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Literature review

Pathogenesis of oral cancer caused by human papilloma virus

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ABSTRACT

Introduction: Oral cancer represents 1-2% of all cancers in the body, 90% of which is correspond to oral squamous cell carcinoma (OSCC). Risk factors traditionally involved in the development of oral cancer are advanced age, male sex, and prolonged expo-sure to habits such as alcohol, tobacco, and betel nut. In recent years, the increasing incidence of OSCC in young patients without exposure to classical risk factors suggests the presence of other possible pathogenic agents, especially the Human Papilloma Virus (HPV).

Objectives: To reveal on the molecular development of OSCC by HPV as an oncovirus and its characteristics.

Results: The studies show the high oncogenic risk presented by HPV subtypes 16 and 18 acting via their E6 and E7 proteins, directly affecting p53, on retinoblastoma (pRb) and other enzymes involved in regulation of the cell cycle like PI3K, thereby altering processes of cellular apoptosis, proliferation and differentiation.

Conclusions: HPV plays an important role as a carcinogen in the onset of OSCC associating a more favorable prognosis compared to other etiologic factors. The process of oncogenesis in the development of OSCC caused by HPV is linked to the high-risk subtypes, as well as the expression of viral proteins E6 and E7, which are responsible for inhibiting the activity of cell cycle tumor suppressor genes.

KEYWORDS

Oral cancer; Human papilloma virus; Oncoproteins; Oncogenesis

INTRODUCTION

Oral cancer comprises 1-2% of all cancers in the body, making it the sixth most common neoplasm worldwide.[1,2] Within this group, the most common entity is oral squamous cell carcinoma (OSCC), which constitutes 90% of all cancers of the oral cavity.[2] The prognosis for OSCC is determined by the stage at diagnosis, following the T (Tumor), N (Metastasis to lymph nodes, M (Distant metastasis) classification.[3] Tumors in the floor of the mouth associates the worst prognosis. The survival rate depends primarily on the tumor stage at the time of diagnosis, generally abut 50% at 5 years. Risk factors traditionally involved in the development of oral cancer are advanced age, male sex, and prolonged exposure to habits such as alcohol, tobacco, and betel nut.[4-8] There are also other predisposing factors like radiation therapy, immunosuppression and chronic irritation.[9] In recent years, different authors have studied infectious carcinogens, specifically the participation of the human papilloma virus (HPV), since there is evidence that it may play an important role in the development of this type of cancer, especially in carcinoma of the cervix.

The increase in the incidence of OSCC in young patients without exposure to classical risk factors suggests the presence of other possible pathogenic agents, especially HPV[9], which is the most common sexually transmitted viral infection, being present in 12-63% of all OSCC cases.[10,11] HPV is widely known to be a pathogenic agent that causes different benign mucocutaneous lesions such as verruca vulgaris, squamous papilloma and condyloma acuminatum.[4,6] In the oral cavity, this virus is responsible for different oral lesions according to its subtype, with 6 and 11 being responsible for squamous cell papilloma and 2 and 4 for verruca vulgaris[2], 13 and 32 for lesions such as Heck's disease or focal epithelial hyperplasia, while subtypes 16 and 18 have a high potential for malignancy affecting the head and neck region (subtypes 31, 33, 51, 55, 58...).[4,6,10]

Some studies show that 70.59% of OSCC are positive to HPV and have shown a higher prevalence in subtype 18 compared to subtype 16.[12] In addition, one study concludes that 48% of OSCC located in the tongue are positive for this virus.[13] A systematic review revealed a lower prevalence of HPV-16 in OSCC (0-2%), being greater in oropharyngeal carcinomas (50-80%).[14]

In general, HPV-associated OSCC occurs more frequently than HPV-negative OSCC in young people, with a mean age difference of 4-10 years. This may be associated with a current increase in the number of sexual partners in young people and adolescents compared to previous decades. OSCC has also been shown to be positive for HPV in individuals who have higher levels of education, being 5 times more frequent in men.[1,15]

TABLE 1. DIFFERENCES BETWEEN HPV-POSITIVE AND HPV-NEGATIVE[3, 6, 16].

Therapy	HPV-positive tumors	HPV-negative tumors
Molecular characteristics	Altered p53, increased expression of p16, decrease in RB expression, degraded p53.	Mutación Mutation in p53, genomic instability.
Pathogenic characteristics	Direct transformation by oncoproteins E6 and E7.	Use of ethanol and tobacco and poor oral hygiene - chronic inflammatory state with free radicals - damage in DNA.
Cellular composition	T Cells (CD3+, CD4+, CD8+, CD34+), NK cells, B cells and monocytes.	Endothelial cells, keratinocytes and fibroblasts in the epidermis.
Epidemiological characteristics	Male, young, Caucasian race, increased number of sexual partners, marihuana use.	Older population, African-Americans, tobacco and ethanol users, poor oral hygiene
Clinical Characteristics	Early T stage with extensive lymph node involvement. Cystic or multilevel tumor phenotype.	Late T stage. Generally, less lymph node involvement.
Metastatic characteristics	Distant metastasis occurs after chemotherapy with a distinct pattern to the lung, liver, bone and other tissues. Requires alternative monitoring strategies.	Local and lung metastasis. Reduction of the distant metastasis pattern in bone, liver and other sites.

Table 2. Histopathology differences between HPV-positive and HPV-negative[6].

HPV-positive tumors	HPV-negative tumors
Not associated with epithelial dysplasia or keratinization.	Keratinization present.
Well differentiated or undifferentiated.	Moderately differentiated.
Has lymphocyte invasion.	Not invaded by lymphocytes.
Lobular growth.	No lobular growth.
Basaloid morphology.	No basaloid variants present.

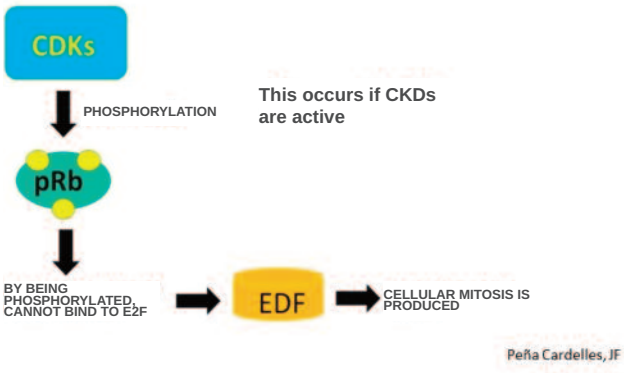

Figure 1. Phosphorylation of pRb.

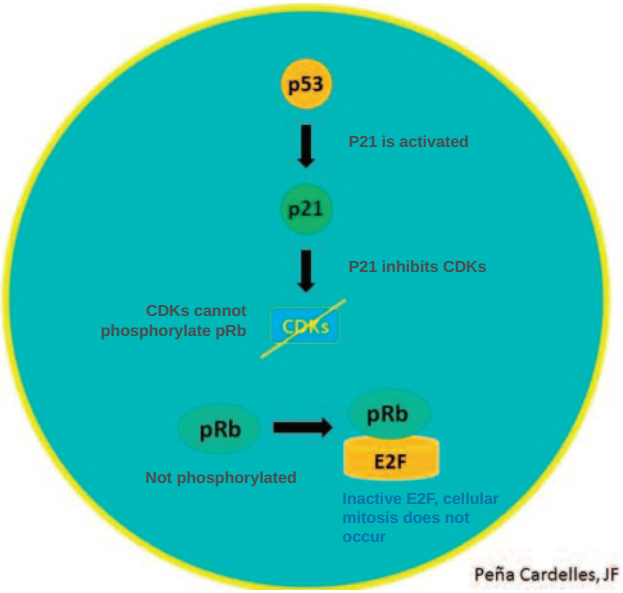

Figure 2. Action of tumor suppression proteins p53 and pRb.

HPV induces a series of changes in chromosomal profiles and gene expression in the tumor lesions where it is present, constituting a different biological type in comparison to tumor lesions associated with traditional risk factors, to the point that patients with HPV-positive tumors have a greater long-term survival rate[5] (Table 1). Histopathologically, there are also differences between HPV-positive and HPV-negative tumors[17] (Table 2).

The purpose of this article is to describe the pathogenesis of OSCC by HPV through a review of the most recent scientific literature, aimed to understand the most important molecular processes responsible for the development of tumor pathology, as well as the specific characteristics of the entity.

HPV AND CARCINOGENESIS

Viruses are microorganisms that need a host cell to complete their lifecycle, making them obligate intracellular parasites. According to this relationship, cells have developed strategies to control viral replication and, at the same time, viruses have developed mechanisms to evade the host cell's defenses.

The defense mechanisms of host cells occur during the cell cycle, which is the process by which the cell can carry out cellular mitosis and replication of its genetic material. The cell cycle comprises different phases: G1, S, G2, M and a fifth phase known as G0 in which the cell remains out of the cell cycle.[3]

Table 3. HPV proteins and their respective functions[19-24].

Protein	Protein function
L1	Largest protein, involved in the virion assembly process.
L2	Essential for the transport of DNA to the interior of the host cell's nucleus.
E1	Helps E2 form a protein complex for replication of the viral DNA.
E2	Viral transcription factor. Helps E1 facilitate replication of viral DNA.
E4	Involved in the modification of viral DNA after transcription.
E5	Regulates growth factors and cell proliferation.
E6	Inhibits p53.
E7	Inhibits pRb, activates E2F, altering the G1/S control point.

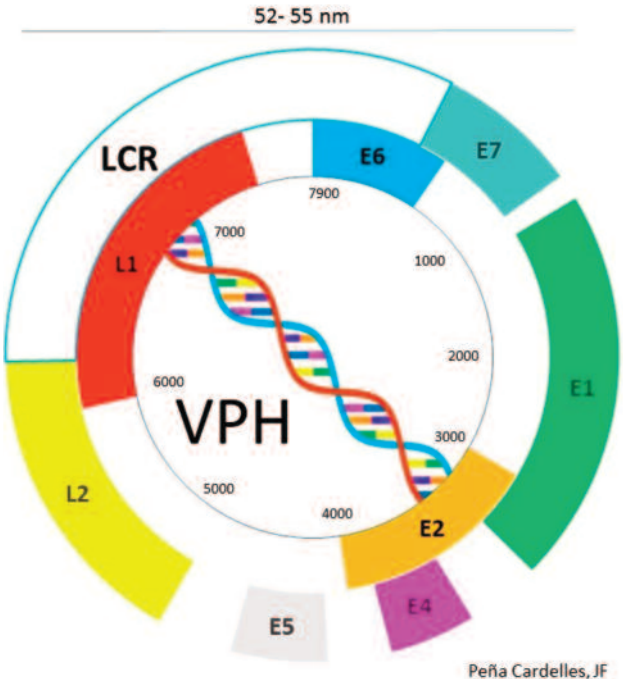

Figure 3. Structure of the human papilloma virus (HPV).

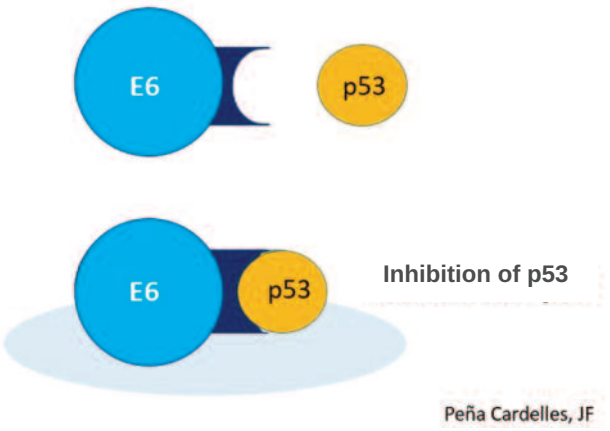

Figure 4. Inhibition of p53 by the E6 viral protein.

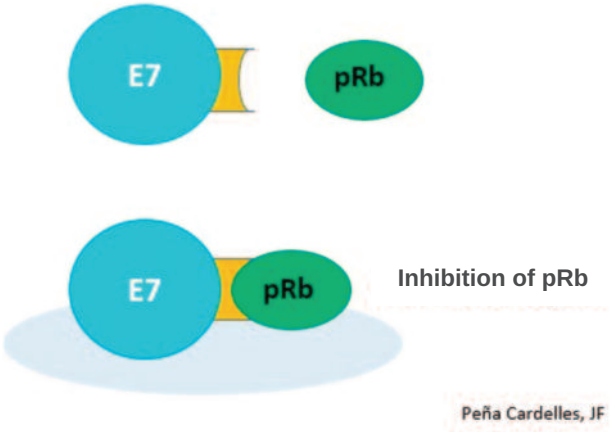

Figure 5. Inhibition of pRb by viral protein E7

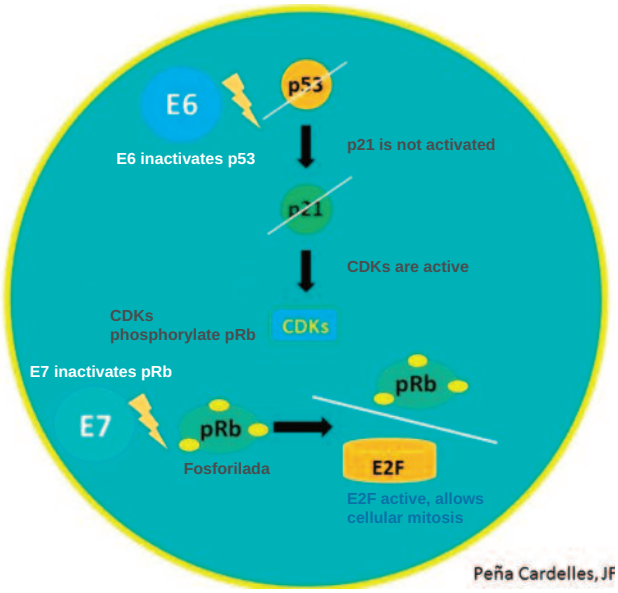

Figure 6. Inhibition of tumor suppression proteins p53 and pRb by viral proteins E6 and E7. Consequences of the mutation occurring in cell DNA due to HPV.

In order to understand the carcinogenesis process caused by HPV, it is important to remember that the tumor suppression protein involved in the cellular cycle is known as p53 (named after its molecular weight). P53 is normally found in small amounts in the cell, but in the face of cell damage, it is synthesized in large quantities. The p53 gene is capable of stopping the cell cycle in the G1, S and G2 phases. In addition, if cell damage continues, it can cause controlled apoptosis of the cell.[3]

P53 acts as a transcriptor in order to activate the p21 gene, which produces the protein p21 capable of inhibiting cyclin-dependent kinases (CDKs), thereby inhibiting the cell's mitotic activity via the retinoblastoma (pRb) protein's hypophosphorylation state (not being phosphorolysed by CKDs). PRb can be found in two states: hypophosphorylated and hyperphosphorylated. In the hypophosphorylated state, pRb is active and can perform its tumor suppressor function by binding and blocking E2F (a protein that, unbound, allows for the

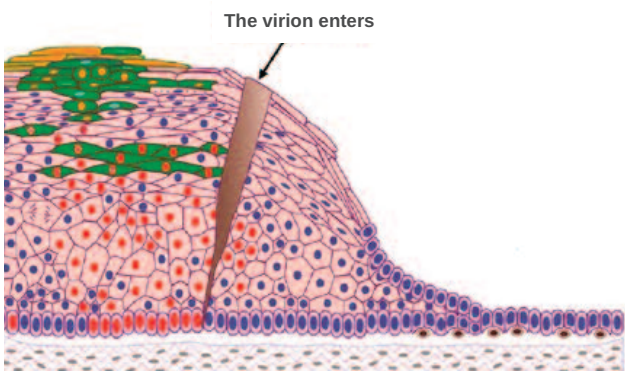

Figure 7. The virion enters the basal membrane through micro-cracks present in the oral mucosa in order to infect basal keratinocytes. Modified from Doorbar et al.[28]

progression of G1 to S), thereby impeding the cell's progression through the cell cycle[3] (Figures 1 and 2).

The process of HPV-related carcinogenesis is related to the cell cycle inside the host cell. HPV is a 52-55 nm virus made up of a double chain of DNA. The virus genome contains three early genes called E (Early), some late genes called L (Late) and some genes called LCR (Long Control Region). The E region is crucial for viral replication and transcription. The L region is responsible for making structural proteins (L1 and L2) that are essential for assembly of the virions. LCR participates in replication and transcription of the viral DNA (Figure 3).

The virus has proteins such as E1 to control its own replication. Upon entry into the cell nucleus, the viral genome produces a mutation in the DNA, inhibiting the E6 protein for p53 and the E7 protein for pRb (the transcription of proteins E6 and E7 become regulated by the viral E2 protein)[3,6,18] (Table 3).

P53, the function of which we specified above (regulation of the cell cycle and apoptosis) will not activate p21 since p53 is inhibited by the E6 viral protein. Therefore, the CDKs will phosphorylate pRb, leaving the E2F transcription factor free (when it is bound to pRb, E2F is inactivated) and leading to both the progression from G1 to S of the cell cycle and cell mitosis[10,25] (Figure 4).

In addition, the E7 gene codes for the E7 protein which inactivates it if bound to pRb (a key protein in avoiding cell mitosis). This prevents it from binding to the E2F transcription factor, thereby promoting progression of the cell cycle[1,5,7,10,25] (Figures 5 and 6).

This functional inactivation of pRb includes increased expression of the p16 tumor suppression protein.[1,25] This protein plays an important role in regulation of the cell cycle and mutations that occur increase the risk of developing various cancers. In fact, according to some studies, the majority of HPV-positive OSCC show an overexpression of the p16 protein.[26] For this reason, various studies have suggested that p16 positivity may be used as a biomarker for HPV-associated tumors and as a prognostic factor for OSCC.[27]

Finally, E5 increases the action of CDKs, thereby promoting proliferation and inhibiting cell differentiation. The E4 protein helps in the assembly of

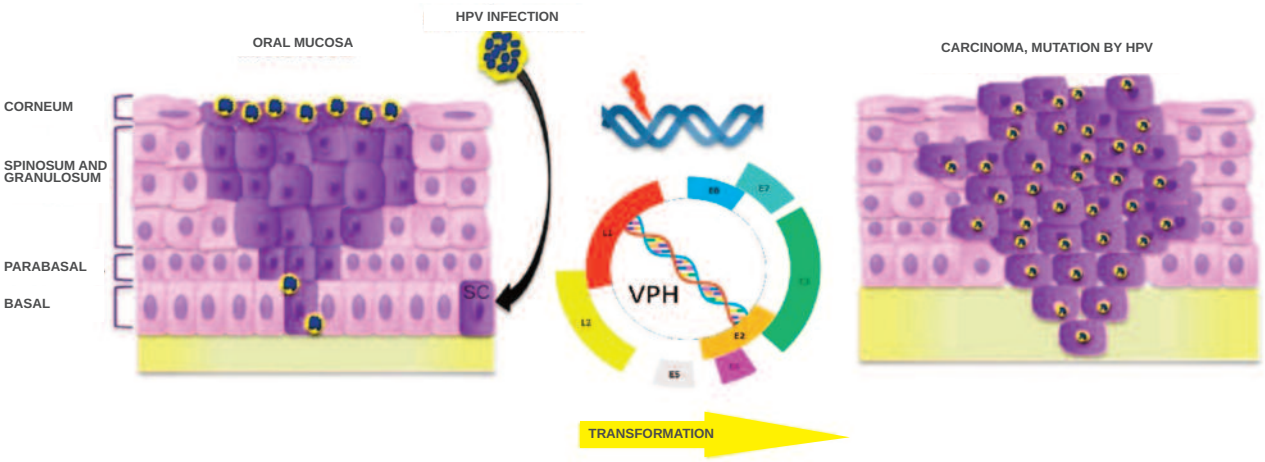

Figure 8. Mitosis of cells with a mutation caused by HPV, until reaching the stratus corneum and making the presence of a tumor in the oral epithelium apparent. Modified from Pullos et. al.[29]

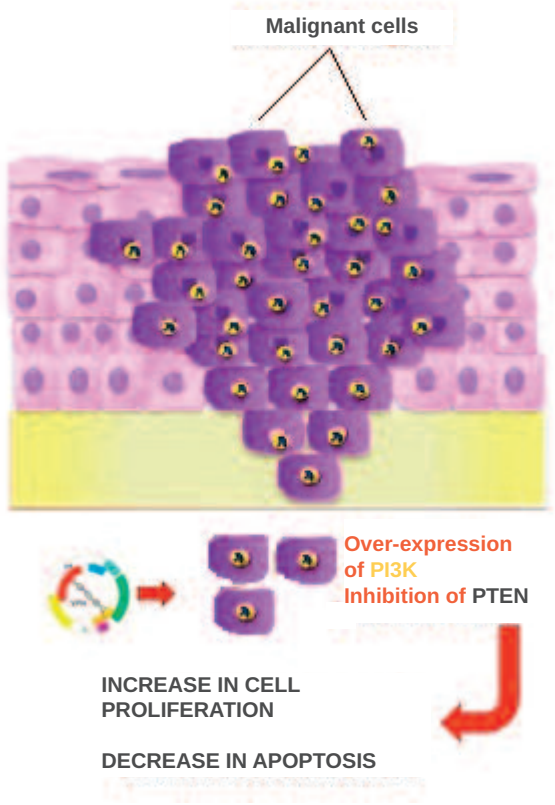

Figure 9. Action of HPV on PI3K and PTEN. Modified from Pullos et. al[29]

proteins L1 and L2 for the formation of virions, as well as the entry of the virus into the cell nucleus.[4,6,10] Thus, there is an infected cell whose genetic material, suppressor genes and tumor suppressor proteins are altered in such a way that it is not capable of controlling its own cell cycle, thereby transforming into potentially malignant cell.

The HPV virion passes through micro-cracks to infect oral basal epithelial cells. Once there, the process of DNA mutation begins inside the host cell. The virion enters the interior of the cell and, through the action of the L2 protein, is capable of integrating its genome into the nuclear DNA structure of the host cell[6] (Figure 7).

When the host cell later divides and starts to differentiate into mature keratinocytes, the DNA alterations increase, as does the number of malignant cells. Finally, the cells, initially the basal cells, begin to increase in number within the epithelial layers until reaching the stratum corneum and the presence of the tumor becomes evident in the oral epithelium (Figure 8).

Several studies have shown that OSCCs likely caused by HPV have a better prognosis than those that are HPV-negative. This can be explained by studying tumor stem cells (TSC). A TSC is defined as a cell within a tumor that can renew itself automatically, supporting tumor growth and generating cancerous cell lines that make up the majority of tumor cells, which is why they are known as tumor-initiating cells or tumorigenic cells. The tumor cells present in OSCCs that express high levels of CD44 antigen may have TSC properties, having increased metastatic potential and higher resistance to treatment. Curiously, the marker for CD44 enrichment is lower in patients with HPV-positive OSCC than in patients with HPV-negative OSCC. An initial idea was that patients with HPV-positive OSCC would respond more favorably to treatment than patients with HPV-negative OSCC because HPV-positive tumors could harbor fewer TSCs. However, several studies revealed that the appearance of TSC is greater in HPV-positive tumors than in HPV-negative tumors. It has been shown that patients with HPV-positive OSCC have a better prognosis and respond more favorably to radiation and chemotherapy than patients with HPV-negative OSCC, probably due to the TSC phenotype or quality regardless of its quantity. They have some properties that make them more susceptible to anti-tumor therapy.[29,30]

The most widely studied route for explaining the existing relationship between HPV and OSCC is inhibition of p53 and pRb. However, other mechanisms of action related to the cell cycle are currently being described and may ultimately explain the appearance of a tumor cell. In this regard, the best prognosis for HPV-related OSCC may also be explained by some studies that investigate the route by which HPV may improve its replication, involving deactivation of DNA repair (DDR), specifically on ATM and ATR kinases. This suppression of DDR may partially explain why HPV-positive cells are more susceptible to radiation therapy since it is not possible to counteract the accumulated damaging process in DNA prior to oncological treatment when DDR is not activated.

Other studies investigate the phosphoinositide 3-kinase (PI3K) signaling route. These enzymes are crucial in numerous cell functions involved in cell growth and

survival, promoting cell proliferation and avoiding apoptosis. It has been confirmed that 55% of cases of HPV-positive carcinoma contain a mutation and overexpression of PI3K. This alteration in PI3K is also related to suppression of phosphatidilin-sitol-3,4,5-triphosphate 3-phosphatase (PTEN), an enzyme considered to be a tumor suppressor that acts as an agonist in the PI3K signally pathway and has been shown to be altered in the presence of HPV[29,32] (Figure 9).

Currently under research is the role played by HPV in autophagia, an intracellular homeostatic process in which aged organelles and long-chain proteins are degrading, which acts as a mechanism of cellular recycling. It has been observed that the virulence of HPV can be mediated by autophagy in such a way that biomolecular inhibition of this process would increase the invasive capability of the virus.[33-35] This is because HPV-16 pseudovirions activate Akt and mTOR pathways in human keratinocytes, thereby inhibiting the first stages of autophagy during interaction of the virus with the cell.[23] The Akt route is an enzyme group that participates in the cell growth and survival process while mTOR regulates cell functions for multiplication and survival.[35,36]

The oncoproteins above-mentioned, E6 and E7, also modulate autophagy through two different pathways. First, E6 causes a restriction of nutrients in keratinocytes that leads to an increase in mTORC1 activity. This inhibits autophagy due to an increase in AKT activity. However, it has been shown that E7 produces the opposite effect, inducing autophagy in keratinocytes.[35] This binds with pyruvate-kinase-M2 (PK-M2), an enzyme that catalyzes the final step of glycolysis. This binding results in the dimerization of PK-M2, restoring nucleic acid synthesis and promoting cell proliferation. This dimerization of PK-M2 results in partial inhibition of glycolysis, which increases its intermediaries[36], thereby promoting synthesis of nucleic acids, lipids and amino acids and increasing autophagy-mediated cell survival mechanisms. This results in rapid cell proliferation and a resulting increase in tumor growth.[35,36] For this reason, it is believed that there may be a balance between oncoproteins E6 and E7 that would determine the role of autophagy in the pathogenesis of head and neck cancer.[34-36]

To a lesser degree, alterations of the tumor suppressor genes such as PBXW7 have been studied. This gene codes for a specific group of proteins called F-box that constitute the ubiquitin ligase complex involved in phosphorylation-dependent ubiquitination.

Ubiquitination is a process by which altered or unusable proteins are destroyed in proteasomes. Therefore, an alteration in this cellular recycling process would contribute to a higher probability of the appearance of potentially tumorous cells.[29]

Another gene that has been confirmed to be altered in the presence of HPV is NOTCH1, which codes for different transmembrane proteins involved in cell growth and in the regulation of interactions that occur with adjacent cells. Mutations in these proteins seem to contribute to alterations of the tumor cycle and promote the appearance of cancer. Viral protein E6 is also considered to have the ability to increase the expression of the EGFR (epidermal growth factor receptor) HBD3 protein. This protein promotes proliferation of keratinocytes in the mucosa, facilitating malignant transformation of the tissue.[8,29]

CONCLUSIONS

HPV plays an important role as a carcinogen in the onset of OSCC with a more favorable prognosis compared to tumors associated with other etiologic factors. The process of OSCC oncogenesis by HPV is determined by its high-risk subtypes, as well as the expression of viral proteins E6 and E7, which are responsible for inhibiting the activity of tumor suppressor genes of the cell cycle.

Other pathways that may be involved in the development of OSCC are currently under research, the majority of which are related to alterations in the cell cycle. It is important to clarify the pathogenic process in order to improve prevention at a clinical level, especially by vaccinating against HPV.

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