1

Human Papillomavirus: Biology and Pathogenesis

José Veríssimo Fernandes[1] and
Thales Allyrio Araújo de Medeiros Fernandes[2]
[1]Federal University of Rio Grande do Norte
[2]University of Rio Grande do Norte State
Brazil

1. Introduction

The human papillomavirus (HPV) is one of the most common causes of sexually transmitted disease in both men and women around the world, especially in developing countries, where the prevalence of asymptomatic infection varies from 2 to 44%, depending on the population and studied region (Sanjosé et al., 2007). Most HPV infection is transient and some studies show that the majority of sexually active individuals are exposed to and acquire infection from this virus at some phase in their lives (Baseman and Koutsky, 2005; Trottier and Franco, 2006). HPV infection is more prevalent in young adults, at the beginning of their sexual activity, with a subsequent decline in the prevalence rate with increasing age, likely as a result of development of an immune response against the virus and reduction of sexual activity (Castle et al., 2005; Fernandes et al., 2009; Chan et al., 2010).

HPV can infect basal epithelial cells of the skin or inner-lining tissues and are categorized as cutaneous types or mucosal types. Cutaneous types are epidermotropic and infect the keratinized surface of the skin, targeting the skin of the hands and feet. Mucosal types infect the lining of the mouth, throat, respiratory, or anogenital tract epithelium (Burd, 2003). Some HPVs are associated with warts while others have been well established as the main risk factor of invasive cervical cancers and their associated pre-cancerous lesions (Clifford et al., 2005; Zekri et al., 2006; Muñoz et al., 2006). However, only few HPV-infected individuals progress to invasive cervical cancer (Burd, 2003). Most infected individuals eliminate the virus without developing recognized clinical manifestation. (Bosch et al., 2008).

Today, more than 150 different HPV types have been cataloged and about 40 can infect the epithelial lining of the anogenital tract and other mucosal areas of the human body. Based on their association with cervical cancer and precursor lesions, HPVs can also be classified as high-risk (HR-HPV) and low-risk (LR-HPV) oncogenic types. LR-HPV types, such as HPV 6 and 11, can cause common genital warts or benign hyperproliferative lesions with very limited tendency to malignant progression, while infection with HR-HPV types, highlighting HPV 16 and 18, is associated with the occurrence of pre-malignant and malignant cervical lesions (Muñoz et al., 2003; Bosch et al., 2002; Bosch et al., 2008). HR-HPV types are also associated with many penile, vulvar, anal, and head and neck carcinomas, and contribute to over 40% of oral cancers (Stanley, 2010).

Persistent infection with HR-HPV is unequivocally established as a necessary cause of cervival cancer (Trottier & Franco, 2006). The critical molecules for initiation and progression of this cancer are the oncoproteins E5, E6, and E7, that act largely by overcoming negative growth regulation by host cell proteins and by inducing genomic instability, a hallmark of HPV-associated cancers (Munger et al., 2004; Moody & Laimins, 2010).

Once HPV transmission to the genital tract occurs through sexual contact, the risk factors for the infection and cervical lesions, including cervical cancer, are the same classic risk factors for other sexually transmitted diseases. The number of sexual partners is the risk factor more consistently associated with genital HPV infection and therefore with cervical cancer. In addition, other indicators of sexual behavior and reproductive activities, heredity, immune and nutritional status, and smoking can contribute in some way to the development of cervical cancer (Tarkowski et al., 2004; Muñoz, 2006; Fernandes et al., 2010).

In this chapter we will discuss the biology and pathogenesis of human papillomavirus, analyzing some specific aspects of their interactions with the infected host and specific host cell components.

2. Biologic properties of HPV

2.1 Structure of viral particle and regulation of gene expression

The human papillomavirus (HPV) is a relatively small non-enveloped virus that contains a double-stranded closed circular DNA genome, associated with histone-like proteins and protected by a capsid formed by two late proteins, L1 and L2. Each capsid is composed of 72 capsomeres, each of which is composed of five monomeric of 55kDa units that join to form a pentamer corresponding to the major protein capsid, L1. The L1 pentamers are distributed forming a network of intra- and interpentameric disulfide interactions which serve to stabilize the capsid (Sapp et al., 1995). In addition to L1, minor capsid proteins with approximately 75kDa exist within the virion and are called the L2 protein. To assemble the viral capsid, the pentamers join to copies of L2 that occludes the center of each pentavalent capsomere. (Jo & Kim 2005; Buck et al., 2008; Conway & Meyers, 2009). Thus, each virion contains 72 copies of the L1, the major component of the capsid, and a variable number of copies of L2, a secondary component of the viral capsid, forming a particle with icosahedra symmetry and approximately 50 to 60 nm in diameter (Burd, 2003; Longworth & Laimins, 2004; zur Hausen, 2009).

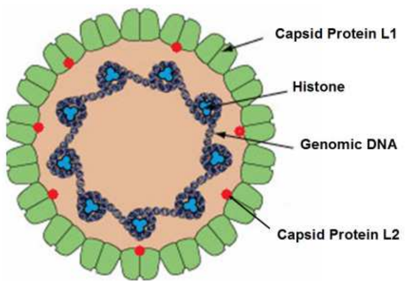


Fig. 1. The structure of HPV. (Adapted from Swiss Institute of Bioinformatics, Viral Zone. - Available in http://viralzone.expasy.org/all_by_species/5.html)

The viral genome of the HPV consists of a single molecule of double-stranded and circular DNA, containing approximately 8000 base pairs and harboring an average of 8 open reading frames (ORFs) (Jo & Kim 2005; Zheng & Baker, 2006). In a functional point of view, the HPV genome is divided into three regions. The first is a noncoding upstream regulatory region (URR) or long control region (LCR) that has regulatory function of the transcription of the E6 and E7 viral genes; The second is an early region (E), consisting of six ORFs: E1, E2, E4, E5, E6, and E7, which encodes no structural proteins involved in viral replication and oncogenesis. The third is a late (L) region that encodes the L1 and L2 structural proteins. The LCR region of the anogenital HPVs ranges in size between 800-900 pb, representing about 10% of the genome, and varies substantially in nucleotide composition between individual HPV types (Fehrmann & Laimins, 2003; Jo & Kim, 2005).

Only one strand of the double-stranded DNA serves as the template for viral gene expression, coding for a number of polycistronic mRNA transcripts. (Stanley et al., 2007). The regulation of viral gene expression is complex and controlled by cellular and viral transcription factors. Most of these regulations occur within the LCR region, which contains cis-active element transcription regulators. These sequences are bound by a number of cellular factors as well as the viral E2 product (zur Hausen, 1996). A large number of cellular transcription factors have been identified and the dysfunction of some of them appears to play a significant role in papillomavirus-linked carcinogenesis (Thierry et al., 1992; Hamid & Gaston, 2009).

The transcription start sites of viral promoters differ depending on the virus type, but, in all types, promoter usage is keratinocyte differentiation-dependent (Smith et al., 2007). The replication origin and many transcriptional regulatory elements are found in the upstream LCR region. The virus early promoter, differentiation-dependent late promoter, and two polyadenylation signals define three general groups of viral genes that are coordinately regulated during host cell differentiation. The E6 and E7 genes maintain replication competence. E1 E2, E4, E5, and E8 are involved in virus DNA replication, transcriptional control, beyond other late functions and L1 and L2, responsible for the assembly of viral particles (Bodily & Laimins, 2011).

The regulation of expression of the late genes in genital HPVs is not well understood. However, it has been shown that the second, or later, promoter is initiated in a differentiation-dependent manner, and thus is activated only when cells are grown in the host’s stratifying/differentiating tissue. Once activated, the later promoter directs transcription from a heterogeneous set of start sites and will serve to produce a set of transcripts that facilitate the translation of L1 and L2 proteins (Smith et al., 2007; Conway & Meyers, 2009). Activation of the later promoter is accompanied by acceleration of viral DNA replication and by high levels of viral protein expression. As a result, virus copy-number amplifies from 50 copies to several thousands of copies per cell. So when a late promoter is activated, the expression of genes will occur, encoding the structural proteins L1 and L2, which join to assemble the capsids and to form virions (Stanley et al., 2007).

2.2 Functions of viral proteins

E1 Protein

The E1 protein represents one of the the most conserved proteins among different HPV types. It has DNA-binding functions and a binding site in the origin of replication localized in the LCR region. It assembles into a hexameric complex, supported by the E2 protein, and the resultant complex has helicase activity and initiates DNA bidirectional unwinding, constituting a prerequisite for viral DNA replication (Wilson et al., 2002; Frattini & Laimins, 1994). The carboxyl terminal domain of E1 has an ATPase/helicase activity and is necessary and sufficient for oligomerization. This domain also interacts with the E2 protein and subunit p70 of DNA polymerase α, but is not sufficient to support replication (Amin et al., 2000). A segment of approximately 160 amino acid residues upstream of the ATPase/helicase domain is the DNA-binding domain (Titolo et al., 2003). A stretch of about 50 amino acids within the amino terminus of E1 acts as a localization regulatory region (LCR) and contains a dominant nuclear export sequence (NES) and a nuclear localization signal (NSL), which are regulated by phosphorylation (Deng et al., 2004).

E2 protein

The E2 open reading frame of HPV gives rise to multiple gene products by alternative RNA splicing. The proteins derived from the E2 gene are involved in the control of viral transcription, DNA replication, and segregation of viral genomes (McPhillips et al., 2006; Kadaja et al., 2009). These different E2 types represent the major intragenomic regulators (Bouvard et al., 1994).

The E2 protein can bind to factors on mitotic chromatin and join the virus genome to host cell chromosomes during mitosis; it contributes to coordinating the HPV DNA replication with host cell chromosome duplication, allowing the viral genomes to be distributed to the daughter cell. This constitutes an important requirement for the persistence of virus DNA in undifferentiated basal cells (McPhillips et al., 2006). Furthermore, the E2 protein interacts with E1 and stimulates viral DNA replication, favoring the binding of E1 to the origin of replication (Seo et al., 1993; Chow et al., 1994).

In lesions containing HPV episomes, the E2 protein directly represses the expression of early genes as a mechanism to regulate the copy number. In addition, it has been reported that HPV E2 proteins are able to repress telomerase promoter activity mediated by the HPV E6 protein (Hamid et al., 2009). Integration of the HPV genome in the host cell chromosome usually disrupts E2 expression, causing a deregulated expression of early viral genes, including E6 and E7, and this event can favor the transformation of human cells and the transition into a malignant state (Romanczuk & Howley, 1992)

In addition to the full-length E2 protein, the infected cells can express an E8^E2C transcript, in which the small E8 domain is fused to the C-terminal domain of E2 (E2C). The full-length E2 protein forms heterodimers with repressor forms of E2, and these E2 heterodimers serve as activators of transcription and replication during the viral cycle. The single-chain E2 heterodimer in the HPV 18 genome initiates genome replication, but is not sufficient for long-term replication of the HPV 18 genome. This is due to the capacity of HPV18 in encoding the repressor E8/E2, which acts as a negative regulator of HPV18 genome replication (Kurg et al., 2010). Moreover, it has been shown that inactivation of E2 in the HPV16 genome increases E6/E7 transcription (Soeda et al., 2006), and that mutation of E8^E2C in the HPV31 or HPV16 genome increases the genome copy number and the E6/E7 transcription, suggesting that the transcriptional repressing by E8^E2C has an important role in viral replication (Lace et al., 2008). It was also noted that the E2C domain not only mediates specific DNA binding but has also an additional role in transcriptional repression by recruitment of co-repressors, such as the CHD6 protein. This suggests that repression of the E6/E7 promoter by E2 and E8^E2C involves multiple interactions with host cell proteins through different protein domains (Fertey et al., 2010).

E4 protein

Despite being considered an early protein, E4 is exclusively located in the differentiated layers of the infected epithelium (zur Hausen, 1996). Although its expression occurs in highly differentiated cells that express the capsid genes and synthesize new progeny virions, and coincides with the onset of vegetative viral DNA replication, E4 is not found in virion particles. The role of this protein in the virus life cycle has not yet been determined, but E4 is not required for transformation or episomal persistence of viral DNA, but interacts with the keratin networks and causes their collapse (Doorbar et al., 1991).

It has been suggested that E4 may have an important role in favoring and supporting the HPV genome amplification, besides regulating the expression of late genes, controlling the virus maturation, and facilitating the release of virions (Londgworth & Laimins 2004). E4 also interacts with and disrupts the organization of intermediate filaments. The role of E4 in providing the release of virus is supported by the association of E4 with the cornified cell envelope (CCE), a highly resistant structure under the plasmatic membrane of differentiated keratinocytes in the stratum corneum. Furthermore, E4 may play role in regulating gene expression and has been shown to induce G2 arrest in a variety of cell types (Londgworth & Laimins 2004).

E5 protein

The E5 protein is a small hydrophobic peptide, approximately 83 amino acids in size that localizes primarily to the endoplasmic reticulum. When expressed alone, HPV E5 has weak oncogenic properties. But in tissue culture assays, HPV E5 can enhance the transforming activity of E6 and E7, suggesting that it may have a supportive role in tumor progression. The localization of E5 to the endoplasmic reticulum suggests its activity may be related to the trafficking of cytoplasmic membrane proteins through this cellular compartment. E5 has also been reported to alter the activity of the epidermal growth factor receptor (EGFR), in addition to reducing the surface levels of major histocompatibility complex (MHC) class I proteins, modulating the MAPK pathway and altering the levels of caveolin 1 (Moody & Laimins, 2010).

The E5 protein varies in length and primary amino acid sequence among the different papillomaviruses, but maintains its hydrophobic nature that promotes fusion between cells (Hu et al., 2009). HPV16 E5 has all the characteristics of fusogenic proteins, including localization in plasma membrane, high level of hydrophobicity, and the ability for dimmers. Moreover, HPV16 E5 has been identified to be necessary and sufficient to induce cell-cell fusion with formation of tetraploid cell and cytokinesis failure (Hu et al., 2009).

The fusogenic activity of the HR-HPV E5 protein contributes to fusion among cells generating aneuploidy with tetraploid cells and chromosomal instability. These events seem to precede and favor integration of HPV genomes, which in turn, leads to expression of viral-cellular fusion transcripts and further enhances expression of the E6-E7 genes, rendering transformed cells strong growth advantages (Ziegert et al., 2003). Thus, the cell fusion HR-HPV E5-induced and cell cycle deregulation seems to have an important role in the early stages of the transformation process. This suggests that HR-HPV E5-induced cell fusion can be a critical event in the early stage of the development of HPV-associated cervical cancer (Gao and Zheng et al., 2010).

As the E5 gene is frequently deleted in cervical cancers, it is believed that the E5 protein may play a role in the early stages of the process of cellular transformation, but is dispensable for the maintenance of malignant transformation (zur Hausen, 1996).

E6 protein

The HPV E6 protein is formed by approximately 150 amino acids and contains two zinc-like fingers joined by an interdomain linker of 36 amino acids, flanked by short amino (N) and carboxy (C) terminal domains of variable lengths (Howie et al., 2009). The best known property of the E6 proteins of HR-HPVs is the ability to bind and degrade the tumor-suppressor protein p53, through the recruitment of the E6-associated protein (E6-AP), a cellular E3 ligase that does not bind to p53 in the absence of E6. Both E6 proteins from HR-HPV and LR-HPV bind to p53, but the interaction is stronger in HR-HPV (Lechner et al., 1994).

The E6 protein can overcome the cell arrest and proapoptotic activities of p53 by targeting p53 for degradation, inactivating the Mdm2 pathway. E6 can also inhibit the transcriptional activities of p53 independently of E6-AP (Thomas et al., 2005). Three different mechanisms have been proposed to explain this p53 inactivation: The first is inhibiting the binding of p53 to its target sequence in the genome; second, E6 may be able to inhibit p53 signaling by maintaining it in cytoplasm; and third, the mechanism employed by E6 to inhibit p53 activity is the abrogation of the transactivation of p53 responsive genes via interaction with either the CBP/p300 or hADA3 histone acetyltransferases. The E6 proteins have been shown to bind to p300, and this interaction inhibits p35 acetylation at p53 dependent sites, leading to decreased expression from p53. However, unlike p300, E6 interaction with hADA3 results in hADA3 degradation (Kumar et al., 2002). E6 may also inhibit p53 activation by blocking the p14/ARF pathway. Thus, E6 is able to modulate transcription of p53-dependent genes by both degradation of p53 and by interaction with the p300 and hADA3 transactivators (Shamanin et al., 2008).

The degradation or blocking of the p53 function inhibit apoptotic signaling that would eliminate the HPV infection cell. There are two major apoptotic pathways that can be triggered by different stresses: the extrinsic and intrinsic pathways. The E6 protein is able to disrupt both pathways to facilitate a cytoprotective environment and prevent cell death (Howie et al., 2009).

In addition, E6 is able to modulate transcription from other cellular signaling pathways as well as potentiating its ability to act as a diverse modulator of host cell signaling. It has been shown that E6 interact with three different proteins, such as a novel protein termed E6-targeted protein 1 (E6TP1) in an E6-AP dependent manner (Wooldridge et al., 2007), beyond another protein with GAP activity, tuberin, that can also be bound and degraded by E6 (Zeng et al. 2008). Furthermore, HR-HPV E6 has been shown to interact with two proteins that are part of the innate immune response to viral infection: interferon regulatory factor-3 (IFR-3) and toll-like receptor 9 (TLR9) (Hasan et al., 2007). Exogenous expression of HPV16 E6/E7 has been shown to inhibit TLR9 transcription, leading to a functional loss of TLR9 signaling pathways within the cell (Hasan et al., 2007).

HR-HPV E6 is also able to interact with members of the PDZ family of proteins, promoting its proteasome-mediated degradation, an activity that seems to be required for induction of cervical cancer (Shai et al., 2007). HR-HPV E6 PDZ binding can mediate suprabasal cell proliferation and this is thought to occur by uncoupling the cell proliferation and polarity control that exist in a differentiated epithelium (Sterlinko et al., 2004). LR-HPV E6 does not contain the PDZ-binding motif and therefore cannot target these proteins. Degradation of PDZ proteins results in cellular transformation due to loss of cell-cell contact and loss of cell polarity (Storrs and Silverstein, 2007). In addition, it has been demonstrated that the degradation of phosphatase PTPN13 by E6 results in anchorage-independent growth and a Ras-dependent invasive phenotype (Spanos et al., 2008).

Another function of the HR-HPV E6 protein that is important for immortalization is their ability to activate the expression of the catalytic subunit of telomerase (hTERT). Thus, the E6 protein is able to promote the maintanance of the telomere, through the action of telomerase. Interestingly, over-expression of hTERT in conjunction with E7 is sufficient to immortalize human primary keratinocytes. The HPV E2 proteins are reported to repress hTERT promoter activity, but the interplay of E6 and E2 during the regulation of this promoter has not been investigated (Hamid et al., 2009).

E7 protein

The E7 protein has around 100 amino acids in length and contains three conserved regions: CR1, CR2, and CR3 (Münger and Howley, 2002). It will induce cellular proliferation by binding to several cellular factors. The best characterized of these interactions is with the RB tumor suppressor and the related family members p107 and p130. The binding of high-risk E7 to pRB disrupts the interaction between pRB and E2F, a family of transcription factors, resulting in the constitutive expression of E2F-responsive genes, such as cyclin A and cyclin E, and promotes premature S phase entry, DNA synthesis, and the progression of cell cycle (Zerfass et al., 1995). Thus, in cells overexpressing the HPV E7 protein, this checkpoint control at G1/S transition is lost and the cells will continue their cell cycle, causing an uncontrolled cellular proliferation. Moreover, E7 induces the degradation of pRb via the proteasome-dependent pathway, using a mechanism that involves association with and reprogramming of the cullin 2 ubiquitin ligase complex (Jo & Kim, 2005; Huh et al., 2007).

HPV E7 can also associate directly with cdk2/cyclin A and cylin E complexes, resulting in an increased cdk2 activity (Nguyen & Münger, 2008). Another action of E7 that contributes to cellular immortalization is its interaction with the CDK inhibitors (CKI) p21 and p27, efficiently neutralizing their inhibitory effects on CDK2 activities, an important factor for G1 to S phase entry and progression (Moody & Laimins, 2010). The ability of E7 to inactivate these CKIs may contribute to its capacity to abrogate TGF-β mediated growth inhibition. Moreover, TGF-β also induces a cdk4/cdk6 specific CKI, P15Inkb, and p15Inkb-induced growth suppression, and these actions may require functional pRB, which is targeted for degradation by E7 (McLaughlin-Drubin & Münger, 2009). High-risk E7 has further been shown to increase the levels of the CDC25A phosphatase, which can induce tyrosine dephosphorylation of CDK2, promoting its activation (Moody & Laimins, 2010).

E7 also affects the expression of S phase genes by directly interacting with E2F factors and with histone deacetylases (HDAC): E7-E2F6 interaction prevents repression of gene expression by E2F6, maintaining a S phase environment conductive for viral replication

(McLaughlin-Drubin et al., 2008), and E7-HDAC binding facilitates HDAC removal at promoters to activate transcription (Longworth & Laimins, 2004).

Another major apoptotic pathway targeted by HPV proteins is anoikis, a form of apoptosis that is triggered when normal cells attempt to divide in the absence of a matrix (Tasaki et al., 2005). E6 and E7 interact with some factors involved with anoikis, such as paxillin, fibulin 1, and p600 (Huh et al., 2005), promoting the prevention of anoikis.

Furthermore, E6 and E7 interfere with the effects of various growth inhibitory cytokines that are induced following infection. High-risk HPV proteins repress the transcription of many IFN-inducible genes (Chang & Laimins, 2000; Kanodia et al., 2007; Tindle, 2002) and block apoptosis binding to TNF receptor 1, inhibiting the formation of the death-inducing signaling complex and consequent transduction of apoptotic signals (Filippova et al., 2002). The exsposure to E7 in a non-inflammatory epithelial environment can also be sufficient to induce a peripheral tolerance to E7 in the cytotoxic T lymphocytes population (Tindle, 2002).

E6 also interacts with the adaptor protein FAS-associated protein with death domain (FADD) and caspase 8 to block cell death in response to FAS and TRAIl. Also, E6 can interfere with induction of the extrinsic and intrinsic (mitochondrial) apoptotic pathways through interactions with the pro-apoptotic Bcl2 members BAK and BAX, as well as by upregulation of the inhibitors of apoptosis such as the inhibitor of apoptosis protein 2 (IAP2, also known as BIRC2) and survivin (also known as BIRC5) (Garnett & Duerksen-Huges, 2006).

L1 protein

The L1 gene corresponds to a sequence of about 1200 base pairs, which encodes a structural protein highly conserved among different HPV types, the (Xu et al., 2006). The L1 protein is formed by five monomeric units of 55kDa that join to form a pentameric structure, totaling 72 per each capsid (Buck et al., 2008). The L1 protein is highly immunogenic and has conformational epitopes that induce the production of neutralizing type-specific antibodies against the virus, which prevent the infection (Carter et al., 2003), making it the target of prophylactic vaccines (Villa et al., 2007; D'Andrilli et al., 2010).

Comparison among L1 sequences of different papillomaviruses suggests a conserved heparin-binding domain at the C-terminus, and the cleavage of this domain from L1 prevents binding to both heparin and human keratinocytes (Culp et al., 2006; Selinka et al., 2007). Thus, it is believed that the L1 major capsid protein contains the major determinant required for initial attachment of the viral particles to cell surface receptors, HSPGs, and therefore has an important role in infection (Schiller et al., 2010).

L2 protein

L2 is a secondary component of viral capsid and it is present in a variable number of copies per each capsid, being located on the inner surface in the central cavity below the pentamers of L1, where they are arranged to form the capsid (Buck et al., 2008). Despite the paucity of L2 in the virion, this protein has recently been shown to have many more functions than a simple structural role. L2 contributes to the binding of virion in the cell receptor, favoring its uptake, transport to the nucleus, and delivery of viral DNA to replication centers. Besides, E2 helps the packaging of viral DNA into capsids and, due to the presence of a usual neutralization epitope in L2 proteins of many papillomaviruses, it may be instrumental in conferring immunity across different types of HPV. L2 also contributes to the interaction of virion in the cell surface. Two distinct regions in the N-terminal protein of L2 interact with the cell surface, and this interaction occurs after an initial low-specificity interaction between L1 and the cell surface. After this, a conformational switch occurs in the capsid, exposing the L2 epitopes and promoting interactions with a more specific secondary receptor. The cleavage of the N-terminus of L2 is necessary for the binding of L1 to the secondary receptor, an indication that L2 has an important role in HPV infection (Schiller et al., 2010) .

Protein	Functions
E1	Viral DNA replication
E2	Control of viral transcription, DNA replication, and segregation of viral genomes.
E4	Favor and support the HPV genome amplification, besides regulating the expression of late genes, controlling the virus maturation, and facilitating the release of virions
E5	Enhance the transforming activity of E6 and E7; Promotes fusion between cells, generating aneuploidy and chromosomal instability; Contribute to immune response evasion.
E6	Bind and degrade the tumor-suppressor protein p53, inhibiting apoptosis; Interact with proteins of the innate immune response, contributing to immune evasion and persistence of virus;Activate the expression of telomerase.
E7	Bind and degrade the tumor-suppressor protein pRB; Increase cdk activity; Affects the expression of S phase genes by directly interacting with E2F factors and with histone deacetylases; Induce a peripheral tolerance in cytotoxic T lymphocytes (CTL) and Downregulate the expression of TLR9, contributing to immune response evasion
L1	Major capsid protein; contains the major determinant required for attachment to cell surface receptors. It is highly immunogenic and has conformational epitopes that induce the production of neutralizing type-specific antibodies against the virus.
L2	Minor capsid protein; L2 contributes to the binding of virion in the cell receptor, favoring its uptake, transport to the nucleus, and delivery of viral DNA to replication centers. Besides, E2 helps the packaging of viral DNA into capsids.

Table 1. The HPV proteins and functions

3. HPV Infection

The HR-HPVs have the ability to infect several types of epithelial cells, but they can cause cancer more frequently in the uterine cervix (Timmons et al., 2010). The cervical cancer arises preferentially in the cervical transformation zone (TZ), located in the boundary between the squamous epithelium of ectocervix and the columnar epithelium of endocervix. Basal cells in the TZ retain the ability to differentiate, a property required for virion production (Crum & McKeon, 2010). The basal cells in TZ are more susceptible to HPV infection in that there are fewer overlying layers than in other locations. In addition, the presence of hormones, such as estrogen and progesterone, that orchestrate cervical changes during menstruation and childbirth, can help both HPV infection and cancer development (Timmons et al., 2010; Roberts et al., 2007; Chung et al., 2008).

It has been reported that two types of cells are present in the basal layer of cervix. The first type comprises the transit amplifying (TA) cells, which are proliferating cells that are able to undergo terminal differentiation. TA cells divide and differentiate, representing the majority of cells in the suprabasal layers. The second class of basal cells is the stem cells, which have unlimited proliferation potential but divide only rarely in order to replenish the TA pool, serving as reserve cells to enable long-term maintenance of the tissue. Only one daughter cell of a stem cell division goes on to become a TA cell, while the other remains a stem cell. It is unclear which cells in the basal layer are the target of HPV infection, and perhaps both cell classes can be infected. If this is true, infection of stem cells could lead to one long-term persistent infection, whereas infection of TA cells could lead to short-term infections, followed by a cure (Jones et al., 2007).

Studies in vitro and in vivo revealed that the L1 major capsid protein contains the major determinant required to the initial attachment of the viral particles to the cell surface receptor, the heparan sulfate proteoglycans (HSPGs). Laminin-5 can also contribute to the binding of viral capsids to the extracellular matrix (ECM) in the epithelial cell lines (Culp et al., 2006; Selinka et al., 2007).

In vivo, the viral particles bound efficiently to regions of the basement membrane (BM) only after these regions had been exposed by mechanical or chemical trauma of the epithelium. The L1 capsid protein binds to HSPGs in segments of the BM exposed after epithelial trauma. After this, L1 undergoes a conformational change that exposes the N-terminus of the L2 minor capsid protein, which is cleaved by furin or the closely related protein convertase (PC) 5 and 6 (Richards et al., 2006). L2 proteolisis exposes a previously occluded surface of L1 that binds to an undetermined cell surface receptor on keratinocytes that have migrated over the BM to close the wound. This receptor is still unknown, but in vitro studies indicate the α6-integrin as a possible candidate (Kines et al., 2009). The cleavage of L2 may be necessary due to the fact that the surface intact of the epithelia apparently contains sulfation patterns that do not bind capsids. Binding to the BM may promote the preferential interaction with basal keratinocytes that are migrating over the exposed BM to close the wound. Thus, papillomaviruses (PV) are the only viruses that initiate the infectious process at an extracellular site (Schiller et al., 2010).

The capsids are internalized via the keratinocytes-surface receptor and subsequently surf toward the cell body. The first phase in infection is the internalization, which usually occurs 2-4 h after cell surface binding (Culp et al., 2004). The pathway involved in internalization and intracellular trafficking is still unclear, but it seems to occur slowly and asynchronously over a span of several hours (Schiller et al., 2010). Clatrin-mediated endocytosis has been pointed out to be like the endocytic pathway for the majority of HPV types. However, some studies suggest that they can enter through a caveolae-mediated pathway and not via clatrin-mediated endocytosis (Smith et al., 2007). On the other hand, it has been proposed that HPV-16 initially enters via clatrin-coated pits but the traffic occurs through caveosomes to eventually reach the endoplasmic reticulum (Hindmarsh et al., 2007; Laniosz et al., 2008). Moreover, it has been suggested that the capsids might be internalized via a novel pathway involving tetraspanin-enriched microdomains (Spoden et al., 2008).

The uncoating is not observed until 8-12 h after cell surface binding, and it seems that L2 has a critical role in the endosome escape (Kamper et al., 2006). The cytoplasm transport along microtubules is mediated by protein complex, and L2 has been found to interact with the microtubule network via the motor protein dynein during infectious entry (Florin et al., 2006). After the entry of the viral genome into the nucleus, the complexes predominantly localize in distinct punctate nuclear domains designated as ND10 bodies or promyelotic leukemia (PML) oncogenic domains (PODs). There is evidence that cell division is required for establishment and expression of the viral genome in the nucleus (Pyeon et al., 2009).

4. Life cycle of HPV

The HPV life cycle begins with infection of stem cells in the basal layer of the epithelium. After the entry in the cells, the virus requires the expression of E1 and E2 genes to maintain a low number of copies of genome. These proteins bind to the viral origin of replication and recruit cellular DNA polymerases and other proteins necessary for DNA replication (Hamid et al., 2009). In the suprabasal layer, the expression of genes E1, E2, E5, E6 and E7 contributes to the maintenance of the viral genome and induces cell proliferation , increasing the number of HPV-infected cells in the epithelium, resulting in a higher number of cells that will eventually produce infectious virions (Hamid & Gston, 2009; Lazarczyk et al., 2009). In the more differentiated cells of this same layer of the epithelium occurs the activation of differentiation-dependent promoter and maintenance of gene expression E1, E2, E6 and E7. Furthermore, there will be activation of the expression of E4 gene, whose product will induce amplification of the viral genome replication, greatly increasing the number of virus copies per cell, at the same time that occurs the expression of genes L1 and L2 (Nakahara et al., 2005; Lazarczyk et al., 2009). In the granular layer, the products of late genes, the major and minor proteins of the viral capsid, L1 and L2 respectively, gather to assembly of the viral capsids and formations of virions, which reach cornified layer of the epithelium and are released (Lazarczyk et al., 2009).

For a better understanding, the life cycle of HPV was divided into two parts: a maintenance phase and differentiation-dependent phase (Bodily & Laimins, 2011).

4.1 Maintenance phase

HPV virions infect cells in the basal epithelial layer that become exposed through microlesions. The viral capsid binds initially to the basal cell layer and infection occurs when activated keratinocytes move into the wound, to the upper layers of the epithelium (Kines et al., 2009). HPV genomes replicate in the nucleus of the basal cell layer, where the viral replication is considered nonproductive and the virus establishes itself as a low-copy-number episome by using the host DNA replication machinery (Moody & Laimins, 2010). In this way, viral proteins are expressed at very low levels in undifferentiated cells, and this contributes to immune avasion and persistence (Bodily & Laimins, 2011).

The maintenance of the viral episome in basal cells is the basic function of the early or maintenance phase of the viral cycle. The expression of E6, E7, E1, and E2 are necessary for continued episomal maintenance. E1 and E2 cooperate to initiate viral DNA replication, whereas E6 and E7 modulate cell-cycle regulators to maintain long-term replication competence (Conger et al., 1999). The E2 protein is probably a major regulator of this process because it is able to make both positive and negative control of the early viral promoter that regulates expression of E6, E7, and E1 as well as E2 itself (Steger et al., 1997).

Following this establishment phase, viral DNA is replicated coordinately with host cell chromosomes, and virus genomes are distributed to the daughter cells. However, in the differentiated keratinocytes of the suprabasal layers of the epithelium, the virus switches to a rolling-circle mode of DNA replication, amplifying its DNA to a high copy number, synthesizing capsid proteins, and assembling the viral particle (Flores et al., 1999).

HPV replication begins when the host cell factors interact with the LCR region of the HPV genome and begin the transcription of the early viral genes, highlighting the E6 and E7. The viral E6 and E7 gene products deregulate the cell cycle, subverting the cell growth-regulatory pathways and modifying the cellular environment in order to faclitate viral replication in a cell that is terminally differentiated and has exited the cell cycle (Syrjânen & Syrjânen, 1999)

4.2 Differentiation-dependent phase

During the maintenance phase in undifferentiated cells, viral proteins are expressed in extremely low levels. However, when HPV-infected cells leave the basal layer, they undergo differentiation and high levels of viral proteins synthesis are induced. This restriction of viral protein synthesis to highly differentiated cells delays the expression of viral antigens to locations less susceptible to the host immune response (Frazer, 2009).

This compartimentalization of gene expression by HPVs constitutes an important strategy to sustain long-term infection, but it creates some problems for the virus. To solve this, the virus forces the cell to remain active in the cell cycle, enabling productive replication in differentiating cells. The viral protein E7 is responsible for maintaining the replication competence in differentiated cells and this is accomplished in part by inactivation of pRB family members (Münger et al., 2004). The activation of the late viral promoter in response to host-cell differentiation occurs in the vicinity of the spinous epithelial layer and is responsible for high levels of viral protein expression. As a result, the virus copy-number amplifies from 50-200 copies to several thousands of copies per cell (Bedell et al., 1991).

The viral proteins E1, E4, and E5 contribute to the activation of late viral functions upon differentiation (Wilson et al., 2005; Fehrmann et al., 2003). The E2-mediated down-regulation of E6 and E7 transcription results in the release of the p53 and pRB cellular proteins, and allows the normal differentiation process of the host cell. Then, a putative late promoter activates the capsid genes, L1 and L2. Finally, the viral particles are assembled in the nucleus, and the complete virions are released when the cornified layers of the epithelium are shed. The virions are shed in an environment with desquamated cells in the absence of lysis or necrosis, and this further contributes to virus persitence because it avoids inflammation (Stanley, 2008).

Most women infected with a specific HPV type will not show evidence of that same type after 6-12 months. It is not known whether the HR-HPV can be detected for periods similar to those for LR-HPV. Some studies show similar duration (Richardson et al., 2003), but others reveal longer durations of infection for HR-HPV types (Franco et al., 1999; Ho et al., 1998). It appears that HR-HPV, particularly HPV16, has a longer time to clearance and is more likely to develop persistent infection (Richardson et al., 2003).

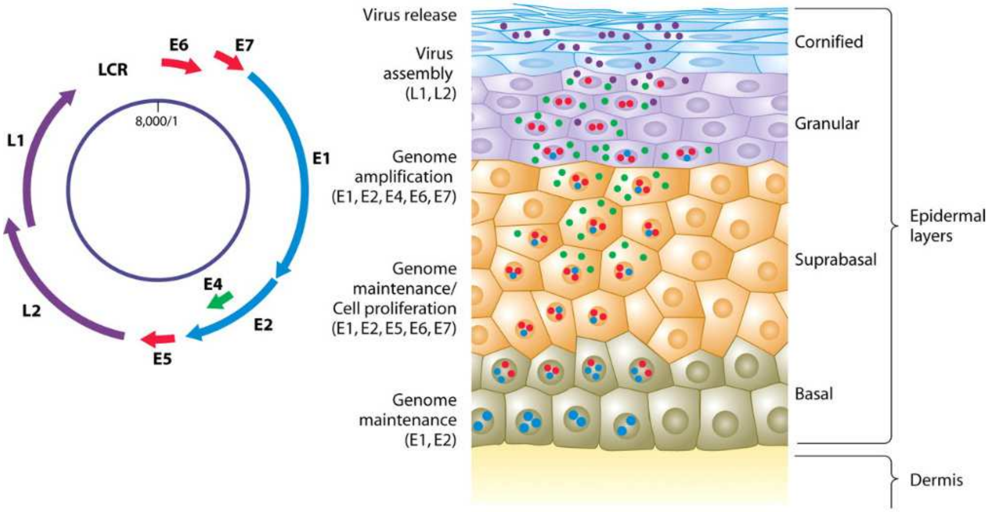


Fig. 2. HPV Cycle life (copied from Lazarczyk et al., 2009, with permission of the author).

5. Pathogenesis

5.1 Persistence x clearance

The infection with HR-HPV typically lasts from 12 -18 months and is eventually cleared by the immune system (Richardson et al., 2003). However, approximately 10% of women fail to clear HPV infections, resulting in a persistent infection. The main consequence of persistent infection with HR-HPV is the development of lesions that may progress to malignancy, and this constitutes the most important risk factor for the development of cervical cancer (Stanley, 2008; Bodily & Laimins; Moody & Laimins, 2010;).

Details about the immune response that results in clearance of HPV infection are still unknown. HPV clearance seems to result in long-term humoral and/or cellular protection against re-infection by the same HPV type; whether the protection is lifelong is not known (Stanley, 2006). Although the term clearance is used when an HPV infection can no longer be detected using sensitive test methods, the HPV presence might not be completely discarded because the latent state of HPV is still poorly understood. Reappearance of HPV from latency even in the absence of definite immunosuppression is common, but most cases are probably benign (Gonzalez et al., 2010). By contrast to HPV infections that clear, the risk of cancer increases dramatically in persistent HPV infections (Schiffman et al., 2010).

It is important to remember that it is not easy to characterize a persistent HPV infection and differentiate persistent infection from healing followed by re-infection, although re-infection with the same HPV type appears to be uncommon. Many studies classify HPV infection as persistent if the HPV was detected in two consecutive follow-up visits 4-6 months apart. However, because the interval between follow-up visits varies among studies and there are many unknown questions regarding the natural history of HPV, it is complicated to distinguish persistent and transience infections. Furthermore, an undetectable HPV infection could be a period of viral latency, in which the HPV levels are below the detectable threshold of current HPV DNA assays, instead of representing a cleared host (Baseman and Koutsky, 2005).

The persistent nature of HPV infection and DNA viral integration into the genome of the cell contributes to increasing the risk of high-grade and malignant lesions because of genomic instability generated. E6 and E7 can induce centrosomal abnormalities resulting in abnormal centrosome reduplication, leading to abnormal numbers of centrosomes Furthermore, abrogation of cell-cycle checkpoints through the targeting of p53 and pRB family members allows retention of cells with chromosomal abnormalities (Münger et al., 2004). This can result in genetic changes that accumulate over an extended period of time until resulting in a combination of genetic abnormalities, allowing cancer development (Bodily & Laimins, 2011).

In benign and malignant HPV lesions, the cellular proliferation increases the demand for nutrients, generating a competition for nutrients and oxygen. To overcome this constraint, both HR-HPV and LR-HPV E7 proteins enhance the levels of the transcription factor Hypoxia-inducible factor-1 (HIF-1), as well as induce the increased expression of HIF-1 target genes under hypoxia conditions (Nakamura et al., 2009). The enhancement of HIF-1 activity results in an increased transcription of a subset of genes that favor angiogenesis, and this induction of angiogenesis is crucial to both persistence and growth of HPV lesions (Bodily & Laimins, 2011).

5.2 Mechanism of immune evasion

HPV infections are chronic, exclusively local and intraepithelial in which the virus remains in the host for many months, even years, during which the mechanisms of host defense apparently remains ignorant of the pathogen for long period of time Stanley, 2009b). So, the immune response to HPV infection is often insufficient to eliminate the virus so that the infected individuals do not heal but develop persistent infection. The main reason for this is an ingenious strategy developed by this virus in which viral DNA replication and virus assembly occur in a cell that will be terminally differentiated and die by natural causes (Staney, 2008). To achieve this lifestyle, HPV must avoid the host defense sytem, and the key to understanding how this occurs is the virus replication cycle which itself is an immune evasion mechanism that inhibits the host´s detection of the virus. The infection and vegetative HPV growth are absulotely dependent upon a complete program of keratinocyte differentiation (Doorbar, 2005).

Papillomavirus late genes also contain codons that mammalian cells rarely use, implying that production of abundant papillomavirus capsid proteins is inhibited in mammalina basal-epithelial cells by the restricted availability of the appropriated tRNAs. The early viral proteins localize mainly to the nucleus, and they are produced in insufficient quantities and/or are not aceesible for immune recognition (Tindle, 2002). Besides, there is viral-induced cytolysis or necrosis, and therefore no inflammation. For most of the duration of the

HPV infectious cycle, there is little or no release into the local milieu of pro-infammatory cytokines, which are important for antigen presenting cell (APC) activation and migration. This way, the central signals to kickstart the immune response in squamous epithelia are absent (Stanley, 2006).

Even in the absence of cellular changes such as cytolysis, necrosis, or cell death, HPV-infected keratinocytes should activate to the production of type 1 interferons, a powerful, generic antiviral and innate immune defense system. The type 1 Interferons, IFN-α and IFN-β, have antiviral, antiproliferative, antiangiogenic, and immunostimulatory properties that act as a bridge between innate and adaptative immunity, activating immature DCs (Le Bon & Tough, 2002). High-risk HPV types actively inhibit the endogenous interferon response, down-regulate toll-like receptors and this combined with the low levels of viral protein generated during the infectious cycle and absence of infammation leads to inefficient activation of the innate immune response, with the consequent ineffectiveness of the adaptive immune response. Thus, the milieu becomes operationally HPV antigen-tolerant and host defences become irrevocably compromised. HPV antigen-specific effector cells are both poorly recruited to the focus and their activity is down-regulated (Stanley, 2009b).

It was demonstrated that infection with HR-HPV, especially HPV 16, downregulates IFN-α inducible gene expression, through E6 and E7 proteins that directly interact with components of the interferon signaling pathways (Konodia et al., 2007). Infected cells with episomal HPV are cleared after exposure to IFN-β, but cells with integrated HPV-DNA are resistant to this antiviral effect (Pett et al., 2006). T-cell response to E2 and E6 are lost or reduced in CIN 3 and carcinoma invasive. Thus, even if HPV antigen-specific cytotoxic T-cells have been generated, regulatory T-cells increasingly dominate the lesion and abrogate the killer defense response (Kobayashi et al., 2004). High-risk HPV infected cervical keratinocytes expressing high level risk of E6 and E7 oncoproteins are not killed in this immunosuppressive tolerante mileu, nad progression to high-grade disease and cancer can result (Stanley, 2009b).

As HPV infections are exclusively intraepithelial, theoretically, an HPV attack would be detected by the professional APC cells of squamous epithelia, the Lanherhans cells (LCs), which are the intraepithelial dendritic cells (DCs). Virus capsid entry is usually an activating signal for CDs, but there is evidence that LCs are not activated by the uptake of HPV capsids. The life cycle of HPV is organized to form a limited viral antigen synthesis in undifferentiated cells, and high-expression is restricted to highly differentiated cells.

HPV replication and release does not cause cell death and inflammation since the differentiating keratinocyte is already programmed to die and this death by natural causes does not act as a danger signal in the infected site (Staley, 2009b). Besides, the absence of viremia, cell lysis, necrosis, or any other signals to trigger an inflammatory response reduces the possibility of an effective immune response in this site (Stanley, 2009a). Thus, the virus becomes pratically invisible to the host who remains indifferent to infection for long periods of time, facilitating the viral persistence (Staley, 2009b)

The healing of the HPV-induced lesions is dependent on the mechanisms of the cell-mediated immune response and is accompanied by interaction of CD8+ and CD4+ limphocytic. Langerhans cells (LCs) are the major dendritic cells (DCs) found in squamous epithelia, and these are probably responsible for triggering an anti-HPV immune response.

The function of LCs is disrupted by HPV at several levels. It has been shown that the infiltration of HPV-infected tissue by LCs and DCs is inhibited by HPV-induced changes in the pattern of cytokine expression (Stanley, 2008). The HPV L2 protein is able to suppress maturation, migration, and cytokine secretion by LCs. Furthermore, the interaction between LCs and keratinocytes can be disrupted by the reduction of E-caderin levels induced by the E6 HPV protein (Ghittoni et al., 2010).

In immunosuppressed patients, HPV infection frequently leads to the appearance of abundant HPV-induced lesions, indicating that the immune system acts to limit HPV infection (Scott et al., 2001). Therefore, in order to persist, HPV must actively suppress both innate and adaptative immune response. One important mechanism of the innate pathway targeted by HPV acting in multiple ways is the interferon response (Samuel, 2001; Stanley, 2008). Keratinocytes constitutively express a low level of interferon-inducible genes in absence of interferon. The cells infected with HR-HPV express E6 and E7, which repress the transcription of many interferon target genes including Stat-1, a transcriptional activator of Interferon-inducible genes (Nees et al., 2001). E6 can bind to and block the action of IRF-3, a regulator of the interferon pathway and also blocks activation of protein kinase R (PKR) as well as the activity of kinase Tyk2, responsible for activating Stat-1, while E7 can bind to IRF-1, that is also a regulator of the interferon pathway (Hebner et al., 2006; Stanley, 2009b). Both E6 and E7 can inhibit expression of the toll-like receptor (TLR9), which is important for sensing doubled-stranded DNA (Hasan et al., 2007).

It is well known that keratinocytes constitutively express low levels of several cytokines that are upregulated following virus infection (Ghittoni et al., 2010). When these cells are infected with HPV show significantly reduced expression of the wide range of inlammatory cytokines including IL-1, IL-6, TNF-α, and TGF-β, at the same time, expression of the anti-inflammatory cytokine IL-10 is increased (Alcocer-Gonzalez et al., 2006; Ghittoni et al., 2010). Thus, HPV infection induces alteration in cytokine production, reducing the ability of immune cells to infiltrate the infected tissue. Keratinocytes constitutively express low levels of interferons α, β, and κ. The expression of interferon κ is suppressed in HPV positive cells and this could contribute to the inhibition of expression of interferon-inducible genes (Rincon-Orozco et al., 2009).

Development of HPV-specific T-cell response is repressed or delayed in HPV-infected patients, this effect being more pronounced in HR-HPV compared with LR-HPV infections (van der Burg and Palefsky, 2009). One reason for this impairment is probably the downregulation of major histocompatribiliy complex (MHC) I expression, probably due to interactions occuring between the viral proteins E6, E7, and E5 and the host cell. Furthermore E7 has been reported to downregulate the transporter associated with antigen processing (ATP), thereby interfering with presentation of antigens via the MHC I pathway (Ghittoni et al., 2010).

The expression of HPV E7 in epithelial cells does not directly impair, but rather slightly increase, MHC clase I expression. E7 expression is nevertheless associated with impairment of IFN-gama-induced enhancement of presentation of endogenous antigen to cytotoxic T lymphocytes (Zhou et al., 2011). Further mechanism of HPV-mediated immune escape involve viral proteins: HPV E7 has high and widespread similarity to several humans proteins, causing a limited immunogenicity (Natale et al., 2000); E6 can downregulate IL-18 expression (Cho et al., 2001); E5 mediate acidification of endossomes, affecting antigen processing and presentation in antigen presentation cells (Straight et al., 1995); E5 also downregulate CD1d, a MHC I-like glycoprotein that presents self or microbial lipid antigen to natural killer – the downregulation of this molecule is utilized by a variety of microbes to evade immune detection (Miura et al., 2010). Finally, natural killer (NK) cell activity is also reduced in patients with HR-HPV infection (Stanley, 2009a; O´Brien and Campos, 2002).

5.3 The role of the physiology of the cervical epithelium

The cervical and anal transformation or transition zones (TZs) are dynamic areas of a few millimeters in size, in which a columnar glandular epithelium coexists with a squamous epithelium, and result from an adaptive process called metaplasia (Mukonoweshuro et al., 2005). These metaplastic conversions are influenced by the acidification of vaginal pH and by trauma such as that resulting from receptive anal intercourse, and can be considered as a stepwise progression of changes. Although these adaptive responses frequently occur at the cervical and anal squamocolumnar junctions, the molecular mechanism underlying the development and the maintenance of the metapastic epithelium are still not completely understood (Herfs et al., 2011).

It is believed that this phenomenon could result from the reprogramming of adult stem cells and that the metaplastic epithelium is associated with a deregulated production of receptors, adhesion molecules, and soluble mediators of the inflammatory response, such as cytokines, chemokines, prostaglandins, and growth factors. These molecules might not only exercise influence epithelial differentiation but also alter the local antiviral immune response, favoring HPV infections. Importantly, a substantial majority of cervical and anal pre-neoplastic lesions develop within the metaplastic microenvironment of TZs (Bodily & Lamins, 2010). This implies that exogenous or endogenous factors specific to the anatomical milieu of squamocolumnar junctions could be conducive to persistent HPV infection (Herfs et al., 2011)

In contrast to normal squamous epithelium, metaplastic epithelia have an altered maturation characterized by a weak expression of several keratin intermediate filaments and cell envelope components such as involucrin and loricrin (Herfs et al., 2008). The primary function of keratins and other cytoskeletal proteins is to provide resistance to mechanical and non-mechanical stresses that can cause cell rupture and death. Thus, because of their immature state, keratinocytes of the squamocolumnar junctions could be more vulnerable to the trauma required for HPV infection (Gu & Colombe, 2007). Therefore, the increased sensitivity of anal and cervical TZs to pre-neoplastic lesions can be attributed to the fact that both the basement membrane and the target actively dividing basal cells for HPV infection could be more accessible in metaplastic areas in which monostratified glandular and pluristratified squamous coexist (Herfs et al., 2011).

Cervical TZs with squamous metaplasia have a higher density of estrogen and progesterone receptor-positive cells compared with normal squamous epithelia. Besides, the cervical TZs are more sensitive to the induction of squamous cell carcinogenesis by estrogen. Among the possible mechanisms by which sex hormones could facilitate HPV-induced carcinogenesis would be the stimulation of expression of E6 and E7 HPV genes, directly and/or indirectly through steroid response elements in the viral genome or still stimulating cellular proliferation (Bhattacharya et al., 1997; Yuan et al., 1999).

It is also possible that hormones sensitize the TZs to persistent HPV infection by altering the local immune microenvironment (Herfs et al., 2011). It has been observed that 17β estradiol can both reduce the migration and/or functional capacity of antigen-presenting cells and promotes the initiation of Th2 immune response, which is generally associated with the progression of the disease (Uemura et al., 2008). Together with these observations, the topography of the cervical TZs is affected by the hormonal status of women, suggesting that sex hormones might not only be involved in the development and maintenance of the metaplastic epithelium but might also be implicated in the high sensivity of TZs to HPV infection and cancer progression (Herfs et al., 2011).

Also observed was a reduction of secretion of soluble factors of innate immune response involved in antiviral defense in the anal and cervical squamocolumnar junctions (Herfs et al., 2010). The β-defensin 2 is weakly expressed in cervical TZs and pre-neoplastic lesions compared with normal exocervical (Hubert et al., 2007). Furthermore, the density of Langerin-positive Langerhans cells (LCs) and their function are significantly altered in the anal and cervical TZs compared with the normal squamous epithelia (Herfs et al., 2008; Giannini et al., 2002) suggesting that keratinocyte-LC interaction could play an important role in the establishment of HPV infection in these regions (Herfs et al., 2011). It was also suggested that a Th2 immunoderivation of immune response could participate in the immunological escape of virus-infected cells (Herfs et al., 2011).

Altering the local immune response, metaplastic cells might not only promote viral infections but might also be involved in the HPV-induced development of cervical and anal carcinoma in the TZs. This could explain, at least in part, why HPV-associated lesions located elsewhere in the anogenital tract outside the TZs, such as the vagina and vulva, are less likely to progress to cancer than those that develop within the TZs. Therefore, the anatomical, histological, physiological, and immunological features of TZs might not only promote the mucosal entry of HPV but also be involved in the HPV-induced development of cervical and anal carcinoma (Herfs et al., 2010).

5.4 The oncogenics activities of HPV

5.4.1 The role of the E5 protein

The hydrophobic E5 protein is mainly found within the Golgi apparatus, as well as in the plasma membranes of HPV-infected cells. The E5 protein has weak oncogenic properties, which results in the increasing expression for the epidermal growth factor receptor (EGFR) (Tsai & Chen, 2003) and in the inhibition of the expression of the major histocompatibility complex (MHC) class I on the plasma membrane modulating the MAPK pathway and altering the levels of caveolin 1 (Moody & Laimins, 2010).

The virus-induced cell fusion mediated by oncogenic viruses is a well-known event among human oncogenic viruses, including HPV, and it seems that this phenomenon plays an important role in the carcinogenesis process (Duelli et al., 2007; Hu et al., 2009). HPV16 E5 has all the characteristics of fusogenic proteins, including the localization of the plasma membrane, the high level of hydrophobicity, and the ability for dimmers. More recently, HPV16 E5 has been identified as necessary and sufficient to induce cell-cell fusion with the formation of the tetraploid cell (Hu et al., 2009).

Aneuploidy with the presence of tetraploid cells is frequently found in precancerous lesions associated with HPV infection. It is reported that expression of either HPV E6 or E7 alone is sufficient to deregulate cytokinesis and consequently produce the tetraploid cell (Heilman et al., 2009). However, it was demonstrated that the formation of these cells is primarily attributed to E5-induced cell fusion, rather than E6, E7, and cytokinesis failure (Ho et al., 2009). Tetraploid cells formed by accident cannot undergo normal mitosis which would trigger p53-dependent cell cycle arrest or apoptosis, whereas oncogenic virus-induced cell fusion is sufficient to induce chromosomal instability when fusion occurs concomitantly with expression of viral oncoproteins capable of perturbing p53 or apoptosis (Duelli et al., 2007).

In vivo and clinical studies reveal that chromosomal instability and aneuploidization seem to precede and favor integration of HPV genomes, which in turn leads to expression of viral-cellular fusion transcripts and further enhances expression of the E6-E7 genes, which renders the strong growth advantages of transformed cells (Ziegert et al., 2003). The cell fusion HR-HPVE5-induced and cell cycle deregulation are two key events for initiation of transformation. This suggests that HR-HPVE5-induced cell fusion can be a critical event in the early stage of development HPV-associated cervical cancer (Gao & Zheng, 2010). As the open reading frame coding E5 is frequently deleted in cervical cancer, it is possible that this viral protein is not required for tumor maintenance, but that it can play a critical role in the early stage of HPV-associated cervical cancer.

5.4.2 The role of the E6 protein

The E6 HPV protein binds not only to cellular p53 and E6-AP but also to a wide range of other cellular proteins, being known a more complete compendium of cellular factors that can interact with this viral oncoprotein. Among the other cellular proteins that interact with E6, the following may be cited: transcription factors such as p300, myc, interferon regulatory (IRF3), autocrine motility factor 1 (AMF-1/gPS2); factors that determine adhesion, cytoskeleton and polarity, such as paxillin, the human homologue of Drosophila disk-large tumor-suppressor gene product (DGL), and membrane-associated guanylate inverted-1 (MAGI-1); apoptosis factors such as the pro-apoptotic Bcl2 and Bak; replication factors and DNA repair factors such as mcm7 and XRCC1; and other cellular proteins such as E6 target protein 1 (E6TP1). In addition, E6 induces telomerase activity by inducing the expression of human telomerase reverse transcriptase (hTERT) (reviewed in IARC, 2007).

HR-HPV E6 proteins have a motif designated as S/TXV at their C-terminal which mediates binding to specific domains on cellular proteins known as PDZ proteins. PDZ domains are approximately 90 amino acid stretches found in a wide variety of cellular proteins. The importance of p53 in the orchestration of the cellular response to damage suffered by DNA as a result of exposure to cytotoxic agents becomes quite evident by the fact that approximately one-half of all human cancers present mutations in the p53 gene (Howie et al., 2009). Normally, p53 protein levels are regulated by the Mdm2 E3 ubiquitin ligase. However, Mdm2-mediated degradation of p53 is inhibited during viral infection and other stress conditions, allowing for stabilization of p53 protein levels and subsequent activation. In contrast, during an HR-HPV infection E6 induces p53 degradation by forming a complex with another E3 ubiquitin ligase, E6-AP. Only E6 HR-HPV is capable of binding to the core region of p53 and this binding of the core region is required for p53 degradation mediated by E6.

Three other mechanisms have been proposed to explain the interaction of the viral E6 protein with p53. The first is by inhibiting the binding of p53 to its site-specific DNA sequence. In the second mechanism, E6 may be able to inhibit p53 signaling independent of protein degradation by means of the sequestration of p53 in the cytoplasm. The third mechanism employed by E6 to inhibit p53 activity is its abrogation of the transactivation of p53 responsive genes via interaction with either the CBP/p300 or hADA3 histone acetyltransferases. The E6 proteins have been shown to bind to p300, and this interaction inhibits p35 acetylation at p53 dependent sites, leading to decreased expression from a p53 (Zimmermann et al., 2000). However, unlike with p300, E6 interaction with hADA3 results in hADA3 degradation (Kumar et al., 2002). E6 may also inhibit p53 activation by blocking the p14/ARF pathway (Shamanin et al., 2008).

Thus, E6 is able to modulate transcription of p53-dependent genes by both degradation of p53 and by interaction with the p300 and hADA3 transactivators. In addition, E6 is able to modulate transcription from other cellular signaling pathways as well as potentiate its ability to act as a diverse modulator of host cell signaling. With respect to G-protein signaling, E6 has been shown to interact with three different proteins, such as a novel protein termed E6-targeted protein 1 (E6TP1), in an E6-AP dependent manner (Lee et al., 2007), beyond another protein with GAP activity, tuberin, which also can be bound and degraded by E6 (Zeng et al., 2008).

High-risk E6 has been shown to interact with two proteins that are part of the innate immune response to viral infection: interferon regulatory factor-3 (IFR-3) and toll-like receptor 9 (TLR9) (Hasan et al., 2007). IRF-3 becomes activated by dsRNA or viral infection, and this activation leads to the transcription of interferon-beta (IFN-β) (Hiscott, 2007). TLR9 becomes activated by viral or bacterial dsDNA derived CpG motifs, and induces cytokine production as a means to defend the cell against the invading organism (Müller et al., 2008). Exogenous expression of HPV16 E6/E7 has been shown to inhibit TLR9 transcription, leading to a functional loss of TLR9 signaling pathways within the cell (Hasan et al., 2007).

The p53 degradation or blocking of its function mediated by E6 has, as a consequence, the inhibition of apoptotic signaling that would otherwise eliminate the HPV infected cell. There are two major apoptotic pathways that can be triggered by different stresses: the extrinsic and the intrinsic pathways. The E6 protein is able to disrupt both pathways to facilitate a cytoprotective environment and prevent cell death, thus highlighting the critical signaling events that a cell undergoes following exogenous or endogenous stress (Howie et al., 2009).

E6 is able to inhibit extrinsic apoptotic signaling at each of the stages, by interacting with TNFR-1, FADD, and caspase-8. It was shown that E6 is able to bind directly to the death receptor TNFR-1 and blocked TNFR-1 DD mediated apoptosis (Filippova et al., 2002). In addition to the TNF pathway, E6 is capable of inhibiting apoptosis stimulated by both Fas and TRAIL pathways. This inhibition is mediated by E6 binding to and degradation of both the FADD adapter protein and the effector caspase-8 (Garnett et al., 2006). As the binding of FADD is not dependent on the conserved PDZ domain of high-risk E6, but rather by a new domain (Tungteakkhun et al., 2008), it is possible that other E6 proteins may inhibit these extrinsic pathways.

HPV E6 proteins have been shown to inhibit intrinsic apoptotic pathway binding to Bak and to induce its proteasomal-dependent degradation (Underbrink et al., 2008). While E6-AP has been shown to play a role in Bak degradation, it has also been proposed that this may not be a universal mechanism for all of the HPV types (Simmonds & Story, 2008). Evidence has shown that Bak degradation is not constitutive, but rather occurs only after apoptotic signals have been initiated, indicating that a Bak conformational change and/or dissociation from its anti-apoptotic partner MCL-1 may be necessary for its interaction with E6 and E6-AP (Underbrink et al., 2008)

Another important effect of E6 in the development of genital cancer is the activation of telomerase reverse transcriptase (hTERT) (Howie et al., 2009). HPV E6 induces histone acetylation at the hTERT promoter, and this acetylation depends on E6-AP (James et al., 2006; Xu et al., 2008). To induce hTERT expression and telomerase activity in keratinocytes, HPV E6/E6-AP requires expression of NFX1-123 (Katzenellenbogen et al., 2007).

In addition to increasing the expression of hTERT, E6 also interacts with other proteins involved in maintaining chromosomal stability within the HPV-infected cell, for example, the minichromosome maintenance 7 (hMCM7) proteins. As MCM7 is involved in licensing DNA replication to ensure a single-round replication per cell cycle, it is thought that E6 interaction with and/or degradation of MCM7 may lead to chromosomal abnormalities in the HPV-infected cell. E6 can also interact with two proteins involved in single-strand DNA break repair: XRCC1 and O(6)-metylguanine-DNA methane transferase (MGMT). XRCC1 to be bound E6; this interaction reduces the ability of XRCC1 to repair metyl metane sulfate (MMS) induced DNA damage (Iftner et al., 2002). E6 interaction with MGMT induces its proteasomal-mediated degradation via E6-AP, which has been hypothesized to sensitize HPV-infected cells to alkylating DNA damage (Srivenugopal & Ali-Osman, 2002). Finally, high-risk E6 mediated p53 loss inactivates the G1 checkpoint. Prolonged proliferation in the absence pf p53 can lead to the loss of the G2 checkpoint, which can result in aneuplody. Together, these interactions may lead to increased genomic instability and accelerate the progression to carcinogenesis (Howie et al., 2009).

Another major apoptotic pathway targeted by HPV proteins is anoikis, a form of apoptosis that is triggered when normal cells attempt to divide in the absence of a matrix (Tasaki et al., 2005). E6 has been shown to bind to paxilin and zyxin, adhesion molecules involved in tethering the cellular cytoskeleton to the extra cellular matrix (ECM) and transmitting signals along the actin network from the ECM to the nucleus. This interaction results in the disruption of actin fibers and a failure to maintain proper cell structure (Howie et al., 2009). HR-HPVE6 proteins also bind to hScrib, a protein involved in epithelial tight junctions, mediating the adhesion of basal cells to the ECM, and at least in some cell types it has been shown that E6 mediates hScrib degradation (Nakagawa & Huibregtse, 2000). Recently, it has been demonstrated that PTPN3, a membrane-bound tyrosine phosphatase that regulates growth factor receptors, is also a PDZ protein that binds and is disrupted by E6 (Jing et al., 2007; Spanos et al., 2008).

5.4.3 The role of the E7 protein

HR-HPVE7 proteins destabilize pRb through its proteosomal degradation via a mechanism that involves association with and reprogramming of the cullin 2 ubiquitin ligase complex by HPV E7 (Huh et al., 2007). The induction of the pRB degradation by HR-HPVE7 proteins and the resulting activation of E2F-mediated transcription represent an important mechanism by which these viruses achieve and maintain S-phase competence in differentiated epithelial cells. HR-HPVE7 proteins, in addition to targeting pRb proteasomal degradation, also contribute to cell cycle deregulation through several additional mechanisms involving cyclin-dependent kinases (cdks), motors that drive the cell division cycle (Zerfass et al., l995).

HPV16 E7 has been shown to interact with and abrogate the growth-inhibitory activities of the cyclin-dependent kinase inhibitors (CKIs) $p21^{CIP1}$ (Jones et al., 1997) and $p27^{KIP1}$ (Zerfass et al., l996), which are induced by anti-proliferative signals, including growth factor withdrawal and loss of cellular adhesion (Fang et al., 1996). The ability of HPV E7 to abrogate CKIs, together with its ability to disrupt the pRB/E2F complex, which results in increased cyclin E and A levels, retains differentiating keratinocytes in a DNA synthesis competent state. HPV E7 can also directly associate with cdk2/cyclin A and cylin E complexes, resulting in increased cdk2 activity (Nguyen & Münger, 2008).

It was demonstrated that HPV16 E7 induces pRb degradation, but the mechanism of cell death depends on the integrity of the p53 tumor suppressor pathway; it does not involve transcriptional activation of canonical p53 transcriptional targets. Intriguingly, E7 expression generally interferes with the transcriptional activity of p53 (Eichten et al., 2002). Furthermore, the mechanism of cell death triggered by HPV16 E7 expression appears to be distinct from classic apoptosis; although caspases are active and DNA is degraded, cell death is mostly caspase independent (Eichten et al., 2004). Although HPV E7 signaling pathways have not yet been molecularly analyzed, HPV 16 E7 expression causes normal human epithelial cells to undergo cell death in response to growth factor deprivation (Zhou & Münger, 2009).

High- and low-risk HPV E7 proteins are associated with the 600 KD retinoblastoma protein-associated factor, p600 (DeMasi et al., 2005; Huh et al.,2005). Although its biological functions have not been fully elucidated in mammalian cells, p600 is implicated as a regulator of anoikis, a form of apoptosis that is triggered when normal cells attempt to divide in the absence of a matrix (Tasaki et al., 2005). Therefore, the interaction between E7 and p600 may deregulate anoikis and protect detached cells from apoptosis, thereby contributing to viral transformation (DeMasi et al., 2007; Huh et al., 2005). Consistent with this idea, HPV16 E7 associates with p600 through the CR1 domain, which is necessary for the transformation capability of HPV16 E7 (DeMasi et al., 2007).

It is known that HPV16 E7 can directly bind to E2F1 and enhance E2F1-mediated transcriptional. E2F1, which plays a role in mediating the transcriptional control of the E2F6 gene, which is unregulated at the G1/S-phase transition, to exert an opposing effect on the activities of E2F-responsive promoters, thereby directing appropriate cell cycle exit and differentiation (Lyons et al., 2006). Interestingly, HPV E7 associates with E2F6 and abrogates its ability to function as a transcriptional repressor (McLaughlin-Drubin et al., 2008), suggesting that the functional deregulation of E2F6 by HPV E7 is needed to counterbalance the up-regulation of E2F6 as a consequence of the activation of E2F1 by E7, thus ensuring that the cells remain in an S-phase-competent state, which is necessary for the viral cycle (McLaughlin-Drubin & Münger, 2009).

Malignant progression mediated by HR-HPVoncogene expression of these cells occurs after prolonged passages in culture or when additional oncogenes, such as *ras* or *fos*, are expressed (Pei et al., 1993). This is comparable to the extended period of time between initial HPV infection and the development of invasive cervical carcinoma. Thus, while the expression of the HPV oncogenes is necessary and sufficient for initiation of cervical carcinogenesis, additional host genome mutations are needed for malignant progression. Indeed, cervical cancer cells have accumulated a wide range of numerical and structural chromosomal abnormalities (Mitelman et al., 2007).

The presence of DNA repairs foci seen in HPV16 E7-expressing cells indicate that E7 may induce double-strand DNA breaks or interfere with break repair. This may facilitate viral genome integration. Consequently, E7 may be a driving force for integration of HR-HPVgenomes into host cellular chromosomes, an event that frequently accompanies malignant progression of high-risk HPV-associated lesions. This may result in double-stranded HPV DNA fragments breaking off of the circular genome and being integrated into the host genome via the endogenous DNA double-strand break (DSB) repair machinery. If the upstream regulatory region is integrated into the host DNA, it may be the site of continued "onion skin" replication as long as the viral E1 and E2 replication proteins are expressed (Kadaja et al., 2007).

Fanconi anemia (FA) patients have an increased incidence of squamous cell carcinomas at sites that are infected by HPVs, and oral cancers arising in FA patients are HPV positive at a significantly higher rate than in the general population. The possible contribution of HPV infection to the increase in incidence of cancer in these patients was reinforced by the demonstration that the FA pathway is activated by HPV16 E7 expression and that the capacity of HPV16 E7 to induce DNA repair foci is enhanced in the FA patient-derived cell lines (Spardy et al., 2007).

Transforming growth factor β (TGF-β) is a potent inhibitor of epithelial cell growth, and acquisition of TGF-β resistance is the hallmark of epithelial tumor cervical carcinoma cell lines. Ectopic HPV16 E7 expression abrogates TGF-β-mediated growth inhibition. Acquisition of TGF-β resistance is a multi-step process, where TGF-β can repress HPV16 E6/E7 expression, which has been correlated to Ski overexpession, but the exact mechanism of this is not yet known (Baldawin et al., 2004). Both $p21^{CIP1}$ and $p27^{KIP1}$ have been implicated in TGF-β-mediated growth inhibition (Datto et al., 1995); and HPV16 E7 ability to inactivate these CKIs may contribute to its ability to abrogate TGF-β-mediated growth inhibition. TGF-β also induces a cdk4/cdk6-specific CKI, P15Inkb, and p15INKB-induced growth suppression may require functional pRB, which is targeted for degradation by HPV16 E7 (MaLac & Münger, 2009).

The tumor necrosis factor- α (TNF-α) is an important part of the immune response mediator that is produced by the cytotoxic T cell in response to a viral infection normal in keratinocytes undergoing G1 growth arrest and cellular differentiation in response to tumor necrosis factor (TNF). HPV E7 also compromises interferon (IFN) signaling through association with and inhibition of the IFN-α-induced nuclear translocation of p48, the DNA-binding component of ISGF-3. Besides, HPV E7 can interfere with interferon regulatory factors (IRFs) associated with IRF-1 and impair its transcriptional activity (Park et al., 2000). Moreover, IFN-γ has been shown to inhibit HPV16 E7 expression, and the IFN-γ-induced suppressor of cytokine signaling-1 (SOCS-1)/JAB can associate with and induce the ubiquitin-mediated degradation of E7 (Kamio et al., 2004). HPV16 E7 may also interfere with insulin-like growth factor (IGF) signaling, which regulates cell survival. HPV16 E7 can associate with IGFP3 and accelerate its proteosome-mediated degradation (Santer et al., 2007).

E7 proteins are also associated with histone modifying enzymes and associated transcriptional co-factors (Bernat et al., 2003). HPV E7 interacts with class I histone deactylases (HDACs), which act as a transcriptional co-repressor by including chromatin remodeling by reversing acetyl of lysin residues on histone. The association between E7 and HDACs results in increased levels of E2F-mediated transcription in differentiating cells possibly influencing S-phase progression. (Longworth et al., 2005). E7 is also associated, directly or indirectly, with histone acetyl transferases (HATs) including p300, pCAF, and SRC1, and has been shown to abrogate SRC1-associated HAT activity (Baldwin et al., 2006). Moreover, the histone methyl transferase, enhancer of zeste homologue 2 (EZH2), has been identified as a transcriptional target of the HPV E7 protein (Holland et al., 2008).

6. Conclusion

HPV is a non-enveloped virus with double-stranded circular DNA genome, protected by an icosahedra capsid forming a particle with about 55 nm. HPV genome is divided into three regions: a long control region (LCR), an early region (E), consisting of six ORFs: E1, E2, E4, E5, E6, and E7, which encodes no structural proteins involved in viral replication and oncogenesis and a late region (L) that encodes the L1 and L2 structural proteins of the viral capsid. The regulation of viral gene expression is controlled by cellular and viral transcription factors. Most of these regulations occur within the LCR region. The virus early promoter, differentiation-dependent late promoter, and two polyadenylation signals define three general groups of viral genes that are coordinately regulated during host cell differentiation. The E6 and E7 genes maintain replication competence, E1 E2, E4, E5, and E8 are involved in virus DNA replication, transcriptional control, beyond other functions. The products of the late genes L1 and L2 are responsible for the assembly of viral particles The HPV life cycle begins with infection of stem cells in the basal layer of the epithelium. After entering the cells, the virus requires the expression of genes E1 and E2 to maintain a low number of genome copies. The expression of E6, E7, E1, and E2 are required for episomal maintenance continued. E1 and E2 act together to initiate replication of viral DNA, while E6 and E7 modulate cell cycle regulators to maintain replication competency in the long-term. The activation of differentiation-dependent promoter leads to an increased production of proteins E1, E2, E5, E6 and E7, resulting in increased cell proliferation and therefore in the number of cells infected with HPV, as well as the number of viral genome copies per cell. Then there is the E4 gene expression that induces genome amplification, at the same time that occurs the expression of genes L1 and L2 and assembly of viral particles. Among the mechanisms that allow the persistence of the virus include a specific differentiation during of the life cycle of the virus, the mechanisms for keeping the number of copies of the genome in undifferentiated cells, angiogenesis, and strategies to evade of both innate and adaptive immune surveillance. In most cases, host defenses prevail and HPV infections resolve themselves. In some cases, however, infections persist for longer periods, allowing the accumulation of additional cellular changes leading to cancer.

The ingenious strategy developed by HPV, in which viral DNA replication and assembly occur only in in terminally differentiated cell and the fact that a local infection and intraepithelial, allows the virus to remain in host for many months, even years, invisible to the host defense mechanism. The HPV achieve this enviable lifestyle through a combination of abilities that contribute to avoid immune response. The viral infectious cycle is confined to the epithelial compartment, there is no viremia or blood-borne spread, and virus particles are eliminated from the mucosal surfaces far from vascular and lymphatic channels. As a result, there is little access to proteins of viruses and virus to the lymph nodes where adaptive immune responses are initiated. Besides, there is no necrosis or cell death virus-induced, and the proinflammatory cytokines that activate APCs in the epithelium are absent. In addition, HPV downregulate interferon responses and disable epithelial LCs. This allows for long uninterrupted periods of viral replication in the epithelium in the absence of host defense mechanisms.This is a high risk strategy for the host when the infection is caused by oncogenic genital HPVs, it increases the risk that the host immune system may become tolerant or unresponsive to viral proteins.
The development of cervical cancer involves a coordinated targeting of multiple pathways involving the HPV oncoproteins, where each one has a distinct role in malignant progression by interacting with many cellular proteins. The oncoproteíns of high-risk HPV usurp or disrupt multiple signaling pathways to maintain the proliferative state in infected cells to facilitate viral replication and persistence. One consequence of this, however, is the accumulation of mutations in cellular genes and increased genomic instability, which results in full transformation. The major viral factors responsible for altering these pathways and mediating the progression to malignancy are the E5, E6 and E7 proteins. The efficient interruption of the functions of p53 and pRb by E6 and E7 is essential for this process. Recent studies have identified other important cellular targets, including telomerase, members of the pathway of DNA damage and important factors for centrosome duplication and signaling proteins. HPV promotes cell proliferation by multiple pathways in the absence of active cellular mechanisms of defense. The new appreciation of the role of other viral proteins, such as E5, in the progression of HPV-induced disease is also emerging. Although the recently introduced vaccines are effective in preventing initial infections caused by the high risk HPV types comprised in the vaccine, they have no effect on existing lesions and cancer, nor will it protect against diseases caused by other HPV types.

7. References

Alcocer-Gonzalez, JM., Berumen, J., Tamez-Guerra, R., Bermudez-Morales, V., Peralta-Zaragoza, O., Hernandez-Pando, R., Moreno, J., Gariglio, P. & Madrid-Marina, V. In vivo expression of immunosuppressive cytokines in human papillomavirus-transformed cervical cancer cells. *Viral Immunology*, Vol. 19, No. 3, (Jun 2006), pp. 481-491, ISSN 0882-8245.

Baldwin, A., Pirisi, L. & Creek, KE. (2004). NFI-Ski Interactions Mediate Transforming Growth Factor ß Modulation of Human Papillomavirus Type 16 Early Gene Expression. *Journal of Virology*, Vol. 78, No. 8, (April 2004), pp. 3953-3964, ISSN 0022-538X.

Baldwin, A., Huh, K-W., & Münger, K. (2006). Human Papillomavirus E7 Oncoprotein Dysregulates Steroid Receptor Coactivator 1 Localization and Function. *Journal of Virology*, Vol. 80, No. 13, (Jul 2006), pp. 6669 – 6677, ISSN 0022-538X.

Baseman, JG., & Koutsky LA. (2005). The epidemiology of human papillomavirus infections. *Journal of Clinical Virology*, Vol. 32, No.4 – Suppl 1, (Mar 2005), pp. S16-S24, ISSN 1386-6532.

Bernat, A., Avvakumov, N., Mymryk, JS. & Banks, L. (2003). Interaction between the HPV E7 oncoprotein and the transcriptional coactivator p300. *Oncogene*, Vol. 22, No. 39, (Sep 2003), pp. 7871-7881, ISSN 0950-9232.

Bhattacharya, D., Redkar, A., Mittra, I., Sutaria, U. & MacRae KD. (1997). Oestrogen increases S-phase fraction and oestrogen and progesterone receptors in human cervical cancer in vivo. *British Journal of Cancer*, Vol. 75, No. 4, (Jan 1997), pp. 554-558, ISSN 0007-0920.

Black, CM., Papp,JR., Markowitz, L., Unger, ER. Tarkowski, TA., Koumans, EH., Sawyer, M & Pierce, A. (2004). Epidemiology of human papillomavirus infection and abnormal cytologic test results in an urban adolescent population. *The Journal of Infectious Disease*, Vol. 189, No. 1, (Jan 2004), pp. 46-50, ISSN 0022-1899.

Bodily J. & Laimins, LA. (2011). Persistence of human papillomavirus infection: keys to malignant progression. *Trends in Microbiology*, Vol. 19, No. 1, (Jan 2011), pp. 33-39, ISSN 0966-842X.

Bodily, M., Beglin, Kyo, S., Inoue, M. & Laimins, LA. (2009). Hypoxia-specific stabilization of HIF-1alpha by human papillomaviruses. *Virology*, Vol. 387, No. 2, (May 2009), pp. 442-448, ISSN 0042-6822

Bosch, FX., de Sanjosé, S. & Castellsagué, X. (2008). Chapter 4 HPV and genital cancer: the essential epidemiology. *Vaccines for the Prevention of Cervical Cancer*, (Jan 2008); 1: med-9780199543458-chapter-4. DOI: 10.1093/med/9780199543458.003.0004.

Bosch, FX., Lorincz, A., Muñoz, N., Meijer, CJLM. & Shah, KV. (2002). The causal relation between human papillomavirus and cervical cancer. *Journal of Clinical Pathology*, Vol. 55, No. 4, (Apr 2002), pp. 244-265, ISSN 0021-9746.

Bouvard, V., Storey, A., Pim, D. & Banks, L. (1994). Characterization of the human papillomavirus E2 protein: evidence of trans-activation and trans-repression in cervical keratinocytes. *EMBO Journal*, Vol. 13, No. 22, (Nov 1994), pp. 5451-5459, ISSN 0261-4189.

Bryan JT & Brown DR. (2000). Association of the human papillomavirus type 11 E1()E4 protein with cornified cell envelopes derived from infected genital epithelium. *Virology*, Vol. 277, No. 2, (Nov 2000), pp. 262-269, ISSN 0042-6822.

Buck CB, Cheng N, Thompson CD, Lowy DR, Steven AC, Schiller JT, Trus BL. (2008). Arrangement of L2 within the papillomavirus capsid. *Journal of Virology*, Vol. 82, No. 11, (Mar 2008), pp. 5190-5197, ISSN 0022-538X.

Burd, EM. (2003). Human papillomavirus and cervical cancer. *Clinical Microbiology Reviews*. Vol. 16, No. 1, (Jan 2003), pp. 1-17, ISSN 1098-6618.

Caberg, J-HD., Hubert, PM., Begon, DY., Herfs, MF., Roncarati, PJ., Boniver, JJ. & Delvenne, PO. (2008). Silencing of E7 oncogene restores functional E-cadherin expression in human papillomavirus 16-transformed keratinocytes. *Carcinogenesis*, Vol. 29, No. 7, (Jul 2008), pp, 1441-1447, ISSN 0143-3334.

Carter, JJ., Wipf, GC., Benki, SF., Christensen, ND. & Galloway DA. (2003). Identification of a human papillomavirus type 16-specific epitope on the C-terminal arm of the major capsid protein L1. *Virology*, Vol. 77, No. 21, (Nov 2003), pp. 11625 -11632, ISSN 0042-6822.

Chan, PK., Chang, AR., Yu, MY., Li, WH., Chan, MY., Yeung, AC., Cheung, TH., Yau, TN., Wong, SM., Yau, CW..& Ng HK. (2010). Age distribution of human papillomavirus infection and cervical neoplasia reflects caveats of cervical screening policies. *International Journal of Cancer*, Vol. 126, No. 1, (Jan 2010), pp. 297-301, ISSN 0020-7136.

Cho, YS., Kang, JW., Cho, M., Cho, CW., Lee, S., Choe, YK., Kim, Y., Choi, I., Park, SN., Kim, S., Dinarello, CA. & Yoon, DY. Down modulation of IL-18 experssion by human papillomavirus type 16 E6 oncogene via binding to Il-18. *FEBS Letters*, Vol. 501, No 2-3, pp. 139-145, ISSN 0014-5793.

Chow LT & Broker TR. (1994). Papillomavirus DNA replication. *Intervirology*, Vol. 37, No. 4, (Jan 1994), pp. 150-158, ISSN 0300-5526.

Chung, S-H., Wiedmeyer, K., Shai, A., Korach, KS. & Lambert, PF. (2008). Requirement for estrogen receptor α in a mouse model for human papillomavirus–associated cervical cancer. *Cancer Research*, Vol. 68, No. 23, (Dec 2008), pp. 9928-9934, ISSN 0008-5472.

Clifford, GM., Rana, RK., Franceschi, S., Smith, JS., Gough, G. & Pimenta, JM. (2005). Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. *Cancer Epidemiology, Biomarkers & Prevention*, Vol. 14, No. 5, (May 2005), pp. 1157-1164, ISSN 1055-9965.

Conger, KL., Liu, J-S., Kuo, S-R., Chow, LT & Wang, TS-F. (1999). Human papillomavirus DNA replication. interactions between the Viral E1 protein and two subunits of human DNA polymerase α/primase. t*he Journal Biological Chemistry*, Vol. 274, N. 5, (Jan 1999), pp. 2696-2705, ISSN 0021-9258.

Conway, MJ. & Meyers, C. (2009). Replication and assembly of human papillomaviruses *Journal of Dental Research*, Vol. 88, N. 4, (Apr 2009), pp 307-317, ISSN 0022-0345.

Crum CP & McKeon FD (2010). p63 in epithelial survival, germ cell surveillance, and neoplasia. *Annual Review of Pathology*, Vol. 5, (Febr 2010), pp. 349-371, ISSN 1553-4006.

Culp, TD., Budgeon, LR. & Christensen ND. (2006). Human papillomaviruses bind a basal extracellular matrix component secreted by keratinocytes which is distinct from a membrane-associated receptor. *Virology*, Vol. 34, No. 1, (Mar 2006), pp,147-159, ISSN 0042-6822.

Culp, TD., Budgeon, LR., Marinkovich, MP., Meneguzzi, G. & Christensen, ND. (2006). Keratinocyte-secreted laminin 5 can function as a transient receptor for human papillomaviruses by binding virions and transferring them to adjacent cells. *Journal of Virology*, Vol. 80, No. 18, (Sep 2006), pp, 8940–8950, ISSN 0022-0345.

D'Andrilli, G., Bovicelli, A., Giordano A. (2010). HPV vaccines: state of the art. *Journal of Cellular Physiology*, Vol. 224, No. 3, (Sep 2010), pp. 567–847, ISSN 0021-9541

Datto, MB., Yu, Y. & Wang, X-F. (1995). Functional Analysis of the Transforming Growth Factor β Responsive Elements in the WAF1/Cip1/p21 Promoter. *The Journal of Biological Chemistry,* Vol. 270, No. 48, (Dec 1995), pp. 28623-28628, ISSN 0021-9258.

DeMasi, J., Huh, K-W., Nakatani, Y. Münger, K. & Howley, PM. (2005). Bovine papillomavirus E7 transformation function correlates with cellular p600 protein binding. *PNAS*, Vol. 102, No. 32, (Aug 2005), pp. 11486 - 11491 ISSN 0027-8424.

DeMasi, J., Chao, MC., Kumar, AS. & Howley PM. (2007). Bovine Papillomavirus E7 Oncoprotein Inhibits Anoikis. *Journal of Virology*, Vol. 81, No. 17, (Sep 2007), pp. 9419 – 9425, ISSN 0022-538X.

De Sanjose, S., Diaz, M., Castellsague, X., Clifford., G., Bruni, L., Munoz, N., & Bosch, FX. (2007). Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infectious Diseases*, Vol. 7, No. 7, (Jul 2007), pp. 453-459, ISSN 1473-3099.

Deng, S-J., Pearce, KH., Kelly, EP., Hartley, A., Stanley, TB., Lobe, DC., Garvey, EP., Kost, TA., Petty, RL., Rocque, WJ., Alexander, KA. & Underwood, MK. (2004). Identification of peptides that inhibit the dna binding, trans-activator, and dna replication functions of the human papillomavirus type 11 E2 protein. *Journal of Virology*, Vol. 78, No. 5, (Mar 2004),pp 2637-2641, ISSN 0022-538X.

DiMaio D,& Mattoon D (2001). Mechanisms of cell transformation by papillomavirus E5 proteins. *Oncogene*. Vol. 20, No. 54, (Nov 2001), pp. 7866-7873, ISSN 0950-9232.

Doorbar, J., Ely, S. Sterling, J., McLean, C. & Crawford, L. (1991). Specific interaction between HPV-16 E1-E4 and cytokeratins results in collapse of the epithelial cell intermediate filament network. *Nature*, Vol. 352, No. 6368, (Aug 1991), pp. 824-827, ISSN 0028-0836.

Duelli, DM., Padilla-Nash, HM., Berman, D., Murphy, KM., Ried, T. & Lazebnik, Y. (2007). A virus causes cancer by inducing massive chromosomal instability through cell fusion. *Current Biology*, Vol. 17, No. 5 (Mar 2007), pp. 431-437, ISSN 0960-9822.

Duesing, S. & Munger, K. (2004). Mechanisms of genomic instability in human cancer: insights from studies with human papillomavirus oncoproteins. *International Journal of Cancer,* Vol. 109, No. 2, (Mar 2004), pp. 157-162, ISSN 0020-7136.

Eichten, A., Westfall, M., Pietenpol, JA. & Munger, K. (2002). Stabilization and functional impairment of the tumor suppressor p53 by the human papillomavirus type 16 E7 oncoprotein. *Virology*, Vol. 295, No. 1 (Mar 2002), pp. 74-85, ISSN 0042-6822.

Eichten, A., Rud, DS., Grace, M., Piboonniyom, SO., Zacny, V. & Munger, K. (2004). Molecular pathways executing the "trophic sentinel" response in HPV-16 E7-expressing normal human diploid fibroblasts upon growth factor deprivation. *Virology*, Vol. 319, No. 1. (Feb 2004), pp. 81-93, ISSN 0042-6822.

Filippova, M., Song, H. Connolly, JL., Dermody, TS. & Duerksen-Hughes, PJ. (2002). The Human Papillomavirus 16 E6 Protein Binds to Tumor Necrosis Factor (TNF) R1 and Protects Cells from TNF-induced Apoptosis. *The Journal Biological Chemistry*, Vol. 277, No. 24, (Jun 2002), pp. 21730 – 21739, ISSN 0021-9258.

Fehrmann F. & Laimins, LA. Human papillomaviruses: targeting differentiating epithelial cells for malignant transformation. *Oncogene*, Vol. 22, No. 33, (Aug 2003), pp. 5201-5207, ISSN 0950-9232.

Fehrmann, F., Klumpp, DJ. & Laimins, LA. (2003). Human papillomavirus type 31 E5 protein supports cell cycle progression and activates late viral functions upon epithelial differentiation. *Journal of Virology*, Vol. 77, No. 5, (Mar 2003), pp. 2819-2831, ISSN 0022-538X.

Fernandes, JV., Meissner, RV., Carvalho, MG., Fernandes, TAAM., Azevedo, PR., Sobrinho, JS., Prado, JC. & Villa, LL. (2010). Prevalence of human papillomavirus in archival samples obtained from patients with cervical pre-malignant and malignant lesions from Northeast Brazil. *BMC Research Notes*, Vol. 3, No. 1, (Jan 2010), pp. 96, ISSN 1756-0500.

Fernandes, JV., Meissner, RV., de Carvalho, MG., Fernandes, TAAM., de Azevedo, PR & Villa, LL. (2009). Prevalence of HPV infection by cervical cytologic status in Brazil. *International Journal of Gynaecology and Obstetrics*, Vol. 105, No. 1, (Apr 2009), pp. 21-24, ISSN 0020-7292.

Fertey, J., Ammermann, I., Winkler, M., Stöger, R., Iftner, T. & Stubenrauch, F. (2010). Interaction of the papillomavirus E8 E2C protein with the cellular CHD6 protein contributes to transcriptional repression. *Journal of Virology*, Vol. 84, No. 18, (Sep 2010), pp. 9505-9515, ISSN 0022-538X.

Filippova, M., Song, H., Connolly, JL., Dermody, TS & Duerksen-Hughes, PJ. (2002). Interaction of the papillomavirus E8 E2C protein with the cellular CHD6 protein contributes to transcriptional repression. *The Journal of Biological Chemistry*, Vol. 277, No. 18, (Jun 2002), pp. 21730-21739, ISSN 0021-9258.

Flores, ER., Allen-Hoffmann, BL., Lee, D., Sattler, CA. & Lambert PF. (1999). Establishment of the human papillomavirus type 16 (HPV-16) life cycle in an immortalized human foreskin keratinocyte cell line. *Virology*, Vol. 262, No. 2, (Sep 1999), pp, 344-354, ISSN 0042-6822.

Florin, L., Becker, ka., Lambert, c., Nowak, T., Sapp, C., Strand, D., Streeck, RE. & Sapp, M. (2006). Identification of a dynein interacting domain in the papillomavirus minor capsid protein L2. *Journal of Virology*, Vol. 80, No. 13, (Jul 2006), pp. 6691-6696, ISSN 0022-538X.

Franco, EL., Villa, LL., Sobrinho, JP., Prado, JM., Rousseau, M-C., Désy, M. & Rohan, TE. (1999). Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *The Journal of Infectious Disease*, Vol. 180, No. 5, (Nov 1999), pp, 1415-1423, ISSN 0022-1899.

Frazer, IH. (2009). Interaction of human papillomaviruses with the host immune system: a well evolved relationship.*Virology*, Vol. 384, No 2, (Feb 2009), pp. 410-414, ISSN 0042-6822.

Gao, P. & Zheng, J. (2010). High-risk HPV E5-induced cell fusion: a critical initiating event in the early stage of HPV-associated cervical cancer. *Virology Journal*, Vol.7, No 238, (Jan 2010), pp. 1-3, ISSN 1743-422X.

Garnett, TO & Duerksen-Hughes PJ. (2006). Modulation of apoptosis by human papillomavirus (HPV) oncoproteins. *Archives of Virology*, Vol. 151, No. 12, (Dec 2006), pp. 2321-2335, ISSN 0304-8608.

Ghittoni, R. Accardi, R. Hasan, U., Gheit, T., Sylla, B. & Tommasino, M.(2010). The biological properties of E6 and E7 oncoproteins from human papillomaviruses. *Virus Genes*, Vol. 40, No. 1, (Feb 2010), pp. 1-13, ISSN 0920-8569.

Giannini, SL., Hubert, P., Doyen, J., Boniver, J. & Delvenne, P. (2002). Influence of the mucosal epithelium microenvironment on Langerhans cells: implications for the development of squamous intraepithelial lesions of the cervix. *International Journal of Cancer*, Vol. 97, No. 5, (Feb 2002), pp. 654-659, ISSN 0020-7136.

González, P., Hildesheim, A., Rodríguez, AC., Schiffman, M., Porras, CP., Wacholder, S., Piñeres, AG., Pinto, LA., Burk, RD & Herrero, R. (2010). Behavioral/lifestyle and immunologic factors associated with HPV infection among women older than 45 years. *Cancer Epidemiology. Biomarkers & Prevention*, Vol. 19, No. 12, (Dec 2010), pp, 3044-3054, ISSN 1055-1065.

Gu, LH & Coulombe, PA. (2007). Keratin function in skin epithelia: a broadening palette with surprising shades. *Current Opinion in Cell Biology*, Vol. 19, No. 1, (Feb 2007), pp.13-23, ISSN 0955-0674.

Hamid, NA., Brown, C. & Gaston K. (2009).The regulation of cell proliferation by the papillomavirus early proteins. *Cellular and Molecular Life Science*, Vol. 66, No. 10, (May 2009), pp. 1700-1717, ISSN 1420-682X.

Hasan, U.A., Bates, E., Takeshita, F., Biliato, A., Accardi, R., Bouvard, V., Mansour, M., Vincent, I., Gissmann, L., Iftner, T., Sideri, M., Stubenrauch, F., Tommasino, M., 2007. TLR9 expression and function is abolished by the cervical cancer-associated human papillomavirus type 16. *Journal of Immunology*, Vol. 178, No. 5, (Mar 2007), pp. 3186-3197, ISSN 1550-6606.

Hasan, UA., Caux, C., Perrot, I., Doffin, A-C., Menetrier-Caux, C. Trinchieri, G., Tommasino, M. & Vlach, J. (2007). Cell proliferation and survival induced by Toll-like receptors is antagonized by type I IFNs. *PNAS*, Vol. 104, No. 19, (May 2007), pp. 8047-8052, ISSN 0027-8424.

Hebner, CM. & Laimins, LA. (2006). Human papillomaviruses: basic mechanisms of pathogenesis and oncogenicity. *Reviews in Medical Virology*, Vol. 16, No 2, (Mar 2006), pp. 83-97, ISSN 1052-9276.

Heilman, SA., Nordberg, JJ., Liu, Y., Sluder, G. & Chen, JJ. Abrogation of the Postmitotic Checkpoint Contributes to Polyploidization in Human Papillomavirus E7-Expressing Cells. *Journal of Virology*, Vol. 83, No. 6, (Mar 2009), pp. 2756 – 2764, ISSN 0022-538X.

Herfs, M., Hubert, P., Kholod, N., Caberg,JH., Gilles, C.,Berx, G., Savagner, P.,Boniver, J. & Delvenne, P. (2008).Transforming growth factor-β1-mediated slug and snail Transcription factor up-regulation reduces the density of langerhans vells in epithelial metaplasia by affecting E-cadherin expression. *American Journal of Pathology*. Vol. 172, No. 5, (May 2008), pp 1391-1402, ISSN 0002-9440.

Herfs, M., Hubert, P., Moutschen, M. & Delvenne, P. (2011). Mucosal junctions: open doors to HPV and HIV infections? *Trends in Microbiology*, Vol. 19, No 3, (Mar 2011), pp. 114-120, ISSN 0966-842X.

Hindmarsh, PL. & Laimins, LA.(2007). Mechanisms regulating expression of the HPV 31 L1 and L2 capsid proteins and pseudovirion entry. *Virology Journal*, Vol. 4. (Feb 2007), pp. 1-12, ISSN 1743-422X

Hiscott, J. (2007).Triggering the Innate Antiviral Response through IRF-3 Activation. *The Journal of Biological Chemistry*, Vol.282, No. 21, (May 2007), pp. 15325-15329, ISSN 0021-9258.

Ho, GY., Bierman, R., Beardsley, L., Chang, CJ. & Burk, RD. (1998). Natural history of cervicovaginal papillomavirus infection in young women. *The New England Journal of Medicine*, Vol. 338, No. 7, (Feb 1998), pp, 423-428, ISSN 0028-4793.

Holland, D., Hoppe-Seyler, K., Schuller, B., Lohrey, C., Maroldt, J., Dürst, M. & Hoppe-Seyler, F. (2008). Activation of the Enhancer of Zeste Homologue 2 Gene by the Human Papillomavirus E7 Oncoprotein. *Cancer Research*, Vol. 68, No. 23, (Dec 2008), pp. 9964 - 9972, ISSN 0008-5472.

Howie, HL., Katzenellenbogen, RA. & Galloway DA. (2009). Papillomavirus E6 proteins. *Virology*, Vol. 384, No. 2, (Feb 2009), pp. 324-334, ISSN 0042-6822

Hu, L., Plafker, K., Vorozhko, V., Zuna, RE., Hanigan, Gorbsky, GJ., Plafker, SM., Angeletti, PC. & Ceresa, PB. (2009). Human papillomavirus 16 E5 induces bi-nucleated cell formation by cell-cell fusion. *Virology*, Vol. 384, No. 1, (Feb 2009), pp. 125-134, ISSN 0042-6822.

Huh, KW., DeMasi, J., Ogawa, H., Nakatani, Y., Howley, PM & Münger, K. (2005). Association of the human papillomavirus type 16 E7 oncoprotein with the 600-kDa retinoblastoma protein-associated factor, p600. *PNAS*, Vol. 102, No. 32, (Aug 2005), pp, 11492-11497, ISSN 0027-8424 .

Huh, KW., Zhou, X., Hayakawa, H., Cho, J-Y., Libermann, TA., Jin, J., Harper, JW. & Munger, K. (2007). Human papillomavirus type 16 E7 oncoprotein associates with the cullin 2 ubiquitin ligase complex, which contributes to degradation of the retinoblastoma tumor suppressor. *Journal of Virology*, Vol. 81, No. 18 (Sep 2007), pp. 9737-9747, ISSN 0022-538X.

Iftner, T., Elbel, M., Schopp, B., Hiller, T., Loizou, JI., Caldecott, KW. & Stubenrauch, F. (2002). Interference of papillomavirus E6 protein with single-strand break repair by interaction with XRCC1. *EMBO Journal*, Vol. 21, No. 17 (Sep 2002), pp. 4741-4748. ISSN 0261-4189.

International Agency for Research on Cancer (IARC). (2007). *IARC Monograph on the evaluation of carcinogenics risks to human – Human Papillomavirus*, World Health Organization, ISBN 978-92-832-1290-4, Lyon, France.

James, MA., Lee, JH. & Klingelhutz, AJ. (2006). HPV16-E6 associated hTERT promoter acetylation is E6AP dependent, increased in later passage cells and enhanced by loss of p300. *International Journal of Cancer*, Vol. 119, No. 8, (Oct 2006), pp. 1878-1885, ISSN 0020-7136.

Jing, M., Bohl, J., Brimer, N., Kinter, M. & Vande Pol, SB. (2007). Degradation of Tyrosine Phosphatase PTPN3 (PTPH1) by Association with Oncogenic Human Papillomavirus E6 Proteins. *Journal of Virology*, Vol. 81, No.5, (Mar 2007), pp.2231-2239, ISSN 0022-538X.

Jo, H. & Kim, JW. (2005). Implications of HPV infection in uterine cervical cancer. *Cancer Therapy*, Vol. 3, (July 2005), pp 419-434, ISSN 1543-9135.

Jones, DL., Thompson, DA. & Munger K. (1997).Destabilization of the RB tumor suppressor protein and stabilization of p53 contribute to HPV type 16 E7-induced apoptosis. *Virology*, Vol. 239, No. 1, (Dec 1997), pp. 97-107, ISSN 0042-6822.

Jones, PH., Simons, BD. & Watt, FM. (2007) Sic transit gloria: farewell to the epidermal transit amplifying cell? *Cell Stem Cell*, Vol. 1, No. 4, (Oct 2007), pp. 371-381, ISSN 1934-5909.

Kadaja, M., Sumerina, A., Verst, T., Ojarand, M., Ustav, E. & Ustav, M. (2007). Genomic instability of the host cell induced by the human papillomavirus replication machinery. *EMBO Journal*, Vol. 26, No. 8, (Apr 2007) 2180-2191, ISSN 0261-4189.

Kadaja, M., Silla MT., Ustav E.& Ustav, M. (2009). Papillomavirus DNA replication from initiation to genomic instability. *Virology*, Vol. 384, No. 2, (Apr 2009), pp. 360-368, ISSN 0042-6822.

Kamio, M., Yoshida, T., Ogata, H., Douchi, T., Nagata, Y., Inoue, M., Hasegawa, M., Yonemitsu, Y. & Yoshimura, A. (2004). SOCS1 [corrected] inhibits HPV-E7-mediated transformation by inducing degradation of E7 protein. *Oncogene,* Vol. 23, No. 17, (Apr 2004), pp. 3107-3115, ISSN 0950-9232.

Kämper, N., Day, PM., Nowak, T., Selinka, H-C., Florin, L., Lydia, JB. John, H., Schiller, JT & Sapp, M. (2006). A membrane-destabilizing peptide in capsid protein L2 is required for egress of papillomavirus genomes from endosomes. *Journal of Virology*, Vol. 80, No. 2, (Jan 2006), pp. 759-768, ISSN 0022-538X.

Kanodia S, Fahey LM, Kast WM. Mechanisms used by human papillomaviruses to escape the host immune response. *Current Cancer Drug Targets*. Vol. 7, No. 1 (Feb 2007), pp. 79-89, ISSN 1568-0096.

Kines, RC., Thompson, CDE., Lowy, DR., Schiller, JT & Day, PM (2009). The initial steps leading to papillomavirus infection occur on the basement membrane prior to cell surface binding. *PNAS*, Vol. 106, No. 48, (Dec 2009), pp. 20458-20463, ISSN 0027-8424.

Kobayashi, N., Takata, H., Yokota S., & Takiguchi, M. (2004). Down-regulation of CXCR4 expression on human CD8+ T cells during peripheral differentiation. *European Journal of Immunology*, Vol. 34, No. 12, (Dec 2004), pp 3370-3378, ISSN 0014-2980.

Katzenellenbogen, RA., Egelkrout, EM., Vliet-Gregg, P., Gewin, LC., Gafken, PR & Galloway, DA. (2007). NFX1-123 and Poly(A) Binding Proteins Synergistically

Augment Activation of Telomerase in Human Papillomavirus Type 16 E6-Expressing Cells. *Journal of Virology*, Vol. 81, No. 8, (Apr 2007), pp. 3786-3796, ISSN 0022-538X.

Kumar, A., Zhao, Y., Meng, G., Zeng, M., Srinivasan, S., Delmolino, LM., Gao, Q., Dimri, G., Weber, GF., Wazer, DE., Band, H. & Band, V. (2002). Human papillomavirus oncoprotein E6 inactivates the transcriptional coactivator human ADA3. *Molecular and Cellular Biolology*, Vol. 22, No.16, (Aug 2002), pp. 5801-5812, ISSN 0270-7306.

Kurg,R., Uusen, P., Vosa, L. & Ustav, M. (2010). Human papillomavirus E2 protein with single activation domain initiates HPV18 genome replication, but is not sufficient for long-term maintenance of virus genome. *Virology*, Vol. 408, No. 2, (Dec 2010), pp. 159-166, ISSN 0042-6822.

Lace, MJ., Anson, JR., Thomas, GS., Turek, LP. and Haugen TH. (2008). The E8∧E2 gene product of human papillomavirus type 16 represses early transcription and replication but is dispensable for viral plasmid persistence in keratinocytes. *Journal of Virology*, Vol. 82, No. 21, (Nov 2008), pp. 10841-10853, ISSN 0022-538X.

Laniosz, V., Nguyen, KC. & Meneses, PI. (2007). Bovine papillomavirus type 1 infection is mediated by SNARE syntaxin 18. *Journal of Virology*, Vol. 81, No. 14, (Jul 2007), pp, 7435 - 7448. ISSN 0022-538X.

Lazarczyk, M., Cassonnet, P., Pons, C., Jacob, Y. & Favre, M. (2009). The EVER proteins as a natural barrier against papillomaviruses: a new insight into the pathogenesis of human papillomavirus infections. *Microbiology and Molecular Biology Reviews,* Vol. 73, No. 2, (June 2009), pp. 348-370, ISSN 092-2172.

Le Bon A. & Tough, DF. Links between innate and adaptive immunity via type I interferon. *Current Opinion in Immunology*, Vol. 14, No 4, (August 2002), pp. 432-436, ISSN 0952-7915.

Lechner MS. & Laimins LA. (1994). Inhibition of p53 DNA binding by human papillomavirus E6 proteins. *Journal of Virology*, Vol. 68, No. 7, (Jul 1994), pp. 4262-4273, ISSN 0022-538X.

Lee, C. Wooldridge, TR. & Laimins, LA. (2007). Analysis of the roles of E6 binding to E6TP1 and nuclear localization in the human papillomavirus type 31 life cycle. Virology, Vol. 358, No. 1, (Feb 2007), pp. 201-1210, ISSN 0042-6822.

Longworth, MS.& Laimins, LA. (2004). Pathogenesis of human papillomaviruses in differentiating epithelia. *microbiology and molecular Biology Reviews*, Vol. 68, No. 2, (Jun 2004), pp. 362 – 372, ISSN 1092-2172 .

Longworth, MS., Wilson, R. & Laimins, LA. (2005). HPV31 E7 facilitates replication by activating E2F2 transcription through its interaction with HDACs. *EMBO Journal*, Vol. 24, No. 10, (May 2005), pp. 1821-30, ISSN 0261-4189.

Lyons, TE. Salih, M. & Tuana, BS. (2006). Activating E2Fs mediate transcriptional regulation of human E2F6 repressor. *American Journal Physiology Cell Physiology*, Vol. 290, No. 1, (Jan 2006), pp. C189 - C199, ISSN 0363-6143.

Mark Schiffman, M. Wentzensen, N., Wacholder, S., Kinney, W., Gage, JC. & Castle, PE. (2011). Human papillomavirus testing in the prevention of cervical cancer. *Journal of the National Cancer Institute*, Vol. 103, No. 5, (Jan 2011), pp. 368-383, ISSN 0027-8874.

McLaughlin-Drubin, ME & Munger, K. (2009). Oncogenic activities of human papillomaviruses. *Virus Research*, Vol. 143, No 2, (Aug 2009), pp 195-208, ISSN 0168-1702

McLaughlin-Drubin, ME., Huh, KW. & Munger, K . (2008). Human papillomavirus type 16 E7 oncoprotein associates with E2F6. *Journal of Virology*, Vol. 82, No. 17, (Sep 2008), pp. 82: 8695 – 8705, ISSN 0022-538X.

McPhillips, MG., Oliveira, JG., Spindler, JE., Mitra, R. & McBride AA. (2006). Brd4 Is required for E2-mediated transcriptional activation but not genome partitioning of all papillomaviruses. *Journal of Virology*, Vol. 80, No. 19, (Oct 2006), pp. 9530-9543, ISSN 0168-1702.

Miura, S., Kawana, K., Schust, DJ., Fujii, T., Yokoyama, T., Iwasawa, Y., Nagamatsu, T., Adachi, K., Tomio, A., Tomio K., Kojima, S., Yasugi, T., Kozuma, S. & Taketani Y. (2010). CD1d, a sentinel molecule bridging innate and adaptative immunity, is downregulated by the human papillomavirus (HPV) E5 protein: a possible mechanism for immune evasion by HPV. *Journal of Virology*, Vol 84, No 22, (Nov 2010), pp. 1114-11623, ISSN 0168-1702.

Mei Xu, M., Luo, W., Elzi, DJ., Grandori,C. & Galloway, DA. (2008). NFX1 Interacts with mSin3A/Histone Deacetylase To Repress hTERT Transcription in Keratinocytes. *Molecular and Cellular Biology*, Vol. 28, No. 15, (August 2008), pp. 4819-4828, ISSN 0270-7306.

Mitelman, F., Johansson, B. & F Mertens, F. (2007). The impact of translocations and gene fusions on cancer causation. *Nature Reviews Cancer*, Vol. 7, No. 4, (Apr 2007), pp. 233-245, ISSN 1474-175X

Moody, CA. & Laimins, LA. (2010). Human papillomavirus oncoproteins: pathways to transformation. *Nature Reviews Cancer*, Vol. 10, No. 8, pp. 550-560, ISSN 1474-175X.

Mukonoweshuro, P., Oriowolo A. & Smith M. (2005). Audit of the histological definition of cervical transformation zone. *Journal of Clinical Patholog*v, Vol. 58, No. 6, (Jun *2005),* pp. 670-672, ISSN 0021-9746.

Münger, K. & Peter M. Howley, PM. (2002). Human papillomavirus immortalization and transformation functions. *Virus Research*, Vol. 89, No. 2, (Nov 2002), pp. 213-228, ISSN 0168-1702

Münger, K., Baldwin, A., Edwards, KM., Hayakawa, H., Nguyen, CL., Owens, M., Grace, M. & Huh, K. (2004). Mechanisms of human papillomavirus-induced oncogenesis. *Journal of Virology*, Vol. 78, No. 21, (Nov 2004), pp. 11451-11460, ISSN 0022-538X.

Munõz, N., Bosch, FX., de Sanjosé, S., Herrero, R., Castellsagué, X., Shah, KV., Snijders, PJF., Chris, JLM. & Meijer, MD. (2003). Epidemilogic classification of human papillomavirus types associated with cervical cancer. *The New England Journal Medicine*, Vol. 348, No 6, (Feb 2003), pp. 518-527, ISSN 0028-4793.

Muñoz, N., Castellsagué, X., de González, AB., Gissmann, L. (2006). Chapter 1: HPV in the etiology of human cancer. *Vaccine*, Vol. 24, Suppl 3, (Aug 2006), pp. 1-10, ISSN 0264-410X..

Nakahara, T., Peh, WL., Doorbar, J., Lee, D. & Lambert, PF. (2005). Human papillomavirus type 16 E1^E4 contributes to multiple facets of the papillomavirus life cycle. *Journal of Virology*, Vol. 79, No. 20, (Oct 2005), pp. 13150-13165, ISSN 0022-538X.

Natale, C., Giannini, T., Lucchese , A., Kanduc, D. (2000).Computer-assisted analysis of molecular mimicry between human papillomavirus 16 E7 oncoprotein and human protein sequences. *Immunology Cell Biology, Vol.* 78, No. 6 (Dec 2000), pp. 580-585, ISSN 0818-9641.

Nees, M., Geoghegan, JM., Hyman, T., Frank, S., Miller, L. & Woodworth, CD. (2001). Papillomavirus type 16 oncogenes downregulate expression of interferon-responsive genes and upregulate proliferation-associated and INF- B-responsive genes in cervical keratinocytes. *Journal of Virology*, Vol. 75, No. 9, (May 2001), pp. 4283-4296, ISSN 0022-538X.

Nguyen, CL. & Munger, K. (2008). Direct association of the HPV16 E7 oncoprotein with cyclin A/CDK2 and cyclin E/CDK2 complexes. *Virology*, Vol. 380, No 1 (Oct 2008), pp. 21-25, ISSN 0042-6822.

O'Brien, PM & Campos, MS. (2002). Evasion of host immunity directed by papillomavirus-encoded proteins. *Virus Research*, Vol. 88, No. 2, (Sep 2002), pp.103-117, ISSN 0168-1702.

Park, J-S., Kim, E-J., Kwon, H-J., Hwang, E-S., Namkoong, S-E. & Um, S-J. (2000). Inactivation of Interferon Regulatory Factor-1 Tumor Suppressor Protein by HPV E7 Oncoprotein. Implication for the E7-mediated immune evasion mechanism in cervical carcinogenesis. *The Journal Biological Chemistry*, Vol. 275, No. (Mar 2000), pp. 6764 – 6769, ISSN 0021-9258.

Pei, XF., Meck, JM., Greenhalgh, D. & Schlegel, R. (1993). Cotransfection of HPV-18 and v-fos DNA induces tumorigenicity of primary human keratinocytes. *Virology*, Vol. 196, No. 2, (Oct 1993), pp. 855-860, ISSN 0042-6822.

Pett, MK., Herdman, MT., Palmer, RD., Yeo, GSH., Shivji,MK., Stanley, MA. & Coleman, N. (2006). Selection of cervical keratinocytes containing integrated HPV16 associates with episome loss and an endogenous antiviral response. *PNAS*, Vol. 103, No. 10, (Mar 2006), pp. 3822-3827, ISSN 0027-8424.

Philip E Castle, PE., Schiffman, M., Herrero, R., Hildesheim, A., Rodriguez, AC., Bratti, MC., Sherman, EM., Wacholder, S., Tarone, R. & Burk, RD. (2005). A prospective study of age trends in cervical Human Papillomavirus acquisition and persistence in Guanacaste, Costa Rica. *The Journal of Infectious Disease*, Vol.191, No. 11, (Jun 2005), pp. 1808-1816, ISSN 0022-1899.

Pyeon, D., Pearce, SM., Lank, SM., Ahlquist, P. & Lambert, PF. (2009). Establishment of human papillomavirus infection requires cell cycle progression. *PLoS Pathogens*, Vol. 5, No. 2, (Feb 2009), pp. 1-9, ISSN 1553-7366.

Richards, RM., Lowy, DR., Schiller, JT. & Day, PM. (2006). Cleavage of the papillomavirus minor capsid protein, L2, at a furin consensus site is necessary for infection. *PNAS*, Vol. 103, No. 5, (Jan 2006), pp.1522-1527, ISSN 0027-8424.

Richardson, H., Kelsall, G., Tellier, P., Voyer, H., Abrahamowicz, M., Ferenczy, A., Coutlée, F. & Franco, EL. (2003). The natural history of type-specific human papillomavirus infections in female university students. *Cancer Epidemiology, Biomarkers & Prevention*, Vol. 12, No. 6, (Jun 2003), pp. 485-490, ISSN 1055-9965.

Rincon-Orozco, B., Halec, G., Rosenberger, S., Muschik, D., Nindl, I., Bachmann, A., Ritter, TM., Dondog, B., Ly, R., Bosch, FX., Zawatzky, R. & Rösl, F. (2009). Epigenetic silencing of interferon-κ in human papillomavirus type 16–positive cells. *Cancer Research*, Vol. 69, No. 22, (Nov 2009), pp. 8718-8725, ISSN 0008-5472.

Roberts, JN., Buck, CB., Thompson, CD., Kines, R., Bernardo, M., Choyke, PL., Lowy, DR. & Schiller, JT. (2007). Genital transmission of HPV in a mouse model is potentiated by nonoxynol-9 and inhibited by carrageenan. *Nature Medicine*, Vol. 13, No. 7, (Jul 2007), pp. 857-861, ISSN 1078-8956.

Romanczuk, H. & Howley, PM. (1992). Disruption of either the E1 or the E2 regulatory gene of human papillomavirus type 16 increases viral immortalization capacity. PNAS, Vol. 89, No. 7, (Apr 1992), pp 3159-3163, ISSN 0027-8424.

Samuel, CE. (2001). Antiviral actions of interferons. *Clinical Microbiology Reviews*, Vol. 14, No. 4, (Oct 2001), pp. 778-809, ISSN 1098-6618.

Santer, FR., Moser, B., Spoden, GA., Jansen-Dürr, P. & Zwerschke, W. (2007). Human papillomavirus type 16 E7 oncoprotein inhibits apoptosis mediated by nuclear insulin-like growth factor-binding protein-3 by enhancing its ubiquitin/ proteasome-dependent degradation. *Carcinogenesis*, Vol. 28, No. 12, (Dec 2007), pp. 2511 – 2520, ISSN 0143-3334.

Sapp, M., Volpers, C., Müller, M. & Streeck, RE. (1995). Organization of the major and minor capsid proteins in human papillomavirus type 33 virus-like particles. *Journal of General Virology*, Vol. 76, No. 9, (Sep 1995), pp. 2407-2412, ISSN 0022-1317.

Schiller, JT., Day, PM. & Kines, RC. (2010).Current understanding of the mechanism of HPV infection. *Gynecologic Oncology*, Vol. 118 (Jun 2010), Suppl 1, S12-17, ISSN 0090-8258.

Scott, M., Nakagawa, M. & Moscicki, AB. (2001). Cell-mediated immune response to human papillomavirus infection. *Clinical and Diagnostic Laboratory Immunology*, Vol. 8, No. 2, (Mar 2001), p. 209 -220, ISSN 1071-412X.

Selinka, H-C., Florin, L., Patel, HD., Freitag, K., Vadim, MS., Makarov, A. & Sapp, M. (2007). Inhibition of transfer to secondary receptors by heparan sulfate-binding drug or antibody induces noninfectious uptake of human papillomavirus. *Journal of Virology*, Vol. 81, No. 20, (Oct 2007), pp. 10970-10980, ISSN 0022-538X.

Seo, YS, Müller, F., Lusky, M., Gibbs, E., Kim, HY., Phillips, B & Hurwitz J. (1993). Bovine papilloma virus (BPV)-encoded E2 protein enhances binding of E1 protein to the BPV replication origin. *PNAS*, Vol. 90, No. 7, (Apr 1993), pp. 2865-2869, ISSN 0027-8424.

Shai, A., Nguyen, ML., Wagstaff, J., Jiang,YH. & Lambert PF. (2007). HPV16 E6 confers p53-dependent and p53-independent phenotypes in the epidermis of mice deficient for E6AP. *Oncogene*, Vol. 26, No 23, (May 2007), pp. 3321-3338, ISSN 0950-9232.

Shamanin, VA., Sekaric, P. & Androphy, EJ. (2008). hAda3 degradation by papillomavirus type 16 e6 correlates with abrogation of the p14arf-p53 pathway and efficient immortalization of human mammary epithelial cells. *Journal of Virology*, Vol. 82, No. 8, (Apr 2008), pp. 3912-3920, ISSN 0022-538X.

Shunsuke Nakagawa, S. & Huibregtse, JM. (2000). Human Scribble (Vartul) Is Targeted for Ubiquitin-Mediated Degradation by the High-Risk Papillomavirus E6 Proteins and the E6AP Ubiquitin-Protein Ligase. *Molecular Cellular Biology*, Vol. 20, No.21, (Nov 2000), pp. 8244- 8253, ISSN 0270-7306.

Simmonds, M. & Storey, A. (2008). Identification of the regions of the HPV 5 E6 protein involved in Bak degradation and inhibition of apoptosis. *International Journal of Cancer,* Vol. 123, No. 10, (Nov 2008), pp. 2260-2266, ISSN 0020-7136.

Smith, JL., Campos, SK. & Ozbun, MA. (2007). Human papillomavirus type 31 uses a caveolin 1- and dynamin 2-mediated entry pathway for infection of human keratinocytes. *Journal of Virology*, Vol. 81, No. 18, (Sep 2007), pp. 9922-9931, ISSN 0022-538X.

Spanos, WC., Hoover, A., Harris, GF., Wu, S. Strand, GL., Anderson, ME., Klingelhutz, AJ., Hendriks, W., Bossler, AD. & Lee JH. (2008). The PDZ binding motif of Human Papillomavirus type 16 E6 induces PTPN13 loss, which allows anchorage-independent growth and synergizes with Ras for invasive growth. *Journal of Virology*, Vol. 82, No. 5, (Mar 2008), pp. 2493-2500, ISSN 0022-538X.

Spardy, N., Duensing, A., Charles, D., Haines, N., Nakahara, T., Lambert, PF. & Duensing, S. (2007). The Human Papillomavirus Type 16 E7 Oncoprotein Activates the Fanconi Anemia (FA) Pathway and Causes Accelerated Chromosomal Instability in FA Cells. *Journal of Virology*, Vol. 81, No. (Dec 2007), pp.13265 – 13270, ISSN 0022-538X.

Spoden, G.,Freitag, K., Husmann, M., Boller, K., Sapp, M., Lambert, C. & Florin L. (2008). Clathrin- and caveolin-independent entry of human papillomavirus type 16--involvement of tetraspanin-enriched microdomains (TEMs). *PLoS One*, Vol. 3, No. 10, (Jan 2008), pp. e-3313, ISSN 1932-6203.

Srivenugopal, KS. & Ali-Osman, F. (2002). The DNA repair protein, O(6)-methylguanine-DNA methyltransferase is a proteolytic target for the E6 human papillomavirus oncoprotein. *Oncogene,* Vol. 21, No. 38, (Aug 2002) 5940-5945, ISSN 0950-9232.

Stanley, MA. (2006). Immune responses to human papillomavirus. *Vaccine*, Vol. 24, Suppl 1, (Mar 2006), pp. S16-22, ISSN 0264-410X.

Stanley, M., Lowy, DR. & Frazer, I. (2006). Chapter 12: Prophylactic HPV vaccines: underlying mechanisms. *Vaccine*, Vol. 24, Suppl 3, (Aug 2006), pp. S106-113, ISSN 0264-410X.

Stanley, MA., Pett, MR. & Coleman, N. (2007). HPV: from infection to cancer. *Biochemical Society Transactions*, Vol. 53, No 6, (Dec 2007), pp. 1456-1460, ISSN 0300-5127.

Stanley, MA. (2008). Immunobiology of HPV and HPV vaccines. *Ginecologic Oncology*, Vol. 109, Suppl 2, (Feb 2008), pp. S15–21, ISSN 0090-8258

Stanley, MA. (2009a). Immune responses to human papilloma viruses. Indian Journal Medicine Research, Vol. 130, No. 3, (Sep 2009), pp. 266-276, ISSN 0971-5916.

Stanley, MA. (2009b). Immunobiology of genital HPV infection. *CME Journal of Gynecologic Oncology*, Vol. 14, pp. 36-43, ISSN 1219-9087.

Stanley MA. (2010). Pathology and epidemiology of HPV infection in females. *Gynecologic Oncology*, Vol. 117, Suppl 2, (May 2010), pp. S5-10, ISSN 0090-8258.

Steger, G & Corbach, S. (1997). Dose-dependent regulation of the early promoter of human papillomavirus type 18 by the viral E2 protein. *Journal of Virology*, Vol. 71, No. 1, (Jan 1997), pp. 50-58, ISSN 0022-538X.

Sterlinko GH, Weber M, Elston R, McIntosh P, Griffin H, Banks L & Doorbar J.(2004). Inhibition of E6-induced degradation of its cellular substrates by novel blocking peptides. *Journal of Molecular Biology.* Vol. 335, No. 4, (Jan.2004), pp 971-985, ISSN 0022-2836.

Storrs, CH. & Silverstein SJ. (2007) PATJ, a tight junction-associated PDZ protein, is a novel degradation target of high-risk human papillomavirus E6 and the alternatively spliced isoform 18 E6. *Journal of Virology.* Vol. 81, No. 8, (Apr 2007), pp. 4080-4090, ISSN 0022-538X.

Straight, SW., Herman, B. & McCance, DJ. (1995). The E5 oncoprotein of human papillomavirus type 16 inhibits the acidification of endosomes in human keratinocytes. *Journal of Virology,* Vol. 69, No.5 (May 1995), pp. 3185 – 3192, ISSN 0022-538X.

Stubenrauch, F., Colbert, AME.& Laimins, LA. (1998). Transactivation by the E2 protein of oncogenic human papillomavirus type 31 is not essential for early and late viral functions. *Journal of Virology*, Vol. 72, No. 10, (Oct 1998), pp. 8115-8123, ISSN 0022-538X.

Syrjänen SM. & Syrjänen KJ. (1999). New concepts on the role of human papillomavirus in cell cycle regulation. *Annals of Medicine*, Vol. 31, No 3, (Jun 1999), pp.175-187, ISSN 0785-3890.

Tasaki, T., Mulder, LCF., Iwamatsu, A., Lee, MJ., Davydov, IV., Varshavsky, A., Muesing, M & Kwon YT. (2005). A family of mammalian E3 ubiquitin ligases that contain the UBR box motif and recognize N-degrons. *Molecular and Celularl Biology*, Vol. 25, No. 16, (Aug 2005), pp. 7120-7136, ISSN 0270-7306.

Thierry, F., Spyrou, G., Yaniv, M. & Howley, P. (1992). Two AP1 sites binding JunB are essential for human papillomavirus type 18 transcription in keratinocytes. *Journal of Virology*, Vol. 66, No. 6, (Jun 1992), pp. 3740-3748, ISSN 0022-538X.

Thomas, MC. & Chiang, CM. (2005). E6 oncoprotein represses p53-dependent gene activation via inhibition of protein acetylation independently of inducing p53 degradation. *Molecular Cell*, Vol. 17, No 2, (Jan 2005), pp, 251-264. ISSN 1097-2765

Timmons, B., Akins, M. & Mahendroo, M. (2010). Cervical remodeling during pregnancy and parturition. *Trends in Endocrinology Metabolism.* Vol. 21, No 6, (June 2010), pp. 353–361, ISSN 1043-2760.

Tindle, RW. (2002). Immune evasion in human papillomavirus-associated cervical cancer. *Nature Reviews Cancer,* Vol. 2, No. , (January 2002), pp. 1-7, ISSN 1474-175X

Trottier, H & Franco, EL. (2006). The epidemiology of genital human papillomavirus infection. *Vaccine*, Vol. 24, Suppl 1, (Mar 2006), pp. S1-15, ISSN 0264-410X.

Tsai, TC. & Chen, SL. (2003) The biochemical and biological functions of human papillomavirus type 16 E5 protein. *Archives Virology*, Vol. 148, No. 8, (Aug 2003), pp.1445-1453, ISSN 0304-8608.

Tungteakkhun, SS., Filippova, M., Neidigh, JW., Fodor, N., & Penelope J. Duerksen-Hughes, PJ. (2008). The Interaction between Human Papillomavirus Type 16 and FADD Is Mediated by a Novel E6 Binding Domain. *Journal of Virology*, Vol. 82, No. 19, (Oct 2008), pp. 9600 – 9614, ISSN 0022-538X.

Uemura, Y., Liu, T-Y. Narita, Y., Suzuki M. & Matsushita, S. (2008). 17β-Estradiol (E2) plus tumor necrosis factor-α induces a distorted maturation of human monocyte-derived dendritic cells and promotes their capacity to initiate T-helper 2 responses. *Human Immunology*, Vol. 69, No. 3, (March 2008), pp. 149-157, ISSN 0198-8859.

Underbrink, MP., Howie, HL., Bedard, KM., Koop, JI. & Galloway, DA. (2008). E6 Proteins from Multiple Human Betapapillomavirus Types Degrade Bak and Protect Keratinocytes from Apoptosis after UVB Irradiation. *Journal of Virology*, Vol. 82, No. 21, (Nov 2008), pp.10408 – 10417, ISSN. 0022-538X.

van der Burg, SH. & Palefsky, JM. (2009) Human immunodeficiency virus and human papilloma virus - why HPV-induced lesions do not spontaneously resolve and why therapeutic vaccination can be successful. *Journal of Translational Medicine*, Vol. 7, No 108 (Jan 2009), pp. 1-8, ISSN 1479-5876.

Villa, LL. (2007). Overview of the clinical development and results of a quadrivalent HPV (types 6, 11, 16, 18) vaccine. *International Journal of Infectious Diseases*, Vol.11, Suppl 2, (Nov 2007), pp. S17-25, ISSN 1201-9712.

White, PW., Titolo, S., Brault, K., Thauvette, L., Pelletier, A., Welchner, E., Bourgon, L., Doyon, L., Ogilvie, WW., Yoakim, C., Cordingley, MG.& Archambault, J. (2003). Inhibition of human papillomavirus DNA replication by small molecule antagonists of the E1-E2 protein interaction. *The Journal of Biological Chemistry*. Vol. 278, No. 29, (Jul 2003), pp. 26765-26772, ISSN 0021-9258

Wilson, R., Fehrmann, F. & Laimins, LA. (2005). Role of the E1∧E4 protein in the differentiation-dependent life cycle of human papillomavirus type 31. *Journal of Virology*, Vol. 79, No.11, (Jun 2005), pp. 6732-6740, ISSN 0022-538X.

Xu, YF, Zhang, YQ., Xu, XM. & Song, GX. (2006). Papillomavirus virus-like particles as vehicles for the delivery of epitopes or genes. *Archives of Virology*, Vol. 151, No. 11, (Nov 2006), pp. 2133-2148, ISSN 0304-8608.

Yuan, F., Auborn, K. & James C. (1999). Altered growth and viral gene expression in human papillomavirus type 16-containing cancer cell lines treated with progesterone. *Cancer Investigation*, Vol. 17, No. 1, (Jan 1999), pp. 19-29, ISSN 0735-7907.

Zekri, AR., Bahnassy, AA., Seif-Eldin, WM., Alam El-Din, HM., Madbouly, MS., Zidan, AZ., El-Hoshy, K., El-Ramly, A. & Abdel-Hamid, NA. (2006). Role of human papilloma virus (HPV) in common and genital warts and its relation to P53 expression. *Journal of the Egyptian National Cancer Institute*, Vol. 18, No 2, (Jun 2006), pp. 117-124, ISSN 1110-0362..

Zerfass, K., Schulze, A., Spitkovsky, D., Friedman, V., Henglein, B. & P Jansen-Durr, P. (1995). Sequential activation of cyclin E and cyclin A gene expression by human papillomavirus type 16 E7 through sequences necessary for transformation. *Journal of Virology*, Vol. 69, No. 10, (Oct 1995), pp. 6389-6399, ISSN 0022-538X.

Zerfass-Thome, K., Zwerschke, W., Mannhardt, B., Tindle, R., Botz, JW. & Jansen-Durr, P. (1996). Inactivation of the cdk inhibitor p27KIP1 by the human papillomavirus type 16 E7 oncoprotein. *Oncogene,* Vol. 13, No. 11, (Dec 1996), pp. 2323-2330, ISSN 0950-9232.

Zheng, L., Ding, H., Lu, Z., Li, Y., Pan, Y., Ning, T. & Ke, Y. (2008). E3 ubiquitin ligase E6AP-mediated TSC2 turnover in the presence and absence of HPV16 E6. Genes to cells : devoted to molecular & cellular mechanisms, Vol.13, No. 3, (Mar 2008), pp. 285–294, ISSN 1356-9597.

Zheng, ZM & Baker, CC. (2006). Papillomavirus genome structure, expression, and post-transcriptional regulation. *Frontiers in Bioscience*. Vol. 11, (Jan 2006), pp. 2286-2302. ISSN 1945-0494.

Zhou, X. & Munger, K. (2009) Expression of the human papillomavirus type 16 E7 oncoprotein induces an autophagy-related process and sensitizes normal human keratinocytes to cell death in response to growth factor deprivation. *Virology*, Vol. 385, No. 1, (Mar 2009), pp. 192-197, ISSN 0042-6822.

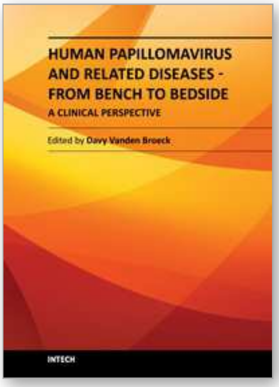
Zhou, F., Legaatt, GR & Frazer IH. (2011). Human papillomavirus 16 E7 protein inhibit inteferon-γ-mediated enhancement of keratinocyte antigen processing and T-cell lysis. *FEBS Journal*, Vol. 278, No 6, (Apr 2011), pp. 955-963. ISSN 1742-464X.

Ziegert, C., Wentzensen, N., Vinokurova, S., Kisseljov, F., Einenkel, J., Hoeckel, M. & Doeberitz MK. (2003). A comprehensive analysis of HPV integration loci in anogenital lesions combining transcript and genome-based amplification techniques. *Oncogene*, Vol. 22, No. 25, (Jun 2003), pp. 3977-3984, ISSN 0950-9232.

Zimmermann, H., Koh, C-H., Degenkolbe, R., O'Connor, MJ., Müller, A., Steger, G., Jason J., Lui, CY., Androphy, E. & Bernard, H-U. (2000). Interaction with CBP/p300 enables the bovine papillomavirus type 1 E6 oncoprotein to downregulate CBP/p300-mediated transactivation by p53. *Journal of General Virology*, Vol. 8, No. 11, (Nov 2000), pp. 2617-2623, ISSN 0022-1317.

zur Hausen, H. (1996). Papillomavirus infections - a major cause of human cancers. *Biochimica et Biophysica Acta*, Vol. 1288, No. 2, (Oct 1996), pp. 55-78, ISSN 0006-3002.

zur Hausen, H. (2009). Papillomaviruses in the causation of human cancers - a brief historical account. *Virology*, Vol. 384, No. 2, (Feb 2009), pp 260-265, ISSN 0042-6822.



Human Papillomavirus and Related Diseases - From Bench to Bedside - A Clinical Perspective
Edited by Dr. Davy Vanden Broeck

ISBN 978-953-307-860-1
Hard cover, 348 pages
Publisher InTech
Published online 20, January, 2012
Published in print edition January, 2012

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 the clinical aspects of HPV and related disease, highlighting the latest developments in this field.