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Development, effectiveness, and future directions of HPV vaccines

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Abstract. Human papillomavirus (HPV) vaccines are vaccines used to prevent sexually transmitted diseases caused by HPV. HPV infection is the leading causation that causing the cervical cancer. Specifically, high-risk-type, for instance, HPV-16 and HPV-18, are also connected with some other cancers. This article summarizes the development mechanism, availability, clinical trials, and problems faced by HPV vaccines. Currently, there were three approved HPV vaccines, including bivalent vaccine, quadrivalent vaccine, and nine-valent vaccine, which can prevent different types of HPV infection. The widely utilization of HPV vaccines has notably diminished the occurrence of diseases that are connected with HPV, especially to guard against cervical cancer. However, research on therapeutic HPV vaccines is still in its early stages, and the results of existing studies in terms of effectiveness and side effects are not ideal. Despite this, therapeutic vaccines remain a promising area in HPV research. This article summarizes the mechanism and effect of preventive HPV vaccines, explores the current status of therapeutic vaccine development, and provides basic information for future HPV vaccine research. Future research should focus on developing more targeted therapeutic vaccines and continue to improve preventive vaccines to cover more high-risk HPV types.

Keywords: HPV, preventive vaccine, therapeutic vaccine.

1. Introduction

The Human Papillomavirus vaccine is a vaccine intended to prevent sexually-transmitted diseases caused by papillomavirus. HPV is capable of causing more than 90% of cervical cancers, and the prevalence and pathology of HPV cancer are results of some factors such as regional differences, HPV genotypes, the study population, the status of HPV vaccination, and the location of anatomic sample collection [1]. HPV-16 and -18 are the main factors causing several different cancers, such as cervix, anus, vagina, penis, vulva, and oropharynx [1]. HPV has adequate carcinogenic power to promote the progress of malignancies and other tumorigenic steps required to produce invasive cancers [1]. In 2018, it was estimated that cervical cancer, the fourth most common cancer among women after breast with 2.1 million cases, colorectal 0.8 million, and lung 0.7 million cases [2]. This highlights the significant influence of cervical cancer on global public health. Until now, in excess of 450 types of HPV have been found [3].

In terms of the carcinogenicity of HPV, various kinds can be classified into two types in general: high risk and low risk types. HPV of high risk types encompass the following: HPV16,18,31,33, 35, 39,45, 51, 52, 56, 58 and 59 [4]. Persistent infection due to high-risk types represents the main causation

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for cervical cancer [5], Currently, three different types of HPV vaccines are approved for sale, which are bivalent vaccine, quadrivalent vaccine, and 9-valent vaccine. Including the first generation of the quadrivalent HPVI6/18/6/11 vaccine (Gardasil) approved by the U.S. Food and Drug Administration (FDA) in June 2006 and the bivalent HPVI6/18 vaccine (Cervarix) approved by the U.S.FDA in October 2009. The second generation of Gardasil 9 was also approved by the US FDA in late 2014. The HPV vaccine has made great progress. The bivalent vaccine human papillomavirus can prevent HPV16 and 18, the quadrivalent human papillomavirus vaccine can prevent HPV16, 18, 6 and 11, and the Gardasil 9 vaccine can prevent HPV6, 11,16, 18, 31, 33, 45, 52 and 58.

Due to the significance of importance of vaccines in preventing HPV-related diseases, this assay aims to illustrate the development mechanism, the availability, the clinical trials, and the problems of HPV vaccine.

2. Mechanism of HPV vaccine

2.1. Principle of HPV infection

HPV sneaks into the basal epithelial cells through tiny wounds in the skin, genital organs, and oropharyngeal regions that are easily accessible. It uses the L1 and L2 capsid proteins as keys to fit into the receptors of these epithelial cells. Once inside, viruses start stripping off their outer layers in the cytoplasm and injects their genome into the core of cells that are infected (Figure 1).

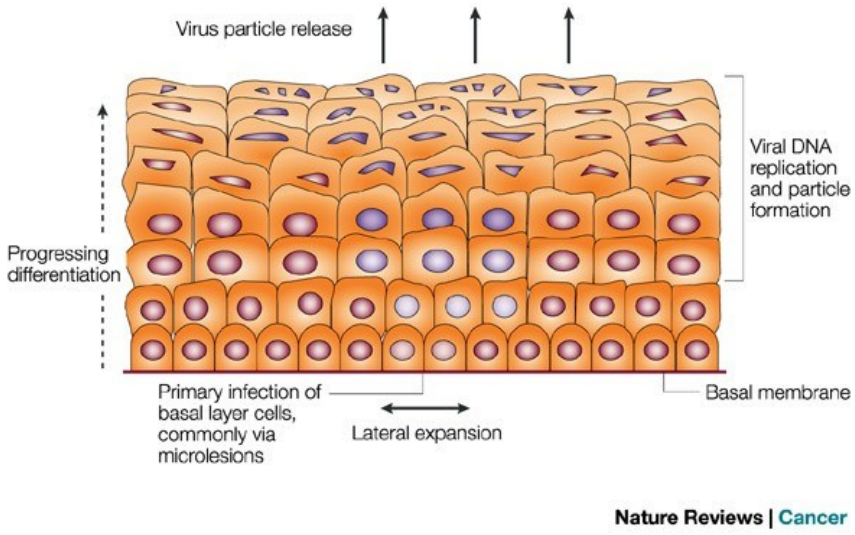

Figure 1. HPV infection process in human body [6].

The infected cell then starts transcribing and copying the virus's genome. Early proteins take the lead role here, regulating the host cell's life cycle and replication processes. These early proteins also oversee the production of later proteins in a way that's tied to cell differentiation. Specifically, L1 and L2 proteins are only expressed in mature squamous cells [6]. In terms of the epithelial cells undergo their final differentiation, the virions also mature and are released along with aging cells. Most infections are cleared by our immune system without any symptoms, sometimes this results in benign cervical lesions that can give rise to cancerous changes [7,8]. This can give rise to low-grade CIN 1 lesions with persistent infection. If left unchecked, these can escalate to high-grade CIN 2/3 lesions, driven by high-risk HPVs. In the worst scenario, ICC may ensue with integration of the virus' genome into our own genetic material Lotus [6].

In typical cases of hrHPV-driven cancer development, the virus' genome becomes part of our chromosomal DNA. This happens during genome linearisation, where something goes wrong with the E2 sequence and this disruption causes two genes—E6 and E7—to be constantly expressed [9]. The E6

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protein is a mastermind behind the destruction of a host apoptosis regulator called p53 and it also switches on telomerase, extending cell lifespan [9].Meanwhile, E7 targets a tumor suppressor protein called pRb for destruction. This sends the cell cycle into overdrive, driving it into the S-phase for rapid genome replication [9]. The combined activities of E6 and E7 throw the cell cycle out of balance, resulting in genomic instability and ultimately, cancer development [6].

2.2. Preventive HPV vaccine

At present, three HPV vaccines are commercially available: Cervarix®, Gardasil^{S} , and Gardasil®9. They all utilize unique properties of the HPV L1 protein to form virus-like particles when expressed singularly in various cell types, which are remarkably similar in both morphology and antigenicity to native virions [10]. These prophylactic vaccines, which have been developed either by attenuation or inactivation of the respective pathogens, have been highly instrumental in reducing the burden due to a number of infectious diseases in the past and resulted in the eradication of small pox and considerably restricted diseases like polio, tetanus, diphtheria, measles among others [11]. However, prophylactic HPV vaccine cannot treat with existing HPV. In contrast, therapeutic HPV vaccine may be able to treat existing infection. Currently developed therapeutic HPV vaccines mainly target E6/E7 as antigens. Cells already infected with HPV are killed by E6 and E7 specificCD8+T cells. Its mechanism of action: The vaccine is first delivered to antigen-presenting cells (APC), which then present E6/E7 epitopes to activate CD8+ cytotoxic T cells and CD4+ helper T cells via surface histocompatibility complex 1 (MHC I) and MHC II, respectively. With help from CD4+ helper T cells, activated HPV antigen-specific CD8+T cells recognize and also kill cells already infected with HPV.

2.3. Therapeutic HPV vaccine

2.3.1. Live vector vaccines

Recombinant bacterial or viral vectors that are live vector vaccines have the ability to replicate inside host cells and they can help achieve dispersion of antigens. These vaccines effectively start antigen presentation and stimulate CD8+ cytotoxic T-cells as well as CD4+ helper T-cells, thereby ensuring robust immunogenicity [12]. Based on experiments, the subcutaneous immunization of mice with recombinant L.tar-L1 has resulted in an increase of IgG1 and IgG2a levels compared to control groups [13]. Notably, this recombinant live vector successfully induced humoral immunity in mice even if there was no aid of any extra medicament [13].

2.3.2. Tumor cell-based vaccines

In order to make tumor cell-based vaccines, tumor cells are separated and generated outside the body to express immune-modulating proteins so their potential to stimulate an immune response inside human bodies increases. Specifically, cytokine genes such as IL-2, IL-12, and granulocyte macrophage colony stimulating factor (GMCSF) are utilized to encourage the differentiation of naive T cells into effector or helper T cells in mice bearing HPV16-induced tumors. These genes are also capable of inducing granulocyte production in vaccines based on tumor cells infected with HPV [14, 15].

2.3.3. DNA vaccine

DNA vaccination works by directly injecting a plasmid into tissues, which carries the DNA sequence of the target antigens for the immune response. This technique relies on the in-situ synthesis of these antigens through the transfection of various cells, including both antigen-presenting and non-antigen-presenting types. The antigens produced are then displayed by MHC class I and class II molecules [16]. Moreover, as a result of this, it results in activating all three of the adaptive immune responses [16]. The existence of full-length complementary DNA offers numerous epitopes, thus surpassing the limitations of MHC restriction encountered in peptide-based vaccines and the plasmid DNA itself boasts unmethylated CpG motifs with the potential to serve as robust immunological adjuvants and DNA vaccines also demonstrate the capability to sustain the process of releasing of antigenic proteins, thus

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bolstering immunological memory [17]. Moreover, DNA vaccines can be genetically modified to express HPV-specific antigenic peptides or proteins, as well as possess a wide range of delivery methods [17]. These properties allow DNA vaccines to present the antigens of HPV to the antigen-presenting cells, thus inducing the in vivo generation of both CD4+ and CD8+ antigen-specific T cell responses [17].

2.3.4. mRNA-LNPs vaccine

It actively targeted tumors by triggering systemic innate immune responses and stimulating tumor-specific immune responses. After intrabody injection, the HPV mRNA-LNPs were effectively taken up by dendritic cells (DCs) in the splenic organ, inducing large amount of type I IFN release, which turned on the systemic innate immune responses. Moreover, these tumor antigen-expressing HPV mRNA-LNPs were taken up by DCs in the tumor microenvironment, thus stimulating tumor-specific effector immune responses [18]. However, such prolonged antigen stimulation was followed by the exhaustion of the CD8+ T cells. This process is marked by a progressively climbing in the expression of numerous inhibitory receptor genes, which ultimately correlates with the functional deterioration of the effector cells [18].

2.4. Summary and prospect of therapeutic HPV vaccine

Therapeutic vaccine has remarkable advantages compared to Prophylactic HPV vaccine, as it has potential to treat with pre-existing HPV. However, currently the therapeutic HPV vaccines are not yet licensed for spectroscocpic use. And the vaccines are still in the stage of clinical research. Therefore, more experiments are needed to prove the safety and effect of therapeutic vaccines.

3. Conclusion

Through sustained research efforts, significant advancements are made in the field of therapeutic HPV vaccines, progressing from bivalent formulations to the more comprehensive nine-valent HPV vaccine. These advancements hold the promise of effectively mitigating a broader spectrum of HPV-related diseases, including some of the most virulent strains. The evolving landscape of preventive cancer vaccines stands as a testament to the improved efficacy in combating HPV infections and underscores the pivotal role of continued research in refining preventive strategies in cancer prevention. Currently, the therapeutic cancer vaccine is still under active investigation, with unremitting endeavors to address its current deficiencies in efficacy and the occurrence of side effects in a substantial portion of recipients. Despite these recognized limitations, the pursuit of developing and enhancing therapeutic cancer vaccines retains considerable potential within the realm of HPV research. This avenue of inquiry embodies a critical aspect of the broader HPV research landscape, underscoring the significance of further exploration and development of therapeutic interventions in cancer treatment. This paper provides a comprehensive overview of the mechanisms and outcomes associated with both preventive HPV vaccines and diverse therapeutic modalities. By offering an exploration of the developmental trajectory of HPV vaccines, this discussion furnishes a foundational understanding of the progress achieved and serves as a catalyst for further advancements in the realm of therapeutic HPV vaccines. Nevertheless, this paper does not mention the research on the feasibility and safety of therapeutic vaccines in human trials. Future HPV vaccine research should focus on developing different, more targeted therapeutic vaccines, as well as developing preventive vaccines that protect against more dangerous types of HPV.

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