Immunotherapy on Breast Cancer: A Brief and Concise Overview

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Abstract

Breast cancer remains the second most widespread and fatal malignancy in females. Scientists can inhibit unregulated cell growth and destruction using newly developed immunotherapy methods like protein kinase B (AKT) Inhibitors. This therapy is designed for prevention rather than fighting tumors head-on with radiotherapy and chemotherapy. This offers less harmful symptoms while still providing effective care. Furthermore, immunology is still in development since many cancers remain resistant to it. Previously, breast cancer has been considered non-immunogenic, but after recent and ongoing clinical trials, data shows discovered vulnerabilities in the molecular level of breast cancer. These studies will lead to developments in life-saving immunology treatments. We aimed to review immunology and how scientists have advanced immunotherapy in breast cancer and discuss ongoing clinical trials.

Introduction:

William B. Coley, the father of immunotherapy, was the first documented person to attempt to manipulate and strengthen a person's immune system. He injected bacteria known as "Coley's toxins" into patients in the hopes of preventing tumor remissions in malignancies. (1) Now, in the 21st century, Coley's concept of using bacteria to boost immune systems has evolved into revolutionary treatments that treat many types of cancers, but not all. Breast cancer remains one of the most fatal malignancies in females, and for years, it has been deemed non-immunogenic. Hormone receptors that express estrogen (ER) and progesterone (PR) are predictable factors that cause breast cancer cells. (2) Analyzing cells with these receptors has led to many key breakthroughs, such as discovering negative and fatal cell cycles. For example, the dysregulation of PI3K/AKT has recently been discovered to cause apoptosis, leading to unregulated cell growth. By looking at more proteins and enzymes in ER + PR cancer cells, we can spot vulnerabilities and create therapies to inhibit and destroy negative processes.

What is Immunotherapy?

First, we must cover the general overview of immunotherapy and why it is so effective against malignant tumors. Immunotherapy can recognize and combat harmful cells by harnessing and enhancing the body's natural immune system. Other treatments, such as radiotherapy or chemotherapy, can damage healthy tissue and cancer cells alike. Still, immunotherapy works by stimulating or modifying the immune system's natural responses, leading to less harmful side effects and pain. This can involve various strategies, including the use of immune checkpoint inhibitors, CAR T-cell therapy, monoclonal antibodies, checkpoint pathway modulators, and more.

Immune checkpoint inhibitors are a revolutionary class of drugs. It has transformed cancer treatment by enhancing the body's natural ability to fight cancer. Checkpoint pathways

are regulatory pathways that ensure physiological immune responses are maintained. When cancerous cells, such as those that express PD-1 or CTLA-4, come into contact with these pathways, they turn off the immune responses like autoimmunity. Immune checkpoint inhibitors ensure that the cancerous cells do not come into contact with regulatory pathways. (Figure 1) (3)

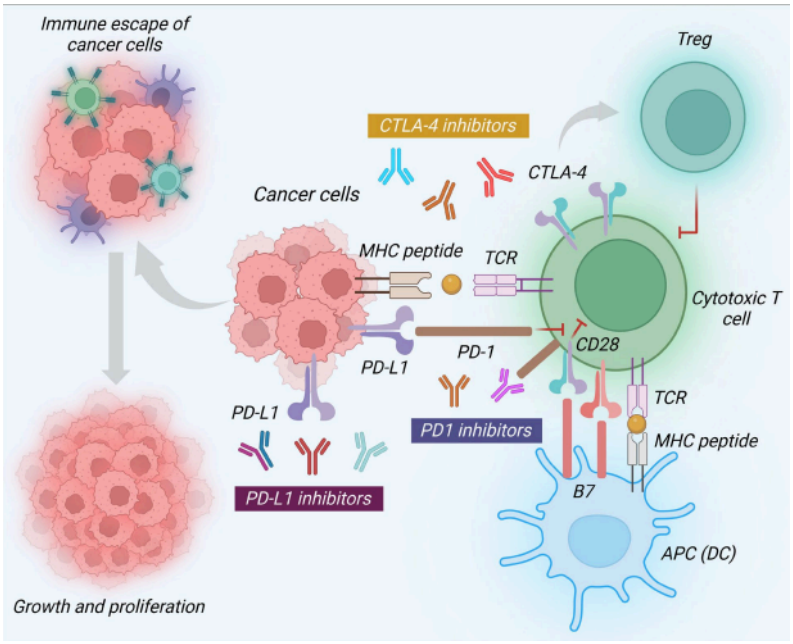

Figure 1. Programmed Death-Ligand 1 (PD-L1) and Programmed cell death protein 1 (PD-1) are molecules that sever T-cell activity. Figure 1 shows how PDL-1 and PD-1 inhibitors are injected to continue T-cell attacks on cancer cells. (3)

CAR T-cell therapy is the process of extracting a patient's T-cells, thymocytes that attack infectious diseases, modifying them to recognize and attack cancer cells, and then injecting them back into the patient. This therapy has shown success in treating blood cancers but has also been limited to treating only blood cancers. (4)

Monoclonal antibodies are laboratory-produced molecules that mimic the body's natural defense system. They are mainly fabricated to attack and target deadly pathogens and cancerous cells. One of the simplest examples is Naked Monoclonal Antibodies. These work by binding to cancer cell antigens and flagging them down for the immune system to attack. These have shown high success rates in certain lymphomas and HER2+ breast cancer (human epidermal growth factor receptor 2). (5)

Similar to Immune Checkpoint Inhibitors, Checkpoint Pathway Modulators are proteins that regulate immune responses against cancer. For example, LAG-3 (Lymphocyte Activation Gene-3) Inhibitors inhibit LAG-3 on T-cell activity. LAG-3 binds to T-cells and makes them exhausted and weak. When checkpoint inhibitors are injected, they can block the binding, and T-cells will have a longer-lasting ability to fight cancerous cells. These inhibitors are an emerging area of immunotherapy, and new work is going on to advance this therapy. (6)

Current Limitations in Immunotherapy on Breast Cancer

Before going over breakthroughs, it is important to understand where immunotherapy stands and what the current limitations are in its use. Certain cancers, particularly those that have numerous mutations, like melanoma, renal cell carcinoma, and non-small cell lung cancer, have shown positive responses to immunotherapy. However, many other cancers, such as pancreatic, prostate, and subtypes of breast cancer, have not responded to these treatments. There are many reasons this might be, and some include the tumor's microenvironment, heterogeneity, and antigenicity.

Many breast cancers have a very immunosuppressive tumor microenvironment (TME). This means that Regulatory T-Cells (TREGS), tumor-associated macrophages, myeloid-derived suppressor cells, and certain cytokines are regulated within the tumor that inhibits immune responses. They inhibit the cytotoxic T-cells and Natural Killer (NK) cells programmed to seek and destroy cancerous cells. TREGS, in particular, produces cytotoxins like Interleukin 10 (IL-10) that promote immune tolerance, allowing the tumor to evade T-cell detection. (7)

Another significant challenge in immunotherapy is its inability to be a universal therapy for masses of cancers. Breast cancer, specifically, has a multitude of subtypes that each need a special treatment type. Its inter- tumor heterogeneity proves a challenge because several strains are based on hormone receptors. As stated before, progesterone receptors and estrogen receptors are just two of the many variants of breast cancer. Each requires different approaches, and many do not have a designated therapy at all yet. Breast cancer's intra-tumor heterogeneity serves as another challenge to overcome since a single tumor can express different mutations and characteristics. This area of diversity can cause some regions of the tumor to respond to immunotherapy, but other parts may evade detection. (8)

The ability of the immune system to recognize and target cancer cells depends upon the presence of antigens. Antigens flag down foreign invaders and decide whether the immune system should attack them. Tumors with high mutational traits usually express a variety of antigens. This means the immune system more easily recognizes them, but there are many cancers; breast cancer expresses low varieties of antigens. This limits the ability of the immune system to recognize and attack, thus making it difficult for immunotherapy to function. (9)

How Immunotherapy is Advancing

A growing amount of evidence proves that breast cancer, a once non-immunogenic tumor, has major vulnerabilities that therapies can target. Breast cancer's notorious TME proves a difficult hurdle to overcome because the immune system is not actively engaged in hormone receptor-positive subtypes. However, this will soon change as prolactin receptors (PRLR) are discovered to trigger several downstream signaling pathways contributing to breast tumor development and growth. (10) can soon create, test, and implement effective immunotherapies by making more discoveries like these.

PRLR AKT proteins play a central role in cell growth and survival, and dysregulation can lead to negative pathways and cell disasters. More specifically, dysregulation of AKT leads to apoptosis, programmed cell death, and, coupled with unregulated cell growth, leads to the development of malignant tumors. (11) The discovery of this pathway is detrimental because we have found out why breast cancer's TME are difficult, and we can point out the weak spots. AKT inhibitors, a recent immunotherapy method, can block the binding site of AKT proteins to their respective enzyme. This means that phosphorylation can no longer happen, and dysregulation can be avoided. Breast cancer cells will stop forming and spreading by using AKT inhibitors to terminate dysregulation. Currently, only a select few inhibitors have been created, and fewer are still being tested. MK-2206, an allosteric AKT inhibitor, is the most recent inhibitor undergoing clinical trials. MK-2206 has been tested on HER2+ breast cancer tumors with the drug trastuzumab. While it proved effective against the tumor, it activated the Human Epidural Growth Factor Receptor 3 (HER3), which caused more unregulated cell growth. MK-2206 has been tested with other drugs, but it did not show as promising results as it did with trastuzumab. This inhibitor will continue to complete trials with other drugs and therapies until a remedy is discovered. (12)

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a protein that attaches to and inhibits T-cell activation. The immune response is thus suppressed, and cancer cells can grow without restraint when CTLA-4 attaches. *Ipilimumab* is a monoclonal antibody that acts as a CTL-4 inhibitor that blocks the suppressive function of CTI-4. When inhibited, T-cell activity resumes, and interleukin-2 (IL-2), a protein that stimulates the growth and activity of white blood cells, is produced. Ipilimumab is an FDA-approved immunotherapy method for treating cancers like melanoma or renal cell carcinoma, but clinical trials are still ongoing for its effectiveness on breast cancer. Recently, in a Phase II trial of Ipilimumab in Triple Negative Breast Cancer (TNBC), Ipilimumab was tested with neoadjuvant paclitaxel on patients with early-stage TNBC. There were high rates of overall pathological response to the drug inhibitor, and it was even effective without PD-L1 expression. (13) Trials show that Ipilimumab has the potential to add TNBC, its first breast cancer subtype, to its approved treatment list.

Conclusion

The recent advancements in immunotherapy have presented a more precise and effective approach to treating and preventing breast cancer. Many immunotherapy methods have been FDA-approved, but there is little to none for breast cancer. Its tumor microenvironments are the biggest challenge, but as technologies and resources gain more ground, scientists can pinpoint weaknesses and develop new drugs and therapies. Immune checkpoint inhibitors, such as AKT inhibitors and Ipilimumab antibodies, have been leading the cause and are still going through the proper trial processes. Although this is a remarkable feat, much about breast cancer is still to be uncovered. The multitude of subtypes like TNBC, HER-2+, and HER-3+ make it challenging to pinpoint one universal treatment. The need for treatments tailored to specific factors and subtypes of breast cancer makes it one of the most

complex and challenging areas of research in oncology. It is urgent to discover a clear understanding of breast cancer to advance treatment methods and lower the recurrence and fatality rates for females.

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