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Review

The anticancer mechanism of human antimicrobial peptide LL-37

Aqeel Ahmad[1*], Mohammed Ali Mullah Fawaz[2]
[1]Department of Medical Biochemistry, College of Medicine, Shaqra University, Saudi Arabia
[2]Department of Microbiology, Sri Sai College of Dental Surgery, Vikarabad, Hyderabad, India

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ABSTRACT

Human antimicrobial peptides LL-37 have a variety of medicinal uses. It has been portrayed that this peptide has robust tumoricidal action in a range of malignancies, particularly ovarian cancer, lung cancer, breast cancer, prostate cancer, pancreatic cancer, malignant melanoma, and squamous cell carcinoma of the skin. It exhibits substantial anticancer action against a range of cancers, including colon cancer, gastric cancer, hematologic malignancy, and oral squamous cell carcinoma (OSCC), in comparison. In this review, we explored in depth the anticancer mechanism of action of LL-37 in numerous sorts of cancer. We have shown how LL-37 impedes colon cancer by eliciting caspase-independent apoptosis. LL-37, in addition, has been noticed to boost tumor-suppressive bone morphogenetic protein signaling in gastric cancer cells via restricting the proteasome, which has been previously reported. In this research, we investigated how DNA methylation interferes with the activity of the human CAMP (Cathelicidin antimicrobial peptide gene) promoter and, as a result, acts as a tumor inhibitor in mouth squamous cell carcinoma. Additionally, how LL-37 inhibits cancer cell development in hematologic malignancy has been explored through caspase-independent but Ca2+/calpain- and AIF-dependent processes.

Introduction

Antimicrobial peptides (AMPs) are short peptides, typically fewer than 100 amino acids in length, generated by all species, from bacteria to humans, that serve as the first line of defense against a wide variety of diseases.[1-2] Numerous AMP have also been synthesized and developed synthetically from naturally existing antimicrobial peptides.[2-7] AMPs are classified into four types based on their structure: (1) alpha-helical; (2) beta-sheet; (3) extended A); and (4) beta-hairpin or loops.[8] The AMP demonstrates many forms of action, including the carpet model, the barrel-stave model, and the toroidal model. The AMPs exhibit a variety of biological actions, including immunomodulation, antiparasitic, antifungal, antibacterial, and anticancer activity, wound healing, and angiogenesis, as well as anticancer and contraceptive activity[9]. Additionally, several AMPs were shown to be very toxic to mammalian cells,

*Corresponding author at: Department of Medical Biochemistry, College of Medicine, Shaqra University, Shaqra-11961, KSA
E-mail address: draqeel@su.edu.sa
https://orcid.org/0000-0002-6003-9404
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limiting their use as therapeutic agents. As a consequence, various efforts to diminish the toxicity of these peptides while retaining their antibacterial effect have been explored.[2,3,5,6]

LL-37 is a human antimicrobial peptide (HAMP) that was noticed in myeloid bone marrow cDNA and alienated from human neutrophils.[10] Cathelicidin exons 1-4 are sited on human chromosome 3p21.[11] LL-37 is manufactured by proteolytic degradation of the hCAP18/LL-37 antecedent protein's C-terminal domain. It has been unearthed that LL-37 is cationic at physiological pH, with a net charge of +6, and is inherently hydrophobic at the N end [12] (Figure-1). The human antimicrobial LL-37 was proven to have biological action against bacteria, fungi, viruses, and parasites.[12] Additionally, LL-37 demonstrated a wide variety of other capabilities, including wound healing, immunomodulation, angiogenesis, cell signaling, apoptosis, and anticancer activity.[12] The growing body of evidence indicates that the human antimicrobial peptide LL-37 protects our urinary system against bacterial infections.[13] Putsep et al. discovered that a deficit in saliva LL-37 correlates with the development of periodontal disease in individuals with Morbus Kostmann.[14] As previously stated, most AMPs, including the HAMP LL-37, had strong anticancer activity. In this assessment, we investigated the impact of LL-37 in the progression and invasion of numerous aspects of cancer, including lung and pancreatic. Also, we have investigated the anticancer effects of LL-37 in several sorts of cancer. Additionally, we investigated the mechanism of action of LL-37 in cancer treatment in several types of cancer.

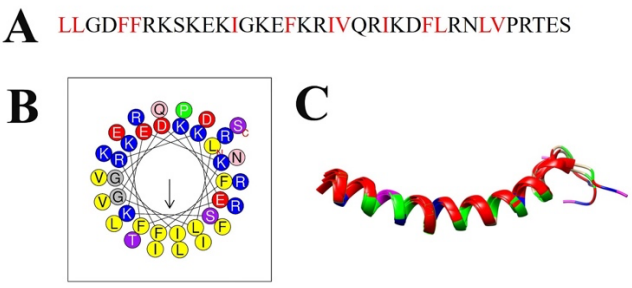

Figure 1: The amino acid sequence, helical wheel plot, and secondary structure of the LL-37 antimicrobial peptide are shown in Figure 1. The sequence of the antimicrobial peptide LL-37 was presented in Figure-1A. The helical wheel projection of human antimicrobial peptide LL-37 was demonstrated in Figure-1B. The hydrophobic (Yellow) and hydrophilic (Blue) amino acids were illustrated in the program (https://heliquest.ipmc.cnrs.fr/cgi-bin/ComputParams.py) (Anionic and cationic amino acid are red and blue respectively). The secondary structure (PDB:2K6O) of LL-37 produced by the UCHF chimera is seen in Figure-1C.

Role of LL-37 in cancer

Cancer is a severe global public healthcare concern, with millions of people dying each year. Radiation treatment, chemotherapy, surgery, hormone therapy, immunotherapy, and chemoradiotherapy are all detrimental to cancer cells under the current cancer care paradigm.[15] Additionally, the cancer treatment approach incorporates RTK or kinase inhibitors, which are available as monoclonal antibodies or small chemical compounds.[16] While these medications are effective against a variety of tumor forms, they may cause serious adverse effects and exhibit high cellular toxicity.[15] Additionally, hypoxic cells are less responsive to a variety of conventional anticancer therapies in cancers that have slowed their development.[17]

Intriguingly, overexpression of the HAMP LL-37 has been found in a diversity of cancers such as lung cancer, breast cancer, ovarian cancer, prostate cancer, malignant melanoma, and skin squamous cell

carcinoma, and these over expressions have been shown to promote the progression and invasion of these cancers.[18] As a result, it has the potential to be employed as a biomarker for some forms of cancer. We already know that the HAMP LL-37 has strong tumorigenic effects in the above-mentioned malignancies, and this has been shown in a variety of ways, which we will not cover in this paper.[19]

Numerous antimicrobial and new peptides have been produced that have considerable anticancer activity against a variety of cancer cell types.[20] Numerous research has evidenced that the HAMP LL-37 has remarkable anticancer activity. The expanding research evidenced that LL-37 expression is reduced in multiple cancers when contrasted to normal tissue. LL-37 is plentifully voiced in healthy colon mucosa but is undetectable in colon cancer tissue. As a result, they may potentially be employed as a biomarker for colon cancer.[21] When colon cancer was treated with the LL-37 peptide hooked up to magnetic nanoparticles, a wider reduction in cell viability as well as a broader prevalence of apoptosis ensued than when the LL-37 peptide was employed alone.[22] The HAMP LL-37 was exhibited to have anticancer efficacy when assessed against gastric cancer, as well. LL-37 amounts in gastric cancer tissue were observed to be much reduced than those seen in healthy gastric cells, according to the findings.[23] Chen et al in 2017 showed that the LL-37 peptide is involved in the suppression of oral squamous cell carcinoma (OSCC).[24] Additionally, it was shown that OSCC expresses less LL-37 than normal oral mucosa tissues, comparable to colon and gastric cancer.[24] Additionally, LL-37 exhibited considerable anticancer activity against cells derived from hematological malignancies. According to the research, the cathelicidin-derived peptide LL-37 peptide is capable of killing malignant cells in Burkitt's lymphoma (BL).[18,25]

Anticancer mechanism of LL-37

Many findings have uncovered that the membranes of malignant cells are anionic, while the membranes of healthy cells are neutral in their charge.[20] In malignant cells, the accessibility of the negatively charged lipid phosphatidylserine, which is situated on the exterior leaflet of the cell membrane, is a crucial contrast between malignant and non-cancerous cells.[26] A variety of explorations have revealed that cancer cell membranes vary from non-cancerous cell membranes in numerous aspects, including the existence of cholesterol and a range of anionic components, among other things.[26] Many cationic AMPs electrostatically interact with negatively charged membranes of cancerous cells and lyse them. Moreover, these cationic peptides form a significant helical structure, and it may probably help in their anticancer activities.[20] The study suggested that LL-37 form significant helical structures which contribute to their biological activities[27] (Figure 1). When cancer cells were contrasted to healthy cells, certain extra membrane components such as sialic acids, proteoglycans, and phospholipids were revealed to be substantially elevated on the exterior of cancer cells.[28] It has been showcased that the number of PGs on the surfaces of malignant cells is far powerful than that on the exterior of healthy cells. All the variables listed above enable the human multifunctional peptide LL-37 to preferentially lyse malignant cells while leaving the normal cells unaffected.[28]

The HAMP LL-37 is known to have a role in the growth and invasion of numerous forms of cancer. Simultaneously, it acts as an anticancer agent against numerous forms of cancer. As a result, the mechanisms discussed above are all-purpose mechanisms of action. Recently, recent research offered numerous novel pathways for particular forms of cancer, which we shall examine in depth below.

P53 is a gene that aids fight cancer. It is on the short arm of chromosome 17 inside the nucleus of cells. It helps manipulate cell progress and cell destruction. Mutations (deletions) in the p53 gene may accelerate the exploration and proliferation of cancer cells throughout the body. Bax and Bak are two nuclear-encoded proteins that operate as proapoptotic factors in higher eukaryotes. Bcl-2 is an antiapoptotic (Oncogenic) protein located on mitochondrial outer membranes. The mitochondrial intermembrane gap

harbors nucleases which include apoptosis-inducing factor (AIF) and endonuclease G. The HAMP LL-37 elevates the quantity of p53 protein in colon cancer possibly engaging the G protein-coupled receptor (GPCR). Increased p53 levels activate the Bax/Bak/ pathway, resulting in a reduction in bcl-2 levels[18] (Figure 2). It is believed that the surge in AIF and EndoG contents in the nucleus is accountable for caspase-independent apoptosis and the restriction of cell expansion.[21] Another way, the HAMP LL-37 halts the progress of the tumor growth factor-1 (TGF-1) epithelial-mesenchymal transition (EMT) of colon cancer cells, which led to less fibroblast availability, less cell propagation of fibroblast-associated colon cancer cells, and less colon tumor growth.[29] Several more pathways contribute significantly to the lowering of colon cancer growth. For instance, LL-37 raises the amount of miR-663a, a kind of microRNA, in colon cancer (Figure 2). This suppresses CXC chemokine receptor type 4 (CXCR4) appearance, culminating in Akt dephosphorylation and cell cycle halt in G2/M in colon cancer cells via p21 stimulation[30] (Figure 2).

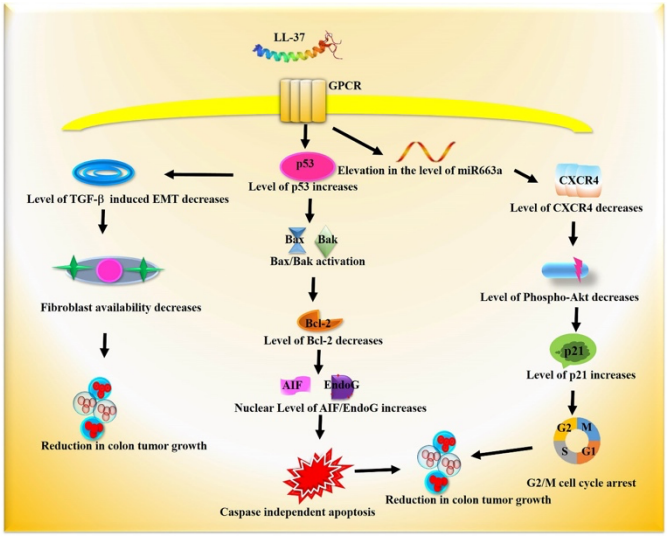

Figure 2: A model illustrating the anticancer mechanism of HAMP LL-37 in colon cancer.

The HAMP LL-37 suppresses gastric cancer cells via BMP-dependent and BMP-independent routes, according to emerging evidence[23] (Figure 3). LL-37, through blocking the proteasome, promotes the tumor-suppressive bone morphogenetic protein (BMP) signaling route in gastric cancer cells, contributing to a diminution in tumorigenesis[23]. Amplification of BMP signaling recruits and phosphorylates Smad 1/5/8, which then creates heterodimers with Smad4, and the ensuing Smads complex stimulates the yield of p21Waf1. Alteration in the expression levels of p21Waf1 and cyclin E2 may culminate in cell cycle stoppage in the G0/G1 phase, according to the researchers.[18] Additionally, they suppress gastric cancer through BMP-independent mechanisms (Figure 3). LL-37 blocks cyclin E2, succumbing in inhibition in the G0/G1 phase and a reduction in the expansion of gastric cancer.[18] The AMP LL-37 from humans illustrates a third manner in which formyl peptide receptor 1 (FPR1) may employ as a tumor moderator in human gastric cancer by limiting angiogenesis[31] (Figure 3).

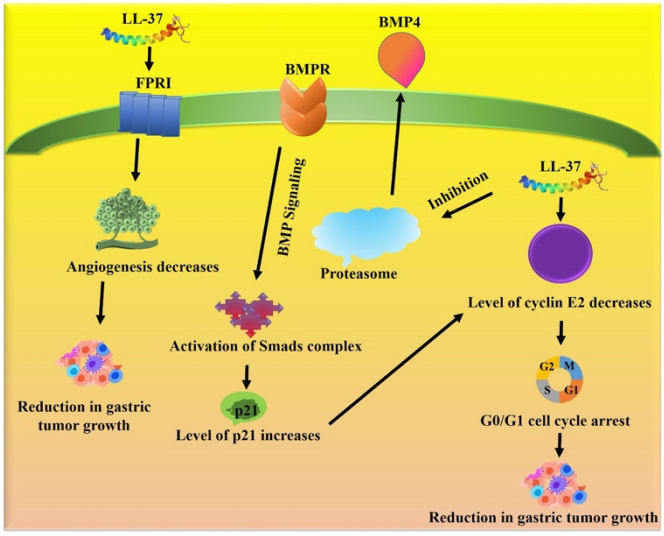

Figure 3: A model exhibiting the anticancer mechanism of HAMP LL-37 in gastric cancer.

It has been evidenced that the HAMP LL-37 inhibits tumor advancement in a range of distinct cancer cells, including OSCC and hematologic malignancy. Consequently, OSCC has a reduced amount of LL-37. It was realized by Chen and colleagues that DNA methylation reduces the human CAMP promoter activity and, as a consequence, acts as a tumor inhibitor in OSCC.[24] Apoptosis, which is not reliant on caspases but rather dependent on Ca2+/calpain and AIF, seems to be the mechanism by which the LL-37 therapy kills Jurkat T leukemia cells.[32] AIF was discovered to be released from mitochondria and enter the nucleus, inducing apoptosis in Jurkat T leukemia cells.[32] Hoffmann et al. illustrated that inflammatory M1 macrophages eradicate expanding B cell lymphoma cells through the generation of the AMP in a vitamin D -dependent fashion. Cathelicidin eliminates cells instantly by precisely aiming at the mitochondria of Burkitt's lymphoma (BL) cells. Vitamin D signaling route stimulation boosts the anticancer activity of tumor-associated macrophages (TAM) and the efficacy of antibody-dependent cellular cytotoxicity (ADCC) towards BL cells.[25]

Conclusion

AMPs have been implicated in the development and invasion of a variety of cancers. However, they also have anticancer action against a variety of cancers. LL-37 showed anticancer activity against a variety of cancer types, including colon cancer, gastric cancer, OSCC, and hematologic malignancy. The LL-37 peptides attack cancer cells in a variety of ways. In colon cancer cells, for instance, a method has been postulated in which LL-37 lights up a GPCR-p53-Bax/Bak/Bcl-2 signaling chain to elicit AIF/EndoG-guided apoptosis. In OSCC, the LL-37 DNA methylation position in the human CAMP promoter region hinders tumor formation. LL-37 inhibits the expansion of Jurkat T leukemia cells in hematologic malignancies by triggering caspase-independent but calpain- and AIF-dependent apoptosis. LL-37 eliminates Jurkat T leukemia cells in hematologic malignancy by eliciting apoptosis via a route that is caspase-independent and calpain- and AIF-dependent.

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Conflicts of Interest

The author declares that there are no conflicts of interest relevant to this article.

Abbreviations

Oral squamous cell carcinoma (OSCC), cathelicidin antimicrobial peptide gene (CAMP), antimicrobial peptides (AMPs), human antimicrobial peptide (HAMP), Burkitt's lymphoma (BL), apoptosis-inducing factor (AIF), endonuclease G (Endo G), G protein-coupled receptor (GPCR), tumor growth factor-1 (TGF-1), CXC chemokine receptor type 4 (CXCR4), epithelial-mesenchymal transition (EMT), tumor-associated macrophages (TAM), antibody-dependent cellular cytotoxicity (ADCC), formyl peptide receptor 1 (FPR1).

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