Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Virology

Human papillomaviruses: shared and distinct pathways for pathogenesis

Denise A Galloway[1] and Laimonis A Laimins[2]

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.

Addresses
[1] Human Biology Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Seattle, WA 98109, USA
[2] Department of Microbiology-Immunology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

Corresponding authors: Galloway, Denise A (dgallowa@fredhutch.org) and Laimins, Laimonis A (l-laimins@northwestern.edu)

Current Opinion in Virology 2015, **14**:87–92

This review comes from a themed issue on **Viruses and cancer**

Edited by **Blossom Damania** and **Paul Lieberman**

For a complete overview see the Issue and the Editorial

Available online 20th September 2015

http://dx.doi.org/10.1016/j.coviro.2015.09.001

Introduction

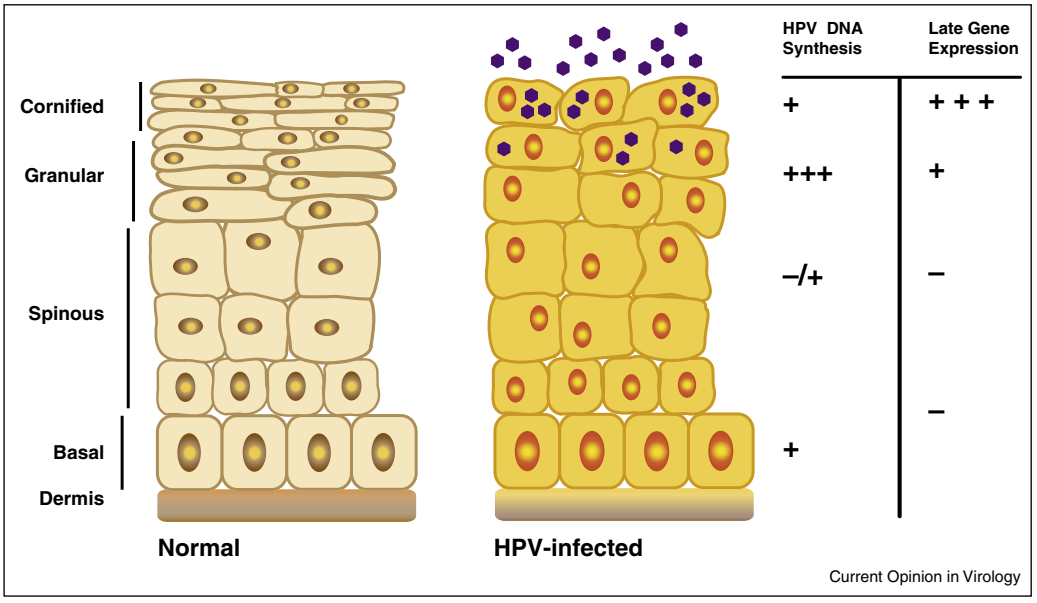
Human papillomaviruses (HPVs) are associated with a spectrum of manifestations ranging from unapparent infections to malignant neoplasias. HPVs are grouped phylogenetically into five genera, alpha, beta, gamma, mu and nu, and are further divided into species [1]. The alpha-papillomaviruses contain viruses 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].

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 kb 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 50–100 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

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.

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••,19••,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 γ-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