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Role of Human Papilloma Virus in Carcinogenesis of Head and Neck Squamous Cell

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) is a malignancy that occur in head and neck region and originates from squamous epithelial cell in the upper respiratory tract mucosa. This malignancy has a high heteregenicity. Carcinogenesis due to HPV infection has a different moleculer pathway from HNSCC without HPV infection.
Methods: We searched Pubmed collection for open access and English language articles publish access from years 2016-2022 with keyword HPV, HNSCC and carcinogenesis.
Results: We had 16 articles that matched from the keywords. The mechanism of HPV leading carcinogenesis in HNSCC because the HPV has a specific protein that can cause malignant transformation in squamous epithelial cells. The E6 protein inactivates the p53 tumor suppressor gene by activating the ubiquitin ligase E6AP causing degradation of p53. The E7 protein inactivates the pRb (protein retinoblastoma) tumpr suppressor protein by blocking the interaction between pRb and E2F, causing E2F depression.
Conclusion: Carcinogenesis and malignant transformation in HNSCC correlated with HPV infection (high risk type) via the E6 and E7 proteins. This combination can causes abnormal cell cycle and leads cells to escape cell cycle control and get a malignant transformation.

Keywords: HPV, Carcinogenesis, HNSCC

Introduction

Squamous cell carcinoma (SCC) of the head and neck is an epithelial malignancy originating from flat epithelial cells of the mucosa in the upper respiratory tract. This cancer accounts for the majority (90%) of malignancies found in the head and neck region.[1] The incidence of head and neck cancer ranks seventh among the most commonly diagnosed cancers globally, comprising approximately 5% of all cancer cases. The global incidence was around 800,000 new cases, with a death toll of approximately 400,000 in 2020.[2] Head and neck cancers exhibit high heterogeneity concerning the primary tumor site, histology, tumor origin, and prognosis.[3]

The epidemiology of head and neck squamous cell carcinoma (HNSCC) has undergone significant changes in recent decades. Major risk factors contributing to the malignancy transformation in the head and neck region include exposure to tobacco (both active and passive smoking) and alcohol consumption, which have synergistic effects.[4] These changes manifest as a decline in the incidence of tobacco-related HNSCC, while the incidence of HNSCC associated with human papillomavirus (HPV) has shown a drastic increase.[5]

Over the past few decades, the etiology of head and neck cancer has been linked to high-risk human papillomavirus (HPV) infections, particularly HPV-16 and HPV-18 in the oropharyngeal region (including tonsils and the base of the tongue). The rise in oropharyngeal cancer incidence related to HPV has been predominantly reported in developing countries, and HPV status strongly correlates with favorable treatment responses and survival rates.[6]

Methods

The literature review adheres to ensuring a comprehensive and transparent investigation into the role of human papillomavirus (HPV) in head and neck squamous cell carcinoma (HNSCC). The literature search from PubMed with keywords related to "HPV" and "head and neck squamous cell carcinoma.

Study selection followed a two-step screening process, with initial screening of titles and abstracts for relevance, followed by a full-text assessment against predefined inclusion and exclusion criteria. As this review is based on previously published studies, ethical approval was not applicable, and all included studies were assumed to have been conducted in accordance with ethical standards. The Methods section provides a structured and rigorous approach to the review, ensuring an analysis of the literature on HPV's role in HNSCC.

Results

We used 16 articles to review the role of HPV in HNSCC carcinogenesis. Review of the extracted literature demonstrated the role of HPV in two various ways was leading malignancy change in epithelial squamous cells from the head and neck region.

Diagnosis of Head and Neck Squamous Cell Carcinoma (HNSCC)

The diagnosis of HNSCC is established based on histopathological examination, where tumor cells with squamous epithelial differentiation are identified, along with invasion into the stroma. Characteristic features of squamous differentiation include keratinization (with or without pearl formation) and the presence of intercellular bridges (Figure 1). Invasion is marked by the disruption of the basal membrane of the surface epithelium and the observation of tumor cell growth downward, forming sheets, islands, or clusters of tumor cells in the underlying tissue. In poorly differentiated cancers, tumor cells typically grow to form sheet-like or ribbon-like structures with large, round nuclei and prominent nucleoli.[7]

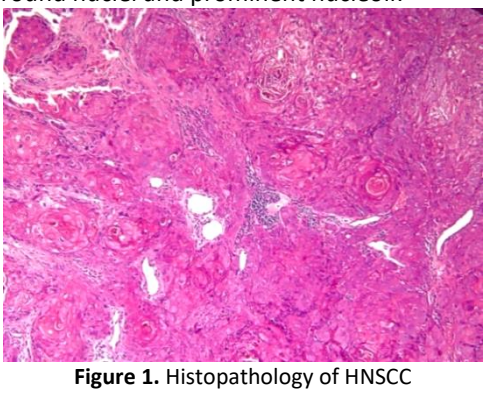

Figure 1. Histopathology of HNSCC

Desmoplastic stromal reactions are associated with tumor cell invasion. Microscopic features include the proliferation of myofibroblast cells, excessive synthesis and deposition of extracellular matrix, and neovascularization. Tumor cells can also infiltrate blood vessels or lymphatics and spread among nerve tissues.[7]

Human Papillomavirus (HPV)

Human papillomavirus (HPV) is a circular, non-enveloped virus with double-stranded DNA. The virus encodes 8-9 proteins in approximately 8000 base pairs, including two regulatory proteins (starting from early genes E1 and E2), three oncoproteins (E5, E6, and E7), and two capsid structure proteins (starting from late genes L1 and L2). HPV has the ability to infect skin or mucosal tissues (Figure 2) HPV infection in head and neck cancer is linked to oral sexual habits, exposing the oral mucosa to the virus.

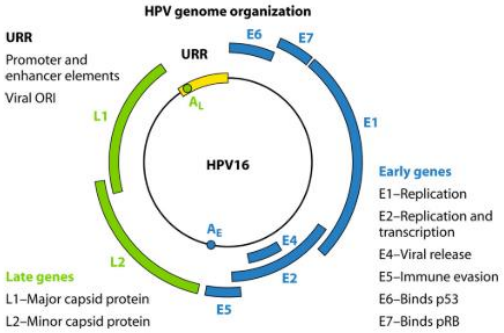

Figure 2. Genome of HPV[8]

There are approximately 179 known HPV genotypes divided in to two categories: low-risk HPV and high-risk HPV. This division is based on the virus's ability to induce normal cell changes into cancer. The most common high-risk HPV types causing cancer are HPV types 16, 18, 31, 33, 35, 45, 51, 52, and 56. HPV types 16 and 18, identified in 80% of HNSCC cases, can cause cancer in the cervix, head and neck, anus, vagina, vulva, and penis.[9] These strains can manipulate cellular pathways in infected cells, inducing uncontrolled proliferation and suppressing apoptosis.

The capsid proteins of HPV, L1 and L2, are responsible for tissue-specific infection. Replication is controlled by E1 and E2 proteins, regulating the transcription of other viral genes.[6] Cells infected with high-risk HPV encode oncoproteins E6 and E7.[10] E6 and E7 oncoproteins cooperate to inhibit apoptosis, promote uncontrolled cell proliferation, and induce genetic instability.[6]

The onset of malignancy begins with the inactivation of the tumor suppressor gene p53 by E6, activating ubiquitin ligase E6AP and resulting in p53 degradation. Meanwhile, E7 inactivates the retinoblastoma tumor suppressor protein (pRb) by blocking the interaction between Rb and E2F, causing E2F repression. Both events lead to the overexpression of p16 and initiate uncontrolled cell growth (Stadler et al., 2008). Both E6 and E7 oncoproteins, encoded by HPV-16, functionally disrupt cell cycle regulation and the DNA repair pathway, inducing genetic and epigenetic changes in the molecular progression of HNSCC (Stadler et al., 2008). The function of E5 protein is not fully understood, but it is believed to cooperate with E6 and E7 in causing malignant transformation and playing a crucial role in evading the immune system.[6]

Discussion

Pathogenesis

In HPV infection, the virus infects primitive/immature keratinocyte cells in the basal layer due to microtrauma, such as mucosal epithelial abrasion that exposes the basal membrane and basal cells. Even in the oropharynx, the virus can enter through epithelial crypts and infect the basal layer without requiring surface epithelial damage.[11] After infecting basal cells, viral DNA replicates, undergoes the cell cycle, and amplifies a number of viral copies to about 50-100 copies per cell. Infected cells leave the primitive compartment and enter the epithelium proliferation compartment (in the spinous and granular layers). Here, a plasmid maintenance phase occurs, where the virus and cell replicate together.

The HPV oncoproteins E6 and E7, especially high-risk types, are crucial components in the transformation of normal cells into malignant ones. The virus's E6 protein can bind to ubiquitin ligase (E6AP) from the host cell and then transfer ubiquitin to the p53 protein, causing p53 damage. The E6-E6AP-p53 complex can block the p21 protein, triggering disruptions in the cell cycle. The E6 protein can also bind to the c-Myc protein, resulting in the upregulation of telomerase reverse transcriptase (hTERT), an enzyme protecting against telomere erosion (Figure 3).[12]

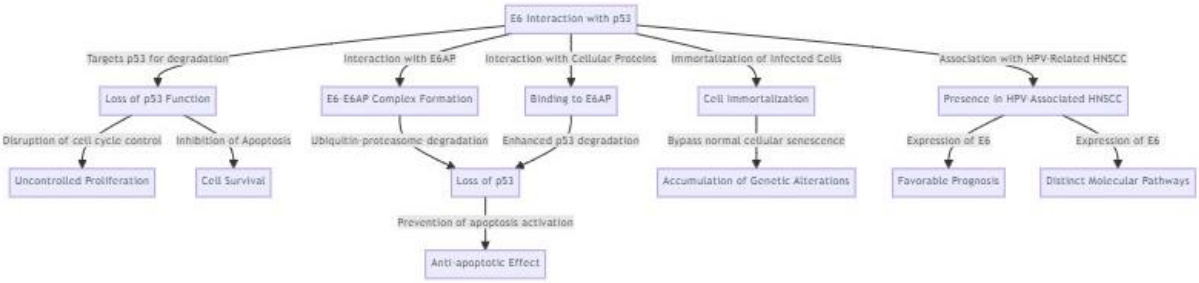

Figure 3: Role of HPV E6 Protein. HPV E6 protein binding to E6AP causes p53 damage. HPV E6 also activates hTERT, preventing telomerase erosion, making the cell immortal and transforming into a cancer cell.[12]

Meanwhile, the HPV E7 protein can bind to the retinoblastoma protein (pRb) and prevent it from forming a complex with the transcription factor E2F. This causes E2F to become free and induces cell cycle progression. The HPV E7 protein also inhibits the function of the p21 protein, a potent cyclin-dependent kinase inhibitor. Loss of the pRb-E2F complex causes overexpression of the p16 protein (Figure 4).[12]

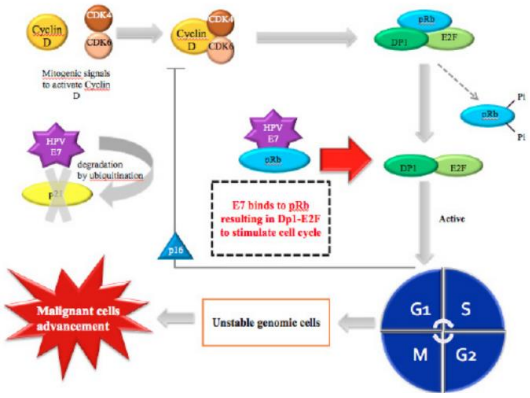

Figure 4: Role of HPV E7 Protein. In the normal state, hypophosphorylated pRb forms a complex with E2F. E2F transcription factors then bind to protein DP1 as a heterodimer and control the cell cycle by regulating the transcription of many genes. Consequently, the cyclin-CDK4/6 complex promotes cell cycle progression through the G1-S phase, resulting in the phosphorylation of pRb. Phosphorylated Rb then releases E2F/DP1 from DNA, allowing entry into the next stage of the cell cycle. Without mitosis signals, the HPV E7 protein also binds to pRb at the restriction point (R), causing the release of the E2F/DP1 complex, thus autonomously driving the cell cycle process. The HPV E7 protein can then degrade the p21 protein, a cell cycle regulator, through ubiquitination.[12]

Under normal conditions, p16 binds to CDK4/CDK6 to inhibit the interaction between cyclin D and CDK4, resulting in Rb hypophosphorylation and cell cycle restriction. In normal epithelial cells, p16 can only be detected in the basal and suprabasal layers where actively proliferating cells are found. In HPV-negative HNSCC, a decrease in p16 expression is observed. In HNSCC, the HPV E7 protein binds to pRb, disrupting p16 regulation. As a compensatory mechanism, overexpression of p16 is observed both in the cytoplasm and nucleus of HPV-infected tumor cells (Figure 5).[12] Both processes can lead to increased p16 expression as a negative feedback due to the absence of pRb that can control the cell cycle. Therefore, the overexpression of p16 is considered a surrogate marker for HPV infection.[13]

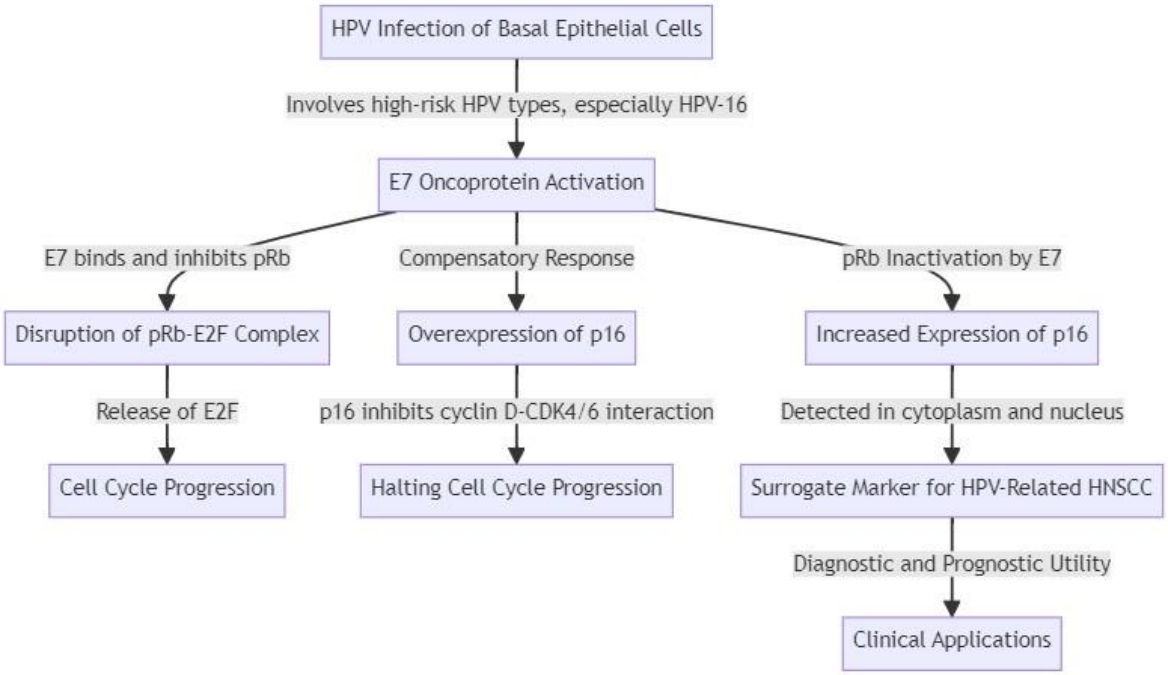

Figure 5. Overexpression of p16 Protein in Infected Cells. In the normal state, p16 inhibits the interaction between cyclin D and CDK4, causing hypophosphorylation of pRb. Meanwhile, the E7 protein causes uncontrolled transcription and translation of the p16 gene by competitively binding to pRb with E2F. As a result, there is a decrease in the levels of the E2F-Rb complex that regulates p16 transcription and translation, leading to the overexpression of p16.[12]

Clinical Implication

The referenced literature offers valuable clinical insights into the diagnosis of head and neck squamous cell carcinoma (HNSCC) resulting from human papillomavirus (HPV) infection. The epidemiological perspectives contribute, shedding light on dynamic trends in oral cancer incidence within the head and neck region. This findings underscore the importance of adapting diagnostic approaches to accommodate evolving etiological factors.[1] In concordance, its emphasize the pivotal role of HPV, particularly high-risk types like HPV-16 and HPV-18, in the carcinogenic process of head and neck cancers.[9] Consequently, a comprehensive diagnosis of SCC in these regions necessitates not only an examination of histological features but also the detection of HPV infection for a thorough understanding.[14]

Another clinical implication is contribute into the prognosis of SCC. HNSCC related to HPV infection has a more favorable outcome compared to those caused by alternative risk factors.[15] This distinction has direct implications for patient management and treatment decisions, advocating for tailored therapeutic approaches based on HPV infection status. Moreover, the utilization of p16 as a surrogate marker, as emphasized by emerges as a valuable diagnostic tool indicating HPV-related head and neck cancers. This serves as a crucial factor for precise risk assessment and aids in treatment planning.[16]

The study underscore the significance of evidence-based management strategies, emphasizing the need for tailored therapeutic approaches grounded in the clinical characteristics of individual patients, including their HPV infection status.[4] This signifies a paradigm shift towards personalized medicine in the diagnosis and treatment of head and neck cancers. In conclusion, the clinical implications of HPV infection on HNSCC diagnosis encompass epidemiological awareness, the centrality of HPV detection, improved prognosis assessment, and the integration of molecular markers like p16 into diagnostic protocols.[4]

Conclusions

The carcinogenesis and malignant transformation of HPV-associated HNSCC (high-risk types) occur through the action of E6 and E7 proteins. The HPV E7 gene can bind to hypophosphorylated pRb, allowing cells to pass the

G1 checkpoint and enter the S phase of the cell cycle. Meanwhile, the E6 gene binds to p53 and ubiquitinates this protein. This combination leads to abnormal cell cycle progression, causing cells to escape cell cycle control and undergo malignant transformation.

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Declarations of competing interest

No potential competing interest was reported by the authors.

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