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VACCINES AS A TREATMENT FOR CANCER- NARRATIVE REVIEW

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ABSTRACT

Background: Cancer is defined as an abnormal growth of cells. Cancer cells are characterized by abnormal structure, functional disorder, and rapid growth compared to normal cells in the body. In recent years, significant progress has been made towards a better understanding of cancer development, which has led to significant advances in cancer treatment. Traditional cancer treatment protocols include radiotherapy, surgery, chemotherapy and proton therapy. Radiotherapy, despite its side effects, remains an important component of cancer treatment for at least 50% of all patients. On the other hand, several new strategies have emerged showing great potential in treating cancer and reducing cancer-related suffering and mortality. These include photodynamic therapy, photothermal therapy, gene therapy and nanomedicine therapy. Gene therapy consists of three different methods including immunotherapy (vaccine therapy, antibody therapy), virus therapy, and gene transfer. Cancer vaccines are designed to treat cancer by training the immune system to recognize infected cells (cancer cells). However, common vaccines are made to prevent infection of normal cells. The aim of this review is to highlight the preventive treatment of cancer with vaccines. **Discussion:** Cancer vaccines urge the immune system to fight cancer cells with the goal of treating the cancer or preventing it from returning after other treatments are completed. Also, some vaccines actually help to prevent some types of cancer. New antigens that arise from cancer-specific mutations represent another class of attractive antigens for therapeutic cancer vaccines. There is great interest in the development and testing of cancer vaccines that target novel antigens. Three types of vaccine platforms are being developed for the treatment of cancer: cell-based vaccines, viral vector vaccines, and molecular vaccines composed of peptides, DNA or RNA. Each of these platforms has advantages and disadvantages and is still under development: Cellular Vaccines, Peptide Vaccines, Viral Vector Vaccines, DNA Vaccines and RNA Vaccines. **Conclusion:** Although preventive anticancer vaccines are still under preclinical investigation, clinical translation is limited by the difficulties of antigenic and suboptimal immunogenicity predictions. The therapeutic anticancer vaccine not only needs to enhance the humoral response and CD4+ T-cell response, but also needs to activate MHCI-mediated CD+8 T-cell responses. The use of small-molecule targeting of the inflammatory signaling cascade (especially in the case of mRNA vaccines), better selection of immunogenic antibiotics, optimization of delivery systems, and selection of appropriate combination therapies will be necessary to ensure the success of anticancer NAVs in the near future.

KEYWORDS: cancer, vaccines, DNA, mRNA

INTRODUCTION

Cancer is defined as an abnormal growth of cells, where cancer cells have abnormal shape, functional disorder, and rapid growth compared to normal cells in the body.[1]

It is not possible to determine a major cause of cancer, but scientists believe that there are several different factors that may cause cancer, such as environmental and genetic factors, and the unique structural features of a person. As for the mechanism of cell transformation into a cancerous cell, scientists believe that this transformation occurs as a result of the combination of several genetic mutations in the genetic material of the cell, especially mutations that affect the part responsible for directing the cell to grow and divide.[2]

Unfortunately, it is a tissue-diverse disease and this diversity represents a major challenge for its specific diagnosis, followed by treatment efficacy.[3]

These data indicate that prostate and breast cancer constitute a significant portion of cancer in men and women, respectively. For children, the highest incidence of cancers is leukemia, and cancers related to the brain and lymph nodes, respectively.[4]

In recent years, significant progress has been made towards a better understanding of cancer development, which has led to significant advances in cancer treatment.[5]

Traditional cancer treatments include radiotherapy, surgery, chemotherapy and proton therapy. Radiotherapy, despite its side effects, remains an important component of cancer treatment for at least 50% of all patients.[6]

Also, chemotherapy (using cytotoxic drugs) inevitably damages the normal tissue surrounding the tumor.[7]

Chemotherapeutic agents target cells with a high basal level of proliferation and regeneration such as cancer cells and rapidly spreading non-tumor cells (in the skin, hair, bone marrow and gastrointestinal epithelium). This causes the high level of toxicity associated with such treatments.[8]

On the other hand, several new strategies have emerged showing great potential in treating cancer and reducing cancer-related suffering and mortality.[9]

These include photodynamic therapy (destruction of cancer cells using a light-sensitive drug activated by specific wavelengths of light), photothermal therapy (using a photothermal agent that activates by producing heat to destroy cancer cells), gene therapy (treatment/modifying of cancer cells using genetic material or stimulating immune cells), nanomedicine therapy (tumour-directed drug delivery).[10]

In gene therapy, cancer is targeted at the genetic level, and this method has a lot of potential. Gene therapy includes a wide range of treatments using genetic materials to modify cancer cells that cause tumor suppression.[11]

This treatment consists of three different methods including immunotherapy (vaccine therapy, antibody therapy), virus therapy, and gene transfer.

Cancer vaccines are designed to treat cancer by training the immune system to recognize infected cells (cancer cells). However, common vaccines are made to prevent infection of normal cells.[12]

With regard to immunotherapy, cancer immunotherapies have gained tremendous interest since the US Food and Drug Administration (FDA) approved six immunotherapies of checkpoint-blocking modifiers and two chimeric antigen receptors T cells (CAR-T).[13]

A brief history about cancer vaccines

The first evidence of cancer immunotherapy dates back to the Iberian papyrus (1550 BC), where the Egyptian pharaoh Imhotep (2600 BC) used compresses and then surgical incisions to treat tumors, which facilitates infection in the desired area and may lead to tumor regression. XVIII and XVIII, multiple forms of cancer immunotherapy have proliferated.[14]

In the eighteenth and nineteenth centuries, contaminated dressings wrapped in ulcerated tumors were used to treat cancer, surgical wounds were left open to facilitate wound infection, and doctors intentionally made suppurating ulcers. One of the most famous effects of microrganism on cancer was mentioned in 1891, when an American surgeon tasted William Cooley Patients with inoperable tumors with *Streptococcus pyogenes* bacteria. Cole developed a toxin containing heat-killed bacteria *Streptococcus pyogenes* and *Serratia sarcoma*, and this treatment was used against sarcoma until 1963.[15]

Cancer immunotherapies aim to activate the host's anti-tumor immunity and modify the tumor suppressor microenvironment, ultimately reducing tumor igenicity and increasing patient survival.[16]

In general, cancer vaccines are considered as an attractive alternative treatment option with both preventive and curative potential. Vaccines that target tumor-associated antigens or tumor-specific antigens (TAAs or TSAs) can specifically attack malignant cells that overexpress the antigens and achieve a chronic therapeutic response due to immune memory. Therefore, cancer vaccines provide a specific, safe and acceptable treatment compared to other immunotherapies.[17]

Steps to use immune cells to fight and target cancer cells[18]

1. We take a sample of the patient's blood, which in turn contains immune cells specialized in targeting cancer cells called T cells.
2. T cells are isolated and activated from the patient sample that we took a while ago
3. Using genetic engineering, large quantities of immune cells are multiplied and produced identical to those in the patient's body
4. A large number of immune cells are grown and prepared to perform their normal functions in fighting cancer
5. These cells are injected into the patient's body
6. T cells target cancer cells through special receptors that are found only on cancer cells and bind to them

7. T cells secrete toxins and enzymes that break down and destroy cancer cells and kill them.
8. Despite significant efforts in this field, clinical translations of cancer vaccines into effective therapies have remained challenging for decades due to the highly variable tumor antigens and related low immune response. However, the US Food and Drug Administration recently approved two preventive vaccines, one for the human papillomavirus (HPV), which is responsible for 70% of cervical cancers, and the other for the hepatitis B virus, which can cause liver cancer. Most encouraging is the immune cell-based vaccine PROVENGE (Sipuleucel-T), which was approved by the FDA in 2010 as the first therapeutic cancer vaccine to treat patients with hormone-resistant prostate cancer.[19]

We know that vaccines are given to healthy people to prevent certain infections such as measles and smallpox. These vaccines use attenuated germs such as viruses or bacteria to trigger an immune response in the body. The immune system's willingness to fight these germs helps prevent bacterial infections in humans. Most vaccines that treat cancer work in the same way, but they prompt the immune system to fight cancer cells in order to treat the cancer or prevent it from returning after other treatments are completed. Also, some vaccines actually help prevent some types of cancer.[20]

The rapidly increasing understanding of the biology of these obstacles has led to new approaches that enable researchers to turn a corner toward developing effective therapeutic cancer vaccines. Much of this new knowledge stems from studies aimed at dissecting the interactions of the immune system and cancer, including elucidating how cancers exploit T-cell checkpoint mechanisms. The development of CPIs (checkpoint inhibitors), the first of which were anti-CTLA-4, Anti-PD-1, and Anti-PD-L1 antibodies, represented a significant advance in cancer medicine.[21]

Cancer Vaccine Antigens

Antigen selection is the single most important component of cancer vaccine design. Ideally, the antigen should be specifically expressed by cancer cells (not in normal cells), which is present in all cancer cells, is essential for the survival of cancer cells (so that cancer cannot escape immune attack by downregulating the antigen), and it must be immunogenic significantly. Few if any of these criteria meet all of these criteria, however there are several classes of antigens that have been used in cancer vaccines.[22]

Types of cancer vaccine antigens

Tumor related antigens

So far, most cancer vaccines have targeted TAAs, which are self-proteins that are abnormally expressed by cancer cells. TAAs include: CT antigens, which are normally expressed only in cells of the immune-privileged sex line, cell line differentiation antigens, which are not ordinarily expressed in adult tissues, and antigens that are overexpressed in tumor cells.[23]

As self-antigens, B cells and T cells that strongly recognize these antigens may have been removed from the immune repertoire by central and peripheral tolerance. Thus the cancer vaccine must "break tolerance" by stimulating TAA-reactive T cells with rare or low residual affinity. Strong adjuvants, co-stimuli, and repeated inoculation have been used to amplify the activation and expansion of autoantigen-reactive T cells, and this is particularly important for low-affinity T cells.[24]

Although the number of peripheral antigen-specific T cells may be useful, the number and quality of TILs (tumor-infiltrating T) is the most relevant measurement, and patient TIL analysis is becoming more and more common in cancer vaccine development.

However in both cases the specific T-cell numbers required for efficacy are currently unknown and will undoubtedly vary depending on antigen, T-cell receptor affinity and tumor type.[25]

A second challenge to target TAAs is that even if they are overexpressed in cancer cells, normal cellular expression may lead to collateral damage. Although cancer vaccines have been accepted so far, in many cases the vaccine has not been effective and may therefore be ineffective.[26]

Chimeric receptor

CAR-T (chimeric receptor-engineered T cell) targets CEA (carcinoembryonic antigen) in severe colitis in a high percentage of patients where this antigen is also expressed in normal intestinal tissue. As therapeutic cancer vaccines become more effective, it will be important to pay close attention to the toxicity of normal cells.[27]

Oncoviral antigens

Viral infections are the cause of 10% of human cancers worldwide, most of which occur in the developing world. Vaccines consisting of HBV surface antigens have been shown to be highly effective in preventing infection and associated disease consequences including HCC (hepatocellular carcinoma). These prophylactic antiviral vaccines work by eliciting the production of potent modulating antibodies that prevent virus entry into host cells, thus preventing virus-mediated tumorigenesis. These preventive vaccines were not effective in treating intrinsic cancer likely because humoral immunity cannot efficiently eliminate large numbers of virus-infected cancer cells, which instead require cellular immune responses.[28]

Neoantigens

New antigens that arise from cancer-specific mutations represent another class of attractive antigens for

therapeutic cancer vaccines. Like viral oncoproteins, the generated antigens are specific to cancer cells and are recognized as foreign by the immune system, and thus reactive immune cells are not excluded by tolerance mechanisms.[29]

There is great interest in the development and testing of cancer vaccines that target novel antigens. Several hotspot mutations that commonly occur in many cancer patients have been shown to encode immunogenic antigens, and adoptive cell therapy and therapeutic vaccines for a few of these mutations have been found to induce clinical and immune responses. However, like cancer mutations, the majority of the antigens generated are specific to each patient and their numbers vary depending on the type of tumor.[30]

Producing a cancer vaccine against the patient's individual developed antigens requires a personalized approach.[31]

- The genome of the patient's tumor is arranged
- Identification of mutations
- Prediction of induced antigens via computerized algorithms (and may be experimentally confirmed for their expression and binding to major histocompatibility complex proteins).
- Then a vaccine is built that expresses the expected new antigens and delivers it to the patient.

In general, three types of vaccine platforms are being developed for the treatment of cancer.[32]

1. Cellular Vaccines
2. Virus vector vaccines.
3. Molecular vaccines consisting of peptides, DNA or RNA.

Each of these platforms has advantages and disadvantages and is still under development.

Types of cancer vaccines

1. Cellular vaccines
2. Peptide vaccines
3. Viral vector vaccines
4. DNA Vaccines
5. RNA Vaccines

1. Cellular Vaccines

Vaccines have been developed that use either killed tumor cells or APCs (autologous antigenpresenting cells) loaded with cancer antigens and have produced some efficacy in patients. The advantage of this approach is that the target antigens do not need to be identified prospectively. Although such vaccines have worked well in mouse tumor models resulting in immune responses and tumor regression, several clinical trials testing GVAX vaccines in prostate cancer, melanoma, pancreatic cancer and lung cancer have shown limited efficacy despite stimulation Immune responses in patients.[33]

2. Peptide Vaccines

Several clinical trials of the peptide vaccine have been conducted with the demonstration of immune responses, but significant clinical benefits have been elusive. Short peptides based on only one antigen are often used that may not be able to overcome antigen heterogeneity, loss of antigen expression within the tumor, or induce robust immune responses. In addition, short peptides do not activate CD4 helper T cells, which are essential for full activation of cytotoxic T lymphocytes.[34]

3. Viral vector vaccines

Many viruses have been exploited as vaccine platforms for cancer. One advantage of virus-based vaccines is that the immune system has evolved to respond effectively to viruses, with innate and adaptive mechanisms working together to elicit a robust and lasting response. Viral pathogen-associated molecular patterns activate pattern recognition receptors to enhance activation of antigen-presenting cells. The most common viral vaccine vectors are derived from poxviruses, adenoviruses, and alphaviruses. A disadvantage of viral vectors is that the antiviral immune response neutralizes the vector, thus limiting vaccination frequency.[35]

4. DNA Vaccines

Cancer DNA vaccines are engineered DNA molecules that encode one or more predetermined TAs, with or without other immune-modifying molecules.

DNA vaccines must pass through the cell membrane of APCs into the cytoplasm and migrate to the nucleus to initiate transcription where the resulting mRNAs travel to the cytoplasm where they are translated into TAs.[36]

These proteins can be degraded by proteasomes and processed by the endoplasmic reticulum as intracellular antigens, which are presented as I MHC-binding peptides.

Alternatively, proteins in endosomes can be degraded as extracellular antigens, producing MHC II-binding peptides.[37]

5. mRNA vaccines

The introduction of mRNA into DCs for adoptive transfer was the first mRNA-based therapeutic cancer vaccine to enter clinical trials.[38]

Whereas, although DC-based mRNA vaccine therapies still account for the majority of mRNA cancer vaccines in clinical trials, IVT mRNA-based immunotherapies delivered by non-viral vectors have been extensively explored recently as a result of promising anti-tumor results that have been gathered from preclinical studies with CureVac, BioNTech and Moderna as campaign lead. A group of IVT mRNA-based immunotherapies examined in clinical trials are mRNAs that encode immunomodulators, which are injected into the tumor or into the nodes to modify the tumor microenvironment.[39]

CONCLUSION

With the recent approval of two mRNA LNP vaccines to prevent COVID-19, mRNA vaccines are experiencing a major explosion in preclinical and clinical research in both the areas of cancer and infectious diseases. The challenges of developing cancer vaccines versus infectious disease vaccines are: First, most infectious disease vaccines are preventative while cancer vaccines are curative.

Although preventive anticancer vaccines are still under preclinical investigation, clinical translation is limited by the difficulties of antigenic predictions and suboptimal immunogenicity. Second, most antigens for infectious diseases (bacterial or viral) are exogenous forms that are usually presented by the MHCII molecule. Vaccines that target these exogenous antigens induce an antibody-mediated humoral response. In some cases the immune response mediated by CD4+ T cells is involved and partially required while CD8+ cytotoxic T cells play an important role in removing malignant cells with somatic mutations. Thus, a therapeutic anticancer vaccine needs to not only enhance the humoral response and CD4+ T-cell response, but also need to activate MHCI-mediated CD+8 T-cell responses, adding to the difficulties of effectively promoting robust anti-tumor immunity.

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