Development Status and trend of HPV vaccine

Shuyang Guo¹*, Yunpeng Wang ²
1: National vaccine & serum institute Beijing, P.R. China 100024
2: National Institute for Food and Drug Control, Beijing, P.R. China 100050

ABSTRACT
Cervical cancer causes significant morbidity and mortality world widely, and human papilloma virus is the major factor that causes cervical cancer incidence. The carcinogenic proteins of HPV can induce malignant metastasis of cervical squamous epithelial cells. There are currently two human papilloma virus prophylactic vaccines listed, but the protection offered by current vaccines is primarily against HPV types used to derive the vaccine. So we review the status and progress of the HPV vaccine in recent years, and the potential clinical application of the vaccine.

HPV and Cervical cancer
HPV infection is the highest incidence of sexually transmitted diseases. In the U.S., there are about 24,900,000 woman infected with HPV virus who in 14 to 59-year-old [1]. Current estimates suggest that 50% to 80% of sexually active adults will be exposed to these viruses during their life-time, resulting in a national prevalence of >20 million infections [2,3] in the U.S.. HPV-DNA can be detected in the presence of more than 99% of cervical tumors [4].

We divide HPV into low-risk and high-risk of each types according to the virulence. The former which includes
HPV 6, 11, 30, 9, 42, 43, 44 and other types, causes genital papilloma, exogenous condyloma class lesions, low-grade cervical intraepithelial neoplasia (CIN); and the latter which includes HPV 16, 18, 31, 33, 35, 51, 52, 56, 58 and other types related to the occurrence of the malignant. HPV16 and 18 are most closely related to the cervical cancer. According to the results of IARC [5], approximately 51.0% of cervical cancer associated with HPV16 infection which cause of squamous cell carcinoma and about 16.2% of cervical cancer associated with HPV 18, which causes adenocarcinoma.

**Pathogenic mechanisms of HPV**

HPV have a circular, double-stranded DNA genome containing about 8000 base pairs and encode two general classes of pro-teins: "early" proteins, which function in the regulation of viral DNA replication (E1, E2), RNA transcription (E2), and cell transformation (E5, E6, E7); and "late" proteins (L1, L2), which are the structural components of the viral capsid [6]. The consistent transcription of E6 and E7 in tumors indicates is an important role for these genes in the transformed state. Related research [7, 8] confirmed that E6 and E7 protein inhibit production of p53 and Rb, promoting the replication of HPV DNA and causing the malignant transformation of cells. In addition, E6 and E7 can interact with many other intracellular molecules to block apoptosis, change cellular transcription, disrupt the normal signal transduction, allowing for uncontrolled growth and providing the potential for malignant transformation [6].

**HPV vaccines**

1. **Prophylactic HPV vaccines**

   The HPV DNA genome is enclosed in a shell or capsid comprised of two proteins L1 and L2; in natural infections serum neutralizing antibodies are made only to the L1 protein [9]. It has been known for >70 years from the pioneering studies of Shope in rabbits that serum neutralizing antibody is protective against viral challenge [10]. Animal studies suggest that virus-neutralizing antibodies can protect the host from infection. Recombinant HPV virus-like particles (VLPs) which display neutralizing epitopes are generated
by overexpression of L1, the major capsid protein of HPV. But L1 can only produce specific antibodies and there is no cross-reactivity as result of its highly conserved, the vaccine is valid only on the part of the crowd. Animal experiments [11] have confirmed that specific B cell epitopes are existed in L2 surface; the neutralizing antibodies may be generated in the skin, mucosal surfaces which generate preventive effect. Therefore, the L1/L2 joint VLP vaccine may have high immune efficiency; this combination vaccine is currently being studied.

Currently, there are two HPV L1 VLP prophylactic vaccines have been approved for selling. These are Gardasil, a quadrivalent HPV 16/18/6/11 L1 VLP vaccine from Merck & Co. Inc and Cervarix, a bivalent HPV 16, 18 L1 vaccines from GSK Biologicals. Gardasil is VLPs of recombinant L1 protein which from yeast fermentation adsorbed on aluminum-containing adjuvant. Cervarix VLPs have been purified in the baculovirus L1 expression system and adsorbed on adjuvant ASO4. Although clinical significance of ASO4 is unclear, but compared to aluminum-containing adjuvant, ASO4 can induce higher antibody response [12]. Both vaccines have shown very high efficacy against cervical intra-epithelial neoplasia in the RCTs [13-15]. In the Phase III RCTs of the quadrivalent vaccine the PP group were women aged 16 – 24 years with<4 lifetime sex partners and naive for ≥1 HPV vaccine genotypes at enrolment through 1 month post the third immunization [9]. The bivalent vaccine in the Phase III RCT has shown, in an interim analysis with a mean follow-up of 14.8 months of women 15 – 25 years of age with≤6 lifetime sex partners and who were DNA negative for the relevant oncogenic HPV type in the vaccine at trial entry, 90.4% efficacy against HPV 16/18 CIN 2+, two cases in the vaccine group, 21 cases in the placebo [16].

2. Therapeutic HPV vaccine

Therapeutic vaccines play a role in treatment process both through cellular immunity and humoral immune. Unlike prophylactic vaccines, therapeutic vaccine generate an immune response through the
epitope of protein (e.g., E6, E7) which encoded by early HPV gene, rather than late genes encoding protein (L1, L2).

2.1 HPV peptide vaccine

Recombinant protein of chemical synthesis peptide vaccine is a choice of therapeutic vaccine. But so far, the peptide vaccine can induce effective responses of anti-tumor T cell is extremely limited. Zwaveling [17] developed a kind of overlap long peptide vaccine which is made of 35 amino acids from HPV16 E7 (43 ~ 77). The vaccine contains the Th and CTL epitopes significantly enhance CTL response in mice. The long peptides can clear HPV16 tumors when used combination with a activation auxiliary substances of dendritic cell (DC). In another study [18], the CIN 2 female patients with HPV16 positive were treatment by E7 fat-soluble peptide vaccine with adjuvant emulsified. Although limited clinical response was observed after inoculation, but T cell specific response of E7 was significantly increased.

2.2 The chimeric virus-like particles

The chimeric virus-like particles are simultaneously containing HPV16 L1 and L2 and E7 part epitope or L1, L2, E6 and partial epitope of the VLP. Chimeric VLP contains the more epitope, it stimulates to generate humoral immunity while activating cellular immune [19]. But anti-late protein antibody exist in serum of infection often inhibit treatment effect of chimeric proteins. So defects of this vaccine need to be further optimized.

2.3 HPV viral vector vaccine

The viral vector vaccine can be used to stimulate the immune response of host and induce the endogenous synthesis of the virus and recombinant proteins to generate a strong T cell response. Daemen [20] used SFV as vector to increase fusion protein production of E6/E7 enhanced mouse CTL and made the growth of tumor regression.

2.4 HPV DNA vaccine

Compared with the conventional vaccines, DNA vaccines have many advantages. DNA vaccine is prepared without peptides, self-replicating vectors,
attenuated pathogens or any adjuvant. Preparation is simple, rapid, low cost, easy to store and relatively safe, therefore it has unique advantages[21]. The DNA vaccine is used in order to obtain protective antibody response against different L1 VLP mixture. It is observed that DNA vaccine can induce neutralizing antibodies in mice and rabbits which play a protective role in immune response. Recently, DNA vaccine which encoding fusion protein of Hsp70, E7 can induce enhanced CTL response and anti-tumor effect in mice[22].

Problems and Prospects

Although the HPV vaccine shows to be effective in animal studies and preclinical experiments, there are still long distances from the large-scale clinical applications. Due to the strict species specificity of the HPV virus, it can not establish the animal model to evaluate vaccine effects effectively. In addition, Short-term and long-term side effects, preparation techniques and economic benefits of HPV vaccine need to be further researched and improved. So we need to conduct more basic research and clinical trials to learn more about HPV and cervical cancer vaccine.

References


