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The Interaction between Human Papillomavirus Proteins and Cytoskeletal Filaments

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1. Introduction

Cancer is a disease in which uncontrolled cell division begins, cell integrity and transmission collapse. Cervical cancer is the second most common cancer among women worldwide. The oncogenic human papillomavirus (HPV) types are the most significant risk factors in its aetiology. HPV causes deformation of genomic integrity, control of cell cycle, cell adhesion and apoptosis by suppressing tumor suppressor genes and interacting with cellular proteins via various proteins on carcinogenesis process. While doing all these functions, HPV undoubtedly interacts with the members of cytoskeleton which enable cellular motility and integrity. This causes deformation of intercellular junction and tissue integrity. Formation of “koilos” which is created by HPV in cells and has an important place in the diagnosis of virus in gynecologic and non-gynecologic samples can be thought as the result of interaction of HPV-cytoskeleton. In this chapter the relation between HPV proteins and members of cytoskeleton will be studied through tumor suppressor genes. First of all HPV genomic structure and HPV proteins will be mentioned generally, then cytoskeleton and its members will be explained together with HPV proteins which they are in interaction with.

2. HPV genomic structure and function

Human papillomaviruses (HPVs) are small, nonenveloped, icosahedral, double-stranded circular DNA viruses belong to the *Papovaviridae* family. HPVs specifically infect keratinized stratified epithelia. The circular DNA approximately 8,000 bp in size, contained within a spherical protein capsid, composed of 72 capsomers. The viral capsid has developed to complete several roles that are crucial to establish viral infection. The HPV genome is enclosed by an icosahedral capsid (T=7) of 55 nm in diameter composed by two structural proteins, the major protein L1 and the minor capsid protein L2 (Horvath et al., 2010; Howley 1996; Longworth & Laimins, 2004; Pr  tet et al., 2007). To date, over 100 different viral types have been recognized and new types are regularly added to this list. These viruses can be classified into mucosal and cutaneous subtypes. Within each of these HPV groups, individual viruses are designated high risk or low risk according to their oncologic potential: high risk viruses such as HPV16,18 are frequently found in carcinomas. Low-risk types are responsible for benign lesions or condylomas (Blachon & Demeret, 2003, Howley 1996; Longworth & Laimins, 2004; Mu  nger et al., 2004, Pr  tet et al., 2007).

HPV types belong to four of those genera, i.e., Alphapapillomavirus, Gammapapillomavirus, Mupapillomavirus and Nupapillomavirus have been associated with cutaneous warts, especially foot and hand warts (Koning et al., 2011). Genitally transmitted HPV types are contained within genus Alfapapillomavirus and viruses from this group, such as HPV 6 and 11, are major sexually transmitted pathogens (Brentijens et al., 2002; de Villiers et al., 2004, Myers et al., 1994 as cited in Doorbar, 2005). These viruses are associated with benign papillomas. Contrary, the high-risk viruses from supergroup A, such as HPV16 and 18, cause mucosal lesions that can progress in some individuals to high-grade neoplasia and cancer (Bosch et al., 2002; Walboomers et al., 1999 as cited in Doorbar, 2005). The second major group of human papillomaviruses (also known as Beta papillomaviruses) are contained within supergroup B such as HPV5. This virus causes inapparent or latent infections in the general population (de Villiers et al., 2004; Myers et al., 1994; Ramoz et al., 2002, as cited in Doorbar 2005). The third major group of human papillomaviruses (also known as Gammapapillomaviruses) are gamma papillomaviruses such as HPV4. This virus cause cutaneous warts in the general population that can superficially resemble those caused by supergroup A papillomaviruses such as HPV2. The remaining group of HPVs are contained within supergroup E (also classified as Mu and Nu-papillomaviruses (de Villiers et al., 2004, Myers et al., 1994 as cited in Doorbar, 2005). Only three human members from this group are known, and all cause cutaneous papillomas in the general population. HPV1 is the most well studied member of this group, and like HPV2 in supergroup A, causes verrucas and palmar warts (Doorbar, 2005).

The HPV genome includes several open reading frames (late and early gene regions and the non-coding long control region (LCR) that encode proteins involved in viral DNA replication (E1 and E2), viral gene expression regulation (E2), virus assembly (E4) and the immortalisation and transformation of infected epithelial cells (E5, E6 and E7; high-risk HPV only). These proteins play a role in genome organization, regulation of gene expression, and cellular transport. HPV proteins and their functions were documented in Table 1. The open reading frames L1 and L2 encode the two capsid proteins (Howley 1996; Pr  tet et al., 2007). These proteins are expressed in the upper layers of infected tissue (Ozbun & Meyers, 1998, as cited in Doorbar, 2005). HPVs L1 and L2 capsid proteins form the structure of the virion and facilitate viral DNA packaging and maturation.

The papillomavirus E1 and E2 proteins play significant roles in viral genome replication. (Munger et al., 2004). The E1 protein also exhibits DNA helicase/ATPase activity (Hughes & Romanos 1993, Longworth & Laimins, 2004). E1 proteins bind to specific DNA elements in the viral origin of replication and assemble into hexameric helicases with the assist of a second viral protein, E2 (Wilson et al., 2002). The viral E2 protein is also crucial for the viral origin of replication (Dao et al., 2006). E2 plays a role in regulating viral transcription from the early promoter and viral genome segregation during cell division (Haugen et al., 1987 as cited in Longworth & Laimins, 2004, Munger et al., 2004).

E6 and E7 oncoproteins, encoded by the oncogenic HPV types, are responsible for malignant transformation. These proteins disrupt normal cell growth and proliferation by binding to tumor suppressors proteins such as p53 and retinoblastoma (pRb) (Burd, 2003, Gammoh et al., 2006). High risk HPV E6 protein interacts with many significant cellular protein. To exemplify these cellular protein, EF-hand calcium-binding protein E6-BP (reticulocalbin 2), the interferon regulatory factor IRF-3, and the focal adhesion protein paxillin (Munger et al.,

HPV proteins	Molecular weights	Functions
L1	55 kDa	Major viral capsid protein. Self-assembly in capsomers and capsids, and interacting with L2. Interacting with cell reseptor.
L2	70 kDa	Minor viral capsid protein. Interacting with DNA. Facilitating virion assembly. Interacting with cell receptor.
E1		Viral genome replication. DNA helicase and ATPase activity. Binding to specific DNA elements in the viral origin of replication and assembling into hexameric helicases with the assist of a second viral protein, E2.
E2	42 kDa	Site-specific DNA binding protein. Viral genome replication . Viral genome expression regulation. Viral genome segregation during cell division. Interacting with and recruits E1 to the origin. Playing a role in regulating viral transcription from the early promoter.
E4		Facilitating virus assembly and release. Interacting with the keratin cytoskeleton and intermediate filaments. Inducing G2 arrest.
E1^E4	10 kDa	Binding and collapsing the cytokeratin network. preventing the progression of cells into mitosis by arresting them in the G2 phase of the cell cycle. Binding to mitochondria. Inducing the detachment of mitochondria from microtubules. Induction of apoptosis.
E5	83 residues	Cellular transformation, and initiation of neoplasia. Being able to activate epidermal growth factor receptor (EGFR) and other protein kinases. Inhibiting apoptosis. Interacting with gap junction proteins.
E6	150 aa	Immortalization and transformation of infected epithelial cells . Disrupting normal cell growth and proliferation by binding to protein p53. Associating with EF-hand calcium-binding protein, E6-BP (reticulocalbin 2), the interferon regulatory factor IRF-3, and the focal adhesion protein paxillin, calcium- binding protein ERC 55 hDLG (the mammalian homologue of the Drosophila discs large tomour suppressor protein), hScrib and MUPP control cell polarity. Leading to the disruption of the actin cytoskeleton and cell matrix interactions. Inducing telomerase. Preventing cell differentiation.
E7	100 aa	Immortalization and transformation of infected epithelial cells. Disrupting normal cell growth and proliferation by binding to protein pRb. Leading to the delocalization of dynein from mitotic spindles via an association with Nuclear Mitotic Apparatus Protein 1 (NuMA). Destabilising centrosomes and causes mitotic defects. Activating cell cycle positive regulators.

Table 1. HPV proteins and their functions.

2004). E6 also binds the p53 as part of a trimeric complex with the cellular ubiquitin ligase, E6AP, leading to the rapid turnover of p53 (Scheffner et al., 1990; Werness et al., 1990 as cited in Longworth & Laimins, 2004).

HPV E7 proteins are low-molecular-weight proteins of approximately 100 amino acids. This oncoprotein encoded by small DNA tumor viruses, they associate with and adjust the functions of cellular protein complexes. The HPV E7 proteins interact with the retinoblastoma (Rb) family of tumor suppressors protein and the related “pocket proteins” p107 and p130. The proteins control the activities of the E2F family of transcription factors that regulate multiple cell cycle transitions as well as other cellular activities (Munger et al., 2004). E7 also binds to other proteins such as p130, p21, p27, cyclin A, cyclin E, the cyclin dependent kinase inhibitor (CKI), TBP, P300/CBP, MPP2, IGFBP-3, Mi2, NuMA (nuclear mitotic apparatus protein 1), p600, and a cellular protein kinase activity (Dyson et al., 1989 as cited in Longworth & Laimins, 2004; Jones and Munger, 1996; Pim and Banks, 2010).

HPV-16 may not only inactivate the tumor suppressor proteins p53 and pRB with its E6 and E7 oncoproteins, respectively, but could also alter other cellular functions through E7 interaction with the cytoskeleton or associated proteins (Rey et al., 2000). Causing both benign and malignant lesions, HPV must first infect the divisible basal cell to induce papilloma formation (Burd, 2003; Flores et al., 2000; Howley 1996; Stanley, 2001). Viral replication occurs concomitantly with epithelial cell differentiation. Entering the basal cell, HPV replicates simultaneously with epithelial cell differentiation and reaches the keratinized cell (Andersson et al., 2005; Burd, 2003; Flores et al., 2000; Hoory et al., 2008; Howley 1996; Stanley, 2001).

The E4 protein is the most abundantly expressed HPV protein. HPV E1^{E4} accumulates in differentiating cells of the upper epithelial layers. It is synthesized from a spliced mRNA, E1^{E4}, which encodes five amino acids from the E1 ORF spliced to the protein encoded by the E4 ORF (Chow et al., 1987; Doorbar et al., 1990; Nasseri et al., 1987 as cited in Raj et al., 2004). The first activity described for the 10-kDa HPV type 16 (HPV16) E1^{E4} protein was its ability to bind and collapse the cytokeratin network (Doorbar et al., 1991 as cited in Raj et al., 2004). Although all of the role of HPV16 E1^{E4} is unclear, previous work has revealed that HPV16 E1^{E4} can interact with keratins and cause the reorganization of the keratin intermediate-filament network (Doorbar et al., 1991 as cited in Wang et al., 2004). The HPV 16 E1^{E4} protein binds to keratins directly and interacts strongly with keratin 18, a member of the type I intermediate-filament family. By contrast, HPV16 E1^{E4} bound only weakly to keratin 8, a type II intermediate-filament protein, and showed no detectable affinity for the type III protein, vimentin (Wang et al., 2004).

The product of the E5 oncogene in HPVs contributes to cellular transformation. HPV16 E5 is a highly hydrophobic protein. It found mainly at the Golgi apparatus and internal membranes (Conrad et al., 1993 as cited in Alonso and Reed, 2002). Little is known about the biological activities of the HPV16 E5 protein or the source of its oncogenicity. It has been shown that E5 is able to regulate epidermal growth factor receptor (EGFR) activation in the presence or absence of ligand, and that expression of the protein in human keratinocytes results in altered gap junction-mediated cell-cell communication (Alonso and Reed, 2002). HPV E5 is also known to interact with growth factor receptors and gap junction proteins and is believed to play a role during the initiation of neoplasia (Yang et al., 2003).

Most benign and low-grade cervical lesions contain HPV DNA in an extrachromosomal state (Durst et al., 1985 as cited in Martinez 2007). However, in most cases of cervical carcinomas the HPV DNA is usually found integrated into the host chromosomes, frequently disrupting the E1 and E2 genes (zur hausen, 2000, 2002; Durst et al., 1985; Meissner et al., 1989 as cited in Martinez 2007). This process result in increased expression of the viral E6 and E7 oncogenes (Yee et al., 1985 as cited in Martinez 2007).

A common feature of Human papillomavirus infection is the appearance of koilocytosis in the differentiated layers of squamous epithelium. Koilocytosis is the most common cytopathic effect and is considered by pathologists to be the major histopathological aspect for determination of HPV infection. Koilocytosis is composed of the presence of abnormal koilocytes. The greatest change caused by HPV in the epithelial cell cytoplasm is called koilos. Koilos means "hollow" in Greek. These koilocytes are squamous epithelial cells that may contain an acentric hyperchromatic nucleus and large clear perinuclear halos that usually occupy a greater volume than that of the cytoplasm (Fornatora et al., 1996; Krawczyk et al., 2008; Miyahara et al., 2011, Safi Oz et al., 2009, Safi Oz, 2010). The multiple nuclei of koilocytes are in fact multilobation of a single nucleus, and this phenomenon is associated with upregulation of gene products related to the G2 chectpoint. On restoration of 3D confocal images, the multinucleated feature of koilocytes was revealed to be multilobation of a single nucleus, as opposed to true multinucleation (Cho, 2005, 2006).

HPV causes various changes through its structural proteins in the cytoplasms and nuclei of the cells and tissues it infects (Krawczyk et al., 2008, Safi Oz et al., 2009, Safi Oz, 2010, Fornatora et al. 1996 as cited in Miyahara et al., 2011). The formation of koilos is influenced by the structural proteins of the virus, cell skeletal filaments, and tumour suppressor genes. Modifications of the cytoskeleton as a result of viral protein expression have been associated with oncogenic transformation by papillomaviruses. HPV proteins are interacted with cell skeletal filaments. Some of these proteins are E6 (HPV16,18), E7 (HPV16,18,38), E5 (high and low risk HPV types), E1^E4 (HPV16), E4 proteins (Lee & Dominguez, 2010; McIntosh et al., 2010; Nguyen 2008; Rey et al., 2000, Safi Oz, 2010; Stanley, 2001; Uribe & Jay., 2009; Yue et al., 2011).

3. HPV proteins in relation with cytoskeletal filaments and interaction mechanisms

Malignant transformation occurs with the alteration of cytoskeleton (Ben-Ze'ev 1997 as cited in Akgul et al., 2009). All these chances occur in different stages of cell cycle. Disruption of cytoskeleton not only means disruption of cytoskeletal organization but also disruption of many cellular functions. In this section, first of all cytoskeleton, its members and functions will be mentioned briefly. Then HPV proteins which are known and thought to have relation with cytoskeleton due to studies carried out until today will be explained. HPV proteins and cellular molecules interacted with cytoskeletal filament disruption were documented in Table 2)

The cytoskeleton is a network of fibers throughout the cell's cytoplasm that helps the cell maintain its shape and gives support to the cell. In addition to providing support for the cell, the cytoskeleton is also involved in cellular motility and in moving vesicles within a cell, as well as assisting in the formation of food vacuoles in the cell. A variety of cellular

organelles are held in place by the cytoskeleton. The cytoskeleton is made up of three different types of protein filaments: microtubules, actin filaments (microfilament) and intermediate filaments. Each type of filament has different mechanical possessions and dynamics, but certain fundamental principles are common to them all (Alberts et al., 2002; <http://biology.about.com/od/cellanatomy/a/aa013108a.htm>).

Actin filaments determine the shape of the cell's surface and are necessary for whole cell locomotion. The actin cytoskeleton is a critical part of the cellular activities such as cell shape, cell division, motility, contraction, focal adhesion, phagocytosis, protein sorting and signal transduction (Lee & Dominguez 2010; Uribe & Jay 2009). Actin filament's usefulness to the cell depends on a large number of accessory proteins that link the filaments to other cell component. These proteins are essential for the control assembly of the cytoskeletal filaments in particular locations (Alberts et al., 2002). Cell movement is an important phenomenon in embryonic morphogenesis, immune surveillance, angiogenesis and tissue repair and regeneration (Hussey et al., 2006; Itoh and Yumura, 2007; McMahon and Gallop, 2005; Puppo et al., 2008; Yamaguchi and Condeelis, 2007 as cited in Lee & Dominguez, 2010). Two transition types (monomeric or G actin and filamentous or F actin) of actin filaments are in cells (Uribe & Jay 2009). Schematic representation of monomeric and filamentous actin were seen in Figure. 1.

The actin filament is asymmetric; actin monomers join the barbed (or +) fast growing end of the filament in the ATP-bound state and depart the filament preferentially from the pointed (or -) end primarily in the ADP state, giving rise to a process known as actin filament treadmilling. The transition between two types of actin is tightly regulated in cells by a large number of Actin-Binding Proteins (ABPs) (Lee & Dominguez, 2010; Uribe & Jay 2009). ABPs carry out a wide range of functions, including actin filament nucleation, elongation, severing, capping, and crosslinking and actin monomer sequestration (Lee & Dominguez 2010). The reorganization of the actin cytoskeleton is regulated in time and space by multiple factor, most notably Rho family GTPases that act as GTP-dependent molecular switches (Raftopoulou and Hall, 2004 as cited in Lee & Dominguez 2010). Among the small GTPases of the Rho family, Cdc42, Rac, and Rho are recognized as the most important regulators of actin assembly, controlling respectively the formation of filopodia, lamellipodia, and stress fibers (Etienne-Manneville and Hall, 2002 as cited in Lee & Dominguez 2010). Signals transmitted through these GTPases lead to localized actin cytoskeleton assembly/disassembly at the plasma membrane, with the actin filaments acting to push the cellular membrane (Hall, 1994 as cited in Lee & Dominguez 2010).

By interacting with paxillin, E6 protein facilitates transformation by disrupting the normal links between paxillin and the actin cytoskeleton by displacing paxillin-LD motif-binding proteins, disrupts the actin filament formation and the regulation of cytoskeleton (Cooper et al., 2007; Safi Oz et al., 2009, Rapp & Chen, 1998, Turner, CE., 2000). In the light of this information, the disruption of actin filament formation and thus, cytoskeleton disruption are believed to affect the formation of koilos around the nucleus (Safi Oz et al., 2009, Rapp & Chen, 1998, Cooper et al., 2007). With HPV disrupting actin filament formation, it is thought that cell shape and division, motility, contraction, focal adhesion and phagocytosis may be influenced.

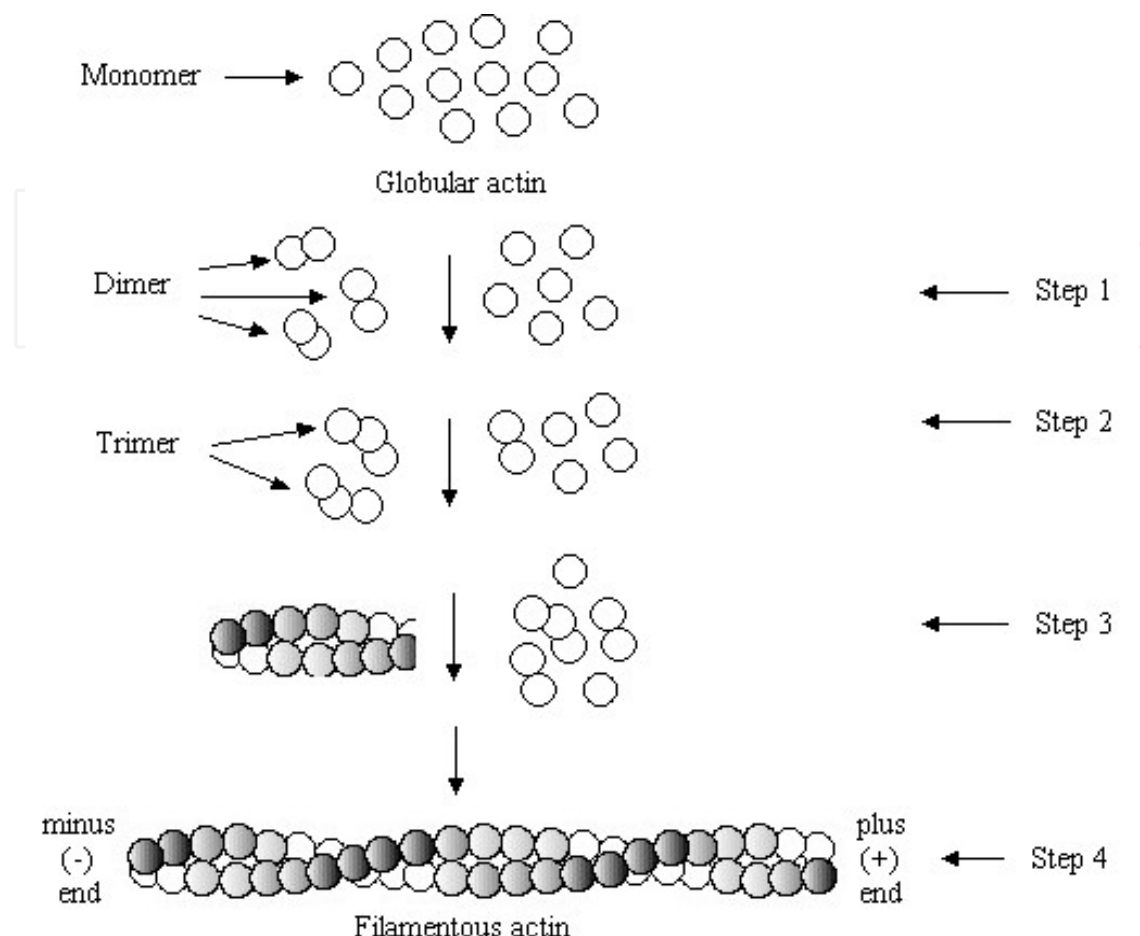


Fig. 1. Schematic representation of monomeric and filamentous actin

The bovine papillomavirus (BPV) E6 oncoprotein also interacts with paxillin and disrupt the actin cytoskeleton. HPV16 E6 binding to paxillin may contribute to the carcinogenic potential of the human papillomavirus (HPV). The association of HPV16 E6 with paxillin was affected by depolymerization of the actin fiber network. Disruption of the actin cytoskeleton is a characteristic of many transformed cells. (Tong & Howley, 1997).

HPVE6 interacted with numerous proteins involved in adhesion, cell architecture and polarity. hDLG (the mammalian homologue of the *Drosophila* discs large tumour suppressor protein), hScrib and MUPP control cell polarity and cellular scaffolds, and their interaction with E6 would lead to deregulation of cytoskeletal organization and cell-cell interactions (Campo, 2005). E6 also interact with the calcium binding protein ERC 55 and the paxillin, interactions that could lead to the disruption of the actin cytoskeleton and cell matrix interactions. Paxillin is a protein associated with focal adhesion kinase (FAK), a kinase that plays a regulatory role in cell migration, and vinculin and involved in the regulation of the cytoskeleton. Paxillin takes role in the regulation of actin cytoskeleton by interacting with other adhesion proteins in the cell such as actopaxin and vinculin. When Human Papillomavirus E6 protein is associated with paxillin, interaction of paxillin with other adhesion proteins therefore formation of actin cytoskeleton is disrupted. (Table 2)

HPV proteins	Cellular molecules	Types of cytoskeletal filaments	Effects
HPV 16 E5	Golgi apparatus Endoplasmic reticulum Cellular membrane	Actin filament	Inhibits endocytotic activity
HPV 16 E6	Paxillin (disrupt paxillin and vinculin, actopaxin interaction)		Disruption of actin filament
	ERC55 (calcium binding protein)		
	hDLG (the mammalian homologue of the Drosophila discs large tumour suppressor protein) hScrib MUPP		
	Tight junction complex		
HPV 16 E7	Unknown		Disruption of actin filament
HPV 38 E7			
HPV 16 E7	Microtubule network (attaches to microtubule network via the motor protein complex dynein) NuMA (Nuclear Mitotic Apparatus Protein 1) / dynein network	Microtubule	Disruption of microtubule motors and HPV associated tumorigenesis. Mitotic errors
HPV 16 L2	Microtubule network (attaches to microtubule network via the motor protein complex dynein)		Disruption of microtubule motors
HPV E4	Cytokeratin	Intermediate filament	Total collapse of the cytokeratin matrix
HPV E1^E4	Cytokeratin DEAD-BAX protein		

Table 2. HPV proteins and cellular molecules interacted with cytoskeletal filament disruption

HPV E6, specifically targets p53 for inactivation in order to promote cell growth and transformation and tumor suppressors such as MAGI-1 and SAP97/hDLG for degradation. HPV E6 also targets numerous cellular proteins involved in a variety of cellular processes such as calcium signaling, cell adhesion, transcriptional control, DNA synthesis, apoptosis, cell cycle control, DNA repair, and small G-protein signaling. (Das et al., 2000, Degenhardt & Silverstein, 2001, Filippova et al, 2002, Gao et al., 1999, Gao et al., 2000, Iftner et al., 2002, Kuhne & Banks, 1998 Tong and Howley, 1997 as cited in Zhang et al., 2007). Cellular targets

for the E6 proteins from high-low risk HPV types are Bak, myc, E6AP, E6BP/ERC55, P300/CBP, PDZ proteins, hTERT, Tyk2, hAda3 (Pim and Banks, 2010). HPV E6 interacts with tight junction complex (Zhang et al., 2007). Tight junction acts as an impermeable barrier that divides epithelial cells into functionally distinct apical and basolateral membrane domains (Yeaman et al., 1999 as cited in Zhang., 2007). Tight junctions consist of several transmembrane proteins (occludin, claudins, and junctional adhesion molecule). All these proteins are associated with at least one of the Zonula occludens proteins (ZOPs). ZOPs bind to the junctional transmembrane proteins linking them to the actin cytoskeleton. So, ZOPs establish a link between the junction site and the cytoskeleton by interacting directly with actin filaments (Fanning et al., 1998, Itoh et al., 1997, Wittchen et al., 1999 as cited in Traweger et al., 2003). ZOPs currently comprising ZO-1, ZO-2, and ZO-3, belong to the family of membrane-associated guanylate kinase homologue (MAGUK) proteins. MAGUK proteins are involved in the organization of epithelial and endothelial intercellular junctions (Traweger et al., 2003 as cited in Bauer et al., 2010). HPV E6 polypeptide binds to MAGUK Proteins (Zhang et al., 2007). The ZO-2 protein is targeted by HPVE6. ZO-2, a 160-kDa phosphoprotein and was found to co-precipitate with ZO-1 in epithelial cells (Gumbiner et al., 1991, Jesaitis and Goodenough, 1994 as cited in Traweger et al., 2003).

ZOPs not only associate with each other but also with components of adherens junctions and gap junctions in cells lacking (Gumbiner et al., 1991, Howarth and Stevenson, 1995 as cited in Traweger et al., 2003). Adherens junction is responsible for cell-cell adhesion (Gumbiner, 1996 as cited in Zhang., 2007). The disruption of adherens junction decreases the phosphorylation of E-cadherin by protein kinase CK2, and this process of downregulation is treated as a common event in carcinogenesis (Serres et al., 2000 as cited in Zhang., 2007). Tight junction disruption and apobasal activity directly contribute to carcinogenesis by deregulating normal proliferation and differentiation programs in epithelial cells (Matter & Balda et al., 2003 as cited in Zhang., 2007). It is also thought that the damage caused by HPV on E6 proteins and tight junctions on carcinogenesis process is important.

HPV-16 may not only inactivate the tumor suppressor proteins p53 and pRB with its E6 and E7 oncoproteins, respectively, but could also alter other cellular functions through E7 interaction with the cytoskeleton or associated proteins. The E7 oncoprotein of Human Papillomavirus type 16 interacts with F-Actin in vitro and in vivo. F-actin is part of cellular structures such as microfilaments and the cell cortex and interacts with several structural and regulatory components. F-actin modifications resulting from viral protein expression will not only affect cytoskeletal organization but can also disrupt several cellular functions (Rey et al, 2000).

Yue et al. showed that HPV38 E7 induces actin stress fiber disruption, and this phenomenon correlates with its ability to down-regulate Rho activity. In addition, HPV38 E7 is able to induce actin fiber disruption by directly binding to the eukaryotic elongation factor 1A (eEF1A) and abolishing its effects on actin fiber formation. Their data support the conclusion that HPV38 E7 promotes keratinocyte proliferation in part by negatively regulating actin cytoskeleton fiber formation and by binding to eEF1A and inhibiting its effects on actin cytoskeleton remodeling (Yue et al., 2011).

The second type of cytoskeletal filament is the microtubule. Microtubules determine the positions of membrane-enclosed organelles and direct intracellular transport. Microtubules

are formed from protein subunits of tubulin (alpha-tubulin and beta-tubulin) (Alberts et al., 2002). Construction of microtubules was seen in Figure 2.

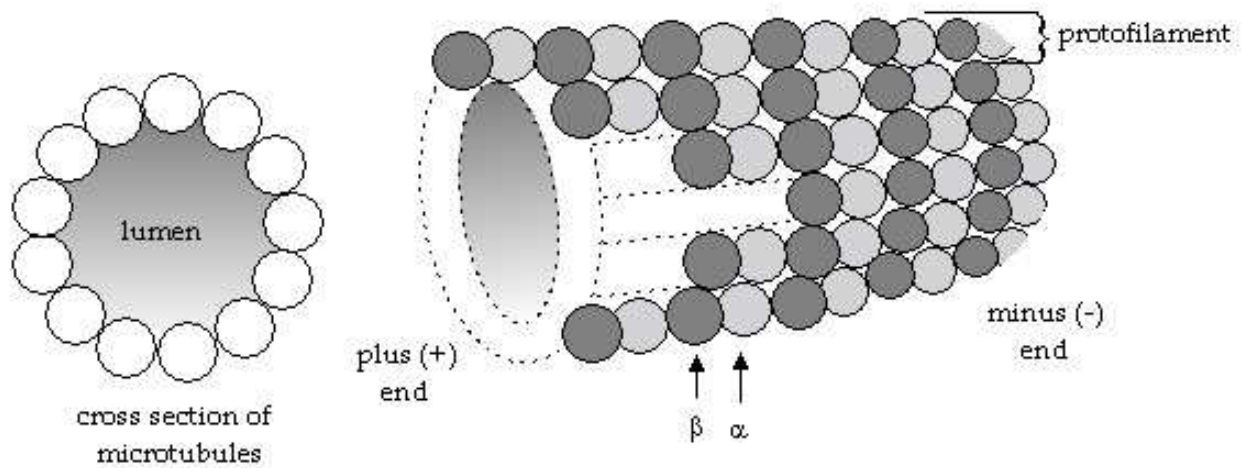


Fig. 2. Construction of microtubules from α and β tubulins

Romani et al. showed that the effect of HPV transformation on cellular cytoarchitecture. Cells from laryngeal papillomas and normal epithelium were cultured *in vitro*. Cytoskeletal components of both types of cells were visualized by immunofluorescence, to determine whether there were any differences in the structure or distribution of the cytoskeleton. The intermediate filaments and actin filaments are altered in the papilloma cells but there isn't significant change in microtubules (Romani et al., 1987). (Table 2) Most of the studies carried out up-to-now are about HPV proteins and motor proteins. HPV16 E7 expression leads to an increased population of mitotic cells with dynein, a minus end-directed microtubule motor protein, delocalized from the mitotic spindle. Dynein is composed of several subunits. The dynein motor complex aids in the positioning of the Golgi complex and mitochondria, along with other organelles, and transports cargo from the endoplasmic reticulum, endosomes, and lysosomes. It is possible that the disruption of microtubule motors by high-risk HPV may contribute to HPV associated tumorigenesis (Nguyen et al., 2008). The other type of motor protein is kinesin. Kinesin uses the energy of ATP hydrolysis to move along a microtubule. These proteins have legs and feet that change conformations by binding and hydrolyzing ATP to walk along the microtubules.

Also HPV16 L2 protein attaches to microtubule network via the motor protein complex dynein (Florin et al., 2006; Schneider et al., 2011). The viral capsid play a critical role in the establishment of the viral infection. The L2 protein is an internally located multifunctional protein with roles in genome encapsidation (Schelhaas et al., 2008, Holmgren et al., 2005 as cited in Horvath et al., 2010). Papillomaviruses enter cells via endocytosis. After endocytic cell entry and egress from endosomes, HPV16L2 goes along with the viral DNA to the nucleus. HPV16 L2 protein may be involved in the intracytoplasmic transport of the viral genome (Florin et al., 2006; Schneider et al., 2011).

The high-risk HPV16 E7 expression leads to the delocalization of dynein from mitotic spindles via an association with Nuclear Mitotic Apparatus Protein 1 (NuMA). The disruption of the NuMA/dynein network may result in mitotic errors (Nguyen, 2008, 2009). It is hypothesized that these event may important role in chromosome alignment and viral persistance (Nguyen & Munger., 2009).

The third type of cytoskeletal filament is the intermediate filament. Intermediate filaments (IFs) provide mechanical strenght and resistance to share stres (Alberts et al., 2002). Intermediate filament-associated diseases clearly represent a significant group of human pathologies, and these pathologies that have given us the best clues to the function of this type of cytoskeleton component (Penky & Lane, 2007). Intermediate filaments are composed of smaller subunits that are themselves elongated and fibrous, but actin filaments and microtubules are made of compact and globular subunits (Alberts et al., 2002).

IFs is a highly elongated, rod-like dimer based on an α -helical coiled-coil structure. Assembly of cytoplasmic IF proteins, such as vimentin, begins with a lateral association of dimers into tetramers and gradually into the so-called unit-length filaments (ULFs) (Strelkov et al., 2003). The molecular organisation of the intermediate filaments is specific for the cell type, the developmental stage and the type of differentiation (McIntosh et al., 2010). Major types of intermediate filament proteins in vertebrate cell are nuclear, vimentin-like, epithelial and axonal IF. Nuclear IF are composed of lamin A, B and C. The nuclear lamins are filamentous proteins, providing the nucleus with a putative skeleton for chromatin attachment (Alberts et al., 2002, Carmo-Fonseca & David-Ferreira, 1990).

Different families of intermediate filaments are keratins, neurofilaments, vimentin-like filaments. Neurofilaments are found in concentrations along the axons of vertebrate neurons. Neurofilament proteins are NF-L, NF-M, NF-H. The vimentin-like filaments are found in muscle, glial cells, many cells of mesenchymal origin and some neurons (Alberts et al., 2002). The most diverse intermediate filament family is that of the keratins. Keratins are major structural proteins in epithelial cells and form the cytoplasmic network of intermediate filaments (Fuchs et al., 1998 as cited in Wang et al., 2004). Every keratin filament is made up of type I (acidic) and type II (neutral/basic) keratin chains (Alberts et al., 2002). The keratin IF network of epidermal keratinocytes provides a protective barrier against mechanical insult, it is also a major player in absorbing stress in these cells (McIntosh et al., 2010). They contain at least 20 members, called keratin 1 (K1) to K20, which are divided into two types according to the sequence and isoelectric point (pI). K9 to K20 are type I (acidic) keratins. The type II keratins, K1 to K8, are neutral or basic. Type I and type II keratins form noncovalent heteropolymers at a 1:1 ratio (Moll et al., 1998 as cited in Wang et al., 2004). Recently, several new functions of keratins have emerged. K8 and K18 prevent Fas- and possibly tumor necrosis factor-induced apoptosis (Caulin et al., 1998, Gilbert et al., 2001, Inada et al., 2001, Ku et al., 2003 as cited in Wang et al., 2004). Keratin intermediate filaments are highly dynamic structures and are reorganized during cellular events such as mitosis and apoptosis (Wang et al., 2004). Diversity of keratins is clinically useful in the diagnosis of epithelial carcinomas, as the particular set of keratins expressed gives an indication of the epithelial tissue in which the cancer originated and thus can help to guide to choise of treatment (Alberts et al., 2002). HPVE4 interacts with the keratin cytoskeleton and intermediate filaments (Campo, 2005). Recent studies have introduced a new protein named E1^{E4} of HPV16 that could disrupt the epithelial cytoskeleton. This protein is

encoded by spliced mRNAs that fuse the two early genes, E1 and E4, which encodes five amino acids from the E1 ORF spliced to the protein encoded by the E4 ORF, and is the most abundantly expressed viral protein in HPV-infected epithelia (Doorbar et al., 1991 as cited in Ohta & Nishiyama, 2011). It has been reported that this protein degrades the cytoskeleton by interacting with epithelial cell proteins (Davy et al., 2002, Nakahara et al., 2002). (Table 2) Doorbar et al showed that expression of the HPV-16 E1^{E4} protein in human keratinocytes (the natural host cell for HPV infection) results in the total collapse of the cytokeratin matrix. Tubulin and actin networks are unaffected by E1-E4, as are the nuclear lamins (Doorbar et al., 1991). The human HPV16 E1^{E4} protein is associated with and reorganises the keratin IF network in cells in culture. HPV16 E1^{E4} was found to effect a dramatic cessation of keratin IF network dynamics by associating with both soluble and insoluble keratin. These observations shed new light on the mechanism of keratin IF network reorganisation mediated by HPV16 E1^{E4} (McIntosh et al., 2010). E1^{E4} also translocates to mitochondria via an N-terminal leucine-rich region and induces the detachment of mitochondria from microtubules. The detached mitochondria then aggregate adjacent to the nucleus (Ohta & Nishiyama, 2011).

HPV16 E1^{E4} protein is the most abundantly expressed viral protein in HPV infected epithelia. HPV E1^{E4} possesses the ability to bind to the cytokeratin network by interacting directly with cytokeratins and to DEAD-box proteins. Keratin association leads to the eventual reorganization of the cytokeratin network *in vivo* as well as *in vitro* (Wang et al., 2004 as cited in Raj et al., 2004). Interestingly, the collapse of the network appears to initiate from the plasma membrane. Once collapsed, the cytokeratin appears as a cluster beside the nucleus.

HPV16 E1^{E4} is also able to prevent the progression of cells into mitosis by arresting them in the G2 phase of the cell cycle.

HPV16 E1^{E4} protein binds to mitochondria after binding to and collapsing the cytokeratin network and induces the detachment of mitochondria from microtubules, causing the organelles to form a single large cluster adjacent to the nucleus. This is followed by a severe reduction in the mitochondrial membrane potential and an induction of apoptosis (Raj et al., 2004).

In addition to the proteins mentioned above, it is expressed that HPV E5 protein contributes to the formation of koilocytes together with E6. The HPV E5 proteins are small (83 amino acids) hydrophobic proteins whose biological functions remain unresolved. These proteins are localized to endosomal membranes and the Golgi but on occasion are found in the cellular membranes (Longworth & Laimins, 2004). This protein associates with Golgi apparatus, endoplasmic reticulum and cellular membrane and inhibits endocytic activity by linking actin cytoskeleton. Although the role of HPV E5 in the cell-cycle is not known completely, it was shown with studies carried out on rodents that it shows low oncogenic activity in addition to major oncoproteins E6 and E7 (Kabsch & Alonso, 2002; Suprynowicz et al., 2008; Yang et al., 2003 as cited in Safi Oz., 2010). E6 protein in low and high risk HPV types aims at p53 and PDZ protein which organizes membrane transport in polarized epithelial cell membrane and may be damaging cell cytoskeleton (Safi Oz 2009, Krawczyk et al., 2008). HPV E5 – cell cytoskeleton association is an issue which requires more detailed biochemical and cellular studies.

4. Conclusion

Here, I summarize recent progress in my understanding of the interaction between Human papillomavirus proteins and their ability to disrupt cytoskeletal filaments. Disruption of cell cytoskeleton causes the occurrence of some important diseases such as cancer. Disruption of cell cytoskeleton both causes the disruption of cellular motility and cellular integrity and failure of important biological events such as cell division, contraction and phagocytosis. Association of various viruses with cell cytoskeleton is a study issue which has been gaining importance in recent years. HPV is included in this group of virus. In the studies of cell cytoskeleton – HPV, HPV16 and 18 which are among the risky group in the sense of cancer formation, become prominent. E6 protein of HPV16 and 18, E5 protein of HPV 16 and E7 protein of HPV38 associate with the members of actin cell cytoskeleton and damages cell cytoskeleton. Moreover, HPV E6 associates through MAGUK (membrane-associated guanylate kinase homologue) proteins with tight junctions which form impermeable barrier between apical and basal membrane domains. Although studies show that actin and intermediate filaments in papilloma cells alter but there are no significant alterations in microtubules; more detailed studies are required on this subject. In association of HPV – microtubule, some studies have been shown in which HPV16 minor capsid protein L2 and E7 link with microtubule network via motor protein dynein. Moreover it was stated that HPV16 E7 causes dynein delocalization via Nuclear mitotic apparatus (NuMa). I am of the opinion that there are few studies upon HPV and kinesine from motor proteins; enlightenment of this subject will direct the association of HPV-microtubule. Comprehensive understanding of HPV-cytoskeleton interaction will offer new insights into the HPV life cycle as well as carcinogenesis. This virus- cytoskeleton interaction will also provide a paradigm for investigating other DNA tumor viruses that share a similar mechanism for interacting with cytokeratin filaments.

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6. References

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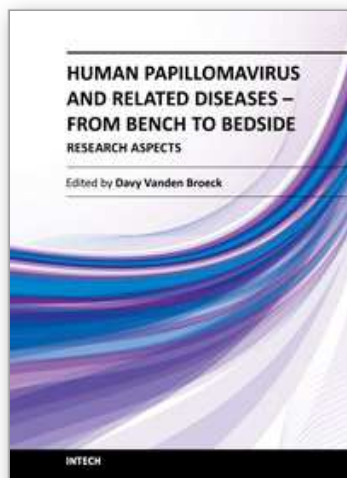
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Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on epidemiological and fundamental research aspects in the area of HPV, and it will update those working in this fast-progressing field with the latest information.

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