awareness that using microscopy and fluorescence labeling to observe and analyze cell.

A necrosis triggered by severe membrane damage is often regarded as direct way of AMPs attack [62]. Carpet, barrel-stave or torodial pore models are often observed in this straight forward way of killing. However, the indirect manner of attack also causes cell death by initiating the apoptosis of cancer cells and most frequently inhibiting the macromolecular synthesis. Some researchers believed that apoptosis of cancer cells is a superior strategy in cancer therapy, especially for apoptosis induction in the process of metastasis which is responsible for increasing therapy failure [1, 2]. Additionally, necrosis may need high level of AMPs or a process of accumulation (reach the threshold) to disrupt membrane structure inducing killing effects, while apoptosis may affect intracellular target and induce cascades reaction under a relative less serve concentration.

Despite the induction of necrosis or/and apoptosis pathway triggered by membrane interfering, several AMPs expressed alternative pathways including the recruitment of immune response, the binding of regulation receptor, the inhibition of synthesis of intracellular macromolecule and the suppression of agiogenesis. These effects are not common features for AMPs, however, play significant synergetic roles regarding the anticancer effects. The synergetic effects of AMPs can also be found among several anticancer trial using conventional drugs. For example, cecropin shows synergetic effect with conventional chemotherapeutics (S-fluorouracil, cytarabine and cytarabine) against variety of cancer cells [30]. By combining melittin, the cytotoxicity of 5-fluorouracil towards cancer cells is promoted while the toxicity on normal cells are reduced [63].

5 Preclinical Investigations of Anticancer AMPs

Promising perspectives have been obtained from preclinical studies on AMPs with anticancer activities in rodent models [64]. These peptides are effective during the trails towards human tumor cells as Xenografts in mice or rats. Cecropin B could significantly inhibit the growth of tumors in mice which were xenografted with human lung cancer cells [65]. Beta-defensin-2

(BD2) is found exhibited antitumor effects in vivo by mediating specific antitumor immunity [66]. In the established SH-SY-5Y neuroblastoma xenografts, LfcinB significantly inhibits the growth of tumor [45]. Similar inhibiton effects of LfcinB can be observed on B16-BL6 melanoma and L5178Y-ML25 lymphoma cells from mouse models [67]. In immuned-deficient mice model, magainin (D-amino acid derivative of magainin) dramatically eliminates majority xenografts of human melanoma cells [68].

Several strategies have been applied to overcome the problems regarding the instability of peptides in the presence of serum or toxicity towards healthy cells. Magainin II were conjugated in polydiacetylene micelles and were able to minimize the size of tumors which is xenograted in mice [69]. A study used a gene vector to introduce *cecropin* into human bladder carcinoma cell line, the expression of peptide in some clones causes a complete suppression of tumorigenicity in nude mice [70]. The transduction domain (proapoptotic DP1peptide) was fused to an AMP to target specific sites in mice xenografts (through locally injection) where rapid apoptosis is triggered, the normal cells is spared from the attack [71].

6 Open Questions on Anticancer Activity of AMPs

Generally speaking, most of studies referring mechanism of AMPs were investigated by involving synthetic membranes or bacteria as model systems [54, 72, 73], which are less complicated in composition and assembling manner. The mechanisms in action may be altered in another model system. Cancer cells differ from each other aside from several general properties. To date, no AMP has been found to be capable of acting to all cancer cell lines [3, 4]. The toxic effects on healthy cells, instability in serum, degradation by proteases and cost for AMPs production are the drawbacks of therapeutic application of many anticancer AMPs [3, 4, 21, 62]. Phase I clinical trials regarding to some membrane lytic AMP also suggest that the short half-life of peptide is the main obstacle that hinders the efficiency of peptide-based therapies [62].

In order to improve the selectivity of AMPs toward cancer cells, the electric charge and hydrophobicity of AMPs are modified to enhance the binding affinity between peptides and the surface of cancer cells. Substitution of L-amino acids with D-amino acids is one technique that can enhance α-helix structure resulting in increased hydrophobicity and improvement of the stability in serum [74, 75]. However, increasing the hydrophobic property is a double-edged sword. Although the toxicity towards cancer cell can be increased by enhancing the hydrophobic property, the hemolytic activity and cytotoxicity towards normal cells are improved as well [76]. One estimate is that increasing the positive charge of AMPs to enhance neoplastic cell selectivity accompanied by controlled hydrophobicity for balancing the hemolysis effect may be a win-win strategy for anticancer drug designing [76].

7 Potential Applications

As mentioned previously, the poor stability in the presence of serum and the promoted concentration used to achieve the bactericidal effects are the major obstacles to hinder the development of AMPs in therapeutic applications [77]. There are multiple strategies to overcome these drawbacks, immobilization of AMPs on the surface of suitable substrate could be advanced approaches [77, 78]. Coupling reaction between AMPs and metal substrates [77, 79], matrix and immersion

loading in the polymerization process [79-81] and the electrostatic attraction between AMPs and polymers [82] can be found as main immobilization methods. Melimine has been covalently immobilized on the surface of glass with two azide linkers (4-azidobenzoic acid (ABA), 4-fluoro-3-nitrophenyl azid (FNA)), the significant reduction of bacterial colonization and killing effect show a promising potential of melimine as an antimicrobial peptide with a broad antibacterial spectrum applied on biomaterial surface [79]. The PEG-AA (poly(ethylene glycol-co-acrylic acid)) microgels could be loaded with a cationic antimicrobial peptide (L5) to further reduce the colonization of *S.epidermidis*. It brings a possible way to modify the surface of materials with irregular plane [81]. Defensin from mosquitoes were embedded into polyelectrolyts multilayer films, with the increasing of defensin layers, the antimicrobial effects of films was promoted 90% compare to control [82]. Though the bactericidal efficacy of AMPs could be compromised due to the covalent binding between substance and peptides (Minimal Inhibition Concentration (MIC) were increased 50-100 fold higher then soluble peptides), the cytotoxicity towards human red cells were declined as well. Additionally, the improvement of long term stability can be observed together with the enhanced resistance of peptides to environmental intervene [77, 79].

Aside from surface modification, electrospinning has been considered as a promising strategy to introduce functional biological molecular (such as protein, peptides) into nanofibrous scaffolds on the surface or interior of the fibers [83-88]. Collagen, chitosan and silk fibroin could be blended with synthetic poly (L-lactide-co-ε-caprolaction) (P(LLA-CL)) to meet the requirement of good mechanical properties and biocompatible activities for skin, nerve and blood vessel tissue engineering [83]. An hydroxyapatite (HA)-kerain nanocomposite could be electrospun into poly (L-lactic acid) (PLLA) fibrous membrane, and the enhancement for bone formation could be observed compared to pure PLLA fibrous membrane [84]. Koh HS et al. [89] reported that laminin was introduced into PLLA nanofibers through three different modifications, including covalently binding, physically adsorbing and blending into PLLA solution before electrospun. The results show that the blended electrospining is the most efficient way to promote the viability and axonal extensions of nerve cells (PC12). Among the above strategies, a long term release and high stability of protein or polymers can be overall summarized accordingly.

Therefore, with appropriate modification and fabrication, AMPs with anticancer effect have promising potential to be applied in clinical use. Peptides with potential function from multiple resources [90-92] can be screened efficiently. Never the less, the balance between stable efficiency and biocompatibility of these functional peptides are the key points for successful and practical application.

Acknowledgement

We would like to thank the Hong Kong Research Grant Council and the Hong Kong Polytechnic University through projects No. PolyU5242/09E and G-YM63. Also, we would like to thank the support of Guangdong Provincial Department of Science and Technology through projects No. 2012B050800002 and 2012B091000143.

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