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overview

The transforming properties of human papillomavirus oncoproteins

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Abstract

Human papillomaviruses (HPV) are very common viruses, often causing benign epithelial lesions but, rarely, also cancer. Only long persistent infection with some carcinogenic or high risk HPV types will progress to high-grade lesions and finally cancer. The oncogenic potential of these HR HPV types relies on the role of their major oncoproteins E6 and E7, which bind, inactivate and degrade the two major cellular tumor-suppressor gene products, p53 and the retinoblastoma tumor-suppressor protein (pRb), respectively. The continuous expression of these early oncoproteins can lead to the transformation and immortalization of infected cells. Both, E6 and E7 co-operate to induce transformation of epithelial cells by interacting with numerous host cell proteins affecting many essential cellular pathways. Herein, the current knowledge on HPV E6 and E7, as well as on the auxiliary E5 oncoprotein is summarized.

INTRODUCTION

Human papillomaviruses (HPV) belong to a family of Papillomaviridae, which are circular double-stranded DNA viruses. There are strictly epitheliotropic infecting either mucosa (Alphapapillomaviruses) or skin (Betapapillomaviruses). There are more than 100 HPV genotypes, of which approximately 40 types infect the anogenital tract mucosa, while the others infect the cutaneous tissues. Most HPV types cause benign epithelial proliferation, while others cause cancer. Therefore, they are classified according to their oncogenic potential into low-risk (LR) HPV types and high-risk (HR) or carcinogenic types (Table 1) *(1)*. The most common LR HPV types 6 and 11 are causing almost 90 % of genital warts (flat and acuminata condylomata), while the most common HR HPV types 16 and 18 are causing more than 70 % cervical cancer cases and most other anogenital cancer as well as oropharyngeal tumours in men and women (reviewed in *(2)*).

The HPV genome contains several early and late open reading frames coding for replication and transcription regulating proteins, E1, E2, E5, E6, E7 and viral capsid proteins, L1 and L2, respectively (Table 2). Two early proteins, E6 and E7 act as a major viral oncoproteins, while the E5 acta as an auxiliary oncoprotein *(1)*.

Both E6 and E7 are small proteins, approximately 18 and 13 kDa in size, respectively, localized in the nucleus *(3)*. The E6 proteins are also found in the cytoplasm and the E7 probably also has a cytoplasmic component *(4)*. The expression of the HR E7 proteins by themselves

TABLE 1

Human papillomvirus (HPV) types and their oncogenic potential (reviewed in *(1)*)

Group	Types	Oncogenic evidence
Alpha HPV		
1	16	Most potent type, causing cancer at several sites
	18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Sufficient evidence for cervical cancer
2A	68	Strong evidence for cervical cancer
2B	26, 53, 66, 67, 70, 73, 82	Limited evidence for cervical cancer
	30, 34, 69, 85, 97	Phylogeneticly related to types with sufficient or limited evidence
3	6, 11	Insufficient evidence
Beta HPV		
2B	5, 8	Limited evidence for skin cancer in patients with *epidermodysplasia verruciformis*
3	Other beta and gamma types	Insufficient evidence

can immortalize human keratinocytes at a low frequency but E6 has no such activity. The combination of E6 and E7, however, is highly efficient at transforming and immortalizing most types of primary cells *(5)*. In addition to E6 and E7, the E5 oncoprotein plays an auxiliary role in cell transformation. Both HR and LR HPV oncoproteins bind they target proteins but HR do it with higher affinity and in addition often degrade them unlike to LR HPV oncoproteins *(6)*.

The transforming properties of HPV oncoproteins lie in the interaction with numerous host cell proteins resulting in the maintenance and the re-entering into the cell cycle, which consequently allows the virus to replicate as it is dependent on the host cell DNA replication machinery. In addition, the E7 protein, together with the E6 oncoprotein of the HR HPV types, is able to interfere with key cellular processes, such as cell cycle, senescence, differentiation, apoptosis and telomere shortening. Furthermore, because of the frequent integration of the HR HPV genome into a host cell chromosome, those two proteins are the only viral proteins that are consistently expressed in HPV associated cancers *(2)*. The HPV E6 and E7 proteins also associate with enzymes that modulate histone acetylation and thus, broadly regulate the transcriptional competence of host cell chromatin *(7)*. In this review, the interactions of HR HPV oncoproteins with cellular target proteins are described.

E6 ONCOPROTEINS

The E6 protein is a small (158 amino acid) oncoprotein found in all human papillomavirus genomes *(8)*. The HR E6 protein is one of the most studied HPV proteins due to its many functions (reviewed in *(9, 10)*) and is found to be interacting with many host cell proteins despite its limited size (**Table 3**). One of the most well known functions of E6 protein is inactivation and degradation of the human p53 tumor-suppressor protein *(11)*. In normal cells p53 is activated upon DNA damage and either activates pathways leading to reparation of DNA damage or activates apoptosis or senescence. Diverse functions of p53 have most recently been reviewed by Reinhardt et al. *(12)*. Inactivation of p53 is necessary for HPV to allow intensive viral DNA replication in the later stages of viral life cycle *(13)* that would otherwise be prevented by p53 activity (Figure 1).

An important control mechanism of the cell cycle occurs during the cell cycle G2-phase, when p53 plays a crucial role during DNA replication. Usually, p53 is maintained at low concentrations by the MDM2-mediated degradation but when replication errors or other DNA damages occurs, the checkpoint kinases CHK1 and CHK2 induce increased p53 activity by phosphorylation of various downstream molecules, including p53 itself. The p53 tetramer acts as a stress-induced transcription factor and induces the expression of $p21^{CIP}$ (p21), which inhibits several cyclin-CDK complexes and stops the cell cycle allowing correction of DNA errors or induction of apoptosis if the damage is too extensive. Besides its crucial role in cell cycle control, p53 is also a master regulator of many other stress-associated cellular functions, and is therefore often inactivated or mutated in many different cancer types *(14)*.

The HR HPV E6 protein targets the p53 protein for proteasomal degradation via interaction with the E6-AP protein *(15)*. However, this is not the only strategy HPV has for inactivating p53 pathway via E6 protein. Thus, HPV E6 proteins additionally target proteins both upstream and downstream of p53. The HPV E6 was found to be interacting with hADA3, GPS2, p150(Sal-2), CBP and p300 all of which proteins act on p53 expression or help in expression of p53 downstream targets *(16–19)*. Furthermore, the HPV E6 interferes with different apoptosis pathways by additional interactions with BAK, procaspase-8, TIP60, DFF40, FADD, GADD34 and TNFR-1 proteins *(20–26)*.

One of the major roles of HPV E6 is to modulate the structure of the epithelial tissue to allow for its life cycle completion in the virus modified upper layer cells where

TABLE 2

Characteristics and function of Papillomavirus type 16 proteins (reviewed in *(1)*)

Protein	Size (a.a.)	Expression	Localisation	Function	Functional domains
E1	649	Early**	Nucleus	Viral DNA replication, DNA helicase, ATP binding, ATPase	Amino-terminal: DNA binding Carboxy-terminal: enzymatic
E2	365	Early***	Nucleus	Origin binding, transcription regulation, auxiliary role in viral DNA replication, and repression of joining viral DNA to host chromosomes	Amino-terminal: transcriptional activity and viral DNA joining Carboxy-terminal: DNA binding and dimerization
E4	95	Early and late	Cytoplasm	Destabilization of cytokeratin filaments	DEAD-box protein binding motif, LLXLL motif
E5	83	Early and late	Endosomal and cell membranes, and Golgi	Mediates mitogenic signalling of growth factors, and auxiliary role in cell transformation	Hydrophobic regions
E6*	158	Early	Nucleus and cytoplasm	Major role in cell transformation; binds E6AP and promotes ubiquitylation and degradation of p53, also binds other cellular proteins, and activates transcription of cellular telomerase	P53 binding domain, PBZ binding domain, four Cys-X-X-Cys motifs
E7*	98	Early	Nucleus and cytoplasm	Major role in cell transformation; binds and inactivates pRb, and interferes with centrosome duplication leading to aneuploidy	LXCXE motif, casein kinase II phosphorilation site, two Cys-X-X-Cys motifs
L1	531	Late**	Diffuse nuclear	Major viral capsid protein	Multimerization domain, L2-binding domain
L2	473	Late	Diffuse nuclear	Minor viral capsid protein	L1-binding domain

a.a., amino acid; * E6 and E7 are the viral genes that are expressed in HPV positive cancers; **prior to productive viral infection; *** required for genome maintenance in persistent infections.

DNA synthesis normally doesn't take place. Thus, the E6 protein is found to interact with many proteins involved in cell-cell adhesion, cell-cell interaction and cell polarity mediating proteins (hDlg, scribble, MAGI-1/2/3, MUPP1, PATJ, PTPN3) *(27–33)*, mostly via binding to the PDZ domain in those proteins and to several proteins involved in epithelial organization and differentiation (fibulin-1, paxillin, zyxin, E6-BP) *(34–37)*. It is known that HPV DNA replication induces DNA damage responses in the cells where the virus is replicating *(38)*, but the E6 protein itself interacts with several proteins directly involved in DNA repair like BRCA1, XRCC1 and MGMT *(39–41)*. In addition, the E6 proteins directly and indirectly target other proteins involved in chromosomal and DNA stability like hTERT, MCM7 and NFX1 *(42–44)*.

The expression of E6 protein in cell culture experiments has also found direct and indirect transcriptional modulation of several host cell promoters: c-myc, prothymosin alpha *(45)*, E-cadherin *(46)* involucrin *(47)* that further deregulate cell cycle control and epithelial organization. Considering the fact that HPV E6 proteins interact with many less well understood transcriptional modulating proteins (E6-TP1, MAML1, TRIP-Br1) *(48–51)* or proteins involved in signal transduction (NHERF1, PKN1, TIP-2/GIPC) *(52–54)*, it is certain that many more promoters are directly and indirectly affected by HPV oncoproteins in infected cells.

The E6 protein can either only interact (BRCA1, CASP8 (Procaspase 8), E6BP, FADD, fibulin-1, karyopherin (Kap) alpha2 adapter, MAML1), inhibit (CBP/p300, DFF40, GADD34/PP1, IRF-3, PATJ, paxillin, TNFR-1, tyk2, XRCC1), degrade (bak, CAL, DLG, E6TP1, GPS2, MAGI-1/3, MCM7, MGMT, MUPP1 (MPDZ), NFX-1, NHERF1, p53, PTPN3, scribble, TIP-2/GIPC, TIP60, tuberin), activate (E6AP, hTERT, PKN1(PKN), TRIP--Br1) or change localisation (Zyxin). Each of this protein--protein action induces different effects in the HPV infected cell through mostly either signal transduction or replication and transcription modulation (listed in Table 3).

Finally, the E6 protein also appears to have some role in immune evasion as it interacts with IRF-3 and tyk-2 proteins both of which are involved in interferon signalling *(55, 56)*.

E7 ONCOPROTEINS

The E7 protein is the major transforming protein of HPV and shares sequence and structural homology with adenovirus E1A protein. Based on this homology, the E7 protein can be divided into three domains: conserved region 1 (CR1, residues 2–15), conserved region 2 (CR2, residues 16–38), which contains the LXCXE motif required for high-affinity binding to retinoblastoma pocket protein (pRb or RB) and other 'pocket proteins' (Table 4), and conserved region 3 (CR3, residues 39–98). CR3 shows little sequence homology to adenovirus E1A but like CR3 of E1A forms a zinc finger structure. However, the E7 protein shares transformation and transactivation functions with E1A protein *(57)*.

TABLE 3

HPV E6 oncoprotein interaction.

Host cell protein	Activity	Role in cell	Reference
p53	Transcription factor	Apoptosis and chromosomal stability	*(11)*
BAK	Interaction with BCL2	Apoptosis	*(20)*
CASP8	Proteolytic activation	Apoptosis	*(21)*
DFF40	DNA fragmentation and chromatin condensation	Apoptosis	*(23)*
FADD	Signal transduction	Apoptosis	*(22)*
GADD34/PP1, TIP60	Translation modulation	Apoptosis	*(24)*, *(26)*
TNFR-1	Signal transduction	Apoptosis TNF alpha signalling	*(25)*
MUPP1 (MPDZ), Zyxin, E6BP	Signal transduction	Cell-cell contact	*(30)*, *(36)*, *(37)*
TRIP-Br1	Translation modulation	Cell cycle	*(50)*
hTERT, MCM7	RNA-directed DNA polymerase activity, replication factor	Chromosomal stability	*(44)*, *(42)*
NFX-1	Translation modulation	Chromosomal stability hTERT regulation	*(43)*
PKN1 (PKN), NHERF1	signal transduction	Cytoskeleton, wnt signalling	*(53)*, *(52)*
BRCA1, XRCC1	DNA binding	DNA repair	*(39)*, *(40)*
MGMT	Cysteine methyltransferase	DNA repair	*(41)*
karyopherin (Kap) alpha2 adapter	Nuclear protein import	E6 nuclear entry	*(90)*
E6TP1, TIP-2/GIPC	Signal transduction	G protein-linked signalling	*(48)*, *(54)*
PTPN3	Signal transduction	Growth hormone signalling	*(32)*
IRF-3, tyk2	Signal transduction	Immunity, JAK-STAT signalling	*(56)*, *(55)*
tuberin	Signal transduction	mTORC1 signalling	*(51)*
MAML1	Translation modulation	NOTCH signalling differentiation	*(49)*
p150(Sal2)	Translation modulation	p53/p21 signalling	*(19)*
ADA3, CBP/p300, GPS2,	Translation modulation	p53 transcription	*(16)*, *(17)*, *(36)*
fibulin-1, MAGI-1/3	Cell adhesion and migration	Cell-cell contact and polarity	*(34)*, *(29)*
DLG, PATJ, paxillin, scribble	Signal transduction	Cell-cell contact and polarity	*(27)*, *(33)*, *(35)*, *(28)*
E6AP	Ubiquitin ligase	Ubiquitination of p53	*(15)*
CAL	Intracellular trafficking	Vesicular trafficking autophagy	*(91)*

The key activity of the E7 protein is to overcome tumour suppressor block controlled by the pRb, while those of E6 protein is to overcome the p53 protective control pathways, which are important in preventing the genetic damage leading to cellular transformation (Figure 1). Thus, these oncoproteins promote genetic instability through induction of cellular proliferation, disruption of cell cycle checkpoints, inhibition of apoptosis, induction of telomerase activity and finally lead to cancer *(2)*. It is clear that high-affinity of E7 protein binding to pRb is not sufficient for transformation and that regions outside the pRb-binding domain must be important for the transforming potential of HR HPV E7 protein. However, how these regions contribute to transformation is poorly understood *(7)*.

In quiescent cells, pRb is present in a hypophosphorylated form and associates with E2F transcription factor, thereby inhibiting their transcriptional activity. Under exposure to a mitogenic signal, complexes of cyclin and cyclin-dependent kinase (CDK) are activated, notably cyclin D1-CDK4 and cyclin D1-CDK6 complexes, which induce pRb phosphorylation leading to the disruption of pRb/E2F complexes. Such activated E2F transcription factors then induce cyclin E and subsequent additional phosphorylation of pRb by cyclin E/CDK2 complex that initiates entry into cell cycle S-phase. The protein $p16^{INK4A}$ (p16) mediates senescence and differentiation by inhibiting cyclin D1/CDK4 and cyclin D1/CDK6 complexes. The interplay between the cyclins, CDKs and their inhibitors determines whether the restriction point can be passed *(14)*.

The E7 binding to pRb, and its related members (p107 and p130) (Table 4), mimics the effects of pRb phosphorylation resulting in the release of active E2F transcription factors, which in turn activate the transcription of a group of genes encoding proteins essential for cell cycle progression. Thus, E7 expressing cells can enter the S phase in the absence of mitogenic signals *(14)*. The E7 also binds and activates complexes of cyclins and CDKs, which control progression through the cell cycle. On the other hand, E6 associates with the ubiquitin-protein ligase E6AP, which then binds to p53 and targets the p53 protein for multi-ubiquitination and consequent proteasomal degradation *(11)*. HPV onco-

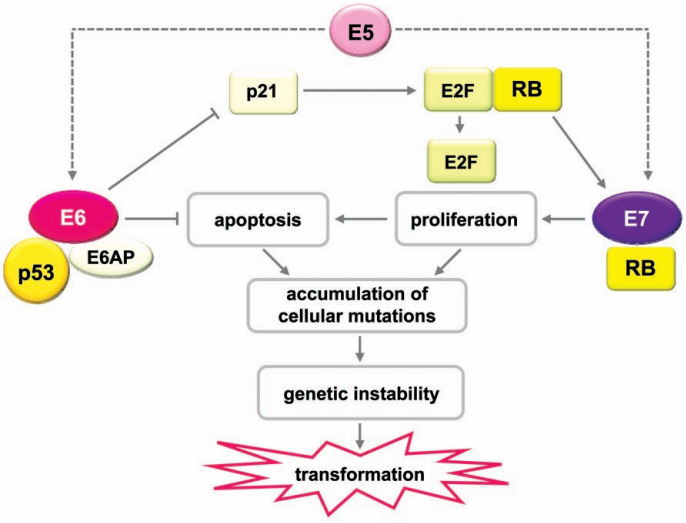

Figure 1. *Essential interaction of HR HPV E5, E6 and E7 oncoproteins and consequences in the infected cell. E7 proteins induce hyperproliferation through inhibition of retinoblastoma (RB) family members and constitutive activation of E2F-responsive genes. E6 proteins inhibit p53-dependent growth arrest and apoptosis. E5 contributes to the actions of E6 and E7 by modulating the transit of signalling proteins through the endoplasmic reticulum. In addition to aberrant proliferation and lack of apoptosis, there is an accumulation of cellular mutations and increased genomic instability resulting with cellular transformation leading to immortalisation*

proteins E7 and E6, both have multiple other functions by binding numerous target proteins and degrading some *via* proteasomal degradation, i.e. family proteins of pRb (p107, p130) *(58)*, and p53 (p63, p73) *(11)*, and p21(CIP1) protein *(59)*.

TABLE 4

HPV E7 oncoprotein interaction.

Host cell protein	Activity	Role in cell	Reference
pRb family proteins (RB, p107, p130)	Tumour suppressor	Disruption of pRb–E2F complexes thereby initiating the E2F mediated transcription	*(14)*
p21	Cell cycle regulator	Binding to and subsequent inactivation of the CDK inhibitor p21	*(14)*
p27	Cell cycle regulator	Binding to and subsequent inactivation of the CDK inhibitor p27	*(92)*
Cyclins A, E	Cell cycle regulators	Regulation of cell cycle binding through pRb, p107, respectively	*(93) (94)*
AP1	Transcription	Interaction with and transactivation of the AP1 family	*(95)*
TBP	Transcription	Deregulation of the TBP mediated transcription	*(96)*
MPP2	Transcription	Activation of MPP2-specific transcriptional activity	*(97)*
HDAC (Mi2b)	Deacetylation	Disruption of pRb–HDAC complex	*(7)*
IRF1	Interferon regulation	Abrogation of transactivation function of IRF1	*(98)*
IGFBP-3	Cell growth	Inactivation of IGFBP-3 contribute to cell transformation	*(99)*
E2F6	Transcriptional repressor	Inactivation of E2F6 leading to extended S-phase of cell cycle	*(100)*
KDM6A, KDM6B	Demethylaton	Demethylaton of promoters of genes for pRb and $p16^{INK4A}$, respectively	*(60)*
Skip	Transcription	Inhibition of Skip function contribute to cell transformation	*(101)*
M2PK	Glycolytic phosphometabolism	Transforming cells by modulation of type M2 pyruvate kinase activity	*(102)*
GAA	Carbohydrate metabolism	Induces the catalytic activity of acid á-glucosidase	*(103)*
NHERF-1 (Na+/H+ exchange regulatory factor 1)	Cell signalling	NHERF-1 degradation that correlates with the activation of the phosphatidylinositol-3'-OH kinase (PI3K)/AKT signalling pathway	*(104)*
p48	Immune evasion	Down-regulation of IFN á-mediated signal transduction	*(105)*
p300, pCAF	Transcription	Abrogates p300 and pCAF associated HAT activity	*(62)*
SRC1	Steroid hormone signalling	Abrogates SRC1 associated HAT activity	*(61)*
p600	Regulator of anoikis	Inhibition of anoikis thereby protect from apoptosis	*(65)*

In addition, the HR HPV E7 binds histone deacetylase (HDAC) in a pRb-independent manner. HDAC binds to the zinc finger region of E7. This zinc finger region specifically binds Mi2b, a component of a HDAC complex, which finally disrupts the Rb–HDAC complex. Both Rb binding and Mi2b/HDAC binding are necessary for E7 to promote cell growth *(7)*.

Furthermore, the HR HPV E7 induces KDM6B and its transcriptional target, cervical carcinoma biomarker, $p16^{INK4A}$, the process is not dependent on pRb inactivation and hence, is not linked to E2F activation *(60)*. Because the HR HPV E7 simultaneously inactivates the critical mediator of $p16^{INK4A}$ induced senescence, pRb, HR HPV E7-expressing cells escape senescence and continue to proliferate, and several known KDM6A- or KDM6B-regulated HOX genes (Homeobox; master regulators of transcriptional programs that maintain cellular identities) are expressed at higher levels in such cells. Hence, the HR HPV E7 expression causes epigenetic reprogramming of host cells at the level of histone methylation *(60)*.

The E7 protein can also associate, directly or indirectly, with histone acetyl transferases (HATs) including p300, pCAF, and SRC1 (Steroid Receptor Coactivator 1; essential component of steroid hormone signalling) *(61) (62)*. It has been shown that HR HPV E7 abrogates SRC1 associated HAT activity *(61)*.

Some studies have suggested that E7 promotes telomere lengthening through the alternative lengthening of telomeres (ALT) pathway, which involves homologous recombination between telomere sister chromatids *(63)*. It is possible that the activation of ALT by E7 is important in maintaining telomere length early in cancer development. This would allow growth of cells that maintain a minimal level of telomerase activity, and is consistent with the notion that E6 plays a part in tumour progression by primarily promoting telomerase activity in high-grade cervical lesions and carcinomas *(3)*.

The p600 protein is a regulator of process of anoikis, a form of apoptosis that is induced by inadequate or inappropriate cell-matrix interactions *(64)*. The HR and LR HPV E7 proteins associate with pRb-associated protein p600 *(65)* results in anoikis resistance in different cell types. Thus, the interaction between E7 and p600 inhibit anoikis and protect detached cells from apoptosis, thereby contributing to viral transformation *(65) (66)*.

The HR HPV E7 expression also causes mitotic abnormalities including chromosomal fusions caused by double stand DNA breaks *(67)*. The presence of DNA repair foci seen in the HR HPV E7 expressing cells indicates that E7 may induce double strand DNA breaks or interfere with break repair. This facilitates viral genome integration, which pointed out E7 as a driving force for the genome integration of HR HPV types into host cellular chromosomes, event that frequently accompanies malignant progression of HR HPV associated lesions *(4)*. In addition to centrosome abnormalities, the E6 and the E7 proteins have been shown to independently bypass mitotic checkpoints, resulting in the accumulation of polyploid cells that can lead to aneuploidy. Abrogation of these checkpoints may be important for viral replication but can also lead to genomic instability in HPV-immortalized cells *(3)*.

E5 ONCOPROTEIN

The E5 oncoprotein is the least studied of the papillomavirus oncoproteins. This very small protein of only 83 amino acids *(68)* is not well conserved among different papillomaviruses *(69)*. It is the major oncoprotein of the bovine papillomaviruses and in human papillomaviruses acts as a supplementary oncoprotein. The protein is highly hydrophobic and associates with the Golgi apparatus endoplasmic reticulum and nuclear membrane *(70)*.

All known functions of the E5 oncoprotein were most recently reviewed by Venute et al. *(71)*. Briefly, E5 is known to reduce the expression of surface HLA molecules leading to improved immune evasion *(72)*. This is mediated by a direct interaction of HLA molecules and E5 proteins, which leads to MHC accumulation in Golgi and reduction on the surface *(73)*. Furthermore E5 interacts directly with Bap31 protein *(74)* that is also involved in vesicular trafficking and MHC molecule delivery to the cell surface *(75)*. Another mechanism of the E5 immune evasion is the over expression of gangliosides on the cell surface, which prevents immunological recognition by T-cells *(76)*. The E5 protein was also found to induce the degradation of Bax and thus have an anti-apoptotic role in viral infection *(77)*

The HR HPV E5 was shown to interact with the 16 kD unit of vacuolar ATPase *(78)* and that this interaction prevents vacuolar acidification, which is supposed to allow better EGF receptor recycling and influence growth factor response and signalling *(79)*. On the other hand BVP1 E5 was shown to directly bind PDGF receptor and activate it without any ligand present *(80)*.

CONCLUSION

The two most important interactions of HR HPV E6 and E7 oncoproteins leading to cell transformation and immortalisation are the binding and degradation of the major tumor-suppressors p53 and pRb, respectively. In addition to many other herein described protein-protein interactions of E6 and E7 oncoproteins, HPV was also found to modulate several important cell signalling pathways such as: mTORC signalling *(81)*, WNT signalling *(82)*, TGF-beta signalling *(83)*, HER/PTEN/Akt pathway *(84)*, ERK-MAP pathway *(85)*, ATM DNA Damage pathway *(86)*, NOTCH-1 signalling *(87)*, WNT signalling *(88)*, TGF-β signalling *(88)*, calcium signalling *(88)*, MAPK signalling *(88)* and insulin signalling *(89)*. This list of protein-protein interactions is probably not complete and future research will probably reveal new pathway targets and enable better understanding of HPV-mediated carcinogenesis.

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