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Molecular Pathogenesis of Human Papillomavirus: Insights into Viral Oncoproteins and Host Integration

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ABSTRACT: Human Papillomavirus (HPV) is a major cause of death from cervical cancer and other anogenital cancers throughout the world. Pathogenicity of HPV is governed by intricate interplay of HPV and host cells mediated primarily by its oncoproteins E6 and E7. These oncoproteins disrupt critical pathways, including those involving tumor suppressors p53 and retinoblastoma (Rb) to induce unregulated cell proliferation and evasion of apoptosis. These mechanisms have been studied in order to develop the different diagnostic tools, such as HPV DNA testing and genotyping, and there are emerging techniques based on E6/E7 mRNA detection and high throughput sequencing. In addition, therapeutic strategies have advanced with the vaccines showing ability to prevent high risk HPV infection and ongoing research to developing targeted therapies to disrupt viral oncoprotein function. New diagnostic and therapeutic approaches to HPV research encompassing an expanding clinical landscape hold promise to reduce incidence of HPV associated malignancies and improve patient outcomes. This review summarizes the molecular pathogenesis of HPV with respect to host cells and discusses its implications for diagnostics and therapeutics, including the need for further development in this area.

INTRODUCTION

Human Papillomavirus (HPV) is a group of over 200 genetically related viruses with a significant public health impact related to an association with benign and malignant lesions. Among these, some, such as the high risk HPV types, in particular the HPVs 16 and 18 are considered the most important with regard to cervical cancer, which is the leading cause of cancer related morbidity and mortality in women around the world. Moreover, HPV is involved in a subset of oropharyngeal cancers, additional anogenital cancers, and merits elucidation of its molecular pathogenesis (1, 2).

As is most of HPV's oncogenic potential, it is mostly due to its viral oncoproteins, E6 and E7. Proteins generated by this multiple sclerosis virus have critical roles in manipulation of host cellular machinery to aid viral replication and persistence. Among eukaryotic viruses, E6 is the only known protein able to bind and promote the degradation of p53, the tumor suppressor protein that normally suppresses cell growth in the face of DNA damage, effectively blocking a normal apoptotic pathway, allowing a virus infected cell to survive. E7 simultaneously interacts with the retinoblastoma protein (Rb), allowing E2F transcription factors released by E7 to drive the cell cycle forward. These actions taken together lead to unregulated cell proliferation which help to develop precancerous lesions and invasive cancers (3, 4).

In addition to the actions of oncoproteins, an elementary event in HPV induced carcinogenesis is the viral DNA integration into the host genome. Futhermore, this integration of virus into the host genome can disrupt host genes and regulatory elements, promote genomic instability and change gene expression profiles further facilitating tumorigenesis. The mechanisms of HPV integration into host DNA and the consequences (of such integration) are areas of intense investigation that provide critical insights into the virus's strategy of inducing oncogenicity (5-8).

Furthermore, the interaction between HPV and the host immune response is complicated. HPV has evolutionary mechanisms that enable it to evade immune detection, including downregulating major histocompatibility complex (MHC) molecules, but host immune response can influence disease progression and outcome in the setting of infection. It is essential to understand these interactions, in order to develop effective vaccines and therapeutic interventions (8-10).

In this review, we cover the molecular pathogenesis of HPV and discuss the mechanisms by which viral oncoproteins drive cellular transformation as well as how viral integration affects cancer development. In the hope of conveying potential future research directions and therapeutic strategies for mitigating the harshness of diseases caused by HPV, we consolidate current knowledge in this area.

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HPV CLASSIFICATION AND GENOMIC STRUCTURE

Depending on genomic characteristics and their associated pathologies, Human Papillomavirus (HPV) are divided into several types. HPVs are classified into those that are low risk, and those that are high risk of causing cancer, mostly based on their potential to do that (1, 2, 11).

1. HPV Types and Their Associated Diseases

- Low-Risk HPV Types: While there are many different types of HPV, these include the so called benign types: HPV 6 and HPV 11 that are mainly linked to genital warts (condylomata acuminata) and to respiratory papillomatosis. These cancer rarely develop into malignancy but can be symptomatic and therefore cause significant morbidity due to their symptomatic lesions (12, 13).
- High-Risk HPV Types: Certain high risk types, most notably HPV 16, HPV 18, HPV 31, HPV 33, HPV 45 and others are specifically associated with various cancers. The vast majority of the cervical cancers, and additional anogenital cancers and oropharyngeal squamous cell carcinomas, are due to HPV 16 and 18. Their oncoproteins' ability to disrupt normal cellular processes is thought to make these types oncogenic (13-15).

2. Genomic Structure of HPV

HPV is a small nonenveloped virus with a circular double stranded DNA genome. The genomic structure includes several key features (16-18):

- Genome Size: Lengths of the HPV genome vary from 7.0 to 8.5 kilobases by type.
- Early (E) and Late (L) Genes:

The genome consist of early (E) and late (L) genes. The early genes (E1, E2, E4, E5, E6, E7) are essential for viral replication, and regulation of viral life cycle, and oncogenesis. As previously discussed, both E6 and E7 are particularly important on account of their oncogenic properties.

Gives rise to the structural proteins which make up the virus capsid (the late genes, L1 and L2). L1 is the major capsid protein and is the main target of vaccine development.

- The late genes (L1 and L2) encode the structural proteins that form the virus capsid. L1 is the major capsid protein and is the primary target for vaccine development.
- Regulatory Elements:
- The HPV genome contains various regulatory regions such as the long control region (LCR), which is crucial for viral replication and transcription regulation. This region contains binding sites for transcription factors and plays a significant role in controlling the expression of early and late genes.
- Integration Sites: In high-risk HPVs, integration into the host genome often occurs at specific sites, leading to the disruption of host genes and regulatory elements that can promote oncogenesis. Integration typically occurs in regions of active transcription and can result in the amplification of oncogenic signals through the dysregulation of nearby host genes.

3. Evolutionary Considerations

HPVs exhibit a high degree of genetic variability, which is significant for their classification and understanding of disease associations. Phylogenetic analyses have helped in grouping HPVs into different genera, such as Alphapapillomavirus (which includes most high-risk types), Betapapillomavirus, and Gammapapillomavirus. These classifications are based on genetic homology and evolutionary relationships, providing insights into the virus's biology and epidemiology (19-21).

Table 1: Classification of Human Papillomavirus (HPV) Types and Associated Diseases

HPV Type	Risk Level	Associated Diseases	Oncogenic Potential
HPV 6	Low-risk	Genital warts, respiratory papillomatosis	Minimal; rarely associated with cancer
HPV 11	Low-risk	Genital warts, respiratory papillomatosis	Minimal; rarely associated with cancer
HPV 16	High-risk	Cervical cancer, oropharyngeal cancer	High; significantly associated with malignancies
HPV 18	High-risk	Cervical cancer, anal cancer	High; significantly associated with malignancies
HPV 31	High-risk	Cervical cancer	Moderate to high; associated with precancerous lesions
HPV 33	High-risk	Cervical cancer	Moderate to high; associated with precancerous lesions
HPV 45	High-risk	Cervical cancer, anal cancer	Moderate to high; associated with precancerous lesions
HPV 52	High-risk	Cervical cancer	Moderate to high; associated with precancerous lesions
HPV 58	High-risk	Cervical cancer	Moderate to high; associated with precancerous lesions

VIRAL ONCOPROTEINS: MECHANISMS OF ACTION

Human Papillomavirus (HPV) is an oncogenic virus, and its viral oncoproteins E6 and E7 are principally responsible for its oncogenic potential. These proteins are important for the transformation (hijacking) of infected host cells to produce uncontrolled cell proliferation and ultimately, cancer. The mechanisms by which these oncoproteins regulate host cellular processes are described in this section (22).

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1. E6 Oncoprotein

- Interaction with p53:

— The E6 protein has one of the primary functions of binding to the tumor suppressor p53. p53 is the essential guardian of genomic integrity, and under normal conditions is responsible for cell cycle arrest and apoptosis in response to DNA damage. Nevertheless, E6 recruits the associated E3 ubiquitin ligase complex and promotes ubiquitination and degradation of p53. The damage to p53 breaks down the DNA damage response and allows cells with damaged DNA to carry on proliferating (23-25).

- Induction of Telomerase Activity:

E6 can also increase telomerase expression, an enzyme that maintains telomere length and (phenotypically) cellular replicative potential. E6 increases cellular immortality, one of the hallmark features of cancer cells by increasing telomerase activity (26, 27).

- Immune Evasion:

Downregulation of MHC class I molecules on infected cells by E6 has been shown to impair the ability of cytotoxic T lymphocytes to recognise and eliminate HPV infected cells. The immune evasion plays an important role in virus' persistence and its oncogenesis (28, 29).

2. E7 Oncoprotein

- Inhibition of Rb Protein:

- Overall, the main protease target for the E7 protein is the retinoblastoma (Rb) tumor suppressor protein. The normal function of Rb prevents cell cycle progression by binding to E2F transcription factors in order to control genes necessary for S phase entry. The E7 protein binds to Rb, inactivating it at which point E2F is released to drive the cell cycle and promote uncontrolled cell division (30).

- Disruption of Cell Cycle Regulation:

E7 disrupts the Rb-E2F pathway, promotes progression through the cell cycle, and is another determinant of genomic instability. The cell cycle is unregulated and can accumulate mutations and chromosomal abnormalities (31).

- Interaction with Cellular Proteins:

Besides directly affecting Rb, E7 can act on other host cellular proteins and oversee cell signaling, apoptosis and differentiation processes. In the example given above, E7 has been demonstrated to bind to cyclin dependent kinase (CDK) complexes responsible for controlling cell cycle transitions and increasing proliferative signals in the host cell (32).

3. Synergistic Action of E6 and E7

- Cooperative Oncogenic Effects:

E6 and E7 have obviously distinct mechanisms of action with the effects synergistic. In addition Rb inactivation by E7, E6 degrades p53, allowing for cell proliferation and survival in the presence of accumulated DNA damage (33).

- Transformation of Host Cells:

By working together, E6 and E7 block cell cycle regulation and induce apoptosis and this is possible because E6 and E7 can stop immune action, in other words prevent the immune system to attack them. The accompanying change of cellular morphology and function characteristic of cancerous cells is evident upon this transformation (22).

4. Implications for Treatment

Understanding the mechanisms through which HPV oncoproteins contribute to cancer development is essential for developing targeted therapies. strategies include:

- Targeting Oncoprotein Interactions:

- Developing inhibitors that block the interactions between HPV oncoproteins and their host targets (e.g., p53 and Rb) could restore normal cell cycle regulation and promote apoptosis in infected cells (34).

- Immunotherapy:

- Harnessing the immune system to target HPV-infected cells through vaccines or therapeutic agents that stimulate an immune response against HPV antigens may enhance elimination of infected cells (35).

- Gene Editing Approaches:

- Techniques such as CRISPR/Cas9 could potentially be used to disrupt the expression of viral oncogenes or restore function to tumor suppressor genes affected by HPV infection (36).

Table 2: Mechanisms of Action of HPV Oncoproteins E6 and E7

Oncoprotein	Target Protein/Pathway	Mechanism of Action	Consequences for Host Cells
E6	p53	Binds to p53 and promotes its ubiquitination and degradation	Disruption of cell cycle arrest and apoptosis; increased survival of damaged cells

	Telomerase	Upregulates telomerase activity	Cellular immortality; allows continued proliferation
	MHC Class I	Downregulates MHC class I expression	Impaired immune recognition and evasion of host immune response
E7	Retinoblastoma (Rb)	Binds to Rb, leading to its inactivation and release of E2F	Deregulated cell cycle progression; promotes entry into S-phase
	Cyclin-Dependent Kinases (CDKs)	Interacts with CDK complexes to influence cell cycle regulation	Enhanced proliferative signals; disruption of normal cell cycle control
	Various host proteins	Alters interactions with multiple cellular pathways	Genomic instability and accumulation of mutations
Combined Action	E6 and E7 Synergy	Cooperative disruption of p53 and Rb pathways	Enhanced transformation of host cells; increased oncogenic potential

HOST CELL INTERACTIONS

Human papillomavirus (HPV) and host cell interaction is a dynamic and complex process both in the infection, replication and oncogenesis. The development of effective therapeutic strategies against HPV associated diseases requires understanding of these interactions. In this section we describe key aspects of how HPV interacts with host cells with a major emphasis on the entry of HPV, evading the immune response and the role of host factors in HPV persistence (37).

1. Mechanisms of Viral Entry

- **Attachment and Entry:**
  - HPV infects epithelial cells by attaching to their surface via interactions with heparan sulfate proteoglycans (HSPGs) and other cellular receptors. The viral genome is then endocytosed through an attachment that follows (38).
- **Endosomal Escape:**
  - To deliver its DNA in the nucleus, HPV must evade out of endosomes once it's inside the cell. In the acidic endosome environment, the viral capsid undergoes conformational change and releases the viral genome into cytoplasm and subsequently the nuclear import of viral genome (39).

2. Immune Response Evasion

- **Downregulation of MHC Molecules:**
  - HPV employs various strategies to evade the host immune response. E6 and E7 oncoproteins can downregulate major histocompatibility complex (MHC) class I molecules on infected cells, reducing their visibility to cytotoxic T lymphocytes and impairing the immune system's ability to target HPV-infected cells (8).
- **Manipulation of Cytokine Responses:**
  - HPV can alter the local cytokine environment to promote an immunosuppressive state, facilitating viral persistence. This includes inducing regulatory T cells (Tregs) that further dampen immune responses against HPV (40).

3. Role of Host Factors in Viral Persistence

- **Cellular Environment:**
  - The presence of specific host factors can influence HPV replication and persistence. For instance, factors that promote cellular proliferation may enhance viral replication, while factors that induce differentiation can lead to a decrease in viral load (8).
- **Genomic Integration:**
  - High-risk HPVs can integrate their DNA into the host genome, often occurring in regions with active transcription. This integration can disrupt host genes and regulatory elements, contributing to genomic instability and facilitating oncogenesis (41).
- **Inflammatory Response:**
  - Persistent infections may trigger chronic inflammatory responses that can contribute to tissue damage and create a favorable environment for cancer development (42).

Table 3: Key Host Cell Interactions with HPV

Interaction Type	Mechanism	Implications for HPV Infection
Viral Entry	Attachment to surface receptors (e.g., HSPGs)	Facilitates viral entry into host cells
	Endocytosis and endosomal escape	Delivers viral genome to the nucleus
Immune Evasion	Downregulation of MHC class I	Reduces immune detection by cytotoxic T lymphocytes
	Induction of regulatory T cells (Tregs)	Damps immune response; promotes viral persistence

Host Factor Influence	Presence of proliferative factors	Enhances viral replication
	Genomic integration into host DNA	Disrupts host genes; contributes to oncogenesis
	Chronic inflammation	Leads to tissue damage; creates a cancer-promoting environment

DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS

The molecular pathogenesis of Human Papillomavirus (HPV) understanding has high implications for diagnostics and therapeutics. HPV is a known major causality of multiple malignancies, especially cervical cancer, thus there is need for efficacious diagnostic tools and therapeutic strategies for early detection, prevention, and treatment of HPV related diseases. This section reviews current diagnostic methods and therapeutic approaches as well as new approaches to the management of HPV infections (43-46).

1. Diagnostic Methods

- **Pap Smear (Cytology):**
  - Cervical cancer screening is commonly performed with a Pap test. Collecting cells from the cervix and checking the cells microscopically for abnormal changes that suggest pre cancerous lesions (dysplasia) or cancer is called Pap test. Effective, but with limitations in sensitivity and specificity, the Pap test.
- **HPV DNA Testing:**
  - HPV DNA testing detects the presence of high-risk HPV types in cervical cells. This method is more sensitive than cytology alone and can identify women at higher risk for developing cervical cancer. DNA tests can be performed alongside Pap tests (co-testing) to improve screening accuracy.
- **HPV Genotyping:**
  - Genotyping allows for the identification of specific HPV types present in a sample. This information is crucial for risk assessment, as high-risk types (e.g., HPV 16, HPV 18) are more strongly associated with progression to cervical cancer.
- **Molecular Biomarkers:**
  - Research is ongoing to identify specific molecular biomarkers associated with HPV infection and oncogenesis. These biomarkers may aid in predicting disease progression and treatment response, enhancing personalized medicine approaches.

Table 4: Emerging Diagnostic Methods for HPV Detection

Diagnostic Method	Description	Advantages	Limitations
HPV E6/E7 mRNA Testing	Detects the expression of E6 and E7 oncogenes	High specificity for cancerous lesions; indicates active infection	Limited availability; requires specialized equipment
Next-Generation Sequencing (NGS)	Comprehensive analysis of HPV genome and variants	Ability to detect multiple HPV types and mutations; detailed profiling	High cost; complex data interpretation
Liquid Biopsy	Analysis of circulating tumor DNA (ctDNA) in blood	Minimally invasive; potential for early detection of malignancies	Sensitivity can vary; not widely established yet
Digital PCR	Highly sensitive method for quantifying HPV viral load	Greater accuracy than traditional PCR; can detect low viral loads	Requires specialized technology and expertise
RNA-Seq for Host Response	Evaluates host gene expression profiles in response to HPV	Provides insights into the host immune response and potential dysregulation	Complex analysis; may require extensive validation
Microarray Analysis	Simultaneous detection of multiple HPV types and biomarkers	High-throughput capability; can identify co-infections	Expensive; may require extensive sample processing

2. Therapeutic Approaches

- **Vaccination:**
  - Vaccines such as Gardasil and Cervarix have been developed to prevent HPV infection. These vaccines target the most common high-risk types (HPV 16, 18) as well as low-risk types (HPV 6, 11). Vaccination has proven effective in reducing the incidence of cervical cancer and other HPV-related diseases (47).
- **Surgical Interventions:**
  - Screening can help find pre-cancerous lesions and, for some, such as those that are pre-cancer, procedures like LEEP or conization might be performed to remove affected tissue to help prevent progression to invasive cancer (48).
- **Chemotherapy and Radiotherapy:**

- Chemotherapy and radiation therapy are standard treatment for patients diagnosed with invasive cervical cancer. They are usually combined in advanced cases for effectiveness of therapy (49).

- **Emerging Targeted Therapies:**
- Targeted therapies directed specifically against the action of HPV oncogenes (E6 and E7) are being researched. These therapies prevent viral protein interaction with host tumor suppressors in an effort to restore normal cellular function (22).

3. Future Directions

- **Personalized Medicine:**
- While advances in genomics and molecular profiling may suggest personalized treatment strategies based on individual patient profiles (such as patient-specific HPV types and host genetic factors), currently the majority of treatment decisions are nonetheless aimed at a general population.

- **Immunotherapy:**
- We are exploring immunotherapeutic approaches to improve the immune response against HPV infected cells. Both therapeutic and preventative vaccines that stimulate an immune response against E6 and E7 oncoproteins are under investigation.

- **Screening Recommendations:**
- Further studies are ongoing to develop screening guidelines for refining the use of simultaneous testing for HPV and cytology in higher or lower risk groups and at various age categories to optimize early detection of cervical cancer.

CONCLUSION

Understanding HPV's molecular etiology has important diagnostic and therapeutic consequences for alleviating the burden of HPV-related disorders. Enhanced screening techniques, efficacious vaccination protocols, and novel therapy regimens offer potential for improving patient outcomes and decreasing the prevalence of cervical and other HPV-related malignancies. Continuously investigation into HPV biology will enhance options for prevention, early detection, and therapy.

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