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Review Article

Host miRNA-Mediated Lineage Control and HPV Transcriptional Regulation: Mechanistic Insights with Environmental Sustainability Perspectives

Nishant Kumar Singh, Agrika Gupta, Aashi Saldhi, Arushi Chowdhary, Prankur Awasthi, Saba Hasan

Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow-226028, India

Corresponding Author
Saba Hasan
Email: shasan@lko.amity.edu

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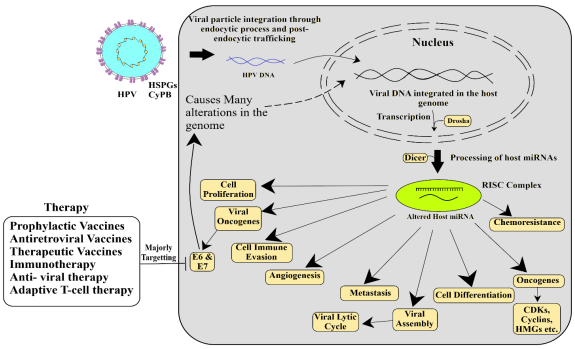
Abstract
Viruses cause 10%–15% of human cancers worldwide. Genomic instability, including DNA damage and the accumulation of mutations and aberrations, is the most common outcome of virus-induced reprogramming. One of the most infectious viruses that causes cancer and spreads sexually is the human papillomavirus (HPV). Mostly HPV causes tumours of the cervix, head and neck, anus, penis, vulva, and vagina. Most HPV infections go away within the first two years. However, in some instances, the infection persists, and the lesions develop into cancerous cells. The E7 and E6 oncoproteins are required for cancer development in high-risk HPV (HR-HPV) types, particularly HPV 18 and HPV 16. Noncoding microRNAs (miRNAs) are involved in post-transcriptional regulation in cervical cancer, as they are in other tumours, resulting in abnormal expression profiles. The miRNAs are small, non-coding, single-stranded post-transcriptional units that play a significant role in the mentioned tumours as tumour suppressors and oncogenes. However, the systemic impact of HPV16 on miRNAs is still unknown. These interactions map potential pathways, allowing possible mechanistic links to be identified. Further, we have discussed the prophylactic vaccines, which are currently in use as a preventive measure, and various therapeutic vaccines are still being developed and under clinical trials. The review paper highlights the functions of various miRNAs in HPV-induced cancers, along with HPV epidemiology, genome structure, stages of pathogenesis, the role of miRNAs in cancers, and recent advances made in the field of therapeutics.

Keywords: *HPV, HR-HPV, HPV 16, miRNAs, cancers, expression.*

GRAPHICAL ABSTRACT



1. Introduction

Cancer is defined by the Mayo Clinic (https://www.mayoclinic.org/) as being caused by gene alterations, which are activated by hormones, microbial agents, smoking, compromised immune systems, and alcohol. The hallmarks of cancer are functional skills gained by human cells during neoplastic progression that are required for malignant tumour formation. These include maintaining evasive growth suppressors, sustaining proliferative signalling, non-mutational epigenetic reprogramming, enabling replicative immortality, tumour-promoting inflammation, avoiding immune destruction, activating invasion and metastasis, polymorphic microbiomes, inducing or accessing vasculature, senescent cells, mutational genome instability, deregulating cellular metabolism, resting cell death, and unlocking phenotypic plasticity [1]. The American Society of Microbiology (ASM) (https://asm.org/articles/2019/january/the-seven-viruses-that-cause-human-cancers) says that the human tumour viruses cause 12% to 20% of malignancies worldwide. Human oncogenic viruses belong to many taxonomic groups. Hepatitis C and human T-cell leukaemia are types of cancer-causing RNA viruses, while hepatitis B, human papillomavirus, Epstein-Barr virus, and Kaposi's sarcoma-associated herpesvirus are DNA viruses [2]. High-risk human papillomaviruses and Epstein-Barr virus are classified as Group 1 (approved) human carcinogens by IARC [3]. Human Papillomavirus (HPV), of the Papillomaviridae family, is a highly specific, genetically heterogeneous DNA virus that attacks both skin and mucosal epithelium [4]. The number of HPV infections varies by geography and demographics [5], and they might be subclinical, resulting in asymptomatic individuals [6]. Sexual contact is the most common method of HPV transmission [7]. Vertical transmission of papillomavirus in babies is possible after birth. Contact-household transmission is the last route of infection. There are currently around 200 forms of HPV, but only one subtype is thought to cause cancer [8]. HPV is classified as Groups 1–4 based on the risk of carcinogenesis (IARC report 2012), and Group 1 or Group 2A with a high risk of carcinogenesis includes 13 types of HPV: HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. In particular, HPV types 16 and 18 are responsible for 70% of the HPV genotypes detectable in cervical cancer (CC). Group 2B, Group 3, or Group 4, with a low risk of carcinogenesis, includes HPV 6 and HPV 11. Typically, this type of HPV is not associated with cancer development but can cause benign lesions such as genital warts (Table 1) [9]. Persistent HPV infection can cause cancer through integration into the host genome, resulting in the activation of viral oncogenes and the loss of late capsid proteins [10]. HPV infects a variety of biological systems, including DNA damage mechanisms, double-strand DNA break repair, intracellular transport pathways, homologous recombination repair, influencing viral genome replication, and host genome integration [11]. Even though the chance of infection decreases with age, young people, especially women aged 20-24 [12], are more likely to contract fatal viruses (World Health Organisation, 2019). HPV viral infections usually resolve after two years, but some high-risk infections can lead to genital warts, cancer, and precancerous lesions (World Health Organisation, 2019). Sex partners, early sexual activity, other diseases (immunosuppression, smoking, etc.), and contraception can lead to infection [13]. The development of systematic cervical cancer screening in middle-income nations has decreased incidence and mortality, while morbidity and mortality rates have increased or remained constant in underdeveloped countries [12]. Various techniques to detect high -risk HPV infection in biological material are available. The HPV vaccine was first approved by the U.S. Food and Drug Administration (FDA) in 2006 for females aged 9 to 26 and in 2009, the approval was expanded to include males [14]. A randomised clinical trial showed protection against 90% of HPV strains. Biomarkers with a precise diagnosis of HPV-positive cervical cancer and an estimation of the dismal prognosis have important clinical value in preventing invasive cancer among women eligible for cancer screening [15]. Small non-coding RNAs known as microRNAs control target genes post-transcriptionally. miRNAs can cause mRNA destruction or translational inhibition depending on their complementarity with the target mRNA sequence [16]. In this review, we have discussed current HPV epidemiological studies, genomic structure, stages of pathogenesis, the role of miRNAs in cancers, HPV - induced cancers, and the role of miRNAs in those

cancers, and HPV therapeutics.

2. HPV genome

According to ICTV, HPV is "a small, non-enveloped, double-stranded circular DNA virus, with a diameter ranging from approximately 52 to 55 nm." [23] In 1949, Strauss et al. used electron microscopy to characterise the icosahedral-shaped virus. Harald zur Hausen[24] received the Nobel Prize in medicine in 2008 for demonstrating a connection between HPV and CC, which resulted in the discovery of two new strains, HPV 16 and 18, from CC biopsies. The upper regulatory region (URR) is the first of the genome's three functional parts, followed by the early region (E) and the late region (L) [25](Fig.1). The life cycle of HPV is associated with host keratinocytes' epithelial differentiation, and basal keratinocytes are infected by HPV through microlesion. The p97 core promoter and silencer/enhancer regions regulate the transcription of ORFs in the viral genome. The virus encodes a complete set of 8 principal proteins divided into 2 types: Early Region Proteins (E1, E2, E4, E5, E6, and E7) and Late Region Proteins (L1 and L2) [26] (Table 2). The primary capsid protein, or L1, oversees the virus's particular cell adherence as well as the host's immunological reaction to the infection. The L1 interacts with proteoglycans during its first contact, which is mostly responsible for HPV entrance. The L1 protein, which self-assembles into virus-like particles (VLPs) and may include a surface cell protein, is highly conserved among HPV types. During the infectious entry, it separates from L2, which stays in combination with HPV DNA, causing the non-enveloped virion to become uncoated. HPV is composed of 72 pentameric capsomeres encased in an icosahedral capsid, and non-coding proteins found in genomic transcripts play a role in the interaction between the virus and its host [7].

HPV subtypes are categorised into HR-HPV and LR-HPV, as mentioned in the introduction above. Pre-neoplastic lesions and carcinomas are known to be strongly associated with the HR variants 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. The LR kinds (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81) tend to create warts, but the HR types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) are known to be strongly connected with pre-neoplastic lesions and carcinomas [27]. HPVs are classified into five genera (alpha (α), beta (β), gamma (γ), mu (μ), and nu (ν) papillomaviruses) based on genetic make-up, evolutionary relationships, and clinical traits. A subgroup of α-papillomaviruses, known as oncogenic HPVs, is trophic for areas of cutaneous, mucosal, and mucocutaneous connections. Whereas β- and γ-papillomaviruses attack the cutaneous skin, HPVs belonging to the μ- and v-genera produce warts on the hands and feet. In the GenBank and EMBL databases, 75% of the genotypes have been sequenced. Papillomavirus genotype α-9 is the most hazardous (Lei).

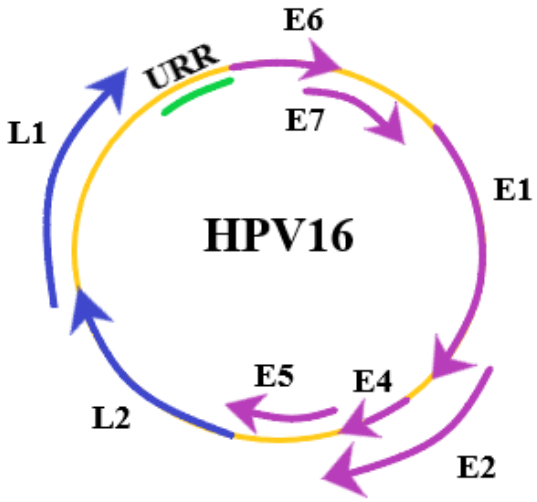


Figure 1. HPV genome structure: URR- upper regulatory region, early proteins- E1, E2, E4, E5, E6, and E7, late proteins- L1 and L2.

3. Stages of HPV pathogenesis in the host cell

The HPV cycle is initiated by penetrating the host's undifferentiated basal epithelial cells. Host receptors and viral antigens must interact for viral penetration. However, morphological similarities are observed, representing proliferative benign or malignant lesions with the skin and anal or vaginal canal or oropharyngeal mucosa [23]. HR-HPV subtypes cause malignant lesions such as squamous cell carcinoma (SCC), whereas LR-HPV subtypes develop minor benign lesions that are condylomatus warts. Host-virus interactions allow viruses to enter undifferentiated epithelial cells. It is caused by high shear stress, chemical shock, and external ingestion. Radiation shock protects the viral genome from oxidative stress. Basal epithelium is infected by the HPV virus with a high mitotic rate despite genetic variability. Cellular elements associated with the viral long control region (LCR) promote post-infection expression in basal epithelial cells [30] (Fig. 2). Viral proteins are created by processing and translating transcripts. The primary viral oncogenes E7 and E6 target pRb and p53, leading to increased proliferation (Fig. 2) of the infected cell. One of the transcription factors, Yin Yang 1 (YY1), contains a zinc finger that may activate, initiate, stop, or repress transcription) [31] and interacts with LCR to control

Table 1. The table is about major HPV infected tumor sites, primary HPV type, HPV reference fraction, worldwide burden, the burden in India, predictive implication of HPV positivity

SL. NO	Tumor Site	Primary HPV Type	HPV Reference Fraction (%)	Worldwide Burden (%)	India Burden (%)	Predictive Implications of HPV Positivity	References
1.	Cervical	16 & 18	More than 90%	70% of cervical cancer	83.2% of cervical cancer	Better prognosis, high sensitivity to radiation and chemotherapy	[17]
2.	Head and neck	16	30%	20% of Head and neck cancer	20% of Head and neck cancer	Better prognosis, potential for de-escalation of therapy	[18]
3.	Vaginal	16	55–64%	4.5% of vaginal cancer	24% of vaginal cancer	Prognosis varies; better outcomes with early-stage detection	[19]
4.	Anal	16	more than 90%	More than 90% of anal cancer	More than 90% of anal cancer	Better response to chemoradiation, potential for targeted immunotherapy	[20]
5.	Vulvar	16 & 33	25–45%	70% of Vulvar cancer	30.3% of Vulvar cancer	HPV-positive cases generally have a better response to treatment	[21]
6.	Penile	6, 16 & 18	63%	50% of penile cancer	more than 50% of penile cancer	HPV-positive tumors tend to be less aggressive, better response to treatment	[22]

HPV oncogene transcription through E6 and E7. YY1 is essential for cancer development, affecting cell cycle, proliferation, differentiation, and apoptosis. According to research, YY1 has a function in CC by regulating E-cadherin expression and HPV-16 E6 and E7 oncoproteins. Elevated YY1 and HPV16 E6 expression, as well as decreased E-cadherin levels, are closely linked to cervical epithelial cell carcinoma and premalignant cervical lesions that proceed to CC. Four distinct lysine-rich heparin-sulphate (HSPG) binding sites in the L1 protein are necessary for successful infection [32]. The L1 and HSPG initially bind in the intraepithelial surrounding, where the cellular protease furin cleaves L2, and the capsid proteins undergo structural changes. Thereafter, HPV is endocytosed after being transported to an internalisation receptor. Via endocytosis, the virus travels in tiny vesicles through the Golgi apparatus and endoplasmic reticulum to reach the nucleus, where a sequence of events and alterations in vesicle structure permit the discharge of the DNA from the virus and its accumulation near the membrane of the

Table 2. Key functions of HPV-expressed proteins.

Serial No.	Protein	Function	Reference
1.	E1	ATP- dependent DNA helicase regulates transcription	[29]
2.	E2	Initiate and regulate HPV proliferation, negative E6 regulator, E1 binding	[26]
3.	E4	Involved in viral release and transmission	[26]
4.	E5	A major oncoprotein in carcinogenesis supports E6 and E7 modulation	[26]
5.	E6	p53 suppressor, tumour development, simulates DNA repair, activates apoptosis	[29]
6.	E7	Activates keratinocyte differentiation, increases accessibility, genomic stability to viral particles, initiates late promoter, degrades pRb, promotes cell cycle progression, and inhibits TLR9 expression, affecting antigen	**[25]**
7.	L1	Capsid protein, encapsulation of viral DNA	[29]
8.	L2	Viral genome to nucleus delivery, complete virus shredding	[25]

nucleus. Viral replication is initiated by the entry of the episomal viral DNA complexed with L2 through nuclear pores into the nucleus and finally finds its home in the ND10 nuclear domains. To start the production phase of the viral life cycle, epithelial cell differentiation is essential for HPV replication. L1 and L2 (capsid proteins) facilitate virion replication. Sequential viral protein synthesis is routinely produced by dedifferentiating basal cells. Hence, latent or active viral replication increases the risk of HPV infection. Thus, the L1 and L2 proteins are necessary for the infection process. Host histones organise DNA into chromatin inside the virus, then enter the nucleus along endocytic pathways. Furthermore, except for the E4 protein, gene expression of early proteins prolongs the viral genome and promotes HPV infection. The viral genome grows because of cell differentiation, and particles are released from the top terminally formed skin layers. Infection with HR-HPV strains can cause integration of the HPV genome within the host [33]. HPV virions enter the extracellular space through trauma-induced microdamage. In some cases, especially inside the uterine mucosa, the virus can pass through the transformation zone and enter the target tissue without mucosal damage. Inflammation, immunosuppression, and antiviral responses influence immune cell infiltration [23]. Additionally, viral proteins encourage deregulation in the host's normal cell cycles (Fig. 2). Viruses alter cellular signalling, disobeying regulatory pathways, to promote viral replication. The virus transitions into replication mode, resulting in the production of excessive viral proteins. Delayed expression of viral proteins in differentiated cells causes delayed antigen expression [7]. Renewing the mucosal epithelium and basal layer requires basal epithelial cells to divide. At the molecular level, cell division is maintained by the hyperexpression of the E6 and E7 proteins. E6 and E7 proteins maintain cell division by integrating the viral genome into the

host genome. The decrease in expression of E2 has detrimental molecular ramifications that raise the risk of HPV-related illnesses and malignancies. Moreover, HPVs promote carcinogenesis through gene and pathway activation, such as the P13K/Akt/mTOR pathway, Notch, RAS, and growth factor-mediated receptors [34].

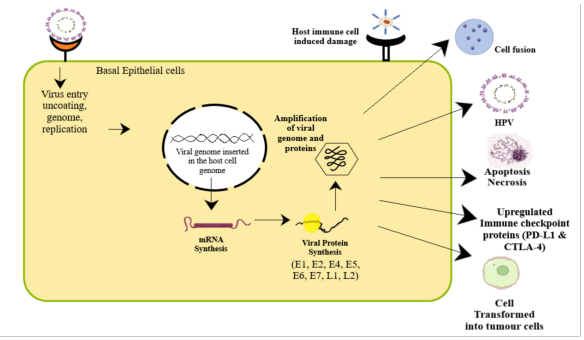


Figure 2. Schematic representation of stages of pathogenesis in HPV infection and the interplay between different mechanisms through which viruses cause host cell damage and disease.

3.1 Chromosomal Alterations

Although HR-HPV E6 and E7 have the potential to immortalise cells, they are not always enough to cause cellular transformation and will not trigger cancer directly. Malignant progression requires additional genetic insults caused by aneuploidy and chromosomal instability, such as chromosome number or shape changes. Aneuploidy emerged as the first genetic change in malignancies more than a century ago. Chromosomal instability (CIN) refers to the continuous rate of chromosome mis segregation, while aneuploidy refers to the aberrant chromosome composition that differs from haploid cells. If aneuploid cells faithfully pass on their aberrant content to every daughter cell, they can remain stable. Bulk DNA sequencing or karyotyping can quantify aneuploidy, although direct detection of mistakes during mitosis makes CIN more difficult to quantify [35]. Since HPV lacks or has reduced p53, it is well adapted to cause CIN, which is present in about 50% of malignancies. Aneuploidy and CIN initially have a detrimental effect on cellular fitness; however, chromosomal alterations in tumours can have a beneficial effect on fitness and can be advantageous to malignancies. CIN promotes tumour formation and drives intratumoral heterogeneity, which can result in treatment resistance and disease progression. It also enables cells to take up advantageous aneuploidy events (deletion of the PTEN tumour suppressor gene on chromosome 10q) [36], eliminate harmful ones, and adapt to various tumour circumstances [35]. The HPV-induced CIN types are listed below in Table 3.

3.2 Epigenetic Regulation

Epigenetics is a post-translational modification (PTM) process that alters gene expression but not the underlying DNA sequence. HPV genomes are structured in virions and infected cells as nucleosomes packed into chromatin. Post-translational histone changes, including acetylation, phosphorylation, and methylation, as well as DNA methylation, regulate HPV genomes. These changes are regulated by a balance of histone readers-methyltransferases (KMTs), acetyltransferases (HATs), and histone erasers-demethylases, and deacetylases (HDAC) [39]. The investigation of HPV31 chromatin revealed considerable chromatin reconfiguration surrounding the late promoter region, signifying accessible DNA regions for transcriptional machinery recruitment. This evidence suggests that viral promoters undergo chromatin restructuring at distinct stages of the viral life cycle. Unexpectedly, epithelial differentiation results in lower YY1 expression and loss of epigenetic inhibition of the early promoter region, which leads to overexpression of HPV18 E6 and E7 [40] Histone acetylation is a reversible and fluid process that modifies chromatin spatial density and is controlled by histone-modifying enzymes such as HATs and HDAC. HDACs eliminate acetyl residues, while HATs acetylate lysine residues. HDAC activity controls the turnover of histone acetylation. HPV16 E7 interacts with HDAC1 and HDAC2 indirectly through Mi2β (the largest protein in the NuRD complex, a chromatin organisation modifier (Chd), belonging to the SNF2 family of helicases) without requiring Rb binding to participate in the nucleosome remodelling and histone deacetylation complex. DNA methylation is an epigenetic marker that occurs when a methyl group is covalently added to the DNA's cytosine ring at position C-5. The E2 protein plays a crucial role in controlling transcriptional activity and HPV genome replication. By attaching to E2-binding sites (E2BS), which are partly palindromic sequences (5′-ACCGN4CGGT-3′) found inside the LCR, E2 controls these viral activities. The E6 and E7 oncoproteins of HPV16 have an impact on DNA methyltransferase DNMT; the E7 protein binds to DNMT1 directly and increases its activity. E7 may start DNMT1 transcription via the pRb/E2F pathway, although the exact mechanism behind this activation is uncertain. DNMT3A and DNMT3B protein levels upregulate high-risk E7 oncoproteins, while the E6 protein inhibits p53, which upregulates DNMT. The activation of the E7 protein's chemical mechanism is still unknown [41]. A chromatin alteration brought

Table 3. Role of HPV in HPV-Induced CINs

Serial No.	HPV-Induced CIN Type	Description/Mechanism	References
1.	Polar Chromosome	Polar chromosomes are chromosomes that are persistently misaligned near spindle poles. The HPV16 E6 oncogene promotes the proteasomal degradation of the mitotic kinesin CENP-E via E6AP-mediated ubiquitination, resulting in polar chromosome misalignment during mitosis. This misalignment contributes to increased chromosomal instability (CIN) in HPV16+ cells, independent of the E7 oncogene, p53, and the E6 PDZ binding domain, but may be further exacerbated by E7-induced reactive oxygen species, causing DNA damage.	[35]
2.	Centrosome Amplification	HPV16 E7 drives centrosome amplification by promoting centriole overduplication during an extended S phase, leading to multipolar spindle formation. E6 contributes by inducing tetraploid cell proliferation after cytokinesis failure. Supernumerary centrosomes can cluster into two spindle poles, enhancing cell survival but increasing chromosomal instability. This centrosome amplification is observed in HPV+ cervical and anal cancers, though rare in head and neck cancer models.	[37]
3.	Chromosome Bridges, Lagging Chromosomes and Micronuclei	HPV16 E6 and E7 promote mitotic abnormalities, including chromosome bridges and lagging chromosomes, in human keratinocytes. E6-induced p53 degradation and E7-mediated Rb breakdown drive cell cycle progression despite DNA damage, leading to chromosomal instability (CIN). Chromosome bridges arise from DNA damage or telomere shortening due to altered telomerase activity, while lagging chromosomes result from improper kinetochore-microtubule attachment. These lagging chromosomes can form micronuclei, which are diagnostic markers for HPV-positive pre-cancerous lesions. E6 and E7 together facilitate CIN and micronuclei formation, bypassing normal cell cycle checkpoints and increasing oncogenic potential in HPV-infected cells.	[38]

on by an HPV infection may result in aberrant gene expression. Tumour suppressor genes, such as p53, are silenced in high-risk HPV-associated lesions due to DNA methylation in CpG island regions. This disturbance may serve as a biomarker for early detection or risk assessment of cervical cancer precursors. Human foreskin keratinocytes (HFKs) express HPV16 E7, leading to greater levels of activation markers such as H3K9 acetylation and H3K4 methylation. These histone modifications rely on E7's Rb and HDAC binding domains. A ChIP study by Zhang et al. reveals that HPV16 E7 enhances histone acetylation on the promoter regions of E2F-responsive genes, cdc25a and E2F1 [42].

3.3 Transcriptional Factors /Translational Regulation or Modification

The long control region (LCR), a non-coding area of around 750 bp that is situated upstream of the E6 gene, controls the transcription of the viral oncogenes for E6 and E7. Enhancer elements located in the central region of the LCR control the expression of early genes from the early promoter (P97 for HPV16 and P105 for HPV18) in a way that is specific to epithelial cells. AP-1, NFI, and TEAD1 are among the transcription factors (TFs) that connect to and stimulate this enhancer element. In chromosomally inserted HPV genomes, the LCR is frequently maintained and controls the expression of viral oncogenes [43]. For this reason, understanding the regulatory processes of LCR-driven transcription is crucial to comprehending the molecular underpinnings of HPV tumorigenesis. In addition to TFs, HPV proteins' post-translational modifications (PTMs) are important for both the viral life cycle and the development of cancer. A consensus phosphorylated site for Casein Kinase II (CKII) is present in HPV E7 in the CR2 homology domain's N-terminal portion of the protein [44]. Because the CKII-phosphorylated S31/S32 residues of E7 have extra negative charges, the LXCXE motif, which is located ahead of the phosphoacceptor site of CKII in E7's CR2, binds pRB and is strongly engaged. Phosphoryl regulation of the E6 oncoprotein is likewise highly pronounced. Studying the interaction between high-risk E6 proteins and Rho-small G protein-activated serine/threonine kinase (PKN), a fatty acid considerably homologous to PKC, was the first way to demonstrate this. While the precise function of PKN phosphorylation in E6 transforming activity remains unclear, the observation of E6 binding to the carboxy-terminal region of PKN raises the possibility that Rho and E6 may interact with PKN simultaneously, thereby enabling E6 to impact Rho-mediated signalling and connecting E6 phosphorylation to either E6-induced immortalisation or the control of the viral life cycle. Proteins that bind serine and phospho-threonine are known as the 14-3-3 family, and they are involved in the control of numerous biological processes, some of which are directly related to the development and aggressiveness of cancer [45]. Phospho-E6 and 14-3-3 seem to interact in a way that depends on 14-3-3 to link the stimulation of stress-induced pathways to E6 phosphorylation and the suppression of p53 transcriptional function. Given that replication takes place in environments with high DDR activation, these findings imply that phosphorylating E6 in these circumstances will help the virus further overcome p53 activity. This process has significant consequences for the viral life cycle. All of these findings—new transcription factors and various ways that the HPV E6 and E7 cancer-causing proteins are phospho-regulated—offer promising new avenues for the development of therapeutic interventions against HPV-induced cancer.

3.4 DNA Damage Repair (DDR)

DNA damage within cells can be repaired using a variety of techniques, which comprise break-induced replication, alternative end-joining (alt-EJ), homology-directed recombination (HR), non-homologous end-joining (NHEJ), mismatch repair, base excision repair, nucleotide excision repair, and other DNA damage tolerance pathways like repriming polymerases and trans lesion synthesis. The three master kinases from the phosphatidylinositol-3-kinase-related kinase (PIKK) family—DNA-dependent protein kinase catalytic subunit (DNA-PKcs), ataxia telangiectasia-mediated (ATM), and ataxia telangiectasia and Rad3-related (ATR)—play a distinguishing role in the DNA damage response (DDR) network. Double-stranded DNA (DSBs) excites the ATM, ATR, and DNA-PKcs kinases, whereas single-stranded DNA (ssDNA) breaks and stresses, while replication activates the ATR kinase [46]. The Laimins, Fradet-Turcott, and Moody laboratories discovered numerous elements of the ATM and ATR DNA damage-sensing pathways, coupled with the homologous recombination DSB repair pathway, which are needed for HPV amplification [47]. Numerous signalling pathways do indeed become hyperactive during amplification, generating major changes in the cellular environment. Topoisomerase 2β-induced DSBs boost HPV replication and contribute to DNA damage signals generated by the virus [48]. HPV stimulation of DNA repair reactions has been

linked to HPV E7-induced replication stress, namely nucleoside pool depletion [49]. This viewpoint is backed by the discovery of replication stress indicators. However, cells responded to HPV E7 expression by increasing nucleoside pools. The TLS pathway aims to minimise replication stress-induced DSBs created by HPV oncogene transcription. It is unclear how HPV oncogenes directly contribute to replication stress-induced DSBs by obstructing TLS or indirectly by raising replication stress exceeding the route's capability[50]. HPV E7 and E6 both damage the TLS route via destabilising p53, with HPV E7 subjecting the TLS route to significant replication stress and HPV E6 directly degrading TLS. The interactions of essential replication proteins make the HPV genome less sensitive to rapid alterations than other viruses. HPV E1, most likely via helicase activity, initiates DNA damage repair (DDR) in HPV replication foci, resulting in viral replication factories that incorporate DNA damage repair proteins. HPV oncogenes are expressed throughout carcinogenesis and amplification, although they seldom reproduce. Even without a target, they can transport DNA repair components away from defective DNA. HPV oncogenes hinder DNA repair mechanisms such as FANCD2 mislocalisation, triggering Fanconi anaemia by repairing DNA cross-links during S-phase and reducing DSB repair by homologous recombination. When homologous recombination fails, they instead repair DSBs employing the microhomology-mediated end-joining pathway [10]. β-HPVs damage DNA repair signals and commonly infect skin beyond the vaginal canal. Like high-risk α-HPVs, they interact with DNA repair factors to prevent cell cycle arrest caused by UV damage. β-HPVs do not require strong amplification or numerous DNA repair factors [51]. β-HPV infections are less associated with carcinogenesis and do not survive in tumours, unlike high-risk α-HPV, which requires ongoing viral gene expression. β-HPV infections can lead to cancer by inhibiting DNA repair pathways, a "hit and run" strategy. Evidence regarding this virus is ambiguous, and a "smoking gun" has proved difficult to locate. Patients with EVER1 and EVER2 mutations may develop non-melanoma skin cancer because of immune inadequacies related to a particular strain of β-HPV. Research on β-HPV has yielded promising findings in the field of basic sciences. E6 from β-HPVs has been linked to skin cancer in individuals with EVER2 and EVER1 mutations, as it affects cellular DNA repair. This reduces the expression of important DNA repair genes, raising the risk of DNA damage [51]. Recent research reveals that β-HPV E6 disrupts the non-homologous end-joining process, which was previously thought to be the most plausible solution for repairing DSBs [52].

3.5 Signalling Pathways

HPVs typically linked to cancer, notably HPV16 and HPV18, encode two late genes (L1 and L2) and six early genes (E1, E2, E4, E5, E6, E7). These proteins help the virus replicate, amplify, and release. The E5, E6, and E7 proteins are critical oncogenes that stimulate host cell proliferation and viral replication. E6 and E7 can integrate into host genomes, whereas E5 is exclusively generated by viral genomes that stay as episomes. The E5, E6, and E7 oncoproteins may govern and change several cell-signalling pathways (Table 4), causing cancer. These molecular pathways play crucial parts in malignant transformation; therefore, targeting them may have therapeutic implications [26].

3.6 Immune Responses

HPV infections cause adaptive and innate immune responses. During infection or intimacy, HPV proteins are displayed on Langerhans cells (LCs), which are specialised antigen-presenting cells. The transition zone has lower LC levels than the exocervix, while squamous intraepithelial lesions (SILs) have a higher LC count despite their ineffectual activity. Furthermore, following HPV16 L1 infection, LCs cease to develop an efficient immune response because of their immunological tolerance. Dendritic cells (DCs) and monocyte macrophages (macrophages) in the skin use MHC molecules to recognise HPV antigens. They are activated by contacts with viral components such as ssDNA, viral RNA, CpG motifs, and TLRs. TLRs trigger innate immune responses, including disease-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) by recognising certain microbial components and producing IFN, defensins, and proinflammatory cytokines that cause local inflammation [60]. Macrophages are stimulated by cytokine emissions and can lyse HPV-affected cells by utilising TNF-α or antibody-dependent cytotoxicity. Keratinocytes emit chemokine monocyte chemotactic protein-1 (MCP-1) in response to TNF-α, which attracts macrophages to infection sites. However, HPV 16's E6 protein blocks its secretion. Similarly, HPV16 E6 and E7 proteins affect the synthesis of MIP-3α. Natural killer (NK) cells are essential to the immune system's early defence; they target viruses and cancer cells without surface MHC molecules. NK cell deficiency in CC patients is caused by downregulation of NK cell receptor expression, resulting in decreased cytotoxic effect against cancer cells, namely NKp30, NKp44, NKp46, and NKG2D. As

a mediator between innate and adaptive immunity, CD1d interacts with CD1d-restricted natural killer T (NKT) cells to activate NKT cells, induce cytokine production, and support adaptive immune responses. On the other hand, HPV6 or HPV16 use the E5 protein to lower CD1d expression during infection, which facilitates immune evasion [61]. While adaptive immunity remains crucial for lesion regression, innate immunity is key for eliminating viral infections. To eradicate low-grade lesions, CD4+ T helper 1 (TH1) cells release IL-2, IFNγ, and CD8+ Tc cells upon recognising HPV oncoproteins E2 and E6. CD4+ TH1 cells regulate high-grade neoplasms by recognising E7 proteins. It takes CD8+ cytotoxic T cells to eradicate the infection and guarantee patient survival [30]. During HPV infection, specialised antigen-presenting cells (APCs) transform HPV proteins into antigenic peptides and present them to CD4+ helper T cells via MHC II molecules on their surface; therefore, they begin an adaptive immune response. T cells produce cytokines such as IL-6, IL-12, IL-1, and TNF-α, which control the immune response and cause local inflammation. CD4+ T cells develop into Th1 and Th2 cells, which promote both cell-mediated immunity and antibody production. Th1 cells produce cytokines and incite CD8+ T cells to differentiate into cytotoxic T lymphocytes (CTL). These CTLs act as effector T cells, killing cancer or CIN cells with HPV antigens [62]. HPV employs various tactics to elude the immune system and promote cancer growth. It evades detection by decreasing viral antigens and altering the production of immune response proteins, allowing it to last longer [63]. Another immune evasion mechanism is the generation of viral particles throughout regular cell shedding in the exterior epithelial layer, which restricts immune cell access and aids HPV in avoiding immune detection. HPV also impacts protein-protein interactions in host cells by modifying protein functions and producing antigen-processing proteins, including PSMB8 and PSMB9. Furthermore, the HPV16 E5, E6, and E7 proteins impede the interferon signalling pathway by interacting with transcription factors (interferon response factors) and typically activating interferon genes [30].

4. Mechanism of HPV-driven carcinogenesis

The fundamental mechanism of HPV-16 and 18-induced cancer growth is already well known. The majority of transforming proteins for HPV types linked to cancer are encoded by the extremely conserved HPV E6 and E7 genes, which are present in nearly all HPV types currently known. After the virus has integrated within the host genome, the expression levels of the E6 and E7 proteins rise substantially. This phenomenon occurs because the E2 gene is disrupted during the virus's transition from circular to linear form. Essential proteins in the cell's machinery that govern the cell cycle and inhibit cancer development interact with E6 and E7 proteins [64]The 100 kDa cellular protein E6-associated protein (E6AP), which is an E3 ubiquitin ligase, interacts with HPV16 E6's conserved LXXLL motif. Once connected to p53's central section, known as the core domain, the E6/E6AP complex quickly ubiquitinates it, causing it to be degraded by proteasomes. Consequently, proapoptotic proteins like BAX, which are physiologically regulated by TP53, are produced less often, and TP53′s regulatory function in the cell cycle is lost [65]. The interaction of E6 and E6AP also contributes to other HPV-induced activities, such as the transcriptional activation of the hTERT (human telomerase reverse transcriptase) gene, which generates the telomerase complex′s catalytic component. Telomeres shrink because of cellular division until they reach a threshold size, which induces replication-dependent senescence in somatic cells, which are typified by minimal to no telomerase activity. In contrast, HPV16-infected cells have tremendous telomerase activity, which permits unrestricted cell division and telomere length maintenance. Because HPV16 E6 associates with E6AP, it can facilitate the NFX1-91 transcriptional repressor's degradation, which in turn activates hTERT transcription. The transcription of p105, a component of the non-canonical NF-kB pathway, is adversely regulated by NFX1-91. Thus, E6-mediated degradation of p105 stimulates the NF-kB signalling pathway. In addition, E6 from beta and other cutaneous HPV types, as well as LR and HR mucosal HPV types, has established a method to block the apoptotic response by causing Bak, a Bcl-2 family member, to degrade. The ubiquitin-proteasome pathway and its association with E6AP also play a role in mediating this activity [66]. Conversely, the retinoblastoma (Rb) tumour suppressor protein interacts with and is rendered inactive by the high-risk HPV strains' E7 oncoprotein. Normally, Rb prevents the cell cycle from proceeding from G1 to S phase. E7 inactivates Rb, disrupting cell cycle control and encouraging unregulated cell proliferation. The interaction between the E7 protein and the cellular RB1 protein releases the powerful transcription factor E2F/DP, which is normally bound to RB1 and inactive during the G1 phase. Thus, the viral protein replicates the physiological conditions of the late G1 phase, when RB1 is phosphorylated to trigger E2F/DP release [58]. E7 possesses three conserved regions (CR1-3), making it related to

adenovirus E1A. CR2 is home to a casein kinase II phosphorylation site as well as an LXCXE motif that interacts with the cell cycle-regulating tumour suppressor pRb1 and associated proteins, p107 and P130. E2F family members (E2F1-3) are under the supervision of pRb1, which keeps cells quiescent. When HPV E7 attaches itself to pRb, it is broken down by proteasomal processes, which in turn triggers the expression of E2F-regulated genes such as cyclin A and E. Cell cycle progression and CDK activity are driven by this activation. HPV16 E7 uses a complex comprising cullin2 to mediate the degradation of pRb. It is unknown, nevertheless, if E7 from different HPV strains uses comparable processes to encourage pRb degradation. The other two pRb-related proteins, p107 and p130, are part of co-repressor complexes that include histone deacetylase enzymes and other E2F family members (E2F4, E2F4, or E2F5). Specific E2F elements are bound by these complexes, which inhibits the expression of certain genes. HPV-16E7 has been demonstrated to destabilise p130, probably changing the E2F complexes' inhibitory activities. Epigenetic modifications linked to gene silencing, such as histone 3 lysine 27 trimethylation (H3K27me3), are caused by interactions between E2F6 and several polycomb complexes [67]. The interaction between HPV16 E7 and E2F6 prevents E2F6 from suppressing the expression of specific genes in cells. In addition to its ability to precisely target E2F complex systems, E7 also binds directly to the CDK inhibitors p21WAF1/CIP1 and p27KIP1, neutralising their inhibitory influences on the cell cycle. Moreover, cyclin A/CDK2 complexes can directly interact with HPV16 E7. When E6 and E7 oncoproteins interact, it can cause cell transformation, which is marked by unchecked cell division and the development of precancerous lesions. Infected cells become incapable of differentiating normally and have genetic and epigenetic changes that accelerate the development of cancer [68]. Oncoproteins E6 and E7 activate the Wnt pathway, increasing β-catenin levels and perhaps promoting gene transcription for cell proliferation. Lower protein levels of the β-catenin degradation inducer (Siah-1) may contribute to this effect. In addition, human HPV-positive tumours have an increase of nuclear β-catenin. Similarly, HPV-infected cells changed NOTCH. E6 oncoprotein regulates the NOTCH pathway by interfering with the interaction of mastermind-like proteins (MAML) and NICD proteins, which are critical components of the Notch signalling system. As a result, NOTCH-targeted genes such as HEY and HES, which serve as powerful transcriptional repressors, decrease their expression. In addition to the carcinogenic potential of the E6 and E7 proteins, viral integration inside the host genome promotes genomic instability [69]. Additionally, E6 and E7 activate the widely recognised carcinogenic pathway, PI3K/AKT/mTOR, in head and neck cancer. Through upstream regulators including RPTK (a type of receptor kinase) and PI3K (phosphoinositide 3-kinase), these viral oncoproteins can activate the Akt pathway, leading to enhanced proliferation [70]. According to multiple studies, HPV-driven oncogenesis may not be the only way the virus contributes to tumour growth. The apolipoprotein B mRNA editing enzymes, or APOBECs, are involved in the noncanonical process of viral (as well as HPV) oncogenicity. The enzymes in concern belong to the APOBEC3 class, which comprises A3A, A3B, A3C, A3DE, A3F, A3G, and A3H deaminases. When the cell's protein machinery identifies foreign nucleic acids, it initiates an interferon-mediated signal cascade that activates these enzymes [71]. AIM2, TLR9, DAI, and RNA polymerase III, among other proteins, have been discovered to detect ssDNA and DSBs, respectively. The foreign DNA's cytidine to uridine deamination is mediated by the overexpressed APOBEC enzymes. Since uridines are unusual DNA nucleosides, the UNG2 glycosylase recognises them and converts them into a simple lesion, which causes the foreign DNA to be subsequently broken down by the uracil excision mechanism [71]. The HPV DNA in infected cells has been shown to be edited by this class of enzymes [72]. When together, these provide a barrier that stops the transfer of DNA across species. Given that the most common mutation in cancer genomes is the C → T transition, it permits conjecture that the APOBEC enzymes produced by the virus may inadvertently cause changes in the host cell's genome that encourage transformation into cancerous cells. The AID deaminase, which plays a key role in B-cell development by inducing somatic hypermutation, has been implicated in cancer development not just in B-cell lymphomas but also in other tumor types. Additionally, APOBEC enzymes have been shown to introduce specific mutations in tumour genomes, creating a distinct mutational signature. APOBEC-induced carcinogenesis is largely responsible for common mutations in the PIK3CA oncogene, such as E542K and E545K [73]. Recent investigations have highlighted the importance and intricacy of APOBEC-related pathways in HPV-associated malignancies; however, it is still unclear if this non-canonical mechanism predominates over mechanisms based on HPV oncoproteins.

Table 4. HPV Early Proteins Activity in Signalling Pathways

Serial No.	Early Protein	Signalling Pathway	Mechanism	Function	References
1.	E5	Fas/FasL Pathway	HPV E5 suppresses the extrinsic apoptosis pathway by reducing Fas receptor expression and inhibiting FasL-induced caspase-8 activation in HaCaT cells. E5 interferes with death receptor activation, including TNF receptors and Fas, which are typically triggered by their respective ligands (e.g., TNF-alpha, FasL). This blockage prevents apoptosis and promotes cell survival. By inhibiting these apoptotic signals, E5 contributes to the persistence of HPV-infected cells and enhances their oncogenic potential.	Influences signal transduction pathways; inhibits endocytic trafficking; increases the activity of signalling cascade emerging from the EGFR in human keratinocytes; activates c-jun expression via the Ras-dependent pathway.	[53]
2.	E6	p53	HPV E6 inhibits the tumour suppressor p53 by binding to E6-associated protein (E6AP) via an LXXLL motif, leading to p53 ubiquitination and proteasomal degradation. This prevents p53-mediated apoptosis in response to DNA damage, contributing to oncogenesis. In human keratinocytes, E6 inactivation allows p53 accumulation, hindering HPV DNA retention and viral propagation, while silencing p53 or expressing wild-type E6 restores HPV amplification, highlighting E6's critical role in carcinogenesis.	A crucial cancer prevention protein; maintains genome integrity; ceases the cell cycle; repairs the damaged DNA; minimizes cell accumulation; induces apoptosis if DNA damage is substantial.	[54]
	E6	PI3K/Akt Pathway	HPV16 E6 inhibits PTEN via PDZ proteins, leading to increased pAkt and cell growth. E6 activates mTOR signaling by binding to E6AP, which degrades the mTOR inhibitor TSC2, although TSC2 levels remain unchanged in E6-expressing cells. E6 also activates upstream kinases like PDK1 and mTOR complex 2,	Control cell growth, cell mobilization, cell proliferation, cell survival, and angiogenesis; associated; correlated with tumour progression, initiation, and metastasis, and drug resistance.	[55][27]

5. Role of miRNAs in cancers

miRNAs are small, single-stranded, noncoding RNA fragments, 21-23 nucleotides in length, controlling

			enhancing Akt phosphorylation. Additionally, E6 prolongs activation of receptor tyrosine kinases (EGFR, insulin receptor, IGFR) and strengthens the growth factor receptor-bound protein 2 (GRB2), leading to activating the PI3K/Akt pathway and improving cell survival and proliferation.		
2.	E6	Wnt Pathway	Human HPV16-positive cancer specimens and initial dysplastic lesions show nuclear β-catenin accumulation, suggesting that the HPV oncogene activates the Wnt pathway. This build-up is associated with tumour growth in cervical cancer patients and HPV infection in cell lines. Silencing the E6 gene in HPV+ cells reduces nuclear β-catenin, showing that E6 regulates the Wnt pathway. E6AP activation necessitates p53 degradation or adherence to PDZ-containing E6 targets.	Regulate differentiation processes; promote cell proliferation due to accumulation of β-catenin; that transcribes a wide range of genes; β-catenin is phosphorylated and ubiquitinated by β-TcRP ubiquitin ligase, leading to its destruction; additionally focuses on positive and negative moderators such as Axin2, Wg, FZD7, DKK-1, and sFRP-2 to produce autoregulation.	[56]
	E6	Notch Pathway	HPV E6 modulates the Notch signaling pathway, leading to increased Notch1 expression and activation in cervical cancer progression. E6 stimulates Notch receptor cleavage, revealing the Notch intracellular domain (NICD), which promotes the PI3K/Akt pathway and induces tumorigenesis. In HPV-positive cell lines, Jagged1 expression is upregulated in late-stage cervical lesions, further activating Notch signaling. Conversely, inhibiting the Notch pathway reduces tumour growth, emphasizing E6's role in driving Notch-mediated cancer development through multiple mechanisms.	Key role in cell differentiation, growth, immune responses, various diseases (cancer), and the development of organs.	[57]
3.	E7	pRb	HPV16 E7 disrupts the Retinoblastoma protein (pRb) by inducing its proteasomal degradation via the cullin 2 ubiquitin ligase complex. This releases E2F transcription factors (E2F1-3), promoting cell cycle progression, reducing apoptosis, and increasing genetic instability. E7 also directly binds and activates E2F1 while inhibiting E2F6. Additionally, E7 inactivates other pRb family members, p130 and p107, disrupting E2F4 and E2F5 regulation, leading to synergistic effects on cell cycle control.	Causes a rise in cell cycle and its regulation, and reduces apoptosis; inhibits the transcriptional inhibitor activity of E2F6.	[58]

	E7	PI3K/Akt Pathway	HPV16 E7 activates the PI3K/Akt pathway by binding and inactivating Rb, increasing Akt activity in keratinocytes. E7 also inhibits protein phosphatase 2A (PP2A), which normally dephosphorylates Akt, by binding to its catalytic and structural subunits, further enhancing Akt signaling.	Reduces reactive oxygen species (ROS) in cells; has a high survival rate in HR-disease-specific patients, an important therapeutic agent.	[59]
3	E7	PI3K/Akt Pathway	These effects are observed in HPV-positive cervical lesions and contribute to cell cycle progression and oncogenesis.This activation leads to increased cytoplasmic retention of p27, reducing its tumour suppressor function.		[59]

cellular functions such as cell division, gene transfer, and differentiation. miRNAs were discovered in 1993 when Victor Ambros and Gary Ruykun found a correlation between 22-bp RNA and LIN-14 that contributes to Caenorhabditis elegans development. miRNAs have been shown to mediate information between physiological and pathological processes and may be transported between cells in exosomes. These RNA fragments are tumour-specific and secreted by oncogenic cells, providing biomarkers [74]. miRNAs are divided into intragenic and intergenic miRNAs depending on where they are found. Intergenic miRNAs are antisense, intronic, junction, and exonic, while intergenic miRNAs are produced from their own promoters. RNA polymerase II creates primary miRNA, fabricated by Drosha (an RNA endonuclease) [75]. miRNAs are transcribed as a single, protracted transcript, with two types of biosynthesis pathways: canonical and non-canonical. They regulate genes through homeostatic regulation and feedback mechanisms [76]. miRNAs are essential for cancer development and progression [77] (Fig. 3). Extracellular miRNAs may be used as cancer biomarkers to predict root cause and prognosis. Cancer cells secrete microvesicles, cytokines, and exosomes to regulate TME (tumour microenvironment). miRNAs regulate cancer initiation, progression, and immune response [78]. miRNAs are involved in carcinogenesis because of tumour suppressor miRNAs and oncogenic miRNAs (Fig. 3). Some upregulated miRNAs operate as tumour-promoting oncomiRs experiencing gain of function in cancer formation, whereas other downregulated miRNAs function as tumour suppressors (TS) enduring loss of function in tumour growth, based on their suppression of a wide range of tumour-suppressive and malignant mRNAs. Epigenetic regulation regulates miRNA expression without altering DNA sequencing. DNA methylation in miRNA sites increases the risk of malignant phenotype. DNA hypomethylation is linked to miRNA target gene promoters [79]. miRNAs and p53 interact to affect the target genes, promoting and preventing miRNA synthesis. miRNAs interact with cell cycle regulators by matching 3'-untranslated regions [80]. miRNAs target critical regulators to encourage cell cycle arrest, such as Cyclin D1, E1, and CDC25A [24]. Although research into the function of noncoding RNAs has advanced significantly, the application of miRNAs as diagnostic biomarkers is still in its early stages. Preanalytical and analytical approaches are essential for miRNA detection, affecting sample collection, storage, transport, and centrifugation parameters [81].

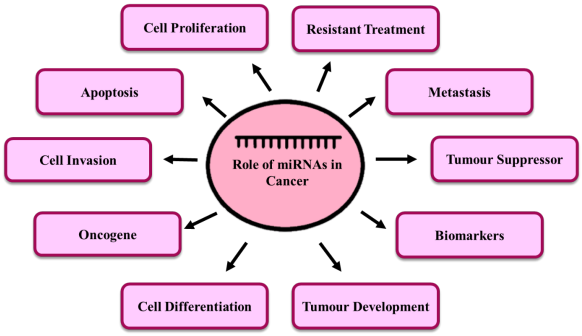


Figure 3. Role of miRNAs in pathways related to cancer like cell proliferation, resistance to treatment, metastasis, inhibition of tumour suppression, regulation of apoptosis, cell invasion, oncogene induction, cell differentiation and tumour development application in biomarkers identification.

6. Types of HPV induced cancers

From inflammation to cancer, the HPV virus has been linked to a variety of diseases. HPV causes infections of skin and mucosa, causing benign lesions [23]. Oncogenic viral proteins E7 and E6 initiate dysregulated cellular regulatory networks [7]. HPVs can modulate the miRNAs expressed by infected cells. Extracellular vesicle synthesis is dysregulated in cancer, and when these vesicles are released into the milieu, they can facilitate tumour growth. The discovery of dysregulated miRNAs in malignancies linked to HPV presents new possibilities for the development of prognostic, therapeutic, and diagnostic biomarkers. Investigations on HPV-induced cancers have been conducted. Some of the HPV-induced cancers have been discussed below.

6.1 Cervical cancer

CC is the most common gynaecologic malignancy, with over 700 deaths per day in developing nations [82]. WHO and the IARC estimated that there were 529,000 new incidences of CC globally in 2008 [24]. HR-HPV types, most commonly 16 and 18, are typically associated with malignancy and its precursor lesions [17]. CC manifests in squamous and glandular cells, which collide in the transformation zone [30]. E6 and E7 proteins promote CC11 by degrading p53 and inactivating pRb [83]. Direct skin-to-skin/mucosal contact is the most common route of HPV transmission [84].

6.1.1 miRNAs involved in cervical cancer

HPV16 E7 oncoprotein upregulates miR-21, encouraging cell growth and invasion (Table 5). miR-21 upregulation in CC may be linked to downregulation of tumour suppressor PTEN and matrix metalloproteinases (MMP), which promotes cellular migration and invasion [85]. The oncogene high mobility group box (HMGB1) promotes inflammation, carcinogenesis, and metastasis in CC. miR-1284, miR-142, and miR-34a can promote CC proliferation, inflammation, and invasion by upregulating HMGB [86]. miR-34a is a tumour suppressor that can be inhibited by activating p53 pathways, potentially leading to CC [87]. miR-155-5p regulates TP53INP1 expression, increasing cell proliferation, and overexpression of CHL1 (Table 5). However, miR-155-5p's effect on CC metastasis has not been thoroughly investigated, and its mechanism is unclear [88]. miR-106b-5p regulates the VEGFA, GSK3B, and PTK2 genes for PI3K-Akt signalling [89]. miR-218 is downregulated in tissues with HR-HPV infection. miR-218 inhibits viability, proliferation, metastasis, and apoptosis (Table 5) in CC [90]. HSP47 and G1/S transition are downregulated by miR-29a, leading to cancer development and YY1 motif growth [85]. he aberrant expression of miR-9 significantly contributes to the development and formation of CC by influencing tumour cell metabolism [87].

6.2 Head and neck cancer

The sixth most prevalent type of cancer to be discovered globally is HNC cancer [92]. HNSCCs are the most common cancers in HNCs. HPV-associated HNSCC and HPV-negative HNSCC are distinct diseases. HPV-associated OSCC has a 28% lower mortality risk than HPV-negative individuals [93]. Smoking, drinking alcohol, and chewing tobacco, microbes, especially Porphyromonas gingivalis [94] They are all linked to HNC.

6.2.1 miRNAs involved in head and neck cancer

miRNAs control cancer stemness and therapeutic efficacy in HNSCCs. miR-155 overexpression promotes OSCC invasion, growth, and metastasis (Table 6). miR-155 levels are higher in people with oral cancer, possibly due to chemoresistance [95]. miR-20a expression is increased in oral HNC but decreased in Cal27 cells (Table 6). Restoring the expression of HPV16 E7 and miR-20a reduces the migration, invasion, and proliferation of Cal27 cells [96]. miR-21 stimulates cell proliferation and inhibits apoptosis, potentially speeding up tumour development by targeting certain genes. Its inhibition restores drug sensitivity, but overexpression might result in resistance. miR-9 is essential for radiosensitivity, angiogenesis, immunity, tumour growth, and metastasis (Table 6). miR-9-5p levels in HPV+HNSCC cells are associated with CAF invasion and higher patient survival rates. miR-363 overexpression inhibits cell migration in HPV-positive HNCs by targeting myosin 1B (MYO1B), and siRNA downregulation of MYO1B in cell lines of HNC [97]; [96] . In the CeRNA (competing endogenous RNA) network, hsa-miR-193-3p controls the target gene PLAU, a biomarker for malignant tumours. It should be used to identify potential HNSCC patients [98].

6.3 Vaginal cancer

Just 10% of all vaginal malignant neoplasms and about 1% to 2% of women worldwide develop primary VC of all malignancies affecting women. The FIGO classifies VC as a primary lesion after ruling out all other causes. HPV is closely linked to VC; however, HPV is becoming increasingly prevalent in younger women due to high human immunodeficiency virus (HIV) rates. Risk factors for VC include high-grade lesions, smoking, immunosuppression, and more [102]. The transitional

Table 5. miRNAs involved in cervical cancer.

Serial No.	miRNA	Expression	Target(s)	Demo–graphics	Patho–logical Specimens	HPV Info	Function	Clinical Potential	Ref
1.	miR-21	Upregulation	E7	Mohebe-Yas Hospital, Tehran, Iran	50 Liquid Based Cytology Samples (LBCs) from women diagnosed with Cervical Intraepithelial Neoplasia (CIN) and Invasive Cervical Cancer (ICC); 46 LBC samples from patients with neither CC nor HPV infection to serve as a negative control; 43 LBC HPV positive samples	HPV16 E7	Encour–ages cell growth and invasion	Potential biomarkers for early detection of CC.	[85]
1.	miR-21	Downregulation	PTEN	Mohebe-Yas Hospital, Tehran, Iran	Same dataset	HPV16 E7	Overexpression of MMP2 and MMP9 encourages cellular invasion and migration	Potential biomarkers for early detection of CC.	[85]
2.	miR-34a	Upregulation	HMGB1	–	–	–	Promotes invasion	–	[86]
2.	miR-34a	Upregulation	p53 pathway	Guizhou Provincial Tumour Hospital, Guizhou, China	116 cervical exfoliated cells from December 2016 to March 2019 (75 CC patients and 41 CIN patients)	HPV16 HPV52 HPV58	Tumour inhibition	Might be related to the occurrence and development of CC	[87]

2.	miR-34a	Downregulation	HMGB1	–	–	–	Stimulates inflammation	–	[86]
3.	miR-1284	Upregulation	HMGB1	Da Ping Hospital, Chongqing, China	CC tissues and adjacent non-neoplastic tissues from 82 patients diagnosed with CC	–	Suppressed CC progression and enhanced chemosensitivity of CC cells	Enhances sensitivity of CC cells to cisplatin via targeting HMGB1	[86]
3.	miR-1284	Downregulation	HMGB1	–	–	–	Assist in carcinogenesis	–	[86]
4.	miR-142	Upregulation	HMGB1	Department of Pathology, Zhongnan Hospital of Wuhan University between 2015 and 2016	Primary tumour tissues and normal tissues from patients between 19–80 years	–	Advocates inflammation	Potential prognostic biomarker and therapeutic target	[86]
4.	miR-142	Downregulation	HMGB1	–	–	–	Stimulates metastasis	–	[86]
5.	miR-155-5p	Upregulation	TP53INP1	Binzhou Central Hospital, Shandong, China	24 CC samples and paratumour tissues	–	Metastasis of carcinoma cells	Potential therapeutic combating metastasis	[91]
5.	miR-155-5p	Downregulation	TP53INP1	–	–	–	Impaired growth, invasion and metastasis of CC cells	–	[91]
6.	miR-106b-5p	Downregulation	GSK3B	–	–	HPV16	CC development by regulating Wnt signaling/β-catenin pathway	Further investigation for validation	[89]
6.	miR-106b-5p	Upregulation	VEGFA	–	–	HR-HPV	Promote migration and proliferation via PI3K/Akt/mTOR	–	[89]

6.	miR-106b-5p	–	PTK2	–	–	HR-HPV	Expression and stability of VEGFA linked to hypoxia	Potential biomarker for prognosis	[89]
7.	miR-218	Upregulation	TPD52	Shanghai Institute of Cell Biology, Shanghai, China	Human cervical epithelial cells (H8 cells) and CC cells (HeLa, SiHa, CaSki, C-33A)	–	Promotion of migration, proliferation, invasion	Regulatory network may act critically in CC	[90]
8.	miR-29a	Downregulation	HSP47	Mohebe-Yas Hospital, Tehran, Iran	Same LBC dataset	HPV16 E7	Inhibiting growth and spread of cancer	Potential biomarker for early detection of CC	[85]
8.	miR-29a	–	G1/S transition	–	–	–	Apoptosis insensibility and uncontrolled cell cycles	–	[85]
9.	miR-9	Downregulation	CC and CIN	Guizhou Provincial Tumour Hospital, China	116 cervical exfoliated cells (75 CC and 41 CIN patients)	HPV16, HPV52, HPV58	Influence metabolism of tumour cells	Expression varies by HPV subtype	[87]

zone of the cervix is vulnerable to HPV due to access to the basal layer [103]. Vaginal microbiota controls the female lower genital tract's immune system. There is no established method for managing and treating VC, leading to a range of therapeutic approaches [102].

6.3.1 miRNAs involved in vaginal cancer

According to Cheng et al., the number of Lactobacillus species in the vaginal microflora is inversely proportional to miRNA expression. miR-130a-3p and miR-23a-3p expression increased in different test groups in a colony not dominated by Lactobacillus species [104]. Moreover, 64% of vaginal cancer cases are HPV-positive, and HPV also plays a significant etiological role in these cases. VC was left out because there were no experimental data on miRNA expression in this study. It is likely because miRNA dysregulation in vaginal cancer is uncommon that no research has been done on it [96].

6.4 Anal cancer

ASCC is connected to anal HPV infection [105]. Men who are HIV-positive and have intercourse with other males (MSM) are at the greatest risk [106]. It is a rare malignancy that affects 3% of gastrointestinal cancers. HIV, immunosuppression, and HSIL are high-risk groups for anal cancer. HPV is the etiological agent for cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia (AIN). HIV-infected patients have more HPVs and anal malignancies [107]. A high number of sexual partners and anal encounters raises

Table 6. miRNAs involved in head and neck cancer

Serial No.	miRNA	Expression	Target(s)	Demographic	Pathological Specimen	HPV Info	Function	Clinical Potential	Ref
1.	miR-155	Upregulation	FOXO3a	Dr. Rakesh Rawal, Department of Life Science, Gujarat University, Gujarat, India	Cisplatin resistant (cisRes) versus cis-sensitive (cisSens) oral cancer cells	–	OncomiR, aids in OSCC's growth, invasion, and metastasis	Combining miR-155 targeting medicines with conventional chemotherapy may help overcome resistance	[95]
2.	miR-20a	Upregulation	OSCC cells	Shanghai Institutes of Biological Sciences, Shanghai, China	Human OSCC Cal27 (tongue SCC) and 2A3 (HPV16-positive pharynx epithelial SCC cells)	HPV16 E7	Suppress OSCC cell proliferation, invasion, and migration	Tumour migration suppressor	[99]
3.	miR-21	Upregulation	HNSCC tissues and cell lines	First Affiliated Hospital of Anhui Medical University	Paired HNC tissue samples from thirty patients	–	Enhances cell progression, induces cisplatin resistance, reduces apoptosis	May help identify better treatment approaches with fewer side effects	[100]
4.	miR-9	Upregulation	NOX4	Third Affiliated Hospital of Harbin Medical University, Harbin, China	111 human HNSCC cell lines SCC090 from 2008 to 2018	HPV+ HNSCC	Radiosensitivity, angiogenesis, immunity, tumour growth, metastasis	Higher, persistent survival rate	[98]
5.	miR-363	Upregulation	MYO1B	Dr. Theresa Whiteside, University of Pittsburgh Cancer Institute, Pittsburgh	41 SCHHN tissues (PCI13, PCI30, JHU028, JHU029)	HPV16 E6 and E7	Inhibits cellular migration in HPV-positive HNC	Further investigation needed	[101]

the risk of HPV infection and malignancy. Additional risk factors include cancers of the lower genital tract, autoimmune diseases, and smoking.

6.	hsa-miR-193-3p	—	PLAU	The Cancer Genome Atlas (TCGA)	72 HPV tumour samples and 43 normal tissue samples	HPV-HNSCC	Biomarker for detecting malignant cancerous cells	Potential biomarker	[98]

6.4.1 miRNAs involved in anal cancer

Among the major challenges in ASCC research are the lack of studies using computer programmes to find miRNAs specific to HPV, HIV , and HPV-HIV co-infection, and technical problems with traditional miRNA isolation and detection tools, as well as in vitro and in vivo tests for anal cancer. Model research on miRNA profiling of HIV and HPV infection is still ongoing [108].

6.5 Vulvar cancer

VSCC is rare but increasing among women under 60, according to an epidemiologic study [109] SCC is the most common type of VSCC, often preceded by dysplastic lesions. Adenocarcinoma, basal cell carcinoma, sarcoma, and anaplastic carcinoma are the remaining cancer types. WHO divides VSCCC into HPV-associated and HPV-independent categories [110]. HPV 16 and 33 subtypes cause 55.5% of HPV-related vulvar malignancies [21]. Younger women are more prone to HPV-associated VC, while older women are more prone to HPV-independent VSCC. Chemotherapy and radiotherapy improve survival for HPV-positive malignancies [111].

6.5.1 miRNAs involved in vulvar cancer

miR-590-5p upregulation in VSCC (Table 7) leads to tumourogenesis [112]. Yang and Wu found that miRNAs can affect VSCC, concluding the upregulation of miR-183-5p, miR-590-5p, and miR-182-5p and the downregulation of miR-103a-3p, miR-603, and miR-107, respectively. miR-590-5p promotes cellular cancerous activity by targeting TGF-RII. miR-4712-5p enhances invasion and proliferation by interfering with PTEN and the downstream p-AKT, cyclin D1, and p-GSK3 signalling pathways. miR-3147 was also shown to function as an oncomiR (Table 7) in VSCC by inhibiting Smad4 [113]. miRNA dysregulation could be used to treat vulvar cancer.

6.6 Penile cancer

In certain regions of Asia, South America, and Africa, penile cancer (PeCa) is classified as an orphan disease that affects 10% of male malignancies. SCC is the most prevalent in PeCa, affecting 95% of cases [115]. PeCa is caused by inflammation, phimosis, and HPV infections. HIV increases PeCa risk and develops intraepithelial neoplasia earlier. Men with HIV have a higher prevalence of HPV infection [116]. HPV DNA was detected in 50.8% of PeCa cases. HPVs 6, 16, and 18 were more frequent [22]. Inguinal lymph node dissection (ILND) is the standard treatment for PeCa [117]. PeCa's molecular aetiology was poorly understood due to its rarity. Molecular approaches were used to investigate the genetic architecture of PeCa.

6.6.1 miRNAs involved in penile cancer

miRNA dysregulation in PeCa disrupts miRNA goals controlling HPV activity [118]. While Barzon et al. 2021 discovered that hypermethylation of the SLIT2 promoter causes miR-218-1 to be downregulated in HPV-positive penile tumours, Ayoubian et al. showed that miR-376b-5p was downregulated in these tumours [119] [120] (Table 8). Various cancer types use miR-211-5p as an important tumour suppressor. PSCC primary tumours have higher levels of miR-21-5p, miR-223-3p, and miR-107. miR-223-3p was activated during metastasis to the lymph nodes (Table 8). Higher miR-107 levels are related to a worse prognosis, whereas higher miR-21-5p and miR-107 levels are associated with a lack of PTEN protein expression [98]; [121]. MMP1, MMP12, and PPARG, as well as hsa-miR-31-5p, hsa-miR-224-5p, and hsa-miR-223-3p, have shown great sensitivity and specificity in distinguishing tumours from non-neoplastic lesions (Table 8) [122]. These miRNAs control the expression of genes such as insulin-like growth factor receptor 1 (IGF1R), MMP9, and PTEN (Table 8) in cancer development [121]. miR-31-5p regulates the androgen receptor (AR) gene in PeCa.

7. HPV therapeutics

HPV vaccinations effectively prevent new infections, but their potential therapeutic benefits remain uncertain (Fig. 4). Millions of people with chronic HPV infection face a dilemma. However, only a few countries have met the WHO target of 90% teenage girl immunisation coverage, indicating low global vaccine coverage. [123].

Table 7. miRNAs involved in vulvar cancer

Serial No.	miRNA	Expression	Target(s)	Demographics	Pathological Specimen	HPV Info	Function	Clinical Potential	Ref
1.	miR-590-5p	Upregulation	TGFβ1 and TGFβ2	Department of Obstetrics, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning, China	30 recently frozen VSCC samples along with surrounding non-cancerous tissues	–	Promotes cellular migration and proliferation and G1/S	A critical therapeutic agent,	[114]
2.	miR-182-5p	Downregulation	–	–	–	–	–	–	–
3.	miR-183-5p	–	–	–	–	–	–	–	–
4.	miR-103a-3p	–	–	–	–	–	–	–	–
5.	miR-107	–	–	–	–	–	–	–	–
6.	miR-603	–	–	–	–	–	–	–	–
7.	miRNA-4712-5p	Downregulation	PTEN	–	30 recently frozen VSCC samples along with surrounding non-cancerous tissues between January 2011 and January 2018	–	Tumour cell invasion and proliferation	Might help in finding a new therapeutic target for VSCC	[114]
8.	miR-3147	Upregulation	Smad4	–	20 VSCC and adjacent non-dysplastic tissues between 2010 and 2017	HPV-	OncomiR	May contribute in the treatment and diagnosis of VSCC in future	[113]

7.1 Prophylactic vaccines

Traditional vaccines aim to prevent infections or diseases. Therapeutic vaccines, however, are designed to treat an existing condition, such as a chronic infection or cancer. Prophylactic vaccines typically target specific pathogens like viruses or bacteria. Utilising recombinant DNA technology, these vaccines are made from pure L1 protein, which forms virus-like particles specific to HPV types by self-assembly. These vaccinations produce antibodies and have a strong immunological response [124]. Prophylactic vaccines are administered before exposure to a pathogen. Preventive vaccinations can protect the tonsils and cervix from infection with the L1 surface protein of the various HPV serotypes [2]. These vaccinations may protect against HPV infections, but are ineffective at curing pre-existing infections because infected basal epithelial cells do not express the

Table 8. miRNAs involved in penile cancer

Serial No.	miRNA	Expression	Target(s)	Demographics	Pathological Specimen	HPV Info	Function	Clinical Potential	Ref
1.	miR-376b-3p	Downregulation	RGS1	Aldemora Bello Cancer Hospital, São Luís, Maranhão, Brazil	22 PeCa samples and five non-tumour adjacent penile tissues from 2013	HR-HPV (16,74,30,49,66)	Tumour suppressor	Potential prognostic marker	[119]
2.	miR-218-1	–	SLIT2	Pathology Unit at the University of Padua, Italy	59 formalin-fixed paraffin-embedded PeCa samples from January 2002 to December 2010	HR-HPV (6 and 11)	Antiproli–fera-tive and apoptotic activity in vitro	An important molecular event in oncogenesis	[120]
3.	miR-21-5p	–	PTEN	Hospital Aldemora Belo and Hospital Presidente Dutra, São Luís, MA, Brazil	50 formalin-fixed paraffin-embedded PeCa specimens from 2013 to 2017	HPV16, 59, 74, 73, 11, 30, 56, 58, 66, 6, 18, 44, 51, 53, 63	Decreases gene expression of PTEN	Important in therapy against PeCa	[121]
4.	miR-223-3p	Upregulation	PPARG	A.C. Camargo Cancer Center, São Paulo, Brazil	59 PeCa, 26 surrounding normal tissues and 16 normal glans	HR-HPV (16 and 18)	Inhibits cell proliferation, induces apoptosis	Potential therapeutic agent	[122]
4.	miR-223-3p	Downregulation	FBXW7	Hospital Aldemora Belo and Hospital Presidente Dutra, São Luís, MA, Brazil	50 formalin-fixed paraffin-embedded PeCa specimens from 2013 to 2017	HPV16, 59, 74, 73, 11, 30, 56, 58, 66, 6, 18, 44, 51, 53, 63	Biomarker for lymph node metastasis	Potential biomarker for lymph node involvement	[121]

target antigens and L1 capsid proteins [103]. Three preventative prophylactic vaccines against HPV are available: nonavalent (Gardasil 9), bivalent (Cervarix), and tetravalent (Gardasil). HR-HPV types 16 and 18 cause about 70% of CCs and a significant portion of other HPV-related cancers. Bivalent and tetravalent HPV vaccines target these types for protection. The 9vHPV vaccination protects against these five HR-HPV

5.	miR-107	Upregulation	–	–	–	–	OncomiR	Potential biomarker for poor prognosis	–
5.	miR-107	Downregulation	PTEN	–	–	–	–	–	–
6.	miR-224-5p	Downregulation	MMP12	A.C. Camargo Cancer Center, São Paulo, Barretos Cancer Hospital, Barretos, and Faculty of Medicine, Botucatu, SP, Brazil	59 PeCa, 26 surrounding normal tissues and 16 normal glans	HR-HPV (16 and 18)	Predictor of poor prognosis	Oncogenic drivers for PeCa development	[122]
7.	miR-31-5p	Upregulation	MMP1	A.C. Camargo Cancer Center, São Paulo, Barretos Cancer Hospital, Barretos, and Faculty of Medicine, Botucatu, SP, Brazil	59 PeCa, 26 surrounding normal tissues and 16 normal glans	HR-HPV (16 and 18)	Prospective indicator of lymph node metastases	Oncogenic indicator of PeCa development	[122]

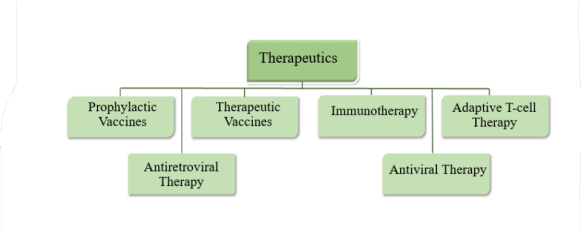


Figure 4. Types of therapeutics used to treat HPV associated tumours.

strains (31, 33, 45, 52, and 58), along with types 16 and 18. Together, these strains are responsible for about 90% of cervical and other HPV-related cancers. About 90% of occurrences of HPV-related genital warts are prevented by the 4vHPV and 9vHPV vaccinations, which also offer protection against HPV6 and 11 [124]. It is not anticipated that a preventive HPV vaccination can eradicate an ongoing, active infection or any aberrant tissue linked to HPV that persists after surgery [125]. Vaccination, however, may be predicted to cure both new infections of HPV caused by distinct types of HPV and reinfections with the same type of HPV, whether by autoinoculation from a nearby or far-off productively infected location or through fresh exposure (i.e., an infected partner).

7.2 Therapeutics vaccines

Therapeutic vaccination elicits an immune response to destroy tumour cells—via tumour antigen [126]. Tumour-specific antigens (TSAs) and tumour-associated antigens (TAAs) are the two main types of tumour antigens. TAAs are self-antigens that the tumour expresses abnormally. To induce an immune response, TAAs must overcome tolerance

mechanisms since they are not fully tumour-specific. Therefore, vaccinations that target TAAs also run the danger of inducing autoimmunity. In contrast, TSAs—which include oncoviral antigens and neoantigens—are completely unique to the tumour and are not immunologically tolerance-tolerant. The vaccination effectiveness of targeting neoantigens has increased due to advances in bioinformatics and genomics. Custom vaccines are required to target specific mutanomes of each tumour but are costly and time-consuming [127]. Four primary HPV vaccines are live vector, whole cell, nucleic acid, and peptide/protein. The main categories of live vector vaccinations include bacterial (Lactobacillus lactis, Lactobacillus casei, Salmonella, and Listeria monocytogenes) and viral (alphaviruses, adenoviruses, and vaccinia) types [128]. Live vector vaccines do not cause neutralising antibodies, allowing repeated immunisations [129]. DNA therapeutic vaccines offer safety, affordability, thermostability, purity, and distribution. RNA vaccination induces an immune response by exposing the body to antigens. Three developed RNA vaccines are self-amplifying (saRNA), conventional non-amplifying (bmRNA), and basic modified conventional non-amplifying mRNA (mRNA). Vaccines based on peptides were recommended to prevent oncogenic modifications by using the antigen HPV E7 oncoprotein as a whole [130]. It stimulates antibody production and contains all HLA epitopes, which prevents MHC restriction. The TA-CIN protein-based vaccine, which contains a fusion protein formed by HPV16 L2, E6, and E7, has advanced to clinical testing. Subunit vaccines are used to induce immunological responses in novel vaccines. Adjuvants can improve vaccine efficacy by providing the right combination. They improve antigen accessibility, enhance immune response, and generate cytokines [131]. Each adjuvant triggers a distinct humoral, cell-mediated, or combined humoral and cell-mediated immune response. For instance, polyinosinic-polycytidylic acid (poly-IC) stimulates the immune response of Th1 cells, CD8+ T cells, and antibodies by activating TLR3 and melanoma differentiation-associated protein 5 (MDA5). [132]. Coffman et al. suggest combining experimentally determined adjuvants with PRR ligands to appropriately direct a desired immune response to better optimise vaccination effectiveness [132]. The most effective way to maximise the benefits of this therapy may be through combination regimens that include immune checkpoint inhibition, therapeutic HPV vaccination, and additional therapies (like novel adjuvants).

7.3 Immunotherapy

Using immunological concepts and techniques, immunotherapy targets the organism's hyper- or hypo-immune condition. To effectively cure various diseases, it seeks to intentionally alter or modify the organism's immune response, either by boosting or lowering it. Immunotherapy strengthens immunosurveillance, increases cytolytic activity, and manages progression. Immune cells (dendritic cells, T-lymphocytes, and myeloid cells) express PD-1 and which suppresses the immune response. Binding of PD-L1 or PD-L2 to their ligand activates PD-1, depletes and hinders the immune response. PD-L1 expression downregulates TIL anticancer responses, making tumour cells resistant to immune surveillance [133]. CC cells can increase immunosuppressive factors in the TME. Immune evasion is linked to local immune system downregulation, including increased regulatory T cells, reduced inflammation, MHC antigen presentation, and checkpoint molecule upregulation [134]. Hence, in addition to targeting tumour antigens, reversing effector T cells or immunosuppression can treat cervical malignancies without HPV [135]. NK cells destroy tumour cells with death ligands, MHC molecules, or oncogenic transformation. NK cells can act as anti-cancer agents through inflammatory cytokines [136]. Further research into allogenic and autologous NK cells to treat anti-NK cells is viable [137]. It has been demonstrated that vorinostat increases MICA expression, enhancing NK cell-mediated cytolytic response [138]. Another treatment, NK cell transplant therapy, can help patients achieve stable disease, partial remission, or complete remission in various malignancies [137]. Immune checkpoint inhibitors (ICIs) and adoptive cell transfer (ACT) are two examples of immunotherapies that have produced long-lasting clinical responses but are only effective in a small percentage of cancer patients. Immunotherapy has transformed cancer treatment and revitalized the field of tumour immunology [139]. Another strategy that seeks to activate the immune system to identify and combat cancer cells is the use of therapeutic vaccinations. Certain malignancies, like prostate and cervical cancer, have favoured vaccinations made from the patient's tumour cells or certain proteins present in cancer cells[24]. The most recent developments in this area include cell treatments that provide a new paradigm for the treatment of cancer, such as CAR-T and CAR-NK. Clinical studies have shown that existing tumours shrink after treatment when human cells are genetically modified to produce T antigens encoded by the Merkel cell polyomavirus.

7.4 Adaptive T-cell therapy

Adoptive T-cell treatments entail collecting, expanding, selecting, and manipulating T cells from a patient ex vivo before reinfusing them back into the patient. TILs, TCRs, and CAR-T cells are the three main modalities of adoptive cell therapy. A myeloablative chemotherapeutic regimen is typically administered before the reinfusion to aid in engraftment. Adoptive cell therapy is a promising immunotherapy approach for cancers linked to HPV due to the tumour-specific nature of HPV viral antigens, which are likely to be consistently present across individuals affected by these tumours [140]. Effector T cell manipulation is key to immunotherapy for malignancies. Many articles have noted the enrichment of TIL in HPV-positive tumours [136]. A diverse population of lymphocytes obtained from a surgically resected material is expanded non-clonally ex vivo in TIL treatment. In the first study, two of the nine patients with metastatic cervical cancer who had this cell infusion experienced sustained full responses, while the other patient experienced a partial response [140]. The patient's own T cells are used in adoptive T-cell therapy to treat cancer. It is then manipulated to make them more effective at eliminating own tumour cells before being given to the patient [141]. It's noteworthy that TCR sequencing of the two full responders revealed T-cell reactivity against neo-antigens and germline antigens, rather than those produced by recognised HPV oncoproteins [142]. In an adoptive T-cell therapy (phase II study), 18 patients with cervical and 11 noncervical HPV-related malignancies were treated at the NIH; response rates were 28% and 18%, respectively, of patients [143]. T cells with a single TCR that have been shown to recognize a particular tumour antigen in an HLA-dependent manner are transduced to create TCR-engineered T cells. This strategy requires patient HLA matching since the technology relies on TCR–MHC pairing. Recently, a phase I/II clinical study targeting an HLA-A*02:01 limited epitope of HPV16 E6 was carried out employing autologous T cells genetically modified to produce a TCR. Of the twelve participants in the experiment, nine were given the maximum dosage of T cells. Out of the nine individuals, two had anal cancer and had both a full and partial response. Resected tissues from responders revealed an interesting increase in E6 TCR T-cell presence for several months after treatment [144]. The use of CAR-T cell therapy is intriguing in HPV-mediated cancers because it targets surface antigens instead of MHC-bound antigens, which overcome defects in the antigen presentation pathway observed in HPV-related malignancies. However, a major barrier to this strategy is the finding of unique and recurring cell-surface antigens in HPV-related malignancies that are not MHC-bound viral antigens. Fortunately, no dose-limiting toxicities were seen, and a significant proportion of patients had stable illness in recent phase I research assessing the safety of CAR-T cells targeted against ERBB in HNSCC [145]. Furthermore, a phase I/II study for cervical cancer is underway (NCT03356795), employing CAR-T cells to target mesothelin, PSMA, Muc1, and GD2. Data from these trials will be used to assess the efficacy of CAR treatments in individuals with cancers who are HPV positive.

7.5 Antiviral therapy and HPV

New avenues for cancer treatment have been made possible by understanding how antiviral immunity, which activates IFN-I and IFN-III, might fight tumours. Preclinical models and clinical trials are currently studying numerous anti-cancer drugs to modify these responses in TME. These drugs can be used as adjuvants for other immunotherapies or as distinct therapies [146]. Antiviral therapy blocks viral enzymes to prevent the virus life cycle. Novel therapeutic substances and techniques are being used to create effective antiviral medicines. Targets for anti-HPV therapeutics have been proposed for various viral proteins, yet HPV proteins lack enzymatic activity outside of viral E1 helicase. Viral elements control basal cell retention in epithelium. Thus, it may be feasible to change the process to clear the viral reservoir from infected tissue sites [24]. Furthermore, numerous viral families, such as reovirus, adenovirus, herpesvirus, and Seneca Valley virus, have been extensively used medicinally. These viruses are known as oncolytic viruses because they can directly cause cancer cell death and tumour regression [146]. The Zika virus (ZIKV), a neurotropic flavivirus that recently caused an epidemic of microcephaly in South America [147], is currently being studied for the treatment of tumours of the embryonal central nervous system. Preclinical models have shown significant oncolytic activity [148]. Notably, CD8+ T cell activation is responsible for at least some of this impact, and this therapy may work in concert with ICB [149]. Talimogene laherparepvec (T-VEC) is the only oncolytic virus approved by some regulatory bodies to treat advanced cutaneous melanoma that is incurable [150]. In response to viral infections, cells create interferon, which causes a variety of changes that limit the spread of viruses and aid in their eventual eradication. In a similar vein, changes that are dependent on interferon are linked to the regulation of tumour development

and the activation of a potent antitumour immune response. Using this justification, interferon has been used to treat a wide range of cancers in the past, such as multiple myeloma, renal cell carcinoma, melanoma, lymphoma, chronic myelogenous leukaemia, and other cancers.

7.6 Antiretroviral therapy and HPV

According to Kelly et al., regular antiretroviral therapy (ART) reduces HR-HPV prevalence in HIV-infected women. According to research by Abel et al., 90% of HIV-positive women on ART had undetectable plasma concentrations, thus lower odds of HPV infection [151]. ART helps people living with HIV (PLWH) maintain healthy immune systems and suppress HIV, in addition to virological suppression. However, the risk of precancerous lesions and HIV infection increases in women with HIV (WLHIV) [152]. HPV 16 is resistant to clearance in women receiving highly active antiretroviral therapy (HAART) The HAART era saw a higher prevalence of ASCC due to HPV infection. HAART resulted in an increase in men's health [106]. In people with HIV, HAART treatment is associated with a reduced risk of cancer compared to no treatment, especially for ADCs. Using HAART is a key factor in reducing the incidence of ADCs in HIV-infected patients. The longer a patient is treated with HAART, the lower their risk of developing ADCs [153]. The protective effect of HAART is primarily due to viral suppression and immune system recovery. Initially, it was believed that HAART had an additional protective effect independent of viral load and CD4 cell count [154].

8. miRNA–Oncogenesis and Environmental Sustainability: The Connections

Environmental hazards contribute to a wide spectrum of health outcomes, from acute infections to chronic and developmental disorders [156, 157]. Emerging research shows that various environmental hazards—including physical (e.g., radiation), biological (e.g., pathogens), and chemical (e.g., air pollution, heavy metals, cigarette smoke, phthalates, and pesticides)—can alter miRNA expression profiles. These exposures often lead to epigenetic modifications that influence miRNA biogenesis and function, thereby modulating cellular stress responses and contributing to the onset and progression of diseases such as cancer, cardiovascular disorders, and neurodegenerative conditions [156]. Understanding the interplay between environmental exposures and miRNA regulation is essential for advancing diagnostic, prognostic, and therapeutic approaches. Oncogenesis via miRNA and environmental sustainability intersect in a variety of ways. miRNA Dysregulation can be a consequence of environmental pollution, thus leading to Cancer: Environmental pollutants—including heavy metals, pesticides, microplastics, endocrine-disrupting chemicals (EDCs), air pollutants, and industrial toxins—can alter miRNA expression, driving oncogenic processes, few examples are: PM2.5 air pollution changes miRNAs linked to lung cancer (e.g., miR-21, an oncomiR), Endocrine disruptors (e.g., BPA, phthalates) upregulate oncomiRs that promote breast or prostate cancer, Cadmium, arsenic, and lead exposure alter miRNAs involved in apoptosis and DNA repair [158]. Microplastics and nanoplastics cause oxidative stress and miRNA dysregulation in animal models. Reducing environmental pollution is a direct strategy to reduce miRNA-mediated carcinogenesis, making public health an integral component of sustainability [159]

8.1 miRNAs as Environmental Biomarkers for monitoring of environmental sustainability:

Due to their circulation in blood, miRNAs are useful as biosensors of environmental damage. Thus, measuring environmental quality and pollutant exposure using miRNA signatures. It is helpful in early detection of cancer risk in exposed populations. Additionally, it can track ecological toxicity in fish, plants, insects, and soil microbes. [160] Climate Change and Ecosystem Stress - Altered miRNA Landscapes: Climate change–related stressors (heat, UV radiation, drought, nutrient loss) influence miRNA expression in humans, animals, and plants. Increased UV upregulates miR-21 and other oncomiRs in skin cells. Heat stress and oxidative damage shift miRNA patterns toward pro-inflammatory, pro-tumour states. Stress-adapted miRNA changes in crops affect food security and agricultural sustainability. Climate resilience strategies (clean air, heat mitigation, sustainable agriculture) indirectly reduce oncogenic miRNA dysregulation. [161]

8.2 Sustainable Agriculture, Food Quality miRNA Exposure:

Plants and animals produce miRNAs that can enter human diets (controversial but explored). Industrial farming introduces pesticides that alter miRNAs in crops, soil organisms, and human agricultural workers, Certain pesticides induce miRNAs associated with leukaemia or lymphoma pathways. Safer, greener agricultural practices help maintain healthy miRNA expression in ecosystems and human populations.

8.3 Green Chemistry Cleaner Industry -Reduced OncomiR Activation:

Sustainable industrial practices (green solvents, reduced emissions) lead to less exposure to mutagenic chemicals, fewer miRNA changes driving tumorigenesis, and reduced long-term cancer burden in populations. This links molecular cancer biology directly to the principles of sustainable development. It has been hypothesized- that exposure to plasticizers causes changes in or the deregulation of a number of oncogenic miRNAs and show that the interaction of plasticizers with several redundant miRNAs, such as let-7f, let-7g, miR-125b, miR-134, miR-146a, miR-22, miR-192, miR-222, miR-26a, miR-26b, miR-27b, miR-296, miR-324, miR-335, miR-122, miR-23b, miR-200, miR-29a, and miR-21, might induce deep alterations. These genotoxic and oncogenic responses can eventually lead to abnormal cell signalling pathways and metabolic changes that participate in many overlapping cellular processes, and the evaluation of miRNA-level changes can be a useful target for the toxicological assessment of environmental pollutants, including plastic additives and plasticizers. [159]. Conservation efforts indirectly reduce oxidative stress in organisms, restore normal miRNA regulatory networks, lower rates of environmentally triggered cancers [162]/

8.4 Integrating Sustainability Molecular Oncology

A unified approach towards reducing the ill effects of environmental pollution, thus mitigating miRNA induced oncogenesis, would involve:

- Regulating pollutants known to disrupt miRNA expression
- Monitoring population miRNA signatures in polluted regions
- Developing environmental strategies informed by molecular epidemiology
- Using sustainability metrics to reduce exposure-driven carcinogenesis.

9. Conclusion

In conclusion, the comprehensive understanding of HPV and its association with various cancers, along with the development of effective therapeutic strategies, sheds light on the advances being made in cancer research and treatment. The discussion covered the epidemiology of HPV-induced cancers, including cervical, head and neck, vaginal, anal, penile, and vulvar cancers, highlighting the role of microRNAs in cancer pathogenesis. The exploration also delves into the HPV genome, stages of pathogenesis, and various therapeutic interventions, such as prophylactic vaccines, therapeutic vaccines, immunotherapy, adaptive T-cell therapy, and antiviral therapy. Additionally, the role of antiretroviral therapy in HIV-infected individuals and its impact on HPV-related diseases was presented. Overall, this in-depth analysis underscores the complexities of HPV-induced cancers and the promising avenues for therapeutic intervention. It points to the need for continued research and development of novel therapeutic modalities to address the complexity of these conditions. The strides made in understanding HPV's role in cancer and the development of effective therapeutic strategies reflect a hopeful future in combating these malignancies. There is enormous potential to further advance our understanding and treatment of HPV-induced cancers, offering better outcomes for affected individuals and paving the way for continued progress in cancer research and treatment. Environmental sustainability plays a preventive role in cancer biology by reducing exposure to environmental agents that dysregulate miRNA expression and drive oncogenesis. Sustainable practices—clean energy, reduced plastics, pollution control, and safer agriculture—help maintain stable epigenetic regulatory networks and reduce global cancer burden

Declaration of Competing Interest

All authors declare there is no conflict of interest in this manuscript

Acknowledgement

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10. References

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