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# Importance of Recombinant Protein L1 Papillomavirus 16 in the Treatment of Uterine Cancer

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## Abstract

More than 100 types of papillomavirus have been identified so far, they are completely tissue-specific. About 5 of these infect the genital area from one person to another through sexual contact. Delayed proteins include L1 and L2, which form the virus capsid. Cervical cancer is the second most common cancer after breast cancer in women worldwide. Human papillomavirus (HPV) accounts for more than 2% of cervical cancers.

Among them, about 15 carcinogenic genotypes have been identified as high-risk genotypes, and genotypes 18 and 16 are the major contributors to 90% of the cancers associated with the virus. Many studies have shown that the expression of E6 and E7 proteins is found in most cervical cancers. Currently, this protein is used as a vaccine. The HPV vaccines available today do not cover all high-risk serotypes and are also very expensive.

Papillomavirus vaccines are generally designed to prevent the spread of the infection and therapeutic vaccines to prevent replication, depending on the stage of the disease that has occurred. The aim of preventive vaccines is to prevent the infection of the virus by stimulating the production of antibodies against it. These vaccines utilize the two proteins L1 and L2 that produce the capsid. Expression of recombinant protein through viral L1 particles in eukaryotic cells produces VLPs that resemble viruses and can stimulate the immune system.

However, studies have shown that VLP induced by both L1 and L2 proteins has a greater preventive role than L1 alone. Viral E1-E2-E6-E7 proteins are commonly used in therapeutic vaccines, and studies in women have shown that the immune response to these proteins often reverses infection and avoids persistent infection.

## Introduction

Cervical cancer is the second most common cancer after breast cancer in women worldwide. Human Papillomavirus (HPV) accounts for more than 2% of cervical cancers. There are more than 100 different types of human papillomavirus with more than 40 species of infectious genotype. Among them, about 2 carcinogenic genotypes have been identified as high-risk genotypes, and genotypes 6, 11, 16 and 18 are the major contributing factors to 90% of cancers of the virus [1].

Human papillomaviruses associated with cervical and rectal cancer include HPV_18, HPV_16, HPV_45, and HPV_31, and these viruses, along with type 5 and type 8 viruses, are also involved in skin squamous cell carcinoma [2]. Papillomaviruses in some cases are found in carcinoma of the vulva, vaginal cancer, penile

cancer, oral cancer [3] also diagnosed with non-melanoma skin cancers [4]. In cervical papilloma infection, low grade dysplasia is not treated pathologically and most of these lesions heal spontaneously. High-grade dysplasia, which is precancerous, usually does not cure itself, and treatment is recommended to prevent cancer.

L1 Protein is the capsid core protein, which accounts for approximately 80% of all virus proteins, and the L2 (small protein) capsid byproduct is approximately 70 kDa. The capsid contains 72 pentamericcapsomers and the pentameric structure is composed of monomeric units of L1 protein.

Viral-like particles or VLPs from different papillomaviruses are produced by the expression of the L1 gene alone along with the L2 protein in mammalian and non-mammalian expression systems. Expression of L1 protein in Escherichia coli produces small virus-like particles. These particles are pentameric and have a faceted structure. These particles well stimulate the immune system and are used as a prophylactic vaccine [5].

The infection results from the inoculation of viral particles into the skin and mucosa, which are called warts in the skin and in the mucosa called condylomas. The incubation period varies from 1 to 2 months. To cause the infection, the virus first infects long-lived epithelial cells, and the basal cells of the epidermis serve as stem cell-like cells as the virus target cells. The virus reaches basal cells through microscopic or macroscopic scratches on the surface of the skin, and then the virus genome is preserved in an epizomial fashion and then expressed. The virus propagates to the top layers and then the virus reaches the top layers simultaneously with cell differentiation and is released into keratinocytes. The presence of the virus in the epidermis layers causes lesions such as paraquatosis, kyphocytosis, papillomatosis [6,7]. The reason for the low frequency of warts in the elderly refers to their immune mechanism that protects them from infection.

One of the most prominent diseases that HPV causes in the respiratory tract is laryngeal papilloma, which is often associated with types 6 and 11 [8].

Papillomaviruses cause a wide range of diseases. Diseases caused by these viruses include skin infections, oral cavity infections, respiratory tract infections, and other cervical cancer after breast cancer is the second most common cause of cancer among women. Despite its worldwide distribution, the virus is widespread in some areas. Most cancers occur in the cervical transformation-prone area, where the inner cervical cylinders intersect with the external cervical squamous cells.

About 2% of cervical cancer cases are squamous cell carcinoma. This cancer develops after a long period.

The severity of the lesion is defined by the degree to which the squamous epithelial cells are replaced by basal cells. Histological classification defines CINI, II, III as mild dysplasia, moderate dysplasia, and severe dysplasia or carcinoma *in situ*. The progression of benign condyloma is towards carcinoma (epithelial cell carcinoma). High-risk papillomaviruses, such as HPV-16, initially work as benign and malignant lesions. In some cases, lesions with severe dysplasia first appear [9].

Oral cancer is a growing global health problem and disease. This disease is very worrying and the incidence of oral cancer is increasing day by day [10]. More than 3% of people with oral cancers (mouth, tongue, part of the nose, throat, lips, and larynx) are all those who use tobacco. According to the World Health Organization, oral cavity carcinomas are the sixth most common cancer in developing countries after lung, prostate, colorectal, gastric and colon cancer in developing countries, and in women the tenth after cancer of the breast, colorectal, lung, stomach, Uterine, cervical, ovarian, bladder, and liver Oral cancer occurs in men more than women, but the ratio of men to women in 1950 was higher of 6 to 1 today to less than 2 to 1 is reached [11].

Human Papillomavirus (HPV), the most common sexually transmitted viral infection among men and women, has been reported to affect about 80% of sexually active adults with at least one type of HPV, causing benign and malignant lesions in the skin and genital tract [12].

The life cycle of the virus is similar to that in adult keratinocytes of this puberty. T-cell responses are important for suppressing and progressing papillomavirus infection. The immune response alone is not enough to kill the virus, but it is capable of inactivating viral particles and preventing the spread of infection. Destruction of infected cells and recovery of virus-induced lesions are mainly mediated by cellular immune responses. Suppression, immune resistance in papillomaviruses is almost proprietary. People who have been suppressed for a variety of physiological and pathological reasons by their immune systems have a high risk of developing persistent HPV infection, and in fact the progression of cancer infection in these individuals is higher and it seems that defects in the immune system may affect the patient's condition. Studies showed that the immune response of CD4 and CD8 cells to E7, E6, and E2 proteins often reverses infection and prevents the development of a persistent infection. However, under normal conditions, the prevention of re-infection infection depends on both B-cell and T-cell immunity [13].

Various vaccines are used to prevent viral infections, including killed virus vaccines, live attenuated viruses, purified protein vaccines, recombinant viral vaccines, peptide and DNA vaccines. In the case of human papillomavirus, due to the lack of cell culture systems and the presence of oncogenes in the viruses of these viruses, the use of live attenuated papillomavirus vaccines or complete inactivated virions containing viral DNA has been restricted [14]. Purified protein vaccines and peptide vaccines also have relatively difficult production and purification methods, and in the case of recombinant viruses they have complex viral delivery systems in addition to the problem of production and purification.

In addition, an immune response against the viral vector may occur that may render the vaccine ineffective. Also, many subunit vaccines are not able to induce T-cell lymphocytes. And finally, the vaccines produced by these methods are expensive for the general population, especially in developing countries, and there are concerns about their health [15].

Use of DNA vaccines is another method of antigen-specific immunotherapy. Untreated plasmid DNA, which is healthy, has low immunogenicity, so unlike viral vectors, it can be used repeatedly. DNA vaccines can be easily prepared in high volume and with high purity, and they also have relatively high stability than proteins and other biological polymers [16]. In addition, DNA therapeutic vaccines are able to induce the responses of T cell lymphocytes that are essential for the prevention and treatment of viral infections. At present, papillomavirus E6 and E7 oncoproteins are the most rational targets for HPV vaccine production because these molecules are the primary viral proteins that are expressed during the development of malignancy in infected cells. In fact, the presence of these molecules seems to be a prerequisite for continuous cell proliferation [17].

One of the problems of DNA vaccines is their limited effect. Several strategies have been employed to increase the efficacy of DNA vaccines, which are brief: the use of targeted antigens for rapid degradation within the cell, the guided antigens for APCs with their fusion with APC receptor ligands, and the chemokine-bound antigens. Or attached to a pathogenic sequence such as tetanus toxin C fragment, simultaneous inoculation with chemokines, co-stimulatory molecules and simultaneous use of oligonucleotides by Chen et al, 2000 [18].

## Methodology

**Preventive vaccines:** Papillomavirus L1 protein expression leads to VLP formation. VLPs resemble viral "empty" particles that form during HPV replication. VLPs induce a strong immune response and are therefore suitable vaccines for administration. In general, VLPs induce a more effective immune response than denatured viruses and soluble proteins.

Recent clinical trials have shown that vaccination with HPV_L1 VLPs results in a protective immune response, including high L1 antiviral titers, specific immune response against various L1 epitopes, and reduced incidence of infection. Recent reports suggest heparan sulfate and dendritic cells at the dendritic cell surface are involved in binding to HPV_L1 VLPs. Dendritic cells are essential for stimulating cellular immunity.HPV_L1 VLPs increase the expression of stimulatory molecules on the surface of dendritic cells and produce cytokines [19].

Chimeric papillomavirus VLPs are another form of VLPs that encapsulate fusion proteins (L1/L2) with epitopes and alien polypeptides in different segments, and are one of the most important forms of VLPs in the delivery of epitopes and polypeptides. Both vaccines can be used as therapeutic and prophylactic vaccines. One of the concerns about DNA vaccines is their limited effect. DNA vaccines, like viral vectors, do not have the ability to replicate and propagate, and this is one of the limitations of these vaccines against viral vectors [20].

L1 protein has been produced in prokaryotic expression systems and the baculovirus system in insect cells has been defined as a suitable model for commercial vaccine production. Merck has developed a quadruple vaccine that includes VLP viruses, HPV_18, HPV_16, HPV_11, HPV_6. The first two types account for approximately 2% of cervical cancer, and the second account for 2% of genital warts [1].

In year 4, Kaufman and his colleagues showed that chimeric parasitic particles containing L1 and E7 can induce specific responses of HLA-restricted T cells [1]. In 2007, Chang and colleagues designed the plasmid L1E7hpSCA1, which contained the E7_L1 gene, and incorporated codons optimized for expression in mammalian cells. They also caused mutations in the E7 gene which in turn reduced its carcinogenicity [21].

HPV E7 DETOX (SIG/E7 DETOX/HSP70) is a vaccine that uses mutant E7 protein (DETOX E7) along with heat shock protein in a vaccine DNA. This vaccine was developed in the year 3 by Liquin et al and is currently in phase 2 therapy [22]. Most vaccine antigens currently under investigation include highly purified recombinant molecules or subunits of the pathogen that, due to their lack of any of the major pathogenic properties, such as immunostimulatory properties, cannot produce innate immune responses.

Immunological adjuvant was first defined by Ramon as a substance that is used in combination with a specific antigen and produces very strong immune responses compared to antigen alone [23].

The vaccine containing the quarter VLP vaccine is now marketed with the support of Merck and is used in some countries in the age group of 9 to 15 years. The other protein is called the L2 capsid and 1/3 of the L1 protein is found in the virus capsid. This protein plays a role in virus capsid accumulation and also has neutralizing epitopes. It is likely that the presence of L2 protein in the vaccine can prevent a wider range of viral types. Although its neutralizing epitopes, similar to L1, do not have the ability to protect, their epitopes induce cross-reactivity [1].

In normal HPV infections, the host has a poor immune response. In contrast, the HPV vaccine produces a strong high-dose immune response.

Papillomavirus vaccines are generally designed according to the stage of the disease that has occurred, preventive vaccines to prevent the spread of the infection, and therapeutic vaccines to prevent replication and replication of the virus.

The aim of preventive vaccines is to prevent the virus infection by stimulating the production of antibodies against it. The L1 and L2 proteins that produce the capsid are used to make these vaccines.

Expression of recombinant protein through viral L1 particles in eukaryotic cells produces VLPs that resemble viruses and can stimulate the immune system [24].

However, studies have shown that VLP induced by both L1 and L2 proteins has a greater preventive role than L1 alone. Two important vaccines that have reached the therapeutic stage are: Servarix vaccine is made from viral L1 particles made in baculoviruses. Gardasil: this vaccine also contains L1 particles made in the yeast system and is the vaccine of alum [25].

Viral E1_E2_E6_E7 proteins are commonly used in therapeutic vaccines, and studies in women have shown that the immune response to these proteins often reverses infection and prevents permanent infection. There have been limited studies of the association of the two L1 and E7 genes in therapeutic vaccines [26].

The L1 protein is produced in prokaryotic and eukaryotic expression systems and the baculovirus system in insect cells has been defined as a suitable model for commercial vaccine production. Merck has developed a quadruple vaccine that includes VLPs of HPV-16, HPV-11, HPV-18, and HPV-6 viruses. The first two types of the virus, together with approximately 70% of cervical cancer, and the second type account for 90% of genital warts [25].

In 2001, Kaufman et al. Showed that chimeric particles containing L1 and E7 can induce specific responses to HLA-restricted T cells [26]. In 2004, Chang et al. designed the plasmid L1E7hpSCA1, which contains the E7-L1 gene, and incorporated codons optimized for expression in mammalian cells. They also caused mutations in the E7 gene, thereby reducing its carcinogenicity [7].

HPV E7 DETOX (SIG/E7 DETOX/HSP70) is a vaccine in which mutant E7 protein (DETOX E7) is used together with heat shock protein in a vaccine DNA. The vaccine was developed in 2006 by Liquin et al and is currently in phase 1 therapy [27]. Most vaccine antigens currently under investigation include highly purified recombinant molecules or subunits of the pathogen that cannot be inherently responsive due to lack of any of the major pathogenic features such as immune stimulatory properties. To provide strong immunity. The immunological adjuvant was first defined by Ramon as a substance used in combination with a specific antigen and elicits very strong immune responses compared to the antigen alone [28].

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Viral E1-E2-E6-E7 proteins are commonly used in therapeutic vaccines, and studies in women have shown that the immune response to these proteins often reverses infection and avoids persistent infection slow. There have been limited studies of the association of the two L1 and E7 genes in therapeutic vaccines [29].

## Results and Discussion

Papillomaviruses are a group of viruses with a 5-kb double-stranded circular DNA genome that tend to epithelial tissue and cause benign cutaneous (wart) and mucosal ulceration. These viruses must infect the basal cells in order to cause a persistent infection. Basal cells are the only proliferating epithelial cells. Studies have shown that virus replication is associated with differentiation of keratinocytes [30]. It is also transmitted through skin-to-skin contact, some papillomaviruses being involved in the development of epithelial malignancies, especially cervical cancer and other genital tract tumors. Papillomaviruses are divided into two types of low-risk and high-risk. Oral cancer is the sixth-most common cancer in the developing world and the third most common cancer in the developing world. Tongue cancer is the most common of these cancers.

Importance of Papilloma Virus Diagnosis in Cervical Cancer: It is a screening program for oral and cervical cancer. Examines the efficacy of HPV vaccines. It is valuable in global epidemiological studies. Progression of the disease is prevented if it is early diagnosed and treated.

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In study Dr. Esmaeili et al in 2019, the L1 gene of genotype 16 was cloned into lactobacilli vector PNZ7021 and its expression was evaluated. For this purpose, a DNA sample from a patient with HPV genotype 16 was extracted and amplified using the specific primers, the L1 gene was amplified and cloned into the pBluescript vector. Subsequently, the L1 gene was cloned into the PNZ7021 vector using banII and HindIII enzymes and transferred to the expression host of Lactobacillus cremoris. The recombinant host was cultured and the expression of the recombinant protein was confirmed by Western blotting [1].

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