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Human papillomavirus and cervical carcinogenesis: Viral mechanism, risk factors, and prevention

Pratibha Kumar, Saumya Khugshal, Vaibhav Kumar Chaubey, Ishita Dimri, Smriti Rai, Anshuman Bisht, [7]Aditi Bisht, Vaishnavi Bijalwan, Priyanshi Rana, [#]Sanjay Gupta, [#]Vijay Kumar, [*]Gourav Kumar.

School of Biosciences, Swami Rama Himalayan University, Jolly Grant, Dehradun, India

Keywords

Cancer, human papillomavirus (HPV), HPV vaccination, lesions, mucosal epithelium

Abstract

The incidence of Human Papillomavirus (HPV) infection is one of the frequently viral infections known worldwide. HPV primarily infects the basal epithelial cells of the cervix, although many types can also infect cutaneous epithelium. Through the method of genetic sequencing there are greater than 200 distinct types that have been recognized. Among them, 40 types can affect mucosal epithelium and induce cellular proliferation. A subset of these mucosal types is "high-risk" and is associated with cellular proliferation leading to cancer. whereas the "low-risk" types typically cause benign lesions. They are primarily transmitted through sexual contacts involving skin-to-skin contact. Mother to child transmission during childbirth is rare. The maximum number of the HPV infections are short lived and are evacuated with 50% resolving within six months by the immune system, and 90% becoming undetectable within one to two years. The risk factor that occurs primarily for the development of cervical cancer is considered to be viral infection only to be resolved with treatment or strong immunological response. Cancer from HPV infection is curable if detected early however it is crucial to take preventive precautions such as safe sexual practices and HPV vaccination. The rate of HPV- related infections and precancerous lesions in many populations is reduced significantly by the vaccine of Human Papillomavirus (HPV).

The review summarizes that the function of Human Papillomavirus (HPV) in cervical carcinogenesis that also include viral mechanisms, risk factors, and preventive strategies of the respective virus.

[*]Corresponding Author: gouravkumar@srhu.edu.in; gouravkmrsinha@gmail.com
[#]Co-Corresponding Author: sanjaygupta@srhu.edu.in; kumarvijay@srhu.edu.in

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1. Introduction

Human papillomavirus (HPV) is a crucial widespread public health issue that cause infection, owing its widespread presence and direct role in causing various cancers, most notably cervical cancer (Okunade, 2020a). All papillomaviruses possess a common genomic organization that set apart from that of polyomaviruses. HPV is transmitted sexually and contributes to about 5% of all cancer cases each year, impacting hundreds of thousands of individuals worldwide. The primary etiological factor for cervical cancer development is caused by most infections that resolve within a year or two, determined infection with high risk of HPV (HR-HPV) genotypes, especially HPV 18 and HPV 16. High-risk HPV infection is involved in an increasing number of non-cervical cancers, such as anogenital and oropharyngeal *tumour* emphasizing the broad oncogenic potential of this virus. The HPV16 contributes to about 50% of cervical carcinoma cases globally (Okunade, 2020b). As per World Health Organization (WHO), one of the key causes of deaths related to cancer among women globally is persisted by cervical cancer and it is extremely impacting low- and middle-income countries. To tackle this public health strain, the World Health Organization (WHO) projected the worldwide initiative in the year 2018 which aimed to scale down cervical cancer incidence (a threshold of 4 per 100,000 women-year) and to direct the target of 90-70-90 targets for the year 2030: fully vaccinating the girls of age 14 by 90%, diagnosis of women with high performance test by the age of 35 to 45, and ensuring 90% of women with HPV infection should get appropriate treatment (World Health Organization, 2024).

The development of cancer caused by high-risk HPV is majorly related to viral oncoproteins E7 and E6. These proteins intervene with normal cellular functions and then it directs the important tumour suppressor proteins that is present in the host cell. The E6 protein expedites the deterioration of the p53 protein, which normally helps control cell cycle checkpoints and apoptosis. Concurrently, the E7 protein suspends the retinoblastoma protein (pRb), leading to rampant cell division through the release of E2 transcription factors. As a result, these disruptions affect the normal regulatory mechanisms of the cell, leading to genomic instability and eventually contributing to malignant transformation, which is key feature of HPV-associated cancers. HPV-related diseases cause a significant burden on global health, which has led to increasing efforts toward prevention, early detection, and treatment. One of the most effective preventive measures is the HPV vaccine, which, to produce antibodies against viral capsid proteins the immune system is stimulated (Okunade, 2020b).

There are some vaccines available which are highly effective in averting interfection with the high-level risk of Human papilloma-virus types. Diagnosis of infection is challenging as the infection often does not show symptoms, especially in men. In women HPV testing can be done by collecting the cells from the cervix for primary analysis and abnormal results may further be confirmed by colposcopy or biopsy to detect precancerous or cancerous changes (Ni et al. 2025).

Vaccination is significantly used to reduce the incidence of infections from HIV and precancerous cervical lesions. In addition to vaccination, screening programs

such as the Papanicolaou (Pap) smear and HPV DNA testing play an important role in detecting precancerous changes at an early stage. Early detection allows timely medical intervention and improves patient outcomes. However, several challenges remain, particularly in achieving equal access to vaccination and screening programs across different regions of the world. Therefore, continued research on HPV pathogenesis, epidemiology, and prevention strategies is essential. This review discusses the current understanding of HPV-associated cervical cancer, involving its molecular mechanisms, disease progression, and available preventive and therapeutic approaches (World Health Organization,2020). This review aims to summarize the recent understanding of infection caused by HPV and its role in cervical cancer development. It also discusses the molecular mechanisms involved in HPV-induced carcinogenesis, along with current strategies for prevention, screening, and treatment.

HPV Epidemiology

Over 90% of anogenital warts account for low-risk HPV genotypes, whereas high-risk strains predominantly types 16 and 18 drive cervical and other anogenital malignancies (Hakim et al. 2025). Malignant progression can occur even in the absence of genomic integration. In fact, the episomal viral forms can drive malignancy all on their own. The retinoblastoma protein (pRb) and tumour suppressors p53 has been directed inactivation by the viral E6 and E7 oncoprotein respectively, loss of these essential checkpoint proteins resulting in unchecked cell proliferation. Uncontrolled cell proliferation and genome instability. This mechanism serves as a primary driver in the pathogenesis of both squamous cell carcinoma and adenocarcinoma. Cancer and anogenital cancer is pioneer to high grade cervical cell abnormality. HPV types of high risk are usually detected in approximately 99% of cervical cancer cases. Five other variants of high-risk HPV types are 52, 45, 58, 31, and 33 which are responsible for another 15% of cervical carcinomas and 11% of all malignancies linked to infection of HPV (Hakim et al. 2025).

The majority of women with infection caused by HPV, even those with high level of risk from HPV type do not develop cancer. Cancer from HPV infection is curable if detected early. Preventative precautions should be taken by people worldwide such as healthy & safe sexual practices and HPV vaccination. HPV vaccination has significantly reduced the incidence of HPV- related infections and precancerous lesions in many populations. There is no particular antiviral treatment that has cure for HPV, the big concern around the world is the high prevalence of genital HPV. One of the studies has evaluated 645 sexually active young females of inner city that are reported prevalence of 54% cervical HPV. In 2008 showed an assessment of 12.7 million cancers arising worldwide that HPV infections are linked to 90% to 93% of anal cancer, 100% of cervical cancers, 63% of oropharyngeal cancers, 40% to 51% of vulvar cancers, and 36% to 40% of penile cancers (Soheili et al. 2021).

To illustrate regional variations in disease burden, data from India which accounts for nearly a quarter of global HPV-related cancer cases provides a clear case study. India contributes to 24% of global HPV related cancer and 7% of the global cancer incidence in 2020. In India it is reported that infection from HPV type 16 and type 18 causes four out of five cervical cancers, making HPV the

most common type of cancer at second place in Indian women. Cervical cancer accounts for 87.6% of all HPV-related cancers in Indian females. While HPV-16 is the most common genotype across India, its prevalence is higher in some regions (e.g. 59-74% in Kolkata, 58-69% in South India). Overall high-risk HPV prevalence varies by region, with a pooled prevalence of 85% found in cervical cancer patients.

Elevated HPV DNA positivity is observed in HIV-positive individuals. HPV infection is high in India due to factors like early marriage, poor genital hygiene, and limited access to screening. However, the introduction of widespread vaccination and improved screening is expected to significantly reduce this burden. A nationwide HPV vaccination program is being launched, targeting girls aged 14 to combat the high burden. The vaccine generally used protects against HPV types 16, 18, 6, and 11. Rates of both new infections and baseline prevalence is associated with a substantially higher burden among HIV-infected populations.

HPV Life Cycle

HPV is a small virus that is non enveloped, having double-stranded DNA, epitheliotropic virus. Because the virus is non-enveloped, it lacks a lipid bilayer and forms a hard outer shell with exceptional stability against heat, detergents, acids and common disinfectant. The structure of the virus includes the outer capsid and the Open Reading Frame (ORF, Figure 1). The later part is further bifurcated into three functional parts namely late region, early region and the non-coding part. The (L1 & L2) which is a structural protein required for assembly of virion is encoded by the late region. Six of the proteins (E1 to E7) that are very important for viral replication and the non-encoding part largely that is directed to as the long control region (LCR) that contains cis elements that are necessarily required for replication and transcription of DNA is encoded by the early region. The differentiation of epithelial cells in the host is linked directly to HPV viral replication (Doorbar et al. 2012).

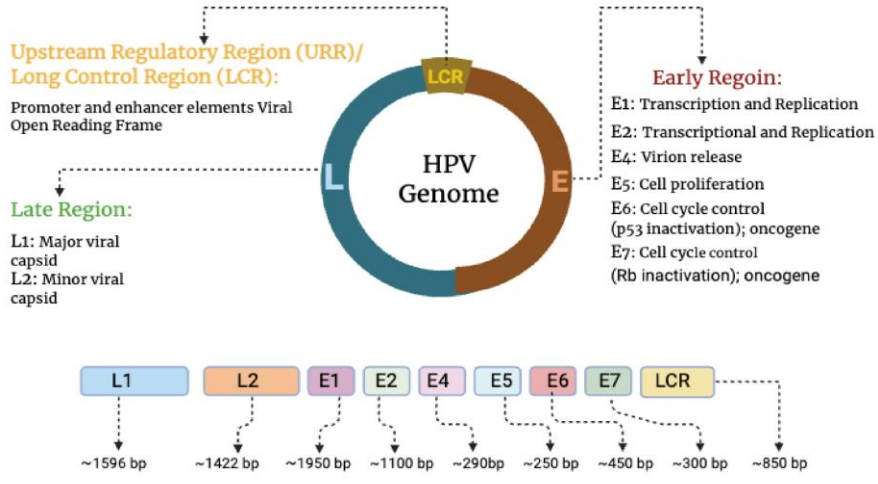


Figure 1. HPV Viral Genome and Gene Function: Genome structure of the circular double-stranded HPV genome, illustrating the structural organization of the Long Control Region (LCR), Early (E1–E7) regulatory/oncogenic regions, and Late (L1–L2) capsid regions.

To successfully produce infectious viral particles, HPV to initially deliver its genomic DNA in mitotically active basal keratinocytes in the stratified epithelium layer followed by the controlled maintenance of low-copy-number viral DNA in dividing epithelial cells and cultivate the high copy number DNA amplification and encapsulation alongside cellular migration up the epithelium toward the terminally differentiated, non-dividing epithelial cells required for viral progeny production. The differentiation of host keratinocytes, starting with infection of basal layer cells through micro-abrasions is linked closely to the life cycle of HPV. The virus establishes its genome, replicates in tandem with the cell, and amplifies its DNA as the cell matures and moves to the surface, releasing progeny virions from shedding epithelial cells (Doorbar et al. 2012). Stratified epithelium's basal layer which is only accessible through micro-wounds or abrasions is infected by HPV particles (virions). The viral genome enters the host nucleus and is established as an episome. In the basal layer, the virus replicates its DNA in low copy number (<100) along with the cell's own DNA division. The phase is relatively silent transcriptionally. As infected basal cells differentiate more into the upper layers (spinous layer), the virus initiates a productive phase. It significantly amplifies its DNA to high copy numbers (thousands of copies). In the topmost layer (stratum corneum) the virus expresses late proteins (L1 & L2) to assemble new virions. They particles are released as the skin/mucous cells shed, causing no cell death (Doorbar et al. 2012).

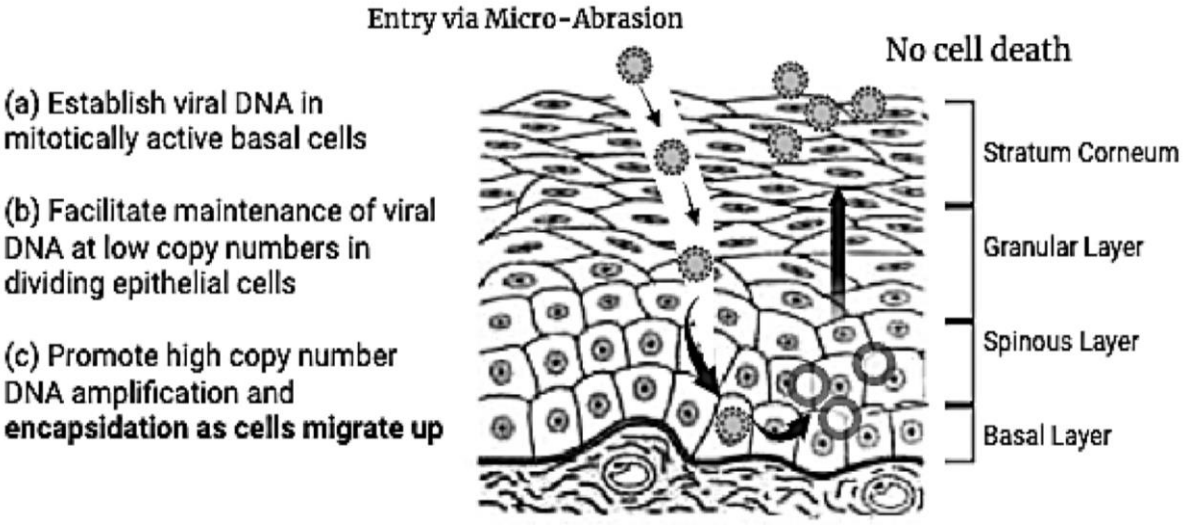


Figure 2. HPV Entry in Cellular Levels: Schematic diagram of HPV infection across different epithelial tissue layers after micro-abrasion in basal membrane, leading viral DNA establishment, maintenance of viral DNA during cell division, and promoting high-copy amplification when cells migrate toward the surface.

The differentiation of host keratinocytes is closely linked to the life cycle of HPV, starting with infection of basal layer cells through micro-abrasions (Figure 2). The virus establishes its genome, replicates in tandem with the cell, and amplifies its DNA as the cell matures and moves to the surface, releasing progeny virions from

shedding epithelial cells (Doorbar et al. 2012). The basal layer of the stratified epithelium which is only accessible through micro-wounds or abrasions is infected by particles of HPV (virions). The viral genome enters the host nucleus and is established as an episome. In the basal layer, the virus replicates its DNA in low copy number (<100) along with the cell's own DNA division. The phase is relatively silent transcriptionally. As infected basal cells differentiate more into the upper layers (spinous layer), the virus initiates a productive phase. It significantly amplifies its DNA to high copy numbers (thousands of copies). In the topmost layer (stratum corneum) the virus expresses late proteins (L1 & L2) to assemble new virions (Figure 3). They particles are released as the skin/mucous cells shed, causing no cell death (Doorbar et al. 2012).

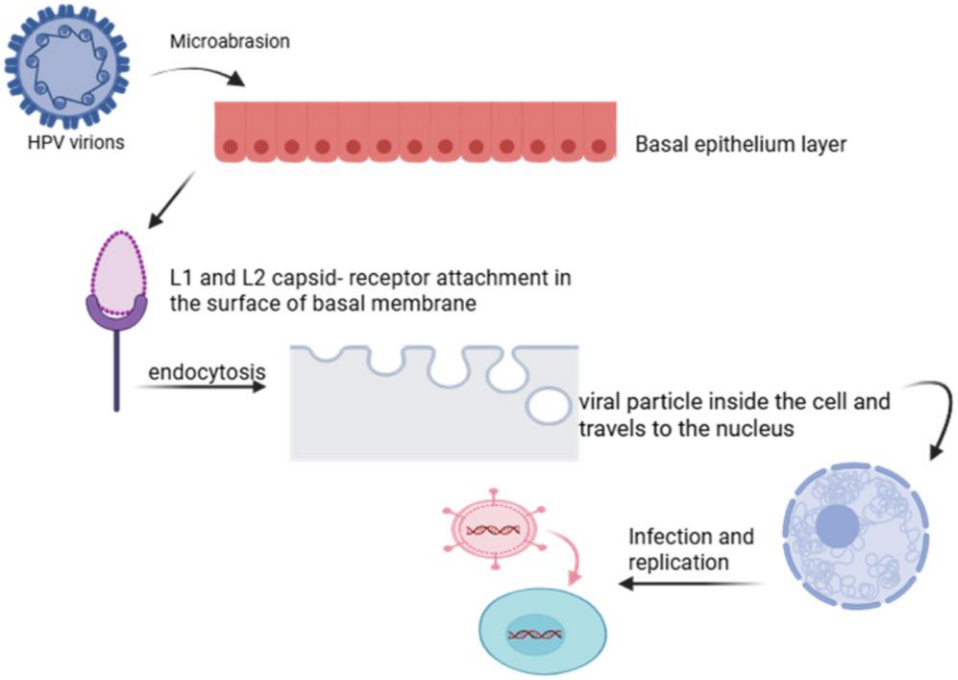


Figure 3. HPV Entry in Host's System: Stepwise cellular mechanism of HPV entry into the host system, showing virions passing through epithelial micro-abrasions, attaching on the basal membrane, and entering into nucleus via endocytosis.

Cervical Cancer

HPV is associated with the most reoccurring malignancy that usually develops from precancerous lesions across ten to twenty years. Cervical carcinoma represents the fourth most prevalent malignancy in women globally. The cervical lesions are categorized into very mild, moderate and very severe dysplasia or carcinoma in situ under the framework of World Health Organization (WHO, Figure 4). In an attempt to standardize treatment abnormalities in the lesions give rise to term cervical intraepithelial neoplasia (CIN). Categorization on CIN grade is mild dysplasia which is CIN1, the moderate dysplasia which is CIN2, and the severe dysplasia which is CIN3. Most recently CIN 2/3 is made by integration of CIN 3 and CIN 3. Infection will occur with at least one type of HR-HPV in 60% of sexually active individuals that have been reported in some studies. The term cervical intraepithelial neoplasia (CIN)

in an attempt to regulate treatment is given rise by abnormalities in the lesions. The cervical cancer is caused by persistent infection primarily with high level of risk from HPV, transformation of healthy cervical tissue into precancerous lesions is followed by invasive cancer. Early stages are usually asymptomatic but later stages typically present with pain in pelvic, post-menopausal bleeding, bleeding mid periods, post-coital bleeding, unusual vaginal discharge, and physical decline (World Health Organized, 2024).

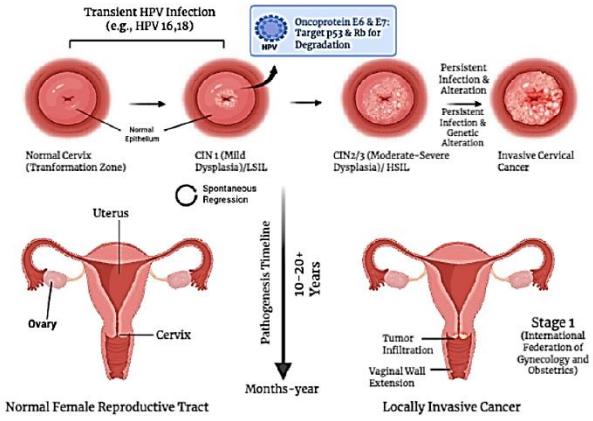


Figure 4. Normal Vs Cervical Cancer: Overview of cervical cancer pathogenesis comparing a normal female reproductive tract to locally invasive cervical cancer, demonstrating the multi-year progression from a transient HPV infection through mild to severe dysplasia (CIN 1-3/LSIL/HSIL) driven by p53 and Rb degradation.

Molecular pathways and immunological evasion in hpv-mediated cervical carcinogenesis

Once the HPV enters the host cells, it is heavily dependent on the microtubules for its journey into the nucleus; the mitotic spindle and astral microtubules of the host cells are used by the virus for physical delivery (Doorbar et al. 2012). HPV primarily infects the basal layer of the skin or mucous membranes. As these moves towards the surface, they naturally stop dividing and start to mature (differentiate) non-dividing cells, turning off their replication machinery. The viral oncoproteins E6 and E7 are used by viruses to drive back into a proliferation (Pal and Kundu, 2020; Vallejo-Ruiz et al. 2024). The viral E6 and E7 oncoprotein actively knock out tumour suppressors p53 and pRb (retinoblastoma protein) respectively, disruption of these regulatory mechanisms promoting uncontrolled cellular proliferation subsequently contributing to malignant transformation. This mechanism is considered central to the development of adenocarcinoma of the cervix and also squamous cell carcinoma. The virus maintains persistent infection through keeping host cells in a state of continuous division (Scarth et al. 2021). While proliferation in the basal layer allows the virus to establish a long-term reservoir as the infected cells divide and pass the viral genome to daughter cells.

HR-HPV persistence depends on a coordinated set of molecular strategies activated by the viral E5, E6, & E7 early oncoproteins (Peng et al. 2024). These proteins corrupt the cell cycle checkpoints, inhibit cellular differentiation, block innate immune sensing, and alter structural transport machinery to maintain viral persistence and drive oncogenic transformation (Pal and Kundu, 2020; Peng et al. 2024; Rasi Bonab et al. 2021).

To inhibit the proper autoimmune reaction in the host by oncoproteins HPV uses different techniques (Rasi Bonab et al. 2021). During the infection specifically the two oncoprotein E7 and E6 are very important for the process called pathogenicity. The process of genetically controlled cell and self-destruction which is a necessity

for cellular development, stability on cellular basis, and understanding of many medical conditions is known as apoptosis (Medda et al. 2021; Rasi Bonab et al. 2021). In the development of HPV- related cervical carcinoma HPV oncoproteins and their associated indicating pathways are significant

JAK/STAT Pathway

The JAK or Janus kinase- STAT is regarded as an important pathway that can influence the responses of the innate immune system (Medda et al. 2021; Rasi Bonab et al. 2021). This pathway is included in the processes of differentiation, apoptosis, cell migration, and proliferation (Figure 5).

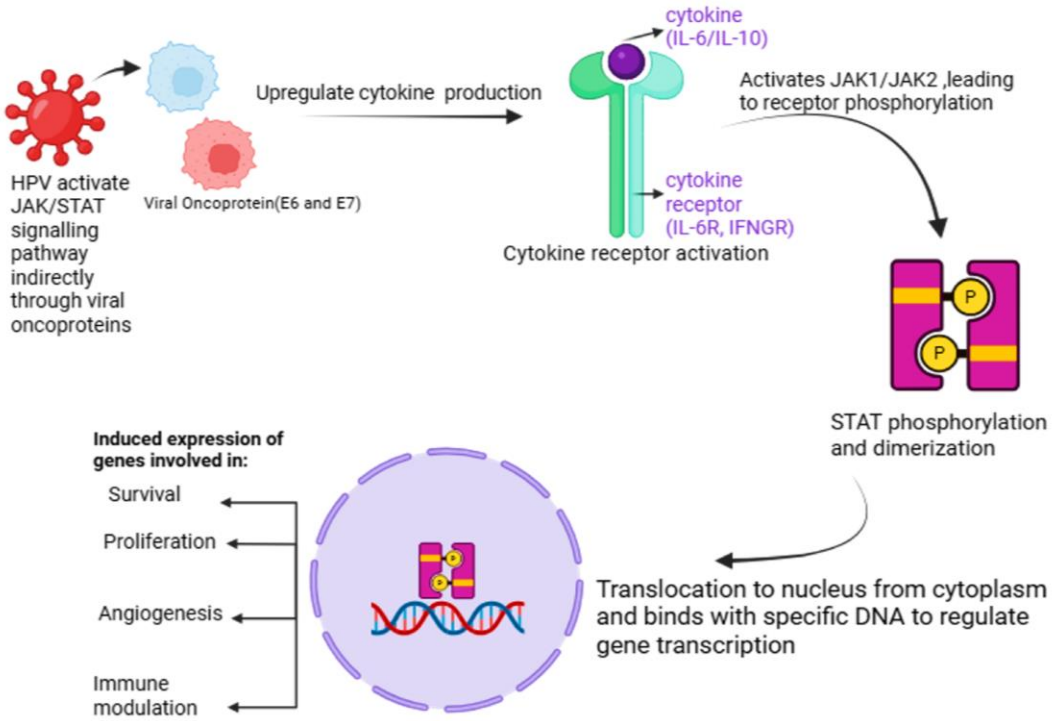


Figure 5. HPV Activated JAK/STAT Pathway in HPV: Diagram illustrating the HPV-activated JAK/STAT signalling pathway, highlighting how viral oncoproteins (E6 and E7) indirectly trigger cytokine upregulation, receptor phosphorylation, STAT dimerization, nuclear translocation, and the subsequent transcription of genes related to proliferation, cell survival, immune modulation, and angiogenesis.

PI3K/AKT Pathway

The regulation of intracellular processes such as protein synthesis and glucose metabolism is linked to action of PI3K (Medda et al. 2021; Rasi Bonab et al. 2021). There are three distinguished types of enzymes depending on first performance, second structure, and the third configuration. The IA group of heterodimers is made up of monitoring subunits that includes p85b, p85a, or p55c, which is attached permanently to a p110b, p110a, or p110d catalytic partner. The process of transformation of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5) triphosphate (PIP3) takes place during the interconnection of regulatory unit with the Receptor tyrosine kinases (RTK) or G-protein-coupled receptors (Rasi Bonab et al. 2021). Ras can similarly trigger the

catalyst subunit directly (Qin et al. 2011; Rasi Bonab et al. 2021). Phosphatase and tensin homolog (PTEN) are capable of downregulating PIP3 and following activation, domain that contain proteins like Pleckstrin Homology (pH) bind to the cell membrane, among which include the kinase B protein which is termed as Akt (Qin et al. 2011; Rasi Bonab et al. 2021). AKT undergoes phosphorylation on Thr308 and Ser473 by PDK1 and DNK-PK, respectively (Medda et al. 2021; Rasi Bonab et al. 2021).

The stimulation of Akt activates the phosphorylation process of FOXO transcription factors (forkhead-box type O), Bcl2 cell agonists, nuclear factor-κB (NF-κB), GSK3b (glycogen synthase kinase-3b), MDM2 (murine double minute 2), and TSC2 (tuberous sclerosis complex 2). Additionally, when tuberous sclerosis complex2 (TSC2) goes under phosphorylation through AKT, the mTOR complex 1 (mTORC1) is triggered (Rasi Bonab et al. 2021). Non-activation of the *signalling* cascade can culminate in apoptosis. During a viral incursion, apoptosis is a potent strategy to completely eradicate viruses. The viruses depend on the functional integrity of the PI3K/Akt *signalling* axis during their reproductive cycle to postpone programmed cell death or halt apoptotic pathways (Peng et al. 2024; Rasi Bonab et al. 2021). This pathway serves as a crucial protective shield against viral attack. Both the E7 and E6 sustain the employment of the pathway through Akt, phosphatase PP2A activates the *signalling* pathway of Akt/mTOR and as well as downregulation (Peng et al. 2024; Rasi Bonab et al. 2021). Via E6, 4E-BP is neutralized but additionally S6K is also switched on which promotes the generation of viral cap-reliant protein (Rasi Bonab et al. 2021). In the hypoxia response, AKT as a vital component, is regarded not just a mechanistic aim of rapamycin (mTOR)/AKT signalling network, but also an effector of many phosphoinositide 3 kinase (PI3K) components (Medda et al. 2021; Rasi Bonab et al. 2021). When cervical carcinoma cells are grown under low-oxygen (hypoxia), Prior research demonstrated that increased potential of AKT/mTORC2/PI3K *signalling* framework can conciliate the repression of HPV oncoproteins like E6 and E7 (Rasi Bonab et al. 2021). Oncoprotein E7 modifies the performance of Akt in the presence of HPV16 and triggers an escalation in the monocyte (keratinocyte) migration associated with P13K/Akt (Rasi Bonab et al. 2021).

Wnt/β-catenin pathway

The Wnt *signalling* cascade is a well-known framework, in growing of primordial germ cells or PGCs its role has been detailed; spanning migration, encompassing proliferation, and differentiation (Rasi Bonab et al. 2021). In numerous of developmental processes, the activity of the Wnt/β-catenin *signalling* cataract is censorious. Similarly, the progression of several types of cancer is associated with this *signalling* pathway (Peng et al. 2024; Rasi Bonab et al. 2021). Wnt ligands bind to the Frizzled/LRP receptor complex to initiate the *signalling* pathway. Wnt release is strictly reliant on the acyltransferase Porcupine. This ligand-receptor interaction triggers a cascade of events that result in cytoplasmic stabilization and translocation of beta-catenin (Rasi Bonab et al. 2021). In contrast to E6, the impact of the E7 oncoprotein on the modulating of Wnt pathways remains largely unexplored. Instead of that, lately, E7 oncoprotein participation in this pathway was recommended (Peng et al. 2024; Rasi Bonab et al.

2021). Prior research indicates that HPV 16, combined with the E6AP to improve Wnt/β-catenin signaling. Additionally, in Wnt-activated cells this partnership enhances Wnt/β-catenin transcription. E6AP alone can constant β-catenin and stimulate Wnt indication, a process dependent on its E3 ligase activity (Bello et al. 2015; Rasi Bonab et al. 2021).

ERK/MAPK pathway

The MAPK/ERK *signalling* pathways consists of a number of different kinase proteins. Signals transfer from the outside of the cell to the nucleus is mediated by these kinases (Qin et al. 2011; Rasi Bonab et al. 2021). A receptor called tyrosine kinase that is present on the surface of the host cell is activated. Receptor activation causes G protein associated with the receptor, such as Ras, to activate the MAPKKK (Raf) (Qin et al. 2011). Subsequent stimulation MAPKK (MEK) and ultimately MAPK (ERK) (Qin et al. 2011; Rasi Bonab et al. 2021). MAPK-mediated pathways enable the transduction between intracellular machinery and extracellular signals. The cell's functional apparatus controls essential biological processes, from cell death to growth and differentiation through these pathways (Medda et al. 2021; Rasi Bonab et al. 2021).. Production of E6 and E7 boosts the activity of various downstream targets within MAPK cascades (Peng et al. 2024; Rasi Bonab et al. 2021). As a result, host cells undergo modification across major steps of carcinogenesis, including invasion, cell migration, and survival without matrix attachment (Rasi Bonab et al. 2021). In cervical *tumours*, Elevating multiple oncogenes by activation of ERK/MAPK pathways. Moreover, the growth of HPV-driven cancers depends on the modulation of two primary *signalling* cascades, EGFR and VEGF, alongside the E5 viral protein (Medda et al. 2021; Rasi Bonab et al. 2021). The E5 protein stimulates the expression of VEGF by activating the ERK *signalling* pathway. It also influences ERK phosphorylation and stabilizes VEGF (Rasi Bonab et al. 2021). HPV-infected cells are protected oppose to autophagy and apoptosis by both the E5 protein and MAPK-ERK pathway (Medda et al. 2021; Rasi Bonab et al. 2021).

YY1 pathway

Yin and Yang 1 are at the helm for managing genes those results in various *signalling* and succession trails of cancer, such as E1A, c-fos, c-myc, p53 and ERBB2 (Rasi Bonab et al. 2021). They also bind directly with various protein that Involved in regulating programmed cell death, like Mdm2, caspases, HDACs, p53, Rb and Ezh2 (Rasi Bonab et al. 2021). Number of growth factors can induce transcription of the YY1 gene, while a bit exerts an inhibitory effect expression. YY1 acts right away on the LCRs of HPV 18 and 16. in the part of the viral regulatory region and numerous cellular functions are supervised by YY1. It has distinct repression and activation domains (Rasi Bonab et al. 2021). δ, NMP-1, NF-E1, UCRBP, and CF1 are the omnipresent cellular counterparts of the YY-1 and have a central role in regulating infection of HPV and E6 and E7 oncogenes. YY-1 can express and a supress gene expression in viral. YY1 inhibition directly results in p53 activation and apoptotic cell death in HPV-infected HeLa cells (Rasi Bonab et al. 2021).

AP-1 pathway

AP-1 is the type of factors whose activities related to

transcription are managed by extracellular and intracellular factors and also viral infection (Medda et al. 2021; Rasi Bonab et al. 2021). Processes involved in cellular like the process called apoptosis, survival, migration, proliferation, growth and differentiation of cell are regulated via AP-1. The cell type, the genetic history of the *tumour*, the stage of the *tumour*, and the differentiation of cell condition characterize the oncogenic or anti-oncogenic, AP-1 via correspondence with the viral promoter of HPV that is located within the region called upstream regulatory region (URR), which accumulate carcinogenesis and promoting the synthesis of E6 and E7 transcripts. (Medda et al. 2021; Rasi Bonab et al. 2021). In cervical *tumours*, c-FOS and JUNB are significant parts of dimers that is related to AP-1, triggered during the expression of the HPV oncogene. Hence, transcription of HPV is produced. AP-1 is targeted via oncoproteins of HPV. As a result, the factor that is responsible for transcription (TF) activation is triggered. For example, c-JUN mediate the expression of E7 protein, and activation of c-JUN are extended via interaction of c-JUN with E7 (Rasi Bonab et al. 2021).

NF-κB pathway

NF-κB operates within negative feedback to limit HPV amplification that can keep the viral copy numbers in control and check the expression of protein called E7 and E6 present in HPV-16(Rasi Bonab et al. 2021). Immortalization of colony-forming and colonic cells via HPV-16 is maximized by impeding NF-κB through an IκB alpha inhibitor. Studies indicate that regulation of NF-κB mediated by HPV-16, E6/E7 help suppress cervical dysplasia at the cervical transformation zone (Rasi Bonab et al. 2021).

CXCL12/CXCR4 pathway

The activation of the CXCL12/CXCR4 *signalling* axis promotes cell proliferation, cell adhesion and cellular migration through phosphorylating AK and various focal adhesion components (Rasi Bonab et al. 2021). It can also cause activation of NF-κB for suppressing apoptosis and cellular increase by the Wnt pathway. The receptor CXCL12 is regulated by the proteins E7 and E6 for virus proliferation and induce cell. This may take place in each case of the two cases low as well as high risk HPVs, which can ultimately cause mutation in CXCR4 and development of the disease (Rasi Bonab et al. 2021). Expressed primarily within the supra basal epithelial layers E6 and E7 modulate CXCL12 concentration, elevating cellular division and viral DNA copy numbers which can be further augmented by CXCR4 mutation. The direct physical engagement between CXCR4 and steady-state concentration and molecular chaperons extends the half-life of E6/E7 oncoproteins (Rasi Bonab et al. 2021).

Treatment and therapies of cervical cancer

The principal goal of cervical carcinoma surveillance is to differntiate high-grade intraepithelial lesions (HSIL) and Early-phase subclinical invasive lesions. Detecting transient lesions exposes patients to unnecessary intervention since most HPV infections and many CIN 1 and CIN 2 clear without intervention. Detecting transient lesions exposes patients to unnecessary intervention since most HPV infections and many CIN 1 and CIN 2 clear without intervention. Documented harms include psychological distress, procedure-related morbidity (e.g. vaginal pain, secondary vaginitis, abnormal vaginal bleeding), heightened maternal complications, particularly premature labor secondary

to cervical management (Fontham et al. 2020) (Fontham et al. 2020). Current preventative measures for sexually active cohorts remain insufficient. This is due to asymptomatic HPV infection and general knowledge gap and understanding about the propagation of HPV infection. At present the accessibility of various HPV vaccines (quadrivalent and 9 valent) has served as a crucial approach for HPV prevention. Authorized HPV vaccines can elicit cross-protective immune responses against strains of oncogene (HPV-18, HPV-31, HPV-16, HPV-45, HPV-33, HPV-58 and HPV-52) significantly lowering overall cancer incidence, and non-oncogenic type 6 & 11 for protection against benign genital lesions. (Fontham et al. 2020; Zhang et al. 2022). Vaccines are regarded as well-tolerated, cost-effectively manufactured, and biochemically stable. Some limitations to the vaccines are that they are expensive and vaccination is recommended within the 9-to-25 age window and before the onset of sexual debut. (Fontham et al. 2020).

Distinct types of treatment are accessible for cervical cancer. The treatments are of more than one type and treatment selection depends on multiple parameters, such as overall health of patient, the cancer's clinical stage and preferences of the patient.

Surgery

Serve as a primary treatment of cervical cancer. The surgical approach is dictated by the anatomical location of the malignancy. Some surgical procedures can be used such as Sentinel lymph node biopsy, cold knife conization, Hysterectomy. Some types under Hysterectomy such as total hysterectomy where the uterus and cervix are resection; surgery required no incision on the abdomen. Surgery incision is known as total laparoscopic hysterectomy.

Radical trachelectomy & Bilateral saplings-oophorectomy

A Radical cervicectomy, nearby tissue, removes the cervix, and the upper of the vagina. After removing the cervix, the part that is remaining of the vagina is attached to the uterus. A specialized bend or stich is located on the uterus; the process is called cerclage, for better help keep the uterus closed during the time of pregnancy (conceiving is still possible even after surgery.

Radiation therapy

X-rays has high energy or other types of radiation are used eradicate cancer cells or keep them from growing further by disintegrate their DNA. Two types include internal radiation therapy (IBRT) and external beam radiation therapy (EBRT). Treatment for cervical cancer involves both external and internal beam radiation and also be used as palliative therapy to overcome symptoms and optimize better quality of life in people with Malignant cervical neoplasm.

Chemotherapy

Commonly known as chemo, deploys cytotoxic or targeted therapies to suppress tumour progression. Chemotherapy can be specified alone or with any other type of treatment. Common medication used to manage cervical carcinoma include Carboplatin, Gemcitabine, Ifosfamide, Cisplatin, Irinotecan, Topotecan, Paclitaxel, and Vinorelbine. Combination of these medications can be used with other which are not mentioned here may also be used.

Immunotherapy

Assist in the individual's immune system fight malignancies. Molecular biomarker testing can be

utilized to forecast clinical response to specific immunotherapeutic agents. Pembrolizumab is known as immunotherapeutic agent that is used to treat patients whose cervical cancer includes the biomarker PD-L1 (Schmidt et al. 2022).

Targeted therapy

It includes agents or other medium to restrain the activity of protein, specific enzymes, or other molecules linked with the growth and spread of malignant cells. Specified therapies are applied in treatment cervical cancer include: Bevacizumab, Tisotumab, vedotin

Therapeutic Cancer Vaccines

The primary aim of therapeutic cancer vaccine is to ease an adaptive immune response against *tumour*-specific antigens (TAAs/TSAs) and *tumour*-associated. Antigens like CEA and MUC1 are significantly upregulated in malignant conditions but still can be detected within normal baseline tissue while TSAs are antigens exclusively produced by *tumour*. These therapies specifically target proteins like E7 and E6 (Lu et al. 2024; Zhang et al. 2022). Various vaccine types (DNA, RNA, peptides and patients' cell-based therapies) have been tested, vaccines alone could not be able to produce results due to low stability and weak immune responses in the body (Zhang et al. 2022; Zhou et al. 2022). Pairing vaccines with immune checkpoints inhibitors (like pembrolizumab or nivolumab) improved overall response rates to between 8% & 42%, it is still unclear that the response from the vaccines or the drug therapies are showing success alone (Schmidt et al. 2022; Zhou et al. 2022). Researchers are now adapting lipid nanoparticles (LNP) technology similar to the delivery system used in Covid-19 mRNA vaccines which has recently shown strong immune response in animal models (mice and monkey) (Zhang et al. 2022; Zhou et al. 2022).

Pattern recognition receptors (PRRs)

PPRs such as NLRs, TLRs and RIG-1 are innate immune sensors that detect molecular warning signs (PAMPs and DAMPs) to trigger inflammatory *signalling* and activate adaptive immunity. PRR *signalling* in frequently dysregulated, specifically, the HPV E7 oncoprotein suppresses STING/NF-kB pathways and type I interferon release to evade immune detection (Gusho & Laimins, 2022). Immune evasion reversed by PRR agonists (e.g. imiquimod, RIG-I agonists or STING agonists) and these are being explored as local as adjuvanted therapies to boost pro-inflammatory cytokines, trigger cancer cel apoptosis, and complement immune checkpoint inhibitors (Zhang et al. 2022). Direct gene-silencing strategies are being used alongside immune modulation, by using RNAs that are non-coding like SiRNAs and CRISPR/Cas9 platforms offer another targeted therapeutic avenue by directly disabling or knocking down E6/E7 oncogenic activity (Deng et al. 2023; Yoshiba et al. 2018).

Other possible treatment modalities comprise of gene silencing (such as TALENs, RNAi, & CRISPR); outside of immunotherapy; with the possibility for tropical applications (Deng et al. 2023; Yoshiba et al. 2018). Clinical case is indicated to evaluate the feasibility and efficacy of these latest modalities in the management of cancer associated with Human Papillomavirus (HPV).

Conclusions

Human Papilloma Virus Infection remains a major health global concern. However, insight into the mechanism of viral infection, natural history and genotype-specific risk profile have greatly benefited the

clinical practices. Although majority of HPV infections are transient and are eradicated by the immune system, persistent high-risk infections are the primary causes of cervical cancer. Combining the primary molecular screening and preventive vaccination have substantially reduced the HPV-mediated cervical cancer burden and made global elimination goal an achievable reality. There are still critical knowledge gaps remaining such as the role of host-virus interactions driving viral persistence and no therapeutic option for pre-existing infection. Keeping these in mind, future research should focus on understanding persistence viral latency and host cell environment and development of targeted therapeutic vaccine and small molecule inhibitors to clear established infection.

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