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HPV and Cervical Cancer: An Investigative Review into Molecular Biology, Immune Evasion and the Implications in Carcinogenesis

Diogo José Horst*

Department of Chemical Engineering, Federal University of São Paulo, Diadema – SP, Brazil

***Corresponding Author:** Diogo José Horst, Department of Chemical Engineering, Federal University of São Paulo, Diadema – SP, Brazil, E-mail: diogohorst@gmail.com

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Abstract

Infection caused by the human papillomavirus (HPV) is common among the sexually active population worldwide. With 200 known genotypes, 15 of them are considered high-risk oncogenic, with types 16 and 18 being most associated with anogenital and head/neck cancers. The cell cycle, consisting of the G1, S, G2, and M phases, is regulated by tumor suppressor genes such as Rb and p53, whose dysregulation can result in continuous replication of damaged cells. High-risk HPVs are related to anogenital neoplasias, and the immune response typically eliminates the initial infection, but HPV avoids immune responses during the productive phase of the infection. Viral proteins, including E1, E2, E5, E6, and E7, play critical roles in virus replication and evasion of the immune system. E1 and E2 affect the immune response, while E6 and E7 interact with tumor suppressor genes, promoting viral replication and inhibiting apoptosis.

Keywords: Cervical Cancer; HPV Infection; Early Detection; Immune Response; Pap Smear; Cytopathology

Introduction

In developing countries, cervical cancer still represents a public health challenge, even with prospects for a cure with early detection. Factors such as HPV type, immunological response, and genetic factors are associated with cervical carcinogenesis. Primary prevention involves reducing the risk of infection by HPV, transmitted mainly sexually.

HPV infection is very common. It is estimated that around 80% of sexually active women will acquire it throughout their lives. Approximately 290 million women worldwide are HPV carriers, 32% of whom are infected with subtypes 16, 18, or both. Comparing this data with the annual incidence of approximately 500 thousand cases of cervical cancer, it is concluded that cancer is a rare outcome, even in the presence of HPV infection. In other words, HPV infection is a necessary, but not sufficient, factor for the development of uterine cervical cancer. Manifesting itself from genital warts to cellular changes that, depending on the host's immunity and the pathogenicity of the agent, trigger neoplastic processes, HPV assumes a marked relevance among young women, with a notable incidence in the age group of 20 to 24 years [1,2].

HPV emerges as a prominent viral agent in public health due to its direct relationship with a wide variety of clinical conditions. As a double-stranded circular DNA virus belonging to the papilloma virus family, HPV has gained relevance due to its association with more than 200 distinct types to date. However, 40 carcinogenic agents have been identified in humans, which raises significant concerns for health professionals [3].

Demonstrating affinity for keratinized squamous epithelium, these viruses have an epitheliotropic propensity, and their life cycle is intrinsically linked to the maturation of squamous cells. The presence of viral DNA sequences in practically 99% of cervical tumors reinforces HPV as the central etiological agent of this neoplasia [1].

Early detection of cellular changes caused by HPV is crucial for preventing cervical cancer. The Pap smear, a cervical cytology technique developed by George Nicholas Papanicolaou, is a valuable tool in this process, allowing the identification of abnormalities before they develop into cancer. Aiming for a comprehensive understanding of these manifestations and their impact on women's health, the investigation seeks to contribute to improving early detection and treatment strategies with the aim of minimizing morbidity and mortality associated with HPV [1,2].

HPVs have the ability to infect basal cells in various epithelial tissues, such as the cervix, anus, and oropharynx, penetrating the basal layer through minor trauma. Viral proteins (E1, E2, E5, E6, and E7) play crucial roles in replication and immune evasion. Proteins such as E1 and E2 affect the immune response, while E6 and E7 interact with tumor suppressor genes, promoting viral replication and preventing apoptosis. Productive infection occurs in the middle layers of the epithelium, where E6, E7, E1, and E2 play fundamental roles in the amplification of the viral genome [4].

The E5, E6, and E7 proteins are central to the effects induced by HPV, interfering with several components of the immune response via interferon (IFN), essential for antiviral defense [4,5].

The E1 protein, central to HPV replication, regulates the immune response by interfering with the expression of genes associated with Toll-like receptor (TLR) signaling, interferon (IFN), and antiviral genes. E2, performing multiple functions, regulates viral replication and impacts the immune response by inhibiting the production of interferon (IFN). The E5 protein, with immunosuppressive functions, influences the expression of IFN and interferon-stimulated genes, favoring HPV replication. E6 and E7, essential in cellular transformation, impact the immune response by promoting viral replication, inhibiting apoptosis, binding to the cell's DNA, and degrading the p53 gene. The research highlights the complexity of the interactions between HPV proteins and the immune system, aiming to contribute to effective prevention and treatment strategies [6-9].

Within this context, this research aims to understand how HPV manipulates the immune system, highlighting the actions of the E1, E2, E5, E6, and E7 proteins. Having the main objective of comprehensively understanding the relationship between human papillomavirus (HPV) infection and the development of cervical cancer, exploring

the molecular mechanisms of infection, and immunological responses.

To this end, the following specific objectives were listed: Investigate the molecular mechanisms involved in the initial HPV infection, with an emphasis on viral proteins. To analyze the interactions between the HPV E6 and E7 viral proteins and components of the interferon pathway, investigate how these interactions contribute to the evasion of the immune system and the promotion of viral replication.To evaluate the role of viral proteins E1, E2, and E5 in regulating the immune response during HPV infection, explore their impact on the immune response.

State of Art

HPV infection is a sexually transmitted infection (STI) that affects a large proportion of the sexually active population worldwide. HPV is a small DNA virus that does not have an external envelope and has an icosahedron-shaped structure (DOORBAR, 2007). The structure of HPV includes a circular, double-stranded DNA genome that has about 8,000 base pairs. The genome is divided into three main parts: six early genes (E1, E2, E4, E5, E6, and E7) that encode essential proteins; two late genes (L1 and L2) responsible for the formation of the viral capsid; and the third part is a long control region (LCR) [10].

To date, there are 200 known HPV genotypes, and 15 have been classified as high oncogenic risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. The different types of high-risk HPV vary in their oncogenicity. The two types widely recognized around the world as the most oncogenic are HPV 16 and 18 [11].

High-risk HPVs have been associated with the development of several diseases, such as anogenital neoplasms, including cervical, vulvar, anal, and penile cancer. They are also related to a subgroup of cancers in the head and neck region, mainly oropharyngeal squamous cell carcinoma (OPSCC). The most common types associated with these diseases are HPV16 and HPV18 [12].

The division of a cell into daughter cells depends on four stages: the G1, S, G2, and M phases. During the G1 phase, the cell accumulates cytoplasmic materials to duplicate the DNA. At the first stop of the cell cycle (called the R checkpoint), the DNA status is checked before the cycle progresses. In the event of any abnormality in the genetic information, it must be repaired first, and in these cases, the cell cycle stops. In the next stages, called S and G2 phases, DNA replicas and the materials necessary for cell duplication are obtained, respectively. The last stage of the M-phase cell cycle is mitosis, that is, cell duplication. After cell division, the DNA code is transcribed in the nucleus into messenger ribonucleic acid. The latter transfers the genetic information to the cytoplasm, where the transfer RNA and the synthetic RNA will be responsible for the synthesis of proteins in the ribosomes [1,13].

The first tumor suppressor gene to be cloned was named the Rb gene after its initial discovery in retinoblastoma. The Rb gene is responsible for the production of a nuclear protein that controls gene expression. When the pRb pathway loses its function, it results in the loss of natural mechanisms for inhibiting cell cycle progression. Another crucial tumor suppressor gene is the p53 gene. When DNA is damaged, the p53 gene is activated, and its protein interacts with other proteins known as CDK/cyclin inhibitors. This set of actions interrupts the cell cycle at the R point during the G1 phase. When DNA repair is not possible, the p53 protein sends signals to other regulatory proteins, such as bax, bcl-2, and c-myc, which induce apoptosis. However, in cases in which the p53 gene loses one of its functions due to the deletion of one of its alleles, the R checkpoint does not occur during the cell cycle. This leads to the continuous replication of damaged cells, causing instability in the genome and the accumulation of mutations [1,14].

HPVs have the ability to infect basal cells in various epithelial tissues, such as the cervix, anus, and oropharynx, penetrating the basal layer through minor trauma. After penetration, the virus's genetic material remains secreted, functioning as an independent compartment. In this state, it exhibits minimal genetic activity and maintains a restricted number of copies, generally ranging from 20 to 100 copies per cell. This process is guided by the viral proteins E1 and E2. Productive infection, in turn, occurs in the middle layers of the epithelium, where initial proteins such as E6, E7, E1, and E2 play fundamental roles in the amplification of the viral genome. E6 and E7, for example, promote

entry into the S phase of the cell cycle and inhibit apoptosis, while E1 and E2 bind to the origin of replication of the HPV genome, enabling its maintenance and amplification during epithelial differentiation [4].

Furthermore, the E5 protein plays a crucial role in stimulating cell proliferation, recycling growth factors, and interfering with the immune response [15]. The main actions performed by each of the early HPV proteins (E1, E2, E5, E6 and E7) in the dysregulation of the antiviral immune response mediated by interferon will be described below. The effect of HPV proteins on interferon (IFN) production and the interferon-stimulated gene (ISG) signaling pathway is a critical point in understanding how the HPV virus manipulates the immune system [4,5].

The E1 protein, central to HPV replication, has been observed not only as a replicative motor but also as a regulator of the immune response (CASTILLO et al. 2014). It interferes with the expression of genes linked to Toll-like receptor (TLR) signaling, interferon (IFN), and antiviral genes, potentially impairing the identification and removal of HPV-infected cells [16].

The E2 protein, which performs multiple functions, including regulating viral replication, also has an impact on the immune response. It can inhibit the production of interferon (IFN) and interferon-stimulated genes, even after activation of IFN-β1. This ability suggests its role in immune system evasion, especially during viral replication and the development of HPV-related cervical cancer [17,18].

The E5 protein, with apparently paradoxical immunosuppressive functions, demonstrates its complexity. It can influence the expression of IFN-β1 and IFN-λ1, as well as interferon-stimulated genes (ISGs), a process that may favor the integration of the viral genome and HPV replication, potentially contributing to cervical cancer [6].

The E6 and E7 proteins emerge as essential regulators of the immune response. E6 interacts with crucial components of the interferon (IFN) pathway, leading to the degradation of IRF-3 and the suppression of IFN-β production, thus promoting viral replication [19]. E7, in turn, interferes with the translocation of the p48 transcription factor, affecting the production of IFN-α and antagonizing the cGAS-STING pathway (cGAS-STING is an interferon-induced protein in which it is produced to identify the presence of DNA virus in the cell cytoplasm), impairing the expression of IFN-β. Both E6 and E7 proteins impact other elements of the IFN pathway, such as the IFN-α receptor, STAT2, and STAT1, triggering a more comprehensive inhibition of the immune response [20-22].

In the upper layers of the epithelium, the L1 and L2 proteins are expressed, forming the viral capsid. Finally, the E4 protein contributes to the release of new viral particles, facilitating the collapse of cytokeratin filaments. It is worth noting that, in most cases, the initial HPV infection is effectively identified and eliminated by the host's immune response [5,10].

Although the E5, E6, and E7 proteins are mainly responsible for the effects induced by HPV, other early proteins also play relevant roles in viral persistence. For example, the E2 protein is essential for the amplification of the viral genome, but it is also associated with the generation of oxidative stress and apoptosis. Furthermore, the presence of the E2 protein is detected in the early stages of carcinogenesis. The E1 gene is not only expressed during productive infections but also throughout cervical carcinogenesis. This is indicated by the high levels of E1 mRNA observed during the progression stages of cervical cancer, suggesting its possible involvement in the carcinogenic process. These additional proteins indicate that although E6 and E7 play a central role in transformation, other HPV proteins can also influence various cellular processes, potentially contributing to virus-mediated immune evasion [23].

HPV induces dysregulation in several components of the immune response in the interferon (IFN) pathway, which is essential for the innate immune response. This is necessary for the virus to complete its life cycle, allowing viral persistence and, in exceptional cases, leading to the development of cancer. Interferons are part of a family of inducible cytokines. When a cell detects the presence of viral DNA, it triggers a series of signals that result in the production of interferon (IFN), an essential protein in the defense against viral infections. IFN acts as a warning signal for nearby cells, preparing other cells to fight the infection and activating signaling pathways that result in the activation of in-

terferon-stimulated genes (ISG) [24,25].

During the HPV genome amplification process, infected cells are detected by the body's immune surveillance mechanisms, which include natural killer (NK), dendritic cells, macrophages, and T and B lymphocytes. However, HPV has been shown to be highly effective in blocking immune responses. As a result, persistent infections become a frequent consequence of the natural history of the disease. Viral persistence paves the way for the integration of the viral genome into the host DNA, leading to the development of cancer, mainly due to the loss of the E2 open reading frame (ORF E2). This, in turn, results in the overexpression of the E6 and E7 oncogenes, triggering the process of cellular transformation [15].

An open reading frame (ORF) refers to a continuous sequence of nucleotides on a strand of DNA or RNA that can be read as a code for the synthesis of a protein. Each gene generally has three main open reading frames, and the E2 ORF here refers to one of these specific regions in the HPV genome, called E2. When "loss of the E2 open reading frame" is mentioned, we are talking about genetic changes that result in the inability to read or translate the genetic information contained in the E2 region. This loss may occur during HPV viral persistence.

The E5 protein also plays a crucial role during the transformation process induced by HPV due to its ability to promote cell proliferation and deregulate the immune response. Furthermore, the E5 protein drives cell proliferation, interfering with the host's immune response; it acts independently and has the ability to form oligomers, such as dimers and hexamers, when expressed in cell membranes, negatively impacting signaling pathways in the immune response. E5 is also associated with the reduction of the apoptosis activation mechanism and immune evasion [8,9].

The discovery that the E6 protein of high-risk HPV is capable of binding to the DNA of the infected cell, inducing the degradation of the p53 gene, led to the suggestion that this inactivation pathway may be directly involved in the neoplastic process that leads to cancer. cervical [8,15].

At this point, the E6 protein plays a role, in turn promoting entry into the S phase of the cell cycle and inhibiting apoptosis by binding to the cell's DNA and inducing the degradation of the p53 gene through the ubiquitin-dependent proteolytic pathway (SCHEFFNER et al., 1990). It has been demonstrated that HPV targets groups of enzymes responsible for the deposition and removal of acetylated marks from histone acetyltransferases (HATs) and histone deacetylases (HDAC) [26].

Methodology

This study uses the narrative-bibliographic review methodology to achieve its objectives. To conduct a bibliographic review, renowned scientific databases were used, such as Pubmed, Scientific Electronic Library Online, and Nature. The descriptors used included “HPV proteins," “HPV infection," “HPV pathophysiology," “HPV E6," “HPV E7," “cervical cancer," “high-risk HPV," and “immune response." Furthermore, the research was carried out on texts available online in Portuguese and English. The book "Citologia Clínica Cérvico-Vaginal" was also consulted, an atlas published in 2012 and available in the FURB library. Statistical data for 2023 were obtained from the official website of the National Cancer Institute [40].

Discussion

As demonstrated by [7], the mechanism by which the HPV-16 E6 protein negatively regulates p53 activity involves the active promotion of p53 degradation through the ubiquitin-dependent proteolytic pathway. However, it was seen that the transcriptional coactivator CBP/p300 is also a target of the Ad E1A and SV40 TAg proteins [27]. Through interaction with specific transcription factors, CBP/p300 regulates a variety of signal-modulated events [28].

The mechanisms by which CBP/p300 activates gene expression include the ability to modify histones and non-histone transcription factors through intrinsic or associated acetyltransferase activity [29]. This may explain, at least in part, why CBP/p300 is the target of SV40 and Ad E1A proteins. Recently published data also demonstrated that CBP/p300 activates p53-dependent transcription. Thus, part of the cell cycle inhibitory properties of CBP/p300 may result from its involvement in p53-regulated events. Indeed, one mechanism by which SV40 and aden-

oviruses can abrogate p53 function is by targeting the p53 cofactor CBP/p300, and, at least for Ad E1A, it has been shown that mutants deficient in CBP binding are no longer able to regulate p53 negatively [30].

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Interestingly, p53-dependent transcriptional down-regulation in vivo is not limited to SV40 TAg and Ad E1A but has also been demonstrated for high-risk HPV E6 proteins (MIETZ et al. 1992). However, to date, no interaction with the transcriptional coactivator CBP/p300 has been described for the HPV E6 oncoprotein. It can be argued that the ability of high-risk HPV E6 proteins to degrade p53 via the E6AP pathway may be sufficient to explain the abrogation of p53 transcriptional activity. However, adenoviruses also have the ability to degrade p53 through the E1B protein [32].

However, this interaction between viral proteins, such as HPV-16 E6, Ad E1A, and SV40 TAg, and the transcriptional coactivator CBP/p300 reveals an intricate mechanism of negative regulation of p53 activity. This interaction results in the abrogation of p53 transcriptional activity, playing a crucial role in cell cycle modulation and, potentially, contributing to neoplastic processes.

It is known that E7 interferes with the translocation of the p48 transcription factor, antagonizing the cGAS-STING pathway [21]. However, this HPV oncoprotein also has the power to bind and inactivate the hypophosphorylated retinoblastoma protein (pRB) [32]. Which eventually leads to the upregulation of p16 INK4A. P16 INK4A is a tumor suppressor protein that inhibits the binding of cyclin-dependent kinases (CDK) -4 or -6 to cyclin D, which regulates cell cycle checkpoints in the G1 phase [33].

Phosphorylation of pRb by G1 cyclin-dependent kinases releases E2F, leading to cell cycle progression into the S phase. Because E7 is able to bind unphosphorylated pRb, it can prematurely induce cells to enter the S phase, arresting the pRb-E2F complexes. More recently, it was discovered that E7 promotes the C-terminal cleavage of pRb by the calcium-activated cysteine protease calpain and that this cleavage is necessary before E7 can promote the proteasomal degradation of pRb. The function of the E7 protein allows HPV replication in the upper layers of the epithelium, where uninfected daughter cells normally differentiate and completely exit the cell cycle [13,34].

Furthermore, E7 binds to the CDK (kinase) inhibitor p27 (ZERFASS-THOME et al., 1996) and CKI p21 [35], confirming the abrogation of cell cycle inhibition. To evade the immune system, E7 also interacts with p48 [36], as well as with Interferon Regulatory Factor 1 (IRF-1) [37].

P600 was identified as a cellular target of E7 that contributes to anchorage-independent growth and cellular transformation [38]. Productively infected cells must express viral gene products in a defined order for infectious virions to be assembled at the epithelial surface.

During productive infection, cell cycle markers such as PCNA and MCMar are confined to the lower epithelial layers, with J. doorbar/lifecycle organization and biomarkers 309, their presence being a direct consequence of E6/E7 activity. The marker identifies cells that are undergoing genome amplification, with the E4 protein being the most abundant member of this group. Virus assembly follows genome amplification and is marked eventually by the appearance of capsid proteins (L1 and L2) in the upper epithelial layers. This suggests that infected cells express each of these markers during epithelial differentiation and that the extent of productive infection can be established by considering the moment and extent of its expression. During neoplastic progression, it appears that two types of changes can occur.

First, viral gene expression becomes dysregulated,

and E6 and E7 levels in basal and parabasal cells increase. Given the known functions of these proteins, this is predicted to be a significant event in stimulating the accumulation of genetic errors in the host cell chromosome. Integration eventually corrects E6/E7 expression in the cell, which further contributes to the chance of progression. The second type of change refers to the regulation of late events, which become progressively delayed as the degree of neoplasia increases. This can be seen by immunostaining as an increase in the thickness of the E7-expressing layers and a reduction in the extent to which E4 is expressed in the upper layers of the epithelium. It has not yet been established whether these two events are linked, as well as the precise mechanisms that regulate such activity [39].

The complex interactions between viral proteins, such as HPV-16 E6, Ad E1A, and SV40 TAg, with the transcriptional coactivator CBP/p300 reveal an intricate mechanism of negative regulation of p53 activity, playing a crucial role in modulating the cellular cycle and potentially contributing to neoplastic processes. The ability of HPV-16 E6 proteins to degrade p53 via E6AP is known, but the discovery that CBP/p300 is also targeted by Ad E1A and SV40 TAg adds complexity to the molecular mechanisms involved. On the other hand, the multifaceted interactions of the HPV E7 oncoprotein outline a complex landscape of cellular evasion and manipulation of the cellular environment. E7 influences the translocation of the p48 transcription factor, antagonizing the cGAS-STING pathway, compromising cell cycle control, and promoting the upregulation of p16 INK4A. The interactions of E7 with p27, p21, p48, IRF-1, and p600 suggest additional strategies for immune evasion and the promotion of cellular transformation.

Conclusions

HPV is a virus significantly capable of evading the host's immune system, facilitating its replication, and contributing to the development of persistent infections, which can lead to cervical cancer. The key mechanisms of E6 and E7 proteins play key roles in inactivating tumor suppressor genes essential for protection against infections and in manipulating the host's immune response, allowing viral persistence.

The present work sought to comprehensively understand the relationship between HPV infection and the development of cervical cancer, exploring the molecular mechanisms of infection, such as immunological responses. It has been demonstrated that HPV, a double-stranded circular DNA virus, is associated with up to 200 different types, 15 of which are considered carcinogenic agents in humans, highlighting types with high oncogenic risk, such as HPV 16 and 18. HPV infection is prevalent, affecting around 80% of sexually active women at some point in their lives.

The relationship between HPV infection and the development of cervical cancer involves exploring the molecular mechanisms of infection and associated immune responses. Throughout this research, it was seen that HPV uses several of its own proteins (E1, E2, E5, E6, and E7) to avoid the immune response by interfering with the interferon pathways. In all, we sought to understand the complexity of the interactions between viral proteins, focusing especially on the E6 and E7 oncoproteins and their influence on the negative regulation of p53 activity, highlighting the role of the transcriptional coactivator CBP/p300 in this process.

Cytopathological changes in the cervix caused by HPV infection, such as dysplasia, most of the time regress spontaneously. However, it is important to be aware that persistent high-risk HPV infections significantly increase the danger of developing cervical cancer. Therefore, it is essential to deepen our knowledge about the pathophysiology of HPV and its immune evasion mechanisms. The relationship between human papillomavirus (HPV) infection and the development of cervical cancer involves exploring the molecular mechanisms of infection and associated immune responses. Throughout this research, it was seen that HPV uses several of its own proteins (E1, E2, E5, E6, and E7) to avoid the immune response by interfering with the interferon pathways. In all, we sought to understand the complexity of the interactions between viral proteins, focusing especially on the E6 and E7 oncoproteins and their influence on the negative regulation of p53 activity, highlighting the role of the transcriptional coactivator CBP/p300 in this process.

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