



Published in final edited form as:

Curr Opin Virol. 2015 October ; 14: 87–92. doi:10.1016/j.coviro.2015.09.001.

Human papillomaviruses: shared and distinct pathways for pathogenesis

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Abstract

Over 200 types of human papillomaviruses (HPV) have been identified that infect epithelial cells at different anatomic locations. HPVs are grouped into five genera with the alpha and beta viruses being the most commonly studied. Members of the alpha HPV genus infect genital epithelia and are the causative agents of many anogenital cancers. Beta HPVs infect cutaneous epithelia and have been suggested as co-factors in the development of non-melanoma skin cancers. Recent studies have shown that activation of DNA damage pathways is important for the productive life cycle of the alpha HPVs while the beta viruses suppress their activation. These differences likely contribute to the varying types of lesions and malignancies that are associated with these viruses.

Introduction

Human papillomaviruses (HPVs) are associated with a spectrum of manifestations ranging from unapparent infections to malignant neoplasias. HPVs are grouped phylogenetically into five genera, alpha, beta, gamma, mu and nu, and are further divided into species[1]. The alpha-papillomaviruses contain viruses that infect mucosal epithelium, some of which are considered high-risk (HR) and others low-risk (LR) based on their association with cancers. The LR-HPVs can cause cutaneous lesions, and other alpha papillomaviruses only cause benign cutaneous infections. HR-HPVs have been conclusively linked to the etiology of anogenital and oropharyngeal cancers[2]. Infection with HR-HPVs is common in young sexually active women and in men, and is generally resolved by an immune response, though latent HPV infection may remain[3,4]. In some cases HR-HPV infections persist causing genetic instability that can progress to invasive cancer if untreated [5,6]. In these cancers the HPV genome persists, generally integrated into host chromosomes, with expression of the E6 and E7 genes [7,8].

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Genus beta HPVs commonly infect the skin[9]. Unlike the genital tract HPVs, serologic evidence indicates that beta HPV infections occur early in life [10]. Several of the genus beta HPVs were initially detected in squamous cell skin cancers (SCSC) from patients with the rare disease epidermodysplasia verruciformis [11], leading to the hypothesis that beta HPVs were causal for SCSC, just as HR-HPVs are causal for anogenital cancers. However integration of beta HPVs and continued expression of the E6 and E7 genes in SCSC has not been reported, indicating that these HPVs are not required for maintenance of the tumor. Similarly, epidemiologic studies have not supplied strong support for a causal association of the beta HPVs with SCSC. Both mechanistic studies on the beta HPV E6 and E7 proteins, and transgenic mouse models are consistent with the beta HPVs being able to act as cofactors with UV damage to promote carcinogenesis [12–15].

Life cycle of human papillomaviruses

The life cycle of human papillomaviruses is dependent upon differentiation of the host-infected cell and cellular replication proteins (Figure 1) [16]. Human papillomaviruses have small double strand genomes of approximately 8 kilobases in length that encode between 6 and 8 genes. None of these genes except for the E1 and E2 encode polymerases, or other replication factors. E1 encodes an origin recognition and helicase protein while E2 facilitates the assembly of E1 complexes on viral DNAs. This makes viral replication dependent largely upon cellular proteins for both the stable maintenance of viral genomes in undifferentiated cells as well as productive replication or amplification in differentiated cells. HPVs infect stratified squamous epithelia and enter cells in the basal layer that become exposed following trauma or wounding. In these cells, viral genomes are maintained as extrachromosomal elements that replicate in S phase in synchrony with cellular replication. Following entry into basal cells, viral genome copy numbers rapidly increase to about 50 to 100 copies per cell on average and this copy number is maintained at similar levels throughout the course of productive infections. Upon differentiation of suprabasal cells, high level replication of viral genomes is induced in a process referred to as amplification and this occurs concurrently with synthesis of the capsid proteins followed by virion assembly and release.

Amplification of HPV genomes requires differentiating cells to remain active in the cell cycle. For the high-risk alpha viruses, amplification also requires the activation of the ataxia telangiectasia (ATM) pathway[17]. In normal cells, the ATM pathway functions to repair double strand DNA breaks, while in HPV positive cells ATM factors such as pCHK2, NBS1 and pSMC1 are constitutively activated and recruited to viral genomes in both undifferentiated and differentiated cells[18–20]. Interestingly, ATM activation is not required for the stable maintenance of episomes in basal cells but is critical for genome amplification in differentiated cells[17]. The levels of a small number of ATM factors that are recruited to HPV genomes including $\frac{1}{5}$ -H2AX, pCHK2 and pNBS1 increase upon differentiation and contribute to regulation of amplification. Members of the homologous recombination repair arm of the ATM pathway such as RAD51 and SMC1 are specifically required for amplification that occurs in G2 and this is when normal recombination repair also occurs[18,19]. Interestingly, activation of the DNA damage pathway is required for productive replication of the polyomavirus SV40 where it acts as a quality control

mechanism to prevent default to a rolling circle mechanism of replication in favor of theta replication[21]. Whether a similar activity is important for HPV genome amplification remains to be determined.

The requirement for ATM activation does not, however, appear to be shared with the beta papillomaviruses and may be restricted to viruses from high-risk alpha subgroup. In fact, beta HPV E6 protein expression results in reduced expression of ATM and ATR, as well as BRCA1/BRCA2[22]. It has been difficult to study the virus lifecycle of LR-HPVs or beta HPVs because it has not yet been possible to develop experimental systems to study replication. However some differences have been noticed by careful examination of infected tissues. Whereas high risk HPVs stimulate proliferation in the basal and parabasal cells, presumably through degradation of pRb and p107[23–25], LR HPVs only stimulate proliferation in the mid-to upper epithelial layers, because their E7 proteins only degrade p130[26]. The E5 protein of alpha HPVs promotes genome amplification, at least in part through stabilization of the EGF receptor[27,28], but this protein is missing in beta HPVs.

Regulation of HPV Gene Expression

Two major viral promoters along with several minor ones regulate viral gene expression during the differentiation-dependent life cycle. The early promoter of high-risk HPVs is located in the Upstream Regulatory Region (URR) and directs initiation of transcription at sites upstream of the E6 open reading frame. HPV transcripts are all polycistronic encoding between 2 and 4 open reading frames and share a common polyadenylation site at the end of the early region. Alternative splicing and leaky scanning translation initiation regulate the differential expression and synthesis of early viral proteins[29]. The HPV E2 proteins are negative regulators of early promoter expression and this is part of a copy number control mechanism that acts by autoregulating expression of the replication proteins E2 and E1[30]. One characteristic of many HPV-positive cancers is that viral genomes are found integrated into host chromosomes so as to retain expression of only the E6 and E7 genes. Integration leads to the loss of E2 expression and high-level transcription of E6 and E7 viral oncoproteins that contributes to malignant progression. Upon differentiation, the late viral promoter is activated by cellular factors and directs initiation of late transcripts from a series of start sites located in the middle of the E7 open reading frame. The late promoter is not a target of E2 repression and its activation induces high levels of expression of the replication proteins E1 and E2 as well as E1[^]E4, E5 L1 and L2. Differentiation-dependent changes in polyadenylation site usage as well as alternate splicing regulate expression of the capsid proteins L1 and L2[31]. Expression of viral proteins is also regulated by microRNAs (miRNAs), however, HPVs do not encode their own miRNAs but rather modulate the expression of cellular miRNAs[32]. These cellular miRNAs regulate a variety of pathways involving proliferation, differentiation and innate immune surveillance. A large number of cellular miRNAs are altered by HPV proteins suggesting that the mechanisms regulating their expression are highly complex. Interestingly, only one miRNA, miR-145, has been shown to directly regulate viral transcription and to be critical for effects on the viral life cycle[33].

The role of high-risk E6 and E7 in viral oncogenesis

The high-risk HPVs are the causative agents of anogenital as well as some oral cancers and the expression of two viral proteins, E6 and E7, is essential for their development[34]. HPVs often integrate into host chromosomes during malignant progression retaining expression only of E6 and E7. The E6 protein interacts with a number of cellular pathways such as those regulating DNA damage repair through its interactions with p53. In normal cells, p53 acts to arrest cells following DNA damage and allow for repair. In HR-HPV infected cells, E6 recruits the cellular ubiquitin ligase UBE3A (E6AP) into a trimeric complex with p53. This results in the ubiquitination of p53 leading to its rapid turnover[34,35]. E6 proteins from the HPVs from the high-risk species also contain PDZ binding domains at their C-terminus that mediate interactions with a number of PDZ domain containing factors that control differentiation and cell polarity. These interactions are regulated by phosphorylation of the E6 PDZ domain and lead to their rapid degradation[36]. The high-risk HPVs E6 proteins bind and degrade the MAGI (membrane-associated guanylate kinase) as well as DLG and Scribble PDZ-domain containing factors implicating these factors as potentially important for oncogenesis. Other binding partners of the high-risk E6 proteins include the acetyl-transferases p300 and CREB[37], which leads to inhibition of p53 acetylation[38]. Finally, E6 proteins activate expression of the catalytic subunit of telomerase, hTert by degrading the transcriptional repressor, NF1-191[35]. Activation of hTert is found in most human cancers and this activity appears largely restricted to the alpha viruses.

The E7 oncoprotein is co-expressed with E6 in HPV-induced cancers and the two act synergistically to promote oncogenesis. During the productive viral life cycle, these two factors are responsible for maintaining differentiating cells active in the cell cycle but also act to promote malignant progression. E7 proteins bind members of the Rb family of proteins with high-affinity which leads to their degradation and constitutive activation of E2F transcription factors[24,25]. High-risk E7 proteins also activate the ATM DNA damage pathway, which occurs through the release of E2Fs from Rb complexes[17]. Interestingly, overexpression of E1 can also activate the DNA damage response in the absence of viral replication and acts by inducing replication from cellular pseudo-origins resulting in stalled replication forks[39]. E7 proteins also bind Cullin 2 ubiquitin ligases as well as class I histone deacetylases (HDACs) and both activities are important for the viral life cycle[25,40]. In addition to E6 and E7, the E5 proteins have been shown to induce tumors in transgenic mice suggesting they may play some role in enhancing the oncogenic activity of E6 and E7 in human cancers. This activity appears to be associated with E5's interactions with EGF receptor[41].

E6 and E7 of the Beta HPVs

The E6 and E7 proteins of the beta HPVs share some similarities with their homologous counterparts in the HR-alpha HPVs, but also have differences. E6 proteins from both genera can target the proapoptotic protein, BAK for degradation and inhibit the apoptotic response to DNA damage[12,42]. Similarly E6 proteins from both genera can bind the transcriptional regulator and histone acetylase, p300[43,44]. However beta E6 proteins bind p300 very tightly, blocking a stabilizing phosphorylation of p300 by AKT, leading to reduced levels of

p300 in beta E6 expressing cells[43]. Unlike HR HPV E6 the beta HPV E6 proteins do not target p53 for degradation. Degradation of p53 by E6 is mediated by its binding to the ubiquitin ligase, E6AP, through a LXXLL motif on E6AP[45]. The beta E6s proteins either bind E6AP very weakly or not at all. Instead the beta E6 proteins bind MAML1, which has a similar LXXLL motif[37,46]. MAML1 is a transcriptional coactivator of Notch regulated genes. The binding of beta E6 proteins to MAML1 blocks Notch signaling. One function of Notch is to promote keratinocyte differentiation and the beta E6 proteins have been reported to perturb differentiation[47].

The alpha and beta E7 proteins all contain an LXCXE motif and bind Rb and the related pocket proteins, p107 and p130[48,49], however their ability to target Rb for degradation is restricted to the HR alpha E7 proteins and an occasional beta E7 protein, such as HPV 38 E7[50]. To varying degrees the Rb/E7 interaction promotes entry into S phase. All of the E7 proteins bind to the ubiquitin ligases UBR4 and KCMF1, though the significance of these interactions for the HPV lifecycle is not known[51].

The beta E6 and E7 proteins have some activities that can promote oncogenesis. Some studies have shown that these genes either singly or in combination can extend the lifespan of keratinocytes[52]. Though most do so only weakly, HPV 38 E6/E7 was shown to immortalize cells [53,54]. Two beta types, HPVs 8 and 38, were shown to promote tumorigenesis in transgenic mice[15,55]. When either the HPV 8 early region, HPV 8 E6 or HPV 38 E6/E7 have been expressed using a K14 promoter they induced epidermal hyperplasia and at low frequency squamous cell carcinomas. Interestingly, UV greatly increased the frequency of SCSC at doses that did not cause tumors in nontransgenic littermates.

UV exposure is the major risk factor for SCSCs leading to the hypothesis that the beta HPVs might inhibit the response to UV damage, allowing cells with mutations to persist. Indeed, blocking apoptosis following UV damage has been shown for several beta HPV types [42,56]. Several beta E6 proteins have been shown to inhibit the repair of UV damage. The ability of HPV 5 and 8 to bind p300 delays the induction of ATR, ATM, their downstream targets CHK1 and CHK2, and BRCA1 and BRCA2[13,22,43]. Although DNA repair foci form they are often delayed and persist longer than it takes to resolve DNA damage in control cells.

Conclusion

Human papillomaviruses are important pathogens that are responsible for a range of effects in humans ranging from unapparent infections to cancers. All HPVs target epithelia tissues and link their productive life cycles to differentiation of the infected host cell. HPVs from different genera have distinct effects on cellular pathways such as those regulating DNA damage and cell cycle control that contribute to the types of lesions as well as cancers that they induce (Table 1). The mechanisms regulating persistent infection and progression to malignancy are fertile areas for future study.

Acknowledgments

DAG and LAL were supported by grants from the NCI and NIAID. We thank Kristina Simanis for her artwork.

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Highlights

1. HPVs infect epithelia cells and link their life cycles to differentiation
2. HPVs are grouped into five genera with the alpha and beta viruses being the most commonly studied.
3. Alpha HPVs are the causative agents of anogenital cancers while beta HPVs have been implicated as co-factors in some skin cancers
4. Activation of DNA damage pathways is important for the productive life cycle of the alpha HPVs while the beta viruses suppress their activation

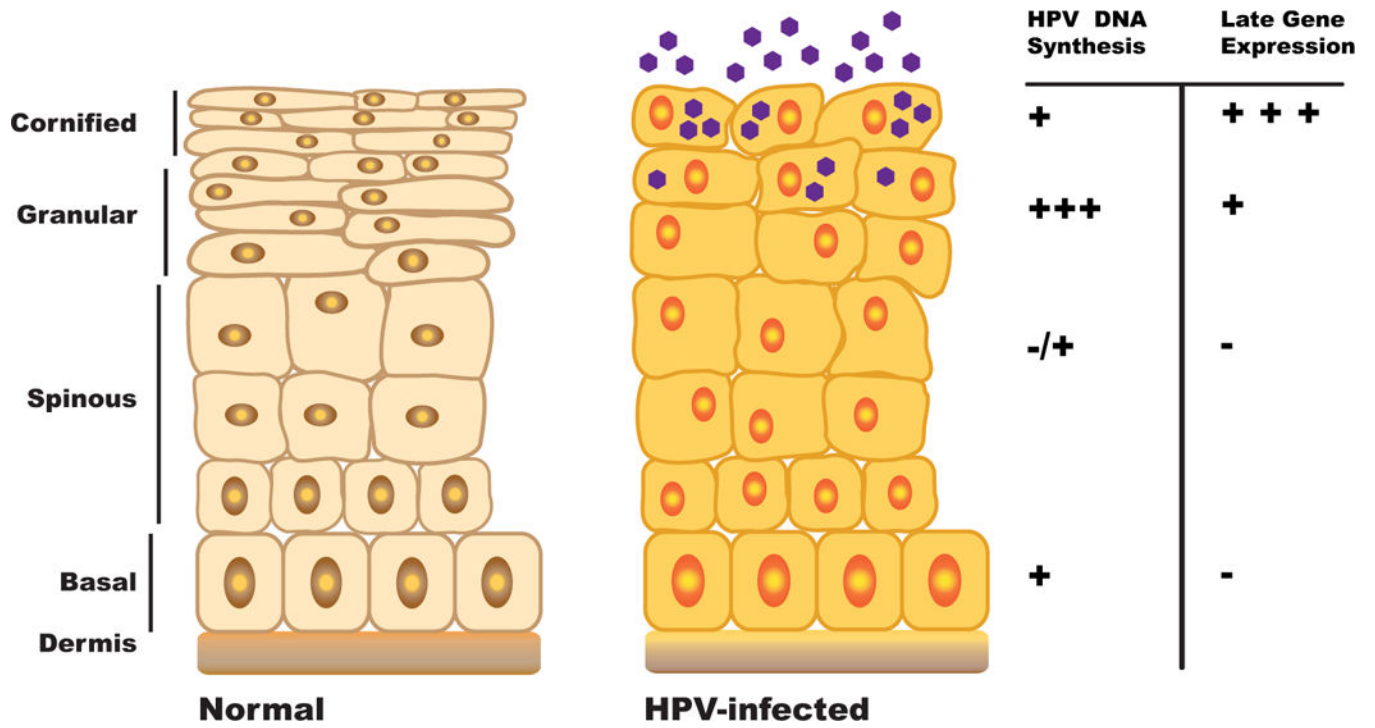


Figure 1. Differentiation-dependent life cycle of human papillomaviruses. HPVs establish persistent infections in basal epithelial cells where viral genomes are maintained as low copy episomes. Productive replication or amplification occurs upon differentiation in suprabasal layers.

Table 1

Differential activities of high-risk alpha and beta papillomaviruses

<u>Beta HPVs</u>	<u>High risk Alpha HPVs</u>
Infect cutaneous epithelia	Infects genital and oral epithelia
Possible association with non-melanoma cancers	Causative agents of cervical cancers
Differentiation-dependent life cycle	Differentiation-dependent life cycle
E6 does not target p53 for degradation	E6 induces p53 degradation through UBE3A
E7 does not affect RB levels	E7 induces degradation of Rb
E6 reduces ATM/ATR signaling	E7 and E1 activate ATM pathway
E6 fails to bind PDZ proteins	E6 binds and degrades PDZ proteins

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