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Multitarget Effects of Cross-Cancer Melittin in Reversing Chemotherapy Resistance in Solid Tumors: Focus on Breast Cancer, Ovarian Cancer, and Non-Small Cell Lung Cancer

Xinxin Wang

School of Health Sciences, Guangzhou Huashang College, Guangzhou, China
heeeunjam1@gmail.com

Abstract. The drug resistance to chemotherapy is a major setback in the management of the solid tumor minimalizing the efficiency of the chemotherapy and the chances of recurrence. This is a significant challenge to cancer treatment because long-term treatment can only be successful with this resistance. Recent research indicates that one of the active polypeptides in the bee venom, Melittin has multi-target effects, which can even reverse drug resistance in various forms of cancer and this points to the use of Melittin as a combination therapy alongside other drugs. In this paper, Melittin showed specific cancer-selective effects on the three common solid tumors namely: breast cancer, ovarian cancer and non-small cell lung cancer. Melittin plays its functions in breast cancer through two of the most important signaling pathways EGFR/HER2 and PI3K/Akt. Melittin interferes with these signaling networks inhibiting the survival of breast cancer cells and can potentially delay tumor growth. Melittin in ovarian cancer has the ability to disturb the lipid section and energy metabolism of cancer cells. Melittin has two vital roles in a non small cell lung cancer (NSCLC), which contributes to its effectiveness as a therapeutic candidate. To begin with, it promotes the natural body processes of apoptosis, which simply initiate self-destruction process among cancer cells. Second, Melittin suppresses anti-death mediation pathways, including the occurrence of NF-Kb, the involvement of which is essential facilitating the survival of cancer cells and their further proliferation. These mechanisms combined, combine to render Melittin an important ally in the fight against chemotherapy resistance, which is one of the main issues in the treatment of solid tumors. In addition to highlighting the promise of Melittin in augmenting traditional chemotherapy, this study forms the basis of designing therapy combinations that target specifically chemotherapy resistance.

Keywords: Melittin, chemotherapy resistance, multi-target effects, cross-cancer types

1. Introduction

Cancer happens to remain one of the most widespread illnesses throughout the globe. As of 2022, approximately 20 million cases were new, and 9.7 million were associated with deaths due to the disease. Some of the leading causes of illness and death due to cancer are lung, breast, and colorectal cancer.

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The present-day methods of treating cancer have such approaches as surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy, yet all of them have their disadvantages. Such treatment methods as chemotherapy, however, continue to be one of the pillars in the treatment of solid tumors, but may lack specificity and may damage normal cells causing severe side effects. The targeted therapies and immunotherapy provide a more specific method of approach, which is a significant advantage. Nonetheless, they have their own challenges: resistance to drugs, expensive nature, and ineligibility to many patients. Chemotherapy resistance has become one of the key obstacles to meet these challenges. It acts as a barrier to good treatment and enhancing the prospective patient outcomes.

In some types of cancer, including non- small cell lung cancer, ovarian cancer and triple-negative breast cancer, chemotherapy resistance is difficult. The initial effect of chemotherapy is rather successful, but the drug resistance to multidrug emerges rapidly. This causes reduced response rate, increased chances of recurrence, and poor patient survival. Better still, there are mechanisms of resistance of each. To say the least, the triple-negative breast cancer is commonly amplified with Mcl-1 and non-small cell lung cancer is commonly mutated with PIK3CA. Such changes are unique and, therefore, challenging to beat drug resistance. Therefore a high priority on cancer research is to find agents that will counter chemotherapy resistance.

Melittin is a natural peptide with actual potential of overcoming that resistance [1]. It acts on various pathways of resistance, and changes drug resistance-related proteins. This paper will explore how Melittin can induce tumors to be sensitized towards chemotherapy and conquer the resistance in these three tumors.

The main topic of this research is to determine the molecular processes of Melittin in controlling the major drug resistance pathways, such as the PI3K/Akt pathway. It also examines the action of Melittin on drug efflux pumps and anti-apoptotic proteins. Melittin has potential as it can reverse the processes that enable cancer cells to evade therapy owing to its ability to be directed to these vital areas. The results have a solid case in favor of Melittin as drug resistance reversal agent and it could have a significant role in the discovery of new adjuvant T. These treatments aim at overcoming drug resistance with various types of cancer. They will contribute to the better results of the treatment process and overcome one of the major challenges of cancer treatment today.

2. Overview of Melittin (MEL)

Melittin is the primary cationic antimicrobial peptide in the venom of bees -comprising approximately half the dry weight of venom. It consists of 26 amino acid residues, and the molecular weight is approximately 2.8 kDa. The peculiarity of this peptide is that it is amphiphilic in its structure due to the uneven distribution of polar and nonpolar amino acids. This arrangement allows Melittin to be soluble in water and act upon cell membranes, which is the most important part of the mechanis.

3. Pharmacological MEL studies

The natural cationic antimicrobial peptide MEL (Melittin) It is multi-target and multi-dimensional, which means that this natural peptide combines the effect of antibacterial and anti-inflammatory effects, anti-tumor and other biological effects, and is not dependent on a specific target (overall functionality). MEL affects the integrity of bacterial cell membranes and prevents Gram-positive bacteria as well as some Gram-negative bacteria (antimicrobial) [2]. It has some anti-inflammatory and analgesic effects and also shows immunomodulatory properties based on the pertinent studies.

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(Anti-inflammatory)Similar to the effects on anti-tumor effects, it entails complex mechanisms. It also shows at the cellular level the interaction of it with the immune system. It is able to address tumor cell membranes, cause tumor cell-apoptosis, and control tumor associated signaling pathways (anti-tumor effects).

3.1. Antibacterial pharmacological activitys

MEL can be considered the representative of natural antimicrobial peptides, having the wide spectrum of antimicrobial activity and limited chances of causing drug resistance. It is attracted to the phospholipid bi-layer of bacterial cell membranes by its cationic nature and interferes with membrane integrity to create pores. This causes cytoplasmic hemorrhage and death of bacteria. It works better against Gram-positive than Gram-negative bacterium because of the outer membrane shield girdle role in the latter.

Gram-positive Staphylococcus aureus, Streptococcus, Gram-negative Escherichia coli and Salmonella and fungi such as Candida albicans and Aspergillus are all antimicrobial spectrum. It is still inhibitory against multidrug resistant strains (e.g.MRSA).

Interaction with antibiotics (penicillin and cephalosporins) improves antimicrobial activity, and hence, enables the reduction in doses of antibiotics and lowers resistance development.

3.2. Immunomodulatory pharmacological effects anti-inflammatory pharmacological effects

MEL controls the inflammatory processes and the activities of immune cells to normalize the immune bodies of the body [3]. Inhibits transcription and release of inflammatory mediators (e.g., TNF-a, IL-1b, IL-6, NO), it blocks the stimulation of inflammatory signalling pathways (NF-bKB, MAPK),which in turn its ability to suppress cyclooxygenase (COX-2) and lipoxygenase (LOX) as well as the synthesis of inflammatory mediators prostaglandins and leukotrienes. Immunomodulatory actions enhance T lymphocytes subset balance, increase their functional capacities of macrophages and phagocytosis, boost antigen presentation capacities, and suppress hyperplastic growth of regulatory T cells (Tregs), stimulate the presence of immunoglobulin secretions and reinforce immune system humoral immune system [3] .

3.3. Additional pharmacological effects

The Melittin also have several pharmacological properties such as analgesic and anticoagulant [4]. Melittin can be used as analgesics and relieves inflammatory and neuropathic pain. It achieves this by preventing the transmission of the pain signals, reducing the excitability of neurons in the dorsal horn of the spinal cord and decreasing the release of the pain mediators such as substance P and calcitonin gene related peptide. In relation to anticoagulation, Melittin in low concentration deter platelet aggregation and increases the time frame of clotting. The mechanism of this effect is the interference of platelet membrane receptors interaction and inhibition of thrombin activity. It is however worth noting that it can cause hemolysis in high concentrations hence attentive dosage should be taken.

3.4. Antiviral effects

Melittin is possible to attach to the viral envelopes and destroy its structure, preventing the viruses such as HIV, influenza and hepatitis B to access and infect host cells. It has a relatively low capability of inhibiting the non-enveloped viruses.

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3.5. Factors which do influence pharmacological effects

Melittin possess peculiar benefits in antitumor and reversal of drug resistance. Nonetheless, there are several limitations to clinical use: lack of stability (resulting in rapid degradation by endogeneous proteins), short half-life (impaired by absence of selectivity between tumor and normal cells), insufficient targeting (incidentally leading to absence of specificity), and low bioavailability (making it clear rapidly upon administration of free forms). This makes it need high dosing in order to be effective and increases the risk of toxicity further. These deficiencies give a proper guideline on how structural change and optimization of delivery system can be realized. To improve the clinical application potential of Melittin, structural modifications are possible e.g. with acetylation or PEGylation or delivery using nanocarrier systems is possible. These are effective strategies to enhance stability, target abilities and minimize hemolytic toxicity [5]. The biologic effects of Melittin are dose-dependent. The primary immunomodulatory effects they have are at low doses, whereas at medium and high doses, they also show strong antitumor activity. Also, the efficacy is determined by the tumor microenvironment factors (acidity and high osmotic pressure) which contribute to the destruction of the tumor cell membrane by Melittin.

4. Multi-target pharmacological activities of Melittin in overcoming chemotherapy resistance

Melittin exhibit anti-tumor effects, yet the most notable feature of them is the reversal of the chemotherapy resistance. These peptides exhibiting distinctive amphiphilic α-helical structure directly insert into tumor cell membranes. They disrupt membrane integrity, triggering an enormous reactive oxygen species buildup and triggering the mitochondrial apoptosis pathway to effectively kill a variety of tumor cells, including drug-resistant ones, which preconditions the resistance to overcome it.

Melittin at the molecular level interferes with some of the most important pathways of drug resistance development in tumor cells. An inelastic thing about it is that it reduces the expression of drug efflux pumps-such as P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP) [6] . These types of pumps expel chemotherapy drugs out of cancerous cells; this lowers the concentration of the drugs, leaving more in the cells, thus causing the drugs to be more effective.

In addition to this, Melittin inhibits vital pro-survival signaling pathways, including PI3K/Akt/mTOR and NF- -B. Such signaling happens to be mostly operational in cancer cells and its presence enables them to survive, proliferate, and be impervious to treatment. The inhibition of these pathways causes the cancer cells to become less resistant and they become more vulnerable to chemo.

Melittin also has potential of attacking tumor stem cells- the cells that seen to be the cause of the cancer persisting and recurrence after treatment. They tend to be more immune to usual cures. Melittin down-regulates several behavioral stem cell markers (such as CD44 and ALDH1) and prevents their self-renewal capability. This reduces the chances of the tumor reoccurring as well as decreases the heterogeneity of the tumor and Melittin is even more appealing as a therapeutic to combat drug resistance.

Melittin has various targets- cell membranes, signaling pathways, tumor stem cells- that provides a solid pharmacological basis of overcoming drug resistance. Its mode of operation is relatively specific to the types of cancers. As an illustrative example, in breast cancer, it interferes with EGFR/HER2 signaling, in ovarian cancer, it disturbs the energy metabolism and lipid balance. This is why this is a common approach to a baseline, unique approach to increase efficacy, and thus Melittin is a unique cross-cancer drug resistance reversal strategy that has a promising future.

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5. Animal experiments of Melittin resistance

It is on this background that, with the ever-growing clinical adversities that are presented by multidrug-resistant bacterial infections, Melittin has shown great potential to be used as natural antimicrobial peptides in fighting drug-resistant bacteria. The corresponding experiments allowed achieving a systematic clarification of its main efficacy results and value of application with the help of simple techniques such as in vitro microdilution antibacterial analyses, validation of in vivo infection models with animals, and the study of molecular biological mechanisms.

In vancomycin-resistant Staphylococcus aureus (VRSA) [7], which is widely the most difficult to treat clinically, scientific studies have demonstrated that Melittin has great antibacterial competencies. The minimal inhibitory concentration (MIC) of Melittin and the minimal bactericidal concentration (MBC) of Melittin have been reported as 0.125 2 0.125 as the lowest possible concentration of Melittin and 0.125 2 0.125 as the lowest possible concentration of PS against different strains of VRSA. Mechanistic investigations confirm that Melittin has its powerful consequences by extracting the integrity of the VRSA cell membranes leading to intracellular material leakages.

A high dose of 16 μg of Melittin directly on an infected wound in a mouse model that simulated the traumatic wounds of third degree was able to eliminate the local VRSA and induce a severe reduction in the inflammatory response in the body. Notably, the involvement of Melittin in the treatment of drug-resistant bacteria-infected wounds rarely caused any severe skin toxicity or hemolysis, which justified the safety and the effectiveness of this compound.

In the case of the most prevalent clinical organism, which is methicillin-resistant Staphylococcus aureus (MRSA). Comparative studies in vitro demonstrated that, Melittin have much stronger antibacterial properties with regard to MRSA than most other Gram-positive bacteria. In vivo experiments also have proven that, in addition to greatly improving the outcome of mice, when having their bacteremia caused by MRSA, and thus, being able to save most severely infected individuals, Melittin also enhance the healing process of MRSA-infected skin wounds, by regulating the local inflammatory environment and stimulating the formation of granulation tissue [8].

In the opposite search of bacterial resistance patterns towards Melittin, a study on the Escherichia coli has shown that overexpression of mrdA gene, the transpeptidase gene of peptidoglycan, had a significant impact on increasing the cross-linking extent of E. coli peptidoglycan. This causes the bacterial cell wall thickening and the shrinkages in the size of the pores hence reducing the fusion of Melittin in penetrating cell wall and their efficiency in binding itself in the cell membrane [9] This process eventually gave resistance to Melittin in E. coli which resulted in an essential theoretical foundation to later genetic engineering adjustments of the arrangement of Melittin to surmount bacterial resistance.

The above chain of experimental findings provided strong basis of the translational implementation of Melittin on the clinical outcomes of multidrug-resistant bacterial infections, also provided fresh perspectives to make diversified therapeutic approaches towards the resistant bacterial infections.

6. Conclusion

The ability of Melttin to precisely control drug efflux into cells by ABC transporters (ABCB1, ABCG2), tumor stem cell resistance functions, and PI3K/Akt/mTOR resistance-relevant signaling pathways can confer their effects to Melttin via a multi-target synergistic mechanism. Efficiently revert chemotherapy resistance phenotypes in breast cancer, ovarian cancer and non-small cell lung

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cancer. The experiments of drug-resistant cells in vitro and the model of tumor carrying animals in vivo treated with this substance proved this substance had a reliable reversal efficacy of drug resistance and had a good biosafety. Its reversal cross-cancer resistance effects show promise as an all-inclusive chemotherapy resistance reverser with new candidate drugs and focused intervention development methods to be utilized in the clinical management of chemotherapy resistance in solid tumors.

Further research is now able to support the potential of Melittin to reverse drug resistance in chemo-resistant models of more solid tumor types to establish the extent to which the cross-cancer effect of Melittin is universal or cancer-specific.

Meanwhile, we will prioritize solving the optimal ratios of dosage and order of administration, in and amongst Melittin and current chemo therapy, which will optimise the chemo sensitivity of drug sore tumours.

We should further optimize the formulations of Melittin such as formulating targeted delivery therapies and conduct comprehensive preclinical toxicity studies. This will contribute to the alleviation of some of the main obstacles to clinical translation, making Melittin progressively closer to application in clinical practice in drug-resistant tumors, and providing new care opportunities to the less-chemo-responsive cancer patients.

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