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Application of mRNA Vaccines in the Treatment of HPV Virus

Zerong Teng

Qingdao No.58 High School of Shandong Province, Qingdao, China
idateng0806@outlook.com

Abstract: Human papillomavirus (HPV), as the main virus causing these cancers, accounts for 5.2% of the global cancer rate. Many preventive vaccines against HPV have already appeared on the market, and nowadays more and more researchers are carrying out more studies on therapeutic vaccines against HPV. The purpose of this paper is to discuss the latest research progress on the pathogenesis of the HPV virus and mRNA vaccines by comparing the different types of mRNA vaccines that have emerged for the treatment of HPV and their mechanisms of action, including the RNA-LPX vaccine, the mHTV-02 vaccine, and the mHTV-03E2 vaccine, and to summarize the clinical progress of these three latest mRNA vaccines. This paper summarizes and introduces these three latest mRNA vaccines and the clinical progress of these three mRNA vaccines. It is found that HPV vaccines are still in clinical trials even though mHTV-03E2 has better therapeutic effects among the three vaccines mentioned above and can target HPV16 and HPV18, providing up to four months of immune protection, even so, this type of therapeutic vaccine still needs more clinical validation and testing, and its real application to life still has a long way to go. Even so, this type of therapeutic vaccine still needs more clinical validation and testing, and there is still a long way to go before it can be truly applied to life.

Keywords: mRNA vaccine, HPV vaccine, therapeutic vaccine, HPV virus, cervical cancer

1. Introduction

Human papillomavirus (HPV) accounts for approximately 5.2% of the global cancer burden. HPV infection is estimated to cause about 530,000 cancer cases annually, the majority of which occur in developing countries, including approximately 720,000 deaths from cervical cancer. Moreover, HPV is a major cause of anal cancer, contributing to about 90% of cases, and is also linked to a small proportion of other cancers such as vulvar cancer. It is important to research about the cancer that caused by HPV virus and find the best way to cure this kind of cancer or prevention of such cancers. It has become a public health issue of global concern. HPV or human papilloma virus is one of the classifications of papillomavirus. It has cyclic double-strand DNA genome. The outer protein coat of the virus consists of two different proteins which is two capsid proteins. The virus coded for 8 major proteins which six of them are in the early zone and two in the late zone [1]. The proteins in early region have different functions. E1 and E2 worked as the replication of HPV virus followed by E6 and E7 proteins act as oncoproteins of cancer. The late stage proteins' primary role is to encode the viral capsid protein such as L1 and L2 protein [2]. The HPV virus primarily infects the epithelial cells of the skin and mucous membranes. The trend of HPV infection is divided into four categories. These

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are direct sexual contact, contact with objects like the infection of condyloma acuminatum, smoke because tissue from the virus may be released into the air during laser treatment of warts, and mother-to-child transmission.

HPV can divide into two phylogenetic genera is the α-HPV and the β-HPV. The α-HPV contain HPV16 and HPV18 which leads most of the example of cervical cancers. The β-HPV can cause the infection of skin. Most of the cure types bit HPV6 and HPV11. Most case only benign warts are produced after viral infection such as some genital warts. Typically, most of human HPV infections are one-time events, usually a variety of benign warts, and are usually cleared by the immune system within 7-12 months. Genital warts rarely lead to lesions that develop into cancer [1]. But some genital infections may turn into cancer if they are not treated in a timely manner. There are various methods to treat HPV-induced precancerous lesions. Additionally, laser therapy, cryotherapy, and cold knife conization are commonly used treatments. For benign warts caused by HPV, medication therapy is also an option. The treatment of Head and Neck cancer (HNC) typically includes surgery, radiotherapy and chemotherapy. However, different combinations of these treatments are used depending on the specific case. This multimodal approach remains the most common strategy for managing head and neck cancer today [3]. Although there are now many new methods of treating cancer caused by HPV, the main clinical treatments are still the ones mentioned above, while the newer methods require further therapeutic validation.

In the current healthcare system, prophylactic vaccines against HPV have made significant progress and development and have been widely introduced for public use. Currently, vaccines preventing HPV-16 and HPV-18 have been approved by the World Health Organization (WHO) and are available in many countries. These vaccines can be administered to individuals aged 15 to 45, regardless of gender. Full immunity requires a series of three doses. Prophylactic HPV vaccines are highly effective in preventing HPV-related diseases, such as genital warts (condyloma acuminatum) and cervical cancer. These vaccines do not contain viral DNA and are non-infectious, as they are composed of virus-like particles (VLPs) made from viral proteins. This ensures they trigger an immune response without infecting cells, providing effective protection [3].

Three types of HPV vaccines are available in various countries: the 9-valent Gardasil9®, 4-valent Gardasil® and 2-valent vaccines Cervarix® [4]. Cervarix 90% effective against pre-cancerous lesions associated with HPV 16 and 18. Reports indicate only a small proportion of individuals—among every 100,000—experience adjuvant-induced autoimmune inflammatory syndrome (AIAS) following HPV vaccination [4]. This suggests that these vaccines have high efficacy and show significant effectiveness in preventing HPV infections. This paper aims to explore the pathogenic mechanisms of HPV, the latest research advancements in HPV-related carcinogenesis, current treatment strategies, and the progress of therapeutic HPV vaccines in clinical development.

2. Application performance of therapeutic HPV vaccines

The E6 and E7 oncoprotein inside the HPV virus is important for maintaining the malignant phenotype of human papillomavirus-positive cancer cells and as an important pathogenic protein of high-risk HPV as a causative agent of cervical cancer [5]. The E6 protein has common structure covering two zinc-related area which can bind with LXXLL peptide that inside the E6AP protein in the host cells. The complex of E6AP can let p53 being inactivated that is a suppressor which can leading cell death and prevent damage cell becoming cancerous. As a result, the p53 will proteolytic degradation [6].

The E7 protein contain 100 amino acids, there are no protein that have extensive sequence as E6 protein even though some sequence motifs that can find in cellular protein like LXCEX sequence [7]. E7 protein can bind with pRb protein in the host cells let it degradation and inactivating. At that time, pRb cannot inhibiting E2F to prevent uncontrolled cell proliferation so the cell cycle progression will

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uncontrolled [5]. The mechanisms by which E6 E7 proteins act together to cause uncontrolled cell proliferation (Figure 1). The single expression of E7 protein will inhibit the pRb so the cellular proliferation will be deregulated p53 protein will response to induced apoptosis and elimination the deregulated cells. If the E6 protein join inside induces the protelytic degradation of p53 cause formation of trimeric complex. The apoptotic response to E7 is blocked, allowing cells to develop under abnormal conditions [5]. These two oncoproteins act as a potential target for intervention of therapeutic vaccine against HPV virus.

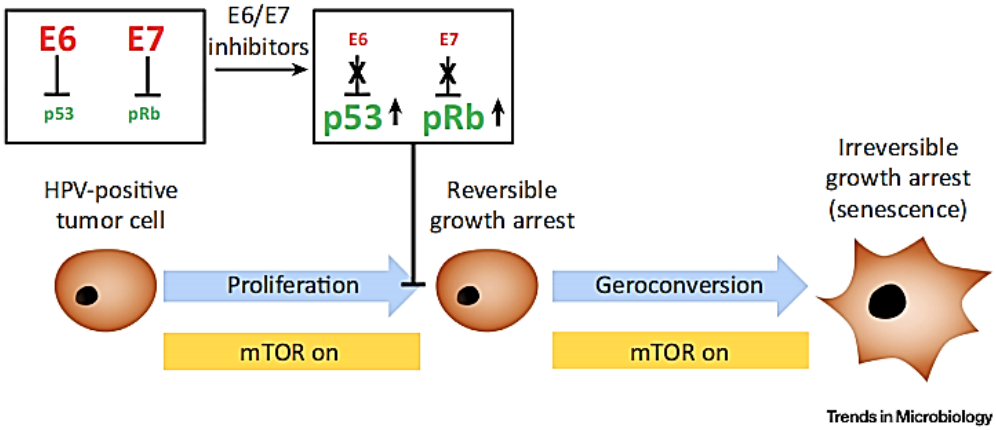

Figure 1: The mechanism of E6 and E7 oncoprotein in HPV virus [5]

2.1. HPV16 E7 mRNA vaccine

Advances in mRNA technology have led to significant progress in the treatment of various cancers with mRNA vaccines, especially in the treatment of human papillomavirus (HPV)-related cancers, due to their unique advantages. Immunotherapy directed against E6 and E7 oncoproteins has significant clinical value. Compared with the traditional HPV vaccine, mRNA can rapidly and accurately encode tumor-specific antigens that have become an ideal candidate for treating HPV-related cancers. In the research, HPV16 E7 mRNA vaccines have been chosen as a strategy for the treatment of HPV-related cancers [8]. The main advantages of mRNA vaccines are their efficient production, low cost and high safety, as they do not integrate into the host genome. mRNA vaccines can activate the immune system by synthesizing the target antigen directly in the body and induce CD8+ T-cell responses, mainly against the HPV16 E7 antigen. T cells encoded by mRNA vaccines can recognize and destroy tumor cells expressing the HPV16 E7 protein. More importantly, the mRNA vaccine can activate dendritic cell T cells to trigger a strong immune response against the tumor. In addition, the efficacy of the HPV16 RNA-LPX vaccine is not only enhanced when used alone, but also when combined with immune checkpoint inhibitors (ICIs), which can further enhance the anti-tumor immune response and thus increase efficacy. In some mouse models, anti-PD-L1 antibodies alone did not improve tumor outcomes, but when combined with the HPV16 E7 RNA-LPX vaccine, the therapeutic effect was significantly improved, resulting in increased complete remission and survival in mice. These results provide a rationale for combining vaccines with ICIs, and the combination of immunotherapies may improve clinical outcomes, especially for patients who do not respond to immune checkpoint inhibitor monotherapy [8].

2.2. mHTV-02 mRNA vaccine

There is a new mRNA occur that targeted both HPV16 and HPV18 related cancers [9]. These vaccines encode the E6 and E7 proteins of these high-risk HPV types, which play a crucial role in tumor

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development, and can target a wider range of HPV virus types compared to the older LPX RNA HPV16 vaccine. This study examined the efficacy of mHTV-02 in eliciting robust immune responses and its therapeutic potential in HPV-associated cancers. The latest study investigates the immunogenicity and therapeutic potential of mHTV-02 in mouse models. The results show that the vaccine elicits a strong antigen-specific immune response, including IFN-γ and IL-2 production, as well as CD8+ T-cell infiltration of tumors. These immune responses lead to tumor regression and prolonged survival of mice.

In addition, the vaccine induces long-lasting T-cell memory responses, which are essential to prevent tumor recurrence. The therapeutic effect of mHTV-02 is particularly strong when administered intramuscularly (i.m.) or intratumorally (i.t.), while intravenous (i.v.) administration has minimal effects on tumor growth or survival. Regarding routes of administration, the latest study highlights the importance of direct administration to the tumor for optimal therapeutic efficacy. Intramuscular and intratumoral injections produced significant therapeutic results, whereas intravenous administration was ineffective. This suggests that local activation of antigen-presenting cells (APCs) near the tumor site plays a crucial role in vaccine efficacy. This study also demonstrates that earlier intervention, especially in the early stages of tumor development, leads to better therapeutic results. Mice treated with mHTV-02 at the earliest stages of tumor growth experienced complete regression and long-term survival, while mice treated at more advanced stages had lower therapeutic efficacy.

The long-term antitumor memory induced by mHTV-02 was investigated. Mice in which the tumor had completely regressed after vaccination were challenged again 54 days later with the same tumor cells. These mice showed complete resistance to tumor growth, demonstrating the establishment of a long-lasting immune memory. This was also confirmed by an increased production of antigen-specific IFN-γ and IL-2, as well as an increased frequency of CD4+ and CD8+ T cells. Overall, mHTV-02 shows promise as a therapeutic vaccine against HPV-related cancers. It effectively triggers a robust and long-lasting immune response, leading to tumor regression and long-term protection. The results also highlight the importance of the mode of vaccine administration, with intramuscular and intratumoral injections being the most effective. Combining mHTV-02 with other immunotherapies, such as PD-1 inhibitors, could further increase its therapeutic potential. This study provides valuable preclinical information that could serve as a basis for future clinical trials and contribute to the development of mRNA vaccines against HPV-related malignancies [9].

2.3. mHTV-03E2 mRNA vaccine

There is a new vaccine called mHTV-03E2 vaccine, a new therapeutic mRNA-based vaccine, was developed to target HPV16 and HPV18, two high-risk strains of human papillomavirus associated with various cancers, including cervical cancer and head and neck cancer [10]. Compared with mHTV-02 can targeted HPV16 as main target, mHTV-03E2 can target both HPV16 and HPV18 at same time. Prophylactic HPV vaccines are designed to prevent initial HPV infection, while therapeutic vaccines such as mHTV-03E2 are designed to treat existing infections and eradicate HPV-induced malignancies. The vaccine uses lipid nanoparticles (LNPs) to deliver mRNA encoding HPV E2, E6 and E7 tumor proteins to the immune system, triggering a robust immune response against HPV-positive tumor cells. The addition of the E2 antigen makes the vaccine even more effective than the previous two vaccines.

Preclinical studies conducted with mHTV-03E2 in a mouse model yielded favorable results. The vaccine elicited a strong specific immune response, particularly by activating CD8+ T lymphocytes, which are essential for tumor regression. In addition, the vaccine produced a durable immune response with memory T cells that persisted for up to 4 months. This suggests that the immune response triggered by the vaccine offers lasting protection against subsequent tumor challenges.

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Given that many conventional therapies do not elicit a durable immune response and that tumor recurrence is common in HPV-positive cancers, this study is of considerable research importance. The therapeutic effect of mHTV-03E2 was dose-dependent, meaning that the higher the vaccine dose, the more pronounced the tumor regression. This result highlights the possibility of optimizing vaccine efficacy by adjusting the dose during clinical application. Importantly, the vaccine was well tolerated in mice and no significant side effects were observed, strengthening the safety of future human studies.

ICIs represent one of the most important advances in cancer immunotherapy, such as anti-PD-L1 antibodies, which block the inhibitory signals used by tumors to evade immune recognition. In animal models, anti-PD-L1 antibodies alone have only a minimal effect on tumor suppression. However, in combination with mHTV-03E2, the therapeutic effect was greatly enhanced. This combination resulted in prolonged survival and complete tumor regression in treated mice. This result suggests that mHTV-03E2 can be effectively used in combination with ICIs to enhance the overall immune response, particularly for tumors resistant to checkpoint-blocking monotherapy.

The combination of mRNA vaccines and ICIs is an attractive avenue for the future treatment of HPV-related cancers. The combination of these two strategies could help overcome the mechanisms used by tumors to bypass the immune system and thus improve treatment outcomes in patients who do not respond well to ICI monotherapy alone. This approach is also in line with the growing trend toward combination immunotherapies, which attack the tumor through different pathways, thus increasing the chances of successful treatment. The results of this study indicate that mHTV-03E2 has great clinical potential for the treatment of HPV-related malignancies [10].

2.4. Comparison of three vaccines

The first two vaccines focus on the HPV related cancers using mRNA vaccine which is mainly target HPV16, but in the third one it using the mHTV-03E2 vaccine which can mainly target both HPV 16 and HPV 18 as really efficient ways and interact E2, E6 an E7 antigens. The key different between these three vaccines are the antigen selection, immune response, therapeutic efficacy and combination with ICIs. The HPV16 E7 RNA-LPX vaccine focuses on the HPV16 E7 antigen and aims to trigger a strong T-cell response against HPV16-positive tumors. Although significant tumor regression has been demonstrated in preclinical models, its efficacy has been limited to HPV16-associated cancers. The mHTV-02 vaccine stimulates a broader immune response by adding HPV16 antigens E6 and E7. E6 plays a crucial role in immune defense by promoting cell proliferation through the degradation of p53, a tumor suppressor protein already mentioned. This is why targeting E6 at the same time as E7 can enhance the therapeutic effect. Both vaccines, however, are limited to HPV16-associated cancers and do not target tumors caused by HPV18, which is also an important pathogen of cervical and other cancers [8, 9].

In contrast, the mHTV-03E2 vaccine represents an important advance, as it acts against both HPV16 and HPV18. In addition to E6 and E7, the E2 antigen has been added. e2 plays a key role in viral replication and transcription Loss of the E2 protein is closely linked to malignant transformation in high-risk HPV infections. By including E2, the mHTV-03E2 vaccine has the potential to offer broader immune protection and potentially prevent viral reactivation, making this type of vaccine more effective than the previous two classes [10]. Another important difference lies in the immune response and durability of protection. While all three vaccines triggered CD8+ T cell activation and tumor infiltration, mHTV-03E2 showed the strongest and longest-lasting immune response: experiments on mice showed that this vaccine enabled memory T cells to maintain immunity for up to four months. In contrast, the first two vaccines did not show the same strong, long-lasting immune activation.

With regard to the combination of ICIs, all three studies examined the synergistic effects of mRNA vaccines with PD-L1 inhibitors. In the first two studies, combination therapy improved tumor control,

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but the mHTV-03E2 vaccine showed the strongest synergy. There is compelling evidence that mHTV-03E2 vaccine is the most effective vaccine candidate for combination immunotherapy of HPV-related cancers [10].

3. Conclusion

The rapid development of mRNA vaccine technology has provided new possibilities for the treatment of HPV-related cancers. The three studies discussed focus on the application of mRNA therapeutic vaccines in HPV-associated malignancies, particularly targeting HPV16 and HPV18, the most high-risk strains. By encoding key antigens such as E6, E7, and E2, these vaccines aim to activate the immune system to eliminate HPV-positive tumor cells. These studies highlight the potential of mRNA vaccines in HPV cancer treatment, especially in inducing antitumor immune responses, enhancing T-cell activity, and combining with ICIs. These three studies demonstrate the great potential of mRNA vaccines in treating HPV-related cancers. As the number of targeted antigens increased fromE7 to E6 and E7 and to E2,E6 and E7 and the vaccine was expanded from HPV16 to HPV16 and HPV18, therapeutic efficacy improved. Combining these vaccines with ICIs further enhanced the immune system's ability to recognize and eliminate tumor cells. Future research directions will focus on optimizing mRNA sequences and delivery systems, determining optimal dosing regimens, conducting clinical trials to assess efficacy in humans, and exploring additional immunotherapy combinations. With continued research, mRNA therapeutic vaccines have the potential to become a new standard for HPV cancer treatment, providing patients with a more effective and safer therapeutic option.

References

[1] *Graham S. V. (2010). Human papillomavirus: gene expression, regulation and prospects for novel diagnostic methods and antiviral therapies. Future microbiology, 5(10), 1493-1506.*

[2] *Furumoto, H., & Irahara, M. (2002). Human papilloma virus (HPV) and cervical cancer. Journal of Medical Investigation, 49(3/4), 124-133.*

[3] *Szymonowicz, K. A., & Chen, J. (2020). Biological and clinical aspects of HPV-related cancers. Cancer biology & medicine, 17(4), 864-878.*

[4] *Roy, V., Jung, W., Linde, C., Coates, E., Ledgerwood, J., Costner, P., Yamshchikov, G., Streeck, H., Juelg, B., Lauffenburger, D. A., & Alter, G. (2023). Differences in HPV-specific antibody Fc-effector functions following Gardasil® and Cervarix® vaccination. NPJ vaccines, 8(1), 39.*

[5] *Hoppe-Seyler, K., Bossler, F., Braun, J. A., Herrmann, A. L., & Hoppe-Seyler, F. (2018). The HPV E6/E7 Oncogenes: Key Factors for Viral Carcinogenesis and Therapeutic Targets. Trends in microbiology, 26(2), 158-168.*

[6] *Zanier, K., ould M'hamed ould Sidi, A., Boulade-Ladame, C., Rybin, V., Chappelle, A., Atkinson, A., Kieffer, B., & Travé, G. (2012). Solution structure analysis of the HPV16 E6 oncoprotein reveals a self-association mechanism required for E6-mediated degradation of p53. Structure (London, England: 1993), 20(4), 604-617.*

[7] *Roman, A., & Munger, K. (2013). The papillomavirus E7 proteins. Virology, 445(1-2), 138-168.*

[8] *Grunwitz, C., Salomon, N., Vascotto, F., Selmi, A., Bukur, T., Diken, M., Kreiter, S., Türeci, Ö., & Sahin, U. (2019). HPV16 RNA-LPX vaccine mediates complete regression of aggressively growing HPV-positive mouse tumors and establishes protective T cell memory. Oncoimmunology, 8(9), e1629259.*

[9] *Wang, J., Ma, L., Chen, Y., Zhou, R., Wang, Q., Zhang, T., Yi, D., Liu, Q., Zhang, Y., Zhang, W., Dong, Y., & Cen, S. (2024). Immunogenicity and effectiveness of an mRNA therapeutic vaccine for HPV-related malignancies. Life science alliance, 7(6), e202302448.*

[10] *Wang, J., Wang, Q., Ma, L., Lv, K., Han, L., Chen, Y., Zhou, R., Zhou, H., Chen, H., Wang, Y., Zhang, T., Yi, D., Liu, Q., Zhang, Y., Li, X., Cheng, T., Zhang, J., Huang, C., Dong, Y., Zhang, W., ... Cen, S. (2024). Development of an mRNA-based therapeutic vaccine mHTV-03E2 for high-risk HPV-related malignancies. Molecular therapy: the journal of the American Society of Gene Therapy, 32(7), 2340-2356.*