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ONCOGENIC POTENTIAL OF PERSISTENT INFECTION WITH HUMAN PAPILLOMAVIRUS

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ABSTRACT

Given that they are a group of small-chain DNA viruses, certain human papillomaviruses (HPVs) may either produce benign sickness or be found in human cancerous tumors. Oncogenic risk strains - as evidenced by the literature - infect epithelial cells so they are detected in the skin and in the mucous membranes (genital, anal, oral and respiratory). The primary risk factor for the formation of many malignant tumors in humans is ongoing human papillomavirus infection, which can occur in many anatomical locations. The most studied are HPV16 and HPV18, because they have the highest carcinogenic activity, while onco-E6 and E7 participate in cell transformation and carcinogenesis induced by HPV, because they are essential factors for immortalization. The current literature is presented in this review which is a critical and comprehensive summary focusing on: the structure and organization of the HPV genome, the cycle of viral infection, focusing on the functional importance of the HPV oncoproteins, E6 and E7, which drive atypical cell proliferation, abnormal, diagnosing precancerous diseases, but also determining the condition, their prevention and the necessary therapy for this type of HPV infection.

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Introduction

A wide number of uncontrolled, diverse viruses (<10 kb) with a double-stranded circular DNA genome make up the Papillomaviridae family, which includes human papillomaviruses (HPV) that infect squamous epithelial cells and cause papillomas in most animals [1]. There are more than 300 distinct forms of papillomavirus in both humans and animals, and the Papillomaviridae family has 49 genes (http://pave.niaid.nih.gov/). Human papillomaviruses are known to exist, and they are classified into 5 phylogenetic genes based on DNA sequence analysis, each with unique life cycle features [2]. Each gender has distinct biological traits as well as genetic features (alpha, beta, gamma, mu, and not HPV). Molecular techniques are utilized to describe viruses, as they have not undergone in vitro cultivation. Of the 150 different strains of HPV, roughly 40 can infect the epithelial lining of the anogenital tract and other mucosal parts of the human body.

HPV can be classified based on its relationship to both benign and malignant anogenital lesions. Examples of these include high-risk oncogenic HR-HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), and low-risk LR-HPV that causes primarily benign lesions affecting anogenital, cervical, and laryngeal papillomas (HPV 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, and 81) [3], with genotypes 6 and 11 being the most common. Every HPV genotype was classified as follows by the International Agency for Research on Cancer (IARC): HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 were classified as carcinogens for humans (group 1); HPV 68 was classified as probably carcinogenic (group 2A), with genotypes 16 and 18

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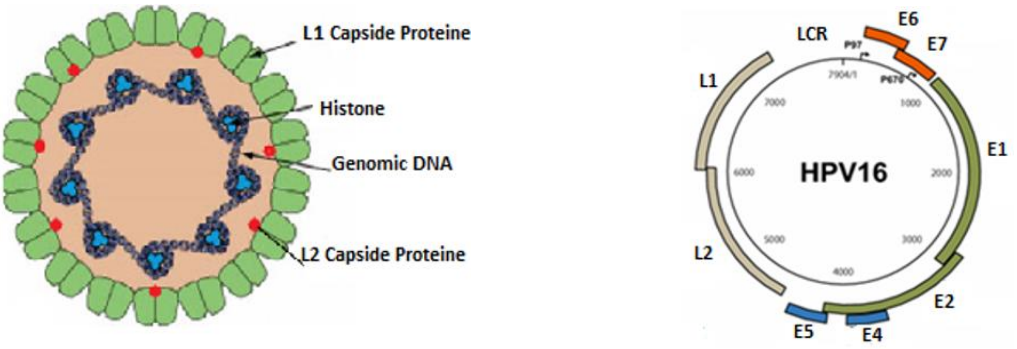
having the highest potential for cancer; HPV 26, 53, 66, 67, 68, 70, 73, 82, etc., were classified as possibly carcinogenic [4]. More than 90% of codylomata are caused by LR-HPV types 6 and 11, which might result in benign hyperproliferative lesions or common genital warts with a very low propensity to become malignant [5].

The most prevalent HPV types found worldwide, encompassing both asymptomatic infections and cervical cancers, are HR-HPV types 16 and 18, which are linked to the development of premalignant lesions and malignant cervical lesions, which account for 70% of cervical cancers [6]. More than 40% of oral cancers are HRV-HPV kinds, which are linked to numerous penile, vulvar, and anal, as well as head and neck carcinomas [7]. Additionally, a number of investigations have demonstrated the existence of high-risk HPV in benign lesions and low-risk HPV in high-grade lesions. The mucous HPV types infect the mucosa of the mouth, throat, respiratory tract, or anogenital epithelium, whereas the cutaneous HPV types target the skin of the hands and feet. The primary risk factor for the development of many human cancers at various anatomical locations is persistent human papillomavirus (HPV) infection [8]. Just a tiny percentage of all known human HPV varieties have been linked to the emergence of cancer. Infectious agent infections are the cause of about 15% of human malignancies, with HPV infections accounting for over one-third of these cases [9]. Cervical cancer and other malignancies of the vaginal, vulvar, anal, rectal, penile, and oropharyngeal regions are strongly linked to HPV infection. According to the statistical data issued by the Centers for Disease Control and Prevention in the period 2008-2012 in the USA of 38,793 new cases of cancer in different parts of the human body (cervix, vagina, vulva, penis, anus, and oropharyngeal), a number of 30,700 cases are associated with the presence of different types of HPV among which 24,600 case are attributed to types 16,18 and 3,800 assigned to types 31/33/45/52/58 [10].

Human Papillomavirus Structure and Genome Organization

The epitheliotropic DNA viruses that infect humans are classified as such because they have a circular double-stranded DNA genome that is 50–60 nanometers in diameter and 8–10 kb in size. These viruses are also linked to proteins that resemble histones and are shielded by two capsids, known as latex L1 and L2 **(Figure 1a)**. The pentamer that corresponds to the main L1 protein capsid is made up of 72 capsomeres, each of which contains five monomer units (55 kDa). The L1 main capsid is stabilized by a network of intra- and interpentamic disulfide connections. The purpose of the virion's minor capsid L2 (75 kDa) proteins is to build the viral capsid by shutting or obstructing each pentavalent capsome's center [11].

According to a study, carcinogenic HPVs express accessory proteins E4, E5, E6, and E7, whereas capsid proteins L1 and L2 and replication factors E1 and E2 are among the four protein classes identified encoded in papillomaviruses that are conserved in origin [12]. These proteins are essential for immune evasion and are carried out during viral replication, which involves altering the prerequisite environment [13]. The P670 promoter is the source of expression for the L1 and L2 late ORFs, which have expression in the upper epithelial layers due to complex joint modifications. The six Open Read Frames (ORFs)—E1, E2, E4, E5, E6, and E7—are expressed from distinct promoters at distinct stages of the epithelial cell differentiating procedure. An uncoded portion of the genome known as the long-range LCR/URR control region/upstream regression region is home to the replication origin and post-transcriptional regulatory sequences that aid in the presentation of viral genes [14]. **Figure 1b** [11] depicts the alpha HPV16 genome organization and the structure of the human papillomavirus.



a) b)

Figure 1. a) Structure of human papillomavirus; b) Genome organization of the high-risk Alpha HPV 16 types

The role and functions of proteins called early in the virus structure and genomic organization [11, 15] are synthesized by domain literature as follows:

- The binding area varies in length and order, but E1 encodes virus-specific helicase DNA that is essential for the replication and amplification of the viral genome;
- E2, is characterized by the potential of binding to sites in both the viral and cellular genomes, the N and C-terminal amino acid sequences are well conserved between the E2 proteins of different papillomaviruses and function in the field of transcription, replication and genomic partitioning. To the advantage of the virus, E2 activities rely on interacting with cellular genetic products and changing their typical roles;

- Both proteins E4 and E5, which exhibit significant sequence variation across types and represent the various tropisms and transmission channels of distinct papillomaviruses, are involved in the evacuation of epithelial epithelium viruses;
- E2 can control the transcriptional level of E6 and E7, which are essential for carrying out the inlet cell cycle in all HPV strains. This process permits the amplification of the genome in the middle epithelial layers and inhibits some components of innate immunity.;
- The L1 protein is the focus of preventive vaccinations because it is immunogenic and contains conformational epitopes that stimulate the generation of certain neutralizing antibodies against the virus, preventing infection.
- By helping the virion attach to the cellular receptor, the L2 protein promotes the virion's absorption, transport to the nucleus, and delivery of viral DNA to the replication sites. E2 further aids in packing viral DNA into capsids.

Human Papillomavirus Infectious Cycle

There is just one method by which the HPV virus spreads, and that method involves stratifying the skin's and mucous membranes' flattened epithelial layer. The HPV life cycle is supplied by the host cell's biology, which is accomplished by micro-abrasion-induced infection of stem cells in the basal layer of the epithelium. Through this technique, one may access self-renewing cells, which in turn stimulate cell proliferation throughout the wound healing process, ultimately leading to the formation of a viral infection. According to the studies carried out and published in the literature [11], the propagation mechanism of the HPV viral infection cycle is presented in **Figure 2** and presents the following stages of propagation:

- The virus has to express the E1 and E2 genes in order to keep the number of genome copies under check once it has entered the cells. In addition to biological DNA polymerases and other proteins necessary for DNA replication, the protein attracts additional proteins to the viral replication origin once it attaches to it.
- Genes E1, E2, E5, E6, and E7 are expressed in the suprabasal layer, which aids in the preservation of the viral genome and promotes cell division. As a result, there are more HPV-infected cells in the epithelium, which means that more cells will produce the later infectious virions.
- The extremely distinct cells that make up the same epithelial layer experience promoter activation, which is dependent on differentiation and preserves the expression of the E1, E2, E6, and E7 genes. The L1 and L2 gene expression rises concurrently with the simultaneous activation of the E4 gene, whose product will cause the amplification of viral genome replication and a marked increase in the number of virus copies on the cell.
- In the granular layer, the major and minor proteins of the viral capsid, L1 and L2, respectively, are formed and discharged to form virions, which reach the stratum corneum of the epithelium. This is the process of assembling viral capsids.

Cycle of life There are two stages to HPV structure: maintenance is the first step, and differentiation is necessary for the second stage. Viral proteins in the maintenance stage are extremely weakly produced in undifferentiated cells and aid in immune evasion and persistence. HPV-infected cells leave the basal layer during the second stage of differentiation, causing high levels of viral protein production and postponing the expression of viral infection markers in areas that are less vulnerable to the host's immune response. According to research, this process establishes a distinct period of infection for HL or HR-HPV types: HR-HPV, particularly HPV-16, has a substantially higher chance of developing a chronic infection and a prolonged elimination period (~ 6–12 months) [16].

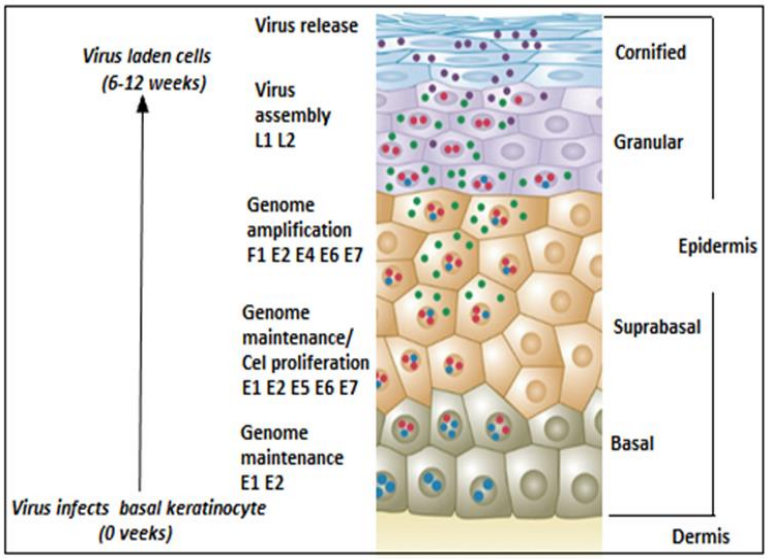


Figure 2. Life cycle of HPV infection (adapted: [11, 17])

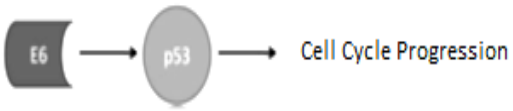
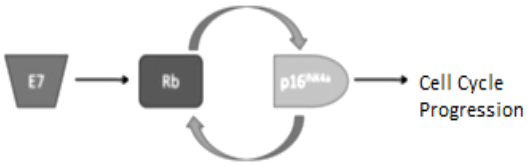
The Role of E6 and E7 Oncoprotein in Carcinogenesis

Research indicates that some kinds of alpha-HPV infect the mucosal epithelium, and the virus reaches the basal epithelial cells by means of microinjection [18]. The virus relies on cell layering and division for reproduction; it lacks its own machinery. From the basal to the suprabasal layers, the epithelium emerges. In this process, the HPV oncoproteins E6 and E7 are essential. The convergent action of many cellular pathways involved in the regulation, maintenance, and cell proliferation to a great extent of the differentiated suprabasal area, which permits amplification of the viral genome, results in control of the cell cycle and apoptosis [8]. The HR-HPV alpha types' typical productive viral life cycle is a tightly controlled and orchestrated process. Viral DNA is haphazardly incorporated into the host genome during chronic infection, leading to cellular immortalization and eventually malignant development.

When compared to the virus's primary proteins, the alpha-HPV E6 and E7 oncoproteins exhibit a high degree of specialization and a low degree of conservation. E6 and E7 inactivate cell cycle checkpoints to increase viral replication in differentiated cells and activate cell proliferation as a result of numerous interactions with cellular proteins [19]. The research's conclusions highlight the fundamental roles of the HPV oncogene mechanism, which include the following: E6-mediated regulation of the enzyme telomerase; E7-mediated degradation of hypophosphorylated retinoblastoma protein (pRb) family members and PDZ domain proteins; and E6-mediated degradation of tumor suppressor protein 53 (p53) [20-22]. **Table 1** displays the oncogenic pathways of HPV E6 and E7 as well as the characteristics of these oncogenes [13, 23].

Cervical cancer is caused by HPV infections. The two oncoproteins, E6 and E7, that the virus encodes are directly involved in the development and maintenance of tumor growth. There is uncertainty regarding the precise function of HPV E6 and E7 proteins in infected basal cells, particularly in the case of low-grade HPV types (like HPV 6 and 11) that are not typically linked to neoplasia and are thought to cause lesions after infecting a basal stem cell at the level of a wound or micro-injury. The E6 and E7 viral proteins are known to have a significant role in promoting basal cell proliferation and parabasic layers in high-risk types that result in neoplasia, particularly in the cervix, where neoplasia may develop [24].

Table 1. Major properties and oncogenic pathways of HPV E6 and E7.

Major properties	Oncogenic pathways of E6 and E7.
E6 • proteasome-mediated degradation of p53 • induction of telomerase expression • degradation of PDZ domain proteins involved in cell polarity • inhibition of innate immune response	
E7 • epigenetic reprogramming of cells by upregulation of KDM6A and KDM6B • abrogation of pRb/E2F pathway by pRb degradation • induction of DDR in differentiated cells to promote viral DNA amplification • inhibition of innate immune response	

Studies have indicated that disruption of E6/E7 expression is undesirable in defining neoplastic grade [20], which is categorized based on the degree of basal cell extension into basal sub-layers [25]. High-risk HPV strains in particular create oncoproteins called E6 and E7, which bind to the normal tumor suppressor proteins p53 and pRb and, over time, can cause mutations. As a tumor suppressor, E6 binds to and destroys p53. The retinoblastoma protein family interacts with E7 and becomes inactive [26]. The E6 and E7 proteins, which are produced from high-risk HPV and are found in premalignant and advanced cervical lesions, are crucial to the development of cancer. The E2 gene encodes a gene that regulates the E6 and E7 genes. HPV circular DNA incorporation into the host genome is a critical step in the malignant transformation process. The E6 and E7 genes express themselves uncontrollably as a result of integration, which frequently takes place at the level of the inactive E2 gene. Together with determining resistance to apoptosis and increasing chromosomal instability, E6 and E7 also interact with the Bax pro-apoptotic protein. E6 oncoprotein also causes the infected cells to become immortal by activating telomerase. E7 specifically targets and changes the phosphorylation state of pRb, another tumor suppressor, rendering it inactive. The transcription factor E2F, which pRb naturally binds to, plays a crucial role in the cell cycle's progression from G1 to S phase due to the engagement of cyclin and cyclin-dependent kinases. Therefore, the p53 tumor protein controls the progression of the cell cycle to the G1 S phase, which is regulated by the p21 protein [27]. E7 contains an inactive E7-pRb complex that prevents E2F from attaching to pRb, enabling E2F to connect to DNA and promote cell division. The various HPV strains carrying the E6 and E7 proteins have varying effects throughout the malignant transformation procedure. While the viruses generated by HPV 6 and HPV 11 are unable to bind to or activate p53 and pRb, HPV 16 and HPV 18 have a significant propensity for carcinogenesis.

The integration of viral genetic material into the host genome is accompanied by alteration of the cervical squamous epithelial morphology, which starts from low-risk intraepithelial lesions in those at high risk, characterized by cytological atypia and abnormal mitotic index. Integration of the viral genome occurs in different chromosomes, but usually in regions that contain genes important for cell viability. It is not necessary to integrate the entire viral genome, but that of the E6 and E7genes is of major importance for carcinogenesis. Cells containing the integrated viral genome exhibit greater growth than normal cells,

leading to cell proliferation and loss of differentiation property. Integration also interrupts the life cycle of the virus so that no more complete virions (unproductive infection) are produced. Although integration is the biological end of the virus, it facilitates perpetual expression of oncoproteins.

Usually, low-risk intraepithelial lesions (LSIL) do not detect integration of HPV DNA, unlike HSIL where viral genetic material is frequently integrated into the host genome. Integration gives HPV an irreversible character. In the absence of treatment, a significant amount of HSIL evolves to cervical cancer, although this process may take years or even decades.

Up to 25% of HPV 16-induced cervical cancers reveal the presence of unintegrated extracromosomal (episomal) DNA, while the HPV 18, 31 and 35 associated HPV carcinomas almost always contain integrated HPV DNA. In epizomal HPV cancers there was demonstrated the existence of YY1 mutations; YY1 elements are the regulatory sites for the transcription factor YY1 that control the activity of a large number of genes. MY1 mutations prevent transcription factor binding and facilitate the expression of E6 / E7 oncogenes with cell cycle accelerating and abnormal cellular proliferation [28].

Prevention and Therapeutic Opportunities

Prevention

The connection between veruciform epidermodisplasia and HPV-related skin cancer was proposed by Stefania Jabłońska in 1972. Harald Zur Hausen proposed the theory that HPV is a major factor in the development of cervical cancer in 1977. After HPV 16 and HPV 18 were linked to cervical cancer in 1983 and 1984 by zur Hausen and colleagues [29], these viruses were identified as carcinogens that affect the growth of this kind of tumor during the course of the next 12 years of study. The subsequent years provided evidence of HPV 16's carcinogenic effects on the oral cavity and oropharynx. The IARC carried out the investigation [30].

HPV infections can resolve spontaneously in 70% of healthy people within a year, and in two years about 90%, other infections are persistent with oncogenic HPV types do not respond immune and have an increased risk of progression to cancer [31]. Due to the greater frequency of HPV-related illness and cancer in immunocompromised people, the innate and adaptive host immune response is crucial in eradicating infected cells. A chronic HPV infection causes squamous intraepithelial lesions, which eventually develop into premalignant, or clinically relevant, cervical cancer in 12 to 15 years [32].

According to research, there are a number of ways to avoid primary and secondary cervical cancer through screening and immunization, which can help lower the incidence of the disease. It suggests that cervical screening can help women who are HPV-positive and have the highest risk of cancer by improving their risk assessment.

The risk of further infection or spread of HPV can be reduced by prevention using safe sex practices and thus reducing the risk of transmission. High-risk strains of HPV can be fought with the three types of vaccine Cervarix, Gardasil and Gardasil. 9. Using high-risk HPV types 16, 18, 31, 33, 45, 52, and 58 together with low-risk HPV types 6 and 11 is the nonvalent HPV vaccination (9vHPV, Gardasil 9) that is used in the US (2014), Canada, Australia, and the European Union (2015) [33]. Five more HPV kinds (types 31/33/45/52/28 through HPV) are present in V503 (HPV 9-valent), which employs VLP particle-like viruses. 90 percent of genital warts and about 90 percent of cervical, vaginal, anal, and HPV malignancies globally can be prevented with the 9vHPV vaccination [34]. Because the infection site is inaccessible, the Pap test is extremely successful in identifying cervical lesions linked to surgically curable HPV in infected individuals. However, this test does not yield the same findings for oropharyngeal cancer (OPC).

Diagnostic Methods

Many techniques are now used for high-risk HPV testing. Using morphological parameters as the reference standard for cervical infections, histological testing is carried out, for instance, by not taking HPV biomarkers into account and by emphasizing simultaneous histological abnormalities. The quantity of aberrant cell extension in the cervical epithelium that corresponds to the three grades of cervical intraepithelial neoplasia (CIN) is shown in **Figure 3**. A histologically verified CIN3 lesion is a clear indication for surgical therapy [35]. Due to its strong consistency with physician readings and ability to be performed with direct brush autosamplers, DNA methylation analysis for high-risk HPV screening in women is an intriguing substitute for cytology. Research revealed that when DNA from clinical specimens was obtained, several HPV PCR tests, or molecular detection techniques, detected more positive samples than s-LA and m-LA [21].

With a high specificity for E6, in particular, the immunological approach known as the Sca Rapid Test approach is utilized to identify E6/E7 on HP6 16/18/45 oncroproteins. Since HPV cannot be grown, tests that rely on finding viral nucleic acids in infected tissues have been developed. The majority of assays identify viral DNA using a variety of amplification methods, demonstrating that cervical cells are infected. The majority of HPV infections are temporary, and an HPV-DNA test's positive predictive value for the development of high-risk cervical lesions is rather low. These two factors represent two significant limitations of DNA-based assays, such as the HPV genotype detection test. Tests based on the identification of messenger RNA for E6/E7 proteins from five high-risk HPV types (16, 18, 31, 33, 45) and then from 14 kinds of HPV oncogenes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) show the oncogenic activity of HPV.

When it comes to predicting the risk of developing cervical cancer, RNA-based assays are more predictive than DNA testing because E6/E7 mRNA directly translate viral activity and correlate with the onset and maintenance of pre-cancerous lesions. Studies have established that E6/E7 mRNA levels rise in proportion to the severity of lesions, meaning that transcription product detection would have a larger prognostic value and could enhance the accuracy and forecast value of HPV DNA in screening [22].

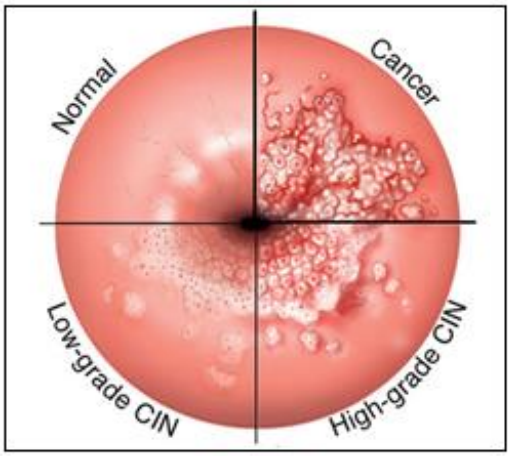


Figure 3. Stages of HPV infection

Therapeutics

It has been found that no effective treatment can be applied for HPV, but it can be associated with carcinogenesis. Some approaches to their inhibition or precise molecular targets (pathways) have been demonstrated, but new methods are needed for known targets and mechanisms [23]. Clinical experiments have shown a novel treatment approach based on CRISPR/Cas9, which involves the silencing of E6 and E7. This process is dependent on the reactivation of TP53 and pRb to cause apoptosis and cellular senescence. **Table 2** compares the features of the CRISPR/Cas9 approach with RNA interference in detail [23].

Research demonstrates and validates the features and potential of this CRISPR-centric technology: a CRISPR/Cas9 sequence that targets E6 mRNA decreases the levels of full-length mRNA and enhances the level of TP53 protein [36]; CRISPR/Cas9 inhibition of E7 as a possible therapeutic intervention for the treatment of cervical cancer [37]; CRISPR/Cas9 targeting the promoter and ORF of E6/E7 transcripts lowers the levels of E6 and E7 mRNA, enhances the level of TP53 protein, lowers the level of RB protein, stimulates apoptosis, and inhibits the growth of SiHa cells; Cas9 exhibits attenuated growth in vivo. 2014 saw the precise engineering of E6/E7 HPV16 or HPV18 mRNAs using CRISPR/Cas9 [38].

Intratumoral treatment resulted in CRISPR/Cas9 activation of apoptosis in vivo and suppression of tumor development. These can all be used as possible adjuvant treatments for cervical cancer. Tools based on CRISPR/Cas9 have also been successfully applied to other creatures and are being researched in a variety of fields, including high-throughput genetic screening, gene knockouts in several species, and targeting pathogens to remove diseases like HBV, HIV, and HPV.

There are patients with tumors that are not infected with HPV, but also patients infected with HPV who later develop cancer, receiving identical treatment. The type and stage of tumors lead to the following treatments: radiotherapy, surgery, chemotherapy or combinations of these methods, etc. The treatment applied to precancerous changes of the cervix is varied, namely: loop electrosurgical excision procedure (LEEP), cryosurgery (freeze -frost); surgical consultation (surgery with a scalpel, laser, or both to remove a cone-shaped piece of tissue from the cervix and cervical canal); electrosurgical excision procedure at the loop or by removing the cervical tissue using a hot wire loop; laser vaporization console (use of laser to destroy cervical tissue).

Table 2. CRISPR/Cas9 approach compared to RNAi

Targets	CRISPR/Cas9	RNAi
Loss-of-function mechanism	Frame shift DNA mutation	Post-transcriptional RNA degradation
Result	Permanent knockout	Reversible knockdown
Transgenes	Cas9 nuclease gRNA	si/shRNA
Guiding sequence	gRNA	si/shRNA
Required sequence information	Transcriptome	Transcriptome
Off-target space	Cuts as monomer	Transcriptome Genome
Transcript variants region	All variants	All variants

Conclusion

Of the multitude of human papillomaviruses (HPV), there are some that cause penile cancer in men, cervical cancer in women, and oropharyngeal cancer in both sexes. Approximately 15% of human cancers are caused by infectious agents and approximately one third are due to HPV infections [9].

Genital warts (condylomata) and low-grade dysplasia are caused by low-risk oncogenic HPVs, while high-risk oncogenic HPVs cause high-grade lesions, such as cervical intraepithelial neoplasia 2+, which is a sign of cervical cancer. HPV E6 and E7 oncoproteins, which cause p53 and pRb to become inactive, are the main viral elements that cause HPV-related malignancies to begin and spread. A potential method for treating cervical cancer is RNA interference using E6 and E7, which have the ability to limit the activity of different molecules. Functions leading to the inhibition of the actions of various molecules, but also RNA interference with E6 and E7 indicate good results for the treatment of cervical cancer.

Therapeutic measures are necessary because prophylactic vaccination requires several steps because it is at the beginning. HPV research and investigations have significantly improved screening and prevention of HPV-induced lesions; however, additional study is required to characterize the biochemistry and epidemiology of numerous HPV types, which will allow for the assessment of the potential risk of persistent infection and the progression to oncogenesis.

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