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HPV and cervical cancer: an investigative review into molecular biology, immune evasion and the implications in carcinogenesis

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.

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Introduction

Cervical cancer remains a public health challenge in underdeveloped nations, despite the possibility of a cure through early identification. Cervical carcinogenesis is linked to factors including HPV type, immune response, and genetics.Primary prevention includes lowering the chance of contracting HPV, which is primarily spread through sexual contact. HPV infection is highly prevalent. Approximately 80% of women who engage in sexual activity are expected to develop it at some point in their life. 32% of the 290 million HPV-positive women in the globe are infected with subtypes 16, 18, or both. This data is compared to the yearly occurrence of over 500,000 instances of cervical cancer, leading to the conclusion that cancer is an uncommon result, even in the event of HPV infection. Put another way, HPV infection contributes to the development of uterine cervical cancer, but it is not a sufficient cause. HPV is becoming increasingly relevant to young women, with a noteworthy frequency in the 20–24 age group. It can manifest in genital warts or cellular alterations that can initiate neoplastic processes based on the host's immunity and the pathogenicity of the agent.[1–3]

Because HPV is directly linked to a wide range of clinical disorders, it becomes a major viral agent in the field of public health management. Being a member of the papilloma virus family, HPV is a double-stranded circular DNA virus that has become more prominent because it has been linked to over 200 different varieties of the virus to date. However, 40 carcinogenic substances have been found in people, which causes medical specialists to have serious worries.[4] These viruses have an epitheliotropic tendency and preference for keratinized squamous epithelium. Their life cycle is inextricably tied to the maturation of squamous cells. Nearly 99% of cervical cancers include viral DNA sequences, supporting HPV's role as the primary etiological agent of this neoplasia.[1]

The prevention of cervical cancer depends on the early diagnosis of cellular alterations brought on by HPV. George Nicholas Papanicolaou's cervical cytology technique, the Pap smear, is an important tool in this process since it enables the detection of abnormalities before they become cancer. With the goal of reducing morbidity and mortality related to HPV, the research aims to improve early identification and treatment options by gaining a thorough understanding of these manifestations and their effects on women's health.

HPVs can penetrate the basal layer by minimal damage and infect basal cells in a variety of epithelial tissues, including the cervix, anus, and oropharynx. The viral proteins E1, E2, E5, E6, and E7 are essential for both immune escape and viral replication. While E6 and E7 interact with tumor suppressor genes to promote viral replication and prevent apoptosis, proteins like E1 and E2 influence the immune response. E6, E7, E1, and E2 are essential for the amplification of the viral genome during productive infection, which takes place in the intermediate layers of the epithelium.[5] The E5, E6, and E7 proteins are crucial to the effects caused by HPV because they interfere with many immune response components through interferon (IFN), which is necessary for antiviral defense.[6] The E1 protein, which is essential to HPV replication, modulates the expression of genes linked to interferon (IFN), Toll-like receptor (TLR) signaling, and antiviral genes, hence controlling the immune response. E2, a multifunctional protein, inhibits the generation of interferon (IFN) to suppress the immune response and control viral proliferation. Due to its immunosuppressive properties, the E5 protein promotes HPV replication by affecting the production of IFN and interferon-stimulated genes. Important players in cellular transformation, E6 and E7 affect the immune system through attaching to the DNA of the cell, preventing apoptosis, stimulating viral replication, and p53 gene degradation. The goal of the research is to contribute to efficient preventative and treatment techniques by highlighting the intricate relationship between HPV proteins and the immune system.[7–10]

In light of this, the goal of this study is to comprehend how HPV modifies the immune system, with a focus on the functions of the E1, E2, E5, E6, and E7 proteins.Its primary goals are to investigate

the molecular processes of infection and immune responses, as well as to gain a thorough understanding of the link between human papillomavirus (HPV) infection and the development of cervical cancer. In order to achieve this, the following particular goals were stated: Examine the molecular processes behind the first HPV infection, paying particular attention to viral proteins. Examine how the interferon pathway's components and the HPV E6 and E7 viral proteins interact to learn more about how these interactions support viral reproduction and immune system evasion. Examine the effects of viral proteins E1, E2, and E5 on the immune system in order to assess how they affect the immune system during HPV infection.

State of art

A significant fraction of the world's sexually active population is afflicted with HPV infection, a sexually transmitted infection (STI). HPV is a little DNA virus with an icosahedron-shaped structure and no exterior envelope.[11] The genome of HPV is made up of roughly 8,000 base pairs of circular, double-stranded DNA. The genome is composed of three main sections: two late genes (L1 and L2) that are involved in the production of the viral capsid; six early genes (E1, E2, E4, E5, E6, and E7) that encode critical proteins; and a lengthy control region (LCR) that makes up the third section.[12] There are 200 known HPV genotypes to date, of which 15-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82-have been identified as high oncogenic risk types. The oncogenicity of the various high-risk HPV strains varies. HPV 16 and 18 are the two kinds that are most commonly acknowledged as being the most carcinogenic worldwide.[13] Numerous illnesses, including anogenital neoplasms, such as cervical, vulvar, anal, and penile cancer, have been linked to high-risk HPVs. Additionally, they have a connection to a subset of head and neck cancers, primarily oropharyngeal squamous cell carcinoma (OPSCC). The most prevalent kinds linked to these illnesses are HPV16 and HPV18.[14]

The G1, S, G2, and M phases are the four stages that determine a cell's ability to divide into daughter cells. In order to duplicate its DNA, the cell gathers cytoplasmic resources during the G1 phase. Before the cell cycle continues, the DNA status is examined at the R checkpoint, which is the first pause in the cycle. The cell cycle ends when there is an anomaly in the genetic code that needs to be fixed before continuing. The subsequent phases, known as the S and G2 phases, are when DNA copies and the components required for cell division are acquired, respectively. In the M-phase cell cycle, mitosis, or cell duplication, is the final stage. The DNA code is translated into messenger ribonucleic acid in the nucleus following cell division. The latter transports the genetic material to the cytoplasm, where the ribosomes' production of proteins is carried out by the synthetic and transfer RNAs.[1,15]

Named after its original discovery in retinoblastoma, the Rb gene was the first tumor suppressor gene to be cloned. The nuclear protein that regulates gene expression is produced by the Rb gene. The lack of natural mechanisms for blocking cell cycle progression occurs when the pRb pathway becomes dysfunctional. The p53 gene is another important tumor suppressor gene. The p53 gene is triggered upon DNA damage, and its product engages in interactions with other proteins referred to be CDK/cyclin inhibitors. During the G1 phase, this series of events disrupts the cell cycle at the R point. The p53 protein triggers apoptosis by sending signals to other regulatory proteins like bax, bcl-2, and c-myc when DNA repair is not feasible. The R checkpoint does not occur during the cell cycle, but, in situations where the deletion of one of the p53 gene's alleles causes the gene to lose one of its functions. As a result, injured cells continue to replicate, which causes genetic instability and the accumulation of mutations.[16]

HPVs can penetrate the basal layer by minimal damage and infect basal cells in a variety of epithelial tissues, including the cervix, anus, and oropharynx. The genetic material of the virus stays secreted after penetration and functions as a separate compartment. It has very little genetic activity in this state and only a small number of copies-usually between 20 and 100 copies per cell. The viral proteins E1 and E2 serve as a guidance for this process. Conversely, productive infection takes place in the intermediate layers of the epithelium, where early proteins like E6, E7, E1, and E2 are crucial for the viral genome's amplification. For instance, E6 and E7 encourage the cell cycle to enter the S phase and prevent apoptosis, whereas E1 and E2 attach to the HPV genome's replication origin to allow for the virus's maintenance and amplification during epithelial differentiation. Moreover, the E5 protein is essential for inducing cell division, recycling growth hormones, and suppressing the immune system.[17] The following will outline the primary functions of each of the early HPV proteins (E1, E2, E5, E6, and E7) in the dysregulation of the interferon-mediated antiviral immune response. Knowing how HPV proteins affect the interferon-stimulated gene (ISG) signaling pathway and interferon (IFN) production is essential to comprehending how the virus affects the immune system.

Important for HPV replication, the E1 protein has been shown to function as an immune response regulator in addition to a replicative motor. Interferon (IFN), Toll-like receptor (TLR) signaling, and antiviral genes are all affected by its interference with their expression, which may make it more difficult to identify and eliminate HPV-infected cells.[18] The multifunctional E2 protein influences the immune response in addition to controlling viral replication. Even after IFN-β1 activation, it can suppress the production of interferon (IFN) and interferon-stimulated genes. This capability raises the possibility of its involvement in immune system evasion, particularly during viral replication and the emergence of cervical cancer linked to HPV.[19,20] The intricacy of the E5 protein is demonstrated by its seemingly counterintuitive immunosuppressive actions. It may enhance the integration of the viral genome and HPV replication by influencing the expression of IFN-β1 and IFN-λ1, as well as interferon-stimulated genes (ISGs), which may contribute to cervical cancer.

The proteins E6 and E7 are recognized as crucial immune response regulators. Through its interactions with key players in the interferon (IFN) pathway, E6 promotes viral replication by degrading IRF-3 and suppressing the generation of IFN-β. (Et al., RONCO, 1998). E7 subsequently obstructs the p48 transcription factor's translocation, which impacts the synthesis of IFN-α and counteracts the cGAS-STING pathway (cGAS-STING is an interferon-induced protein that is generated to detect the existence of DNA virus in the cytoplasm of cells), thereby reducing the expression of IFN-β. The IFN-α receptor, STAT2, STAT1, and other components of the IFN pathway are all impacted by the E6 and E7 proteins, which leads to a more thorough suppression of the immune response.[21–23] The expression of the L1 and L2 proteins forms the viral capsid in the higher layers of the epithelium. Lastly, the E4 protein helps break down cytokeratin filaments by promoting the release of fresh viral particles. It is important to remember that the host's immune system typically recognizes and eradicates the initial HPV infection. While the effects of HPV are mostly caused by the E5, E6, and E7 proteins, other early proteins are also important for the longevity of the virus. For instance, the E2 protein is necessary for the viral genome to multiply,

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but it is also linked to the production of oxidative stress and death. Additionally, the early phases of carcinogenesis are marked by the presence of the E2 protein.

The E1 gene is expressed throughout the development of cervical cancer as well as during productive infections. The high quantities of E1 mRNA seen during cervical cancer advancement phases, which point to its potential involvement in the carcinogenic process, are indicative of this. These other proteins show that whereas E6 and E7 are essential for transformation, other HPV proteins might affect different cellular functions and may even aid in virus-mediated immune evasion.[24] The interferon (IFN) pathway, which is crucial for the innate immune response, is one of the immune response components that HPV dysregulates. This is required for the virus to finish its life cycle, which permits viral persistence and, in rare instances, can result in the growth of cancer. Among the family of inducible cytokines are interferons. A cell's ability to produce interferon (IFN), a crucial protein in the body's defense against viral infections, is dependent on its ability to recognize the presence of viral DNA. IFN serves as a warning sign for surrounding cells, triggering signaling pathways that activate interferon-stimulated genes and enabling other cells to combat the infection.[25,26]

Natural killer (NK), dendritic cells, macrophages, T and B lymphocytes, and other immune surveillance mechanisms identify infected cells throughout the HPV genome amplification process. On the other hand, HPV has been demonstrated to be quite successful at suppressing immune responses. Persistent infections thus become a common outcome of the disease's natural course. Because of the loss of the E2 open reading frame (ORF E2), viral persistence creates the conditions for the integration of the viral genome into the host DNA and the subsequent development of cancer. Thus, the oncogenes E6 and E7 are overexpressed, which starts the process of cellular transformation. A continuous sequence of nucleotides on a strand of DNA or RNA that can be read as a code for protein synthesis is known as an open reading frame (ORF). Every gene typically has three primary open reading frames, and in this case, the term "E2 ORF" refers to one of these particular areas, or E2, in the HPV genome. When the term "loss of the E2 open reading frame" is used, it refers to genetic alterations that render the E2 region's genetic material unreadable or untranslatable. This loss could happen when the HPV virus is still active. Because the E5 protein can stimulate cell division and deregulate the immune response, it is also essential during the HPV-induced transformation process.

In addition, the E5 protein promotes cell division, disrupting the host's immunological reaction. It functions autonomously and can assemble into oligomers, like dimers and hexamers, when it is produced in cell membranes, which has an adverse effect on immune response signaling pathways. E5 is also linked to a decrease in immune evasion and the activation mechanism of apoptosis. The idea that this inactivation pathway may be directly engaged in the neoplastic process that results in cervical cancer arose after it was shown that the E6 protein of high-risk HPV can attach to the DNA of the infected cell and cause the p53 gene to be degraded. Here is where the E6 protein comes into play, helping the cell enter the S phase and preventing apoptosis by attaching to the DNA of the cell and causing the p53 gene to be degraded via the ubiquitin-dependent proteolytic pathway. Histone acetyltransferases (HATs) and histone deacetylases (HDAC) are two categories of enzymes that HPV has been shown to target for the deposition and removal of acetylated marks.

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 (INCA).

Discussion

The active stimulation of p53 degradation via the ubiquitin-dependent proteolytic pathway is the mechanism by which the HPV-16 E6 protein adversely affects p53 function, as shown by Scheffner et al. Nonetheless, it was discovered that the SV40 TAg and Ad E1A proteins also target the transcriptional coactivator CBP/p300.[28] CBP/p300 controls a range of signal-modulated events by interacting with certain transcription factors.[29] Through intrinsic or associated acetyltransferase activity, CBP/p300 can change histones and non-histone transcription factors, activating gene expression.[30] This could help to partially explain why SV40 and Ad E1A proteins target CBP/p300. Additionally, data that was recently released showed that CBP/p300 promotes transcription that is dependent on p53. Therefore, CBP/p300's ability to halt the cell cycle may be partially due to its participation in p53-regulated processes. It is true that SV40 and adenoviruses can inhibit p53 activity by targeting the p53 cofactor CBP/p300. It has also been demonstrated that, in the case of Ad E1A at least, mutants lacking in CBP binding are unable to negatively regulate p53.[31]

Through intrinsic or associated acetyltransferase activity, CBP/p300 can change histones and non-histone transcription factors, activating gene expression. This could help to partially explain why SV40 and Ad E1A proteins target CBP/p300. Additionally, data that was recently released showed that CBP/p300 promotes transcription that is dependent on p53. Therefore, CBP/p300's ability to halt the cell cycle may be partially due to its participation in p53-regulated processes. It is true that SV40 and adenoviruses can inhibit p53 activity by targeting the p53 cofactor CBP/p300. It has also been demonstrated that, in the case of Ad E1A at least, mutants lacking in CBP binding are unable to negatively regulate p53. Remarkably, high-risk HPV E6 proteins have also been shown to exhibit p53-dependent transcriptional downregulation in vivo, in addition to SV40 TAg and Ad E1A. However, the HPV E6 oncoprotein has not yet been shown to interact with the transcriptional coactivator CBP/p300. One may argue that the abrogation of p53 transcriptional activity can be adequately explained by the capacity of high-risk HPV E6 proteins to degrade p53 via the E6AP pathway. Nevertheless, p53 can also be degraded by adenoviruses via 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 indicates a complicated method of negative control of p53 activity. The transcriptional activity of p53 is disrupted as a result of this interaction, which is important for controlling the cell cycle and may even be involved in the development of cancer. E7 is known to obstruct the p48 transcription factor's translocation,

which opposes the cGAS-STING pathway. However, the hypophosphorylated retinoblastoma protein (pRB) can also be bound by this HPV oncoprotein and rendered inactive.[33] This ultimately causes p16 INK4A to be upregulated. Tumor suppressor protein P16 INK4A prevents cyclin-dependent kinases (CDK) -4 or -6 from attaching to cyclin D, which controls cell cycle checkpoints during the G1 phase.[34] When G1 cyclin-dependent kinases phosphorylate pRb, they release E2F, which causes the cell cycle to advance into the S phase. Since E7 can bind unphosphorylated pRb, it can cause cells to enter the S phase too soon, which will stop the pRb-E2F complexes. More recently, it was found that E7 triggers the calcium-activated cysteine protease calpain to cleave pRb at its C-terminus. This cleavage is required in order for E7 to trigger the proteasomal breakdown of pRb. In the top layers of the epithelium, where uninfected daughter cells ordinarily develop and fully exit the cell cycle, HPV replication is made possible by the action of the E7 protein.[35] Moreover, E7 binds to p27, an inhibitor of CDK (kinase)[36] and CKI p21[37] Verifying the reversal of cell cycle suppression. E7 also interacts with p48 in order to avoid the immune system.[38] in addition to Interferon Regulatory Factor 1 (IRF-1).[39]

E7 has been shown to target P600, which aids in cellular transformation and anchorage-independent growth.[40] Infectious virions must assemble at the epithelial surface in a certain arrangement for productively infected cells to express viral gene products. Cell cycle markers, including PCNA and MCMar, are restricted to the lower epithelial layers during productive infection. The presence of J. doorbar/lifecycle organization and biomarkers 309 is a direct result of E6/E7 activity. The E4 protein is the most prevalent member of the collection of markers that identify cells that are undergoing genome amplification. After genome amplification, capsid proteins (L1 and L2) eventually present in the higher layers of epithelium, signaling the beginning of virus assembly. This implies that throughout epithelial differentiation, infected cells express each of these markers, and that the degree of productive infection may be determined by taking into account the timing and intensity of their expression. It seems that there are two kinds of modifications that might happen as a tumor grows. First, dysregulated viral gene expression results in elevated levels of E6 and E7 in basal and parabasal cells. This is expected to be a major event in promoting the accumulation of genetic mistakes in the host cell chromosome, given the known functions of these proteins. E6/E7 expression in the cell is eventually corrected by integration, which raises the likelihood of advancement even more.[41,42]

The regulation of late events, which are increasingly delayed as the degree of neoplasia develops, is the subject of the second type of change. Immunostaining reveals this as a decrease in the amount of E4 expression in the upper layers of the epithelium and an increase in the thickness of the E7-expressing layers. Both the potential connection between these two occurrences and the specific systems controlling such behavior remain unknown. Viral proteins like HPV-16 E6, Ad E1A, and SV40 TAg interact intricately with the transcriptional coactivator CBP/p300 to regulate p53 activity negatively. This mechanism is important for modifying the cellular cycle and may even be involved in the development of cancer. Although it is well known that HPV-16 E6 proteins can degrade p53 via E6AP, the fact that SV40 TAg and Ad E1A can also target CBP/p300 complicates the molecular mechanisms at play. Conversely, the intricate interplay of the HPV E7 oncoprotein delineates a multidimensional terrain of cellular evasion and manipulation of the cellular milieu. E7 affects the p48 transcription factor's translocation, which opposes the cGAS-STING pathway, jeopardizes cell cycle regulation, and encourages p16 INK4A overexpression. E7 interacts with IRF-1, p600, p27, p21, p48, and p21 to propose new tactics for immune evasion and cellular transformation.

Conclusion

The HPV virus possesses remarkable ability to elude the host's immune system, aid in its replication, and facilitate the emergence of recurrent infections that may culminate in cervical cancer. The crucial functions of E6 and E7 proteins include controlling the host's immune system to permit viral persistence and inactivating tumor suppressor genes, which are vital for defense against infections. By investigating the molecular mechanisms of infection, including immune responses, the current study aimed to gain a thorough understanding of the link between HPV infection and the development of cervical cancer. The double-stranded circular DNA virus known as HPV has been shown to be linked to up to 200 distinct varieties, 15 of which are thought to be carcinogenic agents in humans. These types include HPV 16 and 18, which are known to have a high oncogenic risk. Approximately 80% of women who are sexually active have been infected with HPV at some point in their lives. Examining the molecular mechanisms of infection and related immune responses is necessary to understand the connection between HPV infection and the emergence of cervical cancer. It was discovered during this study that HPV interferes with the interferon pathways in order to evade the immune response by using a number of its own proteins (E1, E2, E5, E6, and E7).

All things considered, our goal was to comprehend the intricacy of the relationships amongst viral proteins. We specifically targeted the E6 and E7 oncoproteins and their impact on the suppression of p53 activity, emphasizing the function of the transcriptional coactivator CBP/p300 in this procedure. Dysplasia and other cytopathological abnormalities in the cervix brought on by HPV infection typically go away on their own. But it's crucial to understand that having ongoing high-risk HPV infections greatly raises the risk of developing cervical cancer. Consequently, it is critical to expand our understanding of HPV's pathogenesis and immune evasion strategies. Examining the molecular processes of infection and related immune responses is necessary to understand the connection between human papillomavirus (HPV) infection and the onset of cervical cancer. It was discovered during this study that HPV interferes with the interferon pathways in order to evade the immune response by using a number of its own proteins (E1, E2, E5, E6, and E7). All things considered, our goal was to comprehend the intricacy of the relationships amongst viral proteins. We specifically targeted the E6 and E7 oncoproteins and their impact on the suppression of p53 activity, emphasizing the function of the transcriptional coactivator CBP/p300 in this procedure.

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None.

Conflicts of interest

The author declares that there are no conflicts of interest.

References

1. Consolaro MEL, Stuchi SME. Cervico vaginal clinical cytology text and atlas, São Paulo: Roca ltda. 2012.
2. Cervical cancer: questions and answers. Rio de Janeiro: INCA.

3. Cervical cancer control - prevention actions. INCA.
4. Ahmed MY. Detection of high-risk human papillomavirus in prostate cancer from a UK based population. *Scientific Reports*. 2023.
5. Gyöngyösi E. Transcriptional regulation of genes involved in keratinocyte differentiation by human papillomavirus 16 oncoproteins. *Arc virol*. 2015;160(2):389–398.
6. Schelhaas M. Entry of human papillomavirus type 16 by actin-dependent, clathrin- and lipid raft-independent endocytosis. *PLoS Pathog*. 2012;8(4):e1002657.
7. Herdman M. Interferon-beta treatment of cervical keratinocytes naturally infected with human papillomavirus 16 episomes promotes rapid reduction in episome numbers and emergence of latent integrants. *Carcinogenesis*. 2006;27(11):2341–2353.
8. Scheffner M. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell*. 1990;63(6):1129–1136.
9. Gieswein CE, Sharom FJ, Wildeman AG. Oligomerization of the E5 protein of human papillomavirus type 16 occurs through multiple hydrophobic regions. *Virology*. 2003;313(2):415–426.
10. Hu L, Ceresa B. Characterization of the plasma membrane localization and orientation of HPV16 E5 for cell-cell fusion. *Virology*. 2009;393(1):135–143.
11. Doorbar J. Papillomavirus life cycle organization and biomarker selection. *Dis Markers*. 2007;23(4):297–313.
12. Doorbar J. The E4 protein: structure, function and patterns of expression. *Virology*. 2013;445(1-2):80–98.
13. Manini I, Montomoli E. Epidemiology and prevention of human papilloma virus. *Ann Ig*. 2018;30(4 Suppl 1):28–32.
14. Martel C. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. 2017;141(4):664–670.
15. Liu X. Structure of the human Papillomavirus E7 oncoprotein and its mechanism for inactivation of the retinoblastoma tumor suppressor. *J Biol Chem*. 2006;281(1):578–586.
16. Zimmermann H. The human papillomavirus type 16 E6 oncoprotein can down-regulate p53 activity by targeting the transcriptional coactivator CBP/p300. *J Virol*. 1999;73(8):6209–6219.
17. Wetherill LF. High-risk human papillomavirus e5 onco protein displays channel-forming activity sensitive to small-molecule inhibitors. *J Virol*. 2012;86(9):5341–5351.
18. Bergvall M, Melendy T, Archambault J. The E1 proteins. *Virology*. 2013;445(1-2):35–56.
19. Mcbride A. The papillomavirus E2 proteins. *Virology*. 2013;445(1-2):57–79.
20. Sunthamala N. E2 proteins of high-risk human papillomaviruses down-modulate Sting and IFN-κ transcription in keratinocytes. *PLoS One*. 2014;9(3):e91473.
21. Bortnik V. Loss of HPV type 16 e7 restores cGAS-STING responses in human papilloma virus-positive oropharyngeal squamous cell carcinomas cells. *J Microbiol Immunol Infect*. 2021;54(4):733–739.
22. Lau L. DNA tumor virus oncogenes antagonize the c GAS-STING DNA-sensing pathway. *Science*. 2015;350(6260):568–571.
23. LI S. The human papilloma virus (HPV)-18 E6 onco protein physically associates with Tyk2 and impairs Jak-STAT activation by interferon-alpha. *Oncogene*. 1999;18(42):5727–5737.
24. Bellanger S. Tumor suppressor or oncogene? A critical role of the human papillomavirus (HPV) E2 protein in cervical cancer progression. *Am J Cancer Res*. 2011;1(3):373–389.
25. Mesev E. Decoding type I and III interferon signaling during viral infection. *Nat Microbiol*. 2019;4(6):914–924.
26. Liniger M. TNF-mediated inhibition of classical swine fever virus replication Is IRF1-, NF-κB- and JAK/STAT signaling-dependent. *Viruses*. 2021;13(10):2017.
27. Mietz J. The transcriptional transactivation function of wild-type p53 is inhibited by SV40 large T-antigen and by HPV-16 E6 oncoprotein. *Embo J*. 1992;11(13):5013–5020.
28. Lundblad J. Adenoviral E1A-associated protein p300 as a functional homologue of the transcriptional co-activator CBP. *Nature*. 1995;374(6517):85–88.
29. Janknecht R, Hunter T. Transcription: a growing co activator network. *Nature*. 1996;383(6595):22–23.
30. Ogryzko V. The transcriptional coactivators p300 and CBP are histone acetyl transferases. *Cell*. 1996;87(5):953–959.
31. Somasundaram K, Deiry W. Inhibition of p53-mediated transactivation and cell cycle arrest by E1A through its p300/CBP-interacting region. *Oncogene*. 1997;14(9):1047–1057.
32. Roth J. Inactivation of p53 but not p73 by adenovirus type 5 E1B 55-kilodalton and E4 34-kilodalton onco proteins. *J Virol*. 1998;72(11):8510–8516.
33. Münger K. Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product. *Embo J*. 1989;8(13):4099–4105.
34. Sano T. Expression status of p16 protein is associated with human papillomavirus oncogenic potential in cervical and genital lesions. *The Am J Pathol*. 1998;153(6):1741–1748.
35. Ishikawa M. Overexpression of p16 INK4a as an indicator for human papillomavirus oncogenic activity in cervical squamous neoplasia. *Int J Gynecol Cancer*. 2006;16(1):347–353.
36. Ronco L. Human papillomavirus 16 E6 onco protein binds to interferon regulatory factor-3 and inhibits its transcriptional activity. *Genes Dev*. 1998;12(13):2061–2072.
37. Funk J. Inhibition of CDK activity and PCNA-dependent DNA replication by P21 is blocked by interaction with the HPV-16 E7 onco protein. *Genes Dev.* 1997;11(16):2090–2100
38. Barnard p, Mcmillan N. The human papillomavirus E7 oncoprotein abrogates signaling mediated by interferon- alpha. *Virology*. 1999;259(2):305–313.
39. Um S. Abrogation of IRF-1 response by high-risk HPV E7 protein in vivo. *Cancer Lett*. 2002;179(2):205–212
40. Nakatani Y. P600, a unique protein required for membrane morphogenesis and cell survival. *PNAS*. 2005;102(42):15093–15098.
41. Neto L, Benedito J. Atlas of cytopathology and histology of the cervix. *Medsi*. 2000:164.
42. O'connor MJ. Characterization of an E1A-CBP interaction defines a novel transcriptional adapter motif (TRAM) in CBP/p300. *J Virol*. 1999;73(5):3574–3581.