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Therapeutic Effect Analysis of Cervical Cancer Vaccine

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Abstract. Cervical cancer is a very widespread carcinogenic condition that poses a significant threat to women's health. The primary cause of this condition is mostly linked to persistent infection with high-risk strains of human papillomavirus (HPV), which are recognized for their ability to promote the development of cancer. Due to HPV infection, both therapeutic and preventative HPV vaccinations have been developed. Therapeutic vaccines can eradicate viruses and virus-infected cells by stimulating cellular immunity. Notwithstanding the availability of preventive HPV vaccinations, HPV screening, surgery, radiotherapy, and chemotherapy, the therapeutic effect on cervical cancer patients is limited. Therefore, therapeutic vaccines have emerged as a new treatment option. The cancer-causing proteins E6 and E7, which are consistently detected in cervical cancer and precancerous lesions, are crucial in the progression and sustenance of cervical cancer. Consequently, these cancer-causing proteins present an encouraging opportunity for the research and creation of therapeutic cervical cancer vaccines. The multiple therapeutic vaccines against cervical cancer will be briefly discussed in this article, including their mechanisms, development methods, and clinical effects.

Keywords: Cervical cancer; Therapeutic vaccines; Human papillomavirus.

1. Introduction

According to the WHO, cervical cancer is the fourth most prevalent type of cancer generally. It is also the top cause of cancer deaths in low- and middle-income nations. Around 604,000 new incidences of cervical cancer were reported in the year 2020, resulting in 342,000 fatalities on a global scale [1]. On a worldwide scale, the average age at which cervical cancer is diagnosed is 53 years, whereas the average age at which individuals succumb to the disease is 59 years [2]. Various variables have been identified as potential contributors to an increased susceptibility to cervical cancer. These factors including engaging in premature sex, having numerous sexual partners, tobacco use, prolonged usage of oral contraceptives, immunosuppression, low socioeconomic status, and multiple births. Early symptoms of cervical cancer may include bleeding after sex, increased and sometimes smelly vaginal discharge, or usually no symptoms. As cervical cancer progresses, more severe symptoms may appear, including lower extremity edema, abdominal pain, and vaginal discomfort. There are also more serious symptoms in the later stages, depending on which organs the cancer has metastasized to.

The progression of cervical cancer from normal cervical epithelium occurs via the development of low- and high-grade cervical intraepithelial lesions, with a significant contribution from infection by hrHPV. The majority of HPV infections are transient, disappear within a year or two, and do not result in cervical cancer. A limited proportion of hrHPV infections exhibit persistence, resulting in cervical precancerous tumors lesions that eventually progress to cancer if not well managed. In addition, cancer-prone women may test positive for hrHPV genotypes years before the disease manifests. After hrHPV infects the cervical epithelium, the host genome changes. This silences some factors that cause cancer and makes other factors that cause cancer less effective at the same time. It has been shown that HPV strains 16 and 18 are the major culprits responsible for more than 70 percent of all cases of cervical cavity cancer that occur across the world, so HPV screening and vaccination programs have shown efficacy in the prevention of the illness [3].

The appropriate course of treatment for cervical cancer is contingent upon many variables, including the phase of the disease, the presence of metastasis, the dimensions of the tumor, and the patient's age and overall health status. However, despite the availability of a broad variety of treatments and preventative strategies, cervical cancer continues to be a substantial burden across the globe [1]. At this time, there are three categories of preventive vaccinations that have been approved for use in a variety of countries. Although the efficacy of these three vaccines in preventing the majority of HPV-induced malignancies is well established, they are not very good at getting rid of infections that are already present, and they do not dramatically lower cancer rates. In contrast to prophylactic vaccines, there is ongoing research and development of therapeutic vaccines that aim to activate immune system defenses and eliminate infected cells instead of only focusing on neutralizing antibodies. Hence, therapeutic vaccinations exhibit more promising prospects and provide a greater scope for development in the realm of cervical cancer therapy. This review summarizes the research and development progress, therapeutic effect, current situation, and prospects of cervical cancer therapeutic vaccines.

2. Live Vector-Based Vaccines

Two subcategories of live vector-based immunizations are recombinant viral and bacterial vaccines. These vaccines have the ability to carry HPV antigens, replicate inside host cells, and elicit defenses against HPV. Vector-based vaccines that are administered in a live form has the potential to have increased immunogenicity. The major histocompatibility complex (MHC) class I and class II pathways, help to increase antigen in order to achieve this. The emergence of neutralizing antibody (nAbs) targeting pre-existing bacteria and viruses might potentially limit the use of these vectors and subsequent therapeutic interventions. As further obstacle to the use of live vector vaccines is likely dominance of the vectors' immune response over that of the HPV antigen.

2.1. Bacterial vector-based vaccines

The creation of bacterial vaccinations that can stop cancer is a highly active topic of study. Therapeutic vaccines have been tested using a variety of bacterial vectors, such as Listeria monocytogenes, Clostridium, Bifidobacterium, Salmonella, Mycobacterium, and Bacillus, among others. Among these, Lm has received greater research. The Lm bacteria is of the gram-positive type. The organism is responsible for the production of virulence factors. Several factors contribute to the pathogenicity of the bacterium, including the hemolysin known as listeriolysin O (LLO), the phosphatidylinositol-specific phospholipase C (PI-PLC), the ActA protein responsible for host actin recruitment and polymerization, and internalins that facilitate the attachment of nonphagocytic host cells to the pathogen. ADXS11-001 is a changed version of the Lm bacterium that has been made to make the truncated LLO (tLLO) protein along with the HPV 16 E7 antigen.

Lm has the capacity to replicate in antigen-presenting cells (APCs), in addition to its capability to infect monocytes and macrophages. APCs located in the spleen undertake the process of phagocytosis, engulfing bacteria upon the entry of ADXS11-001 into the circulation. The antigen tLLO-E7 undergoes proteasomal degradation upon its translocation into the cytoplasm, facilitated by the secretion of LLO by ADXS11-011, which enable its escape from the phagolysosome and subsequent localization inside phagosome. The resultant peptides are then given to CD8+ cytotoxic T lymphocytes that are specific for the antigen after being complexed with MHC class I molecules. The extrinsic route is used to process bacteria that are unable to escape the phagolysosome; following the step, the peptides are complexed with the molecules of MHC class II and presented to CD4+ cells that exhibit specificity towards the particular antigen. Helper T cells are stimulated and secrete cytokines, which help the body's defenses go from a protective Th2 response to a cytotoxic Th1 response. Cytotoxic T lymphocytes locate and invade the tumor as a consequence, attacking and eliminating the HPV+ cancer cells.

2.2. Viral vector vaccines

Viral vector vaccines are great oncolytic viruses (OVs) for cervical cancer due to their ability to efficiently infect cells, express encoded antigens, induce immune system responses, be equipped with protective measures, and be targeted against cancer cells. Extensive research has been conducted on the administration of HPV E6 and E7 antigens using adenoviruses.

The adenoviruses (Ads) are large (150 nm or larger), non-enveloped, double-stranded DNA viruses [4]. The potent immunogenicity of adenovirus vectors makes them the perfect choice for applications in immunization and oncolysis. Additionally, as integrin receptors are the majority of human cells' principal receptors for Ads, they may transduce and infect different types of cells, both those that divide and those that don't. Ad vectors are often preserved as cell-free DNA and are not internalized by the infected host, posing no damage. Furthermore, the newest generation of Ad vectors can carry more foreign genes.

The Ads protein's fiber knob domain engages in interactions with receptors on the cell surface, thereby facilitating the process of cellular infection [4]. The virus then gets inside the cell by attaching to cellular integrins, mostly vß3 and vß5, employing the viral penton base's RGD motif, which stands for arginine, glycine, and aspartic acid [4]. The process of transcribing the early and late genes of the Ad virus takes place inside the nucleus of the host cell. This process leads to the synthesis of the virus and its subsequent release from the cell after ingestion and degradation of the viral protein envelope [4]. By altering the genomes of adenoviruses so that they only replicate in tumors, so-called oncolytic adenoviruses (OAds) start to have an anticancer effect [4]. Once the tumor cell that received the infection is lysed, the viral progeny that was released infects nearby cancer cells, and the circulatory system may also aid in spreading the virus to distant metastases. Numerous studies have shown that oncolytic Ads may increase the therapeutic efficiency of conventional cancer treatment drugs and can also elicit immunological responses targeting neoplastic cells via the release of antigens associated with the tumor. Therefore, despite the lack of clinical studies, the utilization of Ads vectors in the therapeutic approach for cervical tumors still offers promising futures and plenty of opportunity for growth.

3. Peptide/Protein-Based Vaccine

Due to the possibility of precisely controlling the immune response utilizing antigens from protein fragments or peptides, as well as the relative simplicity of producing these biomolecules, subunit vaccines are gaining a lot of interest [5].

3.1. Peptide-based vaccines

Peptide-based vaccines have the potential to eradicate cervical cancer by inducing immune responses in cells and using non-self-immunogenic antigen derived from cancer-associated proteins. When presented to CD8+ T cells by MHC I as endogenous antigens, processed in the host's cytoplasm by the proteasome, and then delivered, peptide vaccines cause a cell-mediated immune response. For the production of peptides, synthetic long peptides (SLPs) and minimum peptide epitopes are both viable options. Longer peptides and proteins may simply be synthesized recombinantly, while short peptides can be manufactured at scale utilizing automated synthesis techniques [5]. Short peptides can be exogenously coupled to MHC classImolecules on all nucleated cells and do not need to be processed by professional APCs. On the other hand, since SLPs are too length to fix MHC molecules, specialized APCs are necessary for the collection and presentation of the information. Peptide-based vaccines provide many advantages, especially in respect of their longevity, safety profile, and ease of production and storage. In contrast, the main disadvantages of peptide vaccines are low immunogenicity and poor in vivo stability, thus requiring adjuvants to improve the effectiveness of peptide vaccines in vaccinated populations.

Currently, research and development efforts are focus on creating new therapeutic SLP vaccines aimed at HPV16 (ISA101 and ISA101b). The ISA101 vaccine is made up of HPV-16 E6 and E7

SLPs. Dendritic cells do a great job of breaking down these SLPs. This stimulates CD4+ and CD8+, which leads to the development of an HPV-16-specific anticancer response [6]. ISA101 has been shown to be a successful treatment for pre-malignant vulvar lesions that are positive for HPV-16, resulting in complete remission. The efficacy of this treatment is closely linked to the potency of the lymphocyte reaction, which plays a crucial role in clearing the lesions [6]. Promising outcomes have been seen when administering the ISA101b vaccination to individuals with advanced, recurring, malignant HPV16+ cancer in conjunction with standard radiation therapy or immune-mediated checkpoint blockade with an anti-PD-1 monoclonal antibody. Notably, the vaccine has been observed to elicit strong interferon-γ-producing T cell reactions to the HPV16 E6/E7 antigens, which have been associated with a significant improvement in survival outcomes [7].

3.2. Protein-based vaccines

Protein-based vaccinations provide a notable benefit over peptide-based vaccines due to they include all E6 and E7 epitopes without being limited by MHC class I molecules. However, they also have disadvantages, such as limited immunogenicity and difficult separation and purification processes. Clinical studies for many protein-based vaccines have been undertaken. The recombinant fusion protein known as TA-CIN is composed of the minor capsid protein L2 and two HPV16 oncoproteins called E6 and E7 [8]. The combination of PD-1 inhibition with intratumoral TA-CIN vaccination has a synergistic effect, leading to a substantial increase in specific antigen CD8+ T cell reactions and complete remission of tumors [8].

4. Nucleic Acid-Based Vaccines

Antigens that are coded by either DNA or RNA are used in vaccines made from nucleic acids. Multiple stimuli may elicit powerful MHC I-mediated CD8+ T cell responses owing to their ability to simplify the delivery of several antigens during a single immunization. Nucleic acid-based vaccines are establishing themselves as a viable and captivating platform for the administration of vaccinations. Nucleic acid-based vaccinations have many benefits in comparison to conventional vaccinations. These include their inherent safety profile, ability to elicit a targeted immune response towards the desired antigen, capacity to induce both humoral and cellular immunological reactions, cost-effectiveness in production, and simplified manufacturing processes.

4.1. DNA-based vaccines

DNA-based vaccines are pure plasmid preparations that include one or more targeted DNA sequences that may trigger an immune response against a disease. The host cells take up the introduced DNA once the plasmid DNA preparations have been supplied by a number of methods, which causes the gene to be expressed so that the cell may generate the necessary proteins. APCs display proteins on their cell surfaces after host proteases have converted them into tiny antigenic peptides.

Numerous DNA-based cancer vaccines have been subjected to rigorous preclinical and clinical evaluations, with a particular focus on their use within the context of cervical carcinoma treatment. The therapeutic HPV DNA vaccine GX-188E (tirvalimogene teraplasmid) contains the HPV16 and HPV18 E6 and E7 encoding sequences [9]. GX-188E is capable of targeting and activating dendritic cells. In phase II cervical cancer research, GX-188E showed promising outcomes [9].

4.2. RNA-based vaccines

Recently, messenger RNA (mRNA) vaccination has gained popularity as a DNA vaccine substitute in the realms of infectious disease prevention and cancer therapy. RNA-based vaccines have the capacity to undergo translation inside the cytoplasmic compartment, in contrast to naked DNA-based vaccines, which need transportation to the nucleus for transcription. Additionally, the rate and magnitude of protein expression are generally higher than those of DNA vaccines. RNA-based vaccines are made with non-pathogenic viral vectors and RNA replicon platforms that are derived

from charged single-stranded RNA viruses. One limitation of RNA vaccines is their susceptibility to degradation, since RNA molecules are more prone to enzymatic breakdown compared to DNA. Clinical research on mRNA vaccines has advanced slowly because of issues with stability, the expense of customized production of patient-specific vaccinations, and delivery.

An existing RNA-based vaccine candidate for treating cancers caused by HPV is called RNA-LPX. In preclinical animal models, the therapeutic intervention focuses specifically on targeting the HPV16 E7 protein, and it has been shown that this particular intervention has the capacity to produce durable antigen-specific $CD8^+$ immune responses [10], as shown in Fig. 1. The development of BNT113, a derivative of RNA-LPX encoding HPV16 E6 and E7, included the use of an mRNA backbone and LPX technology that are closely linked. The ongoing clinical trial BNT113 encompasses both Phase I and Phase II. The study primarily centers on individuals who have been diagnosed with head and neck cancer that is linked to the HPV16. The primary aim of this clinical trial is to access the effectiveness and safety of the vaccination. In subsequent studies, the efficacy of the vaccination will be evaluated in individuals afflicted with HPV16-related cervical cancer.

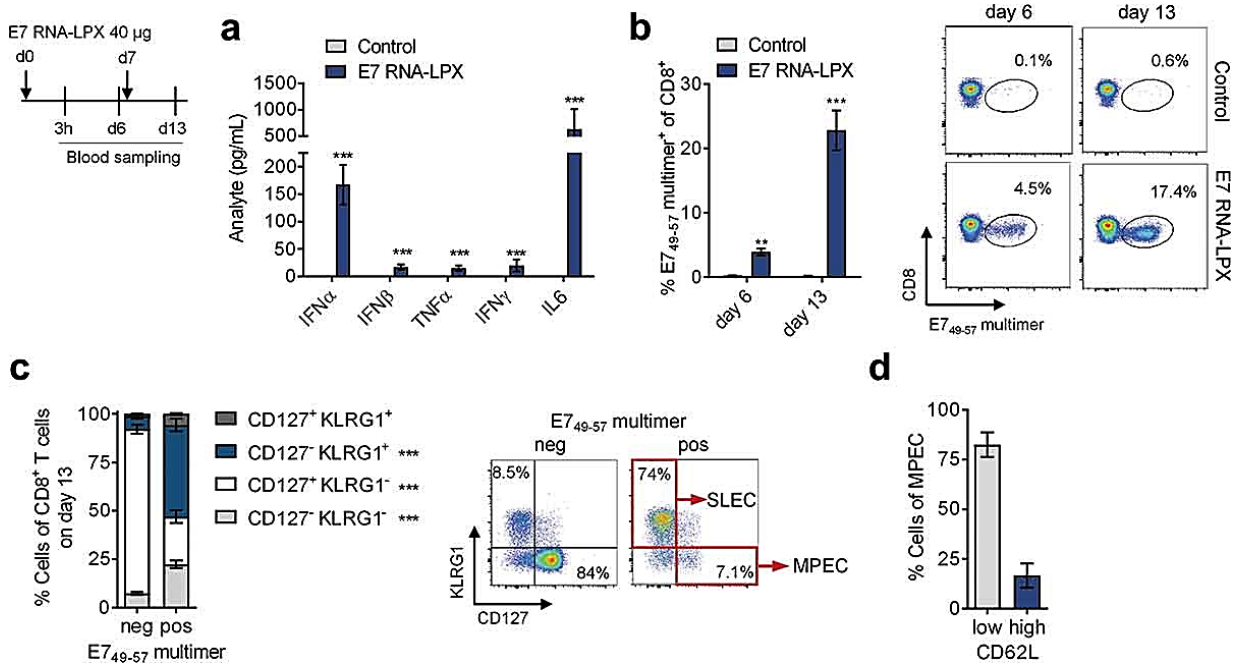

Figure 1. E7 RNA-LPX immune induction of strong antigen-specific effectors and memory $CD8^+$T cell responses in mice [10].

5. Dendritic Cell-Based Vaccines

Vaccines manufactured from entire cells often fall into many categories, one of which is "vaccines based on dendritic cells." Dendritic cells are excellent choices for immunotherapeutic techniques because they cannot only start particular immunological responses in an antigen-dependent way, but they can also establish immune tolerance and control immune homeostasis. DCs possess a high degree of proficiency in the uptake and progression of antigens, which enables them to effectively deliver these antigens to T cells, and they can also boost the efficacy of antigen-specific cancer immunotherapies. The strategy of DC vaccines is to induce immature or mature DCs in vitro, load antigens onto DCs using a variety of methods for various antigen types, and then reinfuse DCs into humans or animals to complete immunity and treat diseases.

Short interfering RNA (siRNAs) targeting molecules that promote apoptosis have been developed to prolong the survival of DCs. The findings of the experiments provide confirmation that the fusion of the functional peptide of Mycobacterium tuberculosis heat shock protein 70 (Hsp70) with the extracellular domain of FPR1, a protein that is seen to be overexpressed in cervical cancer, has the ability to stimulate the maturation of DC and trigger the secretion of IL-12p70, IL-1β, and TNF-α

[11]. On NOG mice, the antitumor activity of autologous DC-activated human cytotoxic T lymphocytes (CTLs) was assessed [11]. The results showed that MTBHsp70-exFPR1-stimulated DCs could boost anti-tumor immunity against cervical cancer [11]. This is a new way to treat cervical cancer with immunotherapy. Although DC vaccines have many advantages, there are also several problems. The identification of the most effective approach for acquiring and processing the novel vaccine, as well as the determination of the most suitable vaccination protocol and a viable combination treatment regimen, remain uncertain. These unresolved issues will have significant implications for the practical implementation of the DC vaccine in clinical settings. In addition, long-term use of DC vaccines may result in T-cell depletion, immune function suppression, or the induction of autoimmune diseases [11].

6. Conclusion

This article offers a comprehensive review of the therapeutic cervical cancer vaccines that are currently being developed and/or are participating in clinical studies for the disease. The development of therapeutic vaccines has proceeded at a much slower pace compared to the development of preventative HPV immunizations. There is no clear connection between the immune responses produced and the clinical outcomes, despite the fact that certain clinical findings have been positive. On the other hand, there are continuing efforts to generate therapeutic vaccinations for cervical cancer. With the knowledge obtained from both ongoing trials and those that have been completed in the past, it is anticipated that therapeutic HPV vaccines will exhibit efficacy in future endeavors. In the foreseeable future, therapeutic HPV vaccinations will likely be accessible in clinical environments, complementing existing treatment modalities such as surgery, chemotherapy, radiation therapy, and similar interventions to address cervical cancer.

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