

Targeting high-risk HPV oncoproteins: Emerging therapeutic strategies and translational challenges

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Abstract

Persistent infection with high-risk human papillomavirus (HPV) is a major cause of cervical and other anogenital and oropharyngeal cancers. The viral oncoproteins E6 and E7 promote malignant transformation through disruption of tumor-suppressor pathways, making them attractive targets for therapeutic intervention. However, the development of effective oncoprotein-directed treatments remains challenging because of their intracellular localization, complex interactions with host proteins, and the difficulty of selectively inhibiting viral functions without affecting normal cellular processes. Emerging approaches include small-molecule inhibitors, gene silencing, genome editing, targeted protein degradation and therapeutic immunotherapy. Although several strategies have demonstrated promising preclinical activity, their clinical applicability remains limited by delivery challenges, off-target effects, tumor heterogeneity and insufficient evidence of durable efficacy. This mini review examines the principal therapeutic approaches targeting high-risk HPV oncoproteins, highlights barriers to clinical translation and discusses opportunities for integrating structural biology, computational drug discovery and experimental validation to accelerate the development of targeted treatments.

Keywords: human papillomavirus, E6, E7, oncoproteins, antiviral drug discovery, HPV-associated cancer

1. Introduction

Persistent infection with high-risk human papillomavirus (HPV), particularly HPV16 and HPV18, contributes substantially to cervical cancer and several other anogenital and oropharyngeal malignancies [1]. Prophylactic HPV vaccines have transformed primary prevention, but they do not reliably eliminate established infections or treat existing HPV-associated lesions [2]. Consequently, therapeutic approaches directed at HPV-driven disease remain an important research priority.

The viral oncoproteins E6 and E7 are central to HPV-mediated carcinogenesis. E6 promotes degradation of the tumor-suppressor protein p53 through interactions involving the cellular ubiquitin ligase E6-associated protein (E6AP), whereas E7 disrupts retinoblastoma protein (pRb)-mediated cell-cycle regulation [3]. Together, these activities promote uncontrolled proliferation, impair apoptosis and facilitate cellular transformation [3,4]. Their continued expression in many HPV-driven cancers creates a potential therapeutic vulnerability.

This mini review examines emerging approaches for targeting E6 and E7, emphasizing the distinction between promising experimental findings and therapies that have demonstrated clinical benefit.

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2. E6 and E7 as therapeutic targets

Targeting E6 and E7 offers a mechanistically attractive approach because these proteins participate directly in maintaining the malignant phenotype of HPV-transformed cells [5,6]. Inhibiting their functions could restore aspects of tumor-suppressor activity while interfering with the molecular processes supporting tumor growth.

Nevertheless, both proteins present substantial drug-discovery challenges. Their functions depend on interactions with multiple cellular partners, and some interaction surfaces are relatively shallow or structurally dynamic. Furthermore, differences between HPV genotypes may influence protein structure, binding interactions and inhibitor activity [7,8]. These considerations complicate the development of compounds with adequate potency, selectivity and activity across clinically relevant high-risk HPV types.

The distinction between inhibiting an oncoprotein and suppressing its expression is also important. Small molecules may interfere with protein–protein interactions or destabilize an oncoprotein, whereas nucleic-acid-based approaches attempt to reduce its production. Therapeutic vaccines and adoptive cellular therapies instead aim to stimulate immune recognition of cells expressing viral antigens. These approaches are complementary but face different developmental and safety requirements.

3. Emerging therapeutic strategies

3.1. Small-molecule inhibition of oncoprotein interactions

Small-molecule inhibitors offer the potential advantages of systemic administration, dose control and access to intracellular targets. For E6, one strategy is to disrupt interactions with E6AP or other host proteins involved in suppressing tumor-suppressor pathways. Interference with the E6–E6AP interaction could reduce E6-mediated p53 degradation and potentially restore p53-dependent cellular responses [9].

Structure-guided drug discovery may support this approach by identifying ligandable pockets, characterizing binding-site geometry and prioritizing compounds for experimental evaluation. Molecular docking, molecular dynamics simulations and binding-energy calculations can help rank candidate molecules, but computational predictions alone do not establish binding affinity, target engagement or biological activity. Biochemical assays, cellular studies and appropriate selectivity controls remain necessary to determine whether a candidate genuinely inhibits the intended interaction.

The HPV E7 oncoprotein represents a critically viable, high-value therapeutic target whose clinical validation is actively being unlocked through advanced drug discovery modalities. Its unique structural properties offer distinct interfaces for both direct and indirect inhibition. Current research leverages these targeted vulnerabilities to develop highly selective modern interventions [10–12]. Contemporary strategies such as targeted protein degraders (PROTACs), synthetic peptide mimics, and downstream pathway inhibitors, are rapidly transitioning from experimental concepts into the next generation of precision oncology treatments for HPV-associated malignancies.

3.2. Gene silencing and genome editing

RNA interference provides an alternative means of suppressing E6 and E7 expression. Small interfering RNAs and related technologies can reduce target messenger RNA, potentially restoring tumor-suppressor pathways and limiting the survival of HPV-transformed cells. However, their therapeutic utility depends on efficient delivery into relevant cells, intracellular stability and sufficient target specificity.

CRISPR-based genome editing has also been investigated as a means of disrupting viral oncogene sequences. Experimental studies suggest that targeting E6 or E7 may impair the viability of HPV-positive cancer cells [13–15]. Nevertheless, delivery efficiency, unintended genomic alterations, immune responses and the possibility of incomplete target disruption remain significant concerns [16].

These approaches require careful evaluation before their safety or effectiveness can be extrapolated to clinical use.

3.3. Targeted protein degradation

Targeted protein degradation seeks to eliminate disease-associated proteins rather than simply inhibit their activity. Technologies such as proteolysis-targeting chimeras (PROTACs) can, in principle, recruit a target protein to cellular degradation machinery [17]. Applied to HPV oncoproteins, this strategy could potentially reduce E6 or E7 abundance and affect multiple downstream oncogenic processes.

However, developing degraders against viral oncoproteins requires suitable target-binding ligands, effective intracellular delivery and appropriate recruitment of the host degradation machinery [18]. The feasibility of this approach must therefore be established experimentally, and it should not yet be interpreted as a clinically validated HPV treatment.

3.4. Therapeutic immunotherapy

Therapeutic vaccines represent a distinct and comparatively advanced avenue for targeting HPV oncoproteins. Unlike prophylactic vaccines, which primarily prevent new infections, therapeutic vaccines aim to stimulate cellular immune responses against antigens expressed by infected or transformed cells. E6 and E7 are attractive targets because their expression is associated with the maintenance of the malignant phenotype in HPV-driven cancers.

DNA-, RNA-, peptide- and viral-vector-based platforms have been investigated, with some candidates demonstrating immunogenicity and encouraging signals of lesion regression in clinical studies [19–22]. Nevertheless, outcomes vary according to vaccine design, disease stage, delivery method and clinical endpoints. Therapeutic vaccines have not become a universally established treatment for HPV-associated disease, and further controlled trials are required.

Other immunotherapeutic approaches, including adoptive T-cell and T-cell receptor-engineered therapies, seek to recognize HPV-derived antigens on tumor cells. These strategies may offer greater specificity in selected patients but are influenced by antigen presentation, tumor immune evasion, patient selection and treatment-associated toxicity. Their development illustrates the importance of integrating viral target biology with host immune mechanisms.

4. Translational challenges and future directions

Despite considerable progress, several obstacles separate experimental findings from clinically useful therapies. First, intracellular delivery remains a major limitation for nucleic-acid therapeutics, genome-editing systems and some protein-targeting approaches. Second, inhibitors must demonstrate selectivity for viral mechanisms without disrupting essential host proteins. Third, activity against one HPV genotype or experimental cell line cannot automatically be extrapolated to other genotypes, tumor sites or patient populations.

A further challenge is the limited comparability of preclinical evidence. Studies differ in target constructs, cellular models, compound concentrations and outcome measures. Apparent restoration of p53 or pRb signaling does not necessarily establish selective oncoprotein inhibition, tumor regression or durable clinical benefit. Future studies should therefore combine direct target-engagement assays with functional measurements, toxicity assessment and validation in biologically relevant models.

Computational methods could accelerate this process by integrating structural modelling, molecular docking, molecular dynamics and chemical-library screening. However, their greatest value lies in prioritizing experimentally testable hypotheses rather than replacing laboratory validation. Combining structural evidence with biochemical assays, cellular studies and pharmacological evaluation could improve candidate selection and reduce premature advancement of poorly characterized compounds.

Combination strategies also warrant investigation. Oncoprotein-directed approaches may complement established cancer treatments or immunotherapies, but potential benefits must be

demonstrated through appropriately designed studies. Ultimately, the most suitable strategy may depend on whether the therapeutic objective is to clear infection, treat precancerous lesions or control established malignancy.

5. Conclusion

E6 and E7 remain compelling targets for developing treatments against high-risk HPV-associated disease. Small-molecule inhibition, gene silencing, genome editing, targeted protein degradation and therapeutic immunotherapy offer complementary routes to interfere with viral oncogenic activity. However, most direct oncoprotein-targeting approaches remain at an experimental stage, and substantial challenges involving delivery, selectivity, validation and clinical translation persist. Progress will depend on rigorous mechanistic studies and coordinated integration of computational prediction, experimental testing and clinical evaluation. Such an approach may help transform promising molecular targets into safe and effective therapeutic options for patients with HPV-associated disease.

Data Availability

All data are contained in the paper.

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Competing Interests

None.

Declaration of Generative AI and AI-Assisted Technologies in the Manuscript Preparation Process

The manuscript's grammar was enhanced using AI.

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