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Evasion of Host Immune Defenses by Human Papillomavirus

Joseph A. Westrich[a], **Cody J. Warren**[a,c], and **Dohun Pyeon**[a,b,*]

[a]Department of Immunology and Microbiology, University of Colorado School of Medicine, Aurora, CO 80045, USA

[b]Department of Medicine, University of Colorado School of Medicine, Aurora, CO 80045, USA

Abstract

A majority of human papillomavirus (HPV) infections are asymptomatic and self-resolving in the absence of medical interventions. Various innate and adaptive immune responses, as well as physical barriers, have been implicated in controlling early HPV infections. However, if HPV overcomes these host immune defenses and establishes persistence in basal keratinocytes, it becomes very difficult for the host to eliminate the infection. The HPV oncoproteins E5, E6, and E7 are important in regulating host immune responses. These oncoproteins dysregulate gene expression, protein-protein interactions, posttranslational modifications, and cellular trafficking of critical host immune modulators. In addition to the HPV oncoproteins, sequence variation and dinucleotide depletion in papillomavirus genomes has been suggested as an alternative strategy for evasion of host immune defenses. Since anti-HPV host immune responses are also considered to be important for antitumor immunity, immune dysregulation by HPV during virus persistence may contribute to immune suppression essential for HPV-associated cancer progression. Here, we discuss cellular pathways dysregulated by HPV that allow the virus to evade various host immune defenses.

1. Introduction

Papillomaviruses (PV) are small DNA viruses that have coevolved for millions of years with various host species, including mammals, reptiles, and birds (Van Doorslaer, 2013). As of now, over 300 PV genotypes have been discovered. Human papillomavirus (HPV) infects mucosal and/or cutaneous skin and causes benign or malignant tumors. Defined as group 1 or 2 carcinogens by the International Agency for Research on Cancer (IARC), ~25 high-risk HPV genotypes are causally associated with multiple human cancers including cervical cancer (CxCa) and oral squamous cell carcinomas (OSCC) (Forman et al., 2012). HPV-associated cancer is a major global health burden causing nearly half a million deaths worldwide every year. Recent studies have shown that HPV-positive OSCC incidence is increasing at an epidemic rate (Chaturvedi et al., 2011; Stein et al., 2014), suggesting that

*Corresponding author. dohun.pyeon@ucdenver.edu (D.P.).

[c]Current address: BioFrontiers Institute, University of Colorado Boulder, Boulder, CO 80303, USA

HPV-positive OSCC will likely comprise the majority of all head and neck cancers (HNC) by 2020 (Auluck et al., 2010; Chaturvedi et al., 2011). This rapid rise in HPV-positive OSCC cases increases the need to improve standard-of-care therapies for this particular subtype of HNC.

While expression of the HPV oncoproteins E6 and E7 quickly inactivates several tumor suppressors, the development of invasive cancer requires many years of viral persistence and disease progression in immunocompetent individuals. Our recent global gene expression analysis of human cervical tissues in different disease stages (normal, early and late precancerous lesions, and cancer) revealed dynamic gene expression changes in a series of cellular pathways, including the cell cycle, translation, mitochondrial energy metabolism, and estrogen signaling (den Boon et al., 2015). Aside from cell cycle- and proliferation-related genes, which are significantly upregulated immediately with high-risk HPV E6 and E7 expression, most host gene expression changes influenced by HPV persistence are slow progressing and accumulating throughout cancer progression. Many of the genes altered slowly and continuously are involved in immune responses and inflammation, such as cytokines and chemokines (den Boon et al., 2015). Our study has further revealed that restoration of the chemokine CXCL14 in mouse OSCC cells, which is downregulated by HPV E7, significantly suppresses HPV-positive OSCC growth *in vivo* by enhancing NK and T cell infiltration into tumor-draining lymph nodes (Cicchini et al., 2016). These results suggest that HPV-mediated immune dysregulation during virus persistence is important to prevent the elimination of HPV-infected cells during cancer progression. Thus, furthering our understanding of virus-directed immune dysregulation would be critical to develop preventive and therapeutic tools for treating virus-associated cancer as well as eliminating virus-infected cells.

2. Host defense mechanisms against HPV

While the majority of the human population acquires HPV infections, only about 10% to 15% of infected individuals establish life-long persistent infection, and only a subset of which has the potential to progress to invasive cancer (Schiffman 2007). This suggests that, for a majority of HPV-infected individuals, host defense mechanisms are largely effective at eliminating initial HPV infection.

2.1. Physical barriers

The unique lifecycle and strict tropism of HPV generates significant physical barriers for virus entry into basal keratinocytes, the native host cells of HPV. To initiate infection, HPV first needs to translocate across skin and mucous membranes, a process that is facilitated by tissue damage. The mucous membrane poses a major physical barrier to virus infection due to the secretion of a viscous protective fluid and antimicrobial peptides found therein. Once HPV reaches the extracellular matrix, extracellular proteases trigger conformational changes in the virus capsid that facilitates virus internalization. Following uptake of virus particles by macropinocytosis, viruses travel along the endocytic pathway to acidic late endosomes/lysosomes, and retrograde traffics through the Golgi to reach the nucleus (DiGiuseppe et al., 2016; Lipovsky et al., 2013; Pyeon et al., 2009; Schelhaas et al., 2012). During intracellular

trafficking, a vast majority of virus particles are degraded and eliminated by host autophagy (Griffin et al., 2013). The nuclear envelope poses another physical barrier to HPV DNA entry into the nucleus. Nuclear envelope breakdown during prometaphase is required for the successful establishment of HPV infection (Pyeon et al., 2009; Schelhaas et al., 2012). Beyond these physical barriers, human α-defensins, particularly α-defensin 5, were found as potent antagonists of HPV infection through inhibition of furin cleavage of the HPV minor capsid protein L2 at the cell surface (Buck et al., 2006; Wiens and Smith, 2015).

2.2. Innate immunity

Once HPV enters a host cell, HPV DNA can be recognized by innate pathogen sensors. Absent in melanoma 2 (AIM2), interferon-γ (IFN-γ) inducible protein 16 (IFI16), and cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS) are cytosolic DNA sensors, while IFI16 also detects foreign DNA in the nucleus (Hornung et al., 2009; Kerur et al., 2011; Li et al., 2013; Unterholzner et al., 2010). Triggering of the AIM2 inflammasome by viral DNA leads to the maturation of caspase-1 and interleukin-1β (IL-1β), which are commonly found activated in HPV16-infected lesions and keratinocytes (Reinholz et al., 2013). IFI16 restricts HPV genome replication and gene transcription by enhancing heterochromatin association with the early and late promoters (Lo Cigno et al., 2015). Further, there is a significant correlation in women between clearance of initial HPV infection and higher expression of nucleic acid-sensing toll-like receptors (TLR3, TLR7, TLR8, and TLR9) as well as TLR2 (Daud et al., 2011). One of the downstream effects of pathogen recognition by pattern recognition receptors (PRRs) is the production of type I interferons (IFN-α and -β). IFN-β treatment hinders HPV entry and promotes clearance of latent HPV episomes in persistently infected cells (Chang et al., 2002; Herdman et al., 2006; Warren et al., 2014). HPV genomes in HPV-positive cervical lesions and IFN-β treated cervical keratinocytes are edited by several IFN-inducible cytidine deaminase APOBEC3 family members (Vartanian et al., 2008; Wang et al., 2014). We and other groups have demonstrated that one of these family members, APOBEC3A, significantly restricts HPV infection (Ahasan et al., 2015; Warren et al., 2015b).

Innate immune cells are also involved in early host responses against HPV infection. HPV infection recruits dendritic (DC), Langerhans (LC), natural killer (NK), and natural killer T (NKT) cells to the HPV-infected microenvironment (Amador-Molina et al., 2013). In addition, plasmacytoid dendritic cells (pDC) have been shown to respond to the presence of HPV16 virus-like particles (VLPs) in CxCa tissue and secrete various cytokines, including IFN-α, IL-6, tumor necrosis factor α (TNF-α), and IL-8 following activation of MyD88-dependent signaling (Bontkes et al., 2005; Lenz et al., 2005; Yang et al., 2004). Additionally, increased HPV infection and HPV-associated cancer incidence has been observed in individuals with various functional NK cell deficiencies (Orange, 2013). Taken together, these findings suggest that the early inflammatory response might be critical for initiating a robust host defense against HPV infection.

2.3. Adaptive immunity

The HPV lifecycle is strictly intraepithelial and virions are produced only from the fully differentiated upper layer of skin. Thus, there is no virus-induced cytolysis or viremia, which

limits the exposure of HPV to systemic immune responses. Nevertheless, results from many studies have agreed that host T cell responses are required to eliminate HPV-infected cells. The regression rate of cervical precancerous lesions strongly correlates with the presence of intraepithelial granzyme B-positive cytotoxic T cells (Woo et al., 2008). A recent study has shown that LCs isolated from women with persistent HPV16 infection can present HPV antigens and activate HPV16-specific $CD8^+$ T cells (Da Silva et al., 2015). Additionally, using the recently established mouse papillomavirus (Mus musculus papillomavirus 1 or MmuPV1) model, Handisurya et al. revealed that productive MmuPV1 infection and papilloma formation require both $CD4^+$ and $CD8^+$ T cell functions; while CD4- or CD8-knockout C57BL/6 mice were resistant to productive MmuPV infection, depletion of $CD4^+$ and $CD8^+$ T cells from immunocompetent mice led to infection and papilloma formation (Handisurya et al., 2014). In addition, UVB irradiation-induced systemic immune suppression causes mice to become highly susceptible to MmuPV1 infection, which ultimately results in the development of squamous cell carcinoma (Uberoi et al., 2016). Taken together, these findings exemplify the pivotal roles of T cell-mediated immune responses in host clearance of HPV infection. The immunogenicity and efficacy of current HPV vaccines further confirmed that HPV infection can also be prevented by antibody-driven immunological memory (Stanley, 2012). However, antibody titers from natural HPV infection are usually too low to show a protective effect, suggesting that HPV efficiently evades the host antibody response during natural infection (Viscidi et al., 2004).

3. Immune evasion by altering host gene expression

In order to evade host immune defenses and establish persistence, HPV modulates host gene expression by deregulating host DNA methylation, histone modification, and transcription factors.

3.1. Deregulation of DNA methylation by HPV

Epigenetic regulation by DNA methylation provides distinct gene expression patterns in different developmental stages, organ tissue types, and disease states (Hochedlinger and Plath, 2009; Kim et al., 2009; Robertson, 2005). DNA methylation also functions as a host defense mechanism. By methylating CpG residues of foreign DNA in eukaryotic cells, pathogen activity can be shut down due to alterations in pathogen transcriptional profiles (Shalginskikh et al., 2013; Waterhouse et al., 2001). HPV DNA is also frequently methylated and viral gene transcription is repressed following DNA methylation (Badal et al., 2003; Kalantari et al., 2004). Previous studies have shown that several pathogens hijack the host DNA methylation machinery to manipulate host transcription to their benefit (Hino et al., 2009; Liu et al., 2013; Silmon de Monerri and Kim, 2014). Interestingly, the HPV oncoprotein E7 interacts with the DNA methyltransferase DNMT1, and stimulates its methyltransferase activity (Burgers et al., 2007) (Fig. 1A). This may partially explain the global changes in the host methylome that we have observed in HPV-positive keratinocytes (Cicchini et al., unpublished results). We have recently shown that expression of the chemokine CXCL14 is downregulated during HPV-associated cancer progression by promoter hypermethylation, in an E7-dependent manner (Cicchini et al., 2016). Since restoration of CXCL14 expression in HPV-positive HNC cells significantly suppresses

tumor growth *in vivo*, HPV E7-mediated CXCL14 promoter methylation may represent an immune evasion strategy during HPV persistence. Our and other studies have shown that CXCL14 induces direct chemotaxis of various immune cells including DCs, LCs, NK, and T cells (Cicchini et al., 2016; Schaerli et al., 2005; Shurin et al., 2005). Additionally, using transgenic mouse models, it has been demonstrated that HPV16 E7 expression in the epidermis creates a strong immunosuppressive area where LC and $CD8^+$ T cell functions are significantly suppressed (Abd Warif et al., 2015; Doan et al., 1999; Tindle et al., 2001). This immune suppression appears to be mediated by an influx of HPV16 E7-induced regulatory T (Treg) cells and tolerization of cytotoxic T cells (Doan et al., 1999; Narayan et al., 2009). In addition to HPV E7, HPV E6 is also involved in deregulation of host DNA methylation. High-risk HPV E6 represses IFN-κ, which is constitutively expressed in keratinocytes and serves to reinforce IFN-stimulated gene expression (Fig. 1A). E6-mediated repression of IFN-κ can be reversed by treatment with a DNA methyltransferase inhibitor (Reiser et al., 2011; Rincon-Orozco et al., 2009). These findings suggest that HPV manipulates host DNA methylation to evade host immune defenses.

3.2. Deregulation of histone modification by HPV

Histone modification is another mechanism of epigenetic reprogramming altered by HPV. Cellular gene expression is tightly regulated by chromosome remodeling through histone methylation, phosphorylation, acetylation, ubiquitination, and sumoylation (Kouzarides, 2007). HPV16 E7 binds to E2F6 and interferes with the formation of E2F6-containing polycomb transcriptional repressor complexes (McLaughlin-Drubin et al., 2008). HPV-mediated modulation of host histone methylation has been well described (McLaughlin-Drubin et al., 2011; McLaughlin-Drubin et al., 2008). Interestingly, HPV38 E7 recruits polycomb protein enhancer of zeste homolog 2 (EZH2) to the TLR9 promoter region, resulting in histone 3 trimethylation at lysine 27 (H3K27me3) and repression of TLR9 transcription (Pacini et al., 2015) (Fig. 1B). Another study has shown that HPV16 E7 recruits histone deacetylase HDAC1 and histone demethylase JARID1B (also known as KDM5B) to the regulatory region upstream of the TLR9 transcriptional start site and reduces H4 acetylation and H3K4me3, leading to downregulation of TLR9 expression (Hasan et al., 2013) (Fig. 1C). Since TLR9 recognizes viral DNA and induces innate immune responses, TLR9 repression may represent an important host immune response pathway antagonized by HPV. Additionally, both high-risk and low-risk HPV E7 proteins inhibit the transcriptional activity of IRF1 by recruiting HDAC1 to promoters that contain IRF1 response elements (Park et al., 2000). Consequently, IRF1 responsive genes, including the ATP-binding cassette (ABC) peptide transporter associated with antigen processing 1 (TAP1), IFN-β, and CCL2, are significantly downregulated in HPV16 E7 expressing cells and mice (Georgopoulos et al., 2000; Um et al., 2002). Consistently, treatment of HPV-positive tumor cells with an HDAC inhibitor increased the surface expression of the major histocompatibility complex class I (MHC-I) molecules, enhancing the susceptibility of tumor cells to E7-specific $CD8^+$ T cells (Lee et al., 2013).

3.3. Modulation of NF-κB by HPV

HPV deregulates the activity of transcription factors to repress proinflammatory cytokine production. Nuclear factor-κB (NF-κB) is one of the most important transcription factors

involved in immune signaling (Ghosh et al., 1998; Lee and Kim, 2007). Accordingly, NF-κB is frequently targeted by many different viruses, including HPV (Brady and Bowie, 2014; Correia et al., 2013; Qu and Lemon, 2010; Vandermark et al., 2012). High-risk HPVs decrease K310 acetylation of NF-κB in keratinocytes by enhancing IFN related developmental regulator 1 (IFRD1) expression, resulting in downregulation of proinflammatory cytokines (Tummers et al., 2015) (Fig. 1D). E7 alone is capable of inhibiting imiquimod-induced NF-κB transactivation of IFN-α, IL-6, and TNF-α (Richards et al., 2015). Impairing the acetylation at K310 in the p65 subunit of NF-κB requires the CR1 and CR3 domains of E7 and leads to reduced nuclear translocation of NF-κB (Richards et al., 2015). An earlier study has shown that HPV16 E6 and E7 also bind to p300/CBP-associated factor (PCAF) and inhibits NF-κB activation, resulting in IL-8 downregulation (Huang and McCance, 2002) (Fig. 1D).

3.4. Transcriptional regulation by HPV through undefined pathways

While tremendous progress has been made in understanding the molecular mechanisms by which HPV deregulates host gene expression, many pathways still remain undefined. Previous studies have shown that E6 and E7 downregulates the expression of proinflammatory cytokines and chemokines, IL-8, IL-18, CCL2, and CCL20 (Cho et al., 2001; Guess and McCance, 2005; Huang and McCance, 2002; Kleine-Lowinski et al., 2003). In addition to repression of proinflammatory gene expression, the HPV oncoproteins E6 and E7 also upregulate expression of immunosuppressive genes in host cells. Previous studies have shown that HPV16 E7 expression *in vivo* is sufficient to trigger local immune suppression (Dunn et al., 1997; Matsumoto et al., 2004). Mittal et al., have revealed that indoleamine 2,3-dioxygenase 1 (IDO1) expression in dermal DCs is highly upregulated by HPV16 E7 expression in mouse skin (Mittal et al., 2013). IDO1 is an IFN-γ-inducible immune checkpoint molecule that promotes the development of functional regulatory T (Treg) cells and acts as a suppressor of antitumor immunity (Bonanno et al., 2012; Munn and Mellor, 2013; Schmidt and Schultze, 2014; van Baren and Van den Eynde, 2015). Drugs targeting the IDO1 pathways are already in clinical trials to reverse cancer-induced immune suppression (Platten et al., 2014). Treg expansion and DC tolerance are also driven by secretion of receptor activator of NF-κB ligand (RANKL) during cervical cancer progression (Demoulin et al., 2015). RANKL is a member of the TNF superfamily that regulates DC maturation and survival and is frequently upregulated in several cancers (Chino et al., 2009; Gonzalez-Suarez and Sanz-Moreno, 2016). Interestingly, while IL-18 is downregulated by HPV16 E6 (Cho et al., 2001), expression of its natural antagonist, IL-18 binding protein (IL-18BP), is significantly increased in primary human keratinocytes expressing either high- or low-risk HPV E7 (Richards et al., 2014). IL-18BP prevents the deleterious effects of excessive IL-18 secretion and reduces activation of primary Th1 $CD4^+$ T cells (Novick et al., 1999; Richards et al., 2014). A proximal gamma interferon activation site (GAS) element in the IL-18BP promoter is responsible for IL-18BP transactivation by E7, indicating that IFN-γ signaling might be critical for increased expression of immunosuppressive genes, including IL-18BP and IDO1. A recent study has shown that transgenic mice expressing HPV16 E7 have increased epidermal secretion of the chemokines CCL2 and CCL5, which recruit mast cells expressing CCR2 and CCR5, the receptors of CCL2 and CCL5, respectively (Bergot et al., 2014). Mast cells in HPV16 E7-

expressing transgenic skin generate an immunosuppressive environment resulting in significantly reduced graft rejection (Bergot et al., 2014). Contrastingly, a previous study has shown that retroviral transduction of HPV16 E6 and E7 almost completely shut down CCL2 expression in primary cervical epithelial cells (Kleine-Lowinski et al., 2003). These conflicting results may be caused by differential effects from expression of both E6 and E7, and E7 alone, or from an *in vivo* mouse model vs. cultured human cells. Interestingly, another study showed that CCL2 expression is downregulated by HPV16 E6 and E7 in primary human keratinocytes, but upregulated by HPV16 E6 and E7 in transformed HaCaT keratinocytes (De Andrea et al., 2007). These results indicate that HPV regulation of CCL2 expression might be complex and different between normal and cancer cells. To better understand the physiological relevance of HPV-induced immune evasion by chemokine deregulation, it is critical to determine the molecular pathways by which HPV modulates expression of these genes.

The HPV E2 protein is a transcription factor, containing DNA binding and transactivation domains (McBride, 2013). Normally, it binds to E2 binding motifs within the viral upstream regulatory region (URR) to regulate early and late gene expression (McBride et al., 1991). However, in addition to viral gene regulation, HPV E2 also regulates the transcription of numerous host genes (Bellanger et al., 2011). A recent genome-wide gene expression analysis revealed that the high-risk HPV E2 protein downregulates Stimulator of Interferon Genes (STING) and IFN-κ expression in primary human keratinocytes (Sunthamala et al., 2014). Downregulation of STING and IFN-κ expression is also observed in HPV-positive patient tissue samples (Sunthamala et al., 2014). STING is an endoplasmic reticulum (ER) adaptor protein induced by cytosolic DNA. STING binds with TANK binding kinase (TBK1) and IFN regulatory factor 3 (IRF3), resulting in phosphorylation of IRF3 and thereby promoting type I IFN production (Tanaka and Chen, 2012). However, it is still unclear if downregulation of STING and IFN-κ expression is directly caused by E2 or indirectly by interactions of E2 with other cellular factors that mediate transcription repression.

4. Immune evasion by dysregulating protein functions

4.1. Protein-protein interaction/sequestration

The HPV oncoproteins E6 and E7 lack enzymatic activity. Instead, they act as adaptor proteins that interact with multiple host proteins, recruit them to desired locations, and hijack their activities to enhance virus replication and persistence, and inadvertently induce malignancy (Roman and Munger, 2013; Vande Pol and Klingelhutz, 2013). HPV E6 and E7 frequently inhibit host protein functions by direct binding. The HPV18 E6 protein directly interacts with non-receptor tyrosine-protein kinase 2 (TYK2), resulting in a reduction of IFN-α-induced phosphorylation in TYK2 and Signal Transducer and Activator of Transcription 2 (STAT2) proteins (Li et al., 1999) (Fig. 2A). TYK2 is a member of the JAK family and is important for signal transduction following receptor binding by various cytokines, including IL-6, IL-12, and type I IFNs. The IFN regulatory transcription factor IRF3 is selectively bound and inhibited by HPV16 E6 protein, while HPV6, HPV11, and HPV18 E6 proteins bind poorly to IRF3 (Ronco et al., 1998). IRF3 plays a central role in

inducing innate immune response against viral infections (Haller et al., 2006). The interaction of HPV16 E6 to IRF3 does not lead to ubiquitination or degradation of IRF3, but significantly represses its activity on target gene transcription and IFN-β production. This suggests that HPV16 E6 binding is sufficient for inhibition of IRF3 functions. Cytosolic DNA can be detected by cGAS, which initiates innate immune signaling through the adapter proteins STING and IRF3 (Cai et al., 2014; Sun et al., 2013). Interestingly, HPV18 E7 antagonizes the activation of the cGAS-STING pathway and limits the production of type I IFNs by binding with STING through its LXCXE motif (Lau et al., 2015) (Fig. 2B). Additionally, HPV16 E7 protein interacts with IRF1, probably at its N-terminal DNA-binding domain, resulting in decreased expression of IRF1 responsive genes, including TAP1, IFN-β, and CCL2 (Park et al., 2000; Perea et al., 2000; Um et al., 2002) (Fig. 2C). IFN signaling is further repressed by HPV16 E7 as it also binds to IRF9, another IFN regulatory factor (Antonsson et al., 2006) (Fig. 2A). IFN signaling lies at the core of antiviral innate immune responses and appears to be heavily targeted by the HPV oncoproteins E6 and E7. Our previous studies have shown that IFN-β treatment significantly inhibits HPV infection in primary and immortalized keratinocytes (Warren et al., 2014; Warren et al., 2015b). These findings indicate that evasion of IFN signaling mediated through HPV E6 and E7 interactions with host proteins might be critical for HPV persistence.

4.2. Posttranslational modification and protein degradation

The mechanisms of host protein degradation by the HPV oncoproteins E6 and E7 are well established (Howley, 2006). However, posttranslational modification of immunoregulatory proteins is relatively understudied. Karim et al. have shown that high-risk HPVs upregulate the cellular protein ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) in keratinocytes (Karim et al., 2013). UCHL1 inhibits K63-linked ubiquitination of tumor necrosis factor receptor-associated factor 3 (TRAF3) resulting in decreased TRAF3-TBK1 complex formation and IRF3 phosphorylation (Fig. 2D). UCHL1 also mediates degradation of the essential modulator of NF-κB, NEMO, and suppresses p65 phosphorylation and NF-κB signaling. HPV16 E6 also induces degradation of pro-IL-1β in a proteasome-dependent manner (Niebler et al., 2013) (Fig. 2E). E6-mediated pro-IL-1β degradation is independent from caspase-1 activation, autophagy, or lysosomal degradation, but requires E6AP expression and poly-ubiquitination of pro-IL-1β. Since the proinflammatory cytokine IL-1β plays important roles in antiviral defense (Gram et al., 2012; Poeck and Ruland, 2012), these results suggest that high-risk HPV suppresses the proinflammatory response by inducing proteasome-mediated degradation of intracellular cytokines. Interestingly, a number of studies have shown that polymorphism in the IL-1β gene cluster is tightly linked to CxCa and HNC risk (Wu et al., 2014; Xu et al., 2013). Specifically, women with IL-1β T-allele containing genotypes show increased risk of CxCa (Dutta et al., 2015). Our unpublished global gene expression data shows that IL-1β expression is significantly downregulated in HPV-positive normal keratinocytes but upregulated in CxCa tissues (Cicchini et al., unpublished results). These results imply that IL-1β may play dual roles in inhibiting HPV infection by its antiviral function in early stages of disease, but facilitating cancer progression through chronic inflammation in late stages.

5. Immune evasion by altered cytoplasmic trafficking of host proteins

5.1. Intracellular sequestration of MHC molecules by HPV

Antigen presentation of viral epitopes by MHC-I molecules is critical to elicit cell-mediated immune responses that eliminate virus-infected cells. In order to escape host recognition, many viruses have various strategies to suppress surface expression of MHC-I molecules (Blagoveshchenskaya et al., 2002; Hewitt, 2003; Jackson et al., 2011), and HPV is no exception. HPV and bovine papillomavirus (BPV) E5s are small transmembrane proteins that bind to several host transmembrane proteins, including MHC-I. E5 binding to MHC-I leads to its downregulation at the host cell surface (Ashrafi et al., 2006; Ashrafi et al., 2005; Ashrafi et al., 2002; DiMaio and Petti, 2013). Upon binding of antigenic peptides delivered by TAP1 in the ER, MHC-I molecules, composed of a heavy α chain and a soluble subunit β2-microglobulin (β2m), traffic through the secretory pathway and imbed within the cell membrane (Donaldson and Williams, 2009). Several quality control mechanisms are involved in this process for accurate antigen presentation. HPV16 E5 physically interacts with the heavy chain of the MHC-I molecule through the hydrophobic region of E5 protein and retains MHC-I in the Golgi and ER (Ashrafi et al., 2006; Ashrafi et al., 2005) (Fig. 3). While HPV16 E5 does not affect expression of the heavy chain and TAP1 proteins, enhanced expression of the MHC I heavy chain by IFN-β treatment restores surface expression of MHC-I molecules. Interestingly, HPV16 E5 specifically downregulates HLA-A and -B expression, but not HLA-C and HLA-E (Ashrafi et al., 2005) (Fig. 3). Our unpublished data showed that HLA-C and HLA-E are the two most transcriptionally downregulated MHC-I molecules in HPV-positive keratinocytes, and this downregulation is dependent on HPV16 E7 expression (Cicchini et al., unpublished results). Further, HPV E5 downregulation of MHC-I molecules at the cell surface correlates with poor $CD8^+$ T cell responses in E5 expressing cells (Campo et al., 2010). An additional study has described a correlation between surface expression of MHC-I molecules and decreased TAP1 expression, suggesting that TAP1 downregulation by E7 may also interfere with MHC-I trafficking (Li et al., 2010). HPV16 E5 also downregulates the surface expression of MHC-II molecules by preventing degradation of the invariant chain that blocks peptide loading (Zhang et al., 2003). Both high-risk HPV16 and low-risk HPV6 E5s also downregulate surface expression of the non-classical MHC molecule CD1d (Miura et al., 2010) (Fig. 3). HPV E5 directly interacts with calnexin in the ER and redirects CD1d to the cytosolic proteolytic pathway (Miura et al., 2010). CD1d expression on the cell surface activates NKT cell responses to various viral, bacterial, and fungal infections (Brigl and Brenner, 2004). Thus, HPV may evade host immune responses by downregulating the surface expression of CD1d. Further investigation is necessary to determine if CD1d presents HPV-related antigens to induce protective antiviral activity.

5.2. Virus trafficking hindered by HPV in antigen presenting cells

The HPV minor structural protein L2 disrupts normal endocytic trafficking of virus particles in DCs and LCs (Fahey et al., 2009). LCs, which are skin resident DCs, uptake L1-only virus-like particles (VLPs) and efficiently induce expression of proinflammatory cytokines and costimulatory molecules leading to the activation of cytotoxic T cell responses (Fausch et al., 2003; Lenz et al., 2001; Rudolf et al., 2001). In contrast, HPV VLPs containing both

L1 and L2 proteins did not activate LCs to present viral antigens (Fausch et al., 2002). Interestingly, HPV16 L2 facilitates internalization of VLPs through interaction with the annexin A2 (ANXA2) heterotetramer (Fahey et al., 2009; Woodham et al., 2014). ANXA2 is associated with S100A10 as a heterotetramer and critical for HPV16 VLP internalization (Dziduszko and Ozbun, 2013; Woodham et al., 2012). Thus, it is likely that HPV16 L2 blocks LC maturation and viral antigen presentation by modulating intracellular trafficking of viral particles. Previously, we have shown that overexpression of the interferon-inducible transmembrane protein 1 (IFITM1) delays viral capsid protein degradation and significantly enhances HPV16 VLP entry into primary keratinocytes (Warren et al., 2014). IFITMs, induced by IFN treatment, inhibit a series of RNA viruses by redirecting virus particles to low-pH late endosomes and lysosomes during intracellular trafficking (Brass et al., 2009; Perreira et al., 2013). These results imply that HPV not only bypasses IFITM restriction but may utilize certain IFN-inducible proteins to facilitate virus infection.

6. Roles of host defense in papillomavirus genome evolution

It is well known that RNA viruses and retroviruses evolve rapidly throughout the course of an infection. Rapid mutation allows these viruses to efficiently evade host immune recognition and develop drug resistance. Viral genome mutation rates determine whether host immune responses clear viral infections, subsequently resulting in dramatic changes in viral fitness and pathogenesis (Pfeiffer and Kirkegaard, 2005; Vignuzzi et al., 2006). Accordingly, virus evolution is driven by strong selective pressures elicited by various host immune defenses (Woo and Reifman, 2012). Compared to the mutation rates of RNA viruses (10^{-4} to 10^{-6} mutations/bp/generation), double-stranded DNA viruses have substantially lower mutation rates (10^{-6} to 10^{-8} mutations/bp/generation). The mutation rate of DNA viruses is approximately a log fold higher than the mutation rates of the human genome (Lauring et al., 2013; Sanjuan et al., 2010). Nevertheless, throughout the course of virus-host coevolution for millions of years, DNA viruses have established large and diverse families that persistently infect countless host species. We and others have identified evolutionary clues within papillomavirus genomes that suggest an important role for host immunity in virus-host coevolution.

6.1. Depletion of CpG dinucleotides in HPV genomes

CpG dinucleotides in viral genomes are frequently targeted for DNA methylation, which negatively affects viral gene expression and occasionally triggers viral genome integration and excision (Karlin et al., 1994). Like other viruses, CpG motifs in HPV genomes can be methylated, and the viral CpG methylation levels in CxCa tissues are negatively correlated with CxCa progression (Badal et al., 2004; Badal et al., 2003). HPV gene transcription is repressed by hypermethylation of the viral upstream regulatory region (URR) (Rosl et al., 1993). An earlier study has shown that *in vitro* methylation of BPV DNA reduces the transformation rate of mouse fibroblasts (Christy and Scangos, 1986). In contrast, other studies have revealed that DNA methylation in the HPV L1 and L2 regions is correlated with HPV integration and cervical malignancies (Kalantari et al., 2004; Kalantari et al., 2010; Mirabello et al., 2012). These results suggest that HPV gene expression and pathogenesis are closely regulated by viral DNA methylation. Additionally, DNA containing

unmethylated CpG dinucleotides is recognized by TLR9 and induces TLR9-mediated antiviral signaling through NF-κB, resulting in type I IFN production (Kumagai et al., 2008). Currently, there is no evidence of direct activation of TLR9 signaling by recognition of unmethylated HPV DNA. However, since TLR9 expression is significantly downregulated in cells expressing the HPV oncoprotein E7 as described above, it is likely that HPV infection and viral gene expression may be influenced by TLR9 responses. Similar to many other small DNA viruses, such as adenovirus and parvovirus, papillomavirus genomes have significantly lower contents of CpG dinucleotides than expected by random chance (Upadhyay et al., 2013; Upadhyay and Vivekanandan, 2015; Warren et al., 2015a). In a recent publication, we calculated the ratio of observed vs. expected (O/E) counts of all dinucleotides in the genomes of all 274 PVs deposited in the Papillomavirus Episteme (PaVE) database (Warren et al., 2015a). We revealed that CpG dinucleotides are the most underrepresented dinucleotide in the genomes of all PV types, except two bird PVs. These results suggest that the loss of CpG dinucleotides in PV genomes may be tied to evolutionary pressures elicited by host DNA methylation and/or TLR9 recognition (Fig. 4A).

6.2. Depletion of TpC dinucleotides in HPV genomes

The TpC dinucleotide motif is preferably targeted by several APOBEC3 (A3) cytidine deaminase family members that convert cytidine (C) to uridine (U) in single stranded DNA and RNA (Chelico et al., 2006; Yu et al., 2004). The human A3 family consists of seven members: A3A, A3B, A3C, A3D, A3F, A3G, and A3H (Jarmuz et al., 2002; LaRue et al., 2009). Of these seven A3 family members, A3A, A3B, and A3H are expressed in skin keratinocytes (Vartanian et al., 2008). A3s were first discovered as important host restriction factors that block the replication of several retroviruses, including human immunodeficiency virus (HIV) (Hultquist et al., 2011; Sheehy et al., 2002; Zheng et al., 2004). Several studies have shown that A3A can eliminate transfected foreign DNA (Stenglein et al., 2010) and restrict several DNA viruses (Chen et al., 2006; Narvaiza et al., 2009). Editing of episomal HPV genomes by A3A, A3B, and A3H in cervical lesions has been demonstrated (Vartanian et al., 2008; Wang et al., 2014). Our recent study has revealed that A3A expression restricts HPV entry in a cytidine deaminase dependent manner (Warren et al., 2015b). Despite its ability to restrict HPV infection, A3A expression is upregulated in HPV-infected keratinocytes as well as HPV-positive CxCa (Warren et al., 2015b). Interestingly, TpC dinucleotides, the preferred dinucleotide target site of many A3s, are dramatically underrepresented in papillomavirus genomes. TpC depletion was most dramatic amongst the *Alphapapillomaviruses* which preferably infect mucosal skin such as the cervicovaginal and oral regions (Warren et al., 2015a). Surprisingly, mucosal skin expresses significantly higher basal levels of all A3 isoforms (except A3B) when compared to cutaneous skin. These findings imply that TpC dinucleotide depletion in *Alphapapillomaviruses* may allow for persistent infection of mucosotropic PV types to avoid A3-mediated antiviral editing (Warren et al., 2015a; Warren and Pyeon, 2015). Additionally, unlike the CpG depletion universally found in the genomes of most papillomavirus types, the degree of TpC dinucleotide depletion varies among PV types infecting different animal species. Taken together, these findings suggest that TpC dinucleotide content variation in PV genomes may limit editing by A3 family members during viral infection and persistence (Fig. 4B).

6.3. Epitope changes in HPV variants

Host adaptive immune responses efficiently neutralize virus particles, eliminate virus-infected cells, and generate immune memory to cope with future infections. Viruses, particularly those with smaller genome capacities, have antigenically altered immune epitopes to evade recognition by adaptive immune cells. On the other hand, viruses with larger genomes encode viral immunomodulatory genes (van de Weijer et al., 2015; Vossen et al., 2002). The rapid accumulation of mutations within the immunodominant epitopes of HIV-1 and hepatitis C virus (HCV) allows for immune escape during the course of an infection, and poses a major challenge to the development of effective vaccines (Goulder et al., 1997; Henn et al., 2012; Timm et al., 2004). Previous studies have described naturally occurring HPV variants in the neutralizing epitopes of L1 and L2 proteins that significantly reduce antigenicity of HPV (Seitz et al., 2013; Yang et al., 2005). For instance, several HPV16 L1 variants isolated from premalignant and malignant cervical tissues show impaired viral capsid assembly, which influences differential B cell class switching and leads to the production of non-neutralizing antibodies (Yang et al., 2005). Although mutations disrupting capsid assembly would diminish viral fitness, they may contribute to virus persistence by evading host immune surveillance (Yang et al., 2005). Additionally, natural epitope variants of the HPV minor capsid protein L2 are also found in high-grade squamous intraepithelial lesions (Seitz et al., 2013). These L2 variants were not efficiently neutralized by anti-L2 antibodies from human sera. Recent studies have also discovered HPV E6 and E7 variants that affect host immune responses (Chagas et al., 2013; Chopjitt et al., 2015). In addition to HPV structural proteins, the HPV oncoproteins E6 and E7 are also potently immunogenic. Several T cell epitopes have been described within E6 and E7, and therapeutic vaccines based on E6 and E7 antigens show promising immune responses (Oosterhuis et al., 2012; Ressing et al., 1995; Welters et al., 2008). A novel E6 variant with an amino acid change in a T cell epitope alters its ability to be bound and presented by MHC-II (Chagas et al., 2013). Additionally, the HPV16 E6 Asian variant upregulates miR-21 expression and suppresses IRF1, 3, and 7 (Chopjitt et al., 2015). These results suggest that variation among HPV genomes may allow for differential evasion of host immune defenses.

7. Conclusion

For optimal control and clearance of HPV infections, both the innate and adaptive arms of the immune response appear to be critical. As described, HPV modulates a series of cellular pathways to evade host immune responses during persistent infection. Some of these mechanisms may lead to virus-mediated immune suppression that creates an immunosuppressive microenvironment in mucosal epithelia, which is vital for cancer progression. Recent clinical trials of novel immunotherapies have promise as cancer therapeutics by reversing tumor-induced immune suppression; however, a majority of treated patients generally do not respond to immune checkpoint inhibitors (Gildener-Leapman et al., 2013; Hamid et al., 2013; Wolchok et al., 2013). Thus, it is very likely that there are additional mechanisms by which tumor cells evade antitumor immune responses. As described above, HPV manipulates various molecular and cellular pathways in host cells to evade host immune surveillance and antiviral immune responses. HPV-mediated immune

suppression during virus persistence might also contribute to tumor cell evasion of antitumor immune responses. Thus, an in-depth understanding of the mechanisms of HPV-associated immune evasion potentially lead to the development of novel immunotherapeutic tools that effectively restore antiviral and antitumor immune responses.

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Highlights

- HPV dysregulates various molecular and cellular pathways to evade host defenses.
- HPV alters transcription of key immune modulators.
- HPV E6 and E7 interacts with core proteins of the interferon pathway.
- HPV E5 and E7 downregulate surface expression of MHC molecules.
- Papillomavirus genome evolution may be driven by virus evasion of host restriction.

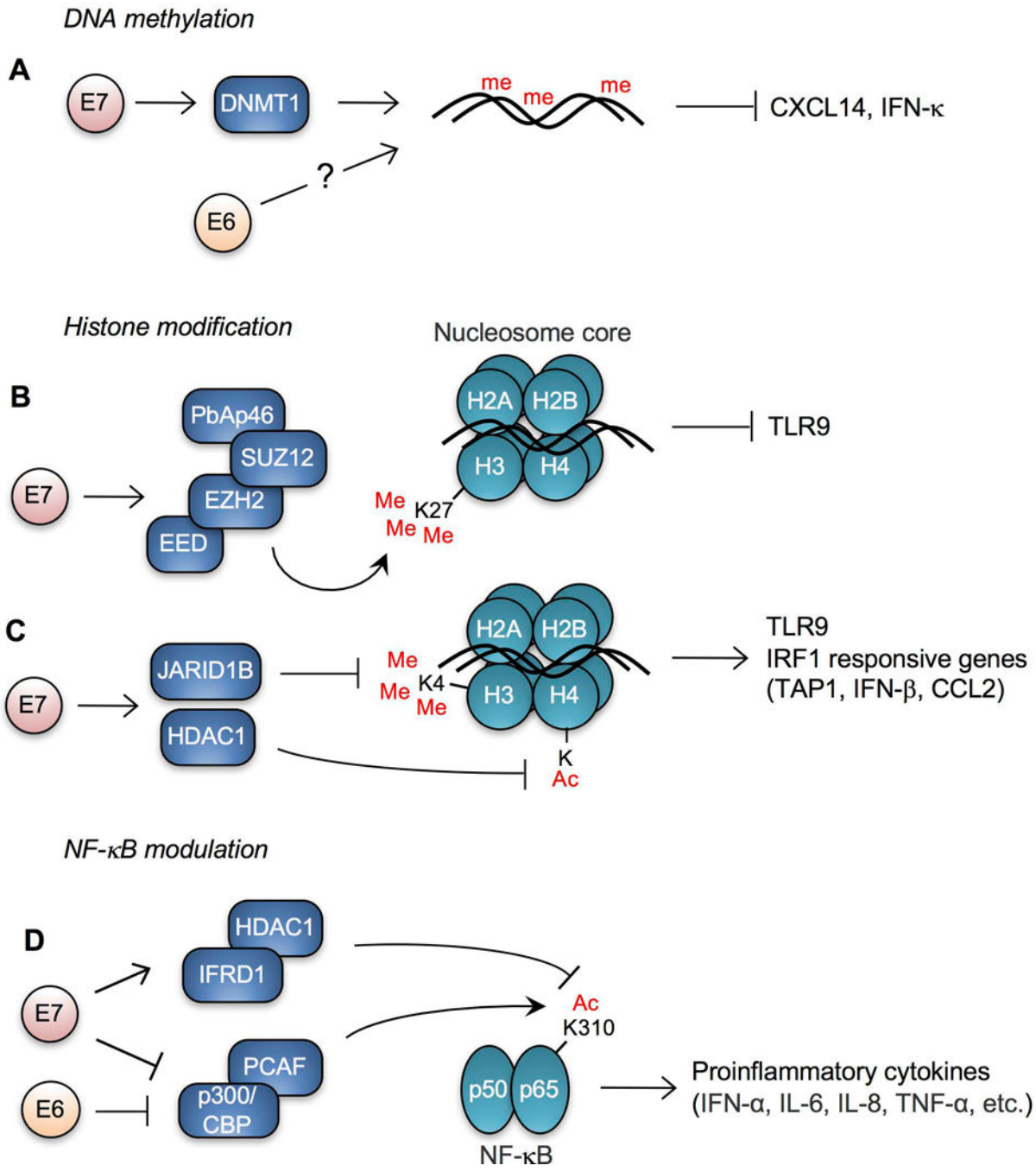

Fig. 1.

HPV alters transcription of key immune modulators. (A) Gene transcription of IFN-κ and CXCL14 is repressed by high-risk HPV E6 and E7, respectively, through DNA methylation. HPV16 E7 interacts with DNMT1 and enhances its activity, but the ability of E6 to influence host DNA methylation is unknown. High-risk HPV E7 represses transcription of TLR9 and/or IRF1 responsive genes by (B) inducing K27 methylation and (C) reducing K4 methylation and acetylation of histone molecules. (D) NF-κB signaling is inhibited by high-

risk HPV E6 and E7 through inhibiting K310 acetylation of p65. me, 5-methylcytidine; Me, methyl lysine; Ac, acetyl lysine; E2BS, E2 binding site.

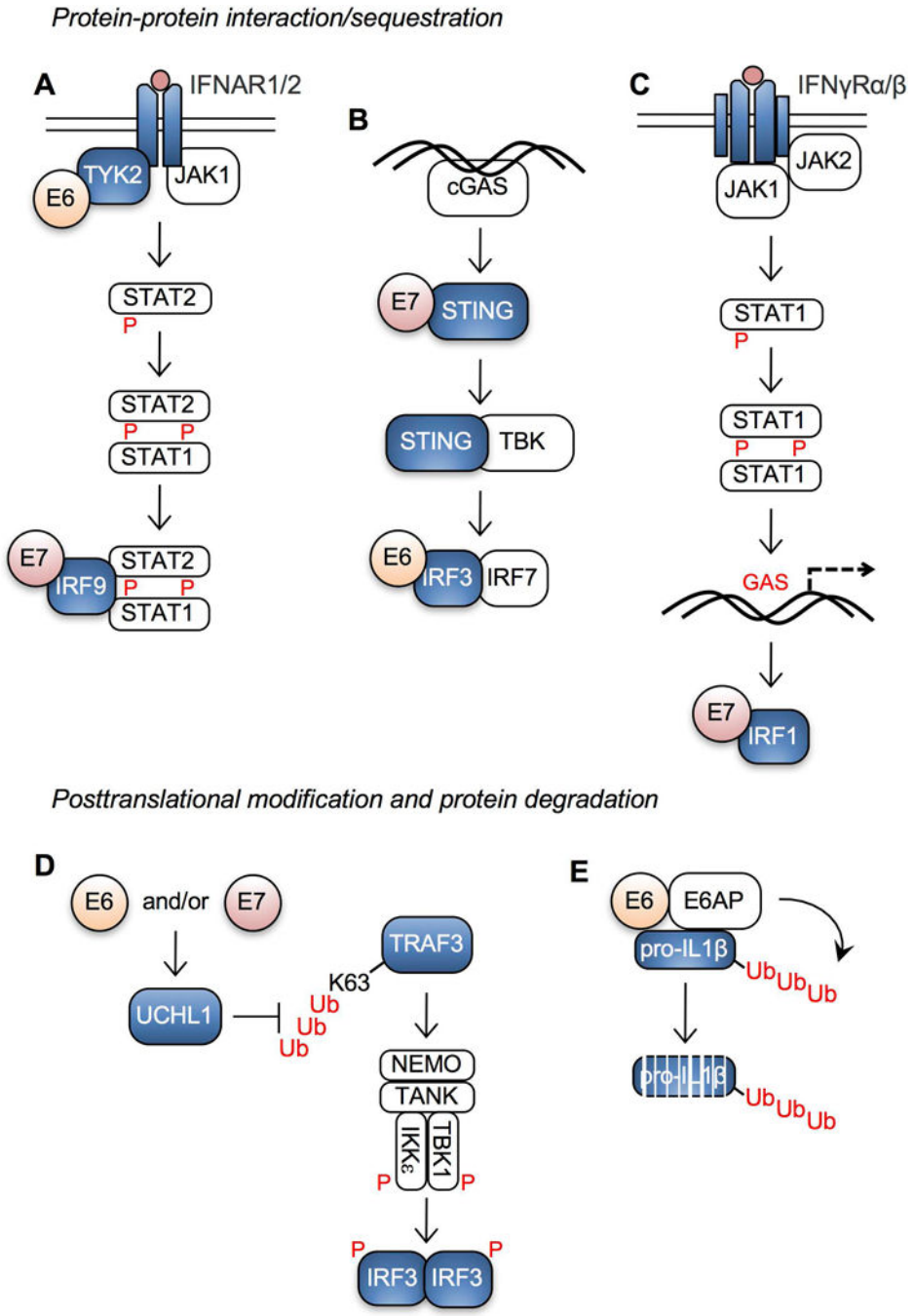

Fig. 2.

HPV E6 and E7 interacts with core components of the interferon pathway. (A) HPV inhibits type I IFN receptor signaling by HPV E6 and E7 interactions with TYK2 and IRF9, respectively. (B) HPV inhibits signaling by the DNA sensor cGAS via high-risk HPV E6 and E7 interactions with IRF3 and STING, respectively. (C) HPV inhibits type II IFN receptor signaling by high-risk E7 interaction with IRF1. (D) The HPV oncoproteins E6 and/or E7 suppress IRF3 activation by inhibiting K63 ubiquitination of TRAF3 through downregulation of UCHL1. (E) Interaction between high-risk HPV E6 and E6AP facilitates

poly-ubiquitination and degradation of pro-IL-1β. P, phosphorylation; GAS, gamma interferon activation site; Ub, ubiquitination.

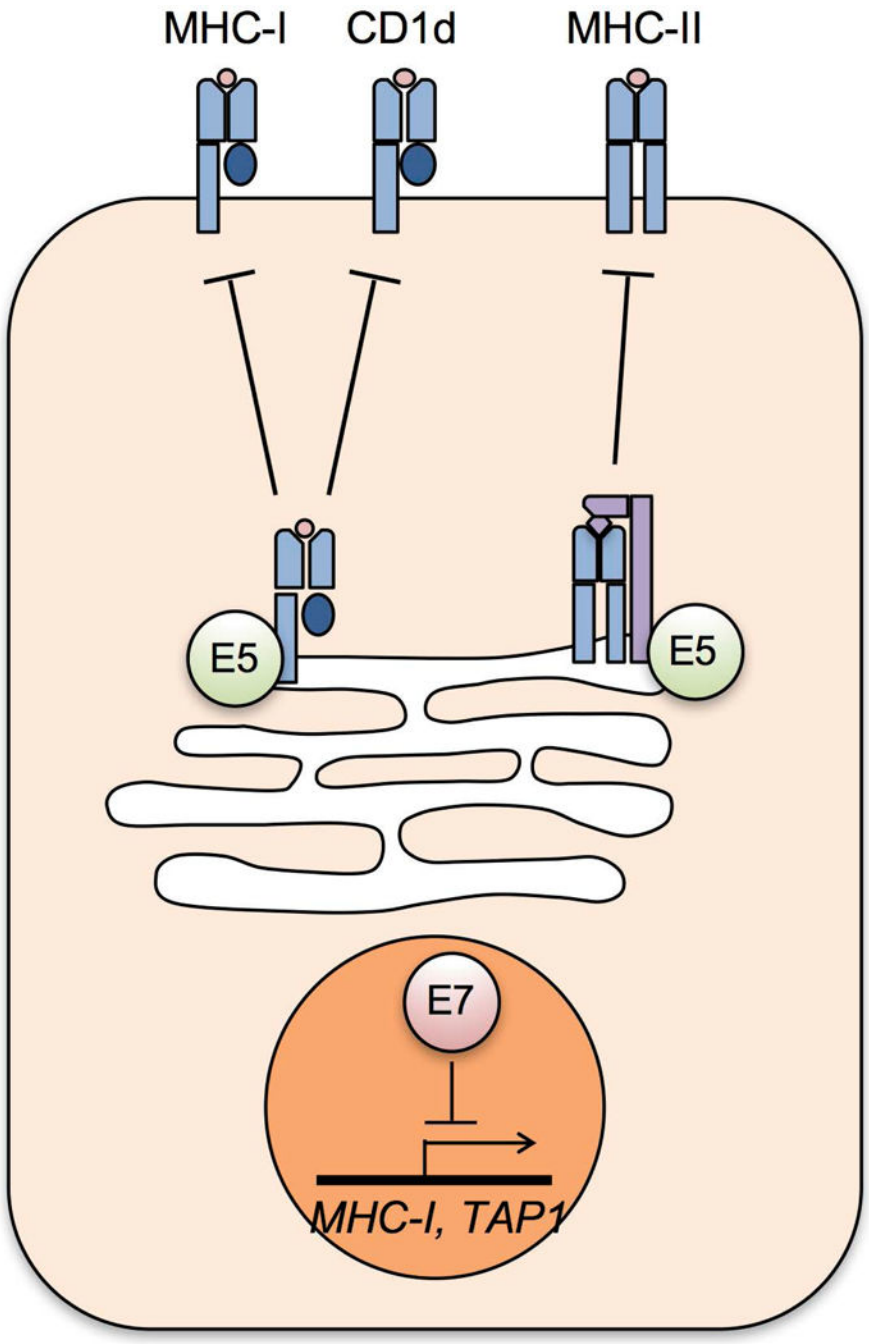

Fig. 3.

HPV E5 and E7 downregulate surface expression of MHC molecules. HPV E5 binds to MHC-I, CD1d, and the invariant chain of MHC-II in the Golgi and ER, preventing their trafficking to the cell surface. High-risk HPV E7 represses transcription of MHC-I genes.

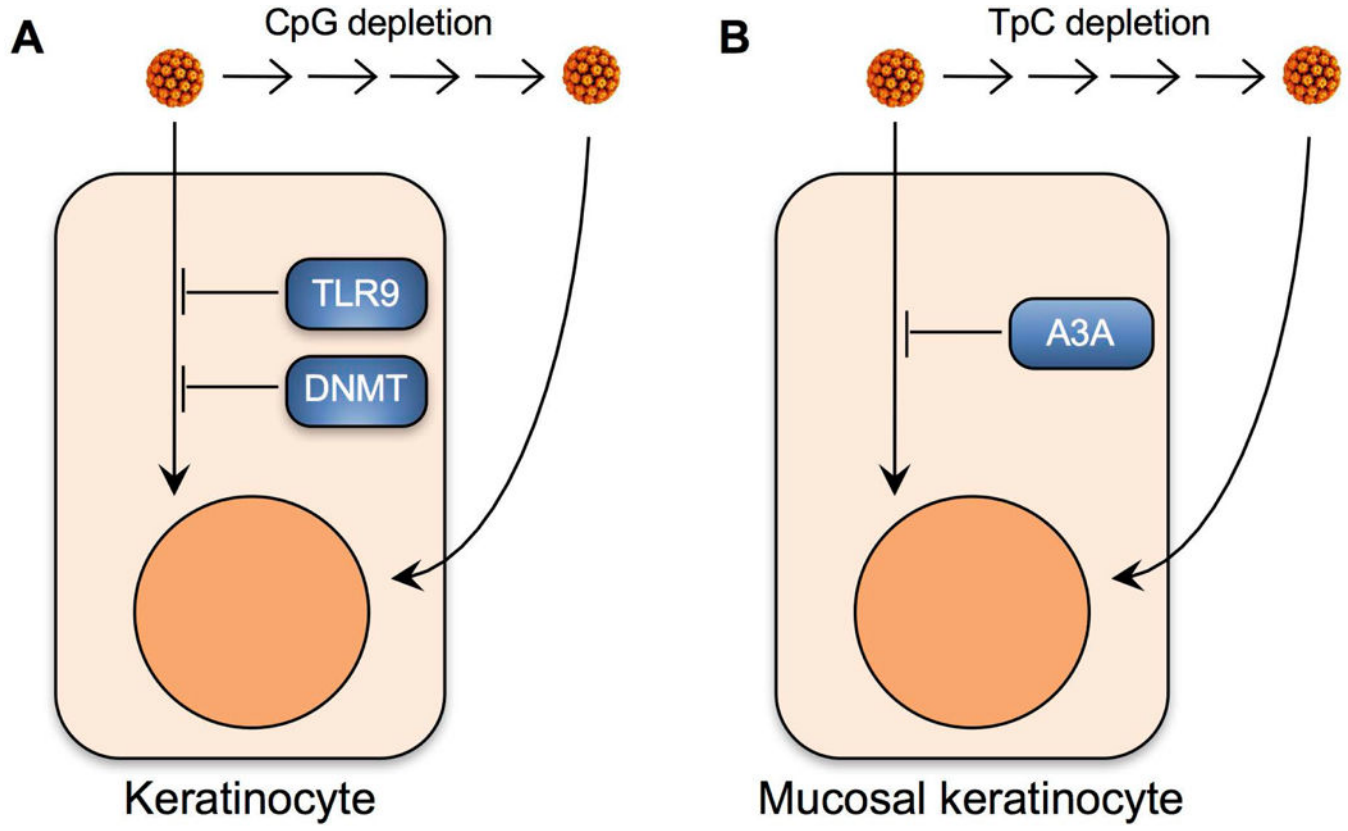

Fig. 4.

Bias in dinucleotide frequencies suggest that host restriction may drive papillomavirus genome evolution. (A) Unmethylated papillomavirus genomes can be recognized by TLR9 and/or targeted for methylation-induced gene silencing. During coevolution with their hosts, papillomaviruses have been selected and enriched for variants that contain reduced CpG motifs. CpG dinucleotide depletion may reflect an important immune evasion strategy. (B) Mucosal skin expresses high levels of nearly all A3 isoforms, including the HPV restriction factor A3A. The *Alphapapillomaviruses* are a genus of papillomaviruses that preferentially infect mucosal skin. TpC depletion amongst the *Alphapapillomaviruses* may allow for evasion of A3A at mucosal sites. DNMT, DNA methyltransferases.