抗菌肽——癌症治疗的新兴方法

吕宇蝶[1] 邵罡[1] 蒙月明[2] 金园庭[1]* 付彩云[2]*

([1]中国计量大学生命科学学院, 杭州 310018;
[2]浙江理工大学生命科学与医药学院, 浙江省家蚕生物反应器和生物医药重点实验室, 杭州 310018)

摘要 抗菌肽是由生物体诱导产生的小分子多肽。大多数抗菌肽在体内发挥着抗微生物和免疫调节的作用。抗菌肽的抗菌机制主要是通过细胞膜穿孔和靶向细胞内细胞器的生理过程。抗菌肽具有促炎和抗炎、皮肤屏障和维持生物体内稳态等免疫调节功能。近年来, 抗菌肽在各种癌症发生发展中的作用研究也取得了很大进展。抗菌肽在生物体内微环境中通过多种信号转导途径, 促进或抑制癌细胞增殖。该综述概述了抗菌肽的分类和生物学作用, 特别是在癌症治疗方面的进展, 以便为癌症治疗提供新的治疗靶点和思路。

关键词 抗菌肽; 分类; 抗菌; 免疫调节; 癌症

Antimicrobial Peptides: An Emerging Category for Cancer Treatment

LÜ Yudie[1], SHAO Gang[1], MENG Yueming[2], JIN Yuanting[1]*, FU Caiyun[2]*

([1]*College of Life Sciences, China Jiliang University, Hangzhou 310018, China*; [2]*Zhejiang Provincial Key Laboratory of Silkworm Bioreactor and Biomedicine, College of Life Sciences and Medicine, Zhejiang Sci-Tech University, Hangzhou 310018, China*)

Abstract Antimicrobial peptides (AMPs) are small molecular peptides that are induced by organisms. Most AMPs play an anti-microbial and immunomodulatory role in the body. The antimicrobial mechanism of AMPs is mainly through cell membrane perforation and physiological processes that target intracellular cells. AMPs have functions in immunomodulatory including pro-inflammatory and anti-inflammatory, skin barriers and maintenance of the homeostasis of the organism. In recent years, the role of AMPs in the development of various cancers has also made great progress. AMPs play an important role in promoting or inhibiting proliferation of cancer cells through multiple signaling pathways in the microenvironment. In this review, we provided a conspectus of the classification and biological roles of AMPs, especially on cancer treatment, in order to provide new therapeutic targets and ideas for cancer therapy.

Keywords antimicrobial peptides; classification; antimicrobial; immunomodulation; cancer

Antimicrobial peptides (AMPs), also known as host defense peptides, are polypeptides produced by organisms that have antibacterial activity and play an important role in many immune systems. To date, more than 3 000 AMPs have been discovered and most AMPs are isolated from animals and plants (http://aps.unmc.edu/AP/main.php). AMPs are short peptides that usually composed of 10-50 amino acids[1]. Hydrophobic amphiphiles and cationic amino acids are spatially arranged. Because of the presence of Lys and Arg residues, many AMPs are cationic peptides, and the net charge is usually +2 to +9[2-3].

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*通讯作者。 Tel: 0571-86835772, E-mail: jinyuanting@cjlu.edu.cn; Tel: 0573-86843336, E-mail: fucy03@zstu.edu.cn
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*Corresponding authors. Tel: +86-571-86835772, E-mail: jinyuanting@cjlu.edu.cn; Tel: +86-573-86843336, E-mail: fucy03@zstu.edu.cn
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Most antibiotics act on intracellular targets, making bacteria more susceptible to mutations[4], while natural AMPs have broad-spectrum resistance to microorganisms, low ability to induce bacterial resistance, indicating that AMPs become the most potential alternative to antibiotics[5]. AMPs have multiple functions such as antibacterial[6-7], antifungal[8-9], antiviral[10-11], and anticancer[12-13], as well as regulation of pro-inflammatory and anti-inflammatory physiological responses through innate and adaptive immunity[14], participating in the regulation of autophagy and apoptosis, maintains homeostasis[15-18].

More importantly, besides a high antimicrobial activity, low cytotoxicity is also a desirable characteristic for AMPs as potential anticancer drug candidates. The microenvironment secretes abundant AMPs such as LL-37 which also play an important role in cancer development[19]. Because of the fact that the plasma membrane components of the cancer cells are changed to be rich of the anion, which provides a basis for the cationic AMPs disrupting the membrane of cancer cell[20]. Accumulated evidence showed that a variety of AMPs have a role in the development of lung cancer[21-23], breast cancer[24-25], prostate cancer[26-27], pancreatic cancer[19], melanoma[28-29], bladder cancer[12], ovarian cancer[30-32], and leukemia[33-35], *etc*.

This review, inspired by a spate of recent studies of AMPs in human diseases and animal models, focuses on the classification and biological roles of AMPs, especially on cancer treatment, in order to provide new therapeutic targets and ideas for cancer therapy.

1 The classification of AMPs

AMPs are widely distributed in six kingdoms including bacteria, archaea, protists, fungi, plants, and animals. According to the source, function, electric charge, composition, and secondary structure, there are different ways to classify AMPs, and some of the classifications are overlapping.

1.1 Classification by source

According to different sources of AMPs, AMPs can be divided into mammalian AMPs, plant AMPs, aquatic biological AMPs, amphibian AMPs, and insect AMPs. Mammalian AMPs consist of defensins and cathelicidins[36-37]. Plant AMPs have been isolated from roots, seeds, flowers, stems, and leaves[38]. Aquatic AMPs are classified into aquatic crustacean and fish AMPs[39-41]. Amphibian skin is exposed to a moist environment, and different amphibian skins secret different AMPs[42]. Insect AMPs are widely distributed, mainly in Diptera, Lepidoptera, Coleoptera, Hymenoptera and Hemiptera[43].

1.2 Classification by function

According to the function of AMPs, AMPs can be divided into antibacterial peptides, antifungal peptides, antiviral peptides, and anticancer peptides. There may be synergistic effects between AMPs and AMPs or AMPs and antibiotics[44]. Antifungal peptides are found in animals, plants, insects, bacteria, and fungi, and some can bind to microbial surfaces and destroy cell walls[9]. Antiviral peptides protect organisms from infection before or after infection of cells[45]. Some AMPs have an anticancer effect. Some AMPs have a variety of functions, including antifungal, antibacterial, and anticancer.

1.3 Classification by electric charge

Depending on the electric charge, there are two types of AMPs, cationic AMPs, and anionic AMPs. Hydrophobicity and amphipathicity of cationic peptides affect the efficiency, pore size, and stability of cell membrane pore formation, but also increase toxicity *in vivo* and *in vitro*[46-50]. Anionic AMPs are negatively charged without basic amino acid residues, which can anchor biofilms through their hydrophobic regions, charge interactions, dissolve and penetrate the membrane[51-53].

1.4 Classification by composition

According to the composition, AMPs can be divided into cecropins, defensins, glycine-rich melittin, and proline-rich bombesin[54]. Most cecropins have 31-39 amino acid cationic AMPs without cysteine to form the helix-hinge-helix structure through the amphiphilic N-terminal and the hydrophobic C-terminal segment[55-56]. Defensins, rich in Cys residues, are divided into three subclasses of α-defensins, β-defensins, and

θ-defensins according to the structure of the disulfide bond, which have very similar tertiary structure[16]. α-defensins are mainly derived from neutrophils, also known as human neutrophil peptides (HNPs, HNP1-4), in which HNP3 can also be found in monocytes, NK cells, and part of mucosal cells[57-58]. β-defensins are isolated from bovine tracheal epithelial cells, and four β-defensins (hBD-1-4) can be induced by the stimulation of microorganism[59-63]. θ-defensins were first discovered in rhesus neutrophils and monocytes with a smaller structure and weaker amphiphilic shapes, but θ-defensins have a significant effect on HIV[64-66]. Melittin is the main component of bee venom. It is composed of 26 amino acids with the hydrophobic amino acid at the N-terminus and a hydrophilic residue at the C-terminus. It can induce the release of anti-inflammatory factors and exert multiple physiological functions; however, it also has strong hemolytic properties[47,67-70]. The Magainin is rich in proline, that is isolated from the skin of Xenopus laevis with broad-spectrum antimicrobial activity[71].

1.5 Classification by secondary structure

According to the secondary structure of AMPs, AMPs can be divided into three categories[72], including the linear peptide with the α-helical structure or the β-sheet structure, and the polypeptide with the ring structure[73-75]. The α-helix structure in AMPs is important for maintaining antibacterial activity, which acts as a membrane solubilizing agent in anti-microbial. But AMPs with highly helical structure will produce hemolysis effects, such as bombesin, cecropin, and melittin[76-78]. AMPs have a β-sheet structure that usually contains disulfide bonds with the number of one to four like the defensin[79-82].

2 The biological activities of AMPs

2.1 Antimicrobial activity

AMPs have a killing effect on microorganisms such as bacteria, fungi, bacterial biofilms, viruses, and parasites, in which the most striking feature is its antibacterial activity[5]. AMPs have two modes of killing microorganism. One is that AMPs act on the membrane to form pores on the cell membrane and impair the integrity of the cell membrane, resulting in the leakage of cell contents and cell death[83]; another is that AMPs target physiological processes in cells to inhibit cell respiration or DNA replication and transcription, and target organelles[84-86].

Most cationic AMPs interact with the surface of bacteria which has negatively charged[50] to damage the cell membrane through the classic models such as barrel-stave model[87], carpet model[88], and toroidal model[89]. The α-helical region of AMPs is bound by a hydrophobic interaction monomer, inserted into the membrane in parallel or vertically to form a barrel wall[90-91]. The carpet model is a kind of detergent-like mechanism that covers the surface of the membrane like a carpet after reaching the threshold concentration by AMPs[92]. The toroidal model is that AMPs are perpendicular to the membrane, but the internal and external structure of the phospholipid membrane is intact[77,93].

After entering the cell, AMPs can inhibit cell wall formation, nucleic acid synthesis, protein synthesis or enzyme activity[50,94]. Proline-rich AMPs bind to ribosomes, interfere with protein synthesis, and induce false protein folding[95-96]. For example, Histatin 5 specifically binds to Candida albicans cell membrane to induce ATP release and pathogen death[97].

Bacteria usually live in the multicellular community of biofilms, and some AMPs also have a good inhibitory effect on biofilms[98-99]. AMPs are often used in conjunction with antibiotics to exert immunomodulatory properties to treat biofilm infections[100-101]. AMPs can destroy viral envelopes, bind viral RNA polymerase complexes, inhibit viral replication, kill viruses, and prevent viral infections[102-104]. It has been reported that NP-1 peptide can interfere with the heparan sulfate receptor site on the plasma membrane of the cell to prevent HSV-2 infection[105].

2.2 Immunomodulatory activity

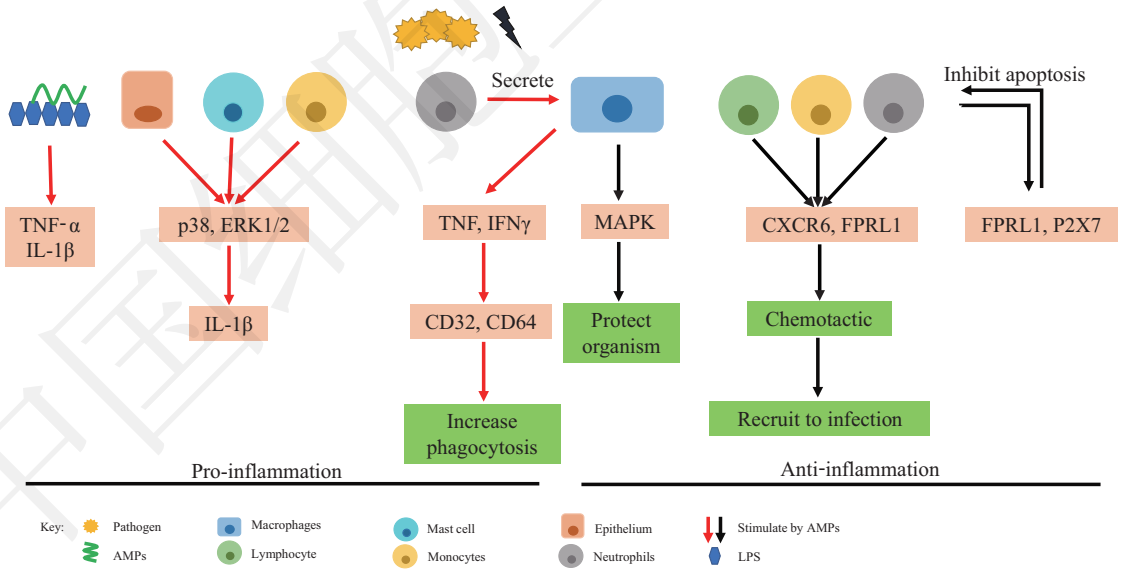
AMPs are part of the human innate immune system and are involved in multiple immune regulations, including anti-inflammatory, pro-inflammatory, skin immune barriers, and maintenance of biological homeostasis[106]. When the pathogen stimulates the body,

the immune response in the body is initiated, and the AMPs play an important role in anti-inflammatory and pro-inflammatory (Fig.1).

AMPs have the function of eliminating infection and regulating inflammation[107]. Host defense peptides such as LL-37, HNP-1, HNP-2, hBD-1, and hBD-2, indirectly promote immune cells like neutrophils, monocytes, and lymphocytes to the inflamed area[108]. The chemotactic properties of defensins and cathelicidins on neutrophils, monocytes, and T cells are mediated by human CC chemokine receptor 6 and formyl peptide receptor-like 1, indirectly promoting immune cell recruitment[109]. LL-37 also up-regulates chemokine MCP-1 and chemokine receptors CXCR-4, CCR2 and IL-10, and inhibits LPS-induced downstream NF-κB pro-inflammatory genes, NF-κB1 (p105/p50), TNF-α induction protein 2 (TNFAIP2) and interleukin (IL)-1β[101,108,110-111]. OH-CATH30 is a kind of AMP isolated from King Cobra protects mice with lethal sepsis by activating MAPK signaling pathway through macrophages[112]. LL-37 not only can kill bacteria but also activates FPRL1 and P2X7 to inhibit neutrophil apoptosis and prolong its lifespan, accompanied by increased reactive oxygen species or induced autophagy[113-114].

However, some studies also showed that AMPs have pro-inflammatory effects. Defensin released from neutrophils can increase bacterial phagocytosis by stimulating the production of TNF and IFNγ by macrophage to increase the expression of CD32 (FcγRIIB) and CD64 (FcγRI)[115]. LL-37 and HBD are conjugated to the G protein-phospholipase C pathway on mast cells, and the pro-inflammatory cytokine IL-18 can also be induced via the p38 and ERK1/2MAPK pathways[116]. LL-37 also induces the activation of p38 and ERK1/2 kinase in monocytes and epithelial cells[117].

Endogenous AMPs protect the skin from infection and accelerate skin proliferation. Studies have shown that LL-37 is strongly expressed in healing skin epithelium and neonatal skin[118-120]. Epidermal keratinocytes develop an innate immune barrier based on hBD and LL-37 during differentiation[121].



当病原体刺激时, 抗菌肽可以激发上皮细胞和免疫细胞产生促炎因子。中性粒细胞分泌的抗菌肽可以激活CD32和CD64, 增加对细菌吞噬作用。促炎反应由红色箭头指示, 抗炎反应由黑色箭头指示。抗菌肽能激活MAPK信号通路来保护生物体。抗菌肽能间接性促使免疫细胞向感染募集以增加抗炎反应。抗菌肽还能激活FPRL1和P2X7受体来抑制中性粒细胞凋亡。

When pathogens stimulate, epithelium and immune cells produce pro-inflammatory factors stimulating by AMPs. Neutrophils secrete AMPs which activate CD32 and CD64 to increase bacterial phagocytosis. The pro-inflammatory response is indicated by a red arrow while the anti-inflammatory response is indicated by a black arrow. MAPK signaling pathway is activated to protect organisms. Immune cells are chemotactic and indirectly recruited to increase anti-inflammatory response. AMPs activate FPRL1 and P2X7 to inhibit neutrophils apoptosis.

图1 抗菌肽的免疫调节活性

Fig.1 The immunomodulatory activity of AMPs

LL-37 and alpha-defensins regulate angiogenesis via endothelial cell adhesion and migration in a fibronectin (FN)-dependent manner[122-123]. AMPs are involved in the regulation of intestinal microbial commensal and pathogenic bacteria interactions in intestinal epithelial cells[124]. One of the AMPs, β-defensin-3, plays a role in mammalian ovarian development via the ERK1/2 pathway[125].

2.3 Anticancer activities

2.3.1 Melanoma In melanoma cells, the over-expression of AMPs LL-37 can induce the binding protein YB-1 expression through NF-κB signaling pathway to promote malignant melanoma cell proliferation, migration, and invasion[126-127]. In melanoma A375 cells, LL-37 can bind to the gene promoter region. If the LL-37 gene is silenced, the transcriptional program associated with histone, metabolism, cellular stress, ubiquitination and mitochondria are changed[128]. LL-37 is an endogenous agonist of the TRLs family, including TRL1-4, which has been shown to have important effects on the proliferation and migration of melanoma cells[129-130].

Other AMPs can inhibit the proliferation of melanoma cells by interfering with the structure of cell membrane and energy metabolism to induce apoptosis and cell cycle arrest. The plant AMP NaD1 promotes destabilization and cleavage of the cell membrane by binding to the plasma membrane phosphatidylinositol 4,5-diphosphate (PIP2) without entering the cell or causing apoptosis[131]. In mouse experiments, it was found that mastoparan, an AMP isolated from the venom of wasp, can kill melanoma cells and induce caspase-dependent apoptosis through the mitochondrial pathway[132]. In addition, the AMPN is in Z reduces the invasion, proliferation, and metastasis of melanoma cells by negatively affection the energy metabolism (glycolysis and mitochondrial respiration) of melanoma cells, increasing the production of reactive oxygen species and causing apoptosis[133]. Spider peptide gomesin can activate the cycle-regulated protein p53/p21 and Hippo signaling pathways, reduce the ratio of G_0/G_1 phase cells, and attenuate MAP kinase pathways to reduce melanoma progression[134]. The cathelicidin-5 with a modified structure inhibits melanoma by both membrane and non-membrane decomposition mechanisms *in vitro* and *in vivo*[135].

2.3.2 Lung cancer Lung cancer is one of the most deadly cancers in the world[136]. Different AMPs have different effects on lung cancer. hCAP-18/LL-37 is highly expressed in human lung cancer tissues and promotes lung cancer development by inducing phosphorylation of epidermal growth factor receptor (EGFR) and activation of downstream MAP kinase signaling pathway[137-138]. Regulation of cathelicidin expression involves bone marrow p65/RelA and soluble factors from tumor cells recruiting inflammatory cells to promote cigarette smoke-induced lung tumor growth[21]. Additional study has also supported the promotion of lung cancer cells by the CRAMP gene, which has a lower tumor burden and longer survival time[139].

Human β-defensin-3 and its mouse homolog Defb14 show the inhibition of tumor growth in tumor model mice. Subcutaneous injection of AMPs in lung cancer mice significantly reduced tumor weight[140]. Tilapia-derived AMP penetrates cells and targets microtubule networks to kill lung cancer cells[141].

2.3.3 Prostate cancer Prostate cancer is the third highest incidence of cancer in men after lung cancer and colorectal cancer[136]. CRAMP, an AMP isolated from prostate cancer cell-derived mouse, regulates the expression of growth factors and cytokines M-CSF and MCP-1, as well as mediates early bone marrow cell differentiation and polarization into primitive M2 macrophages through STAT3/6 signaling pathway to promote cell growth of prostate cancer[142]. CRAMP expression is significantly higher in mouse prostate tumors than in normal tissues, and knockdown of CRAMP decreases proliferation, invasion and type IV collagenase of prostate tumor cells via phosphorylated Erk1/2 and Akt signaling pathway *in vitro*[143].

Lactoferrin is a functional carrier internalizes doxorubicin through receptor-mediated endocytosis into prostate cancer cells to enhance immunity and complement chemotherapy[144]. The AMP of Ranatuerin-2PLx isolated from the skin secretions of the pickerel

frog inhibits the proliferation of prostate cancer cells through inducing apoptosis[145]. The specific human defensin-1 deletion was found in human prostate cancer cells, exogenous human defensin-1 can inhibit prostate cancer cell proliferation, indicating human defensin-1 is a candidate tumor suppressor gene[146].

2.3.4 Breast cancer LL-37 is an important part of the congenital defense in human mammary epithelium[147]. The study founds that LL-37 is strongly expressed in breast cancer cells but not expressed in stromal cells, and the up-regulation of hCAP18/LL-37 is closely related to the expression of ERB2 in breast cancer cells. hCAP18/LL-37 amplifies MAPK signaling through ErbB2 which is stimulated by breast cancer cells to promote breast cancer cell growth and migration[148-149]. LL-37 can act as a partial agonist of IGF-1R, followed by the binding of β-arrestin-1 to IGF-1R to drive intracellular signaling, resulting in increased migration and invasion potential of malignant cells[150]. It has also been reported that LL-37 is an agonist of CXCR4 to enhance breast cancer migration and promote breast cancer development[25]. However, the natural antimicrobial plant defensin PvD1 interferes with the formation of solid tumors in the breast while it can inhibit metastasis of breast cancer cells[151].

2.3.5 Colon cancer LL-37 activates the GPCR-p53-Bax/Bak/Bcl-2 signaling cascade to trigger AIF/EndoG-mediated apoptosis in colon cancer cells, as well as LL-37 induces non-caspase-dependent apoptosis and even inhibits the activity of some related enzymes[152]. LL-37 also inhibits colon cancer development by interfering with EMT (epithelial-mesenchymal transition) and fibroblast-supported proliferation of colon cancer cells[153]. Lactoferrin is involved in colon cancer suppression by apoptosis caused by elevated Fas expression[154]. Circular LfcinB and linear LfcinB exert antitumor activity by differentially activating various signaling pathways including p53, apoptosis and angiogenin signaling. Western blot results confirmed that both bLf and LfcinBs increased the expression of caspase-8, p53, and p21 which are key proteins in tumor suppression[155].

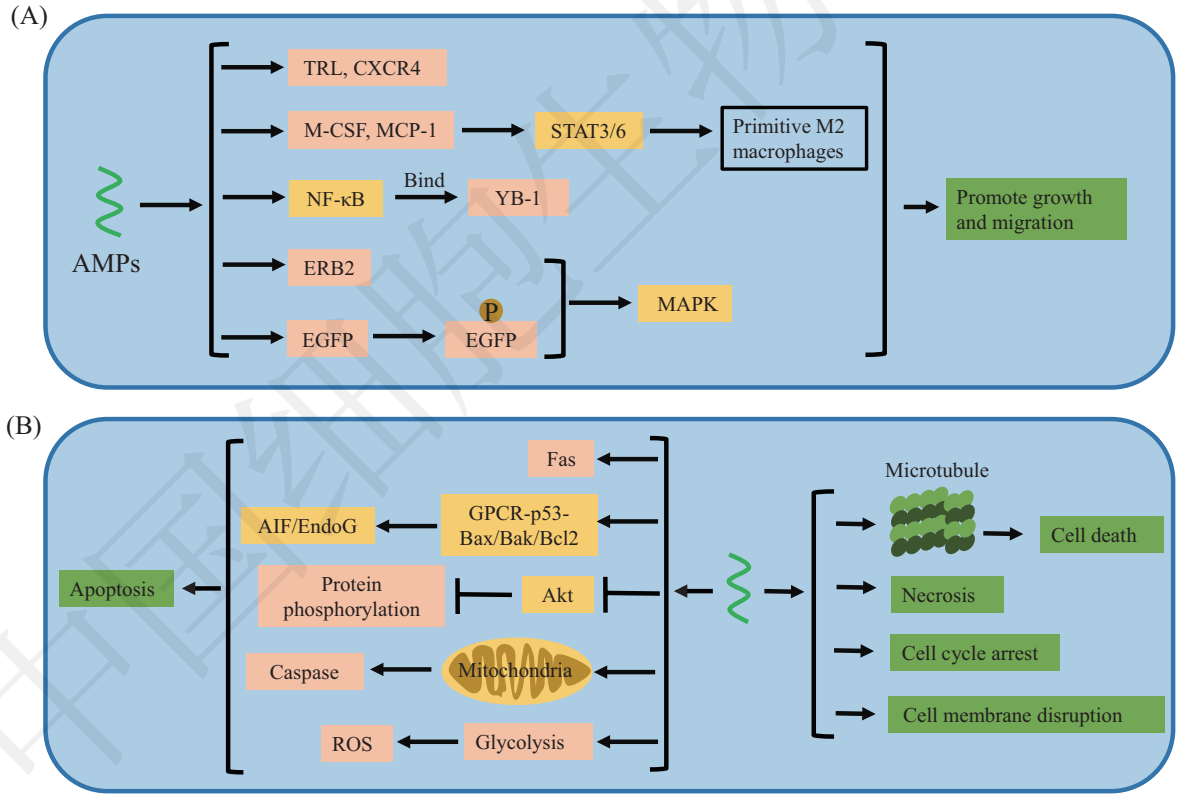
The mechanisms involved in the apoptosis induced by cationic AMPs KT2 and RT2 are accompanied by the down-regulated expression levels of Bcl-2, cyclin B1 and D1, as well as the up-regulated expression levels of p53, cytochrome c, caspase-2, caspase-3, caspase-8, and caspase-9, and cyclin p21[156]. hBD-3, produced by tumor-infiltrating monocytes, inhibits the migration instead of proliferation in colon cancer cells in a dose-dependent manner[157]. HNP1-3 is significantly increased in the plasma of patients with colorectal cancer, suggesting that HNP1-3 is a prognostic assessment marker and a potential marker of chemotherapy of colorectal cancer patients[158].

2.3.6 Gastric cancer Chronic gastritis is associated with tumor formation in the stomach. LL-37 has high expression in gastric inflammation and low expression in gastric tumor tissues, indicating that LL-37 may play an inhibitory role in gastric canceration[159-160]. LL-37 is down-regulated in gastric adenocarcinoma and activates BMP signaling via a proteasome-dependent mechanism to inhibit gastric cancer cell proliferation[161]. LFcinB25 induces the activation of apoptosis-associated caspase-3,7,8,9 and PARP, as well as the increase of autophagy-associated LC3-II and beclin-1 simultaneously during the treatment of LFcinB25 for 2 to 6 hours. Therefore, both apoptosis and autophagy are involved in the early stages of LFcinB25-induced the gastric cancer cell line AGS to death. Later, LC3-II began to decrease, while cleaved beclin-1 increased in a time-dependent manner, indicating that continuous activation of caspase cleaves beclin-1 to inhibit autophagy and thereby enhance apoptosis[162]. Lactoferrin inhibits Akt activation and regulates its downstream protein phosphorylation of apoptosis in SGC-7901 human gastric cancer cells[163]. Melittin induces apoptosis in human gastric cancer (GC) cells via the mitochondrial pathway[164].

CopA3 is an AMP identified from *Copris tripartitus* that causes necrosis of gastric cancer cells primarily through interaction with phosphatidylserine[165]. HNPs 1-3 increase nearly tenfold in gastric cancer tissue and have potential as biomarkers for gastric cancer[166]. Some

synthetic AMPs not only have good antibacterial activity but also have a good inhibitory effect on cancer cells. Treatment of gastric cancer cells with synthetic cationic AMPGW-H1 inhibits cell proliferation by inducing apoptosis and autophagy[167].

2.3.7 Leukemia Polybia-MPI is a short cationic α-helical AMP that is selectively toxic to leukemia cells and has no hemolytic activity. Polybia-MPI targets cell membranes of leukemia cells through plasma membrane perturbation[168]. LL-37-induces apoptosis in Jurkat T leukemia cells by caspase-independent while calpain- and AIF-dependent manner, involving Bax activation then translocation to mitochondria[169]. Lactoferrin triggers apoptosis through the mitochondrial pathway, producing reactive oxygen species to inhibit the proliferation of human leukemia and carcinoma cells[170]. Lactoferrin-derived peptides are concentrated in their helical structural regions, which induce snecrosis in leukemia cell lines (HL-60), and induces apoptosis in Jurkat T cell line via JNK-associated Bcl-2 signaling pathway[171-172]. Another lactoferrin-derived peptide is capable of inducing apoptosis in THP-1 tumor cells by producing intracellular ROS and activating Ca^{2+}/Mg^{2+}-dependent endonucleases[173]. PFR peptide inhibits MEL and HL-60 leukemia cell proliferation by inducing necrosis and cell cycle arrest[174]. The goat AMP ChMAP-28 penetrates the cell membrane and destroys the integrity of leukemia cells to induce necrotic death of leukemia cells[175]. The molecular mechanisms of promotion and inhibition effects of AMPs on the proliferation of various tumors cells were shown in Fig.2.



A: 抗菌肽通过激活STAT3/6、NF-κB和MAPK信号通路来促进癌细胞的生长和迁移。另外, 抗菌肽是TRL和CXCR4的激动剂, 可促进癌症的发展。B: 抗菌肽通过破坏膜结构和靶向细胞内生理反应来抑制癌细胞的增殖。抗菌肽可以通过不同的信号途径诱导癌细胞自噬, 坏死和凋亡。抗菌肽还能通过靶向微管网络和细胞周期来抑制癌症。

A: AMPs promote growth and migration through activating STAT3/6, NF-κB, and MAPK signaling pathways. AMPs are an agonist of TRL and CXCR4 to promote cancer development; B: AMPs inhibit the proliferation of cancer cells by disrupting membrane structure and targeting intracellular physiological responses. AMPs can induce autophagy, necrosis, and apoptosis through the different signal pathway. Targeting microtubule networks and cell cycle are also ways to inhibit cancer.

图2 抗菌肽可以促进或抑制癌细胞的增殖

Fig.2 AMPs can promote or inhibit the proliferation of cancer cells

3 Conclusion

AMPs can kill a variety of microorganisms, and the anti-microbial function is mainly through membrane lysis and targeting intracellular physiological processes. Most of the cationic AMPs act on the membrane to destroy membrane structure and release cell contents with the resultant microorganisms die. AMPs also can interfere with the basic physiological activities of cells, including protein synthesis and mitochondrial function. Although most of the AMPs have the ability to inhibit proliferation of tumor cells by apoptosis, necrosis and autophagy pathway. Recent evidence showed that some AMPs may have anti- and pro-cancer characteristics through complex physiological regulation. For example, LL-37 has been reported to be involved in the development of various cancers, including melanoma, lung cancer, and prostate cancer. LL-37 promotes the proliferation of breast cancer cells indirectly; while LL-37 inhibits the proliferation of the cancer cells in colon cancer and gastric cancer through different pathways. Due to the low cytotoxicity and broad-spectrum activities of AMPs in antibacterial and anticancer, it is urgent to thoroughly investigate the effects and mechanism of AMPs, as well as to develop more efficient agents for cancer therapy.

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