**REVIEW**

## The Effect of Oncogene Proteins of Human Papillomaviruses on Apoptosis Pathways in Prostate Cancer

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**ABSTRACT**

The ability of host cells to activate apoptosis is perhaps the most potent weapon for helping cells eliminate viruses. Human papillomaviruses (HPV) activate several pathways, enabling the infected cells to avoid extrinsic and intrinsic apoptosis pathways. The incapacity of prostatic epithelial cells to induce apoptosis leads to the invasive development of prostate cancer. For the pathogenesis of prostate cancer, several risk factors have been reported; for example, some viruses and infectious diseases have been proposed as causative agents for their relation to prostate diseases. According to several studies, high-risk human papillomaviruses cause malignancy by interfering with the apoptotic and inflammatory pathways; these viruses, such as HPV16 and HPV18, block apoptotic pathways and result in prostate cancer. This review is dedicated to presenting a summary of oncogenes (E5, E6, and E7) HR-HPVs' functions on signaling pathways, inflammation in prostate tumorigenesis, and emphasizing the link between these oncogenes with apoptosis and prostate cancer.

**KEYWORDS**

Apoptosis; inflammation; oncoproteins; prostate cancer

**1 Introduction**

Prostate cancer (PCa) is considered the fifth important cause of death worldwide and the second-most common cancer diagnosed in men [1]. There is not much data on the progression and precise mechanisms associated with PCa; however, several factors might contribute to men getting PCa, including ethnicity, age of more than 50 years, genetic mutations (inherited and acquired), and infections [2]. Moreover, inflammation and chronic infection cause malignancy in some organs, including the liver, stomach, prostate, cervical, and colon [3]. Also, various etiological factors contribute to prostatic inflammation



(prostatitis) induction, such as hormonal variations, infection, dietary factors, and cell injury. The cellular injury resultant may cause a loss of tolerance to prostatic antigens and result in a self-sustaining autoimmune reaction [3,4]. There are approximately 1,400 human pathogens which comprise 220 kinds of viruses; that few of these, referred to oncogenic viruses, are identified to cause malignancy via some strategies. The behavior of the tumor is influenced by virally mediated mechanisms affecting tumor cells and stromal cells in the tumor microenvironment. The virally induced mechanisms include apoptosis suppression, tumor metabolism alternation, anti-tumor immunity alternation, tumor microenvironment inflammation promotion, angiogenesis initiation, cellular proliferation stimulation, enhancing tumor invasion, and metastasis [5]. It is also been observed that HPV infection may impact the occurrence of autoimmunity in people with limited ability and could be related to the inflammation by this virus [6]. It has been indicated that HPV accounts for almost 600,000 cases of cancers (e.g., oropharyngeal, cervix, vulvovaginal, penile, and anal) and genital warts, and recurrent respiratory infection papillomatosis (RRP) of the lungs worldwide. HPV is a sexually transmitted virus that contains more than 200 genotypes, and approximately 40 infect the genital area. It has been shown that the prostate might be a target for HPV infections because of its anatomical location [7]. Even though HPV gene sequences were found in most usual, benign, and malignant prostate tissues [8,9], HPV infection possibly modulates the behavior of PCa cells via affecting apoptosis mechanisms, anoikis, anti-tumor immunity suppression, and resistance mechanisms, which results in metastasis [10]. However, the potential role of HR-HPV infection in PCa development has not yet been established [11]. Apoptosis, known as programmed cell death (PCD), is a tightly regulated process that plays a significant role in adult tissues' growth and homeostasis; it can also function as an antiviral defense mechanism. It has indicated that the deregulation of cell death has a crucial role in developing many diseases, such as cancer. The oncogenic viruses use various pathways to prevent the apoptotic process, permitting the proliferation of damaged and infected cells. In this way, HPV has developed some strategies to evade elimination by apoptosis that allow the infected cells to escape both intrinsic and extrinsic apoptosis pathways [12]. HPVs of all varieties have the same genetic structure and generate eight proteins, containing six early proteins (E1, E2, E4, E5, E6, and E7) and two late proteins (L1 and L2). Antiapoptotic oncoproteins, including E5, E6, and E7 prevalent in high-risk strains, are expected to play a significant role in malignant transformation [13]. During the viral cycle, the HPV E2 protein is a transcription factor that represses the production of viral oncogenes and stimulates viral DNA replication; this protein is explicitly inactivated, in HPV18-associated cancer cells [14]. Proapoptotic proteins E2 and E7 are also considered; as a result, apoptosis and the regulation of the three oncoproteins E5, E6, and E7 are closely linked [13]. It has shown that prostate tumor cells can obtain intracellular survival pathways and variations in chemokine/cytokines and growth factor signal transduction. These characteristics enable them to elude both apoptotic pathways and, promote androgen-independent aggressive behavior, which is resistant to all types of conventional treatment [15]. The recurrent chronic inflammation of unidentified stimuli in the adult prostate has interested a wide range of research to recognize possible infectious factors that might induce prostatic inflammation [16]. Investigations demonstrate that HPV vaccines are efficient for inhibiting infections and lesions which may cause cancer [17]. Understanding the mechanisms of carcinogenesis is essential for therapy, the design of new alternative drugs and vaccine development. This review is dedicated to discussing the effect of HR-HPVs' oncogenes (E5, E6, and E7) on signaling pathways and inflammation in prostate tumorigenesis, emphasizing the relationship of these oncogenes with apoptosis and PCa.

## 2 Oncogenes and Cancer

Natural selection has created cancer barriers, which prevent cancer progression by affecting the genetic makeup of multicellular organisms. Cell cycle arrest, apoptosis, limits on the total number of future cell divisions, cell adhesion, and asymmetric cell division are the five modifications that can be characterized as barriers to metastatic cancer based on current information. Such barriers are distinguished from

constraints, reducing or preventing cancer progression [18,19]. Oncogenic selection refers to selection that promotes the evolution of tumor cells from healthy cells. Also, the oncogenic selection is a primarily destructive process in which cells lose regulatory systems that have been improved through time by natural selection to maintain cells working in the organism's genetic interest. Natural selection encourages the evolution of anti-oncogenesis features, while oncogenic selection favors their abolition [18,20]. The simultaneous compromise of four cancer barriers enhances oncogenesis by allowing the formation of various populations of infected and dividing cells that are also attracted to the tumor's periphery [18].

Furthermore, oncogenic occurrences of infectious causes of human cancers that abrogate barriers are important causes of cancer; however, those that loosen constraints aggravate the problem. It is critical to distinguish between necessary and aggravating factors since inhibiting important reasons will prevent cancer [21,22]. One of the reasons for cancer recurrence is the process of barriers inhibition. In this regard, the diversity of genetic mutations due to mutagenic agents exposure such as radiation and carcinogenic chemicals and interruptions in DNA replication in multicellular organisms lead to the transformation of normal cells into malignant cells [18,23]. Proliferation, survival, angiogenesis, and metabolic-related hallmarks are all conveyed to a tumor cell by oncogenic mutations that constitutively activate RAS, a potent regulator of the MAPK and PI3K-AKT-mTOR cascades. Uncontrolled growth and genetic instability are characteristics of mutations that inactivate the tumor suppressor gene p53 (TP53), a DNA damage-induced activator of growth inhibition and death [24].

Since apoptosis is a cancer-prevention mechanism in most cell types, a malignant cell cannot survive death. However, intact apoptotic systems can still allow oncogenesis in particular cell types if the cell has a high threshold for apoptosis initiation [18,25]. Viruses and bacteria may worsen tumors by enhancing the mutation-driven mechanism of tumorigenesis by increasing the participation of mutagenesis molecules after inflammation [26]. Nevertheless, if they undermine cancer barriers, they may operate as fundamental causes. When a virus can replicate its genome in tandem with a host cell, it can improve its viability while avoiding survival and reproduction. Viruses can get this ability by disabling cancer-fighting mechanisms such as cell cycle arrest, apoptosis, telomerase regulation, and cell adhesion [18,19]. Indeed, research into tumor virus proteins has shown exact strategies for removing oncogenesis barriers [21,27]. Tumor viruses interfere with the system by intervening directly with significant biochemical barriers, such as the p53 and pRB proteins, perhaps because the resultant proliferation helps the tumor viruses survive and reproduce [28].

### 3 Importance of Prostate Cancer

Since the PCa is caused by the accumulation of genetics and epigenetics variations, leading to disabling of inhibitor genes, tumor activated, and oncogenes [29,30]. Many pathologic organisms because of prostate infection induce inflammatory reactions. These agents include vector-borne organisms sexually similar to *Neisseria Gonorrhoea* [31], *Chlamydia trachomatis* [32], *Trichomonas vaginalis* [33], *Treponema pallidum* [34], and bacteria that are transferred via sexual ways, like *Propionibacterium acnes* [35]. Pathogens have been discovered in the prostate; the prevalence and occurrence vary. For example, *Treponema pallidum* is an uncommon cause of granulomatous prostatitis and a unique inflammatory pattern in the prostate. There were many various sexually transmitted illnesses (mostly gonorrhoea), acute prostate inflammation, and prostate abscesses before the discovery and use of antibiotics, which occurred before 1937 [31]. Moreover, several viruses, including HSV2, HPV, HHV8, EBV [36], CMV [37], and BK viruses, can infect the prostate [38]. Although early detection of PCa, which may be at risk of spreading, can be treated before it spreads, this function diminishes the risk of dying from PCa in some men [39].

#### 4 Prostate Cancer and Human Papillomavirus Infection

HPVs, belonging to the *papillomaviridae* family, are small non-enveloped double-stranded circular DNA viruses that form a diverse and large virus group, with more HPV being continuously found. They cause a broad range of diseases, such as invasive tumors. HPV might infect the inner lining of tissues or the epithelial lining of the skin and is classified as mucosal or cutaneous type. The cutaneous HPV, as epidermitrophic types, infect the hand-foot skin and mucosal types of HPV infect the coating of the throat, mouth, anogenital epithelium, or respiratory tract. The mucosal HPV types in the  $\alpha$ -papillomavirus genus are the main reason for cervical, anal, penile, vulvar, oral, and vaginal cancers. Besides, in the  $\alpha$ -papillomavirus genus, benign mucosal HPV types result in benign genital condylomas. The main known HPV genera including alpha-papillomavirus, beta-papillomavirus, gamma-papillomavirus, nu-papillomavirus, and mu-papillomavirus. Also, HPVs may be categorized into low- and high-risk types according to their relationship with precursor lesions and cervical cancer. The HPV 2, 6, 11, 42, 43, and 44 types are considered low risk and high-risk HPV types consist of 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70. A main global health problem worldwide is sexually transmitted infections (STIs). As mentioned above, HPV is a common STI worldwide [4,40], and the earlier is also associated with the etiology of cervical cancer and other anatomical sites [5,7]. The initial assertions of the etiological role of sexually transmitted infections in the progression of PCa date back to the 1950s [16], and some mechanisms were then offered to clarify this connection. PCa is the second most common malignancy in males; in 2008, there were an estimated 903,500 new cancer cases and 258,400 deaths globally, making it the sixth-leading reason of mortality in men [41]. Except for perhaps obesity [3], smoking [2], and a sedentary lifestyle, no variable risk factors have been recognized for PC, despite wide research efforts [42]. Also, the procedure was studied for bacterial infections such as gonorrhea, resulting in PCa via the prostate inflammation and prostate atrophy phases. For viral infections, especially herpes viruses, the transforming features of viruses are more important [17]. Furthermore, numerous sexually transmitted diseases and infections that last longer increase the risk of PCa development due to a higher risk of prostate involvement [43]. According to a recent meta-analysis, Moghoofoei et al. [2] have been reported that there is a significant positive link between HPV (especially genotype 16) infection and the risk of PCa. Moreover, the HPV can influence the biology of PCa and leads to enhanced cancer cells aggressiveness owing to the oncogenic activities of high-risk HPVs and the presence of HPV infection in the specimens of PCa. A few studies have investigated PCa cells' immortalization through the HPV genes. Firstly, Naghashfar et al. [44] reported the expression of HPV18 E6/E7 genes by a retroviral vector prompted the immortalization of PCa cells. Besides, numerous studies reported that knock outting E6 and E7 genes results in apoptosis or susceptibility of cancer cells [45]. Generally, it could be deduced that the HPV oncogenic genes expression is vital for developing cancer induced by HPV. These researches and also a high incidence of HPV in PCa support the hypothesis of the HPV role in PCa progression [45]. Recently, it has been described that the expression level of HPV E7 oncoprotein was considerably greater in HPV-infected PCa samples comparing the HPV-positive prostate control [46]. This possibly shows the key role of HPV oncoproteins in the PCa development, but more researches are required.

#### 5 Human Papillomaviruses and Replication

Papillomavirus particles share a usual non-enveloped icosahedral structure, and the HPV-DNA genome is divided, generally, into three central regions: Early, Late, and Long Control Region (LCR). The late region of papillomavirus genomes encodes L1 and L2 capsid proteins [19], and also the early part encodes six common open reading frames, including E1, E2, E4, E5, E6, and E7 [18].

Moreover, it was shown that integrin  $\alpha$ -6 is the initial candidate of the cellular receptors, and  $\alpha$ -6,  $\beta$ -4, and  $\beta$ -1 are mainly involved in HPV binding. The  $\alpha$ -6 integrin can invoke a transductive signal pathway to

commence replication of DNA in keratinocytes that are very significant for viral replication [30,31]. Additionally, using heparinase, heparan sulfate proteoglycans (HSPGs) on keratinocytes might be eliminated and diminish HPV-11 VLPs binding up to 80%–90%; thus, it indicates that HPVs interact with cell-surface HSPGs [31,32].

HPV uses several pathways for entering the cells; the first pathway is caveolar endocytosis, the second and third pathways are clathrin-mediated endocytosis and clathrin- and caveolin-independent endocytosis. The most common pathway of cell-penetrating is a nonclathrin, noncaveolin pathway which resembles macro-pinocytosis. The low pH encountered in the late endosomal sections is necessary for the exposure of the DNA-virus genome [22,25]. It found 50 to 100 episomal copies per cell in the basal layer of productive warts, indicating that the virus's early genome replication occurs before being retained in infected cells as a stable multicopy plasmid [34,35]. However, reproduction of vegetative viral DNA happens in the differentiated squamous epithelium cells. The E1 and E2 proteins are the first viral proteins to be expressed that are indispensable to initial amplification [9]. The HPV does not encode any other enzymes involved in the replication to amplify the viral genome and should take the host's replication system. The E1 and E2 proteins enroll cellular DNA polymerases and further need extra enzymes for the viral genome replication. Generally, differentiating cells cannot support DNA synthesis, given they have suppressed the cell cycle upon departing the basal epithelial layer. However, HPVs can stimulate cellular replication systems to replicate vegetative viral DNA by E6 and E7 oncogenes. These oncogenes are involved in the virus's life cycle by recovering the cellular environment to allow amplification of the viral genome in differentiated and growth-arrested cells that may usually be inefficient for DNA replication. They accumulate as infectious particles following genome amplification, and capsid proteins such as L1 and L2 are expressed after the genome amplifies. However, the association between genome replication and capsid protein assemblages is not yet fully understood. It is speculated that the infectious virions assembly in the higher epithelial layers needs E2 and the capsid proteins L1 and L2 [34]. In this way, the L1 accumulates inside capsomeres in the cytoplasm before nuclear relocation and is rescued into PML bodies only afterward L2 has combined and displaced the PML component and sp100 [44]. While papillomavirus particles can assemble without L2, the presence of L2 enhances proper packaging [45] and boosts viral infectivity [46]. Finally, virus release demands an effective escape from the cornified cell envelope that the E4 protein might promote. The E4 could interrupt the keratin network and influence the cornified envelope integrity [34]. The genome organization of HPV has been shown in Fig. 1.

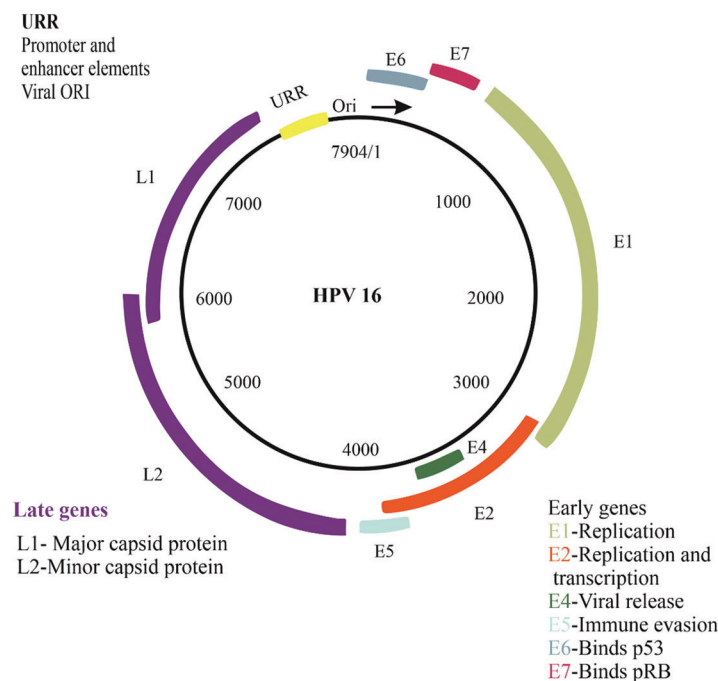
The HPV genome is divided into two regions: early and late, and the placement of each section changes based on the genome's position and when genes are expressed during the viral replication cycle. Early region, which includes E2, E1, E4, E5, E6, and E7, is important in viral propagation and transcription control. L1 major capsid proteins and L2 minor capsid proteins, which encode the virus's structural proteins, make up the late region. The upstream regulatory region (URR), which comprises promoter, enhancer, and viral origin elements, is also in controlling and regulating primary replication transcription. polycistronic transcripts, which utilize the major polyadenylation signal, are generated in this transcription area.

## 6 Oncogenic Activities of HPV

HPV oncoproteins (E5, E6, and E7), as the main drivers of HPV carcinogenesis, are involved in all cancer hallmarks [47,48]. HPV-mediated cancers are highly dependent on the expression of oncogenes (E6 and E7) for survival and continued propagation [49]. The mechanisms of hypermethylation and HPV viral genome integration induce the unbalanced expression of the E5, E6, and E7 oncoproteins that are critical factors for the carcinogenic cascade in human papillomavirus-mediated cancers [6,47]. For instance, interactions of E6, which are related to the malignant progression of human papillomavirus-



infected cells with various host cell proteins, deregulates vital cellular functions and develops numerous cancer hallmarks, leading to the proliferation and survival of genomically defective cancer cells. The HPVs are frequently integrated with premalignant lesions and various oropharyngeal and anogenital cancers; however, this is not part of the virus's life cycle. Integration is a dead-end for a virus because it can no longer form a circular genome that might be assembled and transferred to another host. To present, all HPV integration events that have been thoroughly explored have been roughly linked to HPV oncogenesis [50]. The HPV integration process might be found in premalignant lesions; nevertheless, the cells with integrated HPV enhanced as cells develop into invasive cancer [51]. Generally, integration leads to dysregulated expression of E6 and E7 oncogenes, which stimulates cell proliferation, abolishes cell cycle checkpoints, and results in progressive genetic instability [52]. Human papillomavirus-associated cancers might include either extrachromosomal or integrated viral DNA or both [53].



**Figure 1:** Genome organization of HPV

## 7 Apoptosis and Resistance to Apoptosis in Prostate Cancer

All cancer cells, regardless of the type or region, have cancer hallmarks; that includes angiogenesis and apoptosis evasion [54,55]. One of the significant functions of apoptosis is the inhibition of cancer. Usually, it is the inherent pathway prevented in cancer, but there is a wide range of means to impede apoptosis. Where apoptosis is lost, this allows tumor cells to survive longer and gives additional time for the accumulating mutations that can enhance invasiveness, the progression of tumor cells, stimulation of angiogenesis, interfering with differentiation, deregulation of cell proliferation [56]. Therefore, the apoptosis resistance provided using E6 and E7 oncoproteins might be thought of as a factor contributing to the progression of human cancer. A variety of genes contribute to apoptosis modulation, and among these, the members of the B-cell lymphoma 2 (Bcl-2) family are vigorously involved in cancer pathogenesis. The Bcl-2 expression, as an anti-apoptotic agent, was found to be significantly increased after transfection of cells with E6 and E7. Abnormal Bcl-2 activation aligned with the finding of a significant enhancement in the resistance to apoptosis of cells transfected with E6 and E7 oncoproteins [57]. Tumor cells are resistant to chemotherapeutic drugs by several mechanisms, including defective apoptotic signaling, downregulated

pro-apoptotic signals, and upregulated anti-apoptotic signals [58]. Androgen independent *prostate tumor* cells are highly resistant to therapeutic factors, which activate apoptosis through the caspase cascade [59].

### 8 Modulation of Apoptotic Pathways by HPV Encoded Proteins

Apoptosis is an essential mechanism via which the host could eliminate infectious cells, and also the ability to eschew apoptosis might elevate virus survival [60]. Papillomavirus oncoproteins have been revealed to interfere in apoptotic pathways; for instance, some proteins (e.g., E5 and E6) might protect host cells from apoptosis, whereas E6 has pro-apoptotic attributes, and also E7 might act as an anti-apoptotic or pro-apoptotic factor, based on the cell sort. Overexpression of prominent oncogenes, such as E6 and E7, in cell alteration primarily affects in resistance of changed cells to apoptosis. The capability to eschew apoptosis is the main sign of carcinogenesis [61]. The evasion of apoptosis is one of cancer's essential characteristics, promoting tumor growth and progression of metastases [61,62]. Several studies have revealed that HPVs infection can affect the pathogenesis of PCa. The papillomavirus has been shown to interfere with apoptosis via its oncogenic E5, E6, and E7 proteins, resulting in decreased apoptosis, cell cycle arrest, and cancer in cells [63–66]. It is worth noting that the mechanism of apoptosis involves extrinsic and intrinsic or mitochondria pathways (Table 1).

**Table 1:** HPV oncogenes and the function in apoptosis pathways

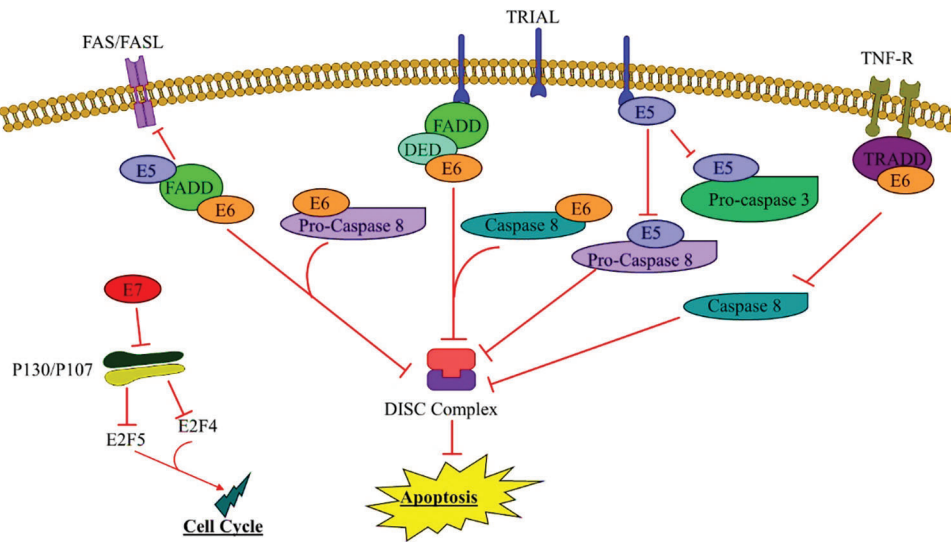
HPV oncogenes	Role in apoptosis pathways and prostate cancer	References
E7	Induction of C-IAP2	[67,68]
	HPV E7 inhibits p53 and p21	[69]
	Prevent working proteins p130 and p107	[70,71]
	Binds to HDAC and Rb and activation of E2F-reactionary genes	[72]
	Can prevent TNF-induced apoptosis in keratinocytes via the expression of C-IAP2	[73]
E6	Destabilizes p63 and p73 with direct impact	[74,75]
	It inhibits p53 activity and reduces apoptosis in the cancer cell	[76,77]
	It can also inhibit TRAIL-induced apoptosis by targeting FADD and caspase-8	[78]
	Activates AKT by binding to p53, p21, and p27 proteins	[79]
	Inactivates PTEN via PDZ proteins	[80,81]
E5	Prevents Fas ligand (FASL or CD95L) from inhibiting FASL, TRAIL-dependent apoptosis	[82,83]
	Prevent TRAIL and prevent the break of pro-caspases-3 and 8 also of PARP	[84]
	Increase the sensitivity of EGFR to EGF stimulation	[85–87]
	Activates AKT, then Bax binding to mitochondria inhibited	[12,66,74]
E2	The E2 protein induces apoptosis	[14]
	The activation of the initiator caspase 8	[14]
	Cleave by caspases as a result of cell death	[14]
	Proapoptotic function	[14]

Note: C-IAP2: cellular inhibitor of protein 2, HDAC: histone deacetylase, AKT: protein kinase B, APAF1: apoptotic protease activating factor 1, EGFR: epidermal growth factor receptor, TRAIL: TNF-related apoptosis-inducing ligand, FADD: FAS Associated via Death Domain, PTEN: phosphatase and tensin homolog deleted on chromosome 10, Bax: Bcl-2 Associated X-protein, Par4: protease-activated receptor 4, PARP: poly ADP ribose polymerase.

## 9 Extrinsic Pathway

The extrinsic apoptotic pathway is activated when receptor trimerization occurs, and adaptor molecules and pro-caspase-8 are recruited to the death-induced signaling complex (DISC). Caspase-8 activation causes downstream executioner caspases-3 and -7 to activate, resulting in cell death/apoptosis [88]. These receptors can also promote cell proliferation, survival, and death. Studies have been shown that HPV oncogenes can inhibit apoptosis induced by interference with apoptotic pathway molecules [89] (Fig. 2). Early genes E5, E6, and E7 systematize are the major infectious agent converting proteins in HPV. These oncoproteins are efficient for transformation and immortalization in primary human keratinocytes *in vitro* [52–54]. Moreover, the E2 protein induces apoptosis; in this way, this apoptotic activity is mediated by the amino-terminal domain. The activation of the initiator caspase-8, part of the extrinsic apoptosis pathway, is required for the apoptotic pathway induced by E2, so caspases cleave E2, leading to cell death. The HPV18 E2 protein may inhibit viral oncogenes' proliferative functions, making E2 inactivation essential for carcinogenic progression [14]. On the other hand, E7 proteins from HPV16 and HPV18 persuade resistance to tumor necrosis factor instead of proliferative result on primary human keratinocytes induction of cellular inhibitor of protein 2 (c-IAP2) has been detected in cells expressing HPV16 E6 and E7 [57]. TNFR interacts with Fas Associated via Death Domain (FADD) and TNFR1-associated death domain protein (TRADD) by its second death in the intracellular region, and this binding eventually activates caspases [90,91]. By binding with complex family proteins (pRB, p130, and p107) and starting E2F-dependent transcription, HPV-E7 can interrupt the G1-S checkpoint and allow the cell to continue into the S phase. The mentioned proteins (pRB, p130, and p107) and their interactions with the E2F transcription factor family members play critical roles in the cell cycle and apoptosis regulation; also, the E7 oncoprotein prevents proteins p130 and p107 function [70,71]. The p130 and p107 adjust E2F Transcription Factor 4 (E2F4) and E2F5, which are critical in cell cycle adjustment [74]. Besides, the E5 alone can result in cancer, augmenting the carcinogenic impression of E6 and E7 [92]. A study proposed that E5 might action a central role in the primary stage of tumorigenesis [93], and inhibits the extrinsic apoptotic pathway by downregulating the Fas receptor and disrupting the development of the DISC [55]. HPV16 E5 can also block Fas-L and TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis by downregulating Fas receptor expression and preventing both recruitment of FADD and forming the DISC [83,94]. Kabsch and Alonso, in their study, demonstrated that E5 prevents Fas-mediated apoptosis by reducing the Fas receptor. Besides, E5 prevents TRAIL signaling by participating in the TRAIL DISC formation, thereby preventing the break of pro-caspases-3, pro-caspases-8, and PARP [84]. Epidermal growth factor receptor (EGFR) is stimulated using several ligands, including EGF and TGF $\alpha$ . The EGF/EGFR can increase cell proliferation and reduce apoptotic cells via AKT, MAPK, and COX-2 proteins [95]. Furthermore, HPV16 E5 promotes EGFR recycling to the cell surface and increases EGFR phosphorylation levels while necessitating EGF binding [96]. It has shown that E5 has a key role in enhanced sensitivity of EGFR to EGF stimulation [85–87]. E6 is another important oncogene of the papillomaviruses that is expressed at high levels, and also it can reduce apoptosis by altering several pathways. Following this fact, the findings indicate that reduction in this gene induces apoptosis in papillomavirus cancer cells [65]. E6 has been shown to prevent apoptosis triggered by TNF, FAS, and TRAIL by accelerating the degradation of pro-apoptotic proteins like FADD and/or procaspase-8, or by interacting with proteins that constitute the DISC [78] (Fig. 2). In early stage, decreased FAS expression or mutations in this gene have been observed in PCa patients. It has also been shown that in PCa malignancy, the loss of TRAILR1 and 2 and the defects in these pathways may be due to the influence of papillomavirus oncogenes [79]. This is followed by the fact that PCU and DU145 PCa cells are sensitive to apoptosis via TRAIL and defects in this pathway lead to further proliferation of cancerous cells, suggesting that the papillomavirus may decrease apoptosis in PCa [90].





**Figure 2:** E5, E6, E7 HPV function in the external pathway

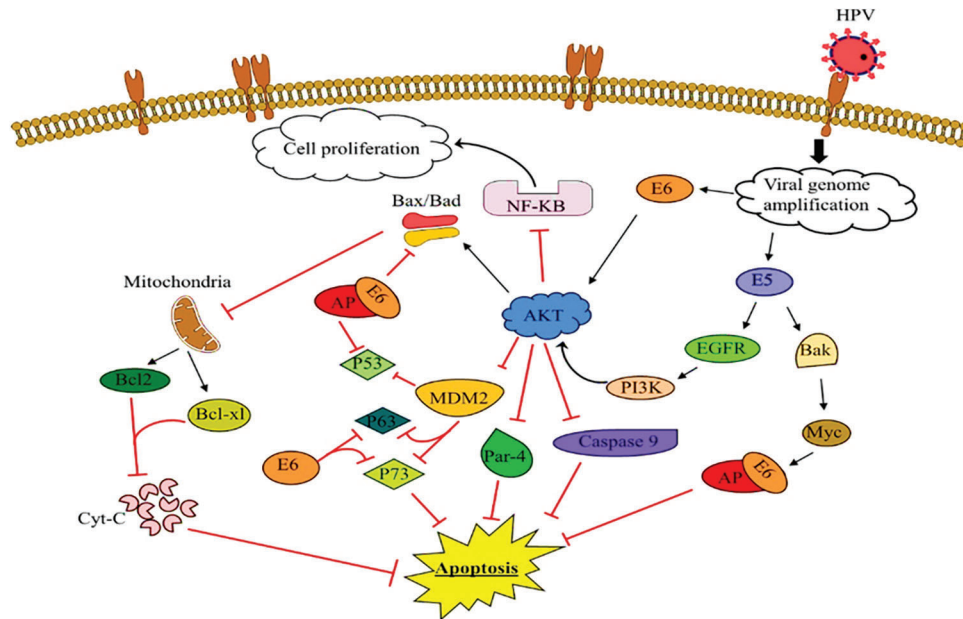
The external pathway begins with private pathways and leads to cell death by inactivating effective caspases. Personal pathways such as the mediator receptor, Fas-L binding to the Fas-L receptor, and downstream pathways inhibit apoptosis. TRAIL route; Oncogenic HPV genes include E5 and E6, which bind to FADD and inhibit apoptosis. Also, E6 HPV binds to the TNFR pathway, leading to its non-binding to tumor necrosis factor (TNF) and TRADD, thereby inactivating caspase-8 and inhibiting apoptosis.

## 10 The Internal Pathway

External stimuli (ultraviolet radiation, oxidative stress, hunger, etc.) trigger the intrinsic apoptotic pathway, which results in pores in the mitochondrial membrane and the release of mitochondrial inner membrane proteins (cytochrome c, SMAC) into the cytosol. Released cytochrome c and pro-caspase-9 create the apoptosome, which activates caspase-9, which subsequently activates downstream executioner caspases-3 and -7, causing apoptosis [88]. Studies have shown that E5, by direct connection, activates AKT, then Bax binding to mitochondria inhibited; as a result, cytochrome C is released and suppresses apoptosis [14,66,74] (Fig. 3). E5 also inhibits apoptosis by directly binding to the p53 tumor suppressor and prevents its function; on the other hand, by binding to Bak, Myc can also inhibit apoptosis via E6AP [12,66,74] (Fig. 3). p53 as a tumor suppressor can inhibit cell propagation through apoptosis, so mutations in the p53 gene have been described in many human tumors, with p53 enhancing or decreasing the expression of its target genes through transcription-dependent function. It has been reported that phosphorylated p53 is activated and can induce apoptosis through increased expression of apoptotic promoter genes such as Bax and Puma [88,97]. Many studies described the ability of HPV-16 E5 to communicate with the EGFR signaling pathway [98–100]. It has indicated that E5 activating EGFR can control cell proliferation, gene transcription, metastasis, and angiogenesis through the PI3 K-Art pathway [101] (Fig. 3).

Binding of E5 HPV oncoproteins to EGFR followed by increased PI3 K activity and AKT production and activation, which resulted in inhibition of increased NF-KB and cell proliferation and inhibition of caspase-9 and Par-4, and finally, they inhibit apoptosis. Also, binding E6 HPV directly to AKT, enhancing AKT activity, inhibiting Bak and Bax activity, and E6 binding through E6AP to Bak led to inhibition of mitochondrial binding and increased Bcl-2 and Bcl-xl, and failure to release cytochrome c

and ultimately inhibit apoptosis. On the other hand, inhibition of MDM2 binding to p53 by increasing AKT, also binding E6 to p53, p63, p73 and inhibiting apoptosis.



**Figure 3:** The function of E5, E6 of HPV in the intrinsic pathway in prostate cancer

Also, HPV-16 E5 can protect cells from UV-induced apoptotic cell death by activating the MAP kinase and PI3 K-Akt pathways [102]. Lastly, the E5 protein may prevent hydrogen peroxide-mediated apoptosis via activating ubiquitin–proteasome-induced degradation of Bax as a pro-apoptotic protein [103]. Thus, the E5 protein could inhibit HPV-infected cells from reacting to apoptotic stimulation [104]. On the other hand, E6 inhibits the intrinsic apoptotic pathway by inactivating p53, Bax, and Bak, which prevents MOMP and the release of cytochrome C [74], and also by directly binding to p63 [75] (Fig. 3). Smeets et al. have been shown that E6 prevents p53 activity and reduces apoptosis in tumor cells [105]. It has been illustrated that E6/E6AP may exclusively target cellular pathways of p53 that are intended to stimulate the transcription of downstream pro-apoptotic proteins such as Bax, Fas, Puma, Apaf-1, and PI3, which are all part of the intrinsic apoptotic cascade [67]. Bak breakdown by E6 prevents the release of apoptosis-inducing factor (AIF) from the mitochondria into the nucleus, preventing UV-induced cell death [106]. E6 also activates AKT by binding to p53, p21, and p27 proteins and reducing their expression; AKT activation prevents Bad, Bax, and caspase-9 activity, and deletion of p21 destroys p53's ability to stop the G1 cell cycle [107,108]. Findings indicate that AKT signaling is involved in TRAIL resistance in the PCa cell. Also in studies showing that Bcl-2 pathways, induced via the activation of AKT and NF-κB pathways might control the sensitivity of TRAIL to PCa cells [74,90]. The AKT has wide downstream aims that control cell duplication, cell growth, angiogenesis, and cell survival [109,110]. Many studies have manifested that E6 may activate the apoptosis pathway via several mechanisms. For example, the E6 inactivates PTEN via PDZ proteins, increasing pAKT and enhancing cell duplication [80–81,111]. There is a p53 mutation in many cancers, and in PCa, the frequency of mutation in p53 is variable [112]; it seems in androgen-independent tumors, the p53 mutation is abundant [113]. Overexpression of p53 blocks androgen signal; however, decreased expression of p53 and increased carcinogenicity of p53 are vital for the progression of PCa [114]. Denmeade et al. [115] have shown that the growth of androgen-dependent PCa is dependent on the balance between androgen p53,

and cutting the balance may be involved in the development of PCa. In humans, there is also a reverse association between the expression of Par4 and Bcl-2 in the benign prostatic tumor epithelium and primary and metastatic PCa [116]. In living cells, AKT kinase activated by E6 has been exposed to phosphorylate Par4 in human prostate tumor cells, leading to par4 silencing and ultimately inhibiting apoptosis. In the end, it can be interpreted that in PCa, various anti-apoptotic pathways such as Bcl-2 are unregulated and p53, Par4 genes are inhibited, and AKT, NF-KB proliferative pathways are also activated [79,117,118]. Moreover, E7 binds to HDAC (histone deacetylase) and Rb and abate their repression of E2F, leading to the activation of E2F-reactionary genes. Besides, E7 as an anti-apoptotic factor, causes the cell to enter the S phase that cellular replication factors are activated [72]. Yuan et al. [73] recently, offered that by the expression of c-IAP2, E7 can prevent tumor necrosis factor (TNF)-induced apoptosis in keratinocytes. Another study found that E7 overexpression in fibroblasts inhibited the release of caspase-8, which postponed Fas and TNF-induced apoptosis [119]. On the other hand, E7, has been reported to play a significant role in interferon-alpha-mediated apoptosis in mouse lymphoma cells and has a pro-apoptotic impact [120]. In genital keratinocytes, overexpression of E7 promotes spontaneous cell death and increases the cells' susceptibility to TNF-induced apoptosis [121]. The intrinsic pathway is controlled using the Bcl-2 protein family [122]. It has been shown that anti-apoptotic Bcl-2 proteins are overexpressed in cancer cells, expressed in 70% of androgen-independent tumors, and reduce the sensitivity of chemotherapy-induced apoptosis cancer cells [123,124]. Besides, it has been reported that p53 can act as an apoptosis suppressor by inhibiting the expression of Bcl-2 protein [125]. Presumably, as the high-risk E6 oncoprotein can inhibit p53, it directly promotes tumor progression by eliminating this protein's inhibitory impact on the Bcl-2 [76]. On the other hand, HPV E5 protein prevents apoptosis via decreasing activity of Bax protein, a pro-apoptotic protein, which can act as a helper for E6/E7 oncoproteins to inhibit apoptosis [123]. A negative correlation between Bcl-2 and p53 has been observed in several cancer cells, but some studies have indicated that the expression of both proteins was increased in HPV-induced cancer cells. A study was conducted by Grace and et al. considerably positive association between the Bcl-2/p53 expression and HPV-mediated squamous cell carcinoma. They suggested that HPV through the deregulation of apoptosis pathways can cause cervical lesions [126]. The theory hypothesized that high-risk HPV E6 oncoprotein causes non-functional Bcl-2 and p53 proteins to co-express in cervical cancer by removing p53's inhibitory impact on Bcl-2 [127]. Wang et al. examined the relationship between p53 and Bcl-2 expression in HPV-positive and HPV-negative breast cancer cases. It was shown that in the HPV positive tumors compared with HPV negative tumors, the p53 and Bcl-2 expression was substantially increased in HPV positive tumors [128]. Another study showed that the activity of Bcl-2 and p53 decreased and increased, respectively, in PCa samples infected with HPV. As well as, they have been reported that there had been a statistically meaningful negative and positive relationship between the measure of E6/E7 expression with that of p53 and Bcl-2, respectively. Therefore, HPV infection possibly assists in tumor development by promoting apoptosis resistance in PCa cells [46]. Survivin is the smallest member of the inhibitor of apoptosis protein (IAP) family which plays a key role in the determination of cell survival via preventing apoptosis, and the survivin expression was enhanced in many cancer types [129]. For example, in PCa, the expression level of survivin was regularly upregulated from low to high grade PCa [130]. Negative regulation of survivin expression by p53 made the hypothesis that by inhibiting p53, HPV-E6 protein leads to overexpression of survivin and subsequently, contributes to the immortalization of cancer cells [131]. Burberry et al. found the expression of endogenous survivin mRNA was increased following the transduction of E6 and E7 into human embryonic fibroblast cells [131]. In one study, Muzio et al. investigated the survivin expression in the oral premalignant lesions and oral cancer infected with HPV. They noticed that the expression level of survivin was considerably high in HPV-positive samples comparing HPV-negative samples. It can be concluded that HPV directly or indirectly influences expression of survivin [132]. Furthermore, Fatemipour et al. reported that the amount of survivin in HPV-infected PCa samples was considerably

higher than in HPV-negative PCa samples. E6, E7, and survivin were also shown to have a substantial favorable connection.

## 11 Conclusion

Proteins E5, E6, and E7 of HPV are contributed to the apoptotic pathway and play a crucial role in the resistance to apoptotic cell death. The virus' capability to escape apoptosis and prevent the extinction of infected cells leads to tumor growth and metastasis, resulting in cancer. HPV infection may induce chronic prostatic inflammation caused by sexually transmitted infections (STIs), which may increase PCa risk. HPV is known as the original etiological factor in cervical cancer studies. Targeting E5, E6, and E7 effectively inhibits apoptosis inflammation and prevents precancerous intraepithelial lesions and their progression to cancer. A thorough understanding of the biology of carcinogenic viruses and host defense mechanisms can facilitate therapeutic approaches. These findings suggest that targeting HPV oncoproteins could be a wise strategy for treating HPV-related cancers. Given that the mechanisms involved in oncogenic virus infection are better known, up-to-date and significant insights into the molecular mechanisms of apoptosis are on the way.

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