Review Article

Comprehensive Analysis of *Papillomavirus* (*PV*) and Its Implications in Cancer: Bridging the Gap between Human and Veterinary Medicine

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How to cite this article: **Naseri A, Matoofi A, Mansouri Ramezani M, Kalantari L, Taherzadeh Amlashi T, Roudaki S, Mohammadian M, Omranzadeh A. Comprehensive Analysis of *Papillomavirus* (*PV*) and Its Implications in Cancer: Bridging the Gap between Human and Veterinary Medicine. Archives of Razi Institute. 2024;79(6):1145-1154.** DOI: 10.32592/ARI.2024.79.6.1145

Article Info:
Received: 20 February 2024
Accepted: 4 April 2024
Published: 31 December 2024

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ABSTRACT

The risk of cancer development posed by papillomavirus (PV) infections is significant, affecting both humans and domestic animals. This underscores the importance of understanding and addressing this viral threat. Recent research has demonstrated the potential of immunotherapies, particularly immune checkpoint blockers (ICBs), in enhancing the immune response against tumor-associated antigens (TAAs) and tumor-related neoantigens, thereby facilitating their neutralization by the immune system. Furthermore, vaccines designed to enhance the immune response against PV-infected cells have yielded promising results, strengthening CD4+ and CD8+ T cell reactions and potentially impeding cancer progression. The oncoproteins E6 and E7, which are notably implicated in the development of malignancies, exert deleterious effects by disrupting tumor suppressor proteins and facilitating immune evasion and tumor proliferation, particularly in high-risk PV genotypes such as HPV-16 and HPV-18. Notwithstanding obstacles such as vaccine hesitancy and concerns regarding vaccine toxicity, PV vaccines have transformed disease prevention strategies, offering a promising avenue in the fight against PV-associated cancers. Advancements in precision medicine and immunotherapy offer promise in the management of advanced PV-related cancers. By identifying and exploiting specific molecular vulnerabilities, while simultaneously bolstering immune responses, these approaches may prove invaluable in combating this disease. This transformative approach has the potential to treat established cancers and prevent their recurrence and progression. Consequently, immunotherapies, therapeutic vaccines, and precision medicine have become the subject of considerable scientific interest due to their capacity to enhance the quality of life and outcomes for individuals afflicted with PV-related cancers. By harnessing the immune system's power and leveraging cutting-edge therapeutic modalities, researchers and clinicians are poised to reshape the landscape of cancer treatment, offering renewed hope and optimism for those affected by PV-associated malignancies. It is therefore imperative that innovative strategies be integrated into clinical practice in order to effectively combat the formidable challenge posed by PV-induced cancers. In conclusion, this review presents a promising direction for combating PV infections and associated malignancies, with the potential to transform the landscape of cancer treatment. By employing immunotherapies, therapeutic vaccines, and precision medicine, researchers and clinicians are positioned to make substantial advancements in the prevention and treatment of PV-related cancers, ultimately enhancing patient outcomes and quality of life.

Keywords: *Papillomavirus*, Cancer Immunotherapy, Virus, Oncogenic Mechanisms, Therapeutic Strategies.

1. Introduction

Significant advancements have been made in the field of cancer therapy; nevertheless, the development of an efficacious treatment remains a challenge (1, 2). Anticancer immunotherapies, including immune checkpoint blockers (ICBs) that utilize monoclonal antibodies, have garnered considerable attention in recent times (3). Immunotherapies elicit immune responses against neoantigens and tumor-associated antigens (TAAs). The use of ICBs and T cell-based immunotherapy for the purpose of immunomodulation has demonstrated considerable potential as a means of treating cancer (5-7). New antigens are present in cancer cells as a result of genetic instability or the presence of agents that cause cancer, including the human papillomavirus (HPV) and hepatitis B virus. Cancer testis antigens (CTAs) and tumor-specific neoantigens are non-tolerogenic, whereas some antigens are tolerogenic, including TAAs and oncofetal antigens (8). In order to develop innovative antitumor strategies, it is essential to develop methods that induce adaptive immune responses against both types of TAAs. It is important to note that different immunotherapies can influence the immune system in varying ways. Passive immunotherapy entails the targeting of tumors directly, without engaging the immune system. In contrast, active immunotherapy presents antigens with the objective of stimulating the immune system (11). A variety of cancer vaccines are currently in use, including those comprising synthetic tumor peptides, dendritic cell-based vaccines, and genetic vaccines (RNA/virus/DNA/bacterial). A safer and more effective anticancer approach can be achieved by the induction of tumor-specific cytotoxic T cells (CD8+ T cells) and the reactivation of preexisting anergic CD8+ T cells. An essential aspect of these endeavors is their impact on public health and scientific advancement, as well as their economic significance as one of the most prevalent classes of immune oncology drugs (IOs) (12). A number of prominent pharmaceutical companies and academic institutions are engaged in research in this area, including Bristol-Myers Squibb, Celgene, and Novartis (13). The development of cancer vaccines is a highly active area of research, with hundreds of clinical trials currently underway. However, the success rates observed to date have been historically low (14). The human papillomavirus (HPV) is a diverse group of viruses comprising over 200 genotypes, each with unique characteristics. The significant clinical consequences of this heterogeneity extend beyond their academic significance. There are numerous high-risk HPV types that are more likely to cause cancer, particularly cervical cancer. Cervical cancer has a high prevalence among females and is associated with significant mortality and morbidity (15). Globally, it is the fourth most common type of cancer among women (16). The principal objective of this systematic review is to examine the anticancer properties of HPV and its effect on cancer. This systematic review will examine the role of HPV in cancer development through an analysis of various studies in this field. The objective of this study is to underscore the significance of HPV vaccines in the prevention of associated diseases. Furthermore, this study aims to achieve optimal vaccine coverage, addressing challenges such as vaccine hesitancy and disparities in access.

2. papillomavirus Overview

In conclusion, the study of papillomaviruses (PV) in various species, including canine (Cf), feline (Fc), and human (H), has revealed significant similarities, particularly in the functional roles of key viral proteins such as E6. The identification of a PDZ domain protein binding motif in CfPV E6, analogous to that observed in HPV16 E6, suggests a potential mechanism for cellular transformation and immune evasion. These findings emphasize the necessity of comprehending PV biology across species to develop efficacious strategies for combating viral infections and associated cancers. Continued research and multidisciplinary collaboration are essential for advancing prevention, treatment, and global elimination efforts of HPV-related diseases, offering the prospect of a healthier future (17). The human papillomavirus (HPV) family comprises a number of viruses that are readily capable of infecting human mucous membranes and epithelial skin cells. Globally, HPV is one of the most prevalent sexually transmitted infections (STIs), with manifestations ranging from benign warts to potentially malignant lesions (18, 19). This comprehensive review addresses several key aspects of HPV.

2.1. Human Papillomavirus Classification and Varieties

A complex taxonomy of HPV is based on both its genetic characteristics and its impact on human health. The HPV virus is a member of the Papillomaviridae family and is classified based on the genetic sequence of the L1 protein in its capsid (20). As a consequence of the genetic variations observed in the L1 gene, distinct HPV genotypes have been delineated, each exhibiting distinctive characteristics and associations. In order to develop effective HPV vaccines, it is of the utmost importance to gain a comprehensive understanding of the genetic diversity of the capsid protein L1. A number of HPV vaccines are currently available, including Gardasil 9, which provides protection against a range of HPV strains that are associated with cancer. Vaccines that target the L1 viral capsid are designed to elicit a robust immune response, thereby reducing the risk of HPV infection and HPV-related disease (21). In accordance with the International Committee on Taxonomy of Viruses (ICTV), HPV is classified into five genera: Alpha, Beta, Gamma, Mu, and Nu-Papillomavirus. A total of over 200 HPV types have been identified within these genera. The pathogenic potential of these HPVs is contingent upon their genetic diversity. Consequently, specific HPV types are regarded as low-risk for causing benign infections such as warts on the skin (HPV-2 and HPV-1) or on the genital area (HPV-6 and HPV-11). High-risk HPV types, such as HPV-16 and HPV-18, have been linked to an increased risk of developing various forms of

cancer, including cervical, vaginal, anal, vulvar, penile, and head and neck cancers. The classification of HPV types is of great consequence with regard to the transmission and development of disease, given its impact on these processes (22). HPV types with low risk typically result in non-life-threatening conditions, whereas HPV types with high-risk, high-risk, or high-risk characteristics cause cancers. In particular, HPV-16 is the most prominent oncogenic HPV type associated with cervical cancer, which has the potential to be a life-threatening disease. Cervical cancer can be caused by high-risk types of HPV transmitted through sexual activity, including vaginal, anal, and oral intercourse. The formulation of effective preventive strategies requires an understanding of how HPV classification, transmission, and effects on cervical cancer can be addressed. The implementation of HPV vaccines and comprehensive screening programs represents a crucial strategy for the prevention of high-risk types of HPV.

2.2. Transmission

The human papillomavirus (HPV) is a highly prevalent virus that has been associated with a number of diseases, including genital warts and cancers. A comprehensive understanding of the modes of transmission of HPV is of paramount importance for public health initiatives, given the contagious nature of the virus and the potential health consequences associated with it. The most common route of transmission is sexual contact; however, other routes exist, including fomite transmission, vertical transmission, non-sexual close contact, and autoinoculation (23). The primary targets of HPV in genital infections are mucosal tissues, including the vulva, cervix, vagina, anus, and penis. Furthermore, the virus has the potential to infect oropharyngeal mucosal tissue during oral sexual intercourse. As a consequence of vertical transmission, a mother infected with HPV during parturition transmits the virus to her newborn. HPV particles are transmitted via maternal genital or oral secretions or the birth canal. The phenomenon of self-inoculation has the potential to facilitate the dissemination of genital warts and common warts on the skin or mucous membranes to novel locations. Warts are highly contagious and, as such, individuals afflicted with them should exercise caution to prevent the spread of the infection to other parts of the body (24). Fomites are defined as contaminated objects or surfaces that have the potential to transmit HPV, although this is not the primary route of transmission. Infected genital or oral secretions have the potential to transmit the virus to fomites. However, the risk of HPV transmission via fomites is comparatively low in comparison to direct skin-to-skin contact. It is possible, particularly in instances where one or both individuals are infected with HPV, for the virus to be transmitted through non-sexual close contact, such as during deep kissing. The use of condoms and vaccinations represent essential strategies for the prevention of HPV infections and related diseases. In order to reduce the burden of HPV-related diseases, it is of the utmost importance to gain a comprehensive understanding of the various modes of HPV transmission.

3. Antitumor Mechanism of Human Papillomavirus

A number of studies have established a causal relationship between HPV and cancer. The majority of HPV-related cancers are attributed to the HPV-16 and HPV-18 genotypes, which are classified as high-risk. The viral genomes are incorporated into the host cell DNA, resulting in the expression of viral oncoproteins E6 and E7. Oncoproteins impede essential cellular processes and are instrumental in the pathogenesis of cancer. Specifically, the anticancer effects of HPV are associated with the immune system and the viral oncoprotein E6, which plays a pivotal role in promoting p53 degradation (25). It has been demonstrated that the E6 oncoprotein downregulates specific factors in certain cancers, thereby inhibiting antitumor activity. The ubiquitin ligases present in a cell's cytoplasm facilitate the degradation of the tumor suppressor protein p53, which is primarily targeted by the E6 protein. Furthermore, E7 impedes the cell cycle by interacting with the retinoblastoma protein (Rb). The inactivation of p53 prevents cells from undergoing programmed cell death and DNA repair. An effective evasion tactic involves the modulation of the interferon pathway, which plays a significant role in antiviral and antitumor immunity. HPV impedes immune responses that could otherwise lead to the eradication of infected cells by disrupting this pathway (27). HPV is capable of evading immune surveillance, which is crucial for its prolonged persistence within host cells and a significant contributing factor to cancer development. Integration of the HPV genome into the host cell's DNA can occur during high-risk HPV infections, leading to significant alterations. The integration of genetic information has been observed to disrupt the normative cellular functions, particularly those regulating cell growth and apoptosis. The integration of viruses results in the expression of viral oncoproteins E6 and E7, which collaborate with host cell proteins to facilitate the proliferation and survival of cells (28). In conclusion, genomic integration results in the survival and proliferation of HPV-infected cells by disrupting the cell division and programmed cell death pathways (Figure 1). In order to develop effective interventions for HPV-associated cancer, it is imperative to gain a comprehensive understanding of these molecular mechanisms. At present, a therapeutic HPV vaccine is not available for clinical use. Nevertheless, a number of vaccines are currently in development that are designed to enhance CD8+ or CD4+ T cell responses. These include peptide, live-vector, protein, and genetic vaccines. Vaccines can be classified into various categories, but multi-epitope vaccines are distinguished by their distinctive design concept. Vaccines comprise cytotoxic T lymphocytes (CTLs), T helper cells (Ths), and B cell epitopes, which are encoded or overlapping in order to induce specific cellular and humoral immune responses (29). Furthermore, multi-epitope vaccines are safe, stable,

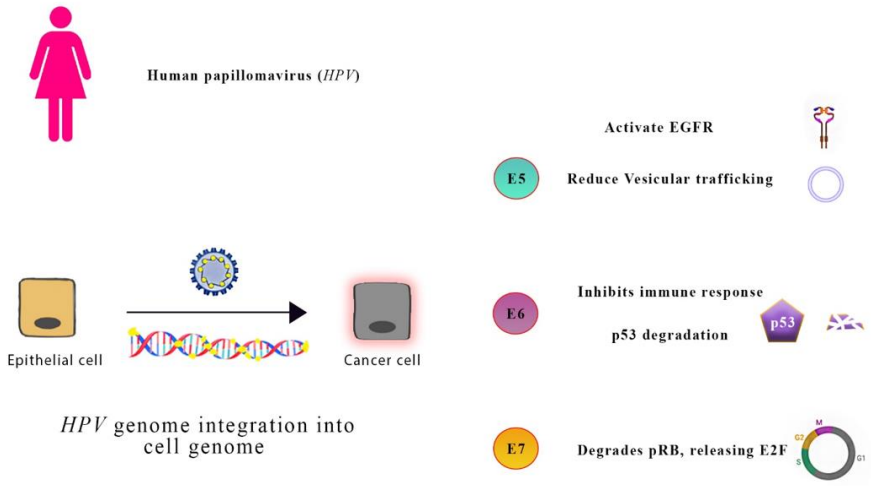

Figure 1: HPV infects basal layer cells and amplifies its genome before releasing virions to complete its life cycle. Disruption of the HPV genome can result in its integration into the cellular genome, leading to overexpression of early oncoproteins (E5, E6, and E7) and subsequent cell transformation. These oncoproteins interact with a number of cellular proteins, including EGFR, PDGFbR, E6AP, PDZ, pRB, and E2F.

and straightforward to store and produce. In conclusion, the study of papillomaviruses (PV) in various species, including canine (Cf), feline (Fc), and human (H), has revealed significant similarities, particularly in the functional roles of key viral proteins such as E6. The identification of a PDZ domain protein binding motif in CfPV E6, analogous to that observed in HPV16 E6, suggests a potential mechanism for cellular transformation and immune evasion. These findings emphasize the necessity of comprehending PV biology across species to develop efficacious strategies against viral infections and associated cancers. Continued research and multidisciplinary collaboration are essential for advancing prevention, treatment, and global elimination efforts of HPV-related diseases, offering hope for a healthier future. To develop clinically effective multi-epitope HPV vaccines, it is necessary to select immunodominant epitopes and implement effective delivery systems (30). HPV-16 E5, E6, and E7 oncoproteins could be used to develop therapeutic vaccines to treat HPV infections and lesions. A vaccine based on the E5 protein has been demonstrated to be an effective method for clearing viruses in premalignant lesions, as the E5 oncoprotein is known to develop in cervical intraepithelial neoplasia. The HPV oncoprotein E6 has been observed to bind to and interact with the p53 tumor suppressor protein. This interaction results in the ubiquitination and subsequent degradation of p53 by the proteasome, effectively inactivating its tumor-suppressive properties (31). The degradation of p53 by E6 is a critical step in the development of HPV-associated cancers, as p53 is normally activated by DNA damage or cellular stress to trigger apoptosis. HPV-infected cells evade programmed cell death by degrading p53, thereby facilitating the acquisition of genetic mutations that contribute to tumor formation. The HPV E7 oncoprotein binds and interacts with the tumor suppressor component pRB (32) (Figure 2). The development of cancer is contingent upon the binding of E7 to pRB, which disrupts the regulation of the cell cycle and precipitates uncontrolled cell proliferation. It is similarly conceivable that E7 may impede the functioning of DNA repair mechanisms, thereby precipitating genomic instability. However, a defining characteristic of cancer is the compromise of genomic integrity. In some individuals, HPV has developed mechanisms to evade immune surveillance and establish persistent infections despite the activation of immune responses (33). Such mechanisms may include immune evasion strategies that interfere with the immune system's ability to detect and eliminate viruses. Furthermore, HPV can create an immune-suppressive microenvironment that impairs the ability of affected immune cells to effectively eliminate infected cells. Furthermore, immunosuppression plays a role in the persistence of viral infections and the development of associated diseases. The introduction of the Gardasil and Cervarix vaccines has resulted in the production of antibodies by the immune system against HPV virus capsid proteins (34). In response to these vaccines, the immune system is trained to recognize and combat HPV. These vaccines prevent HPV infection and enhance the immune system's ability to combat HPV-infected cells, thereby reducing the risk of cancer associated with HPV infection (35). Vaccination represents a pivotal public health strategy for the prevention of diseases associated with HPV, particularly those caused by high-risk HPV types (Figures 1 and 2).

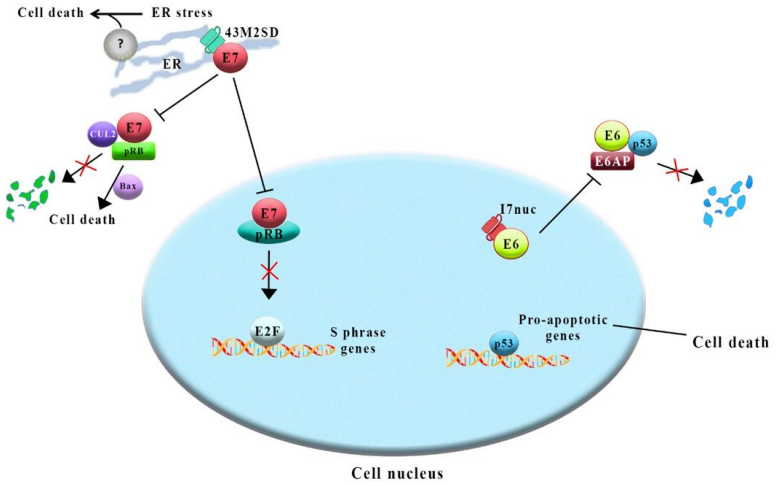

Figure 2: The hypothetical mechanisms of apoptosis induction by anti-16E6 and anti-16E7 intrabodies involve their binding to E6 and E7 proteins, respectively. The binding of scFvI7nuc to E6 inhibits the degradation of p53 in the cytoplasm, resulting in elevated nuclear p53 levels. This, in turn, results in the activation of pro-apoptotic genes, including Puma, Noxa, Bak, and Bax, which ultimately leads to a loss of mitochondrial membrane potential and the subsequent activation of caspase 3, ultimately resulting in cell death. Conversely, the binding of scFv43M2SD to E7 impedes its translocation to the nucleus, thereby restoring the function of the retinoblastoma tumor suppressor protein (pRB) and regulating the activity of E2F transcription factors. Moreover, scFv43M2SD has the capacity to impede the binding of E7 to the CUL2 complex and the subsequent recruitment of pRB for ubiquitination. An increase in pRB levels can directly activate the BAX apoptosis regulator at the mitochondrial level, thereby promoting cell death. Moreover, it is conceivable that scFv43M2SD binding to KDEL receptors in the ER may induce ER stress-related molecules, thereby triggering caspase activation and apoptosis.

4. Clinical Applications

Approximately 25% of global cancer cases are attributable to HPV (36). The HPV-16 E7 antigen is a tumor-associated antigen (TAA) that is frequently expressed in HPV-induced tumors with low immunogenicity. 4-1BBL has been demonstrated to enhance antitumor responses in a DNA vaccine when fused to TAA (37). Nevertheless, the transfection rate remains low, and the antitumor efficacy is limited. The antitumor potential of oncolytic virotherapy is promising, as it can selectively replicate in tumor cells, resulting in cell lysis. It should be noted, however, that the immune system is also capable of utilising tumour cell debris to enhance its antitumour activity. The present study demonstrates that oncolytic adenovirus (OAd) systems can express immunomodulatory molecules, such as SA-4-1BBL fused to E7. In vitro studies have demonstrated that SA/E7/4-1BBL OAd is capable of selectively destroying tumor cells when infected with TC-1 and NIH-3T3 non-tumor cells. The addition of a signal peptide (SP) to both cell lines results in targeted protein expression within the endoplasmic reticulum. Moreover, the fusion of OAd with either E7 or SP has been shown to result in the enhanced therapeutic oncolytic activity of the resulting construct in an HPV-induced cancer murine model. An evaluation of the tumor-suppressing capabilities of a fusion protein, SipB160/HPV-16 E7, derived from HPV-16 and expressed in Salmonella enteric serovar Typhimurium, was conducted in a cervical cancer model (38). The E7 protein was observed to elicit effective cytotoxicity and tumor growth retardation in TC-1 cervical cancer cells when expressed. The data indicated the potential of the SipB160/HPV-16 E7 fusion protein as a therapeutic agent for cancer treatment. Researchers investigate the potential of local cell-mediated immunity (CMI) to treat cervical cancer through mucosal immunotherapy against the HPV-16 E6 protein (39). Lactobacillus casei (L. casei) was engineered to express the HPV-16 E6 antigen, and mice orally administered with L. casei-PgsA-E6 exhibited HPV-16 antigen surface expression. A notable elevation in serum IgG and mucosal IgA levels was discerned in mice that received L. casei-PgsA-E6, in comparison to the control groups, following booster doses. The data indicated that various immune compartments exhibited higher counts of interferon-gamma (IFN-gamma) secreting cells, which suggests a significant increase in cell-mediated immunity (CMI) at both the systemic and local levels. The animals that were immunized with L. casei-PgsA-E6 exhibited a significantly reduced tumor size and a longer survival rate following oral immunization. In depletion experiments, the antitumor effects were dependent on the presence of $CD4^+$ or $CD8^+$ T cells. In light of these findings, it can be concluded that the oral administration of L. casei expressing the E6 protein induces T cell-mediated immunity and exhibits promising antitumor effects. The study introduces a novel approach to developing vaccines to treat HPV-induced cervical cancer by expressing the HPV-16 E7 protein in Nicotiana benthamiana plants using a potato virus X-derived vector (40). Immunization with a crude foliar extract containing E7 resulted in the stimulation of robust humoral and cellular immunity in mice. It is noteworthy that mice

immunized against E7-expressed C3 tumor cells exhibited a reduction in the incidence of cancer development. The study posits that the intrinsic adjuvant-like properties of plants can be harnessed to develop a cost-effective anticancer vaccine, thereby underscoring the potential for the production of such a vaccine in plants. This innovative approach may facilitate the advancement of therapeutic interventions against HPV-induced cervical cancer and provide an economical and scalable production method. Researchers have developed a vaccine comprising HPV-16 E7 peptide and CpG Oligo Deoxy Nucleotide (CpG ODN), formulated with liposomes modified with mannose (41). An antitumor effect was observed, with an inhibition rate of 80% and 78% compared to the control group in a mice model of large TC-1 grafted tumors. The vaccination resulted in an increase in CD4+ and CD8+ T cells and tumors in the spleen, indicating that the vaccine enhanced the immune system. Additionally, the number of macrophages and myeloid-derived suppressor cells was diminished within the tumor microenvironment. The immunosuppressive microenvironment of the tumor was modulated as a result of alterations in cytokine and chemokine expression. Moreover, the vaccine did not result in any significant toxicity to major organs. These findings suggest that mannose-modified liposomes may serve as an effective delivery system for cancer vaccines, potentially enhancing cancer immunotherapy. In order to develop preventative and therapeutic vaccines against the human papilloma virus (HPV), researchers investigated how heat shock proteins could enhance vaccine potency, focusing on the target antigens L1, L2, and E7 (42). Moreover, the researchers investigated the bioactivity of curcumin and nano-curcumin for their anticancer and chemopreventive properties. To assess immune responses and the protective and therapeutic effects of the vaccine, the researchers employed DNA-based and peptide-based vaccine constructs (L1-L2-E7 and HSP70-L1-L2-E7) in a tumor mouse model, combining them with curcumin and nanocurcumin. The results of the therapeutic test indicated that the combination of nano curcumin and the multi-epitope HSP70-L1-L2-E7 vaccine construct significantly reduced the likelihood of HPV-related tumors in mice. The findings indicated that nano curcumin exhibited a greater protective effect than curcumin alone. The study proposes a potential approach for the development of an HPV vaccine based on multi-epitope constructs, curcumin, and nano curcumin. A study conducted by Tang et al. investigated the potential of a self-assembled nanoparticle vaccine to enhance the efficacy of HPV-16-related cervical cancer vaccination (43). An HIV-1 Tat cell-penetrating peptide was combined with an HPV-16 E7 cytotoxic T lymphocyte epitope and granulocyte-macrophage colony-stimulating factor (GM-CSF). As evidenced by DNase I protection tests, transmission electron microscopy, gel retardation, and the resulting nanoparticle formulation, the particle size was observed to be within the range of 20-80 nm. This innovative vaccine demonstrated a marked enhancement in epitope-specific immunity in both in vitro and in vivo models. The administration of nanoparticle Tat-E7/pGM-CSF vaccines has been demonstrated to result in a reduction in tumor growth and an enhancement of long-term survival in prophylactic and therapeutic murine models. These effects were attributed to the priming of memory T cells of the $CD8^+$ type. In conclusion, these results suggest that the combination of pGM-CSF and nanoparticle Tat-E7 represents a promising therapeutic approach for enhancing the potency of peptide-based cervical cancer vaccines. In a study conducted by Li et al. (44), autologous heat shock protein 70 (mHSP70) genes were cloned from mouse liver cells, expressed, and subsequently fused with HPV-16 E7-mHSP70 (E7 at the N-terminus, mHSP70 at the C-terminus) proteins. A murine cervical cancer model, TC-1, which expresses E7, was employed to investigate the inhibition of TC-1 cell growth. In this model, the E7-mHSP70 fusion protein was administered to mice without the use of an adjuvant. It was demonstrated that prophylactic vaccination with E7-mHSP70 provided protection against TC-1 challenges in mice. It is also conceivable that E7-mHSP70 immunotherapy may inhibit the growth of TC-1 tumors in the lung. The present study demonstrated that mice challenged with TC-1 cells could generate an antitumor effect by immunization with E7-mHSP70 protein without any adjuvant. A virus that encodes oncogenic proteins, such as E7, may serve as the basis for cancer vaccines targeting HPV-associated squamous cell carcinomas of the head and neck (SCCHN). A study conducted by Albers et al. (45) demonstrated that the frequencies of HPV-16 E7 T cells in patients with SCCHN were higher than in individuals with HPV-16 who did not develop cancer, as well as in healthy individuals. The immunohistochemical analysis of HPV-16+ SCCHN tumors revealed that these components were further downregulated compared to adjacent normal squamous epithelia, indicating immune escape. It is recommended that HPV-associated SCCHNs be treated with immunotherapy that is specific to E7, as well as strategies that aim to increase the antigen-processing machinery components. In a considerable number of cases, squamous cell carcinomas of the oropharynx (SCCO) are found to harbor HPV-16, which is the etiological agent responsible for the development of cancer. To ascertain the prevalence of HPV-16 E7-specific T cells, Hoffmann et al. (46) conducted a tetramer analysis of peripheral blood lymphocytes from 20 SCCO patients and 20 healthy individuals. No significant differences were observed between the SCCO patient and normal donor groups with regard to CD8+ T cell frequencies. The E711-20 epitope was more frequently expressed by T cells in patients with tumors that expressed HPV-16 E7 and p16. The proliferation of HPV-responsive T cells and their capacity to inhibit tumor growth were demonstrated in vitro when these cells were stimulated with autologous dendritic cells (DCs) infused with HPV-16 E7 epitopes. These findings indicate the presence of precursor T cells specific for the

E711-20 epitope in the circulation of patients with HPV-16+ SCCO, emphasizing the necessity for further investigation into the mechanisms of in vivo tumor elimination and potential strategies for enhancing future HPV-based vaccines in SCCO patients. Sadraeian et al. (47) enhanced the effectiveness of HPV-16-related cervical cancer immunotherapy by combining the E7 protein, an immunotherapy candidate, with a lectin subunit of ricin toxin (RTB). The E7-RTB fusion protein was evaluated in comparison to E7 alone for its capacity to prevent and inhibit tumor development in female mice. The E7-RTB vaccination regimen proved efficacious in protecting mice against the growth of TC-1 cells in both preventive and therapeutic models, exhibiting markedly superior antitumor effects compared to E7 vaccination alone. In light of these findings, HPV-16 E7 therapeutic vaccines in conjunction with immunoadjuvants may offer promising clinical applications and warrant further investigation for future development. An elevated risk of developing cervical cancer and head and neck cancer is associated with infection with the HPV-16 virus. Yan et al. (48) propose a novel DNA vaccine, pConE6E7, which encodes an HPV-16 consensus gene E6/E7, as a means of enhancing antitumor cellular immunity. The construct elicited cellular immune responses specific to HPV-16 E7 at a rate approximately five times higher than that observed with an early-stage E7 DNA vaccine (pE7). A prophylactic dose of the vaccine demonstrated 100% efficacy in preventing the development of tumors expressing HPV-16 oncoproteins E6 and E7. The administration of pConE6E7 resulted in the inhibition or delay of tumor growth in therapeutic studies. Furthermore, immunization with pConE6E7 resulted in the partial overcoming of immune tolerance in E6/E7 transgenic mice. Further investigation of DNA immunogens in vivo may elucidate the mechanisms by which tumor immune rejection is mediated.

5. Future Challenges and Prospective

An increasing number of cancer researchers are investigating the potential of utilizing HPV as a tumor-fighting agent. New research has revealed a complex interaction between HPV and the immune system, which may facilitate the development of novel therapeutic approaches. The development of innovative immunotherapies based on the immunogenic properties of HPV represents one of the most promising prospects in this field of research. Investigators are exploring the potential of eliciting robust immune responses through the use of HPV-specific antigens, particularly those associated with viral capsid proteins L1 and L2. In this method, HPV-infected and transformed cells are targeted and eliminated through the use of the body's natural defense mechanisms, including CTLs (50). Experts are developing therapeutic vaccines with the objective of enhancing or inducing immune responses against HPV, which have the potential to prevent and treat HPV-associated cancers. A novel therapeutic approach based on the use of HPV may prove beneficial for cancer patients in the treatment of their tumors, namely oncolytic virotherapy. The development of oncolytic viruses engineered to enhance their tumor-selective replication, modified from HPV, is being investigated as a potential agent for selectively infecting and destroying cancer cells. Consequently, this approach targets and combats cancer by leveraging HPV's intrinsic capacity to replicate and infect neoplastic tissues. Preclinical studies have yielded promising results, indicating that oncolytic virotherapy may represent a promising treatment option for HPV-related cancers. The advent of molecular biology has facilitated the development of targeted therapeutic approaches to HPV-associated cancers. A number of small molecules and biologics are currently in development with the objective of targeting vital viral oncoproteins, such as E6 and E7. The capacity to impede the activity of these proteins could prevent HPV-transformed cells from proliferating and surviving, thereby facilitating a more precise and tailored approach to treatment. In light of the complexity of HPV-induced carcinogenesis, combination therapies are also being explored. It is feasible to augment the efficacy of treatment while mitigating adverse effects by integrating HPV-targeted therapies with conventional modalities such as chemotherapy and radiation. Despite the numerous challenges that must be addressed, including the necessity for rigorous clinical trials and the potential emergence of resistance mechanisms, HPV-based antitumor strategies remain a promising area of research. The advancement of HPV-centric approaches will necessitate further research, collaboration, and clinical trials to optimize efficacy and combat HPV-associated cancers. The discovery that a previously known oncogene can be used as a therapeutic agent in the context of HPV and antitumor strategies represents an encouraging development in the fight against cancer.

Conclusion

A comprehensive examination of papillomaviruses (PV) across different species, including canines (Cf), felines (Fc), and humans (H), has revealed notable parallels, particularly with regard to the functional roles of crucial viral proteins like E6. It is noteworthy that the discovery of a PDZ domain protein binding motif in CfPV E6, reminiscent of HPV16 E6, provides insights into potential mechanisms underlying cellular transformation and immune evasion in PV infections. These findings highlight the importance of investigating PV biology across species to develop effective strategies for combating viral infections and their associated malignancies. The presence of shared molecular features and pathways across diverse species indicates that PV-associated mechanisms have been conserved through evolution, emphasizing the importance of translational research in this domain. By elucidating the commonalities and differences in the pathogenesis and host interactions of PV, researchers can refine existing prevention and treatment approaches while developing novel interventions tailored to specific viral strains and host susceptibilities. Moreover, interdisciplinary collaboration and knowledge

exchange are essential for accelerating progress in understanding, combating, and ultimately eradicating HPV-related diseases worldwide. By drawing upon insights from a range of disciplines, including veterinary medicine, molecular biology, immunology, and oncology, scientists can develop novel strategies that transcend species boundaries, thereby paving the way for more effective preventive measures, therapeutics, and public health initiatives.

Acknowledgment
Acknowledgments are not applicable in the given context.

Authors' Contribution
Conceptualization: A.O.
Methodology: A.O.
Formal analysis and investigation: All authors.
Writing - original draft preparation: All authors.
Writing - review and editing: All authors.
Funding acquisition: Self-funding.
Supervision: A.O.
All authors checked and approved the final version of the manuscript for publication in the present journal.

Ethics
All applicable international, national, and/or institutional guidelines for the care and use of animals were adhered to.

Conflict of Interest
The authors declare no conflict of interests.

Consent to participate
The participant has not granted consent to participate in the study.
Consent for publication
Publication consent is not applicable in this particular case.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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