

Utilizing the Patient' Immune System to Combat Cancer through DNA Vaccination

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Abstract

One of the most difficult diseases to treat nowadays is cancer. Toxic side effects, the occurrence of concurrent malignancies, the development of resistant mechanisms, and/or the induction of concomitant malignancies frequently limit the effectiveness of standard treatment protocols, which primarily consist of chemo- and radiotherapy, followed or preceded by surgical intervention. This necessitates the creation of therapeutic approaches that are just as effective as conventional therapies while allowing patients to live their lives free from serious adverse effects. In this regard, the advancement of immunotherapy in general and the novel idea of DNA vaccine in particular may offer a means of achieving this objective. Activating humoral and cellular immune responses to target cancer cells using the patient's own immune system have shown early positive outcomes in clinical trials and could lead to a less toxicity conventional therapy regimen in the future. Transferring the plethora of compelling preclinical and early clinical outcomes to an efficient patient therapy is the main issue of this strategy.

Before and during parturition, as well as the two primary physiological processes of parturition: uterine contractions and cervical ripening, the immune system is crucial. White blood cells and the secretions they produce make up the immune system. The cervical tissue is invaded by polymorphic nuclear cells and macrophages, which then release substances like oxygen radicals and enzymes that weaken the cervical matrix and enable softening and dilatation. White blood cells go through chemo taxis, adherence to endothelial cells, diapedesis, migration, and activation during this inflammatory process. Cytokines such tumour necrosis factor and interleukin govern the invasion and production of white blood cells. Cytokine synthesis is impacted by prostaglandins, glucocorticoids, and sex hormones. They modify the target cells as well, changing how those cells react to cytokines. On the other hand, the immune system has a significant impact on how hormones work and how prostaglandins are made. Nitric oxide significantly affects the uterine quiescence during gestation in mammals. In addition, it has anti-adhesive properties on leukocytes and is crucial in controlling the vascular tone of uterine arteries. At term and preterm, cytokines can be identified in the amniotic fluid as well as the maternal and foetal serum. It has been demonstrated that a number of intrauterine cells manufacture these cytokines. The immune system is an extra but essential and underappreciated element in the physiology of delivery because neither white blood cells cytokines nor nitric oxide seems to be the final step for human parturition. Therefore, these mechanisms must be understood by scientists, obstetricians, and anaesthesiologists.

Keywords: Gene therapy; DNA vaccination; Oral delivery; Cancer vaccine; Tumor cells; Clinical trial; Tumor Immunology.

Introduction

A significant portion of all disease-related deaths occur due to cancer, which is a leading cause of death worldwide. Standard cancer treatment involves aggressive chemotherapy and/or radiation that can efficiently kill cancer cells but has the drawback of having serious side effects. Additionally, a lot of cancers are discovered when the tumour has already progressed far enough that treatment options are limited and can only cure a small percentage of patients. A promising method to get the immune system to target tumour cells precisely is cancer vaccination. However, there are a number of issues that must be resolved before cancer vaccines can be used effectively [1]. Patients' immune systems are frequently suppressed by advanced tumour growth, which is exacerbated by prior therapy and ageing. In mouse tumour models, there are signs that young mice are better protected against a lethal tumour challenge, showing improved primary immune responses than older mice. Because the thymus stops producing naive T cells with age, this makes the use of vaccines in patients who are advanced in age challenging [2].

The relationship between the quantity of tumor-infiltrating lymphocytes and a good prognosis provides evidence that the patient's immune system is essential for the capacity to establish an efficient antitumor immune response. Patients with a poor prognosis include those whose immune systems are chronically weakened due to therapy

or other factors. Based on encouraging results in animal models, one strategy uses entire inactivated tumour cells as a source of antigen. The scientific basis for this tactic is the expression of tumor-specific or tumor-associated antigens by both the malignant target cells and the cells employed for vaccination. Numerous antigens that are crucial to successful cell-based vaccination techniques have been discovered, described, and shown to also be expressed on healthy cells. Although the expression is frequently compartmentalised in different tissues and frequently much less intense than on cancer cells, this feature always carries a danger of autoimmunity [3].

Therefore, the ideal cancer vaccine avoids hurting normal cells that express the same antigen and instead targets tumor-specific antigens or tumor-associated antigens, a challenging task. Breaking self-tolerance is crucial for the efficacy of cancer vaccinations since tumor-associated antigens are self-antigens that are overexpressed by tumour cells. In

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Received: 29-Aug-2022, Manuscript No: jmir-22-73888, **Editor Assigned:** 01-Sep-2022, pre QC No: jmir-22-73888(PQ), **Reviewed:** 15-Sep-2022, QC No: jmir-22-73888, **Revised:** 20-Sep-2022, Manuscript No: jmir-22-73888 (R), **Published:** 27-Sep-2022, DOI: 10.4172/jmir.1000159

Citation: Mestecky J (2022) Utilizing the Patient' Immune System to Combat Cancer through DNA Vaccination. J Mucosal Immunol Res 6: 159.

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order to overcome this obstacle, different prime-boost techniques must be used with various formulations of the tumor-associated antigen used in vaccination. This comprises delivery through viral vectors or peptide- or protein-based antigens, which must be combined in order to produce detectable immune responses [4]. The use of self-replicating RNA and DNA vaccines, which were able to disrupt tolerance to tumor-associated self-antigens via implicating pathways of innate antiviral immunity, yielded encouraging findings. These vaccines increase immunogenicity, CD8+ T cell generation, and antigen-specific antibodies without having any unfavourable side effects. It is likely that the effectiveness of the self-replicating vaccines was linked to the caspase-dependent apoptotic cell death of transfected cells and a subsequent uptake of these cells by dendritic cells, even though the production of antigen was not increased in comparison to conventional DNA vaccines (DCs) [5].

Another intriguing method for overcoming some of the above-mentioned challenges is the application of xenogeneic tumor-associated antigens. By utilising a tumor-associated antigen from a different species that shares crucial epitopes and is flanked by xenogeneic protein sequences that further stimulate the antitumor response, the size of an anticancer response is unmistakably improved. By using DNA vaccination to deliver these xenogeneic tumor-associated antigens, an effective method may be developed [6].

Materials and Methods

33 women with large (L: 3 cm) and locally advanced breast cancers (LABCs: T3, 4; N1, 2; M0), engaged in a study of NAC (108 patients enrolled between 2008 and 2011), were investigated using paraffin-embedded slices of breast tumours and tumour-draining ALNs. Core biopsies that were guided by ultrasound provided the histological diagnosis. Multiple core biopsies were taken from each tumour to reduce tumour heterogeneity and sampling inconsistencies. Prior to NAC, a radiopaque coil was implanted into every tumour [7]. If there was no clinical or radiological signs of cancer following NAC, wire-guided excision of the leftover "tumour" was performed (in the instance of breast conservation). To achieve precise localization and histological analysis, the presence of the coil was radio logically confirmed in surgical tissues (wide local excision and mastectomy) [8].

Nine patients were without nodal metastases, while twenty of the twenty-four patients with nodal metastases also had additional pre-NAC ultrasound-guided core needle biopsy samples of metastatic tumours in ALNs [9]. For immunohistochemistry (IHC) analysis, representative tissue sections were employed. At a multidisciplinary meeting, all pre- and post-NAC specimens were discussed, and a decision was made regarding the pathological reaction and available treatments [10].

After NAC, pathological reactions in the surgically removed specimens were evaluated. Histopathological responses in the breast were classified according to well-established and previously published grading standards. Both a 4 (90% elimination of invasive disease) and a 5 (pCR, no residual invasive disease) were assigned as good pathological responses [11]. The best pathological responders were patients who had responses of grades 5 and 4 (GPRs). Poor pathological responses were rated as 3, 2, and 1 (30% reduction of invasive illness, respectively) (no loss of tumour cells). The PPR group consisted of patients who provided these responses. pCR (grade 3: complete disappearance of tumour deposits or replacement by fibrosis in a previously histologically confirmed metastatic ALN), pathological partial response (grade 2: residual metastatic tumour deposits present with evidence of tumour

destruction and replacement by fibrosis), and no pathological response were used to describe the pathological responses in metastatic tumours in ALNs (grade 1: metastatic tumour deposits remain with no evidence of fibrosis). Based on the availability of tissue samples, patient cases were chosen at random to achieve a fair distribution between the compared groups (pCR versus non-pCR) [12].

Discussion

Although the immunosuppressive TME is a significant barrier to the clinical effectiveness of DC cancer vaccines, numerous clinical cancer trials have demonstrated their viability and safety. In this way, attempts to improve the effectiveness of DC vaccines are increasingly concentrating on understanding and reversing the intricate interactions that occur in the TME and lead to immunological dysfunction that can impede T-cell activation and cancer cell death at the tumour bed [13].

Conclusion

A significant portion of cancer treatment failure is explained by drug resistance. Despite efforts, there hasn't been a successful cure for cancer cell drug resistance. Natural products offer a sizable pool for drug discovery, including potential molecules to combat drug resistance [14]. Even though the studies covered in this review lack many specific scientific details, they do demonstrate that many natural products, when used alone or in combination, are effective inhibitors of drug resistance in both laboratory and clinical settings, which offers the scientific and business communities with original insights (many of which are many first reports). All of the herbal formulae as well as several single compounds and herbal ones have already been utilised in clinical settings to treat various disorders, including cancer. Future research may reveal natural remedies for treating cancer cells that are resistant to treatment [15].

Acknowledgments

None

Conflicts of Interest

None

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