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Melittin in Breast Cancer Microenvironment Targeting

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ABSTRACT

In today's society, there are more people dying from breast cancer than ever. In fact, it has been projected that 1 in 39 women will die from breast cancer. Over the years, scientists have developed many forms of treatment to help alleviate some of the symptoms and keep the cancer at bay, such as chemotherapy and immunotherapy. Recently, however, a discovery has been made that could have the most efficacy and effectiveness against breast cancer. Melittin, a cationic peptide found in bee venom, is a 26 amino acid peptide that is being studied in many fields of medicine to be used as a new form of treatment in conjunction with the current forms. It is being tested in cancer research because of a special function that it has: the ability to start apoptosis by punching holes in the actual cell itself. In this paper, we will look at an overview of breast cancer's history and statistics, look through some of the types of treatments that are already being used to fight breast cancer, and analyze five case studies to see how melittin can be used to target the microenvironments of breast cancer cells and figure out which method of treatment melittin will best fit into.

Introduction

In today's society, there are more people dying from breast cancer than ever. In fact, it has been projected that 1 in 39 women will die from breast cancer. Over the years, scientists have developed many forms of treatment to help alleviate some of the symptoms and keep the cancer at bay, such as chemotherapy and immunotherapy. Recently, however, a discovery has been made that could have the most efficacy and effectiveness against breast cancer. Melittin, a cationic peptide found in bee venom, is a 26 amino acid peptide that is being studied in many fields of medicine to be used as a new form of treatment in conjunction with the current forms. It is being tested in cancer research because of a special function that it has: the ability to start apoptosis by punching holes in the actual cell itself. In this paper, we will look at an overview of breast cancer's history and statistics, look through some of the types of treatments that are already being used to fight breast cancer, and analyze five case studies to see how melittin can be used to target the microenvironments of breast cancer cells and figure out which method of treatment melittin will best fit into.

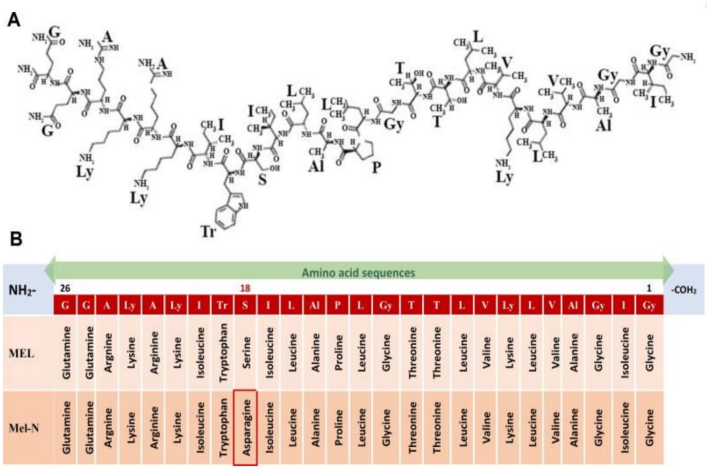

Figure 1. This is a diagram of the molecular structure of melittin.

History of Breast Cancer and Statistics

Breast cancer has a long history in society and it has been one of the most aggressive types of cancer out there. It all starts in 1600 BC when doctors reported a tumor that was present in eight women, and it was said to be untreatable. This was all recorded in a little document called the Edwin Smith Papyrus. This was one of the first types of cancer recorded in history, and there was no possible solution at the time. It became a major problem throughout the years until about the 19th century, when doctors began to understand more about this type of disease. One of the very first successful treatments was invented by two surgeons, Jean Louis Petit and Benjamin Bell. They were able to perform a procedure that involved removing lymph nodes, breast tissue, and some extra chest muscle. More doctors took this procedure even further by simplifying some of the procedures, but they all lead to some post-op complications, such as swelling and soreness. Thankfully, with further advances in research and technology, doctors were able to develop even more effective procedures in the late 20th century. The results were more organized removals and less complications for patients.

The statistics for 2022 predict that about 1 in 8 women will develop breast cancer. This makes it one of the most common types of cancer ever diagnosed in women. Of course, the frequency of cancer within a family varies with who in the family actually has it. However, 85% of breast cancer patients get the disease due to mutations that are completely random, even though there has been no history within the patient's family. In addition, it is predicted that the death rates in women older than 50 have started to decline since 2007, but they have remained steady for women 50 or younger. There have been many risk factors that may determine the likelihood of possessing the disease. Some of the major ones include mutations in the BRCA1 and/or BRCA2 genes, age, less activity, and more related to reproductive health. The statistics show that the trends are showing good signs that the cancer's death rates are decreasing.

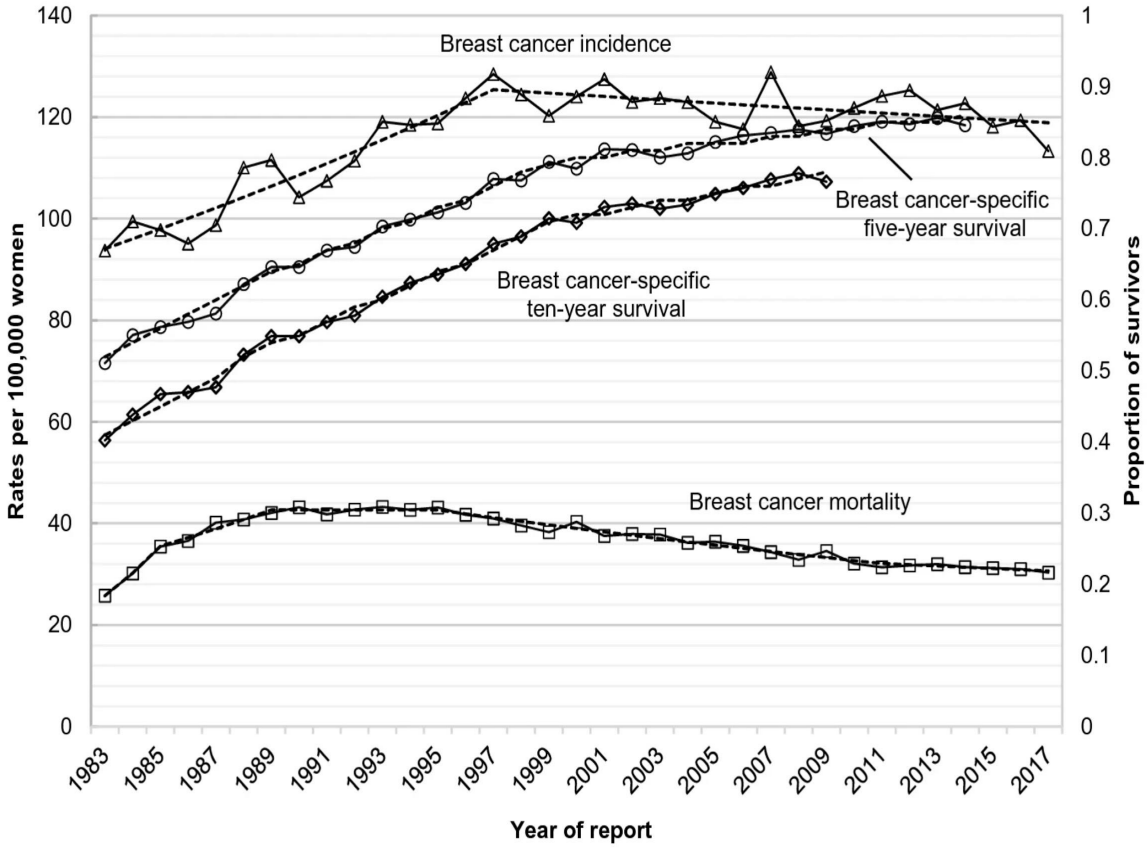

Figure 2. A chart that shows trends of breast cancer survival and mortality rates from the last four decades.

Different Forms of Treatments

Many different forms of treatment have been created to combat breast cancer. One of the very first types of treatment was a surgical procedure formed in the late 19th century. A surgeon named William Halsted performed a procedure that involved excising multiple parts, including the mammary gland and lymphatic tissue. It was basically the removal of a woman's entire breast. The mastectomy, as it was called, set the foundation for the future surgeries to come in the future to make sure that some of the complications that took place, such as rib cartilage damage. There were other surgical procedures that were created in addition to the mastectomy, and another highly regarded one is the lumpectomy. The lumpectomy is less invasive than a mastectomy because it does not involve removing the whole breast, but rather focusing only on the tumor and a portion of the breast tissue. However, a lumpectomy alone does not solve the whole problem, so there must be a supplement to help boost the process of healing from breast cancer. That is where some of the other forms of treatment come into play.

Chemotherapy is another highly effective treatment being used for almost every type of cancer out there, in addition to some bone marrow diseases and immune system issues. It is a drug that utilizes powerful cells to try to eradicate cancer cells in the human body. It can be used as an independent form of treatment for breast cancer, though it can be difficult for patients to keep up with some of the side effects of chemotherapy. It can also be used in addition to some other treatments such as the lumpectomy. Since the doctors remove the majority of the tumor and some of the breast tissue, it's possible that there could still be an area where the cancer lies in the breast, so chemotherapy would be the best treatment to use to help kill off any potential remaining cells.

Figure 3. This is an example of how the drugs used in chemotherapy are kept in a plastic packet.

Endocrine therapy, or hormone therapy, is identical to chemotherapy, but instead of targeting cancer cells themselves, this drug targets the hormones that cancer cells rely on to take form and spread throughout the body. This is another treatment that has been highly regarded among many patients. There is one problem, though: there are more long term side effects in endocrine therapy compared to chemotherapy. It was always believed that hormone therapy was the better option when considering quality of life, but it was later found through more research that women experienced more symptoms over a longer period of time compared to chemotherapy. Nevertheless, endocrine therapy is still a very effective form of chemical treatment used either in conjunction with chemotherapy or independently.

Immunotherapy is not really a form of treatment, but rather a type of training for the body. It helps train the immune system to recognize some of the cancer cells and to try and use the body's power itself to fight them. It is effective because the immune system is a precise defense mechanism, so wherever the cancer cells are, the immune system will target them in that specific location and eventually destroy them. Side effects can vary, however, because every body's immune system is different, so immunotherapy can either yield manageable side effects or possibly catastrophic complications. However, they are not as bad as some of the other treatments listed above, and it is still a reliable form of treatment that can be used by almost anyone.

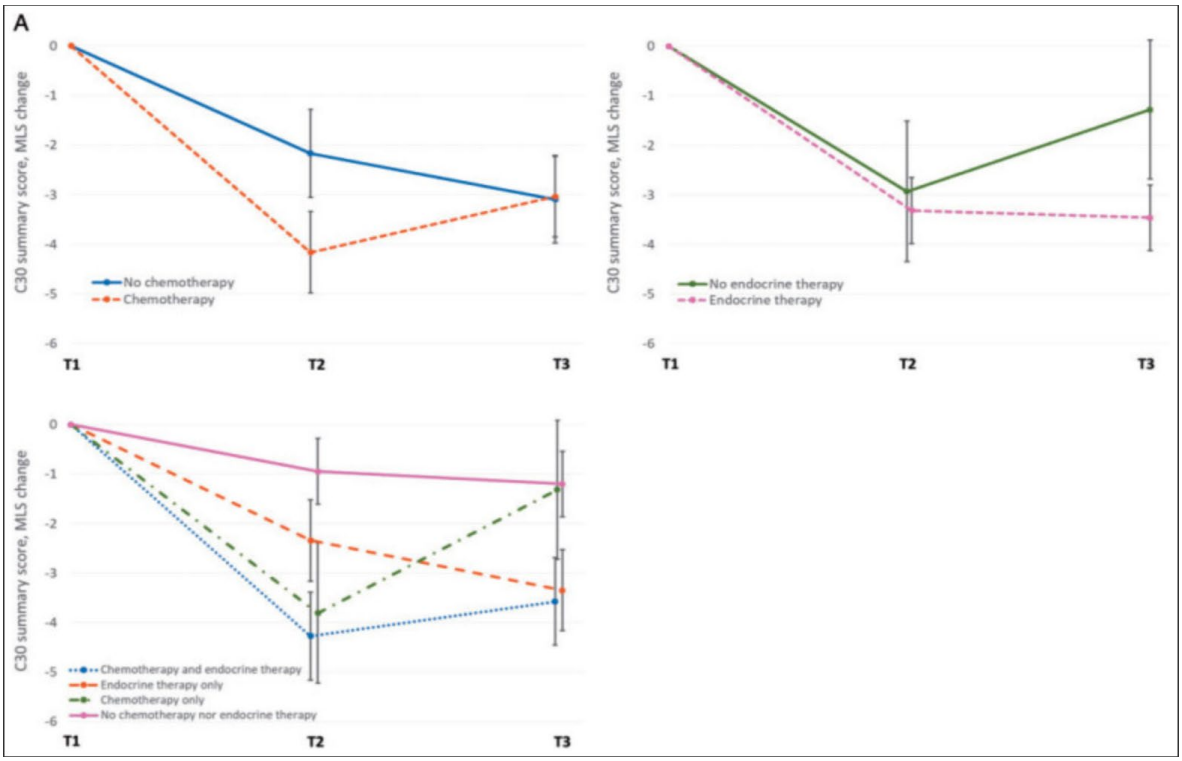

Figure 4. This data shows the previous findings of how endocrine therapy had a higher quality of life score compared to chemotherapy before the new research was published.

Radiation is particularly important because it does not rely on chemicals to target any cancer cells or hormones. Rather, as the name suggests, it utilizes the power of intense rays to kill cancer cells in a patient. Compared to the last two types of treatment, radiation is more comfortable because it is being used in a specific part of the body. However, there can still be some side effects during the process because the radiation may also damage some other healthy cells. There are three different types of radiation: external beam radiation, internal radiation, and systemic radiation. External beam radiation uses beams that are adjusted to focus on the tumor. Internal radiation is a method in which doctors place a solid or liquid that emits radiation within the patient. Finally, in systemic radiation, it is given through a pill or liquid in the mouth or through a vein, respectfully. Those are some of the different types of treatments that are currently being used to help treat breast cancer.

Figure 5. This is a picture of a person undergoing external beam radiation.

Introduction of Melittin

All of those treatments have been used for many years, but recently, a new type of molecule has been talked about within the medical community and studied. Melittin, a cationic peptide, is a molecule that is derived from bee venom and serves a variety of functions at the molecular level due to its 26 amino acids. Melittin's primary functions are to physically puncture cells to exhibit early apoptosis and create that pain sensation people experience after being stung by a bee. In addition, it contributes to the swelling that a person experiences when being stung. It has been used in many fields of medicine, including cardiology and neurology. Being used in oncology is another big advancement in medicine because it can potentially have the ability to cure cancer. Breast cancer has been a big issue from the last few centuries, and although the treatments above have worked very well, melittin is showing promising results in being used as another form of treatment.

There were many case studies published on PubMed that were conducted on human cancer cells, and they have yielded some amazing results that could result in this molecule being incorporated into drugs like pills or liquid medicine. What was most important about these case studies was that they all seemed to focus primarily on the microenvironment and hormone receptors of the tumors. Although immunotherapy has been a focus for many researchers, hormone therapy is still not out of the question because those microenvironments are integral to the development of the tumors. Incorporating melittin into hormone therapy can yield tremendous results because of the nature of melittin in general and how hormone therapy fundamentally works.

One of the first case studies published on PubMed talks about the application of nanoparticles for cancer immunotherapy. One of the issues the study talks about is the time it takes to reserve drugs for those cancer microenvironments. The researchers then decided to identify and use some of the nanoparticles to study and find out whether they can be good candidates for treatment. Along with using some other nanoparticles in the study, the researchers also created a hybrid molecule by using melittin and a lipid. The type of lipid they used was not explicitly stated. They created melittin-NP and they found that by using a size of 20 nm, they were able to get the maximum effects from that molecule. They reported that melittin was able to reduce primary tumor growth by 95% and distant tumor growth by 92%. All of these studies were not only conducted on some human cancer cells, but they were also used on rats as well.

The second case study published on PubMed was a discussion about how melittin can be considered as a candidate for immunotherapy. The researchers were already aware of the nature of melittin and how it could serve well for anticancer treatments. They created a fusion protein composed of melittin and a mutant form of an already existing treatment called IL-2 to observe whether ovarian cancer in women could be hindered. The only problem was that they were unsure whether melittin could actually have characteristics that were beneficial to immunotherapy. In order to find out, they set up a few experiments that involved looking at different types of cancer tissue in vitro and in vivo. For in vivo, they used three different types of human cancer cells: liver, lung, and ovarian. They used rats as the subjects for the in vivo testing. The researchers then injected the fusion protein as they would normally do with immunotherapy. They found that melittin-MIL-2 was able to train the immune system and directly disfigure those cancer cells, and there were much stronger effects on those cells compared to other molecules they had previously studied. In addition, they were able to observe reduced chances of breast cancer. In the end, they were able to conclude that melittin, along with the mutant IL-2 is an exceptional candidate for immunotherapy and it can deliver strong anti-cancer effects, especially in breast cancer.

The third case study deals with melittin and how it can suppress a certain signal transduction molecule in breast cancer cells. The researchers for this study found that HIF-1α was responsible for the development of those microenvironments. Knowing that, they wanted to find a way to hamper the signaling mechanism so it does not trigger that development. After studying about some of the abilities of melittin, the researchers then devised an experiment plan to see whether melittin would be able to prove their hypothesis. They collected a

couple of breast cancer cells and prepared them for the experiment. After that, they decided to use different doses of melittin and the samples were then cultured in its presence. They included a control group that was not treated with melittin. The results showed that when the cancer cells were cultured with melittin, the signaling pathway was interrupted, and the HIF-1α protein levels were significantly lower than in the control groups. The main reason why was because the NFκB gene was not being expressed as much as it was before. In addition, melittin was able to increase the expression of apoptosis because of two different types of signaling mechanisms: TNFA and BAX. They were able to stop two mechanisms responsible for the development of those microenvironments, VEGFA and LDHA. The researchers were then able to conclude that melittin was able to target the microenvironments of breast cancer cells by inhibiting the expression of two signaling mechanisms through apoptosis.

The fourth case study takes on trying to inhibit growth factors for triple-negative breast cancer with melittin. Triple-negative breast cancer is basically a different type of breast cancer with receptors that are different compared to the regular three that are included, which are estrogen, progesterone, and HER2, which is a type of human epidermal growth factor. In this study, the researchers were also unaware about whether melittin could be suitable as an anti-cancer medium. They had already known about some of the anti-cancer effects melittin had against some of the other cancers, such as lung cancer and leukemia, but they wanted to see whether it would work on something as rare as triple-negative breast cancer. They decided to test their hypothesis by extracting venom from honeybees located in Australia to investigate whether the properties of melittin could be used for anticancer purposes. They were able to find out that melittin was powerful against HER2, and inhibiting that growth factor was able to stop the further growth of breast cancer. In addition, melittin was able to reduce the expression of other molecules that were responsible for making the breast cancer cells continue to grow. They then continued to test other things, such as the difference between the concentrations of melittin in honeybees and bumblebees. Nevertheless, the researchers were able to conclude that melittin exhibited characteristics that could prove helpful for anticancer purposes.

The fifth and final case study is a broader look at how melittin could be a possible candidate for immunotherapy. The researchers in this study wanted to find out how to combat the immunosuppressive methods that can be present in some tumors. They were able to do some research and create a bioinspired tumor-inspired nanovehicle, or BTN, that was able to bypass the immunosuppressive nature of those tumors. They created it by combining melittin and a reactive-oxygen species of gemcitabine with a nanovehicle that was based on lipoproteins. They found that the BTN was able to exhibit penetrative qualities using one of melittin's fundamental functions: punching holes in a cell's membrane to start apoptosis early. Otherwise, melittin contributed to a molecule that could have a highly effective and positive impact on cancer therapy.

Conclusion and Determination of Treatment Type for Melittin

After looking at all the different types of case studies, there are a number of things to consider when looking at melittin and how it could fit into the world of cancer treatment. Many studies have looked at different perspectives, whether melittin could fit into immunotherapy because it is able to exhibit qualities that fit very well into that type of treatment. In addition, melittin can also fit into hormone therapy because there are certain cases in which the molecule can directly target hormone receptors that are responsible for the development of the cancer. After much analysis and research, it can be determined that melittin can basically fit into both types of treatment. Many treatments already exist in the world today, and they are all working exceptionally well. At this point in time, there is simply not enough research to determine whether melittin can be able to replace the treatments in total, although that question is still at large and actively being debated. In the present situation, instead of replacing the current forms of treatment due to issues with logistics and the supply chain, it would be better if the molecule could be incorporated into the treatments that are being used right now, and the best types of treatment for melittin to be included in are hormone therapy and immunotherapy. It all depends on the circumstances the

patient faces and what the doctors find is best for them. If a doctor finds out that a tumor has not receded after trying chemotherapy and radiation, then they will go ahead with immunotherapy for the patient. If an ultrasound shows that there is excessive activity in the endocrine system that is benefiting the cancers, then the doctors may recommend hormone therapy. Melittin comfortably fits within those two types of treatments, so using it for both will prove to be a really good advantage against the cancers. Due to their cytotoxic nature, they can act fast and supplement the existing treatments very well. Melittin has always had really strong effects on cancers, and using it to treat breast cancer could potentially signify a revolution in the medical field. It could bring down breast cancer from being one of the deadliest cancers out there by giving safe treatment options to everyone in the world.

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