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Oncogenic Aspects of HPV Infections of the Female Genital Tract

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1. Introduction

Genital human papillomavirus (HPV) infection is a most common sexually transmitted infection among women (Muñoz et al., 2003). The immune system effectively repels most HPV infections, and is associated with strong localized cell mediated immune responses. However, approximately ten percent of individuals develop a persistent infection, with risk of development of high-grade precursor lesions and eventually invasive carcinoma (Stanley, 2006). The causal role of HPV in all cancers of the uterine cervix has been firmly established (zur Hausen, 1999; Walboomers et al., 1999; Bosch et al., 2008). Most cancers of the vulva and vagina are also induced by oncogenic HPV types. In precancerous lesions, most HPV genomes persist in an episomal state whereas, in many high-grade lesions and carcinomas, genomes are found integrated into the host chromosome. Two viral genes, E6 and E7, are invariably expressed in HPV-positive cancer cells. Their gene products are known to inactivate the major tumour suppressors, p53 and retinoblastoma protein (pRB), respectively. In addition, E6 oncoprotein is also capable to up regulate the expression of inhibitors of apoptosis, and E6 and E7 cooperate to effectively immortalise primary epithelial cells. Tumour formation is not an inevitable consequence of viral infection; it rather reflects the multi-step nature of oncogenesis where each step constitutes an independent (reversible or irreversible) genetic change that cumulatively contributes to deregulation of cell cycle, cell growth and survival.

2. Human papillomaviruses

Human papillomaviruses are a large family of small double-stranded DNA viruses which infect squamous epithelia (or cells with the potential for squamous maturation). Papillomaviruses are classified by genotype, and at present, about 130 types have been identified by sequences of the gene encoding the major capsid protein L1 (de Villiers et al.; 2004; Bravo et al., 2010, Van Doorslaer et al., 2011). HPVs can be classified into high or low-risk types depending upon their oncogenic potential. High-risk genotypes 16 and 18 are associated with 70% of cervical carcinoma (Muñoz et al., 2006), and about 80% HPV positive vulval and vaginal carcinoma (Madeleine et al., 1997; Daling et al., 2002; Hampl et al., 2006). Low-risk types 6 and 11 have been isolated in 90% of genital warts (Aubin et al., 2008).

2.1 HPV genome organization

Virus particles consist of about 7900 base-pairs (7.9 kbp) long circular DNA molecules wrapped into a protein shell. The HPV genome can be functionally divided into two regions: Upstream Regulatory Region (URR) and Open Reading Frames (ORFs). URR does not code for proteins but contains cis-elements required for the regulation of the gene expression, replication of the genome, and its packaging into virus particles. ORFs can be divided into the Early Region (E), necessary for the replication, cellular transformation and the control of viral transcription, and Late Region (L) that codes for the capsid proteins that comprises the outer coat of the virus (Figure 1).

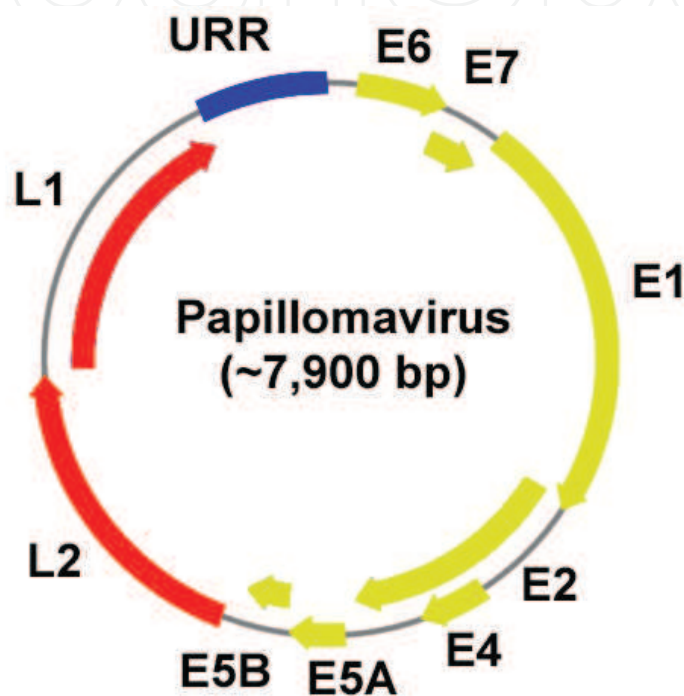


Fig. 1. Schematic presentation of the HPV genome. The non-coding region is the upstream regulatory region (URR). The open reading frames (ORFs) encode the early (E), and late (L) viral proteins. (Adapted from Muñoz et al., 2006).

Within the Early Regions (E) it is possible to distinguish different genes with specific functions. E1 and E2 genes have an important role in basal DNA replication. During viral persistence, the immune system keeps the infection in this state. E2 participates in the regulation of LCR (low-copy repeats) transcriptions, and decreases the expression of E6 and E7. The E4 gene codes for one family of small proteins involved in the transformation of the host cell by producing alterations of the mitotic signals and interacting with keratin. E5 decreases intercellular communication and isolates the transformed cells and interacts with the growth factor's receptors and encourages cellular proliferation. It also stimulates the expression of E6 and E7. E6 is oncogenic, stimulating the growth and transformation of the host cell by the inhibition of protein p53's normal tumour-suppressor function. E7 also acts as an oncogene, inducing cellular proliferation by inhibition of protein pRb. Within the Late Region (L), it is possible to distinguish the L1 gene, which codes for the major capsid protein and can form virus-like particles and L2, which codes for the minor capsid protein (Jones & Wells, 2006).

2.2 Natural history of genital HPV infection

Genital HPV infections are a very common sexually transmitted infection among women with a lifetime risk of 50-80% and have a peak prevalence between ages 18 and 30 (Koutsky, 1997). Most of these infections clear spontaneously. Seventy five per cent of infections clear within a year, and individuals with suboptimal immune responses may be at increased risk of persistent HPV infection and associated malignancy (Stanley, 2006). At present, in the female genital tract about 40 genotypes of HPV can be isolated; nevertheless only 15 types are usually associated with development of carcinoma. Genotypes 16 and 18 have been clearly shown to be predominant carcinogenic human viral agents, but in the majority of cases the presence of HPV alone is not sufficient for the development of neoplasm and different cofactors have been identified: tobacco, other sexually transmitted diseases (e.g. HIV), conditions of temporary immunodeficiency, alterations of hormonal status, beta-carotene deficiency, repeated local traumas, promiscuity and some modalities of sexual behaviour (Au, 2005; Cotton et al., 2007).

2.3 HPV life cycle

HPVs are perfectly adapted to their natural host tissue, the differentiating epithelial cells of skin or mucosa and exploit the cellular machinery for their own purposes. HPVs are undergoing a complete life cycle only in fully differentiated squamous epithelium. These viruses infect the basal cell layer where they establish their small double-stranded DNA genome, as a circular extra-chromosomal element or episome in the nucleus of infected cells. Following the entry into the suprabasal layer, the viral genome replicates and in the upper layers of epidermis complete viral particles are released (Doorbar, 2005). Existence of the viral genome in the infected cell is central to the life cycle of papillomaviruses and their associated pathologies. Maintenance of the viral genome requires the activity of E1 (the replicative helicase of papillomavirus) and E2, the two viral proteins necessary for replication of the HPV genome in conjunction with the host cell DNA replication machinery. As an initiator protein E1 acts both as a DNA binding protein to recognize the viral origin of DNA replication and subsequently as a helicase to unwind the origin and the DNA ahead of the replication fork. In lesions containing HPV episomes, the viral E2 protein directly represses early gene expression as part of a mechanism to regulate copy number. Integration of viral DNA usually disrupts E2 expression, leading to the deregulated expression of early viral genes, including E6 and E7. The expression of viral gene products is closely regulated as the infected basal cell migrates towards the epithelial surface. Genome amplification, which is necessary for the production of infectious virions, is prevented until the levels of viral replication proteins rise, and depends on the co-expression of several viral proteins. Viral persistence leads to clonal progression of the persistently infected epithelium. Events which are still not completely understood lead infected cells to malignant transformation. Tumour formation is not an inevitable consequence of viral infection; it rather reflects the multi-step nature of oncogenesis where each step constitutes an independent (reversible or irreversible) genetic change that cumulatively contributes to deregulation of cell cycle, cell growth and survival (Bosch et al., 2008).

3. HPV DNA replication

The papillomaviruses DNA replication is totally dependent upon the cellular DNA synthesis machinery. The problem for the virus is that the necessary cellular DNA polymerases and replication factors are only available in dividing cells. However, the virus replicates in non-

dividing cells. To solve this problem, HPV encodes proteins that, in the context of the viral life cycle, reactivate cellular DNA synthesis in non-cycling cells, inhibit apoptosis, and delay the differentiation program of the infected keratinocyte, creating an environment permissive for viral DNA replication (Münger & Howley, 2002). The precise details by which this is achieved are not completely understood, but the relevant viral genes are E6 and E7. Rarely, by-product of high-risk HPV replication is the deregulation of growth control in the infected cell and the development of cancer (Swan et al., 1994; zur Hausen, 2002). The HPV episome is replicated by the viral E1 and E2 proteins together with the host DNA replication machinery. E1 acts both as a DNA binding protein to recognize the viral origin and subsequently as a helicase to unwind the DNA ahead of the replication. Structure-function studies have indicated that E1 is a modular protein comprised of a C-terminal enzymatic domain with ATPase/helicase activity, a replication origin DNA-binding domain located in the centre of the protein and the N-terminal regulatory domain. E1 binds to DNA with little sequence specificity. In vitro and in vivo, binding of E1 specifically to the origin is facilitated by its interaction with E2, a transcription/replication factor that binds with high affinity to sites in the viral origin. Assembly of a ternary complex between E1, E2 and the origin serves as a starting point for the assembly of a larger E1 complex that has unwinding activity, most likely a double hexamer necessary for bidirectional unwinding. E1 interacts with DNA replication factors, including the polymerase α -primase and the single-stranded binding protein RPA (Replication Protein A), to promote viral DNA replication (Thierry et al., 2004).

3.1 Inhibitors of HPV DNA replication

Interaction between the E2 protein and E1 helicase of human papillomaviruses is essential for the initiation of viral DNA replication. Research performed by Wang and colleagues (2004) led to the identification of the first small molecule inhibitors of HPV DNA replication. Characterization of their mechanism of action showed that this class of inhibitors binds to E2 and prevents its interaction with the E1 helicase. These inhibitors defined a previously unrecognized small-molecule binding pocket on E2. This class of inhibitors was found to antagonize specifically the E1-E2 interaction in vivo and to inhibit HPV DNA replication in transiently infected cells. These results highlighted for the first time the potential of the E1-E2 interaction as a small molecule antiviral target for the treatment of HPV infections (White et al., 2011). These inhibitors also provided a rare example of a class of small molecules that can antagonize a protein-protein interaction.

4. HPV-induced oncogenesis

The female genital tract, a continuum of squamous epithelium from the vulva to the cervix, is commonly infected by human papillomavirus. The outcome of HPV infection depends on the immune response, the viral genotype (low-risk or high-risk/oncogenic) and the site of infection (the cervical squamo-columnar junction is more susceptible to HPV disease). The key role of HPV in most cancers of the female lower genital tract has been firmly established biologically and epidemiologically (Herrero et al., 2000; Daling et al., 2002; Böhmer et al., 2003; Moscicki et al., 2006).

4.1 Malignant transformation of the lower genital tract

The cervical cancer is marked by a premalignant phase of various grades of cervical intraepithelial neoplasm (CIN) which is a genetically unstable lesion and is characterized by

a spectrum of histological abnormalities. HPV viral integration into the host genomic DNA is associated with progressive genetic instability, and these events play a fundamental role in the progression from low-grade (CIN1) to high-grade (CIN2/3) lesions, and eventually to invasive cervical cancer (ICC). In longitudinal natural history studies, the time from the detection of high-risk HPV to the development of CIN3 is 3–5 years (Herrero et al., 2000), but the progression to ICC takes a further 10–20 years (Moscicki et al., 2006), and probably only 30–40% of CIN3 actually progress to invasive carcinoma (McCredie et al., 2008). Most cancers of the vulva and vagina in younger women are also induced by oncogenic HPV types (Madeleine et al., 1997; Hampf et al., 2006). These cancers are preceded by high-grade vulval intraepithelial neoplasia (VIN2/3) and vaginal intraepithelial neoplasia (VaIN2/3). Compared with cervical cancer, vulval and vaginal cancers develop less frequently.

4.2 Molecular basis of HPV-induced oncogenesis

The HPV DNA usually exists as extrachromosomal plasmid, mostly as a monomeric circular molecule in benign cervical precursor lesions. However, in cervical cancer cells the HPV DNA is integrated in the host genome. During HPV DNA integration, the viral genome breaks in the E1/E2 region. The break leads to the loss of the E2, which encodes proteins including one that inhibits the transcription of the E6 and E7 regions, resulting in increased expression of E6 and E7 oncogenic proteins (Moon et al., 2001). The proteins coded by these genes are multifunctional and interfere with important cell cycle regulatory proteins. Expression of viral oncogenes is tightly controlled in non-differentiated keratinocytes by at least two signalling cascades, one operative at the functional level and the other at the transcriptional level. Integration of the viral DNA could occur, resulting in increased expression of E6 and E7. Additionally, mutations or methylation of host DNA could occur that abrogate the transcriptional control of differentiation and viral gene expression; there is evidence for both of these mechanisms (Pett & Coleman, 2007; Kalantari et al., 2004). The oncoproteins E6 and E7 interact with many cellular proteins and change fundamental cellular functions like cell cycle regulation, telomere maintenance, susceptibility to apoptosis, intercellular adhesion and regulation of the immune response. These effects are in accordance with the essential changes in cell physiology that are acquired during tumour development and that have been proposed by Hanahan & Weinberg (2000). Evading the immune system surveillance has been recognized as an additional basic feature of malignant growth (Katz et al., 2008).

4.3 Regulation of the cell cycle

Maintenance of genetic integrity from one generation to the next requires the accurate replication of chromosomes during the S-phase and their faithful segregation during mitosis. The protein p53 (Figure 2) is known as the “genome’s guardian” (Lane, 1992) and in the case of DNA damage, p53 can provoke the arrest of cellular division to assure the time necessary for DNA repair.

If damage can not be repaired, p53 is able to induce the programmed cellular death (apoptosis) and prevent the propagation of DNA damage in the subsequent generation of cells. The product of another tumour suppressor gene, pRb acts as a repressor of E2F transcription factor (Wu et al., 2000). E2F regulates various genes including those involved in the progression of the cell cycle (the G1-S transition). By binding E2F, pRb prevents the entry into the S phase, providing the time for checking genome integrity (Figure 3). Oncoproteins E6 and E7 cooperatively disrupt the functions of p53 and pRb, with profound

changes in the cell cycle regulation (Vousden, 1993; Tungteakkhun & Duerksen-Hughes, 2008). Furthermore, E6 and E7 proteins can provoke directly DNA mutations of the host cell (Havre et al., 1995; Reznikoff et al., 1996; Moody & Laimins, 2010). As an aberration of virus infection, constant activity of the viral proteins E6 and E7 leads to increasing genomic instability, accumulation of gene mutations, further loss of cell-growth control and ultimately cancer (Münger et al., 1992; Ishiji, 2000).

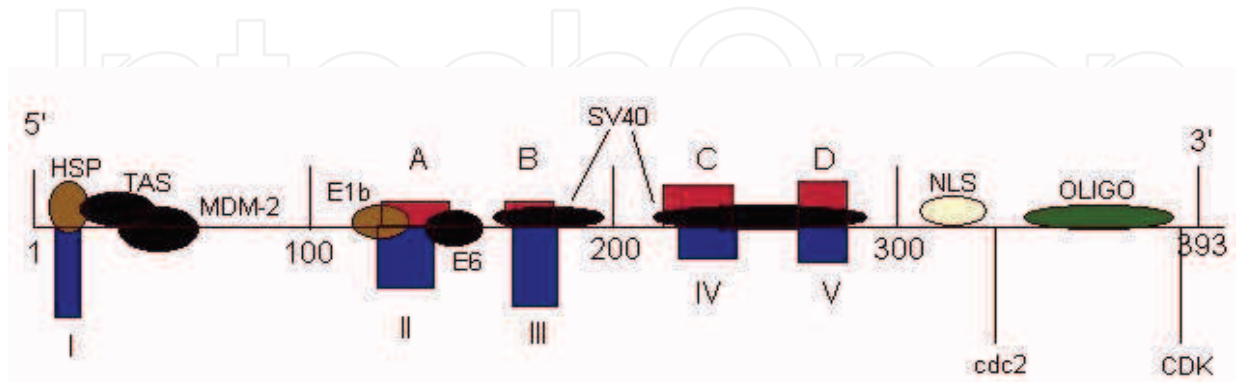


Fig. 2. Structural features of the p53 tumour suppressor gene. The transcription activation site (TAS), heat shock protein binding site (HSP), SV40 large T-antigen binding sites (SV40), adenovirus E1b and papillomavirus E6 binding sites, cellular Mdm2 binding site, nuclear localization signal (NLS), oligomerization domain (OLIGO) and phosphorylation sites (cdc2 and CDK) are indicated. The five evolutionarily conserved domains are labeled HCD I - V and the hot spot regions are HSR A-D (Adapted from Mietz et al., 1992).

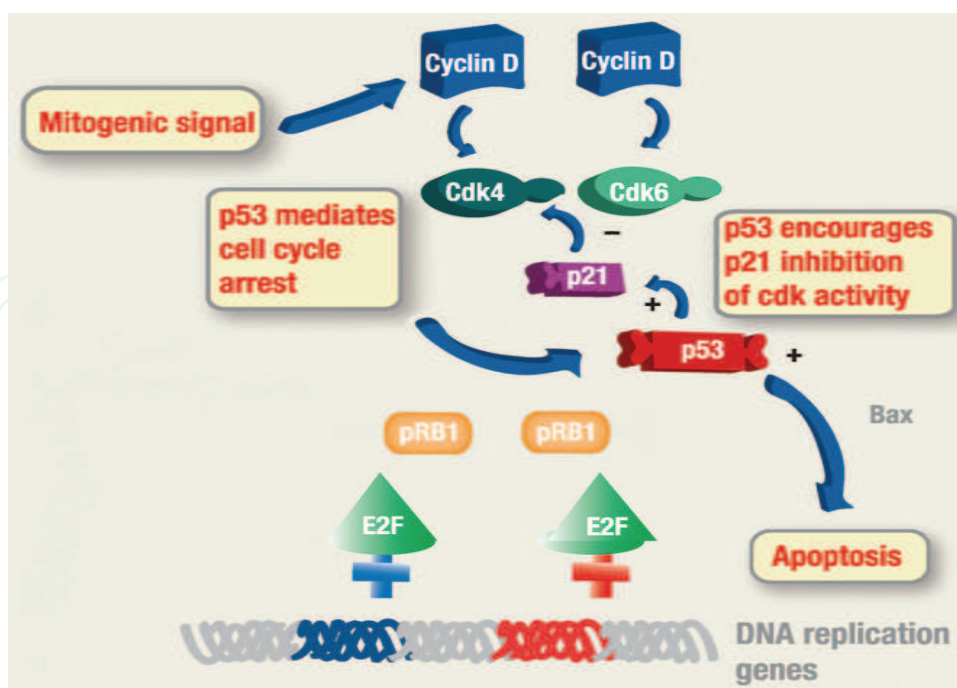


Fig. 3. Regulation of cell cycle: the role of p53 and pRb

4.3.1 Oncoprotein E6 functions

HPV 16 E6 is a 151 amino acid protein with two zinc finger domains. E6 is one of the primary oncogenes of the virus (Rapp & Chen, 1998; Fan & Chen, 2004). E6 together with E7 causes immortalization of cells and plays important roles in malignant transformation. Oncoprotein E6 interacts with numerous cellular proteins (Table 1).

Oncoprotein E6 functions	Investigators, year
Cell immortalization	Band et al., 1990
Binding of E6-AP results in degradation of p53	Tommasino et al., 2003
Antiapoptotic effect	Thomas & Banks, 1998
Chromosomal destabilization	White et al., 1994
Foreign DNA integration	Kessis et al., 1996
Enhancement of DNA mutagenicity	Havre et al., 1995
Activation of telomerase	Klingelhutz et al., 1996
Blockade of interferon	Ronco et al., 1998
E2F-regulated mitotic genes	Thierry et al., 2004
E6 I/E6 II gene expression	Moodley et al., 2003

Table 1. Identified functions of the high-risk HPV oncoprotein E6

E6 targets p53 through recruitment of a cellular E3 ubiquitin ligase - E6 associated protein (E6AP). This trimeric complex leads to p53 degradation by ubiquitin-proteosomal pathway. Besides targeting it for degradation, E6 is capable of binding directly to p53, interfering with its DNA-binding activity (Lechner & Laimins, 1994). In addition, E6 protein blocks apoptosis, alters the transcription machinery and disturbs intercellular interactions, a crucial step towards malignancy. Another important target for E6 is the group of PDZ proteins (Wise-Draper & Wells, 2008). The name is related to the first three members identified: PSD-95 (a post-synaptic density signalling protein), Dlg (the *Drosophila* disc large protein) and ZO1 (the zonula occludens 1 protein with functional roles in epithelial polarity). Only high-risk E6 associates with PDZ proteins. These proteins play important role in cell signalling, cell adhesion and tight-junction integrity (Fanning & Anderson, 1999). Experimental evidence indicates that the interaction of E6 with PDZ proteins is necessary for development of epithelial hyperplasia (Nguyen, 2003).

4.3.2 Oncoprotein E7 functions

HPV 16 E7, a nuclear protein of 98 amino acids, has a casein kinase II phosphorylation site at serine residues 31 and 32 (Firzlaff et al., 1991). E7 interacts with various cellular proteins, most of which are important regulators of the cell cycle, especially the transition from the G1 to S phase (Table 2).

Oncoprotein E7 functions	Investigators, year
Cell immortalization	Münger & Phelps, 1993
Activation of cyclins E and A	Zerfass et al., 1995
Inhibition of pRb-related pocket proteins	Dyson et al., 1992
Induction of apoptosis	Puthenveetil et al., 1996
Inactivation of cyclin-dependent kinase inhibitors	Jones et al., 1997
Foreign DNA integration	Kesis et al., 1996
Enhancement of DNA mutagenicity	Reznikoff et al., 1996
Degradation of tyrosine kinase	Oda et al., 1999
Chromosomal abnormalities	Pett et al., 2004
E2F-regulated mitotic genes	Thierry et al., 2004

Table 2. Identified functions of the high-risk HPV oncoprotein E7

E7 proteins interact with the members of retinoblastoma protein family: pRb, p107 and p130 (also called “pocket proteins”). Most of the pRb functions are related to the repression of the E2F transcription factor. The E7 protein directly binds pRb and targets it for degradation through the ubiquitin-dependant pathway (Boyer et al., 1996). Suppression of Rb function by E7 results in the activation of E2F, and stimulation of the cell cycle progression (Dyson, 1998). E7 is also capable of direct interaction with E2F factors and chromatin modifiers such as histone deacetylases (HDACs), what additionally affects the expression of S phase genes (Hwang et al., 2002; Brehm et al., 1999). E7 protein interacts with cyclin dependent kinases (CDK) inhibitors like p21 and p27. While E6 inhibits p21 transcription by inactivating p53, E7 inhibits p21 functions by direct binding, thus contributing to sustained activity of CDK, such as CDK2. High-risk E7 also increases the expression of CDC25A phosphatase that promotes CDK2 activation (Nguyen et al., 2002). All these effects on cell proliferation are favourable for HPV life cycle and replication but they also contribute to the uncontrolled proliferation of infected cells. Besides disrupting cell cycle control, and allowing the cell division in the presence of DNA damage, E6 and E7 are capable of directly inducing DNA damage (Moody & Laimins, 2010). Thus, in HPV infected cells a deleterious combination could be present: increased DNA damage and impaired response to DNA damage.

4.4 Telomere maintenance

While normal cells have finite numbers of doublings before they become senescent (“Hayflick limit”), malignant cells acquire limitless replicative potential (Hanahan & Weinberg, 2000). The immortality of malignant cells is closely related with telomere maintenance (Shay & Bacchetti, 1997; Hanahan & Weinberg, 2000). The majority of malignant cells achieve telomere maintenance by up-regulation of telomerase, an enzyme that adds hexanucleotide repeats to the 3’ end of DNA strands in the telomere regions.

Telomerase is a ribonucleoprotein complex that contains three subunits: a catalytic subunit - human telomerase reverse transcriptase (hTERT), a RNA subunit and a protein subunit (dyskerin). The expression of hTERT is proportional to telomerase activity in the cells. It has been shown that high-risk E6 protein activates transcription of hTERT. E6 in complex with E6AP or alone interacts with Myc protein (Veldman et al, 2001; Howie et al., 2009). Heterodimer Myc/Max binds to the hTERT promoter and activates its transcription. E6 also affects other hTERT activators including Sp1 which binds to the hTERT promoter and histone acetyltransferases that increase histone acetylation at the hTERT promoter (Oh et al., 2001; James et al., 2006). E6 modulates activity of hTERT repressors as well. The HPV 16 E6/E6AP complex targets hTERT repressor X box-binding protein 1-91 (NFX1-91) for polyubiquitination and degradation. E6 affects binding of two other hTERT repressors - upstream stimulating factors 1 and 2 (USF1 and USF2). Additionally, E6 directly associates with NFX123 that increases hTERT activity by several mechanisms including those on transcriptional and post-translational level (Howie et al., 2009). A second mechanism of telomere maintenance is recombination-based and is termed alternative lengthening of telomeres (ALT) pathway. It has been suggested that the E7 protein affects telomere length through the ALT pathway (Spardy et al., 2008). Thus, a cooperative effect between E6 and E7 could be achieved regarding telomere maintenance and cell immortalization. The E7 effect could be important in early cancer development while E6 might play a role in later phases of oncogenesis (Moody & Laimins, 2010). This is in accordance with the observation that high levels of hTERT expression are found in advanced cervical lesions and invasive carcinomas (Zhang et al., 2004).

4.5 Evading apoptosis

HPV has developed numerous mechanisms that block host-mediated apoptosis. These mechanisms regulate the survival of infected cells thus facilitating the HPV replication cycle. Besides blocking p53 function in regulation of apoptosis, high-risk HPV proteins interact with both extrinsic and intrinsic apoptotic pathways. The extrinsic pathway is triggered by various extracellular signals that activate "death receptors", members of the tumour necrosis factor receptor (TNFR) family. After binding the ligand death receptors form trimers and associate with adaptor molecules and initiator caspases. The result is the formation of the death inducing signalling complex (DISC). DISC activates caspase 8 which cleaves downstream caspases in the apoptotic pathway leading to cell death. High-risk E6 protein interacts with all components of the DISC complex. E6 binds to the death receptor TNFR-1 and blocks its association with adapter molecules (Filippova et al., 2002). Furthermore, E6 can accelerate the degradation of some adapter molecules like FADD and the initiator caspase-8 (Garnett et al., 2006; Howie et al., 2009). The intrinsic apoptotic pathway is activated by various intracellular stressors (DNA damage, oxidative stress and others) and includes mitochondrial permeability transition. Then pro-apoptotic signals dominate changes in mitochondrial membrane are initiated with formation of pores and release of pro-apoptotic proteins. These proteins form an apoptotic signalling complex that results in cleavage of downstream caspases (like caspase-3 and caspase-7), leading to degradation of cellular components. The E6 protein interacts with intrinsic apoptotic pathway signalling by binding Bak, a pro-apoptotic member of Bcl-2 family. E6 binds Bak and induces its degradation through the ubiquitin-proteasome pathway (Thomas & Banks, 1998). The HPV E6 protein is also capable to up regulate the expression of inhibitors of apoptosis, such as survivin and the inhibitor of apoptosis protein 2 (IAP2). The studies of

HPV E7 in regulation of apoptosis obtained variable results; both, anti-apoptotic and pro-apoptotic effects have been found (Garnett & Duerksen-Hughes, 2006). HPV oncoproteins target a number of factors important for anoikis, a specific type of apoptosis that is induced by loss of cell adhesion or inappropriate cell adhesion (Valentijn et al., 2004; Chiarugi & Giannoni, 2008). High-risk HPV proteins bind or are associated with changes in expression levels of fibronectin, fibulin-1, focal adhesion kinase (FAK) and paxillin (Moody & Laimins, 2010). These interactions contribute to the capability of HPV infected cells to become resistant to anoikis and grow in the absence of anchorage to the extracellular matrix and their neighbouring cells. Anchorage independent growth is considered to be a hallmark of malignant phenotypes.

4.6 Escape from immune system surveillance

The major lines of defence against various pathogens are natural mechanical barriers, innate and adoptive immunity. Dendritic cells (DC) are highly specialized antigen presenting cells (APC) that play important roles in innate immunity and provide a link between innate and adoptive immunity. Toll-like receptors (TLR) located in the membrane or inside the DC recognize typical molecular motifs of various pathogens called pathogen-associated molecular patterns (PAMPS). Langerhans cells are main DC of the skin and mucosa, being important detectors at the site of HPV infection. Activated dendritic cells migrate to draining lymph nodes, mature during the migration to highly effective APC and present antigens to naïve T lymphocytes, thereby initiating cell-mediated responses. The activated effector (cytotoxic) cells target infected cells at the site of infection (Stanley, 2006). Indeed, in case of HPV infection in the majority of cases the virus is cleared by cell-mediated mechanisms that are clinically associated with complete remission. However, the time for clearance ranges from months to years suggesting a delay in immune response. Ten to twenty percent of infected persons do not manage to clear the HPV infection and they develop persistent infection that is associated with the risk of high-grade cervical lesions and invasive carcinoma (zur Hausen, 1996; Stanley, 2010). HPV has developed several mechanisms for evading the immune surveillance. The majority of these mechanisms contribute to evading of innate immunity that delays the adoptive immune response. Some of these mechanisms are related with the characteristics of the viral site of infection and some are related to the effects of viral oncoproteins. HPV does not have a lytic phase, and thereby does not cause cell injury that would initiate inflammation and/or immune response. There is no viraemic stage during HPV infection. Therefore both, locally and systemically there is no favourable situation for contact between HPV and the immune system. Hasan and colleagues (2007) have shown that high risk E6 and E7 proteins inhibit TLR9 transcription leading to impaired activation of the innate immune response. Additionally, high-risk proteins interact with interferon regulatory factors (IRF) required for the expression of type I interferons: E6 binds IRF-3 while E7 interacts with IRF-1 (Ronco et al., 1998; Park et al., 2000). Microarray analysis showed that high-risk proteins down-regulate the expression of IFN-inducible genes, including signal transducer and activator of transcription 1 (STAT1) (Chang & Laimins, 2000). One of the possible mechanisms that underlie this phenomenon is direct interaction of HPV 16 E7 with p48-the DNA binding component of the interferon-stimulated gene factor 3 (ISGF3) transcription complex, thus blocking the translocation of this complex to the nucleus (Barnard & McMillan, 1999). Furthermore, HPV proteins interact with the proximal components of interferon-inducible pathways. E6 binds and inhibits the function of tyrosin kinase (Tyk2), a component of the

JAK-STAT signalling pathway that mediates IFN cellular responses (Li et al., 1999). The activity of another interferon-inducible double-stranded RNA protein kinase (PKR) pathway is reduced by synergistic action of E6 and E7 (Hebner et al., 2006). Activated PKR-phosphorylates multiple products leading to various antiviral effects including the inhibition of translation. The reduced activity of this pathway results in the maintenance of viral protein synthesis. Furthermore, it has been shown that interferon induced growth arrest is dependent on p53 acetylation. Post-transcriptional modifications, like acetylation affect p53 stability and increases its transcriptional activity. Besides reducing p53 availability by targeting it for degradation, E6 interacts with p300/CBP that catalyzes acetylation of p53. E6 forms a complex with p300/CBP, thus preventing the acetylation of p53 (Hebner et al., 2007). This mechanism might contribute to the proliferation of HPV infected cells in the presence of interferon (Beglin et al., 2009).

5. Conclusions

Genital HPV infection is a most common sexually transmitted infection of viral origin among women. The association between persistent HPV infection and malignant transformation of the lower female genital tract is well established. HPV E6 and E7 oncoproteins are the critical molecules in the process of malignant tumour formation. Interacting with various cellular proteins, E6 and E7 influence fundamental cellular functions like cell cycle regulation, telomere maintenance, susceptibility to apoptosis, intercellular adhesion and regulation of immune responses. High-risk E6 and E7 cooperatively disrupt p53 and pRb functions with profound changes in the cell cycle regulation. Uncontrolled cell proliferation leads to increased risk of genetic instability; the generator of mutant phenotypes that will contribute to conferring other abnormalities and possible advantages for tumour growth. Furthermore, oncoproteins E6 and E7 are capable of directly provoking DNA damage. Usually, it takes decades for cancer to arise. Thus, cervical carcinogenesis is a multifactorial process involving genetic, environmental, hormonal and immunological factors in addition to HPV infection.

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