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Antimicrobial Peptides of Innate Immune System as a Suitable Compound for Cancer Treatment and Reduction of its Related Infectious Disease

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Abstract
Application of chemotherapy in cancerous children leads to reduction of immune system efficiency. Therefore, these children are prone to various infectious diseases. The excessive use of antibiotics can bring about antibiotic resistant strains. Hence, it is essential to investigate new therapies for this problem. On the other hand, the emergence of resistance against multiple drugs is a major problem in treatments of infection and cancer. Lack of selectivity and negative side effects on normal cells is another associated problem for available drugs. Antimicrobial peptides are important agents that are made by the immune system in response to pathogens. This kind of immune response exists in all animal categories from prokaryotes to humans. Different types of antimicrobial peptides have been identified and isolated from various organisms. These peptides, along with antimicrobial effects, also contain other biological activities such as anticancer, spermicidal, anti-diabetic, growth stimulant, etc. Therefore, these natural compounds can be considered as new therapeutic goals in different areas, especially for the prevention of pediatric infectious disease. Because of anticancer activity, antimicrobial peptides can be used as an effective double functional drug: anti-infective and anti-cancer drugs. There are 2851 antimicrobial peptides from six kingdoms (303 bacteriocins/peptide antibiotics from bacteria, 4 from archaea, 8 from protists, 13 from fungi, 342 from plants, and 2181 from animals) with different activities in various recorded databases and 210 peptides with anticancer/antitumor activity. Most of these peptides are still in the early stages of the study, but in the future, these compounds will have a special place in the medicine basket as the most important and effective drug. In this review, the characteristics and applications of antimicrobial peptides were investigated and their anticancer effects were focused.
Key words: Anticancer, Antimicrobial peptides, Infectious diseases, Immune system, pathogen

Introduction

Antimicrobial peptides are important agents that are made by the immune system in response to pathogens. This kind of immune response exists in all animal categories from prokaryotes to humans. These peptides are usually short and show a wide range of antimicrobial activity. Today, thousands of peptides with antimicrobial activity have been discovered and reported. These peptides are used by a wide range of organisms, including mammals, birds, insects, crustaceans, fish, plants, and microbes (1,2). Some of these compounds are made continuously in the body, while others are synthesized only when the body is attacked by microbes. At the time of the microbes attack, the body's primary defense system increases the synthesis of these compounds to a great extent, and thus the primary barrier to the body acts more efficiently against foreign invasions (3-5). Research has shown that some of these antimicrobial peptides, in addition to intrinsic antimicrobial activity, act as immunosuppressive signals and thus contribute to the immune system's activity

(5). Antimicrobial peptides have many of the characteristics of a new class of antibiotics and can be considered ascomplementary therapeutic to traditional antibiotics. In addition, it has been shown that these compounds neutralize endotoxins. The best use of these peptides in living organisms is the disposal of lethal microbes from the internal system of the body. With the advent of science, these peptides can be extracted and used in vitro as new drug compounds in various industries.

Antimicrobial peptides and different animals

Antimicrobial peptides are made in a variety of gram-positive and gram-negative bacteria. Due to their role in the elimination of other bacterial species, they are known as bacteriocin (6). These peptides destroy other bacteria in the environment in which the host bacterium is present(6,7). The presence of antimicrobial peptides in viruses was first identified by the study of the AIDS virus. These peptides are caused by proteinuria of the protein coating of the virus (8, 9). In insects, antimicrobial peptides are considered as part of the insect defense against invasions of pathogens. Peptides of the insects are cationic and contain less than 100 amino acids. These peptides have a very wide range of activities. The main family of antimicrobial peptides is in the insects, which can be found in Sarcotoxins, Hyphancin, Enbocin, and Spodopsin peptides (10, 11). Thionines and diphencins are two major groups of antimicrobial peptides in plants. In general, plant peptides have cytotoxic activity along with toxic effects on organisms, and in some cases can destroy cancer cells in the laboratory (12-15). Antimicrobial activity of peptides has been observed in crustacean tissues such as shrimp, freshwater crayfish, and marine crabs. The first antimicrobial peptide was extracted from crustaceans from coastal crabs. Antimicrobial peptides are crude proteins rich in proline and in some cases arginine (16, 17). Adolescents have an amazing defense mechanism to deal with environmental stress. These animals are able to secrete toxic and toxic substances during stress. These materials are produced by granular glands distributed at separate points of the skin. Although the composition of these materials can vary among different species, peptides are the main components of these compounds. With the presence of different species among adulthood, the content of skin secretions can include thousands of peptide combinations with different activities. In the absence of mechanical defense systems such as nails, forks, stomachs, teeth, etc., the existence of such a chemical defense system in these animals is vital (18-20). Antimicrobial peptides in mammals are supplied from various sources, such as skin secretions, mucus, neutrophils, and platelet cells. These peptides include diphencin, lactoferrin, lysozyme, and antimicrobial proteins in the platelets. (21, 22).

Statistics

There are 2851 antimicrobial peptides from six kingdoms (303 bacteriocins/peptide antibiotics from bacteria, 4 from archaea, 8 from protists, 13 from fungi, 342 from plants, and 2181 from animals) with different activities in various recorded databases. These recorded peptides are divided to antibiofilm peptide, antiviral peptides, antifungal peptides, antiparasitic peptides, antimalarial peptides , anti-protist peptides, anticancer peptides, antioxidant peptides , chemotactic peptide, insecticidal peptide, protease inhibitor, spermicidal peptide, surface immobilized peptides, and wound healing peptides. Among all these recorded peptides, 210 ones have anticancer/antitumor activity. There are 123 human host defense peptides, 220 from mammals annotated, 1049 active peptides from amphibians, 117 fish peptides, 35 reptile peptides, 40 from

birds, 509 from arthropods, 42 from molluscs, 6 peptides from protozoa, and more. In Figure 1, sources of antimicrobial peptides are shown. As seen in this Figure, the highest number of peptides is discovered from animal source (22-26).

Applications of antimicrobial peptides

Antimicrobial peptides have a wide range of medical applications. These compounds, as new antibiotics, eliminate many infections caused by resistant bacteria. It has been shown that gastrointestinal infections, fungal infections, tetanus, sputum, and jaundice are affected by antimicrobial peptides and can be introduced as a new therapeutic approach (27,28). Antimicrobial peptides are a new hope in preventing the transmission of HIV. In recent years, fourteen peptides derived from skin lesions have been studied on this virus. The study found that these peptides have the ability to control the infection of the HIV virus. Three peptides from these 14 peptides completely inhibit the infection of the virus in concentrations that are not toxic to the target cell. It should be noted that these peptides also inhibit infections caused by the mouse leukemia virus (29-31). It has been shown that cell treatment with these peptides will prevent the integration of viral particles with the target cell and destroy the spread of the HIV virus. On the other hand, these peptides prevent the transmission of the virus by dendritic cells to T cells, so these peptides have provided new hope in the local control of the transmission of AIDS mucosal transmission. Antimicrobial peptides are also a new hope for cancer prevention. Antimicrobial peptides have the ability to bind to negative pregnancy molecules in the target membrane (32,33). The membrane composition of tumor cells differs from the membrane of normal cells. Studies have shown that phosphatidyl serine levels in melanoma and carcinoma cells are higher than normal cells. Such an attribute helps antimicrobial peptides to easily mucus cancerous cells and cause them to die. Some of the most important anti-cancer peptides are Defensin, Magainins, and the Cecropin family (1, 34-36). The use of other antimicrobial peptides produces sprays for patients with cystic fibrosis. Due to increased chloride concentration, the level of antimicrobial peptides in the lungs decreases and the individual is more affected by the infection of opportunistic bacteria such as pseudomonas aeruginosa. Through genetic engineering, antimicrobial peptides can be altered so that they are less affected by high salt concentrations (4). Generally, anti-microbial peptides are very diverse. These peptides have very high antimicrobial effects on a wide range of bacteria, viruses, and fungi, while the peptides are important components of the immune system in different animal species (5-7); therefore, in recent years, the study of this type of peptides has attracted a lot of attention..

Antimicrobial peptides and infectious diseases

Chemotherapy drugs cause immune deficiency following cancer treatment that lead to development of infectious diseases, especially in children. Indiscriminate use of antibiotics for treatment of these infections leads to development of resistant microbial strains (37,38). This status is more important for children's infections. So, the prevalence and treatment of recurrent infections in children after chemotherapy regarding to suppress the immune system, is a big challenge. Meanwhile, pay attention to antimicrobial peptides and their derivatives is very important and hopeful (39-41).

Antimicrobial peptides and cancer treatment

However many drugs are available, treatments of infection and cancer face a major problem: the emergence of resistance against multiple drugs. Many medications induce such problems (42). The cause of the selective effect of some antimicrobial peptides on cancer cells is due to the nature of the membrane of these cells. Lack of selectivity and negative side effects on normal cells is another associated problem for available drugs (43). These problems are more noticeable in children with cancer. So, it's necessary to develop new antineoplastic and antimicrobial therapies, with higher selectivity, leading to fewer side effects. In between, several antimicrobial peptides have considered due to their ability to kill or inhibit the growth of a variety of microorganisms and tumor cells. Some antimicrobial peptides can also be anticancer agents (44-47). These bifunctional peptides have increased in recent years. For example, Aurein 1.2, a peptide identified from the frog *Litoria aurea*, has broad-range activity toward bacteria and anticancer activity against 55 different cancer cell lines in vitro, without any significant cytotoxic activity (48). Changes in the cell membrane have important role in the progression of cancer, as they play a key role in the cell's response to its environment. Difference between cell membrane of normal and cancerous cells likely lead to the ability of certain antimicrobial peptides without toxicity on normal cells. The best reported mechanism for anticancer activity of these peptides is electrostatic interactions between cationic peptides and anionic cancerous cell membrane components Cancer cell membranes typically carry a net negative charge due to a higher than normal expression of anionic molecules. addition, the negative membrane potential of cancer cells may also contribute to the selective cytotoxic activity of ACPs (49-52).

There are various antimicrobial peptides with anticancer activity. Some of these antimicrobial peptides with selective antitumor mechanisms were summarized in table 1.

There different natural and synthetic peptides that developed and entered to clinical trials phase as new anticancer drug. ANG-4043, CLS-001, MBI-226, GRN-1201, ICT01-2588, ICT03-Es5, ICT04-CYP, ITK-1, WT-2725, CLS-001, MBI-226, DPK-060, LL-37 , LTX109, NP-213, PXL-01, SGX-942, and MK-4261 are some these developed peptides (53-69).

Future perspective

It seems that antimicrobial peptide develops as suitable anticancer and anti-infective drugs in future. Determination of the exact mechanism of interaction of antimicrobial peptides with cancer cells and their selectivity characteristics must be done in future studies. The effect of amino acid sequences and structure of peptides must be also determined with detail. Another obstacle and challenge for application of antimicrobial peptides is cost. Now, the purification and synthesis of these peptides are expensive. Despite all these challenges, in the near future, antimicrobial peptides have been developed and optimized for anticancer activity. These native peptides can be an economically viable and therapeutically superior alternative to the current generation of chemotherapeutic drugs because of their both potent antimicrobial and anticancer activities.

Conclusion

Suitable cancer treatments require development of strategy with high selectivity and efficacy. Current techniques (surgery, radiation, and chemotherapy) lead to severe side-effects. Antimicrobial peptides as member of innate immune systems have suitable properties for new anticancer drugs. Due to antimicrobial activity, antimicrobial peptides may also be used for the

prevention of infection after chemotherapy, especially in cancerous children. Hence, antimicrobial peptides are potent future chemotherapy cancer drug due to their important properties such as short time-frame of interaction, low toxicity, mode of action, specificity, good solubility, and good tumor penetration.

Table 1. Some important antimicrobial peptides with anticancer activity from various sources.

AMP name	Source
Alpha-defensin-1	Human
Cecropin A	Silk moth
Lactoferricin B	cattle
Alloferon 1	insects
Alloferon 2	insects
Antiviral protein Y3	insects
Aurein 2.5	frog
Aurein 2.4	frog
Aurein 2.3	frog
Aurein 2.2	frog
Aurein 2.1	frog
: Aurein 1.2	frog
Aurein 1.1	frog
Dermaseptin-B2	frog

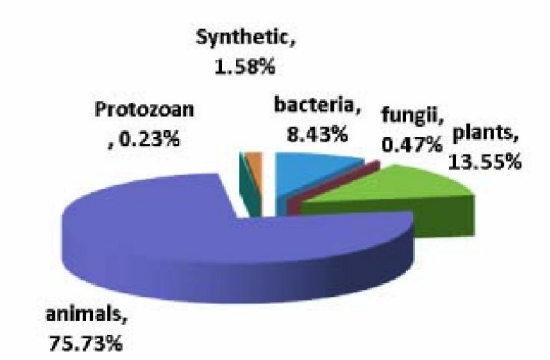

Figure 1. Frequency of antimicrobial peptides based on their

Conflict of interest

The authors report no conflict of interest.

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