

The emerging role of vaccines in cancer therapies

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Abstract. Globally, there is a severe public health issue with cancer. Comprehensive funding has been provided for the creation of medicinal vaccines against cancer. The efficiency of vaccines in preventing bacterial and viral illnesses has been demonstrated. Over the past 200 years, they have averted many fatal diseases and saved countless lives. Vaccines protect against diseases brought on by viruses and bacteria by exposing recipients to attenuated or inactivated pathogens. Thereby, the individual's immune system can identify the antigen and behave. DNA vaccines, mRNA vaccines, and synthetic peptide vaccines are just a few of the innovative vaccinations created in recent years using modern biotechnology. Immune adjuvants or drug delivery systems are utilized to enhance immunogenicity through extensive immune system research, tests on animal models, and clinical trials of vaccines. This review paper will discuss therapeutic cancer vaccine mechanisms and cancer vaccine delivery methods.

Keywords: Therapeutic Cancer Vaccines, Immune Response, Delivery System.

1. Introduction

One of the most significant issues with global public health is cancer. The second top causes of mortality in the United States are cancer (23.1% of all deaths) and cardiovascular disease (26.0% of all deaths) [1]. The development of highly effective therapeutic cancer vaccines has received extensive support [1]. The American Cancer Society annually analyzes cancer incidence, mortality, and survival rates. Additionally, it estimates the annual number of cancer deaths and new cases. While cancer incidence rates for women have stayed steady over the decades, rates for males have declined by about 2% per year. There were almost 2,629,200 fewer cancer deaths between 1991 and 2016 (a 27% decrease in the cancer death rate). The gap in cancer mortality rates has gradually narrowed across ethnic groups but widened among the rich and poor segments of society. Mortality rates from cervical cancer are twice as high in poorer areas than in wealthier areas. In particular, it is indicated that cancer treatment strategies should receive high priority [2].

Among the many cancer treatment possibilities, therapeutic vaccinations have drawn the most attention. Compared to conventional treatments like surgery or chemotherapy, this is because those therapeutic vaccinations produce an immune response that persists in suppressing the tumor. Therapeutic vaccines made of DNA, mRNA, and synthetic peptides trigger autoimmune reactions by triggering antigen-presenting cells (APCs) and cytotoxic T lymphocytes that are specific for the antigen in question (CTLs). Tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs) are the main targets of therapeutic vaccinations, which instruct the patient's immune system to identify and eradicate tumor cells. TSAs are derived from typical protein sequences that have been somatically mutated. TSAs are a suitable subject for cancer immunotherapy because of their uniqueness. Nevertheless, personalized immunotherapies must be created because mutant cell cancers differ from one another. Despite having the same organizational structure, TAA is less immunogenic and self-antigen tolerant [1]. However, effective delivery systems can enhance immunogenicity by increasing the efficiency of antigen uptake and processing by APCs. An overview of the immunological reactions to therapeutic cancer vaccines composed of synthetic peptides, DNA, and mRNA is given in this review paper. Cell-based delivery, lipid-based delivery, polymer-based delivery, peptide-based delivery, and virus-like particle delivery are also summarized.

2. Current types of cancer vaccines

2.1. DNA vaccine

The DNA vaccine has received wide attention and has been thoroughly studied since it was first proposed in the 1990s. DNA vaccine contains a genetically modified plasmid carrying a DNA sequence encoding an antigen that is injected into the muscle site and elicits a response from the humoral and cell-mediated immune response. The inoculated DNA sequence is expressed on the myocytes and APCs. The protein is produced on the cell surface and processed as an endogenous antigen via the MHC class I pathway. The cytotoxic T cell is stimulated by the antigen on the cell surface. Furthermore, pass on to the MHC class II pathway and initiation adaptive immunity [3]. The tumor antigens have been divided into two main categories: tumor-specific shared antigens and tumor-specific unique antigens. Because of this, cancer DNA vaccines need to target different types of antigens to allow for treatment and thus achieve the desired therapeutic result [4]. Since the DNA vaccine is a relatively new type of vaccine with a relatively low economic cost, simple storage conditions, and comprehensive immune response, it has been widely applied in clinics such as cancer, tuberculosis, HIV, and other diseases. However, the further study still needs to improve the restriction that only protein immunogens can be used. Despite the constructive results in small animal experiments, it shows poor immunogenicity in large animal models and humans [3,4]. The US Food and Drug Administration's Center for Biologics Evaluation and Research (CBER/FDA) now oversees the clinical development of regulatory DNA vaccines. The laws and guidelines are first considered, and then the vaccine policy should be developed. The DNA vaccine's safety and immunogenicity are then determined using data from animal model testing, after which human clinical trials may be carried out [3].

2.2. mRNA vaccine

mRNA vaccine is a recent mode of vaccination that functions by using messenger RNA (mRNA) encoding microbial antigens. The procedure of designing an mRNA vaccine includes: studying mRNA tumor vaccines by finding genes with amino acid sequences that can encode antigenic proteins in tumor cells. Afterward, the mRNA vaccine is encapsulated in lipids and enters the body's immune cells, dendritic cells, where it stays in the cytoplasm rather than moving into the nucleus to interfere with the normal nucleic acids of the body's cells. When the mRNA fragment is read by the cell ribosome of the viral surface protein, it is generated and appears on the dendritic cell's surface. When the dendritic cell contacts the helper T cell, the surface proteins are presented to the immune system, and the body's autonomic immune system is activated. Many antibodies are produced through the transfer of information between the B-cell and helper T-cell. At the same time, cytotoxic T cells kill the virus-infected cells [5]. Compared with DNA vaccines, the mRNA vaccines have better immunological properties, safety, and flexibility. These characteristics have distinguished them as a top candidate for the development of cancer therapy. Furthermore, mRNA vaccines have no likelihood of infection or insertional mutagenesis. Since mRNA is not infectious and is not integrated. Moreover, mRNA can be degraded during normal cellular activity. Its immunogenicity can be down-regulated, hence increasing safety. Meanwhile, the mRNA is adjusted to be more stable for effective and rapid in vivo delivery, which enables mRNA vaccines an excellent opportunity to develop quickly, effectively, and affordably for mass production [6].

2.3. Synthetic peptides of cancer vaccine

Since the immune system can detect tumor cells, the technology of synthetic peptide vaccines, which can destroy tumor cells by guiding the patient's immune system, has been highly anticipated. Synthetic peptide vaccines have single or multiple long or short sequences of amino acids as tumor antigens. Synthetic peptide vaccines must be paired with vaccine adjuvants because the peptides alone are poorly immunogenic. Consequently, adjuvants are needed to control the release of peptides and enhance antigen expression [7]. The two most popular adjuvants for synthetic peptide vaccines are

incomplete Freund's adjuvant (IFA) and equivalent Montanide ISA-51. Short (9-11 amino acid) peptides with IFA or Montanide in clinical trials against melanoma do not perform satisfactorily. The reason for this may be the loss of function or the absence of specific T cells at the site of vaccination. Long peptides, 16 amino acids, with Montanide show high levels of immunogenicity. It effectively stimulates T-cell immune function to fight against tumor cell telomerase reverse transcriptase (TERT) [8].

There have been many synthetic peptide vaccines that eliminate tumors by stimulating CD8+ cytotoxic T cells in the immune system; CD4+ TH cells have also been reported to be stimulated against tumors. Early research and clinical evidence demonstrated that CD4+ T cells could promote tumor protection. Furthermore, there have been some positive results in the use of adoptive T-cell therapy for melanoma [7,8].

3. The delivery system of vaccines

3.1. Cell-based delivery of tumor antigen vaccine

Dendritic cell-based therapeutic cancer vaccines are well-known among cell-based delivery technologies for tumor antigen vaccines. Dendritic cells' primary job is to identify and absorb antigens like bits of bacteria, viruses, and cancer cells. After processing, antigenic peptides are presented to the cell membrane surface via MHC. They also migrate to the nearby lymph nodes where T cells are clustered and deliver antigenic information to the corresponding T cells. In the meantime, dendritic cells upregulate the expression of co-stimulatory factors on the cell surface, stimulating t-cell activation, proliferation, and aggregation. This induces the activation of an adaptive immune response. Dendritic cell vaccines are mainly based on the highly potent antigen-presenting ability of dendritic cells [9].

The first generation of dendritic cell cancer vaccines is delivered to T cells by dendritic cells containing synthetic antigenic peptides, antigen-encoded mRNA, or DNA, as well as the patient's own inactivated tumor cells or lysates. The DC cancer vaccine has been shown to have high safety and feasibility in early clinical trials and mouse models. There are many therapeutic uncertainties regarding the type of adjuvant, the patient's immune system's condition, the route of vaccination, and the immune target [9,10]. Recent research in dendritic cell vaccines has been directed towards enhancing the immunogenicity of dendritic cells and triggering more potent CD8+ T cells through vaccines. Activating naive T cells or programmable memory T cells allows naive T cells to develop into cytotoxic T cells. When combined with DC cytokines like IL-12 and IL15, dendritic cells exhibit tumor peptides via CD80, CD70, and 4-1BB to promote the development of naive T cells into cytotoxic T cells at lymphoid organs [9].

3.2. Lipid-based delivery

Liposomes are currently significantly widely studied nanocarriers for nanoparticle delivery. Phospholipids have a lipophilic tail and a hydrophilic head. In this regard, liposomes are characterized by closed vesicles composed of phospholipid bilayers [11]. Liposomes are broadly selective, non-toxic, non-immunogenic, and suitable for intra-biological degradation. In their capacity to transport both antigen and adjuvant to the same antigen-presenting cells, liposomes are highly valued as vaccine carriers. This triggers a high-intensity immune response. Capable of adequate protection of encapsulated antigens and controlled slow release of antigens. Significantly improves the therapeutic index of the vaccine and reduces negative responses [11, 12].

Charged liposomes have structural stability as well as modulate the surface properties of liposomes. The slow, long-term release of antigens is made possible by the interaction of positively charged liposomes with negatively charged cell membranes. The use of positively charged 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) for delivery of plasmid DNA enables rapid maturation of stimulated DCs and then enhances the cellular immune response [12].

3.3. Polymer-based delivery

Natural polymers are readily available as well as a renewable resource. As a natural polymer, Chitosan is gaining attention because of its high utility, biodegradability, absorbability, and permeability. It is electrostatically bound to negatively charged proteins or plasmid DNA to form polymer composites for use in vaccine adjuvants or delivery vehicles. Chitosan derivatives, which are created by chemically altering chitosan, typically exhibit antibacterial action in addition to being non-toxic. Antigen-loaded chitosan nanoparticles enhance the stimulation of APCs and release pro-inflammatory cytokines [13-15].

Hydrogel polymers are used for delivering vaccine molecules that can be administered orally, injected intramuscularly, or released into the organism via transcutaneous tissue through a system of hydrogels to contain. These delivery methods have yielded positive results in experimental animal models. Different hydrogel delivery methods elicit immune responses with various outcomes. For example, the "hydrogel patch" delivers antigenic proteins into the epidermis and encourages the production of IgG in the region, eliciting an immunological response [16].

3.4. Peptide-based delivery

Due to the antigenic character of peptides, they can trigger a comprehensive and targeted immune response. Adjuvants must be used with peptide vaccinations to produce the intended outcomes. Short peptides are less immunogenic since they elicit protective immune responses by adopting a minimum number of viral components. However, the binding of numerous identical short peptides can increase their immunogenicity. The lipid core peptide (LCP) method, which improves immune stimulation and autonomous adjuvants by mixing peptides with poly-lysine cores, has been applied in several vaccine trials [17]. Peptides, the primary mode of delivery for RNA vaccines, are positively charged and interact with nucleic acids via electrostatic forces. Protamine, a polycationic peptide found in various animal sperm nest tissues, can be used as the delivery system of mRNA vaccines. It lowers the cost of storage and safeguards mRNA from RNase destruction. Protamine-mRNA complexes, on the other hand, serve as adjuvants. Therefore, activating TLR7 can result in immunogenicity [18].

3.5. Virus-like particle

Virus-like particles (VLPs) have often been called "empty shells" because they lack the viral genome despite having the same organizational structure as viruses. Through TLRs and pattern recognition receptors, VLPs activate the innate immune system (PRRs), thus triggering strong humoral responses and IgM and enhancing APCs by cross-presentation of MHC I and II. This unique structure significantly contributes to medical development [19]. VLPs are formed by the organization of single or multiple proteins. VLPs can self-assemble and morphologically resemble nature viruses; nevertheless, they are genetically devoid of disease-causing components and cannot be replicated. Currently, five VLPs vaccines have been approved [19].

VLPs are transformed into cVLPs by genetic or chemical fusions that alter the surface expression of VLPs, which then stimulate the response of the immune system to external proteins. SV40 VLPs are formed by inserting specific exogenous peptides on the surface of VP1. SV40 VLPs can mount DNA and protein antigens while acting as natural adjuvants to stimulate the innate immune system. They deliver antigens and stimulate CTLs without the need for synthetic adjuvants [19]. When delivered by VLPs, DNA can be orally administered into the GI mucosa. VLPs constructed of the open reading frame 2 (ORF2) of HEV have received plasmid DNA in vitro; mucosal and systemic immune responses against the HEV virus are intense in mouse models. HPV VLP vaccines can deliver and express plasmid DNA in vivo and in vitro. Both mucosal and systemic cellular and humoral immune systems can be activated by an oral HIV-VLP vaccination supplied with access to HEV-VLP [19].

The longevity and cellular accessibility of siRNA vaccines are enhanced by polyethyleneimine (PEI)-coated VLPs (PEI-AAV2-VLPs) produced from adeno-associated virus type 2 (AAV2). The electrostatic properties of PEI are protective and improve cellular intake and enhance the efficiency

of siRNA delivery. When utilized in the therapy of breast cancer, PEI-AAV2-VLPs can prevent siRNA from enzymatic breakdown and cause MCF-7 breast cancer cell death [19].

4. Conclusions

Data from animal models and clinical trials of therapeutic cancer vaccines have yielded promising results, heralding cancer vaccines' unlimited possibilities. The action of vaccines is improved and enhanced by combining adjuvants and delivery systems that promote immune responses. Different types of immune vaccines are combined with various delivery systems to achieve the desired therapeutic effect. VLPs are considered safe in vaccine development and can enhance the uptake of antigens by APCs [19]. Even so, addressing immune tolerance and proper delivery of vaccine material is one of the primary issues of delivery systems. At the same time, therapeutic cancer vaccines require an in-depth understanding of the immune system mechanisms [19-21]. It is undoubtedly great news that therapeutic cancer vaccines are being developed, considering cancer is one of the most challenging diseases of modern times. Despite a recent decline in cancer mortality rates, there is still a need to increase cancer prevention awareness among the underprivileged. In low-income communities, basic medical examinations, smoking cessation initiatives, and information about cancer prevention should be strengthened [21].

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