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A review on Novel Insights of Breast Cancer Vaccines

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ABSTRACT

Cancer vaccines are on the verge of success. It is a unique approach wherein patient's immune system is dynamized to mount an immune response against the tumor mass thus, an anti-tumor effect is exhibited. Due to the down-regulation of immune system caused by the check-points such as CTLA-4 and PDL-1, cancer cells escape the immune system and began its uncontrolled growth and ultimately turns into a tumor. Even though the other treatments are available for the breast cancer chemotherapy but still the mortality and relapse incidents are sky-high. So a more personalized pharmakon is developed so as to arouse an immune response against the tumor. The main aim for developing cancer vaccines is breast cancer is to exhilarate patient's own immune system so as to kill cancer cells with minimal side-effects. Appended leverage of using immunotherapy includes meticulous specificity, low toxicity, and the potential for permanent treatment effect due to immunologic memory. Various types of vaccines have been developed using different mechanism such as DNA vaccine, dendritic cell vaccine, and tumor cell vaccine, hyper-acute vaccine but their agenda is common that is to prompt an immune response against tumor.

Keywords: Cancer, Vaccine, Immunotherapy, Tumor cell, DNA vaccine, Genetic modification.

INTRODUCTION

Breast cancer is one of the most common malignancy amongst various other cancers impacting around 2.1 million women each year and is a prominent cause of death all over the world. According to American Cancer Society, the overall expected number of new cases in the year 2019 is 2,68,600 amongst women and 2,670 cases amongst men [1]. Breast cancer is basically an uncontrolled growth of cells either in the lobules, which are the milk producing cells in the breast, or in the ducts that carries the milk from lobules to nipples. Sometimes, this uncontrolled growth can also occur in the fibrous tissue or fatty tissue of the breast, but principally it originates from the lobules or ducts and then affect the surrounding tissue. Depending upon its ability to impinge the surrounding tissue, it is classified as invasive or non-invasive breast cancer [1, 2]. The cancer is said to be invasive when it show the metastasis, thereby, affecting the nearby tissue and can even travels to the distant organs such as lungs and liver. Lymph nodes present in the breast is the main route through which the cancer spreads. Once the tumor cells begins to affect the lymph nodes, it spreads throughout the body and can even blocks the drainage of interstitial fluid and causes the swelling to the breast tissue. While non-invasive cancer remains confined to a localized space and do not affect its surrounding tissue cells thereby the tumor is benign and can be treated easily [2].

A normal cell always need a stimuli to show uncontrolled growth, so in order to grow in the breast region, tumor cells need certain agents that exaggerate their growth. These agents are basically the proteins that bind to human epidermal growth factor receptor-2 which is responsible for promoting the growth of cancer cells and the female sex hormones such as estrogen and progesterone which helps to exacerbate the condition. Depending upon the type of receptorspresent on the tumor cells, the breast cancer is further classified into four molecular subtypes which are as follows [1, 3].

1) HR+/HER2-: In this type of cancer, tumor cells contain receptors for estrogen and progesterone and thus is said to be hormonal receptor positive but do not contain HER2 on its surface. This type of cancer is also termed as Luminal-A type breast cancer and can be treated easily with hormonal therapy such as with antagonist of estrogen and progesterone receptors [1].

2) HR-/HER2+: Here tumor cells do not contain any hormonal receptor, however does have HER2 and therefore said to be hormonal receptor negative but HER2 positive [1, 3]. Since human epidermal growth factor is said to be responsible for promoting the tumor growth, recent advances in immunotherapy have made it possible to target HER2 directly using vaccines such as DNA vaccine, dendritic cell vaccine etc.[4, 5].

Such vaccines which targets human epidermal growth factor receptors are collectively called as anti-HER 2 vaccines [6].

3) HR+/HER2+: In this cancer, the tumor cells contain both the hormonal receptors as well as HER2 and estrogen, progesterone and agonist of HER2 are the potential agents that are causing the cell to divide and grow uncontrollably. Therefore, by using antagonist of female hormones and HER2, this cancer can easily be controlled and treated.

4) HR-/HER2-: This cancer neither contain hormonal receptors nor have HER2. Therefore, this type is called as triple negative cancer because the tumor cells lack receptors for estrogen, progesterone as well as for proteins that bind on HER2. Hormonal therapy is ineffective in this type and is considered as the most difficult cancer to treat as the stimuli that is causing the growth of cells is unknown [1, 2, 3].

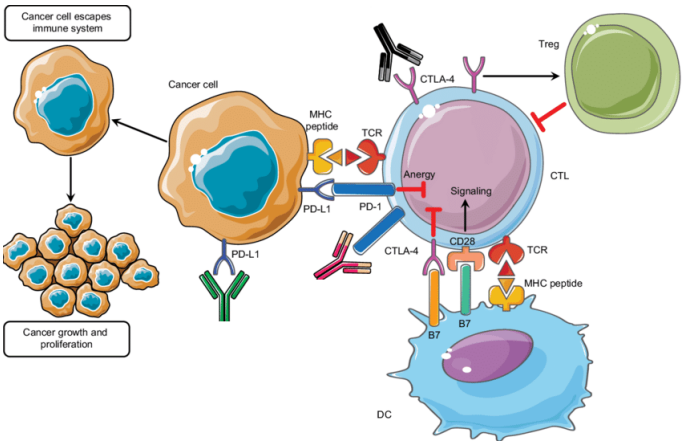

Figure 1: Dendritic Cell-Based immunotherapy

BREAST CANCER VACCINE

Until now, breast cancer can be treated with different curative approaches such as ablation, surgery, radiotherapy,chemotherapy and with more peculiar approach like hormonal therapy but even with these therapeutic options mortality rates and relapse incidents are tremendously sky-high [7]. According to the American Cancer Society, approximately 627,000 women died in the year 2018 [1]. Therefore, need is felt for the development of more actualized-pharmacon based on stimulating person's own immune system. Thus, breast cancer vaccines came into existence.

Breast cancer vaccine has been developed in order to treat cancer with minimal side effects. Breast cancer vaccine is basically a classic example of personalized-medicine based on prompting patient's immune system against tumor. Different type of vaccines are made such as DNA vaccine, dendritic cell vaccine, and a vaccine containing mouse gene, that is tumor-cell vaccine, and checkpoint inhibitors that blocks the action of CTLA-4 and PDL-1[7]. The main aim of developing the vaccine is to activate the immune system and to increase the responsiveness of immune system against tumor cells in breast tissue. Breast cancer vaccination is a promising strategy for activating an immune response against cancer [9]. Many vaccines are currently under clinical trials in Phase I & II and are being tested in combination with other therapies. To date, only NeuVax vaccine which is an anti-HER 2 vaccine have completed the phase III clinical trials and is successfully in preventing the breast cancer relapse [8]. Per contra, NeuVax with other combinational strategies is still under trials so as to the HER 2 positive breast cancer. Different type of vaccines used to prompt the immune system are discussed as follow:

1. **DNA Vaccine against HER-2 tumor:** DNA vaccine contain a plasmid which contain genes that encodes for tumor- antigens [10, 11] When this vaccine is injected into the patient's body, it draws the attention of APCs to direct the immune system to target the antigen based cancer cells. Nonetheless, the success of vaccine depends upon type of antigen specificity. HER-2 is a protein receptor obliged for exacerbating the tumor growth. Also, it is responsible for transformation of cancer cells. Apart from this, receptor is present on the cell membrane and can effectively be targeted. Normally, body treats HER2 as a self-molecule. To mount an immune response, only specific epitopes are selected using recombinant technology so as to combat the mechanism of self-tolerance [12, 13, 14]. DNA vaccine against HER2 is found to be successful as it has reduced the size of tumor in transgenic mice [15, 16]. Other types of DNA vaccines that are now under clinical trials are Polyepitope DNA vaccine, Neoantigen DNA vaccine, Chimeric DNA vaccine etc.

2. **Dendritic Cell Vaccine:** Dendritic cells are antigen presenting cells which are present throughout the body and are responsible for activating and directing T-cells and B-cells towards their target [11,14]. However, due to failure of dendritic cell to recognize the antigens containing tumor cells, they escape this surveillance mechanism of immune system. So, dendritic cell vaccine contains the dendritic cells which modified outside the body, that is, dendritic cells are loaded with cancer specific antigen outside the body in ex-vivo condition [14, 17, 20]. When the modified form of dendritic cells are injected back into the body, they presents a tumor specific antigen on its surface to the cytotoxic T-cells and therefore, successfully generates an immune response to target the tumor mass. The circulating dendritic cells are isolated from patient's body by apheresis and are then subjected to maturing factors which assist in the process of maturation so as to have an enhanced expression [17, 18, 19]. These matured dendritic cells are then injected back into patient so as to mount an immune response against cancer. These vaccines has been approved for human use and are found to very effective.

3. **Hyper-Acute Breast Cancer Vaccine:** This vaccine contain killed cells of breast tumor. Tumor cells are first killed using a radiation and are then genetically modified using a mouse gene called as murine alpha-(1,3) Galactosyltransferase [21,22]. The genetic modification is required for the many reasons. One such reason is because cancer cells develops from person's own healthy cells, therefore, in order to arouse an immune response, it is necessary to increase the antigenicity. Thus, a mouse gene is added and this gene is responsible for producing a specific protein-sugar pattern, specifically, alpha (1,3) Galactosyl-epitopes on the surface of glycolipids and glycoproteins [21, 22]. This sugar-protein pattern is responsible for graft rejection during organ transplantation from non-primate models. These genetically modified cells with enhanced antigenicity when are injected back into the patient, immune system gets activated and start targeting the tumor mass breast in the breast tissue, thus, decreases the tumor size and helping in eradicating the tumor from breast. This vaccine is currently under clinical trials in Phase II.

4. **Immune Check Point Blockers:** Immune check-point inhibitors are a form of immunotherapy which targets the immune check-points that are important regulators of the immune system [27]. Thus, to understand this therapy, it is necessary to understand the role of these checkpoints in the regulation of immune system.

Immune System- check-points: - Immune system is a critical regulator for human body that removes all the cells which show abnormality through apoptosis. As cancer cells shows abnormality in the growth patter but still escapes the destruction by the immune system due to several factors. One such factor is that tumor develops from person's own healthy cells due to which they lack the antigenicity [24, 28]. Immune system is capable of differentiating between the 'self" and "foreign" antigen by possessing a mechanism called as self-tolerance, that is, immune system shows tolerance to self-antigen and do not initiate any immune response against them [28]. This mechanism works because of the presence of certain check points on immune system which actually downregulates the immune cells, thereby, preventing them from mounting a response against self-antigen [30]. CTLA-4 also called as

CD152 protein receptor is one such check point that down regulates the immune system [28, 30]. In order to get activated, T-cells receptor not only needed to get bind to the epitope but also needs a second signal from APCs and this is called as co-stimulation and this co-stimulatory response is given by co-stimulatory proteins such as CD28 which bind to CD86 on antigen presenting cells (APCs) and mounts an immune response [24, 31]. So, this CTLA-4 is homologous to CD28 and possesses more affinity towards CD86, thereby, prevent the binding of CD28 with CD86 [24]. As a co-stimulatory response is not produced, T-cells remains inactivated and thus, do not initiate the immune response. Another check point on immune system is PDL-1 [30, 31]. That recognizes the tumor's antigen as a self-antigen and assists the escape of cancer cells from an immune system through a phenomenon known asanergy [24, 28]. Also, minor population of CD4+ T-cells called as regulatory T-cells, suppresses the activity of other T-cells, thereby, protects the tumor cells from an attack by immune cells. Thus, check points such as CTLA-4 and PDL-1 are responsible for downregulating the immune response against cancer cells and upregulates the tumor growth. So by inhibiting these checkpoints, working of immune system is enhanced and thus is able to kill the cancer cells on first place. CTLA-4 and PDL-1 inhibitors prevent them from binding to CD86 and allows the binding of co-stimulator CD28 with CD86 of MHC-1 so as send a co-stimulatory signal to activate the cytotoxic T-cells against the cancer cells [26]. One such inhibitor of CTLA-4 is ipilimumab which is approved in 2011 by FDA and it inhibits the immune system's tolerance towards cancer cells and thus provides a potentially useful immunotherapeutic strategy for the patients with cancer.

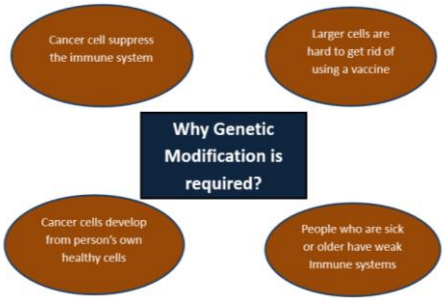

Figure 2: Rationale behind Genetic Modification

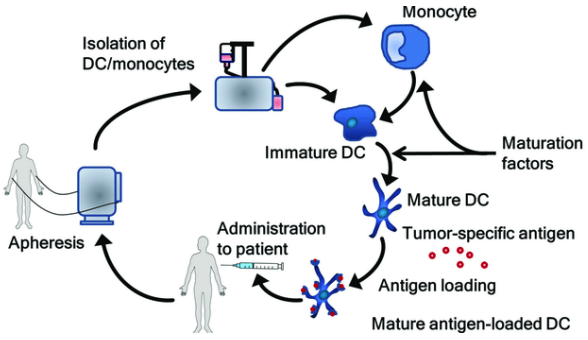

Figure 3: Role of Checkpoints in Downregulation of Immune system

CONCLUSION

With the advancement in the field of immunology, various types of immunological strategies are adopted to brush-off breast cancer which includes the development of different type of vaccines such as DNA vaccine, hyper-acute vaccine, dendritic-cell vaccine, and check-point blockade. Out of these, only dendritic cell vaccine is used in the market while all other vaccines that are designed to kill the cancer cells are currently under clinical trials in Phase II or Phase III. To date, only NeuVax have successfully completed clinical Phase III trials and are being used in the therapeutic treatment against breast cancer.Apart from vaccines, another approach has also being used which involves the inhibition of check-points. One such inhibitor is ipilimumab which is a monoclonal antibody approved by FDA in year 2011which prevents the down regulation of check-points. In consideration of the damaging effect of other therapeutic approaches, the development of immunotherapy against breast cancer was of utmost importance. In nutshell, the use of immune-therapeutic strategy in combating the cancer growth and preventing the relapse seems to be very promising and a novel approach.

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