

Progress of research on human papilloma virus vaccine application

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Abstract. Human papillomavirus (HPV) infection is a huge and serious topic in China and around the world with innumerable infections every year, which seriously endanger the lives of women all over the world. This article focuses on the pathogenesis of HPV, the types of HPV vaccines and their mechanism of action, as well as an analysis of the existing problems and an outlook on the future. Great progress has been made globally in order to decrease the HPV infection rate of women around the world, and this article provides additional possibilities for the development of future vaccines and solutions to existing problems.

Keywords: hpv virus; vaccine.

1. Introduction

Sexually active women often contract HPV in their lives. For many women, the infection is still asymptomatic, which is cleared through immune system. Nonetheless, some women develop persistent HPV infection, which may in-depth develop to cervical cancer and high or low grade cervical intraepithelial neoplasia (CIN), or to some extent degenerate [1-2]. During the progression of many lesions associated with HPV to cancer, HPV viral DNA could be integrated into host genome. Numerous early (E5, E4, E2 and E1) together with late (L1 and L2) genes are frequently deleted during this process.

For the HPV oncogenes E7 and E6, E2 is a negative regulator. Loss of E2 in the process of integration results in high E7 and E6 expression, which are considered to be oncogenic effects of damage associated with HPV. Oncoproteins E7 and E6 are needed for initiation and maintenance of malignancies related to HPV and are hence expressed and existed in the transformed cells [3]. Additionally, therapeutic HPV vaccines against E7 and E6 can bypass the problem of immune tolerance to autoantigens since these viruses encode heterologous oncogenic proteins in humans. Because of such factors, for the therapeutic HPV vaccines, the oncogenic proteins HPV E7 and E6 are the desired targets [4].

The HPV vaccine is the best way to protect against HPV infections. Nevertheless, despite the prophylactic HPV vaccines have been largely successful and have created leaps and strides in the prevention of HPV infection together with the diseases related to HPV, diseases related to HPV still carry a significant burden worldwide.

Apart from that, there are also several problems exist which impede people get hpv vaccination.

Therefore, this work reviews the research progress of HPV vaccine in recent years. Firstly, we introduced the basic knowledge about vaccine, especially HPV vaccine mechanism. Then we give 4 types of advanced HPV vaccines and their application.

2. Hpv vaccine and its pathogenic mechanism

2.1. History of hpv vaccine development

Cervical cancer, as the most common malignant tumors, it is one of the deadliest and most preventable malignancies in women. The development of development of HPV vaccination to reduce the cervical cancer incidence is of great importance. It is also is currently considered by authoritative health institutions or organizations worldwide as a cost-effective It is also a key strategy and an

important tool for global health authorities or organizations. Since 2006, Merck's Gardasil Since 2006, Cervarix and Gardasil, such two quadrivalent HPV vaccines have been approved for clinical application. Cervarix (GlaxoSmithKline, UK) and Gardasil 9 (Merck, USA) are different prophylactic vaccines. (Merck, USA) and Cervarix (GlaxoSmithKline, UK) have been approved and marketed in more than 100 countries worldwide. Universal vaccination is expected to prevent 90 percent of cancers of the vulva, cervix, anus and vagina. Vulvar, vaginal and anal cancers [5]. Although effective but still insufficient, the and no therapeutic HPV vaccine has been marketed so far. China's domestic HPV vaccine development in China started late, and no relevant domestic vaccine has been market, from July 2016, the bivalent HPV vaccine (Cirex®) received our national After the approval of the Drug Administration for marketing, the quadrivalent HPV vaccine (GadaxiuXiu®) and nine-valent HPV vaccine (Gator Xiu 9®) were also launched in China in May 2017 and April 2018, respectively [6]. In addition, in 2007, Australia was the first country to offer free quadrivalent vaccination to young women and girls aged 12-18, thus reducing the incidence rate of female genital warts aged 21-30 years from 11.3% in 2007 to 11.3% in 2011.

The incidence rate of female genital warts between the ages of 21 and 30 reduced from 11.3% in 2007 to 3.1% in 2011 [6], which is the first step towards free HPV vaccination.

The first step towards free HPV vaccination has made a significant contribution to reducing HPV infection and increasing HPV vaccination rates.

2.2. Mechanisms of vaccine development

Preclinical and clinical trials have developed and tested several kinds of therapeutic vaccines involving peptides or proteins, live vectors, cell vaccines together with nucleic acids. Clinical trials are of great significance to assess whether therapeutic HPV vaccines can control HPV infection as well as the diseases associated with HPV. Most of such vaccines target HPV oncoproteins E7 and E6 for the delivery of diverse forms of E7 and E6 antigens to antigen-presenting cells (APCs) to respectively activate HPV antigen-specific CD4 + helper T cells or CD8 + cytotoxic T cells (Fig. 1). A significant idea is that E7 and E6 antigens require to be treated and digested into the smaller peptides with proteasome prior to they appeared on MHC class I APCs for the CD8 + T cell activation. Nevertheless, not all the fragments of antigenic protein peptide are loaded onto the molecules of MHC and identified with antigen-specific T cells [7]. In such short peptides, only a few involve antigenic fragments (epitopes) sequences that can bind the molecules of MHC having high affinity and next interact with antigen-specific T cell receptors (TCRs) to trigger immune responses [8-9]. The great majority of therapeutic vaccines are designed for the sake of eliciting an immune response against E7 antigen. The basic principle is that E7 antigen has better immunological characteristics in comparison with E6 antigen in the preclinical models.

Immunity activated by therapeutic HPV vaccine. Due to the use of different types of HPV therapeutic vaccines, various forms of the antigen enter into system. The transfection of DNA plasmids encoding HPV E7 and E6 oncoproteins into DCs was conducted with infected live transformation vector vaccines or DNA vaccines. Such antigens are subsequently transcribed into the RNA; nonetheless, with RNA vaccines, the RNA is also introduced into the cells. Moreover, transcriptional RNA is converted into antigen-presenting proteins or peptide. The dendritic cell can also take antigenic proteins or long peptides through the phagocytosis after vaccination with a peptide or protein. Proteasomes process them into short peptides and load them onto an endoplasmic reticulum (ER) MHC class I molecule for presentation to T cell receptors on the CD8+ T cells. Besides, tumor cells or dendritic cells can be produced in vitro, expressed with the essential costimulatory molecules on the MHC class I molecules, and transported back into body as a whole-cell vaccine via adoptive transfer into the primary T cells. Endosomal proteases was applied for degraded the antigenic peptides or proteins ingested by DCs into smaller fragments. Endosomes involving small antigenic peptides can be subsequently fused to exosomes involving class II MHC molecules, in this time, the antigenic molecules can be loaded onto class III MSC molecules.

Afterwards, the MHC class II antigenic peptide compound is converted to the surface of cell, which is presented to T-cell receptors on the CD4⁺ T cells.

3. Four types of advanced vaccines

3.1. Therapeutic HPV vaccines based on live vector

Based on vectors themselves, they are classified as viral and bacterial vectors, which are continuously replicated in body and facilitate the antigen propagation, initiating an immune response in the cell. Live HPV therapeutic vaccines based on vector vectors have high immunogenicity and can result in strong humoral and cellular immune responses [10]. Unluckily, there are potential safety risks related to the live vector vaccines, particularly in immunocompromised individuals. Furthermore, the efficacy of the immune response is limited by the application of repeated immunization with the same vector. Commonly used bacterial vectors are: *Lactobacillus casei*, *Lactobacillus plantarum* together with *Lactobacillus lactis*. Commonly used viral vectors are: adenovirus, adeno-associated virus, alphavirus, and poxvirus.

3.2. Therapeutic HPV vaccines based on peptide and protein

Peptides and proteins involving HPV antigens are treated by DCs and presented to MHC class II or MHC class I molecules for the stimulation of the cellular immune response of cytotoxic CD4⁺ or CD8⁺ T cells. Vaccines based on protein and peptide have the advantage that they are stable, safe and easy to produce. Nevertheless, vaccines based on peptide, with low immunogenicity need lipids or other adjuvants (for instance Toll-like receptor ligands, cytokines, and chemokines) to improve vaccine efficacy, activate adaptive and innate immune responses, and further facilitate CD8⁺ cytotoxic T cell responses. Moreover, despite vaccines based on peptide have MHC specificity, vaccines based on protein involve all human leukocyte antigen (HLA) epitopes, hence avoiding the MHC restrictions [11]. Nevertheless, vaccines based on protein have low immunogenicity and are primarily presented with the MHC class II pathway, activating antibody production without generating a cytotoxic T lymphocyte (CTL) response, meaning that they face some challenges in mass generation and treatment of diseases related to HPV.

3.3. Nucleic acid-based therapeutic HPV vaccines

DNA vaccines are stable, safe and easy to manufacture and can maintain antigen expression in cells longer, in comparison with protein or RNA vaccines, but there are DNA-coding genes E6 and E7, which can lead to a potential risk of cell transformation; RNA replicons are able to self-replicate, potentially resulting in sustained antigen expression levels and improved immunogenicity. Nonetheless, one shortcoming of RNA replicon is low stability.

3.4. Whole-cell-based therapeutic HPV vaccines

DCs exert an essential role in the regulation of immune system and are generally considered to be the most efficient specialized antigen presenting cells (APCs) [11]. The evolution of DC-based vaccines has been driven by an increase in knowledge of DC biology and methods of DC preparation in isolation. The DC-based HPV vaccine involves ex vivo loading of HPV antigens onto DCs and delivering these DCs to infected hosts. One superiority of DC vaccine is that DCs can utilize as the natural adjuvant to improve the efficacy of antigen-specific cancer immunotherapy. There are some limitations, however, namely that they are technically laborious and therefore difficult to mass-produce. Furthermore, different cultivation techniques may induce inconsistent quality of vaccine, lack of vaccine assessment criteria, and the most effective drug delivery route has yet to be determined. In order to generate vaccines based on tumor cells, tumor cells were separated and manipulated in vitro for the expression of immunoregulatory proteins, which may in-depth improve their immunogenicity in vitro. One superiority of vaccines based on tumor cell is that they do not require

to be strictly restricted and therefore can cover a broader range of tumor antigens. HPV has famous tumor specific antigens, thus the use of vaccines based on tumor cell is unlikely to be the most convenient immunotherapy for the treatment of cancers related to HPV. Vaccines based on tumor cell also have the risk of patients being implanted with novel cancers. The property of these vaccines and their underlying risks need adjusting the purity and potency of each vaccine, making it costly and time-consuming to produce. These factors have prevented the development and clinical testing of HPV vaccines based on tumor cells.

4. Practical application issues

4.1. Who the vaccine is intended for

Bivalent vaccines (Cervarix, Cialis) have been approved globally and in China for women aged 9 to 45 years; Quadrivalent vaccine (Gardasil) is approved globally for men aged 9 to 26 and women aged 9 to 45, and in China for women between ages of 20 and 45; The nine-valent vaccine (Gardasil-9, Gardasil-9) is approved globally for men aged 9 to 15 and women aged 9 to 26, and in China for women between the ages of 16 and 26. The WHO has recommended HPV vaccination as the primary means of primary prevention of cervical cancer for girls aged 9 to 14 years who have not had sex; China's Guidelines for Comprehensive Prevention and Control of Cervical Cancer recommend that the best target for HPV vaccination is girls aged 13 to 15 years. Studies have shown that the younger the age, the more effective the vaccination. In Sweden, the incidence rate of the CIN (grade II or higher) reduced by 64% in women aged <17 years compared with those who were not vaccinated; for women aged 17-19 years and 20-29 years, the incidence decreased by only 25% and 14%, respectively, compared with those who were not vaccinated, which may be related to the younger the age of sexual intercourse and the less chance of being infected with HPV[12].

4.2. The hpv vaccination methods

HPV vaccine was injected intramuscularly in three times, the second injection was one to two months after the first injection, and the third injection was at least six months after the first injection [13]. The three vaccines have different properties, components, and populations, and each recipient should complete the immunization program with the same vaccine whenever possible, but if the previously used vaccine is unknown or unavailable, any HPV vaccine can be utilized to finish an immunization program. HPV vaccines can be administered with other live and inactivated vaccines, but with different syringes and at different sites.

4.3. Immunization effect of hpv vaccine

HPV is mainly sexually transmitted, and prophylactic HPV vaccines are not effective in patients with pre-existing HPV infection and cervical cancer, but are highly effective in people without HPV infection. 80% of cervical cancer incidence can be reduced in women aged 11-13 years after vaccination with the cervarix vaccine (Cervarix, produced by GlaxoSmithKline, GSK) . Among women of appropriate age, 98% of CIN grade II and above (CIN II+) can be prevented by Gardasil quadrivalent vaccination, and 90% of CIN II+ can be prevented by Cervarix bivalent vaccination.

The bivalent and quadrivalent vaccines also provide cross-protection against HPV31/33/45[14].The nine-valent vaccine is effective against HPV6/11/16/18-associated infections, precancerous.

The protection against HPV6/11/16/18-associated infections, precancerous lesions and cervical cancer was comparable to that of quadrivalent vaccine, and the protection rate against HPV31/33/45/52/58-associated CIN II/III, cervical adenocarcinoma in situ or cervical cancer could reach 97.1% (95% CI: 83.5 to 99.9) [15].

After three doses of the three vaccines according to the immunization schedule, the seropositivity rate of the vaccinees reached almost 100%, and the antibody level could be maintained for more than 4 years. The antibody levels could be maintained for more than 4 years.

5. Summary

Cervical cancer is the only cancer known to be vaccine-preventable worldwide, and it is also a cancer with a very high incidence, so it is urgent to vaccinate women against hpv. This article describes the pathogenesis of the hpv virus and some feasible means of prevention, as well as a vision of future trends in prevention.

However, there are many practical problems that need to be faced in the marketing and application of cervical cancer preventive vaccines. First, the cost of vaccination is not acceptable to everyone, and there are still many limitations to mass application. To achieve large-scale application in developing countries, appropriate national subsidy policies are needed to achieve higher coverage. Second, due to the different beliefs and cultural levels of various regions, ethnic groups, and religions, there are different perceptions of HPV preventive vaccination for young women, which is also a problem encountered in vaccination. Third, awareness of the preventive vaccine in schools and communities and good publicity among the public, students and parents can help strengthen parents' motivation for vaccination and increase the vaccination rate of young women. Fourth, since the preventive HPV vaccine surveillance was launched, no safety problems have been found and no related diseases have occurred, which helps to reduce the concerns about vaccination. Fifth, if cervical cancer preventive vaccination is common, the corresponding screening should also be actively coordinated, otherwise, it leads to some people mistakenly believing that screening is not needed, which instead increases the incidence of cervical cancer, and the preventive vaccine cannot guarantee 100% prevention rate. Sixth, the question of whether vaccines can be mixed, especially when someone is unsure which vaccine they have received and needs further injections, has not been answered. Thus, there are a variety of issues that are currently being faced that still need to be actively addressed.

The high-risk HPV was determined as a causative factor for numerous diseases may result in the progress of HPV therapeutic vaccines. The recent advances in this field, together with those mentioned in this review, is conducive to the elimination of HPV and malignancies associated with HPV and the seed movement of malignancies. Diverse targeting approaches of HPV E6 and E7 oncoproteins, which represent outstanding targets of tumor-specific antigens and HPV therapeutic vaccines, have been discussed in this review. Our previous research, along with that of other researchers in this area, this indicates that the present HPV vaccines in this review have both limitations and advantages. Further clinical researches are needed to confirm the anti-tumor effect of HPV vaccine.

The HPV vaccine is expected to continue to be successful in the next few years as efforts to enhance and develop treatment strategies continue. It can be expected that therapeutic HPV vaccines will be available clinically in the near future and will be provided together with other available treatments to control diseases related to HPV.

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