Virology 445 (2013) 138–168

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

The papillomavirus E7 proteins

Ann Roman [a,b,*], Karl Munger [c,**]

[a] Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
[b] Department of Microbiology, University of Washington, Seattle, WA 98105 USA
[c] Division of Infectious Diseases, Brigham and Women's Hospital, Department of Medicine, Harvard Medical School, Boston, MA 02115, USA

ARTICLE INFO

Available online 31 May 2013

Keywords:
Viral life cycle
Regulation of transcription
Regulation of cell cycle checkpoints
Transformation
Viral oncology
Cervical cancer

ABSTRACT

E7 is an accessory protein that is not encoded by all papillomaviruses. The E7 amino terminus contains two regions of similarity to conserved regions 1 and 2 of the adenovirus E1A protein, which are also conserved in the simian vacuolating virus 40 large tumor antigen. The E7 carboxyl terminus consists of a zinc-binding motif, which is related to similar motifs in E6 proteins. E7 proteins play a central role in the human papillomavirus life cycle, reprogramming the cellular environment to be conducive to viral replication. E7 proteins encoded by the cancer-associated alpha human papillomaviruses have potent transforming activities, which together with E6, are necessary but not sufficient to render their host squamous epithelial cell tumorigenic. This article strives to provide a comprehensive summary of the published research studies on human papillomavirus E7 proteins.

Introduction

Unlike most review articles that are written from a particular perspective and evaluate the literature accordingly, this article lists and summarizes many of the countless research papers that have been published over the years focused on biochemical properties and biological activities of human papillomavirus (HPV) E7 proteins. The intent is to be comprehensive and to present information as unbiased as possible, rather than providing a critical assessment and synthesis of this literature. A number of excellent and comprehensive reviews on E7 have been published (Ghittoni et al., 2010; Klingelhutz and Roman, 2012; McLaughlin-Drubin et al., 2012; McLaughlin-Drubin and Munger, 2009; Moody and Laimins, 2010; Pim and Banks, 2010; Wise-Draper and Wells, 2008) and this article is to complement these reviews by providing unfiltered and undigested information. The goal is to empower investigators to connect to the primary literature so that they can apply their own filters and criteria to assess the "credibility" of the information in question. To maximize accessibility of the information, most of the information is organized and presented as tables.

The quality and usefulness of future versions of this article depends upon crowdsourcing: missing or misinterpreted information should be brought to the authors' attention and will be corrected in revised versions of these tables and/or updated version of this article. The most effective and efficient way to communicate changes will be to prepare a Table or Figure in the same format as used here and send it as an attachment to E7PAVEreview@gmail.com.

The HPVs are divided into genera (e.g., alpha, beta, mu, and gamma), species (groupings of types within a genus) and types based on amino acid identity, with types being the most closely related (de Villiers et al., 2004). The alpha papillomaviruses cause mucosal and cutaneous disease while the beta, mu and gamma papillomaviruses cause cutaneous disease. Additionally, the alpha genus is divided into low-risk and high-risk types based on outcome of infection, with the former causing benign papillomas and the latter lesions that can progress to carcinomas (zur Hausen, 2002). This review is a compendium of the biochemical and biological activities of E7 proteins encoded by high-risk alpha papillomavirus types (HPV16 and 31 in genus 9; HPV18 in genus 7), the low-risk alpha papillomavirus types (HPV6 and 11 in genus 10); the beta types (HPV5, 8 and 20 in genus 1; HPV38 in genus 2; HPV49 in genus 3); a mu type (HPV1); and gamma types (HPV4 in genus 1 and HPV108 in genus 6).

Human papillomavirus E7 proteins

Amino acid sequences

HPV E7 proteins consist of approximately 100 amino acid residues. There are no cellular proteins that share extensive sequence similarities to E7, even though some E7 sequence motifs, most notably the LXCXE sequence, are also found in cellular

* Correspondence to: 1100 Fairview Avenue North, Mail Stop C1-015, Seattle, WA 98109, USA. Fax: +1 206 667 5815.
** Correspondence to: 181 Longwood Avenue, MCP 861, Boston, MA 02215,. Fax: 1 617 525 4283.
E-mail addresses: aroman@fhcrc.org (A. Roman), kmunger@rics.bwh.harvard.edu (K. Munger).

0042-6822/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.virol.2013.04.013

proteins (Defeo-Jones et al., 1991). The amino terminus contains two regions of sequence similarity to the adenovirus (Ad) E1A proteins. Relative to Ad E1A, these E7 sequences correspond to a small portion of conserved region (CR) 1 and nearly the entire CR2 (Phelps et al., 1988). This sequence similarity extends to the simian vacuolating virus 40 large tumor antigen (SV40 T) (Fig. 1) (Figge and Smith, 1988) and provided a mechanistic explanation for the functional similarities between Ad E1A and HPV16 E7 that were discovered early on (Matlashewski et al., 1987; Phelps et al., 1988).

The CR1 and CR2 homology domains are conserved between different HPV E7 proteins and are separated by a non-conserved sequence of variable size and amino acid composition. The CR2 domain is followed by a second poorly conserved sequence followed by the conserved carboxyl terminal zinc-binding site, which consists of two CXXC domains separated by 29 to 30 amino acid residues (Barbosa et al., 1989; McIntyre et al., 1993) (Fig. 1).

Papillomavirus E6 proteins contain two copies of a similar zinc-binding motif. The HPV16 E7 C-terminal domain can be replaced with the zinc-binding domain derived from E6 without apparent loss of function (Mavromatis et al., 1997). It has been suggested that E6 and E7 might have evolved from a common ancestor (Cole and Danos, 1987; Van Doorslaer et al., 2009). Consistent with such a model, some papillomaviruses encode E7 but no E6 proteins (Ahola et al., 1986; Chen et al., 2007; Nobre et al., 2009) whereas other papillomaviruses encode E6 but no E7 proteins (Gottschling et al., 2011; Stevens et al., 2008a, 2008b). In some cases E7 proteins contain functional domains that in other papillomaviruses are encoded by the E6 proteins. The Rhesus monkey papillomavirus 1 (MmPV1), which causes anogenital tract lesions similar to alpha HPVs, for example, encodes an E7 protein with a C-terminal PDZ binding motif (XS/TXV), which is a hallmark of high-risk alpha HPV E6 proteins (Tomaic et al., 2009).

Some E7 proteins, including HPV16 E7 migrate slower on SDS polyacrylamide gels than predicted from their molecular mass. This is attributed to the high content of acidic amino acid residues, particularly within the CR1 and CR2 homology domains (Armstrong and Roman, 1992, 1993; Heck et al., 1992; Munger et al., 1991). Neutralization of the negative charges by chemical modification of free carboxyl groups by 1-Ethyl-3-[3-dimethyl-aminopropyl]carbodiimide (EDC) restored electrophoretic migration of HPV16 E7 to the predicted molecular mass (Armstrong and Roman, 1993). In addition, the commonly used protease inhibitors, tosyl-L-lysine chloromethyl ketone (TLCK) and tosyl-L-phenylalanine chloromethyl ketone (TPCK), can chemically modify the conserved cysteine residue in the E7 CR2 homology domain (cysteine at residue 24, C24, in HPV16) causing slower migration on SDS polyacrylamide gels (Stoppler et al., 1996).

Excellent antibodies exist for detection of untagged HPV16 E7: the ED17 antibody recognizes an epitope near the LXCXE domain and will not detect a deletion of residues 21–24 (del 21–24) whereas the 8C9 antibody recognizes an epitope in the CR1 homology domain and will not detect the del 6–10 mutant (Psyrri et al., 2004). In addition, epitope tagging has been widely used. Amino-terminal tagging of HPV16 E7 can affect E7 stability and binding to cellular proteins such as p600 (UBR4) and such tagged forms can be transformation defective (Huh et al., 2005;

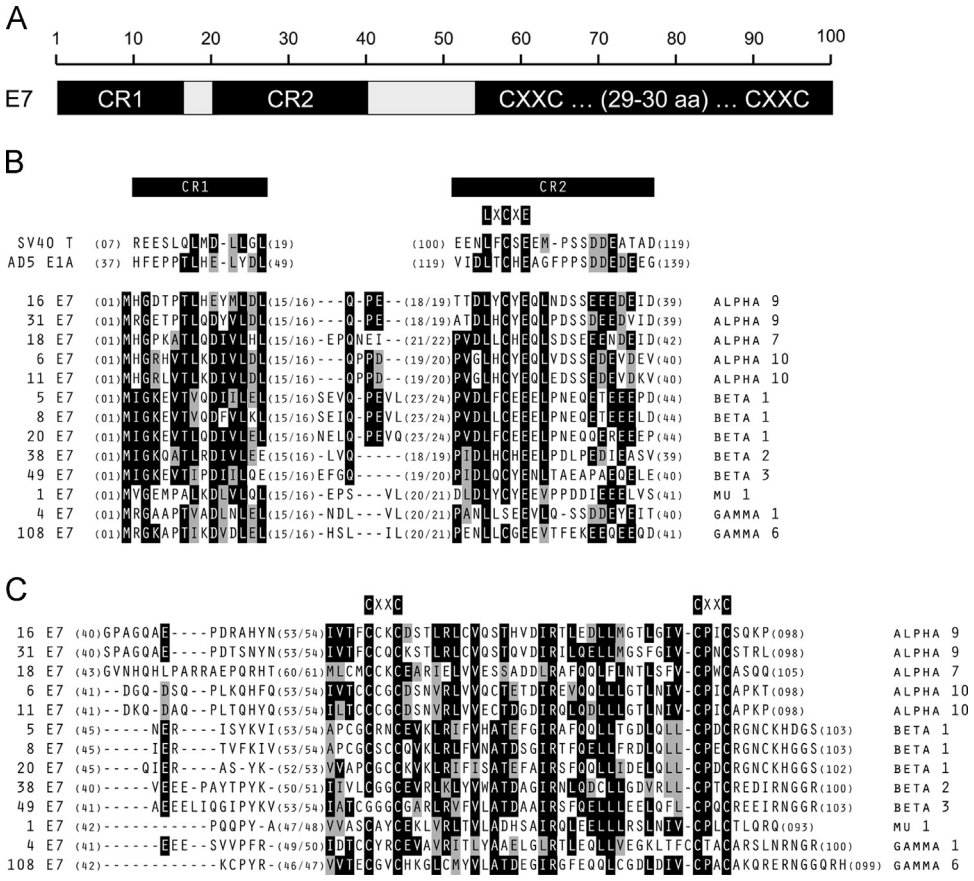

Fig. 1. Sequence alignment of various HPV E7 proteins. (A) Schematic representation of the conserved sequence elements in a generic E7 protein. Conserved regions (CR) are shown as black boxes, variable sequences are shown in gray. (B) The HPV E7 amino terminus contains two sequence elements that are similar to CR1 and CR2 of the adenovirus type 5 E1A protein (Ad5 E1A) and related sequences in the simian vacuolating virus 40 large tumor antigen (SV40 T). The position of the highly conserved LXCXE motif in CR2 is shown. (C) The HPV E7 C-terminus contains two CXXC motifs that form a zinc-binding site. The one letter code for amino acid (aa) residues is used; X denotes any amino acid. Identical amino residues are highlighted by black boxes, amino acid residues with chemically similar side chains are marked with gray boxes. See text for details.

Reinstein et al., 2000). In contrast, fusing epitopes to the C-terminus does not appear to affect biological activity (Huh et al., 2005). On occasion, an estrogen receptor derived tag (ER) that allows for conditional activation of E7 has been added to the C-terminus (Genovese et al., 2008; Smith-McCune et al., 1999).

Subcellular localization

Felix Wettstein's group was the first to detect the HPV16 E7 protein in cervical carcinoma lines. They showed that HPV16 E7 localized to the soluble cytoplasmic fraction (Smotkin and Wettstein, 1987). Nuclear localization of E7 has also been reported (Greenfield et al., 1991; Guccione et al., 2002; Sato et al., 1989; Smith-McCune et al., 1999) and low-risk but not high-risk HPV E7 proteins can associate with PML bodies (Guccione et al., 2002). HPV16 E7 was also detected in the nucleolus (Zatsepina et al., 1997).

Consistent with nuclear and cytoplasmic E7 pools and activities, the HPV16 E7 protein contains nuclear localization as well as nuclear export sequences and can shuttle between the two cellular compartments (Knapp et al., 2009). It enters the nucleus through nuclear pores using a RAN dependent pathway that does not depend on classical karyopherins. Nuclear import is independent of retinoblastoma tumor suppressor protein (pRB) binding but the nuclear localization sequence has not been identified (Angeline et al., 2003). The HPV16 E7 nuclear export sequence has been mapped to amino acid residues 76–84, which are well conserved in HPV E7 proteins (Fig. 1) (Knapp et al., 2009). RAN dependent, karyopherin independent nuclear import has also been reported for HPV11 E7 and the C-terminal zinc-binding domain was necessary for nuclear transport (Piccioli et al., 2010).

Post-translational modifications

Phosphorylation

Early studies indicated that HPV16 is heavily phosphorylated on serine residues (Smotkin and Wettstein, 1987). The HPV16 E7 protein contains a consensus phosphorylation site for casein kinase II (CKII; EC 2.7.11.1) in the CR2 homology domain (Barbosa et al., 1990; Firzlaff et al., 1989). This motif is conserved in SV40 T and Ad E1A CR2 domains as well as in other alpha HPV E7 proteins (Fig. 1) and some cellular LXCXE domain containing proteins (Defeo-Jones et al., 1991). CKII phosphorylation was reported two times faster for HPV18 E7 than HPV16 E7, which in turn was two times faster than HPV6 E7 (Barbosa et al., 1990).

A complex of macrophage-inhibitory related factor protein (MRP) 8 and 14 functions as a CKII inhibitor and causes decreased CKII HPV16 E7 phosphorylation. MRP 8/14 levels were detectable in normal but not in HPV immortalized human keratinocytes with a concomitant four fold increase in CKII activity in HPV immortalized cells (Tugizov et al., 2005).

S-phase-specific phosphorylation of Serine 71 in the HPV16 E7 C-terminal domain has also been described but the kinase is unknown (Massimi and Banks, 2000). Although HPV16 E7 carrying a mutation at this site has been tested for altered biological activity, thus far only one assay has detected loss of function (see Table 9).

The HPV6 E7 protein can be in vitro phosphorylated by protein kinase C (PKC; EC 2.7.11.13) on threonine 7 in the CR1 homology domain. Even though this residue is well conserved amongst many HPV E7 proteins, the PKC recognition sequence [$(R/K_{1-3}/X_{2-0})$-S/T-$(X_{2-0}/R/K_{1-3})$] is not conserved and the high-risk HPV16 E7 is not PKC phosphorylated under similar experimental conditions (Armstrong and Roman, 1995). However, phosphorylation of HPV16 E7 at threonine residues 5 and 7 by dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A; EC 2.7.12.1) has been described and linked to increased E7 stability and transforming activity (Liang et al., 2008).

Ubiquitination

HPV16 E7 has a short half-life of less than 1 h (Smotkin and Wettstein, 1987) and is degraded by the proteasome. A lysine-less HPV16 E7 mutant was efficiently degraded through a ubiquitin dependent mechanism, suggesting that HPV16 E7 can be amino terminally ubiquitinated followed by proteasomal degradation (Reinstein et al., 2000). Ubiquitination of the HPV16 E7 protein by Ubch7 (UBE2L3) and a Cullin 1/Skp2-containing E3 ubiquitin ligase has also been described (Oh et al., 2004a). Amino terminal ubiquitination and proteasomal degradation has also been documented for HPV58 E7, which contains no lysine residues (Ben-Saadon et al., 2004). Studies with estrogen-receptor (ER) fused HPV E7 proteins showed that low-risk HPV6 and 11 E7 proteins are also ubiquitinated but have a somewhat longer metabolic half-life than similarly tagged high-risk HPV16 and 18 E7 proteins. Non-conserved HPV11 E7 lysine residues 39 and 43 were identified as targets for ubiquitin modification but their mutation to arginine residues caused decreased protein stability demonstrating that ubiquitin modification of these residues is not essential for rapid proteasomal degradation (Genovese et al., 2011).

Other modifications

HPV E7 proteins have been reported to associate with transglutaminase 2 (TGM2; EC 2.3.2.13). HPV18 E7, but not HPV16 E7, is polyaminated at glutamine residues 87 or 88 in the C-terminal domain. HPV18 E7 polyamination interferes with pRB binding and functional inactivation (Jeon et al., 2003).

Evidence for additional post-translational modification of HPV16 E7 is provided by the detection of three isoforms designated as E7a1 (17.5 kDa, IEP 4.68), E7a (17 kDa, IEP 6.18) and E7b (16 kDa, IEP 6.96). These isoforms show differential localization to the nuclear and cytoplasmic compartments (Valdovinos-Torres et al., 2008).

HPV E7 structures

Early glycerol gradient sedimentation studies with HPV16 E7 expressed in cervical cancer lines provided evidence that HPV16 E7 was present in macromolecular complexes (Smotkin and Wettstein, 1987). HPV16 E7 forms a very stable extended structure (Alonso et al., 2002) even though the amino terminal CR1/CR2 homology sequences represent an intrinsically disordered domain (Garcia-Alai et al., 2007). E7 dimerization through the C-terminal zinc-binding domain was observed when the protein was expressed in *Escherichia coli* (McIntyre et al., 1993) or *Saccharomyces cerevisiae* (Clemens et al., 1995; Todorovic et al., 2011). Detailed studies with purified recombinant HPV16 E7 showed that E7 can form tetramers (Clements et al., 2000) and higher order oligomers (Alonso et al., 2004), which may have chaperone activity (Alonso et al., 2006), although the dimeric form was predicted to be prevalent at physiological E7 concentrations (Clements et al., 2000). Multimerization does not inhibit pRB binding (Alonso et al., 2006; Clements et al., 2000). Metal substitution studies with the E7 C-terminal zinc-binding domain provided evidence for a compact, highly shielded zinc-thiolate complex as evidenced by luminescence of the Cu(I)–E7 derivative (Roth et al., 1992) similar to that observed with Cu(I)-metallothioneins (Beltramini et al., 1989).

Three-dimensional structures of the zinc-binding C-terminal domains of HPV1 and HPV45 E7 have been reported (Liu et al., 2006; Ohlenschlager et al., 2006). The structure of the C-terminal HPV1 E7 domain encompasses amino acids 44–93 and was solved by X-ray crystallography. It forms a dimer with a unique zinc-

Table 1
Biological activities of alpha HPV E7.

Biological process	High-risk HPV E7 (HPV16, 18, or 31)	Low-risk HPV E7 (HPV6 or 11)	References
Viral replication			
Maintains extrachromosomal HPV genomes	+ (HPV31 only)	+	Flores et al. (2000), McLaughlin-Drubin et al. (2005), Oh et al. (2004b), Thomas et al. (1999)
Amplifies HPV genomes	+	ND	Flores et al. (2000) and McLaughlin-Drubin et al. (2005)
Transformation			
Transforms permanent rodent cells	+	−	Banks et al. (1990), Barbosa et al. (1990), Edmonds and Vousden (1989), Phelps et al. (1988), Vousden et al. (1988), Watanabe et al. (1990), Watanabe et al. (1992)
Transforms primary rodent cells in cooperation with RAS	+	−	Banks et al. (1990), Chesters et al. (1990), Firzlaff et al. (1991), Jewers et al. (1992), Massimi et al. (2008), Phelps et al. (1988), Storey et al. (1990b)
Immortalizes primary human epithelial cells (often, but not always, in cooperation with E6)	+	<	Halbert et al. (1991, 1992), Jewers et al. (1992), Melillo et al. (1994), Munger et al. (1989a), Sedman et al. (1991), Wazer et al. (1995)
G1/S control			
Induces DNA synthesis	+	+	Banks et al. (1990), Morris et al. (1993), Watanabe et al. (1992)
Induces PCNA in suprabasal cells	+	<	Cheng et al. (1995)
Induces cell DNA synthesis in suprabasal cells	+	<	Cheng et al. (1995), Chien et al. (2000), Collins et al. (2005), Flores et al. (2000), Genovese et al. (2008)
Bypasses growth arrest	+	−	Demers et al. (1996), Helt and Galloway (2001), Nguyen et al. (2002), Ruesch and Laimins (1997), and Schulze et al. (1998)
Abrogates $p27^{KIP1}$ inhibition of CDK2 activity	+	ND	Zerfass-Thome et al. (1996)
Mediates cyclin E/CDK2 phosphorylation of p107	+	ND	McIntyre et al. (1996)
Abrogates $p21^{CIP1}$ inhibition of CDK2 activity	+	<	Funk et al. (1997), Helt et al. (2002), Jones et al. (1997a)
Increases levels of $p21^{CIP1}$	+	−	Martin et al. (1998)
Abrogates C/EBPα-mediated growth arrest, independent of $p21^{CIP1}$	+	+	Muller et al. (1999)
Induces polα, and cyclin E in suprabasal cells	+	ND	Chien et al. (2000)
Abrogates $p16^{INK4A}$-mediated G1 arrest	+	ND	Giarre et al. (2001)
Abrogates RAF-induced growth arrest by AKT-mediated mislocalization of $p21^{CIP1}$	+	ND	Westbrook et al. (2002)
Activates CDK2 complexes	+	+	He et al. (2003)
Increases expression of E2F2	+	ND	Longworth et al. (2005)
Mislocalizes $p27^{KIP1}$ to the cytoplasm	+	ND	Charette and McCance (2007)
Abrogates Miz-1-mediated transcription of $p21^{CIP1}$	+	−	(Morandell et al. (2012)
Mitotic processes			
Abrogates mitotic spindle checkpoint	+	−	Thomas and Laimins (1998)
Causes multipolar mitoses/aberrant centrosome duplication	+	−	Duensing et al. (2000), Duensing and Munger (2003)
Induces tetrasomy	+	−	Southern et al. (2004), Southern et al. (2001)
Induces anaphase bridges	+	ND	Duensing and Munger (2002)
Decreases recruitment of γ-tubulin from cytoplasm to centrosomes	+	ND	Nguyen et al. (2007)
Disrupts NuMA/dynein network and induces prometaphase delay	+	+	Nguyen and Munger (2009)
Activates CHK2	+	ND	Moody and Laimins (2009)
Promotes mitotic entry	+	ND	Spardy et al. (2009)
Abrogates postmitotic checkpoint	+	ND	Heilman et al. (2009)
Upregulates PLK4 transcription	+	−	Korzeniewski et al. (2011)
Prolongs G2	+	ND	Banerjee et al. (2011)
Upregulates cytoplasmic cyclin B, hyperphosphorylates CDK1 and phosphorylates CDC25C in suprabasal cells (induces prolonged G2 phase in suprabasal cells)	+	+ (only cyclin B analyzed	Banerjee et al. (2011)
Engages mitotic spindle checkpoint	+	ND	Yu and Munger (2012)
Upregulates CDT1	+	ND	Fan et al. (2013)
Cell death/survival			
Induces cell death in response to confluence and/or serum deprivation	+	ND	Jones et al. (1997b)
Abrogates IGFBP-3-mediated apoptosis	+	ND	Mannhardt et al. (2000)
Activates PKB/AKT	+	+	Menges et al. (2006), Pim et al. (2005)
Abrogates Siva-1 mediated apoptosis	+	ND	Severino et al. (2007)
Disrupts Siva-1: Bcl-X_L complex formation	+	ND	Severino et al. (2007)
Activates calpain	+	ND	Darnell et al. (2007)
Activates caspase 3 and 7 in differentiated cells	+	+	Moody et al. (2007)
Abrogates apoptosis through maintenance of activated GSTP1	+	ND	Mileo et al. (2009)
Induces autophagy in HFKs in response to metabolic stress	+	ND	Zhou and Munger (2009)

Table 1 (*continued*)

Biological process	High-risk HPV E7 (HPV16, 18, or 31)	Low-risk HPV E7 (HPV6 or 11)	References
DNA damage/repair			
Induces double strand DNA breaks	+		Duensing and Munger (2002)
Activates the FA pathway	+	−	Spardy et al. (2007)
Differentiation/senescence			
Delays differentiation	+	+	Collins et al. (2005), Flores et al. (2000), Jones et al. (1997a), Zhang et al. (2006)
Abrogates pRB-induced flat cell morphology	+	ND	Brehm et al. (1999), Gonzalez et al. (2001), Helt and Galloway (2001)
Enhances C/EBPα-mediated differentiation	+	ND	Muller et al. (1999)
Abrogates senescence	+	+ (PML-induced senescence	Bischof et al. (2005), DeFilippis et al. (2003), Psyrri et al. (2004), Wise-Draper et al. (2005)
Upregulates senescence inhibitor, DEK	+	−	Wise-Draper et al. (2005)
Metabolism			
Shifts the equilibrium of M2 pyruvate kinase (M2-PK) to the less active, dimeric form	+	ND	Zwerschke et al. (1999)
Activates allosteric acid α-glucosidase	+	ND	Zwerschke et al. (2000)
Increases intracellular alkalinization potentially due to increased activity of the Na^+/H^+ exchanger protein	+	ND	Reshkin et al. (2000)
Cytokine modulation			
Abrogates TGF-β-mediated repression of the c-myc promoter	+	ND	Pietenpol et al. (1990)
Abrogates TGF-β-mediated growth arrest	+	ND	Lee et al. (2002b), Pietenpol et al. (1990)
Disrupts the formation of the ISGF3 (STAT1, STAT2, IRF-9) complex	+	ND	Barnard and McMillan (1999)
Inhibits cellular response to IFN-α	+	+	Barnard et al. (2000)
Abrogates IRF-1-mediated transactivation	+	+	Park et al. (2000), Perea et al. (2000)
Inhibits TNFα-mediated cell cycle arrest	+	ND	Basile et al. (2001), Boccardo et al. (2010)
Inhibits TNFα-mediated epithelial differentiation	+	ND	Basile et al. (2001)
Inhibits TNFα-induced apoptosis when protein synthesis is inhibited	+	ND	Basile et al. (2001), Thompson et al. (2001)
Inhibits TRAIL-induced apoptosis when protein synthesis is inhibited	+	ND	Basile et al. (2001)
Suppresses STAT-1	+	−	Hong et al. (2011), Thomas et al. (2001)
Abrogates TGF-β-mediated activation of a SMAD-responsive promoter	+	+	Habig et al. (2006), Lee et al. (2002b)
Inhibits TNFα-induced NFκB activity	+	ND	Spitkovsky et al. (2002) Vandermark et al. (2012)
Increases expression of VEGF and IL-8	+	ND	Walker et al. (2011)
Protein stability			
Increases steady state level of p53			Demers et al. (1994b), Jones et al. (1997b), Seavey et al. (1999)
Destabilizes pRB	+	−	Berezutskaya et al. (1997), Boyer et al. (1996) Demers et al. (1994a), Jones and Munger (1997)
Destabilizes p107	+	−	Gonzalez et al. (2001), Helt and Galloway (2001) Jones and Munger (1997)
Stimulates S4A proteasome subunit ATPase activity	+	ND	Berezutskaya and Bagchi (1997)
Destabilizes p130	+	+	Genovese et al. (2008), Gonzalez et al. (2001), Helt and Galloway (2001), Zhang et al. (2006)
Targets IGFBP-3 for proteasomal degradation	+	ND	Santer et al. (2007)
Recruits pRB to a cullin 2 ubiquitin ligase complex that contains ZER1	+ (HPV16 only)	−	Huh et al. (2007), White et al. (2012)
Destabilizes claspin	+	ND	Spardy et al. (2009)
Targets NHERF-1 for E6-mediated degradation	+	ND	Accardi et al. (2011)
Stabilizes HIF-1α	+	ND	Bodily et al. (2011b)
Stabilizes cyclin B during mitosis	+	ND	Yu and Munger (2012)
Transcription			
Transactives AdE2 promoter through E2F	+	+	Edmonds and Vousden (1989), Firzlaff et al. (1991), Phelps et al. (1992), Storey et al. (1990b), and Watanabe et al. (1990)
Disrupts pRB but not p107 E2F complexes	+	ND	Arroyo et al. (1993), Chellappan et al. (1992), Huang et al. (1993), Wu et al. (1993), Zerfass et al. (1995)
Upregulates p107/E2F-responsive B-myb promoter	+	+	Armstrong and Roman (1997), Lam et al. (1994)
Enhances c-jun-mediated transactivation	+	ND	Antinore et al. (1996)
Activates the c-fos promoter	+	−	Morozov et al. (1997)
Upregulates cyclin E promoter/mRNA	+	ND	Martin et al. (1998), Vogt et al. (1999)
Induces $p14^{ARF}$	+	ND	Bates et al. (1998)
Stimulates M phase phosphoprotein 2 (MPP2)-mediated transcription	+	-	Luscher-Firzlaff et al. (1999)
Represses MHC I promoter	+	−	Georgopoulos et al. (2000), Li et al. (2009)
Represses TAP-1 and LMP-2 promoters	+HPV18 only	+HPV6; −HPV11	Georgopoulos et al. (2000), and Heller et al. (2011)
Abrogates Skip-mediated transcriptional transactivation	+	ND	Prathapam et al. (2001)
Activates E2F1-dependent, pRB-independent transcription	+	<	Hwang et al. (2002)

Table 1 (*continued*)

Biological process	High-risk HPV E7 (HPV16, 18, or 31)	Low-risk HPV E7 (HPV6 or 11)	References
Abrogates binding of SMAD to DNA	+	ND	Lee et al. (2002b)
Activates the p73 promoter	+	-	Brooks et al. (2002)
Upregulates the CDC25A promoter	+	ND	Nguyen et al. (2002)
Abrogates BRCA 1 inhibition of ER-α transcriptional activity	+	ND	Zhang et al. (2005)
Abrogates BRCA1 inhibition of E Box transcriptional activity	+	ND	Zhang et al. (2005)
Abrogates BRCA1 repression of hTERT	+	ND	Zhang et al. (2005)
Enhances c-myc dependent transcriptional transactivation	+	–	Wang et al. (2007)
Represses TLR9 promoter	+	ND	Hasan et al. (2007)
Abrogates E2F6 mediated transcriptional repression	+	+	McLaughlin-Drubin et al. (2008)
Induces the hTERT promoter	+	ND	Liu et al. (2008)
Upregulates Nucleophosmin	+	ND	McCloskey et al. (2010)
Activates HIF-1-mediated transcription	+	ND	Bodily et al. (2011b)
Co-activation, epigenetic control			
Abrogates BRG-1-mediated transcriptional repression of c-fos	+	ND	Lee et al. (2002a)
Abrogates p300 transcriptional co-activation function	+	<	Bernat et al. (2003)
Down-regulates steroid receptor coactivator 1 (SRC-1)-mediated transcription	+	+	Baldwin et al. (2006)
Relocalizes SRC-1 to the cytoplasm			
Abrogates FHL2 co-activation of beta-catenin and Fos/Jun -dependent promoters	+	ND	Campo-Fernandez et al. (2007)
Stimulates DNMT1 activity	+	ND	Burgers et al. (2007)
Decreases the number of E2F6-PcG complexes	+	ND	McLaughlin-Drubin et al. (2008)
Induces EZH2	+	+	Holland et al. (2008)
Upregulates SIRT1	+	ND	Allison et al. (2009)
Represses E-cadherin promoter through a DNMT-1-dependent mechanism	+	ND	Laurson et al. (2010)
Upregulates KDM6A/B	+	ND	McLaughlin-Drubin et al. (2011)
Induces $p16^{INK4A}$ expression through H3K27 demethylation	+	ND	McLaughlin-Drubin et al. (2011)
Modulation of cellular miR expression			
Downregulates miR-203	+	ND	Melar-New and Laimins (2010)
Induces miR-16-1	+	ND	Zheng and Wang (2011)
Other activities			
Increases levels of cyclin E throughout the cell cycle	+	ND	Martin et al. (1998)
Elevates levels of CDK activity	+	–	Martin et al. (1998)
Decreases polymerization of actin	+	ND	Rey et al. (2000)
Abrogates TAP-1-mediated ATP-dependent peptide transport into the ER	ND	+	Vambutas et al. (2001)
Induces membrane type 1 metalloproteinase and activation of MMP2	+	ND	Smola-Hess et al. (2005)
Inhibits NM23 expression/activities	+	ND	Mileo et al. (2006)
Enhances AKT-dependent HFK migration	+	ND	Charette and McCance (2007)
Upregulates MMP-9 activity	+	ND	Cardeal et al. (2012)

FA, Fanconi anemia; H3K27, lysine 27 on histone H3; HFK, primary human foreskin keratinocytes; miR, micro-RNA; ND, not done; and PcG, polycomb group complex.

binding fold that is not closely related to the E6 zinc-binding domain structure (Nomine et al., 2006). Many of the highly conserved amino acid residues in the C-terminal domain are surface exposed (Liu et al., 2006). The structure of the entire HPV45 E7 protein was solved by nuclear magnetic resonance spectroscopy (NMR). The amino terminal domain is unfolded and C-terminal zinc-binding domain is involved in dimer formation (Ohlenschlager et al., 2006). There is good general agreement between the two structures.

Biological activities of alpha HPV E7 proteins

Interest in the HPV E7 protein was driven by early observations that E6 and E7 were the only two high-risk alpha HPV genes that are consistently expressed in human cervical carcinoma derived cell lines. The high-risk alpha HPV E7 protein scored as the major transforming protein in "standard" rodent cell based transformation assays (morphological transformation of NIH3T3 mouse fibroblasts and, similar to Ad E1A, cooperation with RAS to transform primary baby rat kidney cells). The recognition that E7 shares two blocks of sequence similarity with CR1 and CR2 of Ad E1A provided the biochemical framework for many of the following studies into "adenovirus E1A-like activities" of HPV E7 proteins.

The various biological activities that have been reported for high-risk and low-risk alpha HPV E7 proteins are listed in Table 1. While we have endeavored to indicate when a particular biochemical or biological activity is true for only one HPV type, the reader should be aware that a "+" in a column does not necessarily indicate similar modes of action for different viruses. For example, while both HPV16 and 18 E7 destabilize pRB, the mechanisms must be different (White et al., 2012); and although both HPV16 E7 and HPV6 E7 destabilize p130, there appear to be distinct mechanisms (Barrow-Laing et al., 2010). The reader is reminded to consult the primary literature to evaluate the experimental data in this Table.

It is important to note that the oncogenic activities of the high-risk alpha HPV E7 proteins represent functions related to the viral life cycle and/or arise as a consequence of a specific replication strategy that these viruses have adopted to establish a long-term persistent infection and/or produce viral progeny. Although the papillomaviruses are thought to initially infect undifferentiated epithelial cells where the viral genome is maintained at a low copy number, the productive phase of the life cycle takes place in the differentiated compartment, where cells would have normally exited the cell cycle. Since papillomaviruses are small and do not encode enzymes required for replication, the viruses must hijack cellular pathways if the virus is to propagate. Viral life cycle phenotypes observed when E7 expression is disrupted in the context of the intact genome are listed in Table 2. The main function of the HPV E7 proteins is generally thought to be to retain differentiating cells in a DNA synthesis competent state. However, for at least some of the viruses, E7 is also required for maintenance of the viral genome in undifferentiated cells. As seen in Table 1, E7 affects many cellular processes, running the gamut from cell cycle entry to cell death that would be pertinent to completion of the virus cycle. As will be seen in subsequent tables, E7 accomplishes this through direct or indirect interactions with an ever-expanding number of proteins. The relevance of those interactions to the virus life cycle remains, in many cases, to be established.

Experimental analyses of the viral life cycle generally involve studies with monolayer human primary keratinocytes induced to differentiate by the addition of calcium or suspension in methylcellulose. Alternatively, in vitro engineered skin-like organotypic structures are produced by growing confluent keratinocytes at the air-liquid interface on an artificial dermis or a reconstituted dermis to form a structure that recapitulates key aspects of epithelial differentiation and allows for viral genome amplification, late gene expression and production of viral progeny in differentiated layers of the epithelium. An important caveat, however, is that these in vitro models for skin differentiation have a very limited life span, i.e. even in the organotypic cultures, the skin-like structure is formed but then rapidly disintegrates. Hence these experimental systems do not truly mimic the "steady state" maintenance of squamous epithelia with continuous asymmetric division of basal epithelial cells (a) to maintain the basal layer and (b) to produce a continuous supply of differentiating cells to replace the terminally differentiated, denucleated squames that are continuously shed. Hence potential biological activities of E7 that may be related to long-term persistent infection cannot be studied.

Association of HPV E7 with cellular and viral proteins

The biochemical basis of the transforming activities of HPV E7 proteins initially was enigmatic since E7 lacked sequence motifs characteristic of enzymes or DNA binding transcription factors. However the observed functional and amino acid sequence similarity to Ad E1A, also known to lack intrinsic enzymatic or specific DNA binding activities, suggested similarities in the mechanisms of action of these two classes of viral proteins (Phelps et al., 1988). The Harlow and Branton groups published intriguing studies revealing that Ad E1A associated with specific cellular proteins and some of these proteins associated through CR1 and CR2 sequences that were known to be essential for cellular transformation (Egan et al., 1988; Harlow et al., 1986). The identification of the 110kd protein interacting with Ad E1A through CR2 sequences as the retinoblastoma tumor suppressor gene product pRB, supported the concept that Ad E1A transforms cells through association with cellular proteins (Whyte et al., 1988). SV40 T (DeCaprio et al., 1988) and later the HPV16 E7 oncoprotein (Dyson et al., 1989) were also shown to associate with pRB through the conserved LXCXE sequence motif within CR2 (Fig. 1).

The similarities between HPV16 E7 and Ad E1A/SV40 T were further elucidated with the construction of chimeric proteins. The HPV16 E7 CR1 homology domain could functionally be replaced with the related Ad E1A or SV40 T domains (Brokaw et al., 1994). Interestingly, Ad E1A was able to functionally complement HPV16 E7 mutants in CR1 and CR2 and conversely HPV16 E7 was able to functionally complement a pRB binding defective CR2 Ad E1A mutant but was unable to complement a p300 binding defective Ad E1A mutant in CR1 (Davies and Vousden, 1992).

An early example of the functional significance of interaction of HPV16 E7 with pRB was the demonstration that an HPV16 E7 mutated in the CR2 pRB binding sequence could be complemented by E2F1 when cooperating with HPV16 E6 to immortalize HFKs; a mutation in either CR1 or the CR2 CKII site, could not be complemented (Melillo et al., 1994). The concept that Ad E1A, SV40 T and HPV16 E7 each exerts its biological activities through association with and functional reprogramming of host cellular regulatory proteins or protein complexes is now firmly established and a large number of cellular proteins have been reported to associate with HPV E7.

Table 3 lists these proteins together with the method that was originally used to discover a given interaction. There was no attempt to distinguish between direct and indirect interactions. Some proteins including E2F transcription factors and cyclin/cyclin-dependent kinase (cdk) complexes have been reported to interact both directly and indirectly with E7 and the criteria that different research groups use to classify a given interaction as "direct" or "indirect" are quite different. This table attempts to be comprehensive and unbiased. Readers will need to consult the primary literature to critically evaluate by their own criteria whether a given interaction may be biologically relevant or not.

In addition to the proteins listed in Table 3, a large number of other HPV E7-associated cellular proteins have been discovered by several groups who performed large-scale yeast two hybrid screens and/or characterized HPV E7-associated cellular protein complexes by immunoaffinity purification followed by mass

Table 2
Loss of E7 expression through insertion of a translation termination linker: effects on the viral life cycle.

HPV	Phenotype	References
HPV16	Retains ability to maintain extrachromosomal HPV genomes in undifferentiated NIKS cells	Flores et al. (2000)
	Fails to amplify viral DNA, induce unscheduled DNA synthesis, increase the level of expression of p53, $p21^{CIP1}$, and mdm2, disrupt differentiation and induce apoptosis in differentiated NIKS cells	Flores et al. (2000)
	Reduces expression of L1	Flores et al. (2000)
HPV18	Retains ability to maintain extrachromosomal HPV genomes	McLaughlin-Drubin et al. (2005)
	Fails to amplify HPV DNA and produce infectious virus	McLaughlin-Drubin et al. (2005)
HPV31	Retains ability to transiently replicate extrachromosomal HPV genomes	Thomas et al. (1999)
	Fails to stably maintain extrachromosomal HPV genomes	Thomas et al. (1999)
HPV11	Fails to stably maintain extrachromosomal HPV genomes	Oh et al. (2004b)

NIKS; spontaneously immortalized human foreskin keratinocytes (Allen-Hoffmann et al., 2000)

Table 3
Cellular Proteins Reported to be Associated with HPV E7.

Gene name	Original name	Entrez Gene #	Method	High risk	Low risk	References
	Actin filamentous (F-actin)		GST	+	ND	Rey et al. (2000)
ATM	ATM	472	Co-IP	HPV31	ND	Moody and Laimins (2009)
BRCA1	BRCA1	672	GST/Co-IP	+	ND	Zhang et al. (2005)
CAPN1	Mu-Calpain	823	Co-IP	+	ND	Darnell et al. (2007)
CCNA1	Cyclin A	8900	Peptide bdg, GST	+	ND	Dyson et al. (1992), McIntyre et al. (1996)
CCNE1	Cyclin E	898	GST	+	ND	McIntyre et al. (1996)
CDK2	CDK2	1017	E7 peptide bdg; GST	+	+	He et al. (2003), McIntyre et al. (1996), Nguyen and Munger (2008)
CDKN1A	$p21^{CIP1}$	1026	GST/Co-IP	+	< /−	Funk et al. (1997)
CDKN1B	$p27^{KIP1}$	1027	YTH	+	< (GST)	Zerfass-Thome et al. (1996)
CENPC	CENP-C1	1060	YTH	+	−	Yaginuma et al. (2012)
CHD4	Mi2	1108	GST, YTH,	+	ND	Brehm et al. (1999)
CHUK	IKK-α	1147	Co-IP	+	ND	Spitkovsky et al. (2002)
CUL1	Cullin 1	8454	GST	+	ND	Oh et al. (2004a)
CUL2	Cullin 2	8453	AP-MS	HPV16 only	−	Huh et al. (2007)
CUL3	Cullin 3	8452	AP-MS	+	+	White et al. (2012)
CSNK2	Casein kinase II		Kinase assay	+	<	Barbosa et al. (1990), Firzlaff et al. (1989)
DNAJA3	hTid-1	9093	YTH	+	<	Schilling et al. (1998)
DNMT1	DNMT1	1786	GST	+	ND	Burgers et al. (2007)
DYRK1A	DYRK1A	1859	Co-IP	+	ND	Liang et al. (2008)
E2F1	E2F1	1869	GST/ivT	+	<	Hwang et al. (2002)
E2F6	E2F6	1876	AP-MS	+	+	McLaughlin-Drubin et al. (2008)
ENC1	Enc1	8507	AP-MS	HPV18/45 only	−	White et al. (2012)
EP300	p300	2033	GST	+	<	Bernat et al. (2003)
FHL2	FHL2	2274	GST	+	ND	Campo-Fernandez et al. (2007)
FOXM1	MPP2	2305	YTH	+	ND	Luscher-Firzlaff et al. (1999)
GAA	Acid α-glucosidase	2548	YTH	+	ND	Zwerschke et al. (2000)
GSTP1	GSTP1	2950	GST	+	ND	Mileo et al. (2009)
HDAC1	HDAC1	3065	GST	+	ND	Brehm et al. (1999)
HDAC2	HDAC2	3066	GST	+	ND	Brehm et al. (1999)
HIF1A	HIF1α	3091	Co-IP	+	+	Bodily et al. (2011b)
HTRA1	HtrA1/Prss11	5654	Co-IP	+	ND	Clawson et al. (2008)
IGFBP3	IGFBP-3	3486	YTH	+	<	Mannhardt et al. (2000)
IKBKB	IKK-	3551	Co-IP	+	ND	Spitkovsky et al. (2002)
IRF1	IRF-1	3659	YTH	+	+	Park et al. (2000)
IRF9	p48	10379	GST	+	ND	Antonsson et al. (2006), Barnard and McMillan (1999)
JUN	c-jun	3725	GST; YTH	+	ND	Antinore et al. (1996)
KAT2B	pCAF	8850	YTH	+	+	Avvakumov et al. (2003), Huang and McCance (2002)
KCMF1	KCMF1	56888	AP-MS	+	+	White et al. (2012)
MYC	c-myc	4609	YTH	+	+	Wang et al. (2007)
NCOA1	SRC1	8648	Co-IP	+	+	Baldwin et al. (2006)
NME1	NM23-H1	4830	YTH	+	ND	Mileo et al. (2006)
NME2	NM23-H2	4831	YTH	+	ND	Mileo et al. (2006)
NUMA1	NuMA	4926	Co-IP, GST	+	<	Nguyen and Munger (2009)
PKM	M2-PK	5315	YTH	+	-	Zwerschke et al. (1999)
PML	PML	5371	GST	+	+	Bischof et al. (2005)
PPP2R1/PPP2CA	PP2A	5519/5515	GST/ivT	+	+	Pim et al. (2005)
PSMC1	S4, 26S proteasome	5700	YTH	+	ND	Berezutskaya and Bagchi (1997)
RAN	Ran	5901	GST	+	ND	Angeline et al. (2003), De Luca et al. (2003)
RB1	pRB	5925	Co-IP	+	<	Berezutskaya et al. (1997), Boyer et al. (1996), Dyson et al. (1989), Firzlaff et al. (1991), Helt and Galloway (2001), Jones and Munger (1997), Munger et al. (1989b)
RBL1	p107	5933	Peptide bdg	+	<	Dyson et al. (1992), Gonzalez et al. (2001), Helt and Galloway (2001), Zhang et al. (2006)
RBL2	p130	5934	Peptide bdg	+	<	Dyson et al. (1992), Helt and Galloway (2001), Zhang et al. (2006)
SIVA1	Siva-1	10572	YTH	+	ND	Severino et al. (2007)
SMAD1	SMAD-1	4086	GST	+	+ (HPV1, 8, 11)	Habig et al. (2006)
SMAD2	SMAD-2	4087	GST	+	+ (HPV1, 8, 11)	Habig et al. (2006)
SMAD3	SMAD-3	4088	GST	+	+ (HPV1, 8, 11)	Habig et al. (2006)
SMAD4	SMAD-4	4089	GST	+	+ (HPV1, 8, 11)	Habig et al. (2006)
SMARCA4	BRG-1	6597	GST	+	-	Lee et al. (2002a)
SNW1	Skip	22983	YTH	+	<	Prathapam et al. (2001)
TAF1C	TAF-110	9013	GST	+	ND	Mazzarelli et al. (1995)
TAP1	TAP1	6890	Co-IP	+	+	Vambutas et al. (2001)
TGM2	TGase2	7052	YTH/GST	+	+	Jeon et al. (2003)
TBP	TBP	6908	GST	+	+	Mazzarelli et al. (1995)
TUBG1	γ-tubulin	7283	Co-localization	+	ND	Nguyen et al. (2007)
UBR4	p600	23352	AP-MS	+	+	Huh et al. (2005)
ZBTB17	Miz-1	7709	YTH	+	+	Morandell et al. (2012)
ZER1	ZER1	10444	AP-MS	HPV16 only	−	White et al. (2012)

AP-MS, affinity purification/mass spectrometry; bdg, binding; Co-IP, Co-immunoprecipitation; GST, Co-affinity purification through association with a glutathione-*S*-transferase fusion protein; ivT, in vitro translation; YTH, yeast two-hybrid.

spectrometry. Multiple methods exist to filter such data and to identify "high-confidence interactors". These studies have been critically reviewed (White and Howley, 2013) and the primary data can be accessed in the form of supplementary tables with the respective publications (Rozenblatt-Rosen et al., 2012; White et al., 2012) and in Gulbahce et al., 2012 for the complete dataset of HPV16 E7 associated proteins in HeLa cells performed by Huh and colleagues (Huh et al., 2005). In the absence of further biological validation, these data are best viewed as "hypothesis-generating".

HPV E7 proteins have also been reported to associate with viral proteins. In addition to forming homodimers and higher order complexes (see the section entitled HPV E7 structures), HPV E7 proteins can associate with HPV E2 proteins (Gammoh et al., 2006; Wang et al., 2012) and the Adeno-Associated Virus (AAV) Rep78 protein (Hermonat et al., 2000).

Mutations and phenotypes of alpha HPV E7s

One of the advantages of working with viral proteins is that it is straightforward to perform mutational genotype/phenotype analyses. Several groups performed extensive mutagenic analyses on HPV16 E7 mostly targeting residues conserved between HPV E7, Ad E1A and/or SV40 T, highly conserved residues in high-risk HPV E7's and/or residues that were different in low-risk and high-risk HPV E7 proteins (Banks et al., 1990; Edmonds and Vousden, 1989; Phelps et al., 1992; Watanabe et al., 1990). A more recent large-scale mutagenic analysis of the C-terminal domain was inspired by the available 3 dimensional structure of E7 and targeted both predicted surface exposed and non-exposed residues (Todorovic et al., 2011).

An important caveat when interpreting phenotypes of E7 mutants concerns protein stability, conformation and localization. Very few studies have exhaustively addressed protein stability of the various mutants although many contemporary studies document steady state levels in a given assay. Concerns about stability and conformational alterations are somewhat ameliorated when a given mutant retains some E7 activity. As noted in the section entitled Amino acid sequences, studies with epitope tagged or other fusion proteins also have to be viewed with caution since fusing heterologous sequences to the E7 amino terminus can alter HPV16 E7 stability and function.

There is a further caveat when interpreting E7 mutant phenotypes. As will become clear in the subsequent tables, more than one protein binds to a particular amino acid sequence of E7. Therefore, it is not trivial to implicate a given protein as responsible for a specific function. Further experiments will be needed to establish the identity of the effector protein.

Mutations and phenotypes of high-risk alpha HPV E7 proteins

Tables 4–9 summarize biochemical (Tables 4, 6 and 8) and biological (Tables 5, 7 and 9) readouts, with high-risk alpha HPV E7 mutants in the CR1 homology domain (Tables 4 and 5), CR2 homology domain (Tables 6 and 7) and C-terminal zinc-binding domain (Tables 8 and 9), respectively. The location of the mutations is depicted in Figs. 2–4. The most comprehensive collection of mutations and their biochemical and biological studies exists for HPV16 E7. Therefore, studies with other high-risk alpha HPVs are listed when unique, informative mutants were tested or when results differ substantially from studies performed with HPV16 E7.

Mutations and phenotypes of high-risk alpha HPV E7 proteins

The low-risk HPV E7 proteins show generally no or decreased activity in most standard transformation assays. Hence these proteins were "natural transformation defective mutants". Thus, in addition to standard mutagenic analyses, which are summarized in Table 10 and Fig. 5, some investigators have constructed chimeric high-risk/low-risk E7 proteins. Studies with HPV6/HPV16 chimeric E7 proteins showed that the C-termini could be swapped without causing dramatic alterations in transforming activity and that the amino terminus, particularly the CR1 homology domain, contained sequences that accounted for the unusual electrophoretic migration of HPV16 E7 (see the section entitled Amino acid sequences) whereas the CR2 homology domain appears to determine pRB

Table 4
High-risk alpha HPV E7 CR1 mutants: biochemical properties.

HPV type	Phenotype	References
HPV16		
H2P	Retains binding to pRB or p107	Banks et al. (1990), Demers et al. (1996)
	Retains binding to TBP	Phillips and Vousden (1997)
	Retains binding to HDAC	Brehm et al. (1999)
	Retains binding to IGFBP-3	Mannhardt et al. (2000)
	Retains binding to Skip	Prathapam et al. (2001)
	Fails to block binding of pRB to E2F	Helt and Galloway (2001)
	Reduces binding to p300	Bernat et al. (2003)
	Fails to bind p600	Huh et al. (2005)
	Fails to bind cullin 2 complex	Huh et al. (2007)
	Retains binding to DNMT1	Burgers et al. (2007)
	Fails to bind to FHL2	Campo-Fernandez et al. (2007)
del 3–5 (GDT)	Retains binding to pRB	Brokaw et al. (1994)
del 6–8 (PTL)	Retains binding to pRB	Brokaw et al. (1994)
del 6–10 (PTLHE)	Retains binding to pRB or p107	Brokaw et al. (1994), Demers et al. (1996), Munger et al. (1989b), Phelps et al. (1992)
	Retains binding to S4 subunit of the proteasome	Berezutskaya and Bagchi (1997)
	Retains binding to $p21^{CIP1}$	Jones et al. (1997a)
	Retains binding to HDAC	Brehm et al. (1999)
	Retains binding to E2F/cyclin A complex	Arroyo et al. (1993)
	Very limited binding to IRF-1	Park et al. (2000)
	Fails to bind p600	Huh et al. (2005)
	Retains binding to E2F6	McLaughlin-Drubin et al. (2008)
	Retains binding to NuMA	Nguyen and Munger (2009)
del 9–11 (HEY)	Retains binding to pRB	Brokaw et al. (1994)
del 12–14 (MLD)	Retains binding to pRB	Brokaw et al. (1994)

binding efficiency and transformation (Heck et al., 1992; Munger et al., 1991; Pater et al., 1992). Such studies revealed that changing a conserved aspartate residue (D) in HPV16 E7 to a glycine (G) caused a dramatic decrease in pRB binding and transformation whereas mutation of the conserved corresponding G to a D converted HPV6 E7 into a transforming protein (Heck et al., 1992; Sang and Barbosa, 1992).

Chimeric HPV11/HPV16 E7 proteins were constructed to map key determinants of HPV16 E7 required to reduce major histocompatibility complex class I (MHC I) expression. Such studies showed that the C-terminus of HPV16 E7 was responsible for negatively regulating MHC I transcription. A more detailed analysis documented a critical role for amino acids 78, 80, and 88 in the HPV16 E7 C-terminal domain (Heller et al., 2011).

Table 5
High-risk alpha HPV E7 CR1 mutants: biological activities.

HPV type	Phenotype	References
HPV16		
H2D	Reduces transformation	Watanabe et al. (1990)
H2P	Reduces BRK immortalization, transformation	Banks et al. (1990)
	Retains ability to transactivate the B-myb promoter	Lam et al. (1994)
	Fails to bypass growth arrest induced by differentiation, DNA damage, growth in suspension, or TGF-β	Demers et al. (1996), Schulze et al. (1998)
	Fails to destabilize pRB, p107, p130	Helt and Galloway (2001), Jones and Munger (1997)
	Fails to increase Cyclin E levels	Martin et al. (1998)
	Fails to degrade IGFBP-3 and reduces ability to abrogate IGFBP-3-mediated apoptosis	Mannhardt et al. (2000)
	Fails to bypass pRB-induced quiescence in SAOS2 cells	Helt and Galloway (2001)
	Fails to extend HFK lifespan	
	Fails to induce tetrasomy in monolayer and raft cultures	Southern et al. (2004)
	Fails to inhibit TNF-α-induced growth arrest	Boccardo et al. (2010)
H2P in the context of the intact genome	Inefficient immortalization of HFKs	Bodily et al. (2011a)
	Viral genomes may be extrachromosomal or integrated	
	Retains ability to produce late transcripts	
	Loss of differentiation-dependent reduction of pRB	
del 3–5 (GDT)	Reduces ability to transform primary rodent cell in cooperation with RAS.	Brokaw et al. (1994)
	Retains ability to transactivate AdE2 promoter	
D4R	Increases electrophoretic mobility of E7 protein	Armstrong and Roman (1992)
T5T7/DD	Greatly reduces phosphorylation by DYRK1A	Liang et al. (2008)
	Enhances ability to promote cell proliferation	
del 6–8 (PTL)	Substantially reduces transformation of primary rodent cell in cooperation with RAS	Brokaw et al. (1994)
	Retains ability to transactivate AdE2 promoter	
del 6–10 (PTLHE)	Substantially reduces transformation	Brokaw et al. (1994), Phelps et al. (1992)
	Reduces transactivation of AdE2 promoter	
	Reduces ability to transactivate cAMP-dependent c-fos promoter	Morosov et al. (1994)
	Fails to bypass growth arrest induced by differentiation, DNA damage, or TGF-β	Demers et al. (1996)
	Fails to induce apoptosis in confluent or serum deprived cells	Jones et al. (1997b)
	Fails to stabilize p53	
	Fails to destabilize pRB	Berezutskaya et al. (1997), Jones et al. (1997b)
	Fails to increase Cyclin E levels	Martin et al. (1998)
	Retains ability to inhibit IFN-α activity	Barnard et al. (2000)
	Very limited ability to abrogate IRF-1-mediated transactivation	Park et al. (2000)
	Retains ability to block binding of pRB to E2F	Helt and Galloway (2001)
	Reduces ability to bypass pRB-induced flat SAOS2 phenotype	Gonzalez et al. (2001)
	Retains ability to induce abnormal centrosome duplication	Duensing and Munger (2003)
	Fails to transactivate the E2F	Psyrri et al. (2004)
	Fails to induce DNA synthesis in HPV E2	
	Fails to rescue HPV E2-expressing HeLa cells from senescence or apoptosis	
	Fails to induce tetraploidy in monolayer and raft cultures	Southern et al. (2004)
	Retains ability to abrogate E2F6-mediated transcriptional repression but fails to disrupt E2F6-polycomb complexes	McLaughlin-Drubin et al. (2008)
	Fails to inhibit TNF-α-induced growth arrest	Boccardo et al. (2010)
del 6–10 (PTLHE) in the context of the intact genome	Fails to delay HFK differentiation	Collins et al. (2005)
	Retains ability to maintain extrachromosomal copies of HPV genome in undifferentiated HFKs	
	Reduces ability to induce E2F-responsive MCM7 promoter in suprabasal cells	
	Reduces ability to induce cellular DNA synthesis in suprabasal cells	
del 9–11 (HEY)	Reduces ability to transform primary rodent cell in cooperation with RAS.	Brokaw et al. (1994)
	Retains ability to transactivate AdE2 promoter	
del 12–14 (MLD)	Substantially reduces ability to transform primary rodent cell in cooperation with RAS.	Brokaw et al. (1994)
	Reduces ability to transactivate AdE2 promoter	
HPV31		
H2P in the context of the intact genome	Retains ability to transiently replicate extrachromosomal copies of viral genomes	Thomas et al. (1999)
	Loses ability to maintain extrachromosomal copies of the viral genome	
HPV18		
H2P	Retains ability to mediate cyclin E/cdk2 phosphorylation of p107	McIntyre et al. (1996)

BRK, baby rat kidney cells; cAMP, cyclic AMP; HFK, primary human foreskin keratinocytes; SAOS2, pRB/p53 defective human osteosarcoma cell line (ATCC Number: HTB-85)

Table 6
High-risk HPV E7 CR2 mutants: biochemical activities.

HPV tpye	Phenotype	References
HPV16		
del 15–17 (LQP)	Retains binding to pRB	Brokaw et al. (1994)
del 18–20 (ETT)	Reduces binding to pRB	Brokaw et al. (1994)
D21G	Substantially reduces binding to pRB	Heck et al. (1992)
D21S	Retains binding to pRB or p107	Demers et al. (1996)
	Retains binding to TBP	Phillips and Vousden (1997)
del 21–24 (DLYC)	Fails to bind pRB and p107	Demers et al. (1996), Jones et al. (1997b), Munger et al. (1989b), Phelps et al. (1992)
	Fails to bind E2F/cyclin A complex	Arroyo et al. (1993)
	Retains binding to S4 subunit of the proteasome	Berezutskaya and Bagchi (1997)
	Retains binding to hTid-1	Schilling et al. (1998)
	Fails to bind IRF-1	Park et al. (2000)
	Retains binding to E2F1	Hwang et al. (2002)
	Retains binding to BRG-1	Lee et al. (2002a)
	Retains binding to p600	Huh et al. (2005)
	Retains binding to cullin 2 complex	Huh et al. (2007)
	Fails to binding γ-tubulin	Nguyen et al. (2007)
	Retains binding to CDK2 complexes in pRB family member knockout cells	Nguyen and Munger (2008)
	Reduces binding to CDK2 complexes in pRB family member proficient cells	
	Retains binding to E2F6	McLaughlin-Drubin et al. (2008)
	Retains binding to NuMA	Nguyen and Munger (2009)
	Fails to bind phosphorylated ATM	Moody and Laimins (2009)
C24G	Substantially reduces binding to pRB and p107	Demers et al. (1996)
	Retains binding to c-jun	Antinore et al. (1996)
	Reduces binding to TBP	Phillips and Vousden (1997)
	Retains binding to HDAC via Mi2β	Brehm et al. (1999)
	Retains binding to IGFBP-3	Mannhardt et al. (2000)
	Fails to bind acid α-glucosidase	Zwerschke et al. (2000)
	Retains binding to p107	Gonzalez et al. (2001)
	Retains binding to Skip	Prathapam et al. (2001)
	Substantially reduces binding to p300	Bernat et al. (2003)
	Retains binding to PML IV	Bischof et al. (2005)
	Retains binding to DNMT1	Burgers et al. (2007)
	Fails to bind γ-tubulin	Nguyen et al. (2007)
	Fails to bind FHL2	Campo-Fernandez et al. (2007)
	Retains binding to Miz-1	Morandell et al. (2012)
C24S	Substantially reduces binding to pRB	Munger et al. (1989b), Phelps et al. (1992)
	Retains binding to E2F/cyclin A complex	Arroyo et al. (1993)
E26G	Fails to bind E2F/cyclin A complex	Arroyo et al. (1993)
	Fails to bind pRB but retains binding to p107	Demers et al. (1996)
	Reduces binding to TBP	Phillips and Vousden (1997)
	Retains binding to γ-tubulin	Nguyen et al. (2007)
	Fails to bind HIF-1α	Bodily et al. (2011b)
E26Q	Substantially reduces binding to pRB	Munger et al. (1989b), Phelps et al. (1992)
	Retains binding to S4 subunit of the proteasome	Berezutskaya and Bagchi (1997)
N29D30/PP	Retains binding to pRB	Giarre et al. (2001)
D30EEEEDE33-37/QQQQQQ	Reduces binding to pRB	Firzlaff et al. (1991)
S31R	Reduces binding to pRB	Barbosa et al. (1990)
S31S32/AA	Fails to bind F-actin	Rey et al. (2000)
S31S32/RP	Minimally reduces binding to pRB	Barbosa et al. (1990), Firzlaff et al. (1991), Heck et al. (1992)
S31S32/CC		
S31S32/AA		
S31S32/DD		
S31S32/RP	Reduces binding to TBP	Phillips and Vousden (1997)
S31S32/AA		
S31S32/DD	Retains binding to HDAC	Brehm et al. (1999)
S31S32/RP	Reduces binding to TBP	Phillips and Vousden (1997)
	Fails to bind Skip	Prathapam et al. (2001)
	Reduces binding to p300	Bernat et al. (2003)
S31S32/GG	Reduces binding to pRB	Jones et al. (1997b)
del 31–32 (SS)	Retains binding to pRB	Phelps et al. (1992)
S32W	Minimally reduces binding to pRB	Barbosa et al. (1990)
E35D36/DH	Minimally reduces binding to pRB	Barbosa et al. (1990)
del 35–37 (EDE)	Retains binding to pRB	Munger et al. (1989b), Phelps et al. (1992)
	Retains binding to E2F/cyclin A complex	Arroyo et al. (1993)
	Retains binding to $p21^{CIP1}$	Jones et al. (1997a)
	Retains binding to S4 subunit of the proteasome	Berezutskaya and Bagchi (1997)
	Retains binding to hTid-1	Schilling et al. (1998)
	Retains binding to HDAC	Brehm et al. (1999)
	Retains binding to CDK2 complexes in pRB family member proficient or deficient cells	Nguyen and Munger (2008)
D36H	Retains binding to pRB	Demers et al. (1996)
HPV31		
del 22–26 (LHCYE)	Fails to bind pRB	Longworth and Laimins (2004)
	Retains binding to HDAC 1/2	
HPV18		
Point mutations in aa 25–32 (PxDLLCxE)	Fails to bind CENP-C	Yaginuma et al. (2012)
del 24–27 (DLLC);	Fails to bind pRB or p107	Chien et al. (2000)
C27S	Fails to bind pRB and retains binding to p107	Chien et al. (2000)
E35E36E37/QQQ	Retains binding to pRB and p107	Chien et al. (2000)

F-actin, filamentous actin.

Table 7
High-risk alpha HPV E7 CR2 mutants: biological activities.

HPV type	Phenotype	References
HPV16		
del 15–17 (LQP)	Substantially reduces transformation of primary rodent cell in cooperation with RAS	Brokaw et al. (1994)
	Reduces ability to transactivate AdE2 promoter	
del 18–20 (ETT)	Substantially reduces transformation of primary rodent cell in cooperation with RAS	Brokaw et al. (1994)
	Reduces ability to transactivate AdE2 promoter	
D21G	Substantially reduces transformation of primary rodent cell in cooperation with RAS	Heck et al. (1992)
D21S	Retains ability to transform permanent rodent cells	Edmonds and Vousden (1989)
	Retains ability to bypass growth arrest induced by differentiation, DNA damage, or TGF-β	Demers et al. (1996)
	Retains ability to inhibit TNF-α-induced growth arrest	Boccardo et al. (2010)
del 21–24 (DLYC)	Fails to abrogate TGF-β repression of c-myc promoter	Pietenpol et al. (1990)
	Substantially reduces ability to transactivate AdE2 promoter	Brokaw et al. (1994), Phelps et al. (1991, 1992),
	Substantially reduces transformation of primary rodent cell in cooperation with RAS	Brokaw et al. (1994), Phelps et al. (1992)
	Reduces ability to transactivate cAMP-dependent c-fos promoter	Morosov et al. (1994)
	Fails to bypass growth arrest induced by differentiation, DNA damage, or TGF-β	Demers et al. (1996), Helt and Galloway (2001)
	Fails to destabilize pRB, p107, p130	Helt and Galloway (2001), Jones et al. (1997b)
	Fails to stabilize p53	
	Fails to induce cell death in response to confluence or serum/growth factor deprivation	Jones et al. (1997b)
	Reduces ability to inhibit $p21^{CIP1}$	Jones et al. (1997a)
	Fails to increase cyclin E levels	Martin et al. (1998)
	Fails to induce abnormal centrosome duplication/centriole synthesis	Duensing et al. (2000), Duensing and Munger (2003), Korzeniewski et al. (2011)
	Fails to inhibit IFN-α activity	Barnard et al. (2000)
	Fails to abrogate IRF-1-mediated transactivation	Park et al. (2000)
	Fails to block binding of pRB to E2F	Helt and Galloway (2001)
	Fails to extend HFK lifespan	
	Fails to bypass pRB-induced flat SAOS2 phenotype	Gonzalez et al. (2001)
	Fails to abrogate TGF-β activation of SMAD-responsive promoter, bind SMADs and inhibit binding of SMADs to DNA	Lee et al. (2002b)
	Retains ability to activate E2F1-dependent, pRB-independent transcription	Hwang et al. (2002)
	Retains ability to abrogate BRG-1-mediated repression of the c-fos promoter and BRG-1-induced flat cell formation in SW13 cells	Lee et al. (2002a)
	Retains ability to be imported into the nucleus via a RAN-dependent pathway	Angeline et al. (2003)
	Fails to rescue E2-expressing HeLa cells from apoptosis or senescence	Psyrri et al. (2004)
	Fails to transactivate the E2F-responsive cyclin A promoter	
	Fails to induce DNA synthesis in HPV E2-expressing HeLa cells	
	Fails to induce tetrasomy in monolayer or raft cultures	Southern et al. (2004)
	Retains ability to abrogate E2F6-mediated transcriptional repression and disrupt E2F6-polycomb complexes	McLaughlin-Drubin et al. (2008)
	Fails to transactivate the E2F-responsive polycomb group EZH2 histone methyltransferase gene	Holland et al. (2008)
	Fails to increase expression of hTERT promoter	Liu et al. (2008)
	Fails to increase FANCD2-containing alternative lengthening of telomeres (ALT)-associated promyelocytic leukemia bodies (APBs)	Spardy et al. (2008)
	Retains disorganized metaphase phenotype (prometaphase delay)	Nguyen and Munger (2009)
	Fails to promote mitotic entry	Spardy et al. (2009)
	Fails to destabilize claspin	
	Fails to inhibit TNF-α-induced growth arrest	Boccardo et al. (2010)
	Retains ability to upregulate KDM6A/B histone H3 lysine 27-specific demethylases	McLaughlin-Drubin et al. (2011)
	Fails to increase PLK4 transcription	Korzeniewski et al. (2011)
	Fails to bind HIF-1α	Bodily et al. (2011b)
	Retains ability to increase HIF-1α-mediated transcription	
	Fails to inhibit cyclin B degradation	Yu and Munger (2012)
del 21–24 (DLYC) in the context of the intact genome	Fails to induce E2F-responsive MCM7 promoter in suprabasal cells	Collins et al. (2005)
	Fails to induce cellular DNA synthesis in suprabasal cells	
	Retains ability to maintain extrachromosomal copies of HPV genome in undifferentiated HFKs	
	Fails to delay HFK differentiation	
	Fails to immortalize HFKs	Bodily et al. (2011a)
C24G	Fails to transform permanent rodent cells	Barbosa et al. (1990), Edmonds and Vousden (1989), Watanabe et al. (1990)
	Substantially reduces ability to transactivate AdE2 promoter	Edmonds and Vousden (1989), Watanabe et al. (1990)
	Retains CKII phosphorylation	Barbosa et al. (1990)
	Fails to upregulate B-myb promoter	Lam et al. (1994)
	Not required for E7 nuclear localization	Fujikawa et al. (1994)
	Fails to bypass growth arrest induced by differentiation, serum starvation, DNA damage, or TGF-β	Demers et al. (1996), Nguyen et al. (2002)
	Retains ability to enhance c-jun-mediated transactivation	Antinore et al. (1996)

Table 7 (*continued*)

HPV type	Phenotype	References
	Fails to bypass growth arrest induced by differentiation, serum starvation, DNA damage, or TGF-β	Demers et al. (1996), Nguyen et al. (2002)
	Retains ability to enhance c-jun-mediated transactivation	Antinore et al. (1996)
	Fails to destabilize pRB but retains ability to destabilize p107	Gonzalez et al. (2001), Jones and Munger (1997)
	Fails to increase cyclin E levels	Martin et al. (1998)
	Retains ability to abrogate C/EBPα-mediated growth arrest and enhance C/EBPα-mediated differentiation	Muller et al. (1999)
	Fails to bypass pRB-induced flat SAOS2 phenotype	Brehm et al. (1999), Gonzalez et al. (2001)
	Retains ability to degrade IGFBP-3 and to abrogate IGFBP-3-mediated apoptosis	Mannhardt et al. (2000)
	Fails to activate acid α-glucosidase	Zwerschke et al. (2000)
	Fails to induce intracellular alkalinization	Reshkin et al. (2000)
	Fails to transactivate the p73 promoter	Brooks et al. (2002)
	Fails to abrogate RAF-induced growth arrest and relocalize $p21^{CIP1}$	Westbrook et al. (2002)
	Fails to upregulate CDC25A promoter	Nguyen et al. (2002)
	Fails to activate AKT in undifferentiated and differentiated HFKs	Menges et al. (2006), Westbrook et al. (2002)
	Reduces ability to abrogate p300-mediated HPV E2 transactivation	Bernat et al. (2003)
	Retains ability to induce abnormal centrosome duplication	Duensing and Munger (2003)
	Fails to increase acetylation of histone H3 on E2F-regulated promoters	Zhang et al. (2004)
	Retains ability to induce tetrasomy in monolayer and raft cultures	Southern et al. (2004)
	Fails to abrogate PML IV-mediated senescence	Bischof et al. (2005)
	Fails to disrupt PML IV:CBP-mediated p53 acetylation and p53-mediated transcription	
	Fails to bind HIF-1α	Bodily et al. (2011b)
	Retains ability to increase HIF-1α-mediated transcription	
	Retains inhibition of Miz-1-dependent $p21^{CIP1}$ transcription	Morandell et al. (2012)
C24G in the context of the intact genome	Reduces ability to immortalize HFKs	Jewers et al. (1992)
	Very inefficiently immortalizes HFKs	Bodily et al. (2011a)
	Causes reduced levels of viral transcripts in undifferentiated HFKs	
	Fails to produce late viral transcripts in differentiated HFKs	
	Fails to decrease pRB levels in differentiated cells	
	Fails to produce virus particles	
C24S	Fails to transform primary rodent cell in cooperation with RAS	Phelps et al. (1992)
	Substantially reduces ability to transactivate AdE2 promoter	
	Reduces ability to transactivate cAMP-dependent c-fos promoter	Morosov et al. (1994)
	Fails to degrade pRB	Berezutskaya et al. (1997)
E26G	Retains ability to upregulate B-myb promoter	Lam et al. (1994)
	Not required for E7 nuclear localization	Fujikawa et al. (1994)
	Fails to bypass growth arrest induced by differentiation, DNA damage, or TGF-β	Demers et al. (1996)
	Fails to increase cyclin E levels	Martin et al. (1998)
	Fails to destabilize pRB	Gonzalez et al. (2001)
	Retains ability to destabilize p107	
	Fails to bypass pRB-induced flat SAOS2 phenotype	
	Fails to transactivate the p73 promoter	Brooks et al. (2002)
	Retains ability to induce abnormal centrosome duplication	Duensing and Munger (2003)
	Fails to inhibit TNF-α-induced growth arrest	Boccardo et al. (2010)
	Retains ability to increase HIF-1α-mediated transcription	Bodily et al. (2011b)
E26G in the context of the intact genome	Retains ability to immortalize HFKs	Jewers et al. (1992)
	Fails to immortalize HFKs	Bodily et al. (2011a)
ND29/30PP	Fails to destabilize pRB	Giarre et al. (2001)
	Fails to abrogate $p16^{INK4A}$-mediated G1 arrest	Giarre et al. (2001)
S31G	Retains ability to transform primary rodent cells in cooperation with RAS	Storey et al. (1990a)
S31R	Reduces ability to transform established rodent cells	Edmonds and Vousden (1989)
S31S32/RP	Fails to induce S phase proteins in differentiated HFKs	Bodily et al. (2011a)
S31S32/AA		
S31S32/DD		
	Fails to be phosphorylated by CKII	Barbosa et al. (1990)
S31S32/AA	Reduces transformation of established rodent cells	Barbosa et al. (1990)
S31S32/DD	Fails to be phosphorylated by CKII	Firzlaff et al. (1991)
	Retains ability to transactivate the AdE2 promoter	Firzlaff et al. (1991)
	Fails to abrogate Skip-mediated transcriptional transactivation	Prathapam et al. (2001)
S31S32/AA	Reduces transformation of primary rodent cells in cooperation with RAS	Firzlaff et al. (1991), Heck et al. (1992)
	Fails to abrogate C/EBPα-mediated growth arrest and to enhance C/EBPα-mediated differentiation	Muller et al. (1999)
S31S32/GG	Reduces ability to bypass growth arrest induced by differentiation, DNA damage, or TGF-β	Demers et al. (1996)
	Reduces ability to destabilize pRB	Jones et al. (1997b)
	Reduces ability to stabilize p53	
	Reduces ability to induce cell death in response to confluence or serum deprivation	
	Reduces ability to transactivate the E2F	Psyrri et al. (2004)
	Reduces ability to induce DNA synthesis in HPV E2	
	Reduces ability to rescue E2-expressing HeLa cells from apoptosis or senescence	
	Fails to induce tetrasomy in monolayers but retains ability in raft cultures	Southern et al. (2004)
	Retains ability to immortalize HFKs	Bodily et al. (2011a)

Table 7 (*continued*)

HPV type	Phenotype	References
S31S32/AA or DD in the context of the intact genome	Reduces ability to produce viral particles but particles are infectious	
S31S32/RP in the context of the intact genome	Loses *cis* element required for late viral gene expression	Bodily et al. (2011a)
	Retains ability to support extrachromosomal replication of HPV genomes in monolayers	
	Reduces ability to produce viral particles but particles are infectious	
del 31–32	Retains ability to transform primary rodent cells in cooperation with RAS	Phelps et al. (1992)
S32A	Somewhat reduces transformation	Barbosa et al. (1990), Storey et al. (1990a)
E35D36/DH	Retains ability to transform rodent cells	Edmonds and Vousden (1989)
	Retains ability to be phosphorylated by CKII	Barbosa et al. (1990)
del 35–37 (EDE)	Retains ability to transform primary rodent cells in cooperation with RAS	Phelps et al. (1992)
	Substantially reduces CKII phosphorylation	
	Reduces ability to transactivate cAMP-dependent c-fos promoter	Morosov et al. (1994)
	Retains ability to degrade pRB	Berezutskaya et al. (1997)
D36H	Retains ability to bypass growth arrest induced by differentiation or TGF-β	Demers et al. (1996)
HPV31		
D21G in the context of the intact genome	Retains ability to transiently replicate extrachromosomal HPV genomes	Thomas et al. (1999)
	Fails to maintain extrachromosomal HPV genomes	
del 22–26 (LHCYE) in the context of the intact genome	Somewhat reduces ability to stably maintain extrachromosomal HPV genomes	Longworth and Laimins (2004)
	Significantly reduces growth rate	Longworth and Laimins (2004)
	Fails to extend life span	
	Fails to amplify HPV genomes upon differentiation	
	Fails to post-transcriptionally increase E2F2 in differentiated cells	Longworth et al. (2005)
C24G in the context of the intact genome	Fails to transiently replicate extrachromosomal HPV genomes	Thomas et al. (1999)
	Fails to maintain extrachromosomal HPV genomes	
S31S32/AA in the context of the intact genome	Retains ability to transiently replicate extrachromosomal HPV genomes	Thomas et al. (1999)
	Retains ability to maintain extrachromosomal copies of HPV genomes	
HPV18		
del 24–27 (DLLC)	Fails to mediate cyclin E/cdk2 phosphorylation of p107	McIntyre et al. (1996)
	Fails to induce unscheduled DNA synthesis in suprabasal cells	Chien et al. (2000)
	Fails to induce polα mRNA	
	Fails to upregulate PCNA or cyclin E, or $p21^{CIP1}$	
	Fails to upregulate cytoplasmic cyclin B in suprabasal cells	Banerjee et al. (2011)
	Fails to upregulate cytoplasmic inactive CDC25C in suprabasal cells	
C27G	Fails to mediate cyclin E/cdk2 phosphorylation of p107	McIntyre et al. (1996)
C27S	Fails to induce unscheduled DNA synthesis in suprabasal cells	Chien et al. (2000)
	Fails to induce polα mRNA	
	Fails to upregulate PCNA or cyclin E, or $p21^{CIP1}$	
S32S34/QQ	Fails to be phosphorylated by CKII	Chien et al. (2000)
	Fails to upregulate PCNA, cyclin E, $p21^{CIP1}$	
	Reduces ability to target p130 for degradation	Genovese et al. (2008)
	Fails to induce suprabasal DNA synthesis	
	Fails to upregulate expression of cytoplasmic inactive CDC25C in suprabasal cells	Banerjee et al. (2011)
E35E36E37/QQQ	Retains ability to increase polα mRNA	Chien et al. (2000)
	Fails to induce PCNA, cyclin E, and $p21^{CIP1}$	
	Fails to be phosphorylated by CKII	
	Fails to induce suprabasal DNA synthesis	
	Reduces ability to target p130 for degradation	Genovese et al. (2008)
	Fails to upregulate cytoplasmic cyclin B in suprabasal cells	Banerjee et al. (2011)

cAMP, cyclic AMP; HeLa, HPV18 positive human cervical adenocarcinoma line (ATCC Number CCL-2); HFK, primary human foreskin keratinocytes; SAOS2, pRB/p53 defective human osteosarcoma cell line (ATCC Number: HTB-85); SW13 human adrenal gland/cortex carcinoma line (ATCC Number CCL-105).

Studies with alpha HPV E7 peptides

Studies with peptides yielded important insights into many aspects of HPV E7 biology and biochemistry. Early studies by Rawls and colleagues made use of synthetic versions of full length HPV16 E7 as well as isolated domains and allowed clean mapping of the ability to induce DNA synthesis, to transcriptionally activate the Ad E2 promoter, and to bind zinc ions (Rawls et al., 1990) (Table 11). A later study with smaller peptides encompassing the LXCXE domains provided information regarding the minimal domain necessary for pRB binding (Jones et al., 1990) (Table 11). Subsequently, the structure of the minimal peptide bound to a pRB fragment was solved (Lee et al., 1998). Many studies also took advantage of synthesizing E7 peptides as fusions in *E. coli* to identify E7 associated cellular proteins (see Table 3) or to rapidly map domains necessary for interactions of E7 with cellular proteins (Table 11).

Cutaneous HPV E7 proteins

Beta, mu and gamma HPVs are associated with infections of keratinized, cutaneous epithelia. A recent study however, identified a large number of beta and gamma HPVs in the oral mucosa, potentially suggesting that these cutaneous viruses may also colonize a mucosal niche (Bottalico et al., 2011).

Cutaneous HPVs have attracted less experimental attention than alpha HPVs because they are mostly associated with benign warts. Some beta HPVs associated warts, however, can undergo malignant progression to invasive squamous

Table 8
High-risk alpha HPV E7 C-terminal mutants; biochemical activities.

HPV type	Phenotype	References
HPV16		
E46A	Retains binding to p600	Huh et al. (2005)
	Retains binding to cullin 2 complex	Huh et al. (2007)
A50S	Retains binding to pRB	Demers et al. (1996)
Y52A	Retains ability to dimerize	Todorovic et al. (2012),
	Reduces binding to pRB	Todorovic et al. (2011)
del 52–56 (YNIVT)	Fails to bind Skip	Prathapam et al. (2001)
	Retains binding to p300	Bernat et al. (2003)
	Reduces binding to Miz-1	Morandell et al. (2012)
del 52–57 (YNIVTF)	Reduces binding to hTid-1	Schilling et al. (1998)
N53D	Retains ability to dimerize	Todorovic et al. (2012),
	Fails to bind cullin 2	Todorovic et al. (2011)
	Reduces binding to pRB	
V55T	Fails to dimerize	Todorovic et al. (2012),
	Fails to bind cullin 2	Todorovic et al. (2011)
	Increases binding to pRB	
V55F57M84/AAA	Reduces binding to GSTP1	Mileo et al. (2009)
F57A	Fails to dimerize	Todorovic et al. (2012),
	Increases binding to pRB	Todorovic et al. (2011)
C58C91/GG	Retains binding to pRB and p107	Demers et al. (1996)
	Retains binding to $p27^{KIP1}$	Zerfass-Thome et al. (1996)
	Reduces binding to TBP	Phillips and Vousden (1997)
	Retains binding to IRF-1	Park et al. (2000)
	Fails to bind acid α-glucosidase	Zwerschke et al. (2000)
	Fails to bind BRG-1	Lee et al. (2002a)
	Fails to bind TGase 2	Jeon et al. (2003)
	Fails to dimerize	Todorovic et al. (2011)
C59S	Retains ability to dimerize	Todorovic et al. (2012),
	Reduces binding to pRB	Todorovic et al. (2011)
K60E	Retains ability to dimerize	Todorovic et al. (2011)
D62K	Retains ability to dimerize	Todorovic et al. (2012),
	Increases binding to pRB	Todorovic et al. (2011)
S63D	Retains ability to dimerize	Todorovic et al. (2012),
	Fails to bind cullin 2	Todorovic et al. (2011)
	Reduces binding to pRB	
T64D	Retains ability to dimerize	Todorovic et al. (2012),
	Reduces binding to pRB	Todorovic et al. (2011)
L65A	Fails to dimerize	Todorovic et al. (2011)
L65R66L67/AAA	Retains binding to p300	Bernat et al. (2003)
R66E	Retains ability to dimerize	Todorovic et al. (2012),
	Fails to bind cullin 2	Todorovic et al. (2011)
	Increases binding to pRB	
L67R	Retains partial or full binding to pRB	Avvakumov et al. (2003), Brehm et al. (1999)
	Fails to bind HDAC and Mi2β	Brehm et al. (1999)
	Fails to bind pCAF	Avvakumov et al. (2003)
	Reduces binding to PML IV	Bischof et al. (2005)
	Retains ability to dimerize	Todorovic et al. (2011)
C68V69Q70/AAA	Retains binding to p600	Huh et al. (2005)
	Fails to bind cullin 2 complex	Huh et al. (2007)
	Retains binding to E2F6	McLaughlin-Drubin et al. (2008)
V69A	Fails to dimerize	Todorovic et al. (2011)
S71I	Retains binding to pRB and p107	Demers et al. (1996), Jones et al. (1997b)
	Retains binding to HDAC	Brehm et al. (1999)
	Retains binding to IRF-1	Park et al. (2000)
	Retains binding to BRG-1	Lee et al. (2002a)
	Retains binding to TGase 2	Jeon et al. (2003)
	Retains binding to pCAF	Avvakumov et al. (2003)
T72D	Retains ability to dimerize	Todorovic et al. (2012),
	Fails to bind cullin 2	Todorovic et al. (2011)
H73E	Retains ability to dimerize	Todorovic et al. (2012)
	Fails to bind cullin 2	Todorovic et al. (2011)
V74T	Retains ability to dimerize	Todorovic et al. (2012,
	Increases binding to pRB	Todorovic et al. (2011)
del 75–77 (DIR)	Retains ability to degrade pRB	Helt and Galloway (2001)
	Retains binding to p300	Bernat et al. (2003)
I76A	Fails to dimerize	Todorovic et al. (2011)
R77E	Fails to dimerize	Todorovic et al. (2011)
	Reduces binding to pRB	
del 78–85 (TLEDLLMG)	Reduces binding to hTid-1	Schilling et al. (1998)
L79A	Fails to dimerize	Todorovic et al. (2011)
del 79–83 (LEDLL)	Fails to bind TBP	Massimi et al. (1997)
	Fails to bind M2-PK	Zwerschke et al. (1999)
	Significantly reduces binding to IGFBP-3	Mannhardt et al. (2000)
	Fails to bind acid α-glucosidase	Zwerschke et al. (2000)
	Retains binding to p300	Bernat et al. (2003)
	Retains binding to p600	Huh et al. (2005)
	Fails to bind FHL2	Campo-Fernandez et al. (2007)
	Fails to bind cullin 2 complex	Huh et al. (2007)
	Retains binding to E2F6	McLaughlin-Drubin et al. (2008)
	Fails to bind NuMA	Nguyen and Munger (2009)
	Reduces binding to Miz-1	Morandell et al. (2012)
E80D81/KK	Retains ability to dimerize	Todorovic et al. (2011)
L82L83/RR	Fails to bind HDAC	Brehm et al. (1999)
	Reduces binding to PML IV	Bischof et al. (2005)
	Fails to bind DNMT1	Burgers et al. (2007)
L82L83M84G85/ AAAD	Retains ability to dimerize	Todorovic et al. (2011)
M84S	Retains ability to dimerize; Increases binding to pRB	Todorovic et al. (2011)
G85A	Retains ability to dimerize;	Todorovic et al. (2012,
	Reduces binding to pRB	Todorovic et al. (2011)
T86D	Fails to dimerize	Todorovic et al. (2011)
L87A	Fails to dimerize	Todorovic et al. (2011)
I89V90/AA	Fails to dimerize	Todorovic et al. (2011)
C91G	Reduces dimerization	Todorovic et al. (2011)
	Fails to bind c-jun	Antinore et al. (1996)
	Fails to bind HDAC	Brehm et al. (1999)
	Fails to bind BRCA1	Zhang et al. (2005)
	Reduces binding to PML IV	Bischof et al. (2005)
C91S	Fails to bind S4 subunit of the proteasome	Berezutskaya and Bagchi (1997)
	Significantly reduces binding to hTid-1	Schilling et al. (1998)
	Retains binding to p600	Huh et al. (2005)
	Fails to bind cullin 2 complex	Huh et al. (2007)
	Fails to bind E2F6	McLaughlin-Drubin et al. (2008)
	Fails to bind NuMA	Nguyen and Munger (2009)
	Increases binding to HIF-1α	Bodily et al. (2011b)
del 91–94 (CPIC)	Significantly reduces binding to hTid-1	Schilling et al. (1998)
P92A	Retains ability to dimerize	Todorovic et al. (2012, 2011)
	Increases binding to pRB	
I93T	Retains ability to dimerize	Todorovic et al. (2012),
	Increases binding to pRB	Todorovic et al. (2011)
Q96K97P98/EEA	Retains ability to dimerize	Todorovic et al. (2012,
	Reduces binding to Cullin 2	2011)
HPV31		
L67R	Fails to bind HDAC 1/2/3	Longworth and Laimins (2004, 2005)
	Retains binding to phosphorylated ATM	Moody and Laimins (2009)
	Increases binding to HIF-1α	Bodily et al. (2011b)
C68V69Q70/AAA	Retains binding to HDAC 1/2 and pRB	Longworth and Laimins (2004)
S71C	Retains binding to pRB and HDAC 1/2	Longworth and Laimins (2004)
del 79–83 (LQELL)	Retains binding to HDAC 1/2	Longworth and Laimins (2004)
L82L83/RR	Retains binding to HDAC 1/2	Longworth and Laimins (2004)
G91G	Retains partial binding to HDAC 1/2	Longworth and Laimins (2004)
HPV18		
C65S	Reduces binding to Zn^{2+} by 50%	McIntyre et al. (1993)
C65C98/SS	Fails to bind Zn^{2+}	McIntyre et al. (1993)
del 65–68/98–101 (CCKC/ CPWC)	Fails to bind c-myc	Wang et al. (2007)
C98S	Reduces binding to Zn^{2+} by 50%	McIntyre et al. (1993)

TGase 2, transglutaminase 2.

Table 9
High-risk alpha HPV E7 C-terminal mutants; biological activities.

HPV type	Phenotype	References
HPV16		
E46A	Retains ability to destabilize pRB, p107, p130 Retains ability to block binding of pRB to E2F Retains ability to bypass DNA damage checkpoints Retains ability to extend HFK lifespan	Helt and Galloway (2001)
A50S	Retains ability to bypass growth arrest induced by differentiation, DNA damage, or TGF-β Retains ability to destabilize pRB Retains ability to transactivate the E2F-responsive cyclin A promoter Retains ability to induce DNA synthesis and block senescence in HPV E2-expressing HeLa cells Reduces ability to rescue E2-expressing HeLa cells from apoptosis or senescence	Demers et al. (1996) Psyrri et al. (2004)
	Significantly reduces ability to induce tetrasomy in monolayer and raft cultures	Southern et al. (2004)
H51A	Retains ability to destabilize pRB Retains ability to block binding of pRB to E2F Retains ability to bypass DNA damage checkpoints	Helt and Galloway (2001)
Y52A	Retains ability to transform primary rodent cells in cooperation with RAS Reduces ability to overcome cell cycle arrest	Todorovic et al. (2011)
del 52–56 (YNIVT)	Significantly reduces ability to abrogate Skip-mediated transcriptional transactivation Reduces inhibition of Miz-1-dependent $p21^{CIP1}$ transcription	Prathapam et al. (2001) Morandell et al. (2012)
del 52–57 (YNIVTF)	Fails to stimulate MPP2 (FOXM1)-dependent transcription	Luscher-Firzlaff et al. (1999)
N53D	Retains ability to transform primary rodent cells in cooperation with RAS Fails to overcome cell cycle arrest	Todorovic et al. (2011)
del 54–61 (IVTFCCKC)	Retains ability to transactivate the AdE2 promoter Fails to transform permanent rodent cells	Watanabe et al. (1990)
V55T	Increases ability to transform primary rodent cells in cooperation with RAS Fails to overcome cell cycle arrest	Todorovic et al. (2011)
V55F56M84/AAA	Reduces protection of GSTP1 from inactivation through oxidation Reduces protection of cells from JNK-mediated apoptosis in response to UV	Mileo et al. (2009)
F57A	Retains ability to transform primary rodent cells in cooperation with RAS Fails to overcome cell cycle arrest	Todorovic et al. (2011)
C58C91/GG	Reduces ability to transform permanent rodent cells	Edmonds and Vousden (1989)
	Retains ability to transactivate the B-myb promoter	Lam et al. (1994)
	Fails to bypass growth arrest induced by differentiation, DNA damage, or TGF-β	Demers et al. (1996)
	Fails to abrogate $p27^{KIP1}$-mediated inhibition of CDK2	Zerfass-Thome et al. (1996)
	Fails to abrogate IRF-1 mediated transactivation	Park et al. (2000)
	Fails to abrogate BRG-1-mediated repression of the c-fos promoter and BRG-1-induced flat cell formation in SW13 cells	Lee et al. (2002a)
	Reduces ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
C59S	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
K60E	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
D62K	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
D62S63T64/AAA	Retains ability to destabilize pRB Retains ability to block binding of pRB to E2F Retains ability to bypass DNA damage checkpoints	Helt and Galloway (2001)
S63D	Retains ability to transform primary rodent cells in cooperation with RAS Fails to overcome cell cycle arrest	Todorovic et al. (2011)
T64D	Increases ability to transform primary rodent cells in cooperation with RAS Fails to overcome cell cycle arrest	Todorovic et al. (2011)
L65A	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
L65R66L67/AAA	Retains ability to block binding of pRB to E2F	Helt and Galloway (2001)
del 65–72 (LRLCVQST)	Fails to stimulate MPP2 (FOXM1)-dependent transcription	Luscher-Firzlaff et al. (1999)
R66A	Retains ability to destabilize pRB Retains ability to block binding of pRB to E2F Retains ability to bypass DNA damage checkpoints	Helt and Galloway (2001)
R66E	Increases ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
L67R	Fails to bypass pRB-induced quiescence in SAOS2 cells Fails to abrogate growth arrest induced by serum deprivation Fails to upregulate CDC25A promoter	Brehm et al. (1999) Nguyen et al. (2002)
	Fails to transactivate E2F-dependent promoters	Avvakumov et al. (2003)
	Fails to increase acetylation of histone H3 on E2F-regulated promoters	Zhang et al. (2004)
	Fails to abrogate PML IV-mediated senescence	Bischof et al. (2005)
	Fails to induce centriole overduplication Fails to increase PLK4 transcription	Korzeniewski et al. (2011)
	Fails to increase HIF-1α-mediated transcription	Bodily et al. (2011b)
	Reduces ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
L67R in the context of the intact genome	Retains ability to immortalize HFKs Retains ability to maintain extrachromosomal copies of viral genomes Retains ability to activate late viral transcription in differentiated cells May be compromised in ability to decrease pRB level and induce cell cycle proteins Fails to produce viral particles.	Bodily et al. (2011a)
C68V69Q70/AAA	Retains ability to destabilize pRB, p107, p130 Retains ability to block binding of pRB to E2F	Helt and Galloway (2001)

Table 9 (*continued*)

HPV type	Phenotype	References
	Retains ability to abrogate pRB-induced flat SAOS2 cell morphology	
	Fails to bypass DNA damage checkpoints	
	Fails to extend HFK lifespan	
	Fails to inactivate $p21^{CIP1}$	Helt et al. (2002)
	Fails to bypass differentiation-induced growth arrest	
	Limited increase in FANCD2-containing alternative lengthening of telomeres (ALT)-associated promyelocytic leukemia bodies (APBs)	Spardy et al. (2008)
	Retains ability to abrogate E2F6-mediated transcriptional repression and decrease E2F6-PcG complexes	McLaughlin-Drubin et al. (2008)
	Retains ability to inhibit TNF-α-induced growth arrest	Boccardo et al. (2010)
C68V69Q70/AAA in the context of the intact genome	Retains ability to immortalize HFKs	Bodily et al. (2011a)
	Retains ability to maintain extrachromosomal copies of viral genomes	
	Retains ability to activate late viral transcription in differentiated cells	
	May be compromised in ability to decrease pRB level and induce cell cycle proteins	
	Reduces ability to produce viral particles but particles are infectious.	
V69A	Reduces ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
S71I	Retains ability to transform permanent rodent cells	Edmonds and Vousden (1989)
	Retains ability to be phosphorylated by CKII	Barbosa et al. (1990)
	Retains ability to bypass growth arrest induced by differentiation, DNA damage, or TGF-β	Demers et al. (1996)
	Retains ability to destabilize pRB	Jones et al. (1997b)
	Retains ability to stabilize p53	
	Retains ability to abrogate cell death induced by confluence or serum deprivation	
	Retains ability to abrogate IRF-1-mediated transactivation	Park et al. (2000)
	Retains ability to abrogate BRG-1-mediated repression of the c-fos promoter and BRG-1-induced flat cell formation in SW13 cells	Lee et al. (2002a)
	Retains ability to abrogate pRB-induced flat SAOS2 cell morphology	Avvakumov et al. (2003)
	Retains increased acetylation of histone H3 on E2F-regulated promoters	Zhang et al. (2004)
	Significantly reduces ability to induce tetrasomy in monolayer and raft cultures	Southern et al. (2004)
T72D	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
T72H73V74/AAA	Retains ability to degrade pRB	Helt and Galloway (2001)
	Retains ability to block binding of pRB to E2F	
	Retains ability to override DNA damage checkpoints	
H73E	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
V74T	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
del 75–77 (DIR)	Retains ability to block binding of pRB to E2F	Helt and Galloway (2001)
	Retains ability to degrade pRB	
I76A	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
R77A	Retains ability to degrade pRB	Helt and Galloway (2001)
	Retains ability to block binding of pRB to E2F	
	Retains ability to override DNA damage checkpoints	
R77E	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
L79A	Reduces ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
del 79–83 (LEDLL)	Fails to shift the equilibrium of M2 pyruvate kinase (M2-PK) to the less active, dimeric form	Zwerschke et al. (1999)
	Fails to degrade IGFBP-3 and to abrogate IGFBP-3-mediated apoptosis	Mannhardt et al. (2000)
	Fails to activate acid α-glucosidase	Zwerschke et al. (2000)
	Retains the ability to destabilize pRB, p107, p130	Helt and Galloway (2001)
	Retains ability to block binding of pRB to E2F	
	Retains ability to abrogate pRB-induced quiescence of SAOS2 cells	
	Fails to bypass DNA damage checkpoints	
	Fails to extend HFK lifespan	
	Fails to inactivate $p21^{CIP1}$	Helt et al. (2002)
	Fails to bypass differentiation-induced growth arrest	
	Fails to inhibit TBP binding to DNA	Maldonado et al. (2002)
	Limits increase in FANCD2-containing alternative lengthening of telomeres (ALT)-associated promyelocytic leukemia bodies (APBs)	Spardy et al. (2008)
	Retains ability to abrogate E2F6-mediated transcriptional repression and decrease E2F6-PcG complexes	McLaughlin-Drubin et al. (2008)
	Fails to induce disorganized metaphase phenotype (prometaphase delay)	Nguyen and Munger (2009)
	Retains ability to inhibit TNF-α-induced growth arrest	Boccardo et al. (2010)
	Reduces inhibition of Miz-1-dependent $p21^{CIP1}$ transcription	Morandell et al. (2012)
	Fails to inhibit cyclin B degradation	Yu and Munger (2012)
del 79–86 (LEDLLMGT)	Fails to stimulate MPP2 (FOXM1)-dependent transcription	Luscher-Firzlaff et al. (1999)
E80Q	Fails to repress MHC I expression	Heller et al. (2011)
E80D81/KK	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
	Fails to overcome cell cycle arrest	
E80E81/QQ	Gains ability to be polyaminated by TGase 2	Jeon et al. (2003)
L82L83/RR	Fails to abrogate PML IV-mediated senescence	Bischof et al. (2005)
	Fails to disrupt PML IV:CBP-mediated p53 acetylation and p53-mediated transcription	
L82L83M84G85/AAAD	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
M84S	Reduces ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
G85A	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
	Fails to overcome cell cycle arrest	

Table 9 (*continued*)

HPV type	Phenotype	References
T86D	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
L87A	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
I89V90/AA	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
C91G	Limits ability to transform permanent rodent cells	Edmonds and Vousden (1989)
	Fails to immortalize HFKs	Jewers et al. (1992)
	Fails to enhance c-JUN-mediated transactivation	Antinore et al. (1996)
	Fails to abrogate BRCA1 inhibition of ER-α-mediated transcription	Zhang et al. (2005)
	Fails to abrogate PML IV-mediated senescence	Bischof et al. (2005)
	Reduces ability to cooperate with RAS to transform primary rodent cells	Todorovic et al. (2011)
C91G in context of intact genome	Fails to immortalize HFKs	(Jewers et al. (1992),
	Reduces efficiency of immortalization of HFKs	(Bodily et al. (2011a)
	Retains ability to maintain extrachromosomal HPV genomes	
	Retains ability to produce late viral transcripts	
	Reduces proliferation and retention of nuclei in organotypic rafts	
C91S	Fails to stimulate S4A proteasome subunit ATPase activity	Berezutskaya and Bagchi (1997)
	Retains ability to degrade pRB	Gonzalez et al. (2001)
	Retains ability to induce abnormal centrosome duplication	Duensing and Munger (2003)
	Fails to abrogate E2F6-mediated transcriptional repression and decrease E2F6-PcG complexes	McLaughlin-Drubin et al. (2008)
	Fails to increase HIF-1α-mediated transcription	Bodily et al. (2011b)
C91S in context of intact genome	Retains ability to immortalize HFKs	Bodily et al. (2011a)
	Retains ability to maintain extrachromosomal HPV genomes	
	Retains ability to decrease the level of pRB	
	Retains ability to produce late viral transcripts in differentiated HFKs	
	Reduces proliferation and retention of nuclei in organotypic rafts	
del C91-94 (CPIC)	Substantially reduces ability to transactivate the AdE2 promoter	Storey et al. (1990a), Watanabe et al. (1990)
P92A	Increases ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
I93T	Retains ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
Q96K97P98/EEA	Reduces ability to transform primary rodent cells in cooperation with RAS	Todorovic et al. (2011)
	Reduces pRB degradation	
HPV31		
L67R in the context of the intact genome	Fails to stably maintain extrachromosomal HPV genomes	Longworth and Laimins (2004)
	Fails to extend life span	
	Fails to increase E2F2 transcription and to inhibit binding of HDAC 1/3 to E2F2 promoter in differentiated cells	Longworth et al. (2005)
C68V69Q70/AAA in the context of the intact genome	Retains ability to stably maintain extrachromosomal HPV genomes	Longworth and Laimins (2004)
	Retains ability to extend life span.	
	Limits ability to amplify viral DNA upon differentiation	
S71C in context of intact genome	Retains ability to stably maintain extrachromosomal HPV genomes	Longworth and Laimins (2004)
	Retains ability to extend life span	
	Retains ability to amplify HPV genomes upon differentiation	
del 79–83 (LQELL) in the context of the intact genome	Some reduction in the ability to stably maintain extrachromosomal copies of viral genomes	Longworth and Laimins (2004)
	Retains ability to extend life span	
	Fails to amplify HPV genome upon differentiation	
L82L83/RR in the context of the intact genome	Retains ability to extend life span	Longworth and Laimins (2004)
	Somewhat reduces ability to stably maintain extrachromosomal HPV genomes	
	Fails to amplify HPV genomes upon differentiation.	
C91G in context of intact genome	Significant reduces ability to stably maintain extrachromosomal copies of viral genomes	Longworth and Laimins (2004)
	Fails to immortalize cells	
HPV18		
C65S	Fails to cooperate with RAS to transform primary rodent cells	McIntyre et al. (1993)
C65C98/SS	Fails to cooperate with RAS to transform primary rodent cells	McIntyre et al. (1993)
del 65–68/98–101 (CCKC/ CPIC)	Fails to enhance c-myc dependent transcriptional transactivation	Wang et al. (2007)
Q87Q88/RR	Fails to be polyaminated by TGase 2	Jeon et al. (2003)
C98S	Fails to cooperate with RAS to transform primary rodent cells	McIntyre et al. (1993)

BRK, baby rat kidney cells; HFK, primary human foreskin keratinocytes; UV, ultraviolet; SAOS2, pRB/p53 defective human osteosarcoma cell line (ATCC Number: HTB-85); SW13 human adrenal gland/cortex carcinoma line (ATCC Number CCL-105); TGase2, transglutaminase 2.

cell carcinomas (SCCs), particularly in chronically immunosuppressed patients or in individuals affected by Epidermodysplasia verruciformis (EV), a rare autosomal recessive genetic disease. EV-associated cancers were the first malignant tumors that were linked to HPV infections (reviewed in Pfister (2003)). Very few cell-based assays have been described to analyze the potential transforming activities of beta HPV E7 proteins. Table 12 lists biological and biochemical activities and a limited amount of mutational genotype/phenotype data for this group of viruses.

Chimeras between the alpha HPV16 E7 and the mu HPV1 E7 have also been informative. While both E7 proteins bind pRB with high efficiency, only HPV16 E7 degrades it. Studies with chimeras revealed that the HPV16 E7 CR2 domain, in the background of HPV1 E7 could degrade pRB while swapping the HPV1 E7 CR2 domain into the HPV16 E7 background resulted in loss of ability to

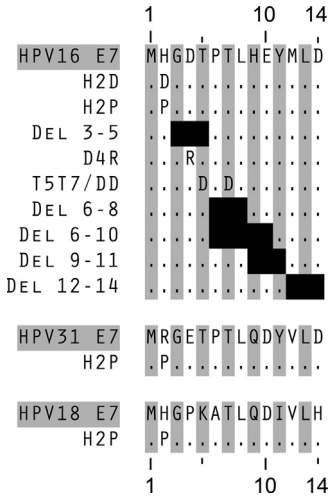

Fig. 2. Schematic representation of the HPV E7 CR1 mutants described in Tables 4 and 5. Amino acid residues 1–14 of HPV16, 31 and 18 E7 are shown. The one letter code for amino acid (aa) residues is used. Black boxes denote deletions (del).

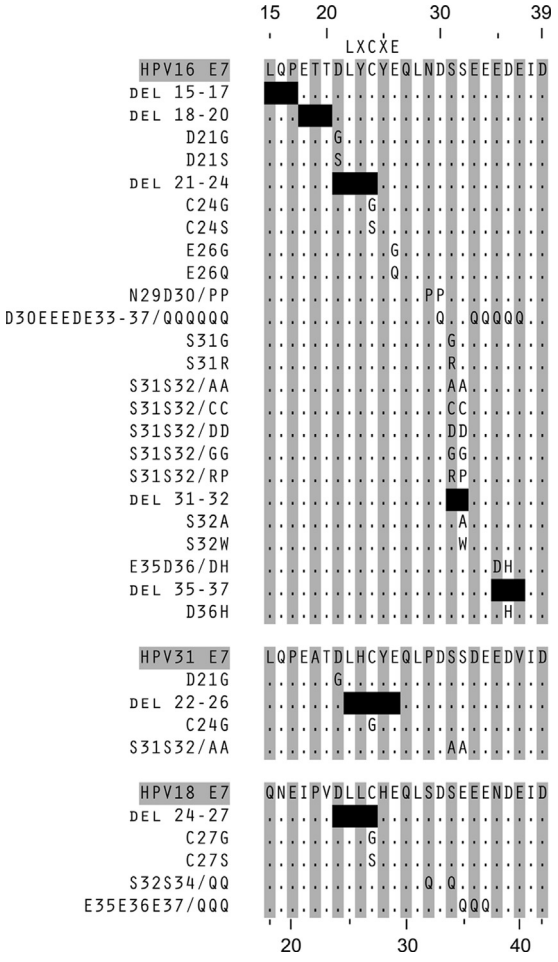

Fig. 3. Schematic representation of the HPV E7 CR2 mutants described in Tables 6 and 7. Amino acid residues 15–39 of HPV16 and HPV31 E7 and amino acid residues 18–42 of HPV18 E7 are shown. The position of the LXCXE motif is indicated. The one letter code for amino acid (aa) residues is used; X denotes any amino acid. Black boxes denote deletions.

degrade pRB. Subsequent experiments narrowed the critical sequence to Q27LN29 in HPV16 E7 CR2 (compared to E29VPP32 in HPV1 E7—see Fig. 1) (Giarre et al., 2001).

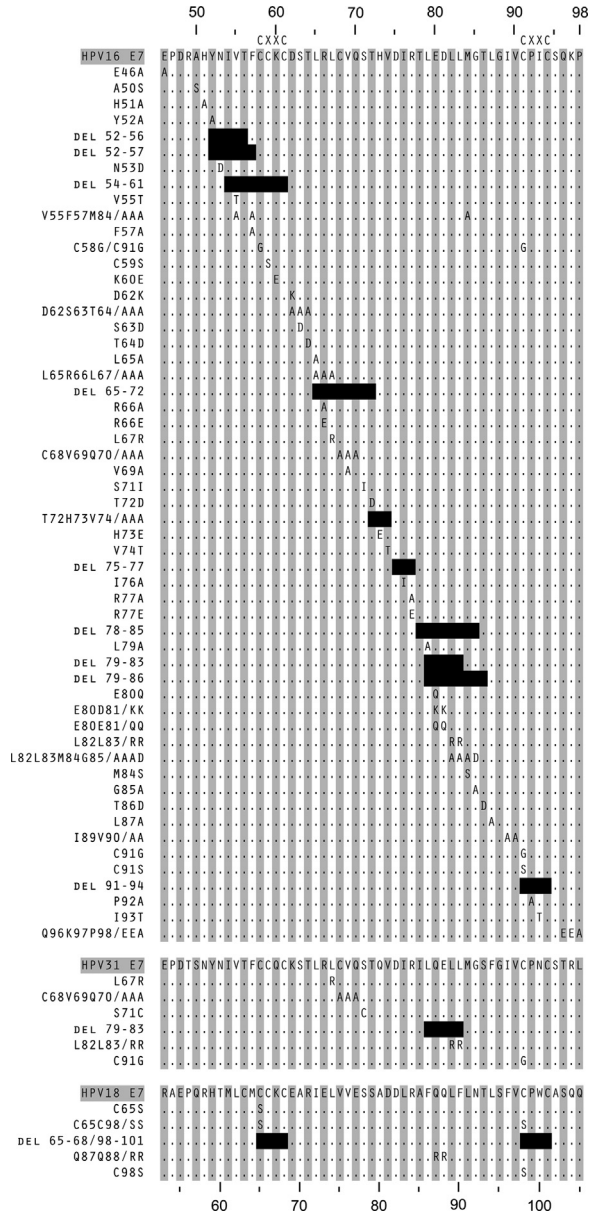

Fig. 4. Schematic representation of the HPV E7 C-terminal mutants described in Tables 8 and 9. Amino acid residues 46–98 of HPV16 and HPV31 E7 and amino acid residues 53–105 of HPV18 E7 are shown. The positions of the CXXC motifs are indicated. The one letter code for amino acid (aa) residues is used; X denotes any amino acid. Black boxes denote deletions.

Genetically engineered mouse models

Papillomaviruses are highly species specific and there are no infectious heterologous animal models for HPV life cycle and pathogenesis studies. Genetically engineered mouse models (GEMMs) with expression of alpha and beta HPV subgenomic fragments targeted to basal epithelia recapitulate key phenotypes of the diseases that these viruses can cause upon infection of the human host (Arbeit et al., 1996; Brake and Lambert, 2005; Schaper et al., 2005; Viarisio et al., 2011). GEMMs expressing HPV E7 in basal epithelial cells have not only validated results from cell-based experiments but in many cases have also provided novel insights (Balsitis et al., 2006, 2005, 2003; Schaeffer et al., 2004; Shin et al., 2009, 2012b). Of particular interest are studies that document that E7 is the major driver of GEMMs for HPV-associated cervical (Jabbar et al., 2009) and anal (Thomas et al., 2011) cancers. The results from such studies are summarized in Table 13.

Table 10
Low-risk alpha HPV mutants: biological and biochemical activities.

HPV type and region	Mutation	Phenotype	References
HPV6			
CR1	H2R4H5/AAA	Retains binding to p130 Fails to destabilize p130 Fails to decrease/delay differentiation	Zhang et al. (2006)
CR1	R4D	Retains binding to pRB Retains ability to be phosphorylated by CKII	Sang and Barbosa (1992)
CR1	R4V6K9/DPH	Retains ability to transactivate the AdE2 promoter in BRKs and HFKs	Armstrong and Roman (1997)
CR1/CR2	R4V6K9G22H24/ DPHDY	Super transactivates (greater than HPV16 E7) the AdE2 and B-myb promoters in HFKs	Armstrong and Roman (1997)
CR1/CR2	R4V6K9V37E39/DPHDI	Retains ability to transactivate the AdE2 promoter in BRKs and HFKs	Armstrong and Roman (1997)
CR1/CR2	CR1/CR2 R4V6K9G22H24V37E39/ DPHDYDI	Gains transactivation ability comparable to HPV16 E7 on the AdE2 promoter in BRKs and HFKs	Armstrong and Roman (1997)
CR1	T7A	Retains ability to be phosphorylated by CKII Fails to be phosphorylated in vitro by PKC	Armstrong and Roman (1995)
CR1/CR2	T7G22H24/DDY	Super transactivates the AdE2 and B-myb promoters in HFKs	Armstrong and Roman (1997)
CR1/CR2	T7G22H24/ADY	Gains transactivation ability comparable to HPV16 E7 on the AdE2 and B-myb promoters in HFKs	Armstrong and Roman (1997)
CR1	K9D10/AA	Retains binding to p130 Retains ability to destabilize p130 Retains ability to decrease/delay differentiation	Zhang et al. (2006)
CR2	G22D	Increases binding to pRB Retains ability to be phosphorylated by CKII Gains ability to transform permanent rodent cells	Sang and Barbosa (1992)
		Gains ability to destabilize pRB Increases binding to p107 Increases binding to p130	Zhang et al. (2006)
CR2	G22D in context of chimeric E7 with HPV6 E7 N-terminus and HPV16 E7 C-terminus	Increases binding to pRB Increases transformation of BRK cells in cooperation with RAS	Heck et al. (1992)
CR2	G22H24/DY	Gains transactivation ability comparable to HPV16 E7 on the AdE2 promoter in BRKs and HFKs	Armstrong and Roman (1997)
	G22H24V37E39/DYDI	Gains transactivation ability comparable to HPV16 E7 on the AdE2 promoter in BRKs and HFKs	Armstrong and Roman (1997)
CR2	C25A	Fails to bind p130 Fails to destabilize p130 Fails to decrease/delay differentiation	Zhang et al. (2006)
CR2	V30N	Retains binding to pRB Increases ability to be phosphorylated by CKII	Sang and Barbosa (1992)
CR2	D31A	Retains binding to p130 Retains ability to destabilize p130 Retains ability to decrease/delay differentiation	Zhang et al. (2006)
CR2	S32S33/AA	Fails to be phosphorylated by CKII Retains ability to be phosphorylated in vitro by PKC	Armstrong and Roman (1995)
CR2	V37D	Retains binding to pRB Increases ability to be phosphorylated by CKII	Sang and Barbosa (1992)
CR2	V37E39/DI	Retains ability to transactivate the AdE2 promoter in BRKs Loses ability to transactivate the same promoter in HFKs	Armstrong and Roman (1997)
C-term	K49T	Somewhat increases ability to induce unscheduled suprabasal DNA synthesis	Genovese et al. (2011)
C-term	K49R	Somewhat increases ability to induce unscheduled suprabasal DNA synthesis	Genovese et al. (2011)
C-term	L67R	Retains binding to p130 Fails to destabilize p130 Fails to decrease/delay differentiation	Zhang et al. (2006)
HPV11			
CR2	G22D	Increases binding to p130 Reduces ability to destabilize p130 Somewhat increases ability to induce unscheduled suprabasal DNA synthesis	Genovese et al. (2011)
CR2	G22K39K42/DEA	Gains increased ability to induce unscheduled suprabasal DNA synthesis comparable to HPV16 E7	Genovese et al. (2011)
CR2	G22K39K42/DRR	Gains increased ability to induce unscheduled suprabasal DNA synthesis comparable to HPV16 E7	Genovese et al. (2011)
CR2	del 22–25 (GLHC)	Fails to destabilize p130 Fails to induce suprabasal DNA synthesis	Genovese et al. (2008)
CR2	S32S33/NQ	Fails to be phosphorylated by CKII Reduces ability to destabilize p130 Fails to induce suprabasal DNA synthesis	Genovese et al. (2008)
CR2/C-term	K39K42/EA	Somewhat increases ability to induce unscheduled suprabasal DNA synthesis	Genovese et al. (2011)
CR2/C-term	K39K42/RR	Somewhat increases ability to induce unscheduled suprabasal DNA synthesis	Genovese et al. (2011)

Table 10 (*continued*)

HPV type and region	Mutation	Phenotype	References
		Increases binding to and destabilization of p130	
C-term	Q78T	Retains inability to repress MHC I expression	Heller et al. (2011)
C-term	Q78Q80/TE	Retains inability to repress MHC I expression	Heller et al. (2011)
C-term	Q78Q80N88/TEG	Partially gains ability to repress MHC I expression comparable to HPV16 E7	Heller et al. (2011)
C-term	Q80E	Retains inability to repress MHC I expression	Heller et al. (2011)
C-term	Q80N88/EG	Partially gains ability to repress MHC I expression	Heller et al. (2011)
C-term	N88G	Partially gains ability to repress MHC I expression	Heller et al. (2011)

BRK, baby rat kidney cells; and HFK, primary human foreskin keratinocytes.

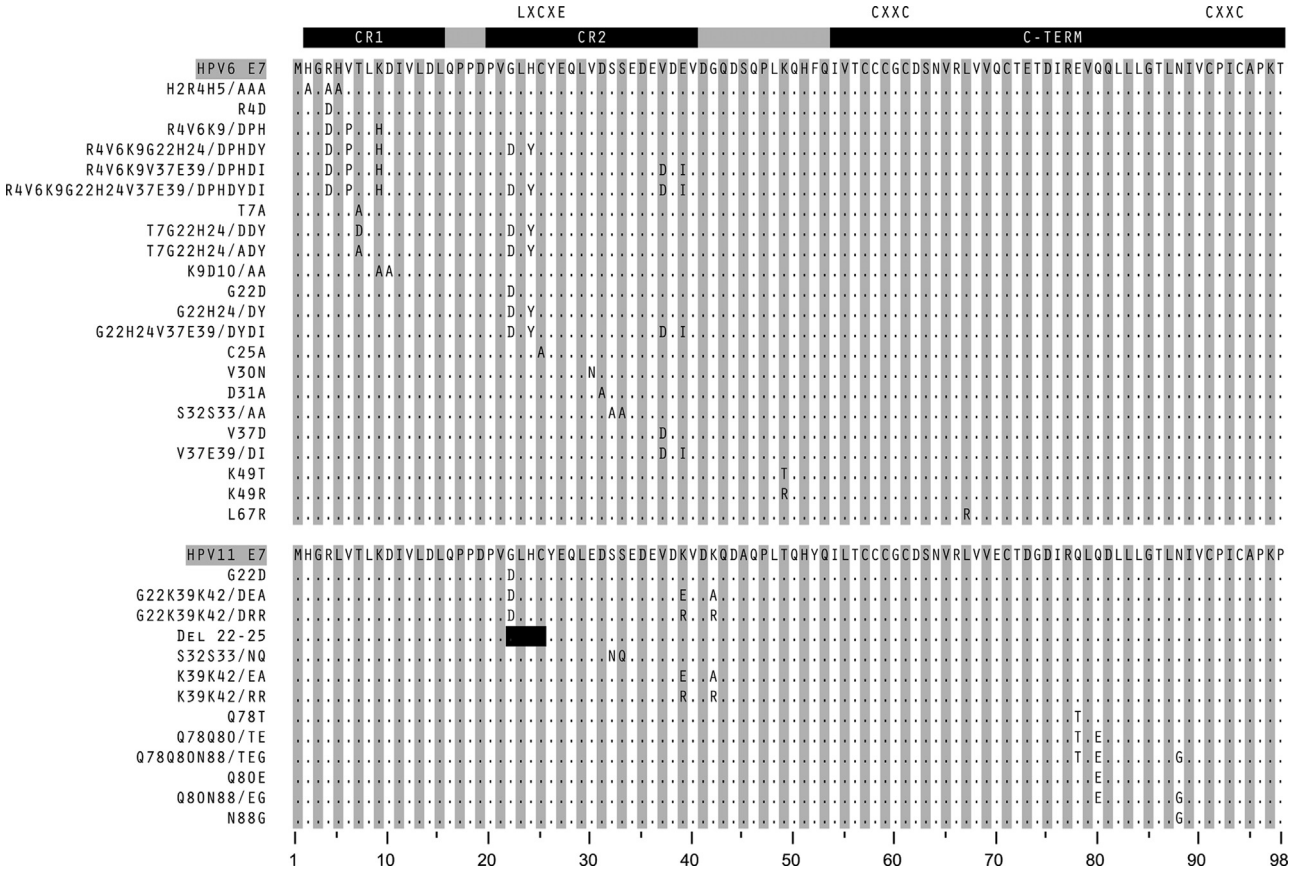

Fig. 5. Schematic representation of the low-risk alpha HPV E7 mutants described in Table 10. A schematic structure of E7 is shown on top with CR1, CR2 and conserved C-terminal domains indicated in black and the non-conserved regions shown in gray. The positions of the LXCXE motif in CR2 and CXXC motifs in the C-terminus are indicated. The one letter code for amino acid (aa) residues is used; X denotes any amino acid. Black boxes denote deletions.

Table 11
Experiments with HPV16 E7 derived peptides.

HPV16 E7 Peptide	E7 domain	Activity	References
aa 1–98	CR1/CR2/C-term	Induces cellular DNA synthesis Activates the Ad E2 promoter Binds Zn^{2+}	Rawls et al. (1990)
Overlapping 12-mers from aa 1–10	CR1	Low efficiency binding to Siva-1	Severino et al. (2007)
aa 1–17	CR1	Fails to bind $p27^{KIP1}$	Zerfass-Thome et al. (1996)
aa 1–36	CR1/CR2	Fails to bind DYRK1A	Liang et al. (2008)
aa 1–38	CR1/CR2	Fails to bind BRCA1	Zhang et al. (2005)
aa 1–40	CR1/CR2	Fails to induce cellular DNA synthesis Fails to activate the Ad E2 promoter Fails to bind Zn^{2+}	Rawls et al. (1990)
del 1–38	CR1/CR2	Binds $p21^{CIP1}$	Funk et al. (1997)
aa 2–32	CR1/CR2	Binds pRB, p107, p130 and cyclin A	Dyson et al. (1992)
aa 2–41		Fails to bind MPP2 (FOXM1) Fails to stimulate MPP2 (FOXM1)-dependent transcription	Luscher-Firzlaff et al. (1999) Luscher-Firzlaff et al. (1999)

Table 11 (*continued*)

HPV16 E7 Peptide	E7 domain	Activity	References
del 9–48	del in CR1/CR2	Retains binding to cdk2 (via cyclin A)	He et al. (2003)
del 9–38	del in CR1/CR2	Loses ability to activate cdk2	He et al. (2003)
Overlapping 12-mers from aa 10–30	CR1/CR2	Fail to bind to Siva-1	Severino et al. (2007)
aa 16–41	CR2	Localizes to nucleus, like full length E7	Fujikawa et al. (1994)
aa 18–38	CR2	Fails to bind $p27^{KIP1}$	Zerfass-Thome et al. (1996)
aa 21–29	CR2	Minimal E7 peptide that inhibits E7/pRB binding	Jones et al. (1990)
aa 20–29 D21N	CR2	Fails to inhibit E7/pRB binding	Jones et al. (1990)
aa 20–29 Y23F	CR2	Fails to inhibit E7/pRB binding	Jones et al. (1990)
aa 20–29C24S	CR2	Fails to inhibit E7/pRB binding	Jones et al. (1990)
aa 20–29 Y25F	CR2	Fails to inhibit E7/pRB binding	Jones et al. (1990)
aa 20–29 E26Q	CR2	Fails to inhibit E7/pRB binding	Jones et al. (1990)
aa 20–29 Q27N	CR2	Retains ability to inhibit E7/pRB binding	Jones et al. (1990)
Overlapping 12-mers from aa 22–42	CR2	Fails to bind to Siva-1	Severino et al. (2007)
aa 25–36	CR2	Binds IRF-9	Antonsson et al. (2006)
aa 16–98	CR2/C-term	Severely defective for cellular DNA synthesis Severely defective for Ad E2 activation Binds Zn^{2+}	Rawls et al. (1990)
aa31–98	CR2/C-term	Necessary for disruption of pRB/E2F-1 complex	Huang et al. (1993), Patrick et al. (1994), Wu et al. (1993)
Overlapping 12-mers from aa 37–69	C-term	Significant binding to Siva-1	Severino et al. (2007)
aa 38–98	C-term	Binds BRCA1	Zhang et al. (2005)
	C-term	Binds DYRK1A	Liang et al. (2008)
aa 39–98	C-term	Binds $p27^{KIP1}$	Zerfass-Thome et al. (1996)
aa 39–98	C-term	Fails to induce cellular DNA synthesis Fails to transactivate the Ad E2 promoter Binds Zn^{2+}	Rawls et al. (1990)
delta 40–98	del C-term	Fails to bind $p21^{CIP1}$	Funk et al. (1997)
aa 42–98	C-term	Binds MPP2 (FOXM1)	Luscher-Firzlaff et al. (1999)
	C-term	Retains the ability to stimulate MPP2 (FOXM1)-dependent transcription	Luscher-Firzlaff et al. (1999)
aa 62–84	C-term	Required for binding to DNMT1	Burgers et al. (2007)
aa 67–98	C-term	Fails to induce cellular DNA synthesis Fails to transactivate the Ad E2 promoter Binds Zn^{2+}	Rawls et al. (1990)
Overlapping 12-mers from aa 70–84	C-term	Fails to bind Siva-1	Severino et al. (2007)
Overlapping 12-mers from aa 79–99	C-term	Significant to maximal binding to Siva-1	Severino et al. (2007)

aa, amino acid residue.

Table 12
Biological and biochemical activities of E7 proteins encoded by cutaneous (beta, gamma, mu) HPVs.

Genus	HPV type	Phenotype	References
Beta			
Beta 1	**HPV5 E7**	Binds pRB with low efficiency Fails to transform established rodent cells Fails to immortalize primary rodent cells Weakly transforms primary rodent cells in cooperation with RAS.	Yamashita et al. (1993)
		In organotypic raft cultures: Significantly delays/disrupts HFK differentiation in the presence of E6	Boxman et al. (2001)
		In organotypic raft cultures: Causes hyperkeratosis and papilla-like structures Moderately increases suprabasal proliferation Results in co-expression of Cyclin E and $p16^{INK4A}$ in suprabasal cells.	Westphal et al. (2009)
		Upregulates lipocalin-2 in primary adult keratinocyte monolayers and in differentiated layers of organotypic raft cultures.	Akgul et al. (2011)
		Reduces pRB levels	Buitrago-Perez et al. (2012)
	HPV5 E7 del 26–29 (DLFC)	Fails to reduce pRB levels.	Buitrago-Perez et al. (2012)
Beta 1	**HPV8 E7**	Fails to transform established rodent cells	Schmitt et al. (1994), Yamashita et al. (1993)
		Binds pRB with low efficiency Fails to immortalize primary rodent cells Very weakly transforms primary rodent cells in cooperation with RAS.	Yamashita et al. (1993)
		Weakly immortalizes primary human foreskin keratinocytes Modestly transactivates the AdE2 promoter	Schmitt et al. (1994)
		In organotypic raft cultures: Causes hyperkeratinization and suprabasal PCNA expression Causes invasion of epidermal cells into artificial dermis.	Akgul et al. (2005)
		Upregulates MT-1-MMP expression and activates MMP-1, 2, 8	Akgul et al. (2005), Smola-Hess et al. (2005)
		Binds SMADs	Habig et al. (2006)

Table 12 (*continued*)

Genus	HPV type	Phenotype	References
		Abrogates TGF-β-mediated transactivation Reduces pRB levels Does not alter p53 or $p21^{CIP1}$ levels Causes abnormal keratin expression Causes polyploidy	Akgul et al. (2007)
		In organotypic raft cultures: Moderately increases suprabasal proliferation Results in co-expression of Cyclin E and $p16^{INK4A}$ in suprabasal cells.	Westphal et al. (2009)
		In organotypic raft and monolayer cultures: Upregulates lipocalin-2.	Akgul et al. (2011)
		Binds C/EBPβ (GST/Co-IP) Inhibits C/EBPβ-mediated transactivation of CCL20 promoter in keratinocytes Inhibits Langerhans cell migration.	Sperling et al. (2012)
	HPV8 E7 del 79–83 (FQELL)	Reduces binding to C/EBPβ Fails to inhibit C/EBPβ-mediated transactivation of CCL20 promoter	Sperling et al. (2012)
Beta 1	**HPV12 E7**	Fails to cooperate with RAS to transform primary rodent cells	Massimi et al. (2008)
Beta 1	**HPV14 E7**	Binds, and in the presence of E6, destabilizes pRB Fails to activate E2F-responsive genes Fails to immortalize HFKs in the presence of E6	Cornet et al. (2012)
Beta 1	**HPV20 E7**	In organotypic raft cultures: Causes some delay/disruption of differentiation in the presence of E6	Boxman et al. (2001)
		Binds pRB with low efficiency Fails to destabilize pRB Fails to abrogate NIH 3T3 growth arrest induced by serum deprivation	Caldeira et al. (2003)
		In organotypic raft cultures: Moderately increases suprabasal proliferation; Fails to cause co-expression of cyclin E and $p16^{INK4A}$ in suprabasal cells	Westphal et al. (2009)
		In organotypic raft cultures: Upregulates lipocalin-2	Akgul et al. (2011)
		Fails to activate NF-κB Binds Iκκα (Co-IP) Attenuates NF-κB-mediated transcription	Hussain et al. (2011) Byg et al. (2012)
Beta 1	**HPV24 E7**	Fails to cooperate with RAS to transform primary rodent cells Binds pRB, and in the presence of E6, partially degrades pRB Causes modest, if any, increase in expression of E2F-responsive promoters, in the presence of E6 Fails to immortalize HFKs in the presence of E6.	Massimi et al. (2008) Cornet et al. (2012)
Beta 1	**HPV36 E7**	Fails to cooperate with RAS to transform primary rodent cells Binds pRB, and in the presence of E6, partially degrades pRB Causes modest, if any, increase in expression of E2F-responsive promoters, in the presence of E6 Fails to immortalize HFKs in the presence of E6.	Massimi et al. (2008) Cornet et al. (2012)
Beta 2	**HPV22 E7**	Binds, and in the presence of E6, destabilizes pRB Fails to activate E2F-responsive genes Fails to immortalize HFKs in the presence of E6	Cornet et al. (2012)
Beta 2	**HPV38 E7**	In organotypic raft cultures: Causes some delay/disruption of differentiation in the presence of E6	Boxman et al. (2001)
		Extends life span of primary human fibroblasts and keratinocytes Binds to pRB with high efficiency Destabilizes pRB in NIH 3T3 and primary human fibroblasts Abrogates NIH 3T3 growth arrest induced by serum deprivation Induces anchorage independent growth in NIH 3T3 cells	Caldeira et al. (2003)
		In organotypic raft cultures: Causes parakeratosis and altered expression of keratins Increases suprabasal proliferation Fails to cause co-expression of cyclin E and $p16^{INK4A}$ in suprabasal cells	Westphal et al. (2009)
		Upregulates lipocalin-2 in keratinocyte monolayers and in differentiated layers of organotypic raft cultures	Akgul et al. (2011)
		Binds to eEF1A (GST; Co-IP) Downregulates Rho activity Causes disruption of stress fibers (F-actin) dependent on CKII, MEK, ERK signaling and eEF1A binding	Yue et al. (2011)
		Binds pRB and enhances phospho-pRB levels in the presence of E6 Activates E2F-responsive genes in the presence of E6 Immortalizes HFKs in the presence of E6	Cornet et al. (2012)
		Binds Iκκα (Co-IP) Attenuates NF-κB-mediated transcription	Byg et al. (2012)
Beta 3	**HPV49 E7**	Fails to cooperate with RAS to transform primary rodent cells Binds pRB and enhances phospho-pRB levels in the presence of E6 Activates E2F-responsive genes in the presence of E6 Immortalizes HFKs in the presence of E6.	Massimi et al. (2008) Cornet et al. (2012)

Table 12 (*continued*)

Genus	HPV type	Phenotype	References
Gamma			
Gamma 1	**HPV4 E7**	In organotypic raft cultures: Causes hyperkeratosis and altered expression of keratins Significantly increases suprabasal proliferation Fails to cause co-expression of cyclin E and $p16^{INK4A}$ in suprabasal cells	Westphal et al. (2009)
		Binds pRB through C-terminal sequences (aa 39–100)	Wang et al. (2010)
		Upregulates lipocalin-2 in primary keratinocyte monolayers but not in differentiated layers of organotypic raft cultures	Akgul et al. (2011)
		Binds Iκκα (Co-IP) Attenuates NF-κB-mediated transcription	Byg et al. (2012)
Gamma 6	**HPV108 E7**	In organotypic raft cultures: Causes a dysplastic phenotype	Nobre et al. (2009)
Mu			
Mu 1	**HPV1 E7**	Binds pRB with high efficiency Transforms permanent rodent cells Fails to immortalize primary HFKs; Fails to transactivate the Ad E2 promoter	Schmitt et al. (1994)
		Inability to abrogate C/EBPα-mediated growth arrest	Muller et al. (1999)
		Inhibits cellular response to IFN-α	Barnard et al. (2000)
		Fails to destabilize pRB Only partially abrogates pRB-mediated senescence in SAOS2 cells	Gonzalez et al. (2001)
		Fails to abrogate $p16^{INK4A}$-mediated G1 arrest	Giarre et al. (2001)
		Fails to upregulate MT-1-MMP expression	Smola-Hess et al. (2005)
		Binds SMADs Abrogates TGF-β-mediated transactivation	Habig et al. (2006)
		In organotypic raft cultures: Destabilizes p130 Induces unscheduled DNA synthesis in suprabasal cells	Genovese et al. (2008)
		In organotypic raft cultures: Causes hyperkeratosis and dyskeratosis Significantly increases suprabasal proliferation Fails to cause co-expression of cyclin E and $p16^{INK4A}$ in suprabasal cells	Westphal et al. (2009)
		Upregulates lipocalin-2 in primary adult keratinocyte monolayers but not in differentiated layers of organotypic raft cultures.	Akgul et al. (2011)
		Binds to p300 with low efficiency	Fera and Marmorstein (2012)
	HPV1 E7 P31P32PI35/SSE	Enhances binding to p130 Enhances destabilization of p130 in monolayer and cells induced to differentiate Increases induction of suprabasal DNA synthesis Gains ability to be phosphorylated by CKII	Genovese et al. (2008)

Co-IP, Co-immunoprecipitation; GST, Co-affinity purification through association with a glutathione-*S*-transferase fusion protein; NIH 3T3, immortalized murine fibroblasts; SAOS2, pRB/p53 defective human osteosarcoma cell line (ATCC Number: HTB-85).

Table 13
Biological activities of HPV E7 in genetically engineered mouse models (GEMMs).

Expression site	Transgene	Phenotype	References
Eye			
Lens-specific αA crystallin promoter	HPV16 E7	Induces cell proliferation, decreases differentiation and apoptosis in the differentiated lens	Pan and Griep (1994)
	HPV16 E7	Crossed with $E2F1^{-/-}$ mice: Partial loss of ability to disrupt differentiation	McCaffrey et al. (1999)
	del 21–24 (DLYC)	Fails to perturb development in the lens	Pan and Griep (1994)
Retinal photoreceptor cell specific IRBP promoter	HPV16 E7	Induces p53-dependent apoptosis-mediated retinal degeneration	Howes et al. (1994)
Basal epithelial cells			
Skin cancer model: Keratin K14 promoter in FVB mice			
	HPV16 E7	Induces high incidence of squamous epithelial hyperplasia/delayed differentiation Induces low incidence of malignant skin tumors	Herber et al. (1996)
	HPV16 E7	Abrogates inhibition of DNA synthesis in response to ionizing radiation	Song et al. (1998)
	HPV16 E7	Acts as a promoter of skin carcinogenesis	Song et al. (2000)
	HPV16 E7	Deregulates Mmp2, 12, 14, 19 and 27 genes in E7 induced skin cancer.	Ibarra Sierra et al. (2012)
	HPV16 E7	When crossed with Rb conditional knock out mice: Causes pRb-independent dysplasia and increased proliferation	Balsitis et al. (2003)
	HPV16 E7	When crossed with $Rb^{\Delta LXCXE}$ knock in mice: Fails to cause epithelial hyperplasia, stimulate cellular DNA synthesis, abrogate DNA damage induced cell cycle arrest or upregulate $p21^{Cip1}$ Retains ability to delay differentiation resulting in expansion of the spinous layer	Balsitis et al. (2005)
	HPV16 E7	When crossed with $p53^{-/-}$ mice: Retains ability to upregulate $p21^{Cip1}$ but at a reduced level	Balsitis et al. (2005)
	HPV16 E7	When crossed with $p19^{Arf-/-}$ mice: Retains ability to upregulate $p21^{Cip1}$ and p53	Balsitis et al. (2005)
	del 6–10 (PTLHE)	Fails to cause epithelial hyperplasia and benign tumors	Gulliver et al. (1997)
		Fails to abrogate the DNA damage response to radiation	Song et al. (1998)

Table 13 (*continued*)

Expression site	Transgene	Phenotype	References
	del 21–24 (DLYC)	Fails to cause epithelial hyperplasia and benign tumors	Gulliver et al. (1997)
		Fails to abrogate the DNA damage response to radiation	Song et al. (1998)
Cervical carcinoma model: Keratin K14 promoter plus estrogen (0.05 mg/60 days) for 6 months in FVB mice			
	HPV16 E7	Causes multifocal microinvasive cervical carcinomas, increases the number of centrosomes in premalignant lesions, and induces p53 In combination with E6 (which also increases the number of centrosomes but only causes low grade dysplasia), causes large, invasive cancers, and greater numbers of centrosomes/cell	Riley et al. (2003)
	HPV16 E7	Significantly deregulates Dmbt1, Gli1 and 17βHsd2 genes in E7 induced cervical carcinoma	Ibarra Sierra et al. (2012)
	HPV16 E7	When crossed with $Rb^{\Delta LXCXE}$ knock in mice: Fails to stimulate suprabasal DNA synthesis and abrogate DNA damage response to radiation Intermediate ability to up-regulate Mcm7 gene in suprabasal layers Retains ability to induce cervical carcinomas but without dysplasias	Balsitis et al. (2006)
	HPV16 E7	Increases expression of $p21^{Cip1}$ in the suprabasal compartment When crossed with $p21^{Cip1-/-}$ mice: Increases the incidence of cervical disease relative to that seen in $p21^{Cip1-/-}$ mice, but incidence is comparable to that seen in $p21^{Cip1}$ proficient mice.	Shin et al. (2009)
	HPV16 E7	When crossed with mice carrying a constitutively active β-catenin transgene: Causes higher incidence of cervical carcinomas than with either transgene alone	Bulut et al. (2011)
	C68V69Q70/AAA	Reduces ability to induce unscheduled DNA synthesis in suprabasal cells Retains ability to degrade pRB family members and upregulate Mcm7 and $p16^{Ink4a}$ Fails to inactivate $p21^{Cip1}$ and cause severe cervical disease	Shin et al. (2009)
Cervical carcinoma model: Keratin K5 or 14 promoter plus estrogen (0.05 mg/60 days) for 7–10 months in FVB mice			
	Repressible HPV16 E7	When repressed, results in reversion of the acute phenotype and of dysplasia/cancer, whether in the presence or absence of E6	Jabbar et al. (2009), Jabbar et al. (2012)
Cervical carcinoma model: Keratin K14 promoter in mixed genetic background			
	HPV16 E7	8 months estrogen (0.05 mg/60 days): Causes unscheduled DNA synthesis, high incidence of high grade dysplasia and low incidence of cancer In the absence of stromal but presence of epithelial ERα: Fails to cause unscheduled DNA synthesis, high grade dysplasia or cancer	Chung et al. (2013)
Cervical carcinoma model: Conditional knockout of all three Rb family members plus estrogen (0.05 mg/60 days) for 6 months in FVB mice			
	No transgene	Fails to recapitulate the E7-mediated cancer phenotype but does result in a high incidence of high grade dysplasia Partially recapitulates the E7-mediated induction of unscheduled DNA synthesis Totally recapitulates the E7-mediated abrogation of the DNA damage response	Shin et al. (2012b)
Head and Neck Cancer model: Keratin K14 promoter plus low dose 4-NQO in FVB mice			
	HPV16 E7	Only partially degrades pRb Increases DNA synthesis in basal cells and induces unscheduled DNA synthesis in suprabasal cells Causes high incidence of carcinomas and increases expression of Mcm7 and $p16^{Ink4a,}$ similar to that seen when E6 is expressed along with E7	Strati and Lambert (2007)
	HPV16 E7	Induces DNA damage foci When crossed with $FancD^{-/-}$ mice: Enhances induction of DNA damage foci and increases incidence of carcinomas	Park et al. (2010)
Head and Neck Cancer model: Conditional knockout of pRB plus low dose 4-NQO in FVB mice			
	No Transgene	Fails to increase DNA synthesis in basal cells but does recapitulate the E7-mediated induction of unscheduled DNA synthesis in suprabasal cells Causes only a low incidence of carcinomas but does recapitulate the E7-mediated increase in expression of Mcm7 and $p16^{Ink4a,}$	Strati and Lambert (2007)
Head and Neck Cancer model: Knockout of pRB and p107 plus low dose 4-NQO in FVB mice			
	No Transgene	Recapitulates the E7-mediated head and neck disease phenotype and increased expression of Mcm7, $p16^{Ink4a}$ and Ezh2	Shin et al. (2012a)
Head and Neck Anal Cancer Model: Keratin K14 promoter plus DMBA in FVB mice			
	HPV16 E7	Causes high incidence of anal cancer (mostly highly differentiated) with increased expression of Mcm7, $p16^{Ink4a}$ similar to that seen when E6 is expressed along with E7 Induces unscheduled suprabasal DNA synthesis, upregulates Mcm7, and abrogates radiation induced growth arrest, similar to that seen when E6 is expressed along with E7	Thomas et al. (2011)

DMBA, 7,12-Dimethylbenz(a)anthracene; 4-NQO, 4-Nitroquinoline *N*-oxide; and mutations are all in the HPV16 E7 gene.

Acknowledgments

We sincerely apologize to those authors whose contributions we may have missed. Please submit such data to E7PAVEreview@gmail.com so that it can be included in updated versions of this chapter. The work on HPV E7 biology and biochemistry in our laboratories has been supported over the years by Public Health Service grants CA081135, CA066980, and CA141583 (KM) and AI031494, AI49254, CA124314, AI078489 and VM-56 (AR).

References

Accardi, R., Rubino, R., Scalise, M., Gheit, T., Shahzad, N., Thomas, M., Banks, L., Indiveri, C., Sylla, B.S., Cardone, R.A., Reshkin, S.J., Tommasino, M., 2011. E6 and E7 from human papillomavirus type 16 cooperate to target the PDZ protein Na/H exchange regulatory factor 1. J. Virol. 85, 8208–8216.

Ahola, H., Bergman, P., Strom, A.C., Moreno-Lopez, J., Pettersson, U., 1986. Organization and expression of the transforming region from the European elk papillomavirus (EEPV). Gene 50, 195–205.

Akgul, B., Bauer, B., Zigrino, P., Storey, A., Mauch, C., Pfister, H., 2011. Upregulation of lipocalin-2 in human papillomavirus-positive keratinocytes and cutaneous squamous cell carcinomas. J. Gen. Virol. 92, 395–401.
Akgul, B., Garcia-Escudero, R., Ghali, L., Pfister, H.J., Fuchs, P.G., Navsaria, H., Storey, A., 2005. The E7 protein of cutaneous human papillomavirus type 8 causes invasion of human keratinocytes into the dermis in organotypic cultures of skin. Cancer Res. 65, 2216–2223.
Akgul, B., Ghali, L., Davies, D., Pfister, H., Leigh, I.M., Storey, A., 2007. HPV8 early genes modulate differentiation and cell cycle of primary human adult keratinocytes. Exp. Dermatol. 16, 590–599.
Allen-Hoffmann, B.L., Schlosser, S.J., Ivarie, C.A., Sattler, C.A., Meisner, L.F., O'Connor, S.L., 2000. Normal growth and differentiation in a spontaneously immortalized near-diploid human keratinocyte cell line, NIKS. J. Invest. Dermatol. 114, 444–455.
Allison, S.J., Jiang, M., Milner, J., 2009. Oncogenic viral protein HPV E7 up-regulates the SIRT1 longevity protein in human cervical cancer cells. Aging (Albany NY) 1, 316–327.
Alonso, L.G., Garcia-Alai, M.M., Nadra, A.D., Lapena, A.N., Almeida, F.L., Gualfetti, P., Prat-Gay, G.D., 2002. High-risk (HPV16) human papillomavirus E7 oncoprotein is highly stable and extended, with conformational transitions that could explain its multiple cellular binding partners. Biochemistry 41, 10510–10518.
Alonso, L.G., Garcia-Alai, M.M., Smal, C., Centeno, J.M., Iacono, R., Castano, E., Gualfetti, P., de Prat-Gay, G., 2004. The HPV16 E7 viral oncoprotein self-assembles into defined spherical oligomers. Biochemistry 43, 3310–3317.
Alonso, L.G., Smal, C., Garcia-Alai, M.M., Chemes, L., Salame, M., de Prat-Gay, G., 2006. Chaperone holdase activity of human papillomavirus E7 oncoprotein. Biochemistry 45, 657–667.
Angeline, M., Merle, E., Moroianu, J., 2003. The E7 oncoprotein of high-risk human papillomavirus type 16 enters the nucleus via a nonclassical Ran-dependent pathway. Virology 317, 13–23.
Antinore, M.J., Birrer, M.J., Patel, D., Nader, L., McCance, D.J., 1996. The human papillomavirus type 16 E7 gene product interacts with and trans-activates the AP1 family of transcription factors. EMBO J. 15, 1950–1960.
Antonsson, A., Payne, E., Hengst, K., McMillan, N.A., 2006. The human papillomavirus type 16 E7 protein binds human interferon regulatory factor-9 via a novel PEST domain required for transformation. J. Interferon Cytokine Res. 26, 455–461.
Arbeit, J.M., Howley, P.M., Hanahan, D., 1996. Chronic estrogen-induced cervical and vaginal squamous carcinogenesis in human papillomavirus type 16 transgenic mice. Proc. Natl. Acad. Sci. USA 93, 2930–2935.
Armstrong, D.J., Roman, A., 1992. Mutagenesis of human papillomavirus types 6 and 16 E7 open reading frames alters the electrophoretic mobility of the expressed proteins. J. Gen. Virol. 73 (Part 5), 1275–1279.
Armstrong, D.J., Roman, A., 1993. The anomalous electrophoretic behavior of the human papillomavirus type 16 E7 protein is due to the high content of acidic amino acid residues. Biochem. Biophys. Res. Commun. 192, 1380–1387.
Armstrong, D.J., Roman, A., 1995. Human papillomavirus type 6 E7 protein is a substrate in vitro of protein kinase C. Biochem. J. 312 (Pt 3), 667–670.
Armstrong, D.J., Roman, A., 1997. The relative ability of human papillomavirus type 6 and human papillomavirus type 16 E7 proteins to transactivate E2F-responsive elements is promoter- and cell-dependent. Virology 239, 238–246.
Arroyo, M., Bagchi, S., Raychaudhuri, P., 1993. Association of the human papillomavirus type 16 E7 protein with the S-phase-specific E2F-cyclin A complex. Mol. Cell. Biol. 13, 6537–6546.
Avvakumov, N., Torchia, J., Mymryk, J.S., 2003. Interaction of the HPV E7 proteins with the pCAF acetyltransferase. Oncogene 22, 3833–3841.
Baldwin, A., Huh, K.W., Munger, K., 2006. Human papillomavirus E7 oncoprotein dysregulates steroid receptor coactivator 1 localization and function. J. Virol. 80, 6669–6677.
Balsitis, S., Dick, F., Dyson, N., Lambert, P.F., 2006. Critical roles for non-pRb targets of human papillomavirus type 16 E7 in cervical carcinogenesis. Cancer Res. 66, 9393–9400.
Balsitis, S., Dick, F., Lee, D., Farrell, L., Hyde, R.K., Griep, A.E., Dyson, N., Lambert, P.F., 2005. Examination of the pRb-dependent and pRb-independent functions of E7 in vivo. J. Virol. 79, 11392–11402.
Balsitis, S.J., Sage, J., Duensing, S., Munger, K., Jacks, T., Lambert, P.F., 2003. Recapitulation of the effects of the human papillomavirus type 16 E7 oncogene on mouse epithelium by somatic Rb deletion and detection of pRb-independent effects of E7 in vivo. Mol. Cell. Biol. 23, 9094–9103.
Banerjee, N.S., Wang, H.K., Broker, T.R., Chow, L.T., 2011. Human papillomavirus (HPV) E7 induces prolonged G2 following S phase reentry in differentiated human keratinocytes. J. Biol. Chem. 286, 15473–15482.
Banks, L., Edmonds, C., Vousden, K.H., 1990. Ability of the HPV16 E7 protein to bind RB and induce DNA synthesis is not sufficient for efficient transforming activity in NIH3T3 cells. Oncogene 5, 1383–1389.
Barbosa, M.S., Edmonds, C., Fisher, C., Schiller, J.T., Lowy, D.R., Vousden, K.H., 1990. The region of the HPV E7 oncoprotein homologous to adenovirus E1a and Sv40 large T antigen contains separate domains for Rb binding and casein kinase II phosphorylation. EMBO J. 9, 153–160.
Barbosa, M.S., Lowy, D.R., Schiller, J.T., 1989. Papillomavirus polypeptides E6 and E7 are zinc-binding proteins. J. Virol. 63, 1404–1407.
Barnard, P., McMillan, N.A., 1999. The human papillomavirus E7 oncoprotein abrogates signaling mediated by interferon-alpha. Virology 259, 305–313.
Barnard, P., Payne, E., McMillan, N.A., 2000. The human papillomavirus E7 protein is able to inhibit the antiviral and anti-growth functions of interferon-alpha. Virology 277, 411–419.
Barrow-Laing, L., Chen, W., Roman, A., 2010. Low- and high-risk human papillomavirus E7 proteins regulate p130 differently. Virology 400, 233–239.
Basile, J.R., Zacny, V., Munger, K., 2001. The cytokines tumor necrosis factor-alpha (TNF-alpha) and TNF-related apoptosis-inducing ligand differentially modulate proliferation and apoptotic pathways in human keratinocytes expressing the human papillomavirus-16 E7 oncoprotein. J. Biol. Chem. 276, 22522–22528.
Bates, S., Phillips, A.C., Clark, P.A., Stott, F., Peters, G., Ludwig, R.L., Vousden, K.H., 1998. p14ARF links the tumour suppressors RB and p53. Nature 395, 124–125.
Beltramini, M., Giacometti, G.M., Salvato, B., Giacometti, G., Munger, K., Lerch, K., 1989. Luminescence emission from Neurospora copper metallothionein. Time-resolved studies. Biochem. J. 260, 189–193.
Ben-Saadon, R., Fajerman, I., Ziv, T., Hellman, U., Schwartz, A.L., Ciechanover, A., 2004. The tumor suppressor protein p16(INK4a) and the human papillomavirus oncoprotein-58 E7 are naturally occurring lysine-less proteins that are degraded by the ubiquitin system. Direct evidence for ubiquitination at the N-terminal residue. J. Biol. Chem. 279, 41414–41421.
Berezutskaya, E., Bagchi, S., 1997. The human papillomavirus E7 oncoprotein functionally interacts with the S4 subunit of the 26 S proteasome. J. Biol. Chem. 272, 30135–30140.
Berezutskaya, E., Yu, B., Morozov, A., Raychaudhuri, P., Bagchi, S., 1997. Differential regulation of the pocket domains of the retinoblastoma family proteins by the HPV16 E7 oncoprotein. Cell Growth Differ. 8, 1277–1286.
Bernat, A., Avvakumov, N., Mymryk, J.S., Banks, L., 2003. Interaction between the HPV E7 oncoprotein and the transcriptional coactivator p300. Oncogene 22, 7871–7881.
Bischof, O., Nacerddine, K., Dejean, A., 2005. Human papillomavirus oncoprotein E7 targets the promyelocytic leukemia protein and circumvents cellular senescence via the Rb and p53 tumor suppressor pathways. Mol. Cell. Biol. 25, 1013–1024.
Boccardo, E., Manzini Baldi, C.V., Carvalho, A.F., Rabachini, T., Torres, C., Barreta, L.A., Brentani, H., Villa, L.L., 2010. Expression of human papillomavirus type 16 E7 oncoprotein alters keratinocytes expression profile in response to tumor necrosis factor-alpha. Carcinogenesis 31, 521–531.
Bodily, J.M., Mehta, K.P., Cruz, L., Meyers, C., Laimins, L.A., 2011a. The E7 open reading frame acts in cis and in trans to mediate differentiation-dependent activities in the human papillomavirus type 16 life cycle. J. Virol. 85, 8852–8862.
Bodily, J.M., Mehta, K.P., Laimins, L.A., 2011b. Human papillomavirus E7 enhances hypoxia-inducible factor 1-mediated transcription by inhibiting binding of histone deacetylases. Cancer Res. 71, 1187–1195.
Bottalico, D., Chen, Z., Dunne, A., Ostoloza, J., McKinney, S., Sun, C., Schlecht, N.F., Fatahzadeh, M., Herrero, R., Schiffman, M., Burk, R.D., 2011. The oral cavity contains abundant known and novel human papillomaviruses from the Betapapillomavirus and Gammapapillomavirus genera. J. Infect. Dis. 204, 787–792.
Boxman, I.L., Mulder, L.H., Noya, F., de Waard, V., Gibbs, S., Broker, T.R., ten Kate, F., Chow, L.T., ter Schegget, J., 2001. Transduction of the E6 and E7 genes of epidermodysplasia-verruciformis-associated human papillomaviruses alters human keratinocyte growth and differentiation in organotypic cultures. J. Invest. Dermatol. 117, 1397–1404.
Boyer, S.N., Wazer, D.E., Band, V., 1996. E7 protein of human papilloma virus-16 induces degradation of retinoblastoma protein through the ubiquitin-proteasome pathway. Cancer Res. 56, 4620–4624.
Brake, T., Lambert, P.F., 2005. Estrogen contributes to the onset, persistence, and malignant progression of cervical cancer in a human papillomavirus-transgenic mouse model. Proc. Natl. Acad. Sci. USA 102, 2490–2495.
Brehm, A., Nielsen, S.J., Miska, E.A., McCance, D.J., Reid, J.L., Bannister, A.J., Kouzarides, T., 1999. The E7 oncoprotein associates with Mi2 and histone deacetylase activity to promote cell growth. EMBO J. 18, 2449–2458.
Brokaw, J.L., Yee, C.L., Munger, K., 1994. A mutational analysis of the amino terminal domain of the human papillomavirus type 16 E7 oncoprotein. Virology 205, 603–607.
Brooks, L.A., Sullivan, A., O'Nions, J., Bell, A., Dunne, B., Tidy, J.A., Evans, D.J., Osin, P., Vousden, K.H., Gusterson, B., Farrell, P.J., Storey, A., Gasco, M., Sakai, T., Crook, T., 2002. E7 proteins from oncogenic human papillomavirus types transactivate p73: role in cervical intraepithelial neoplasia. Br. J. Cancer 86, 263–268.
Buitrago-Perez, A., Hachimi, M., Duenas, M., Lloveras, B., Santos, A., Holguin, A., Duarte, B., Santiago, J.L., Akgul, B., Rodriguez-Peralto, J.L., Storey, A., Ribas, C., Larcher, F., del Rio, M., Paramio, J.M., Garcia-Escudero, R., 2012. A humanized mouse model of HPV-associated pathology driven by E7 expression. PLoS One 7, e41743.
Bulut, G., Fallen, S., Beauchamp, E.M., Drebing, L.E., Sun, J., Berry, D.L., Kallakury, B., Crum, C.P., Toretsky, J.A., Schlegel, R., Uren, A., 2011. Beta-catenin accelerates human papilloma virus type-16 mediated cervical carcinogenesis in transgenic mice. PLoS One 6, e27243.
Burgers, W.A., Blanchon, L., Pradhan, S., de Launoit, Y., Kouzarides, T., Fuks, F, 2007. Viral oncoproteins target the DNA methyltransferases. Oncogene 26, 1650–1655.
Byg, L.M., Vidlund, J., Vasiljevic, N., Clausen, D., Forslund, O., Norrild, B., 2012. NF-kappaB signalling is attenuated by the E7 protein from cutaneous human papillomaviruses. Virus Res. 169, 48–53.
Caldeira, S., Zehbe, I., Accardi, R., Malanchi, I., Dong, W., Giarre, M., de Villiers, E.M., Filotico, R., Boukamp, P., Tommasino, M., 2003. The E6 and E7 proteins of the cutaneous human papillomavirus type 38 display transforming properties. J. Virol. 77, 2195–2206.

Campo-Fernandez, B., Morandell, D., Santer, F.R., Zwerschke, W., Jansen-Durr, P., 2007. Identification of the FHL2 transcriptional coactivator as a new functional target of the E7 oncoprotein of human papillomavirus type 16. J. Virol. 81, 1027–1032.
Cardeal, L.B., Boccardo, E., Termini, L., Rabachini, T., Andreoli, M.A., di Loreto, C., Longatto Filho, A., Villa, L.L., Maria-Engler, S.S., 2012. HPV16 oncoproteins induce MMPs/RECK-TIMP-2 imbalance in primary keratinocytes: possible implications in cervical carcinogenesis. PLoS One 7, e33585.
Charette, S.T., McCance, D.J., 2007. The E7 protein from human papillomavirus type 16 enhances keratinocyte migration in an Akt-dependent manner. Oncogene 26, 7386–7390.
Chellappan, S., Kraus, V.B., Kroger, B., Munger, K., Howley, P.M., Phelps, W.C., Nevins, J.R., 1992. Adenovirus E1A, simian virus 40 tumor antigen, and human papillomavirus E7 protein share the capacity to disrupt the interaction between transcription factor E2F and the retinoblastoma gene product. Proc. Natl. Acad. Sci. USA 89, 4549–4553.
Chen, Z., Schiffman, M., Herrero, R., Desalle, R., Burk, R.D., 2007. Human papillomavirus (HPV) types 101 and 103 isolated from cervicovaginal cells lack an E6 open reading frame (ORF) and are related to gamma-papillomaviruses. Virology 360, 447–453.
Cheng, S., Schmidt-Grimminger, D.C., Murant, T., Broker, T.R., Chow, L.T., 1995. Differentiation-dependent up-regulation of the human papillomavirus E7 gene reactivates cellular DNA replication in suprabasal differentiated keratinocytes. Genes Dev. 9, 2335–2349.
Chesters, P.M., Vousden, K.H., Edmonds, C., McCance, D.J., 1990. Analysis of human papillomavirus type 16 open reading frame E7 immortalizing function in rat embryo fibroblast cells. J. Gen. Virol. 71 (Part 2), 449–453.
Chien, W.M., Parker, J.N., Schmidt-Grimminger, D.C., Broker, T.R., Chow, L.T., 2000. Casein kinase II phosphorylation of the human papillomavirus-18 E7 protein is critical for promoting S-phase entry. Cell Growth Differ. 11, 425–435.
Chung, S.H., Shin, M.K., Korach, K.S., Lambert, P.F., 2013. Requirement for stromal estrogen receptor alpha in cervical neoplasia. Horm Cancer 4, 50–59.
Clawson, G.A., Bui, V., Xin, P., Wang, N., Pan, W., 2008. Intracellular localization of the tumor suppressor HtrA1/Prss11 and its association with HPV16 E6 and E7 proteins. J. Cell. Biochem. 105, 81–88.
Clemens, K.E., Brent, R., Gyuris, J., Munger, K., 1995. Dimerization of the human papillomavirus E7 oncoprotein in vivo. Virology 214, 289–293.
Clements, A., Johnston, K., Mazzarelli, J.M., Ricciardi, R.P., Marmorstein, R., 2000. Oligomerization properties of the viral oncoproteins adenovirus E1A and human papillomavirus E7 and their complexes with the retinoblastoma protein. Biochemistry 39, 16033–16045.
Cole, S.T., Danos, O., 1987. Nucleotide sequence and comparative analysis of the human papillomavirus type 18 genome. Phylogeny of papillomaviruses and repeated structure of the E6 and E7 gene products. J. Mol. Biol. 193, 599–608.
Collins, A.S., Nakahara, T., Do, A., Lambert, P.F., 2005. Interactions with pocket proteins contribute to the role of human papillomavirus type 16 E7 in the papillomavirus life cycle. J. Virol. 79, 14769–14780.
Cornet, I., Bouvard, V., Campo, M.S., Thomas, M., Banks, L., Gissmann, L., Lamartine, J., Sylla, B.S., Accardi, R., Tommasino, M., 2012. Comparative analysis of transforming properties of E6 and E7 from different beta human papillomavirus types. J. Virol. 86, 2366–2370.
Darnell, G.A., Schroder, W.A., Antalis, T.M., Lambley, E., Major, L., Gardner, J., Birrell, G., Cid-Arregui, A., Suhrbier, A., 2007. Human papillomavirus E7 requires the protease calpain to degrade the retinoblastoma protein. J. Biol. Chem. 282, 37492–37500.
Davies, R.C., Vousden, K.H., 1992. Functional analysis of human papillomavirus type 16 E7 by complementation with adenovirus E1A mutants. J. Gen. Virol. 73 (Pt 8), 2135–2139.
De Luca, A., Mangiacasale, R., Severino, A., Malquori, L., Baldi, A., Palena, A., Mileo, A. M., Lavia, P., Paggi, M.G., 2003. E1A deregulates the centrosome cycle in a Ran GTPase-dependent manner. Cancer Res. 63, 1430–1437.
de Villiers, E.M., Fauquet, C., Broker, T.R., Bernard, H.U., zur Hausen, H., 2004. Classification of papillomaviruses. Virology 324, 17–27.
DeCaprio, J.A., Ludlow, J.W., Figge, J., Shew, J.Y., Huang, C.M., Lee, W.H., Marsilio, E., Paucha, E., Livingston, D.M., 1988. SV40 large tumor antigen forms a specific complex with the product of the retinoblastoma susceptibility gene. Cell 54, 275–283.
Defeo-Jones, D., Huang, P.S., Jones, R.E., Haskell, K.M., Vuocolo, G.A., Hanobik, M.G., Huber, H.E., Oliff, A., 1991. Cloning of cDNAs for cellular proteins that bind to the retinoblastoma gene product. Nature 352, 251–254.
DeFilippis, R.A., Goodwin, E.C., Wu, L., DiMaio, D., 2003. Endogenous human papillomavirus E6 and E7 proteins differentially regulate proliferation, senescence, and apoptosis in HeLa cervical carcinoma cells. J. Virol. 77, 1551–1563.
Demers, G.W., Espling, E., Harry, J.B., Etscheid, B.G., Galloway, D.A., 1996. Abrogation of growth arrest signals by human papillomavirus type 16 E7 is mediated by sequences required for transformation. J. Virol. 70, 6862–6869.
Demers, G.W., Foster, S.A., Halbert, C.L., Galloway, D.A., 1994a. Growth arrest by induction of p53 in DNA damaged keratinocytes is bypassed by human papillomavirus 16 E7. Proc. Natl. Acad. Sci. USA 91, 4382–4386.
Demers, G.W., Halbert, C.L., Galloway, D.A., 1994b. Elevated wild-type p53 protein levels in human epithelial cell lines immortalized by the human papillomavirus type 16 E7 gene. Virology 198, 169–174.
Duensing, S., Lee, L.Y., Duensing, A., Basile, J., Piboonniyom, S., Gonzalez, S., Crum, C. P., Munger, K., 2000. The human papillomavirus type 16 E6 and E7 oncoproteins cooperate to induce mitotic defects and genomic instability by uncoupling centrosome duplication from the cell division cycle. Proc. Natl. Acad Sci. USA 97, 10002–10007.
Duensing, S., Munger, K., 2002. The human papillomavirus type 16 E6 and E7 oncoproteins independently induce numerical and structural chromosome instability. Cancer Res. 62, 7075–7082.
Duensing, S., Munger, K., 2003. Human papillomavirus type 16 E7 oncoprotein can induce abnormal centrosome duplication through a mechanism independent of inactivation of retinoblastoma protein family members. J. Virol. 77, 12331–12335.
Dyson, N., Guida, P., Munger, K., Harlow, E., 1992. Homologous sequences in adenovirus E1A and human papillomavirus E7 proteins mediate interaction with the same set of cellular proteins. J. Virol. 66, 6893–6902.
Dyson, N., Howley, P.M., Munger, K., Harlow, E., 1989. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. Science 243, 934–937.
Edmonds, C., Vousden, K.H., 1989. A point mutational analysis of human papillomavirus type 16 E7 protein. J. Virol. 63, 2650–2656.
Egan, C., Jelsma, T.N., Howe, J.A., Bayley, S.T., Ferguson, B., Branton, P.E., 1988. Mapping of cellular protein-binding sites on the products of early-region 1A of human adenovirus type 5. Mol. Cell. Biol. 8, 3955–3959.
Fan, X., Liu, Y., Heilman, S.A., Chen, J.J., 2013. Human papillomavirus E7 induces rereplication in response to DNA damage. J. Virol. 87, 1200–1210.
Fera, D., Marmorstein, R., 2012. Different regions of the HPV-E7 and Ad-E1A viral oncoproteins bind competitively but through distinct mechanisms to the CH1 transactivation domain of p300. Biochemistry 51, 9524–9534.
Figge, J., Smith, T.F., 1988. Cell-division sequence motif. Nature 334, 109.
Firzlaff, J.M., Galloway, D.A., Eisenman, R.N., Luscher, B., 1989. The E7 protein of human papillomavirus type 16 is phosphorylated by casein kinase II. New Biol. 1, 44–53.
Firzlaff, J.M., Luscher, B., Eisenman, R.N., 1991. Negative charge at the casein kinase II phosphorylation site is important for transformation but not for Rb protein binding by the E7 protein of human papillomavirus type 16. Proc. Natl. Acad. Sci. USA 88, 5187–5191.
Flores, E.R., Allen-Hoffmann, B.L., Lee, D., Lambert, P.F., 2000. The human papillomavirus type 16 E7 oncogene is required for the productive stage of the viral life cycle. J. Virol. 74, 6622–6631.
Fujikawa, K., Furuse, M., Uwabe, K., Maki, H., Yoshie, O., 1994. Nuclear localization and transforming activity of human papillomavirus type 16 E7-beta-galactosidase fusion protein: characterization of the nuclear localization sequence. Virology 204, 789–793.
Funk, J.O., Waga, S., Harry, J.B., Espling, E., Stillman, B., Galloway, D.A., 1997. Inhibition of CDK activity and PCNA-dependent DNA replication by p21 is blocked by interaction with the HPV-16 E7 oncoprotein. Genes Dev. 11, 2090–2100.
Gammoh, N., Grm, H.S., Massimi, P., Banks, L., 2006. Regulation of human papillomavirus type 16 E7 activity through direct protein interaction with the E2 transcriptional activator. J. Virol. 80, 1787–1797.
Garcia-Alai, M.M., Alonso, L.G., de Prat-Gay, G., 2007. The N-terminal module of HPV16 E7 is an intrinsically disordered domain that confers conformational and recognition plasticity to the oncoprotein. Biochemistry 46, 10405–10412.
Genovese, N.J., Banerjee, N.S., Broker, T.R., Chow, L.T., 2008. Casein kinase II motif-dependent phosphorylation of human papillomavirus E7 protein promotes p130 degradation and S-phase induction in differentiated human keratinocytes. J. Virol. 82, 4862–4873.
Genovese, N.J., Broker, T.R., Chow, L.T., 2011. Nonconserved lysine residues attenuate the biological function of the low-risk human papillomavirus E7 protein. J. Virol. 85, 5546–5554.
Georgopoulos, N.T., Proffitt, J.L., Blair, G.E., 2000. Transcriptional regulation of the major histocompatibility complex (MHC) class I heavy chain, TAP1 and LMP2 genes by the human papillomavirus (HPV) type 6b, 16 and 18 E7 oncoproteins. Oncogene 19, 4930–4935.
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 40, 1–13.
Giarre, M., Caldeira, S., Malanchi, I., Ciccolini, F., Leao, M.J., Tommasino, M., 2001. Induction of pRb degradation by the human papillomavirus type 16 E7 protein is essential to efficiently overcome p16INK4a-imposed G1 cell cycle arrest. J. Virol. 75, 4705–4712.
Gonzalez, S.L., Stremlau, M., He, X., Basile, J.R., Munger, K., 2001. Degradation of the retinoblastoma tumor suppressor by the human papillomavirus type 16 E7 oncoprotein is important for functional inactivation and is separable from proteasomal degradation of E7. J. Virol. 75, 7583–7591.
Gottschling, M., Bravo, I.G., Schulz, E., Bracho, M.A., Deaville, R., Jepson, P.D., Van Bressem, M.F., Stockfleth, E., Nindl, I., 2011. Modular organizations of novel cetacean papillomaviruses. Mol. Phylogenet. Evol. 59, 34–42.
Greenfield, I., Nickerson, J., Penman, S., Stanley, M., 1991. Human papillomavirus 16 E7 protein is associated with the nuclear matrix. Proc. Natl. Acad. Sci. USA 88, 11217–11221.
Guccione, E., Massimi, P., Bernat, A., Banks, L., 2002. Comparative analysis of the intracellular location of the high- and low-risk human papillomavirus oncoproteins. Virology 293, 20–25.
Gulbahce, N., Yan, H., Dricot, A., Padi, M., Byrdsong, D., Franchi, R., Lee, D.S., Rozenblatt-Rosen, O., Mar, J.C., Calderwood, M.A., Baldwin, A., Zhao, B., Santhanam, B., Braun, P., Simonis, N., Huh, K.W., Hellner, K., Grace, M., Chen, A., Rubio, R., Marto, J.A., Christakis, N.A., Kieff, E., Roth, F.P., Roecklein-Canfield, J., Decaprio, J.A., Cusick, M.E., Quackenbush, J., Hill, D.E., Munger, K., Vidal, M.,

Barabasi, A.L., 2012. Viral perturbations of host networks reflect disease etiology. PLoS Comput. Biol. 8, e1002531.
Gulliver, G.A., Herber, R.L., Liem, A., Lambert, P.F., 1997. Both conserved region 1 (CR1) and CR2 of the human papillomavirus type 16 E7 oncogene are required for induction of epidermal hyperplasia and tumor formation in transgenic mice. J. Virol. 71, 5905–5914.
Habig, M., Smola, H., Dole, V.S., Derynck, R., Pfister, H., Smola-Hess, S., 2006. E7 proteins from high- and low-risk human papillomaviruses bind to TGF-beta-regulated Smad proteins and inhibit their transcriptional activity. Arch. Virol. 151, 1961–1972.
Halbert, C.L., Demers, G.W., Galloway, D.A., 1991. The E7 gene of human papillomavirus type 16 is sufficient for immortalization of human epithelial cells. J. Virol. 65, 473–478.
Halbert, C.L., Demers, G.W., Galloway, D.A., 1992. The E6 and E7 genes of human papillomavirus type 6 have weak immortalizing activity in human epithelial cells. J. Virol. 66, 2125–2134.
Harlow, E., Whyte, P., Franza Jr., B.R., Schley, C., 1986. Association of adenovirus early-region 1A proteins with cellular polypeptides. Mol. Cell. Biol. 6, 1579–1589.
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. J. Immunol. 178, 3186–3197.
He, W., Staples, D., Smith, C., Fisher, C., 2003. Direct activation of cyclin-dependent kinase 2 by human papillomavirus E7. J. Virol. 77, 10566–10574.
Heck, D.V., Yee, C.L., Howley, P.M., Munger, K., 1992. Efficiency of binding the retinoblastoma protein correlates with the transforming capacity of the E7 oncoproteins of the human papillomaviruses. Proc. Natl. Acad. Sci. USA 89, 4442–4446.
Heilman, S.A., Nordberg, J.J., Liu, Y., Sluder, G., Chen, J.J., 2009. Abrogation of the postmitotic checkpoint contributes to polyploidization in human papillomavirus E7-expressing cells. J. Virol. 83, 2756–2764.
Heller, C., Weisser, T., Mueller-Schickert, A., Rufer, E., Hoh, A., Leonhardt, R.M., Knittler, M.R., 2011. Identification of key amino acid residues that determine the ability of high risk HPV16-E7 to dysregulate major histocompatibility complex class I expression. J. Biol. Chem. 286, 10983–10997.
Helt, A.M., Funk, J.O., Galloway, D.A., 2002. Inactivation of both the retinoblastoma tumor suppressor and p21 by the human papillomavirus type 16 E7 oncoprotein is necessary to inhibit cell cycle arrest in human epithelial cells. J. Virol. 76, 10559–10568.
Helt, A.M., Galloway, D.A., 2001. Destabilization of the retinoblastoma tumor suppressor by human papillomavirus type 16 E7 is not sufficient to overcome cell cycle arrest in human keratinocytes. J. Virol. 75, 6737–6747.
Herber, R., Liem, A., Pitot, H., Lambert, P.F., 1996. Squamous epithelial hyperplasia and carcinoma in mice transgenic for the human papillomavirus type 16 E7 oncogene. J. Virol. 70, 1873–1881.
Hermonat, P.L., Santin, A.D., Zhan, D., 2000. Binding of the human papillomavirus type 16 E7 oncoprotein and the adeno-associated virus Rep78 major regulatory protein in vitro and in yeast and the potential for downstream effects. J. Hum. Virol. 3, 113–124.
Holland, D., Hoppe-Seyler, K., Schuller, B., Lohrey, C., Maroldt, J., Durst, M., Hoppe-Seyler, F., 2008. Activation of the enhancer of zeste homologue 2 gene by the human papillomavirus E7 oncoprotein. Cancer Res. 68, 9964–9972.
Hong, S., Mehta, K.P., Laimins, L.A., 2011. Suppression of STAT-1 expression by human papillomaviruses is necessary for differentiation-dependent genome amplification and plasmid maintenance. J. Virol. 85, 9486–9494.
Howes, K.A., Ransom, N., Papermaster, D.S., Lasudry, J.G., Albert, D.M., Windle, J.J., 1994. Apoptosis or retinoblastoma: alternative fates of photoreceptors expressing the HPV-16 E7 gene in the presence or absence of p53. Genes Dev. 8, 1300–1310.
Huang, P.S., Patrick, D.R., Edwards, G., Goodhart, P.J., Huber, H.E., Miles, L., Garsky, V. M., Oliff, A., Heimbrook, D.C., 1993. Protein domains governing interactions between E2F, the retinoblastoma gene product, and human papillomavirus type 16 E7 protein. Mol. Cell. Biol. 13, 953–960.
Huang, S.M., McCance, D.J., 2002. Down regulation of the interleukin-8 promoter by human papillomavirus type 16 E6 and E7 through effects on CREB binding protein/p300 and P/CAF. J. Virol. 76, 8710–8721.
Huh, K., Zhou, X., Hayakawa, H., Cho, J.Y., Libermann, T.A., Jin, J., Harper, J.W., 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. J. Virol. 81, 9737–9747.
Huh, K.W., DeMasi, J., Ogawa, H., Nakatani, Y., Howley, P.M., Munger, K., 2005. Association of the human papillomavirus type 16 E7 oncoprotein with the 600-kDa retinoblastoma protein-associated factor, p600. Proc. Natl. Acad. Sci. USA 102, 11492–11497.
Hussain, I., Fathallah, I., Accardi, R., Yue, J., Saidj, D., Shukla, R., Hasan, U., Gheit, T., Niu, Y., Tommasino, M., Sylla, B.S., 2011. NF-kappaB protects human papillomavirus type 38 E6/E7-immortalized human keratinocytes against tumor necrosis factor alpha and UV-mediated apoptosis. J. Virol. 85, 9013–9022.
Hwang, S.G., Lee, D., Kim, J., Seo, T., Choe, J., 2002. Human papillomavirus type 16 E7 binds to E2F1 and activates E2F1-driven transcription in a retinoblastoma protein-independent manner. J. Biol. Chem. 277, 2923–2930.
Ibarra Sierra, E., Diaz Chavez, J., Cortes-Malagon, E.M., Uribe-Figueroa, L., Hidalgo-Miranda, A., Lambert, P.F., Gariglio, P., 2012. Differential gene expression between skin and cervix induced by the E7 oncoprotein in a transgenic mouse model. Virology 433, 337–345.
Jabbar, S.F., Abrams, L., Glick, A., Lambert, P.F., 2009. Persistence of high-grade cervical dysplasia and cervical cancer requires the continuous expression of the human papillomavirus type 16 E7 oncogene. Cancer Res. 69, 4407–4414.
Jabbar, S.F., Park, S., Schweizer, J., Berard-Bergery, M., Pitot, H.C., Lee, D., Lambert, P. F., 2012. Cervical cancers require the continuous expression of the human papillomavirus type 16 E7 oncoprotein even in the presence of the viral E6 oncoprotein. Cancer Res. 72, 4008–4016.
Jeon, J.H., Choi, K.H., Cho, S.Y., Kim, C.W., Shin, D.M., Kwon, J.C., Song, K.Y., Park, S.C., Kim, I.G., 2003. Transglutaminase 2 inhibits Rb binding of human papillomavirus E7 by incorporating polyamine. EMBO J. 22, 5273–5282.
Jewers, R.J., Hildebrandt, P., Ludlow, J.W., Kell, B., McCance, D.J., 1992. Regions of human papillomavirus type 16 E7 oncoprotein required for immortalization of human keratinocytes. J. Virol. 66, 1329–1335.
Jones, D.L., Alani, R.M., Munger, K., 1997a. The human papillomavirus E7 oncoprotein can uncouple cellular differentiation and proliferation in human keratinocytes by abrogating p21Cip1-mediated inhibition of cdk2. Genes Dev. 11, 2101–2111.
Jones, D.L., Munger, K., 1997. Analysis of the p53-mediated G1 growth arrest pathway in cells expressing the human papillomavirus type 16 E7 oncoprotein. J. Virol. 71, 2905–2912.
Jones, D.L., Thompson, D.A., Munger, K., 1997b. Destabilization of the RB tumor suppressor protein and stabilization of p53 contribute to HPV type 16 E7-induced apoptosis. Virology 239, 97–107.
Jones, R.E., Wegrzyn, R.J., Patrick, D.R., Balishin, N.L., Vuocolo, G.A., Riemen, M.W., Defeo-Jones, D., Garsky, V.M., Heimbrook, D.C., Oliff, A., 1990. Identification of HPV-16 E7 peptides that are potent antagonists of E7 binding to the retinoblastoma suppressor protein. J. Biol. Chem. 265, 12782–12785.
Klingelhutz, A.J., Roman, A., 2012. Cellular transformation by human papillomaviruses: lessons learned by comparing high- and low-risk viruses. Virology 424, 77–98.
Knapp, A.A., McManus, P.M., Bockstall, K., Moroianu, J., 2009. Identification of the nuclear localization and export signals of high risk HPV16 E7 oncoprotein. Virology 383, 60–68.
Korzeniewski, N., Treat, B., Duensing, S., 2011. The HPV-16 E7 oncoprotein induces centriole multiplication through deregulation of Polo-like kinase 4 expression. Mol. Cancer 10, 61.
Lam, E.W., Morris, J.D., Davies, R., Crook, T., Watson, R.J., Vousden, K.H., 1994. HPV16 E7 oncoprotein deregulates B-myb expression: correlation with targeting of p107/E2F complexes. EMBO J. 13, 871–878.
Laurson, J., Khan, S., Chung, R., Cross, K., Raj, K., 2010. Epigenetic repression of E-cadherin by human papillomavirus 16 E7 protein. Carcinogenesis 31, 918–926.
Lee, D., Lim, C., Seo, T., Kwon, H., Min, H., Choe, J., 2002a. The viral oncogene human papillomavirus E7 deregulates transcriptional silencing by Brm-related gene 1 via molecular interactions. J. Biol. Chem. 277, 48842–48848.
Lee, D.K., Kim, B.C., Kim, I.Y., Cho, E.A., Satterwhite, D.J., Kim, S.J., 2002b. The human papilloma virus E7 oncoprotein inhibits transforming growth factor-beta signaling by blocking binding of the Smad complex to its target sequence. J. Biol. Chem. 277, 38557–38564.
Lee, J.O., Russo, A.A., Pavletich, N.P., 1998. Structure of the retinoblastoma tumour-suppressor pocket domain bound to a peptide from HPV E7. Nature 391, 859–865.
Li, H., Zhan, T., Li, C., Liu, M., Wang, Q.K., 2009. Repression of MHC class I transcription by HPV16E7 through interaction with a putative RXRbeta motif and NF-kappaB cytoplasmic sequestration. Biochem. Biophys. Res. Commun. 388, 383–388.
Liang, Y.J., Chang, H.S., Wang, C.Y., Yu, W.C., 2008. DYRK1A stabilizes HPV16E7 oncoprotein through phosphorylation of the threonine 5 and threonine 7 residues. Int. J. Biochem. Cell. Biol. 40, 2431–2441.
Liu, X., Clements, A., Zhao, K., Marmorstein, R., 2006. Structure of the human Papillomavirus E7 oncoprotein and its mechanism for inactivation of the retinoblastoma tumor suppressor. J. Biol. Chem. 281, 578–586.
Liu, X., Roberts, J., Dakic, A., Zhang, Y., Schlegel, R., 2008. HPV E7 contributes to the telomerase activity of immortalized and tumorigenic cells and augments E6-induced hTERT promoter function. Virology 375, 611–623.
Longworth, M.S., Laimins, L.A., 2004. The binding of histone deacetylases and the integrity of zinc finger-like motifs of the E7 protein are essential for the life cycle of human papillomavirus type 31. J. Virol. 78, 3533–3541.
Longworth, M.S., Wilson, R., Laimins, L.A., 2005. HPV31 E7 facilitates replication by activating E2F2 transcription through its interaction with HDACs. EMBO J. 24, 1821–1830.
Luscher-Firzlaff, J.M., Westendorf, J.M., Zwicker, J., Burkhardt, H., Henriksson, M., Muller, R., Pirollet, F., Luscher, B., 1999. Interaction of the fork head domain transcription factor MPP2 with the human papilloma virus 16 E7 protein: enhancement of transformation and transactivation. Oncogene 18, 5620–5630.
Maldonado, E., Cabrejos, M.E., Banks, L., Allende, J.E., 2002. Human papillomavirus-16 E7 protein inhibits the DNA interaction of the TATA binding transcription factor. J. Cell. Biochem. 85, 663–669.
Mannhardt, B., Weinzimer, S.A., Wagner, M., Fiedler, M., Cohen, P., Jansen-Durr, P., Zwerschke, W., 2000. Human papillomavirus type 16 E7 oncoprotein binds and inactivates growth-inhibitory insulin-like growth factor binding protein 3. Mol. Cell. Biol. 20, 6483–6495.
Martin, L.G., Demers, G.W., Galloway, D.A., 1998. Disruption of the G1/S transition in human papillomavirus type 16 E7-expressing human cells is associated with altered regulation of cyclin E. J. Virol. 72, 975–985.
Massimi, P., Banks, L., 2000. Differential phosphorylation of the HPV-16 E7 oncoprotein during the cell cycle. Virology 276, 388–394.
Massimi, P., Pim, D., Banks, L., 1997. Human papillomavirus type 16 E7 binds to the conserved carboxy-terminal region of the TATA box binding protein and this contributes to E7 transforming activity. J. Gen. Virol. 78 (Pt 10), 2607–2613.

Massimi, P., Thomas, M., Bouvard, V., Ruberto, I., Campo, M.S., Tommasino, M., Banks, L., 2008. Comparative transforming potential of different human papillomaviruses associated with non-melanoma skin cancer. Virology 371, 374–379.
Matlashewski, G., Schneider, J., Banks, L., Jones, N., Murray, A., Crawford, L., 1987. Human papillomavirus type 16 DNA cooperates with activated ras in transforming primary cells. EMBO J. 6, 1741–1746.
Mavromatis, K.O., Jones, D.L., Mukherjee, R., Yee, C., Grace, M., Munger, K., 1997. The carboxyl-terminal zinc-binding domain of the human papillomavirus E7 protein can be functionally replaced by the homologous sequences of the E6 protein. Virus Res. 52, 109–118.
Mazzarelli, J.M., Atkins, G.B., Geisberg, J.V., Ricciardi, R.P., 1995. The viral oncoproteins Ad5 E1A, HPV16 E7 and SV40 TAg bind a common region of the TBP-associated factor-110. Oncogene 11, 1859–1864.
McCaffrey, J., Yamasaki, L., Dyson, N.J., Harlow, E., Griep, A.E., 1999. Disruption of retinoblastoma protein family function by human papillomavirus type 16 E7 oncoprotein inhibits lens development in part through E2F-1. Mol. Cell. Biol. 19, 6458–6468.
McCloskey, R., Menges, C., Friedman, A., Patel, D., McCance, D.J., 2010. Human papillomavirus type 16 E6/E7 upregulation of nucleophosmin is important for proliferation and inhibition of differentiation. J. Virol. 84, 5131–5139.
McIntyre, M.C., Frattini, M.G., Grossman, S.R., Laimins, L.A., 1993. Human papillomavirus type 18 E7 protein requires intact Cys-X-X-Cys motifs for zinc binding, dimerization, and transformation but not for Rb binding. J. Virol. 67, 3142–3150.
McIntyre, M.C., Ruesch, M.N., Laimins, L.A., 1996. Human papillomavirus E7 oncoproteins bind a single form of cyclin E in a complex with cdk2 and p107. Virology 215, 73–82.
McLaughlin-Drubin, M.E., Bromberg-White, J.L., Meyers, C., 2005. The role of the human papillomavirus type 18 E7 oncoprotein during the complete viral life cycle. Virology 338, 61–68.
McLaughlin-Drubin, M.E., Crum, C.P., Munger, K., 2011. Human papillomavirus E7 oncoprotein induces KDM6A and KDM6B histone demethylase expression and causes epigenetic reprogramming. Proc. Natl. Acad. Sci. USA 108, 2130–2135.
McLaughlin-Drubin, M.E., Huh, K.W., Munger, K., 2008. Human papillomavirus type 16 E7 oncoprotein associates with E2F6. J. Virol. 82, 8695–8705.
McLaughlin-Drubin, M.E., Meyers, J., Munger, K., 2012. Cancer associated human papillomaviruses. Curr. Opin. Virol. 2, 459–466.
McLaughlin-Drubin, M.E., Munger, K., 2009. The human papillomavirus E7 oncoprotein. Virology 384, 335–344.
Melar-New, M., Laimins, L.A., 2010. Human papillomaviruses modulate expression of microRNA 203 upon epithelial differentiation to control levels of p63 proteins. J. Virol. 84, 5212–5221.
Melillo, R.M., Helin, K., Lowy, D.R., Schiller, J.T., 1994. Positive and negative regulation of cell proliferation by E2F-1: influence of protein level and human papillomavirus oncoproteins. Mol. Cell. Biol. 14, 8241–8249.
Menges, C.W., Baglia, L.A., Lapoint, R., McCance, D.J., 2006. Human papillomavirus type 16 E7 up-regulates AKT activity through the retinoblastoma protein. Cancer Res. 66, 5555–5559.
Mileo, A.M., Abbruzzese, C., Mattarocci, S., Bellacchio, E., Pisano, P., Federico, A., Maresca, V., Picardo, M., Giorgi, A., Maras, B., Schinina, M.E., Paggi, M.G., 2009. Human papillomavirus-16 E7 interacts with glutathione S-transferase P1 and enhances its role in cell survival. PLoS One 4, e7254.
Mileo, A.M., Piombino, E., Severino, A., Tritarelli, A., Paggi, M.G., Lombardi, D., 2006. Multiple interference of the human papillomavirus-16 E7 oncoprotein with the functional role of the metastasis suppressor Nm23-H1 protein. J. Bioenerg. Biomembr. 38, 215–225.
Moody, C.A., Fradet-Turcotte, A., Archambault, J., Laimins, L.A., 2007. Human papillomaviruses activate caspases upon epithelial differentiation to induce viral genome amplification. Proc. Natl. Acad. Sci. USA 104, 19541–19546.
Moody, C.A., Laimins, L.A., 2009. Human papillomaviruses activate the ATM DNA damage pathway for viral genome amplification upon differentiation. PLoS Pathog. 5, e1000605.
Moody, C.A., Laimins, L.A., 2010. Human papillomavirus oncoproteins: pathways to transformation. Nat. Rev. Cancer 10, 550–560.
Morandell, D., Kaiser, A., Herold, S., Rostek, U., Lechner, S., Mitterberger, M.C., Jansen-Durr, P., Eilers, M., Zwerschke, W., 2012. The human papillomavirus type 16 E7 oncoprotein targets Myc-interacting zinc-finger protein-1. Virology 422, 242–253.
Morosov, A., Phelps, W.C., Raychaudhuri, P., 1994. Activation of the c-fos gene by the HPV16 oncoproteins depends upon the cAMP-response element at -60. J. Biol. Chem. 269, 18434–18440.
Morozov, A., Shiyanov, P., Barr, E., Leiden, J.M., Raychaudhuri, P., 1997. Accumulation of human papillomavirus type 16 E7 protein bypasses G1 arrest induced by serum deprivation and by the cell cycle inhibitor p21. J. Virol. 71, 3451–3457.
Morris, J.D., Crook, T., Bandara, L.R., Davies, R., LaThangue, N.B., Vousden, K.H., 1993. Human papillomavirus type 16 E7 regulates E2F and contributes to mitogenic signalling. Oncogene 8, 893–898.
Muller, C., Alunni-Fabbroni, M., Kowenz-Leutz, E., Mo, X., Tommasino, M., Leutz, A., 1999. Separation of C/EBPalpha-mediated proliferation arrest and differentiation pathways. Proc. Natl. Acad. Sci. USA 96, 7276–7281.
Munger, K., Phelps, W.C., Bubb, V., Howley, P.M., Schlegel, R., 1989a. The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. J. Virol. 63, 4417–4421.
Munger, K., Werness, B.A., Dyson, N., Phelps, W.C., Harlow, E., Howley, P.M., 1989b. Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product. EMBO J. 8, 4099–4105.
Munger, K., Yee, C.L., Phelps, W.C., Pietenpol, J.A., Moses, H.L., Howley, P.M., 1991. Biochemical and biological differences between E7 oncoproteins of the high- and low-risk human papillomavirus types are determined by amino-terminal sequences. J. Virol. 65, 3943–3948.
Nguyen, C.L., Eichwald, C., Nibert, M.L., Munger, K., 2007. Human papillomavirus type 16 E7 oncoprotein associates with the centrosomal component gamma-tubulin. J. Virol. 81, 13533–13543.
Nguyen, C.L., Munger, K., 2008. Direct association of the HPV16 E7 oncoprotein with cyclin A/CDK2 and cyclin E/CDK2 complexes. Virology 380, 21–25.
Nguyen, C.L., Munger, K., 2009. Human papillomavirus E7 protein deregulates mitosis via an association with nuclear mitotic apparatus protein 1. J. Virol. 83, 1700–1707.
Nguyen, D.X., Westbrook, T.F., McCance, D.J., 2002. Human papillomavirus type 16 E7 maintains elevated levels of the cdc25A tyrosine phosphatase during deregulation of cell cycle arrest. J. Virol. 76, 619–632.
Nobre, R.J., Herraez-Hernandez, E., Fei, J.W., Langbein, L., Kaden, S., Grone, H.J., de Villiers, E.M., 2009. E7 oncoprotein of novel human papillomavirus type 108 lacking the E6 gene induces dysplasia in organotypic keratinocyte cultures. J. Virol. 83, 2907–2916.
Nomine, Y., Masson, M., Charbonnier, S., Zanier, K., Ristriani, T., Deryckere, F., Sibler, A.P., Desplancq, D., Atkinson, R.A., Weiss, E., Orfanoudakis, G., Kieffer, B., Trave, G., 2006. Structural and functional analysis of E6 oncoprotein: insights in the molecular pathways of human papillomavirus-mediated pathogenesis. Mol. Cell. 21, 665–678.
Oh, K.J., Kalinina, A., Wang, J., Nakayama, K., Nakayama, K.I., Bagchi, S., 2004a. The papillomavirus E7 oncoprotein is ubiquitinated by UbcH7 and Cullin 1- and Skp2-containing E3 ligase. J. Virol. 78, 5338–5346.
Oh, S.T., Longworth, M.S., Laimins, L.A., 2004b. Roles of the E6 and E7 proteins in the life cycle of low-risk human papillomavirus type 11. J. Virol. 78, 2620–2626.
Ohlenschlager, O., Seiboth, T., Zengerling, H., Briese, L., Marchanka, A., Ramachandran, R., Baum, M., Korbas, M., Meyer-Klaucke, W., Durst, M., Gorlach, M., 2006. Solution structure of the partially folded high-risk human papilloma virus 45 oncoprotein E7. Oncogene 25, 5953–5959.
Pan, H., Griep, A.E., 1994. Altered cell cycle regulation in the lens of HPV-16 E6 or E7 transgenic mice: implications for tumor suppressor gene function in development. Genes Dev. 8, 1285–1299.
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. J. Biol. Chem. 275, 6764–6769.
Park, J.W., Pitot, H.C., Strati, K., Spardy, N., Duensing, S., Grompe, M., Lambert, P.F., 2010. Deficiencies in the Fanconi anemia DNA damage response pathway increase sensitivity to HPV-associated head and neck cancer. Cancer Res. 70, 9959–9968.
Pater, M.M., Nakshatri, H., Kisaka, C., Pater, A., 1992. The first 124 nucleotides of the E7 coding sequences of HPV16 can render the HPV11 genome transformation competent. Virology 186, 348–351.
Patrick, D.R., Oliff, A., Heimbrook, D.C., 1994. Identification of a novel retinoblastoma gene product binding site on human papillomavirus type 16 E7 protein. J. Biol. Chem. 269, 6842–6850.
Perea, S.E., Massimi, P., Banks, L., 2000. Human papillomavirus type 16 E7 impairs the activation of the interferon regulatory factor-1. Int. J. Mol. Med. 5, 661–666.
Pfister, H., 2003. Chapter 8: Human papillomavirus and skin cancer. J. Natl. Cancer Inst. Monogr., 52–56.
Phelps, W.C., Bagchi, S., Barnes, J.A., Raychaudhuri, P., Kraus, V., Munger, K., Howley, P.M., Nevins, J.R., 1991. Analysis of trans activation by human papillomavirus type 16 E7 and adenovirus 12S E1A suggests a common mechanism. J. Virol. 65, 6922–6930.
Phelps, W.C., Munger, K., Yee, C.L., Barnes, J.A., Howley, P.M., 1992. Structure-function analysis of the human papillomavirus type 16 E7 oncoprotein. J. Virol. 66, 2418–2427.
Phelps, W.C., Yee, C.L., Munger, K., Howley, P.M., 1988. The human papillomavirus type 16 E7 gene encodes transactivation and transformation functions similar to those of adenovirus E1A. Cell 53, 539–547.
Phillips, A.C., Vousden, K.H., 1997. Analysis of the interaction between human papillomavirus type 16 E7 and the TATA-binding protein, TBP. J. Gen. Virol. 78 (Part 4), 905–909.
Piccioli, Z., McKee, C.H., Leszczynski, A., Onder, Z., Hannah, E.C., Mamoor, S., Crosby, L., Moroianu, J., 2010. The nuclear localization of low risk HPV11 E7 protein mediated by its zinc binding domain is independent of nuclear import receptors. Virology 407, 100–109.
Pietenpol, J.A., Stein, R.W., Moran, E., Yaciuk, P., Schlegel, R., Lyons, R.M., Pittelkow, M.R., Munger, K., Howley, P.M., Moses, H.L., 1990. TGF-beta 1 inhibition of c-myc transcription and growth in keratinocytes is abrogated by viral transforming proteins with pRB binding domains. Cell 61, 777–785.
Pim, D., Banks, L., 2010. Interaction of viral oncoproteins with cellular target molecules: infection with high-risk vs low-risk human papillomaviruses. APMIS, 118; 471–493.
Pim, D., Massimi, P., Dilworth, S.M., Banks, L., 2005. Activation of the protein kinase B pathway by the HPV-16 E7 oncoprotein occurs through a mechanism involving interaction with PP2A. Oncogene 24, 7830–7838.
Prathapam, T., Kuhne, C., Banks, L., 2001. The HPV-16 E7 oncoprotein binds Skip and suppresses its transcriptional activity. Oncogene 20, 7677–7685.
Psyrri, A., DeFilippis, R.A., Edwards, A.P., Yates, K.E., Manuelidis, L., DiMaio, D., 2004. Role of the retinoblastoma pathway in senescence triggered by repression of

the human papillomavirus E7 protein in cervical carcinoma cells. Cancer Res. 64, 3079–3086.
Rawls, J.A., Pusztai, R., Green, M., 1990. Chemical synthesis of human papillomavirus type 16 E7 oncoprotein: autonomous protein domains for induction of cellular DNA synthesis and for trans activation. J. Virol. 64, 6121–6129.
Reinstein, E., Scheffner, M., Oren, M., Ciechanover, A., Schwartz, A., 2000. Degradation of the E7 human papillomavirus oncoprotein by the ubiquitin-proteasome system: targeting via ubiquitination of the N-terminal residue. Oncogene 19, 5944–5950.
Reshkin, S.J., Bellizzi, A., Caldeira, S., Albarani, V., Malanchi, I., Poignee, M., Alunni-Fabbroni, M., Casavola, V., Tommasino, M., 2000. Na+/H+ exchanger-dependent intracellular alkalinization is an early event in malignant transformation and plays an essential role in the development of subsequent transformation-associated phenotypes. FASEB J. 14, 2185–2197.
Rey, O., Lee, S., Baluda, M.A., Swee, J., Ackerson, B., Chiu, R., Park, N.H., 2000. The E7 oncoprotein of human papillomavirus type 16 interacts with F-actin in vitro and in vivo. Virology 268, 372–381.
Riley, R.R., Duensing, S., Brake, T., Munger, K., Lambert, P.F., Arbeit, J.M., 2003. Dissection of human papillomavirus E6 and E7 function in transgenic mouse models of cervical carcinogenesis. Cancer Res. 63, 4862–4871.
Roth, E.J., Kurz, B., Liang, L., Hansen, C.L., Dameron, C.T., Winge, D.R., Smotkin, D., 1992. Metal thiolate coordination in the E7 proteins of human papilloma virus 16 and cottontail rabbit papilloma virus as expressed in Escherichia coli. J. Biol. Chem. 267, 16390–16395.
Rozenblatt-Rosen, O., Deo, R.C., Padi, M., Adelmant, G., Calderwood, M.A., Rolland, T., Grace, M., Dricot, A., Askenazi, M., Tavares, M., Pevzner, S.J., Abderazzaq, F., Byrdsong, D., Carvunis, A.R., Chen, A.A., Cheng, J., Correll, M., Duarte, M., Fan, C., Feltkamp, M.C., Ficarro, S.B., Franchi, R., Garg, B.K., Gulbahce, N., Hao, T., Holthaus, A.M., James, R., Korkhin, A., Litovchick, L., Mar, J.C., Pak, T.R., Rabello, S., Rubio, R., Shen, Y., Singh, S., Spangle, J.M., Tasan, M., Wanamaker, S., Webber, J.T., Roecklein-Canfield, J., Johannsen, E., Barabasi, A.L., Beroukhim, R., Kieff, E., Cusick, M.E., Hill, D.E., Munger, K., Marto, J.A., Quackenbush, J., Roth, F.P., DeCaprio, J.A., Vidal, M., 2012. Interpreting cancer genomes using systematic host network perturbations by tumour virus proteins. Nature 487, 491–495.
Ruesch, M.N., Laimins, L.A., 1997. Initiation of DNA synthesis by human papillomavirus E7 oncoproteins is resistant to p21-mediated inhibition of cyclin E-cdk2 activity. J. Virol. 71, 5570–5578.
Sang, B.C., Barbosa, M.S., 1992. Single amino acid substitutions in "low-risk" human papillomavirus (HPV) type 6 E7 protein enhance features characteristic of the "high-risk" HPV E7 oncoproteins. Proc. Natl. Acad. Sci. USA 89, 8063–8067.
Santer, F.R., Moser, B., Spoden, G.A., Jansen-Durr, 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 28, 2511–2520.
Sato, H., Watanabe, S., Furuno, A., Yoshiike, K., 1989. Human papillomavirus type 16 E7 protein expressed in *Escherichia coli* and monkey COS-1 cells: immunofluorescence detection of the nuclear E7 protein. Virology 170, 311–315.
Schaeffer, A.J., Nguyen, M., Liem, A., Lee, D., Montagna, C., Lambert, P.F., Ried, T., Difilippantonio, M.J., 2004. E6 and E7 oncoproteins induce distinct patterns of chromosomal aneuploidy in skin tumors from transgenic mice. Cancer Res. 64, 538–546.
Schaper, I.D., Marcuzzi, G.P., Weissenborn, S.J., Kasper, H.U., Dries, V., Smyth, N., Fuchs, P., Pfister, H., 2005. Development of skin tumors in mice transgenic for early genes of human papillomavirus type 8. Cancer Res. 65, 1394–1400.
Schilling, B., De-Medina, T., Syken, J., Vidal, M., Munger, K., 1998. A novel human DnaJ protein, hTid-1, a homolog of the Drosophila tumor suppressor protein Tid56, can interact with the human papillomavirus type 16 E7 oncoprotein. Virology 247, 74–85.
Schmitt, A., Harry, J.B., Rapp, B., Wettstein, F.O., Iftner, T., 1994. Comparison of the properties of the E6 and E7 genes of low- and high-risk cutaneous papillomaviruses reveals strongly transforming and high Rb-binding activity for the E7 protein of the low-risk human papillomavirus type 1. J. Virol. 68, 7051–7059.
Schulze, A., Mannhardt, B., Zerfass-Thome, K., Zwerschke, W., Jansen-Durr, P., 1998. Anchorage-independent transcription of the cyclin A gene induced by the E7 oncoprotein of human papillomavirus type 16. J. Virol. 72, 2323–2334.
Seavey, S.E., Holubar, M., Saucedo, L.J., Perry, M.E., 1999. The E7 oncoprotein of human papillomavirus type 16 stabilizes p53 through a mechanism independent of p19(ARF). J. Virol. 73, 7590–7598.
Sedman, S.A., Barbosa, M.S., Vass, W.C., Hubbert, N.L., Haas, J.A., Lowy, D.R., Schiller, J.T., 1991. The full-length E6 protein of human papillomavirus type 16 has transforming and trans-activating activities and cooperates with E7 to immortalize keratinocytes in culture. J. Virol. 65, 4860–4866.
Severino, A., Abbruzzese, C., Manente, L., Valderas, A.A., Mattarocci, S., Federico, A., Starace, G., Chersi, A., Mileo, A.M., Paggi, M.G., 2007. Human papillomavirus-16 E7 interacts with Siva-1 and modulates apoptosis in HaCaT human immortalized keratinocytes. J. Cell. Physiol. 212, 118–125.
Shin, M.K., Balsitis, S., Brake, T., Lambert, P.F., 2009. Human papillomavirus E7 oncoprotein overrides the tumor suppressor activity of p21Cip1 in cervical carcinogenesis. Cancer Res. 69, 5656–5663.
Shin, M.K., Pitot, H.C., Lambert, P.F., 2012a. Pocket proteins suppress head and neck cancer. Cancer Res. 72, 1280–1289.
Shin, M.K., Sage, J., Lambert, P.F., 2012b. Inactivating all three rb family pocket proteins is insufficient to initiate cervical cancer. Cancer Res. 72, 5418–5427.
Smith-McCune, K., Kalman, D., Robbins, C., Shivakumar, S., Yuschenkoff, L., Bishop, J. M., 1999. Intranuclear localization of human papillomavirus 16 E7 during transformation and preferential binding of E7 to the Rb family member p130. Proc. Natl. Acad. Sci. USA 96, 6999–7004.
Smola-Hess, S., Pahne, J., Mauch, C., Zigrino, P., Smola, H., Pfister, H.J., 2005. Expression of membrane type 1 matrix metalloproteinase in papillomavirus-positive cells: role of the human papillomavirus (HPV) 16 and HPV8 E7 gene products. J. Gen. Virol. 86, 1291–1296.
Smotkin, D., Wettstein, F.O., 1987. The major human papillomavirus protein in cervical cancers is a cytoplasmic phosphoprotein. J. Virol. 61, 1686–1689.
Song, S., Gulliver, G.A., Lambert, P.F., 1998. Human papillomavirus type 16 E6 and E7 oncogenes abrogate radiation-induced DNA damage responses in vivo through p53-dependent and p53-independent pathways. Proc. Natl. Acad. Sci. USA 95, 2290–2295.
Song, S., Liem, A., Miller, J.A., Lambert, P.F., 2000. Human papillomavirus types 16 E6 and E7 contribute differently to carcinogenesis. Virology 267, 141–150.
Southern, S.A., Lewis, M.H., Herrington, C.S., 2004. Induction of tetrasomy by human papillomavirus type 16 E7 protein is independent of pRb binding and disruption of differentiation. Br. J. Cancer 90, 1949–1954.
Southern, S.A., Noya, F., Meyers, C., Broker, T.R., Chow, L.T., Herrington, C.S., 2001. Tetrasomy is induced by human papillomavirus type 18 E7 gene expression in keratinocyte raft cultures. Cancer Res. 61, 4858–4863.
Spardy, N., Covella, K., Cha, E., Hoskins, E.E., Wells, S.I., Duensing, A., Duensing, S., 2009. Human papillomavirus 16 E7 oncoprotein attenuates DNA damage checkpoint control by increasing the proteolytic turnover of claspin. Cancer Res. 69, 7022–7029.
Spardy, N., Duensing, A., Charles, D., Haines, N., Nakahara, T., Lambert, P.F., Duensing, S., 2007. The human papillomavirus type 16 E7 oncoprotein activates the Fanconi anemia (FA) pathway and causes accelerated chromosomal instability in FA cells. J. Virol. 81, 13265–13270.
Spardy, N., Duensing, A., Hoskins, E.E., Wells, S.I., Duensing, S., 2008. HPV-16 E7 reveals a link between DNA replication stress, fanconi anemia D2 protein, and alternative lengthening of telomere-associated promyelocytic leukemia bodies. Cancer Res. 68, 9954–9963.
Sperling, T., Oldak, M., Walch-Ruckheim, B., Wickenhauser, C., Doorbar, J., Pfister, H., Malejczyk, M., Majewski, S., Keates, A.C., Smola, S., 2012. Human papillomavirus type 8 interferes with a novel C/EBPbeta-mediated mechanism of keratinocyte CCL20 chemokine expression and Langerhans cell migration. PLoS Pathog. 8, e1002833.
Spitkovsky, D., Hehner, S.P., Hofmann, T.G., Moller, A., Schmitz, M.L., 2002. The human papillomavirus oncoprotein E7 attenuates NF-kappa B activation by targeting the Ikappa B kinase complex. J. Biol. Chem. 277, 25576–25582.
Stevens, H., Rector, A., Bertelsen, M.F., Leifsson, P.S., Van Ranst, M., 2008a. Novel papillomavirus isolated from the oral mucosa of a polar bear does not cluster with other papillomaviruses of carnivores. Vet. Microbiol. 129 (108–116).
Stevens, H., Rector, A., Van Der Kroght, K., Van Ranst, M., 2008b. Isolation and cloning of two variant papillomaviruses from domestic pigs: Sus scrofa papillomaviruses type 1 variants a and b. J. Gen. Virol. 89, 2475–2481.
Stoppler, H., Stoppler, M.C., Adduci, A., Koval, D., Schlegel, R., 1996. The serine protease inhibitors TLCK and TPCK react with the RB-binding core of HPV-18 E7 protein and abolish its RB-binding capability. Virology 217, 542–553.
Storey, A., Almond, N., Osborn, K., Crawford, L., 1990a. Mutations of the human papillomavirus type 16 E7 gene that affect transformation, transactivation and phosphorylation by the E7 protein. J. Gen. Virol. 71 (Pt 4), 965–970.
Storey, A., Osborn, K., Crawford, L., 1990b. Co-transformation by human papillomavirus types 6 and 11. J. Gen. Virol. 71 (Pt 1), 165–171.
Strati, K., Lambert, P.F., 2007. Role of Rb-dependent and Rb-independent functions of papillomavirus E7 oncogene in head and neck cancer. Cancer Res. 67, 11585–11593.
Thomas, J.T., Hubert, W.G., Ruesch, M.N., Laimins, L.A., 1999. Human papillomavirus type 31 oncoproteins E6 and E7 are required for the maintenance of episomes during the viral life cycle in normal human keratinocytes. Proc. Natl. Acad. Sci. USA 96, 8449–8454.
Thomas, J.T., Laimins, L.A., 1998. Human papillomavirus oncoproteins E6 and E7 independently abrogate the mitotic spindle checkpoint. J. Virol. 72, 1131–1137.
Thomas, J.T., Oh, S.T., Terhune, S.S., Laimins, L.A., 2001. Cellular changes induced by low-risk human papillomavirus type 11 in keratinocytes that stably maintain viral episomes. J. Virol. 75, 7564–7571.
Thomas, M.K., Pitot, H.C., Liem, A., Lambert, P.F., 2011. Dominant role of HPV16 E7 in anal carcinogenesis. Virology 421, 114–118.
Thompson, D.A., Zacny, V., Belinsky, G.S., Classon, M., Jones, D.L., Schlegel, R., Munger, K., 2001. The HPV E7 oncoprotein inhibits tumor necrosis factor alpha-mediated apoptosis in normal human fibroblasts. Oncogene 20, 3629–3640.
Todorovic, B., Hung, K., Massimi, P., Avvakumov, N., Dick, F.A., Shaw, G.S., Banks, L., Mymryk, J.S., 2012. Conserved region 3 of human papillomavirus 16 E7 contributes to deregulation of the retinoblastoma tumor suppressor. J. Virol. 86, 13313–13323.
Todorovic, B., Massimi, P., Hung, K., Shaw, G.S., Banks, L., Mymryk, J.S., 2011. Systematic analysis of the amino Acid residues of human papillomavirus type 16 e7 conserved region 3 involved in dimerization and transformation. J. Virol. 85, 10048–10057.
Tomaic, V., Gardiol, D., Massimi, P., Ozbun, M., Myers, M., Banks, L., 2009. Human and primate tumour viruses use PDZ binding as an evolutionarily conserved mechanism of targeting cell polarity regulators. Oncogene 28, 1–8.

Tugizov, S., Berline, J., Herrera, R., Penaranda, M.E., Nakagawa, M., Palefsky, J., 2005. Inhibition of human papillomavirus type 16 E7 phosphorylation by the S100 MRP-8/14 protein complex. J. Virol. 79, 1099–1112.
Valdovinos-Torres, H., Orozco-Morales, M., Pedroza-Saavedra, A., Padilla-Noriega, L., Esquivel-Guadarrama, F., Gutierrez-Xicotencatl, L., 2008. Different Isoforms of HPV-16 E7 Protein are Present in Cytoplasm and Nucleus. Open Virol. J. 2, 15–23.
Vambutas, A., DeVoti, J., Pinn, W., Steinberg, B.M., Bonagura, V.R., 2001. Interaction of human papillomavirus type 11 E7 protein with TAP-1 results in the reduction of ATP-dependent peptide transport. Clin. Immunol. 101, 94–99.
Van Doorslaer, K., Sidi, A.O., Zanier, K., Rybin, V., Deryckere, F., Rector, A., Burk, R.D., Lienau, E.K., van Ranst, M., Trave, G., 2009. Identification of unusual E6 and E7 proteins within avian papillomaviruses: cellular localization, biophysical characterization, and phylogenetic analysis. J. Virol. 83, 8759–8770.
Vandermark, E.R., Deluca, K.A., Gardner, C.R., Marker, D.F., Schreiner, C.N., Strickland, D.A., Wilton, K.M., Mondal, S., Woodworth, C.D., 2012. Human papillomavirus type 16 E6 and E 7 proteins alter NF-kB in cultured cervical epithelial cells and inhibition of NF-kB promotes cell growth and immortalization. Virology 425, 53–60.
Viarisio, D., Mueller-Decker, K., Kloz, U., Aengeneyndt, B., Kopp-Schneider, A., Grone, H.J., Gheit, T., Flechtenmacher, C., Gissmann, L., Tommasino, M., 2011. E6 and E7 from beta HPV38 cooperate with ultraviolet light in the development of actinic keratosis-like lesions and squamous cell carcinoma in mice. PLoS Pathog. 7, e1002125.
Vogt, B., Zerfass-Thome, K., Schulze, A., Botz, J.W., Zwerschke, W., Jansen-Durr, P., 1999. Regulation of cyclin E gene expression by the human papillomavirus type 16 E7 oncoprotein. J. Gen. Virol. 80 (Pt 8), 2103–2113.
Vousden, K.H., Doniger, J., DiPaolo, J.A., Lowy, D.R., 1988. The E7 open reading frame of human papillomavirus type 16 encodes a transforming gene. Oncogene Res. 3, 167–175.
Walker, J., Smiley, L.C., Ingram, D., Roman, A., 2011. Expression of human papillomavirus type 16 E7 is sufficient to significantly increase expression of angiogenic factors but is not sufficient to induce endothelial cell migration. Virology 410, 283–290.
Wang, J., Zhou, D., Prabhu, A., Schlegel, R., Yuan, H., 2010. The canine papillomavirus and gamma HPV E7 proteins use an alternative domain to bind and destabilize the retinoblastoma protein. PLoS Pathog. 6, e1001089.
Wang, X., Qi, M., Yu, X., Yuan, Y., Zhao, W., 2012. Type-specific interaction between human papillomavirus type 58 E2 protein and E7 protein inhibits E7-mediated oncogenicity. J. Gen. Virol. 93, 1563–1572.
Wang, Y.W., Chang, H.S., Lin, C.H., Yu, W.C., 2007. HPV-18 E7 conjugates to c-Myc and mediates its transcriptional activity. Int. J. Biochem. Cell. Biol. 39, 402–412.
Watanabe, S., Kanda, T., Sato, H., Furuno, A., Yoshiike, K., 1990. Mutational analysis of human papillomavirus type 16 E7 functions. J. Virol. 64, 207–214.
Watanabe, S., Sato, H., Komiyama, N., Kanda, T., Yoshiike, K., 1992. The E7 functions of human papillomaviruses in rat 3Y1 cells. Virology 187, 107–114.
Wazer, D.E., Liu, X.L., Chu, Q., Gao, Q., Band, V., 1995. Immortalization of distinct human mammary epithelial cell types by human papilloma virus 16 E6 or E7. Proc. Natl. Acad. Sci. USA 92, 3687–3691.
Westbrook, T.F., Nguyen, D.X., Thrash, B.R., McCance, D.J., 2002. E7 abolishes raf-induced arrest via mislocalization of p21(Cip1). Mol. Cell. Biol. 22, 7041–7052.
Westphal, K., Akgul, B., Storey, A., Nindl, I., 2009. Cutaneous human papillomavirus E7 type-specific effects on differentiation and proliferation of organotypic skin cultures. Cell. Oncol. 31, 213–226.
White, E.A., Howley, P.M., 2013. Proteomic approaches to the study of papillomavirus-host interactions. Virology 435, 57–69.
White, E.A., Sowa, M.E., Tan, M.J., Jeudy, S., Hayes, S.D., Santha, S., Munger, K., Harper, J.W., Howley, P.M., 2012. Systematic identification of interactions between host cell proteins and E7 oncoproteins from diverse human papillomaviruses. Proc. Natl. Acad. Sci. USA 109, E260–267.
Whyte, P., Buchkovich, K.J., Horowitz, J.M., Friend, S.H., Raybuck, M., Weinberg, R.A., Harlow, E., 1988. Association between an oncogene and an anti-oncogene: the adenovirus E1A proteins bind to the retinoblastoma gene product. Nature 334, 124–129.
Wise-Draper, T.M., Allen, H.V., Thobe, M.N., Jones, E.E., Habash, K.B., Munger, K., Wells, S.I., 2005. The human DEK proto-oncogene is a senescence inhibitor and an upregulated target of high-risk human papillomavirus E7. J. Virol. 79, 14309–14317.
Wise-Draper, T.M., Wells, S.I., 2008. Papillomavirus E6 and E7 proteins and their cellular targets. Front. Biosci. 13, 1003–1017.
Wu, E.W., Clemens, K.E., Heck, D.V., Munger, K., 1993. The human papillomavirus E7 oncoprotein and the cellular transcription factor E2F bind to separate sites on the retinoblastoma tumor suppressor protein. J. Virol. 67, 2402–2407.
Yaginuma, Y., Eguchi, A., Yoshimoto, M., Ogawa, K., 2012. The PxDLLCxE sequence in conserved region 2 of human papilloma virus 18 protein E7 is required for E7 binding to centromere protein C. Oncology 83, 210–217.
Yamashita, T., Segawa, K., Fujinaga, Y., Nishikawa, T., Fujinaga, K., 1993. Biological and biochemical activity of E7 genes of the cutaneous human papillomavirus type 5 and 8. Oncogene 8, 2433–2441.
Yu, Y., Munger, K., 2012. Human papillomavirus type 16 E7 oncoprotein engages but does not abrogate the mitotic spindle assembly checkpoint. Virology 432, 120–126.
Yue, J., Shukla, R., Accardi, R., Zanella-Cleon, I., Siouda, M., Cros, M.P., Krutovskikh, V., Hussain, I., Niu, Y., Hu, S., Becchi, M., Jurdic, P., Tommasino, M., Sylla, B.S., 2011. Cutaneous human papillomavirus type 38 E7 regulates actin cytoskeleton structure for increasing cell proliferation through CK2 and the eukaryotic elongation factor 1A. J. Virol. 85, 8477–8494.
Zatsepina, O., Braspenning, J., Robberson, D., Hajibagheri, M.A., Blight, K.J., Ely, S., Hibma, M., Spitkovsky, D., Trendelenburg, M., Crawford, L., Tommasino, M., 1997. The human papillomavirus type 16 E7 protein is associated with the nucleolus in mammalian and yeast cells. Oncogene 14, 1137–1145.
Zerfass, K., Levy, L.M., Cremonesi, C., Ciccolini, F., Jansen-Durr, P., Crawford, L., Ralston, R., Tommasino, M., 1995. Cell cycle-dependent disruption of E2F-p107 complexes by human papillomavirus type 16 E7. J. Gen. Virol. 76 (Pt 7), 1815–1820.
Zerfass-Thome, K., Zwerschke, W., Mannhardt, B., Tindle, R., Botz, J.W., Jansen-Durr, P., 1996. Inactivation of the cdk inhibitor p27KIP1 by the human papillomavirus type 16 E7 oncoprotein. Oncogene 13, 2323–2330.
Zhang, B., Chen, W., Roman, A., 2006. The E7 proteins of low- and high-risk human papillomaviruses share the ability to target the pRB family member p130 for degradation. Proc. Natl. Acad. Sci. USA 103, 437–442.
Zhang, B., Laribee, R.N., Klemsz, M.J., Roman, A., 2004. Human papillomavirus type 16 E7 protein increases acetylation of histone H3 in human foreskin keratinocytes. Virology 329, 189–198.
Zhang, Y., Fan, S., Meng, Q., Ma, Y., Katiyar, P., Schlegel, R., Rosen, E.M., 2005. BRCA1 interaction with human papillomavirus oncoproteins. J. Biol. Chem. 280, 33165–33177.
Zheng, Z.M., Wang, X., 2011. Regulation of cellular miRNA expression by human papillomaviruses. Biochim. Biophys. Acta 1809, 668–677.
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 385, 192–197.
zur Hausen, H., 2002. Papillomaviruses and cancer: from basic studies to clinical application. Nat. Rev. Cancer 2, 342–350.
Zwerschke, W., Mannhardt, B., Massimi, P., Nauenburg, S., Pim, D., Nickel, W., Banks, L., Reuser, A.J., Jansen-Durr, P., 2000. Allosteric activation of acid alpha-glucosidase by the human papillomavirus E7 protein. J. Biol. Chem. 275, 9534–9541.
Zwerschke, W., Mazurek, S., Massimi, P., Banks, L., Eigenbrodt, E., Jansen-Durr, P., 1999. Modulation of type M2 pyruvate kinase activity by the human papillomavirus type 16 E7 oncoprotein. Proc. Natl. Acad. Sci. USA 96, 1291–1296.