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The Interaction Between Human Papillomavirus and Other Viruses

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Abstract

The etiological role of human papillomavirus (HPV) in anogenital tract and head and neck cancers is well established. However, only a low percentage of HPV-positive women develop cancer, indicating that HPV is necessary but not sufficient in carcinogenesis. Several biological and environmental cofactors have been implicated in the development of HPV-associated carcinoma that include immune status, hormonal changes, parity, dietary habits, tobacco usage, and co-infection with other sexually transmissible agents. Such cofactors likely contribute to HPV persistent infection through diverse mechanisms related to immune control, efficiency of HPV infection, and influences on tumor initiation and progression. Conversely, HPV co-infection with other factors may also harbor anti-tumor effects. Here, we review epidemiological and experimental studies investigating human immunodeficiency virus (HIV), herpes simplex virus (HSV) 1 and 2, human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), BK virus (BKV) JC virus (JCV), and adeno-associated virus (AAV) as viral cofactors in or therapeutic factors against the development of genital and oral HPV-associated carcinomas.

Keywords

papillomavirus; HIV; herpesvirus; polyomavirus; parvovirus

1. Introduction

The oncogenic properties of papillomaviruses are related to replication strategies occurring in terminally differentiating epithelia of skin and mucosa (Doorbar, 2007). Papillomaviruses specifically infect basal cells of stratified squamous epithelial through microlesions or wounds in the epithelium (Roberts et al., 2007). Proliferating basal cells will eventually differentiate. HPV produces the viral oncoproteins E6 and E7 to induce an S-phase like environment in quiescent, differentiated cells. E6 and E7 stimulate cell cycle progression via

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degradation of the cell cycle gatekeepers, p53 and retinoblastoma proteins (Rb), respectively. Differentiated cells support the productive phase of the viral lifecycle activating late gene expression, genome amplification, and viral assembly. In the uppermost epithelial layers, progeny virions are sloughed off as part of the normal epidermal renewal process.

Establishment of chronic or persistent HPV infection with one of the high-risk HPV types is a major predisposing risk factor in the development of HPV-associated carcinomas (Bosch et al., 2002). HPV has been causally linked to a subset of cancers arising in the anogenital tract and oropharynx. Over 95% of cervical carcinomas (squamous cell carcinomas and adenocarcinomas) are attributed to HPV infection, while the prevalence of HPV in oropharyngeal squamous cell carcinomas (OSCC) shows a more varied association ranging between 45–87% (Gillison et al., 2015). However, these infections typically resolve on their own and are cleared by the immune system. Transformation by high risk HPV types requires persistent infection, high level expression of the viral oncogenes E6 and E7, and accumulation of cellular mutations over time (Moody and Laimins, 2010). Persistent, high level expression of E6 and E7 is often associated with integration of the viral genome where disruption of the E2 coding region leads to deregulated expression of E6 and E7 oncoproteins, yet viral genome integration is not a prerequisite for cancer. Since less than 1% of women infected with high-risk HPV types will develop cancer, additional biological and environmental cofactors, such as immune status, hormonal changes, parity, dietary habits, tobacco usage, and co-infection with other sexually transmissible agents have been implicated in the development and progression of HPV-associated cancers (Castellsague et al., 2002). Indeed, a history of prior sexually transmitted infections that include human immunodeficiency virus (HIV), herpes simplex virus, *Neisseria gonorrhea*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* has been linked to a reduced ability to clear HPV or an increased risk of acquisition of HPV infection (Grce et al., 2004). Interactions between HPV and viruses and microbes that share a similar epithelial niche could enhance HPV replication and persistence and accelerate cancer progression. This chapter will review the evidence for a number of viruses that have been proposed as potential risk factors in HPV-associated cancers.

2. Human Immunodeficiency virus and HPV

Human immunodeficiency virus (HIV) is a member of the Retroviridae family of viruses and is the etiological agent of acquired immunodeficiency syndrome (AIDS). Antiretroviral therapy has improved the health and survival of HIV-positive patients. However, HIV-infected individuals have a greater risk of developing AIDS-defining and non-AIDS-defining malignancies, including HPV-associated cancers.

HIV is primarily transmitted at mucosal surfaces upon sexual contact (Hladik and McElrath, 2008). While HIV exhibits tropism for a number of cell types, including monocytes, dendritic cells, and epithelial cells, its primary target is the CD4+ T lymphocyte (Perez et al., 2011). HIV depletes CD4+ T cells through a variety of mechanisms, leading to immunodeficiency (Doitsh et al., 2014; Finkel et al., 1995; Garg et al., 2012; Gougeon et al., 1996; Huang et al., 2008; Jekle et al., 2003; Muro-Cacho et al., 1995; Rosok et al., 1998).

Due to the critical role of the host immune response in clearing HPV infection, the effects of HIV on the immune system are thought to influence HPV pathogenesis.

Focusing on cervical cancers, HIV infection has positively correlated with a prevalence of persistent HPV infections and increased incidence of low-grade and high-grade cervical intraepithelial lesions (CIN) and invasive cervical carcinoma (De Vuyst et al 2008). In the United States, HIV-infected women with T cell counts less than 200 have a 7-fold increased incidence of cervical carcinoma compared to the general population (Abraham et al., 2013). Worldwide, HIV-infected women also demonstrate an increased incidence of invasive cervical carcinoma with standardized incidence ratios (SIR) ranging from 2 – 40. (De Vuyst et al., 2008). Antiretroviral treatment and immune reconstitution has shown clearance of HPV, reduction in HPV persistence, and regression of low grade CIN (Blitz et al., 2013; Konopnicki et al., 2013). However, antiretroviral therapy has been shown to confer little to no protection in the prevalence of HPV-associated squamous cell cervical carcinomas in HIV-infected women (Frisch et al., 2000). Thus, HIV infection confers lifelong risk for the development of HPV-associated cervical cancer.

Oral HPV infection is also more prevalent in HIV-infected individuals compared to HIV-negative individuals with HPV16 being the most commonly HPV type detected (Beachler et al., 2012; Cameron et al., 2005). Over 60% of HIV-positive individuals with oropharyngeal tumors were shown to be HPV-positive (D'Souza et al., 2014), and tonsillar cancers, the majority of which are HPV-positive, have been shown to occur at statistically higher levels (SIR 1.5 to 4) in both men and women infected with HIV (Chaturvedi et al., 2009; Frisch et al., 2000; Shiels et al., 2009). Similar to what has been observed in cervical cancer, antiretroviral therapy did not reduce the risk of developing invasive tonsillar carcinoma in a 10-year study period (Frisch et al., 2000). An increased incidence of HPV-associated oral warts has also been described for individuals on antiretroviral therapy (Greenspan et al., 2001).

The basis for HIV infection enhancing HPV-associated cancer is suggested to involve several mechanisms that together increase the acquisition and persistence of high-risk HPV types. The state of immunosuppression induced by HIV infection impairs the ability to clear HPV infection (Palefsky, 2009). Low CD4 T cell counts represent a strong correlate for infection with high-risk HPV types (Lacey, 2005). In addition, HIV may enhance susceptibility of individuals to acquiring HPV infection by disruption of the mucosal epithelial barrier, which could then facilitate access and entry of HPV to basal epithelial cells (Reusser et al., 2015). Indeed, inflammatory cytokines produced by cells exposed to HIV glycoproteins disrupted tight junction formation and epithelial barrier function (Nazli et al., 2010). Furthermore, exposure to HIV glycoproteins was experimentally shown to enhance susceptibility of basal cells in oral and anal epithelia to infection with HPV pseudovirions (Tugizov et al., 2013). In addition to HIV being a risk factor in HPV-associated cancers, HPV infection has also been suggested to be a risk factor for HIV infection. In both men and women worldwide, infection with any HPV type has been shown to double the risk for HIV infection (Houlihan et al., 2012). Interestingly, the risk of HIV infection following HPV better correlated with non-persistent HPV infections, defined by the detection of a HPV genotype at a single visit or by loss of the HPV genotype at follow-

up visits (Averbach et al., 2010; Smith-McCune et al., 2010). Furthermore, the degree of cytological dysplasia did not correlate with HIV infection, suggesting that HPV infection induced a local inflammatory response and recruitment of immune cells susceptible to HIV infection (Denny et al., 2012). Therefore, HPV vaccination programs will not only protect against HPV-associated cancers, but reduce the risk for HIV infection as well.

3. HPV and Herpesviruses

Herpesviruses consist of a group of large, enveloped double-stranded DNA viruses that establish life-long persistent infections in their host. Lifelong infection is achieved through the establishment of latent infections in long-lived cells, with evasion of immune surveillance. The replicative phase can involve a variety of cells, with herpesvirus replication generally occurring in the epithelium. Most human herpesviruses are shed and transmitted in saliva, exhibiting life-long residence in the oral cavity, but can also be sexually transmitted. Thus, several human herpesviruses share similar routes and sites of infection as HPV. These include herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), human cytomegalovirus (HCMV), and Epstein-Barr virus (EBV).

3.1 Herpes simplex viruses-1 and -2 in HPV-associated carcinoma

HSV-1 and -2 are related viral genotypes distinguished by antigenic differences of their envelope glycoproteins. While both viruses cause common infections worldwide, HSV-1 is more seroprevalent than HSV-2, with HSV-1 antibodies detected in 50% of persons in developed countries and up to 90% of persons in developing countries (Wald and Corey, 2007). HSV-2 seropositivity varies widely in different populations with seropositivity ranging between 15% to 80% (Wald and Corey, 2007). HSV-1 and HSV-2 are transmitted by close personal contact with an individual shedding the virus. Although both HSV-1 and HSV-2 can infect oral or genital mucosa, HSV-2 is typically associated with genital herpes. However, the proportion of genital HSV-1 infections has increased due to changes in sexual practices. HSV infection of the epithelial mucosa supports viral replication, followed by infection of sensory nerve endings where the virus is transported to either the dorsal root, sacral, and trigeminal ganglia depending on the site of infection. HSV neuronal infection harbors the latent virus for the lifetime of the host with periodic viral reactivation that re-seeds infection of the mucosal epithelium for productive viral replication and shedding. Primary infection or viral reactivation can manifest without any symptoms or be symptomatic with the appearance of ulcerative or vesicular lesions in the oral and genital mucosa. Thus, it has been suggested that HSV oral and genital infections may be predisposing factors for HPV infection. Possible mechanisms include HSV infection allowing HPV better access to the basal cell layer for the establishment of infection. Alternatively, HSV replication in the tissues where HPV also replicates may directly or indirectly influence the persistence, clearance, and/or oncogenic activities of HPV.

Several epidemiological studies have been conducted to determine the association of HSV infection with HPV-associated cervical and oral cancers. In regards to cervical cancer, HSV-2 seropositive women have been shown to have a 2- to 9-fold increased risk of developing cervical squamous cell carcinoma or adenocarcinoma (Castellsague et al., 2002;

Hildesheim et al., 1991; Rawls et al., 1968; Slattery et al., 1989; Smith et al., 2002). HSV-2 specific antigens and DNA have been detected in exfoliated cells from dysplastic/cancerous cervical tissues at higher frequency than in normal tissues (Pacsa et al., 1976; Prakash et al., 1985). HSV-2 co-infection with the high-risk HPV types 16 and 18 has been observed in approximately 25–30% of CIN and 13–25% of invasive cervical squamous cell carcinoma and adenocarcinomas compared to 0–4% of normal cervical tissues (Di Luca et al., 1987; Zhao et al., 2012). HSV-1 has also been implicated in cervical cancer (Finan et al., 2006). However, a number of studies have shown a lack of association with HSV-1 or -2 in cervical carcinogenesis (Lehtinen et al., 2002; Munoz et al., 1995). In head and neck cancers (HNSCC), similar inconsistent associations between HSV-1 and HPV have been observed. However, in one study where a small subset of HPV-positive HNSCC cases were co-infected with HSV-1, co-infection correlated with decreased survival following chemoradiation. Thus, the presence of HSV could be a prognostic indicator for outcomes following therapy (Rautava et al., 2012) or serve as a serological biomarker for increased risk.

In vitro studies have provided some evidence for how HSV can act as a cofactor in HPV-associated malignancies. The idea of HSV as an oncogenic cofactor was suggested by early studies showing increased tumor incidence in rats treated with smokeless tobacco (snuff) and HSV-1 infection, compared to either snuff or HSV-1 alone (Hirsch et al., 1984; Larsson et al., 1989). Furthermore, HPV16-immortalized human keratinocytes transfected with HSV-2 subgenomic fragments formed squamous cell carcinomas in immunocompromised mice (DiPaolo et al., 1998). In vitro, HSV has been shown to alter aspects of the HPV life cycle upon co-infection. The presence of either HSV-1 or -2 in HPV18-transfected HeLa and A431 cells was shown to increase HPV integration and enhance HPV replication (Hara et al., 1997). In organotypic raft culture, HPV-positive cervical epithelial cells infected with either HSV-1 or HSV-2 exhibited significant cytopathic effects associated with HSV replication (Meyers et al., 2003). HSV-infected, HPV-positive organotypic raft cultures had undetectable E2 and reduced E6 and E7 mRNA levels; however, HPV DNA copy number and replication were maintained (Meyers et al., 2003). From these studies we can propose than HSV may act in an opportunistic manner, replicating in HPV-infected tissues and influencing HPV gene expression. Subsequent tissue repair, deregulated HPV oncogene expression and DNA replication, or HPV integration would be the early carcinogenic events that would not rely on the continued presence of HSV, setting up a scenario for HSV “hit-and-run” oncogenesis (Cox et al., 1993).

Deciphering the role of HSV in HPV-associated cancers is clearly needed with the recent FDA approval of an oncolytic HSV-1 for treatment of melanoma. T-Vec (talimogene laheraprepvec) is a second-generation HSV-1 virus engineered with deletions in the HSV-1 γ34.5 and α47, which attenuate neurovirulence and enhance replication in cancer cells. T-Vec also carries an insertion of the human granulocyte-macrophage colony-stimulating gene in the HSV genome to enhance tumor specific immunity (Hu et al., 2006; Senzer et al., 2009). T-Vec has been tested in a phase I/II clinical trial with head and neck cancers and, in conjunction with chemotherapy, resulted in tumor responses in 82% of patients. Almost half of the patient tumor samples were HPV-positive. No patient developed local recurrences within the follow-up time of 29 months (Harrington et al., 2010). Future studies will

determine the efficacy of T-Vec in the treatment of head and neck cancers and cervical cancers.

3.2 Human cytomegalovirus in HPV-associated carcinoma

Human cytomegalovirus (HCMV) is a prevalent herpesvirus that infects 60 to 90% of adults worldwide. HCMV has a broad tropism infecting mononuclear cells, fibroblasts, endothelial and epithelial cells. Similar to HSV, HCMV uses the epithelium as a site for replication with viral shedding found in saliva, cervical secretions, and urine (Waner et al., 1977), and has likewise been implicated as a cofactor in HPV-mediated carcinogenesis. Indeed, HCMV DNA has been detected in 45% of cervical carcinoma in-situ as well as invasive cervical carcinoma, compared to only 17% in normal cervical tissues (Marinho-Dias and Sousa, 2013). Similar to HSV, HCMV co-infection with HPV16 or HPV18 was more frequent in high grade CIN and invasive carcinoma than in normal or control cervical tissues (Baldauf, 1996; Shen et al., 1993) The presence of HCMV in HPV16-positive cervical tumors correlated with a 2-fold increase in lymph node metastasis (Chen et al., 1996) and has also been associated with integrated forms of HPV16 in cervical lesions (Szostek et al., 2009). An association between HCMV infection and oral cancer is still lacking, limited by the few epidemiological studies and small sample size (Saravani et al., 2015; Yang et al., 2004).

Although HCMV is not a typical human tumor virus, some early studies implicated HCMV infection with malignant transformation of human embryonic lung cells (Geder et al., 1976). HCMV infection was also capable of inducing cervical dysplasia and carcinoma in mice (Heggie et al., 1986). A confounding issue was that malignant transformation occurred in the absence of a viral protein or was not always associated with the presence of the viral genome (Nelson et al., 1984). Studies have also shown that HCMV infection can induce cellular mutations and sensitivity to genotoxic agents that could enhance cellular transformation following infection (Albrecht et al., 1997). These observations led to the suggestion that HCMV might contribute to oncogenesis via a “hit-and-run” mechanism (Shen et al., 1997). More recently, HCMV infection has been shown to induce DNA strand breaks specifically on chromosome 1q42 to 1q21 in the absence of viral gene expression (Fortunato et al., 2000). In the years that followed, HCMV has been detected in a variety of cancers such as gliobastoma multiforme and colon, prostrate and breast carcinomas, with inconsistent associations also documented (Cobbs et al., 2002; Harkins et al., 2002; Herbein and Kumar, 2014; Samanta et al., 2003). HCMV, like other herpesviruses, possesses viral activities that modulate cell cycle, cell survival and apoptosis, endothelial adhesion, migration, and invasion, angiogenesis, and immune evasion. However, the incomplete association of HCMV observed in various cancers, including those associated with HPV, has proposed HCMV provide “oncomodulatory” activities that enhance tumor progression. Activation of cellular signaling pathways following HCMV infection results in secretion of cellular and viral growth factors and cytokines, which can affect the tumor microenvironment and malignant phenotype of tumor cells. (Michaelis et al., 2009).

3.3 Epstein-Barr virus in HPV-associated carcinoma

Epstein-Barr virus (EBV) is a human DNA tumor virus, associated with B cell and epithelial malignancies. EBV typically infects B lymphocytes and epithelial cells establishing life-long

persistent infections. Memory B cells harbor the latency phase of the viral lifecycle, while differentiated epithelial cells support the replicative phase. EBV's oncogenic potential is well established as demonstrated by EBV infection immortalization of B cells in vitro. EBV encodes a number of viral oncogenes that include EBV encoded nuclear antigens (EBNA) 1, 2, 3A, 3B, and 3C and the latent membrane proteins (LMP) 1 and 2 required for B cell immortalization. In epithelial cell infection, the oncogenic capabilities of EBV are less understood, yet EBV is an etiological factor in nasopharyngeal carcinoma (NPC) and a subset of gastric carcinoma. The shared epithelial tropism linked with its oncogenic potential also has suggested EBV as a potential cofactor in HPV-associated cancer.

EBV can infect cervical epithelial cells (Sixbey et al., 1983), has been detected in cervical washings (Sixbey et al., 1986), and has been implicated as a potential cofactor in the development of cervical carcinoma. In cervical cancer, PCR detection of EBV DNA or RNA is found in more than 60% of invasive squamous cell carcinoma (Aromseree et al., 2015; Khenchouche et al., 2013; McCormick et al., 2015; Santos et al., 2009; Sasagawa et al., 2000). A correlation between the detection of EBV and lesion severity has also been observed, with EBV detected in 8–14% of normal samples, 12.5% of low grade CIN lesions, and 21–38% of high grade CIN lesions (Khenchouche et al., 2013). While PCR is more sensitive, RNA in situ hybridization (ISH) can discriminate whether EBV is present in epithelial tumor cells versus infiltrating B lymphocytes in the stroma. The EBV encoded RNAs (EBERs) are an abundantly expressed, non-coding RNA routinely used for clinical detection of EBV by ISH (Gulley and Tang, 2008). Positive EBER-1 ISH signals have been detected in the carcinoma cells of approximately 50% of invasive cervical carcinoma, 35% of high grade CIN lesions, and 10% of normal cervical tissues (Landers et al., 1993; Sasagawa et al., 2000). In addition, the EBV oncoproteins EBNA-2 and LMP1 were frequently detected in both invasive cervical carcinoma and high grade CIN lesions (Sasagawa et al., 2000). A confounding issue with the association of EBV in cervical cancer is that not all the tumor cells are positive for EBV. A low EBV copy number less than 1 copy per cell was observed in cervical tumors, and EBER ISH positive cells were only detected in a subset of tumor nests (Sasagawa et al., 2000). Furthermore, EBV has been detected in normal squamous and glandular epithelial tissue adjoining the tumor and in B lymphocytes infiltrating the tumor or the stroma, and not in dysplastic or tumor cells, questioning whether EBV has any role in cervical cancer or is merely a passenger (Payne et al., 1995; Shoji et al., 1997). However, EBV may play an indirect role by interfering with the immune response to HPV-transformed cells through the production of the viral BCRF1 gene product, an interleukin-10 homolog (Al-Daraji and Smith, 2009; Polz-Dacewicz et al., 2016). Similarly, EBV gene products can be secreted in exosomes, such that EBV-infected bystander cells could influence the tumor, tumor environment, and immune responses to HPV (Meckes et al., 2013; Pegtel et al., 2011). Whether EBV has direct or indirect effects on cervical cancer, the presence of EBV alongside HPV16 in cervical smears has also been shown to correlate with a 5 to 7-fold increased likelihood of HPV integration into the host genome, suggesting that the presence of EBV may enhance genomic instability of HPV-infected cervical epithelial cells. (Kahla et al., 2012; Szostek et al., 2009).

Like other herpesviruses, EBV is a life-long resident of the oral cavity, replicating in oropharyngeal epithelial cells and shed in saliva. The continual presence of EBV in the oral

cavity has long suggested EBV oncogenic activities as a cofactor in oral cancers. Furthermore, HPV-positive OSCC typically involves the tonsil and base of tongue (BOT) (Dahlstrand and Dalianis, 2005; Licitra et al., 2002), which are in close proximity to lymphoid rich regions known to harbor EBV. In OSCC, EBV has been detected at variable rates (15–100%) with some studies unable to detect significant levels of EBV (Bagan et al., 2008; Cruz et al., 1997; D'Costa et al., 1998; Iamaroon et al., 2004; Kobayashi et al., 1999; Sand et al., 2002; Tsang et al., 2003). Geographical and ethnic differences have been suggested to explain the varied association of EBV with OSCC. Regions endemic for NPC, an EBV-associated head and neck cancer, correlate with a higher frequency of EBV in OSCC (Jalouli et al., 2012). In some cases, EBV has been localized to tumor cells using less sensitive methods such as EBER ISH and LMP1 immunohistochemistry. Curiously, expression of LMP1 has also been detected in cancerous oropharyngeal tissues, in the absence of EBER expression (Gonzalez-Moles et al., 2002; Kobayashi et al., 1999), raising the possibility of an EBER-negative form of latent EBV infection (Bonnet et al., 1999; Sugawara et al., 1999). Indeed, oral epithelial tissues with severe dysplasia exhibited greater EBER expression by ISH as compared to OSCC, which suggests a role for EBV early in tumorigenesis rather than at late stages (Kikuchi et al., 2016).

Only a few studies have correlated the presence of EBV with HPV in OSCC. PCR detection of EBV and HPV in oropharyngeal tumors has shown the presence of both viruses in approximately 15% to 20% of OSCC (Jalouli et al., 2012; Polz-Gruszka et al., 2015). In our study, focusing on tonsillar and base of tongue squamous cell carcinomas, laser capture microdissection (LCM) was used to specifically isolate carcinoma cells from oral tumor samples, followed by reverse transcription quantitative PCR (RT-qPCR) to detect the EBV EBER transcripts (Jiang et al., 2015). The absence of infiltrating B cells in EBV-positive samples was confirmed by RT-qPCR amplification of the CD20 B cell specific transcript. In our OSCC cohort, 75% of tonsillar SCC and 90% of BOT SCC were HPV-positive, with HPV16 being detected in 8/9 samples examined. EBV EBER transcripts were detected in 42% and 80% of tonsillar and BOT SCCs, respectively. EBV and HPV co-infection was observed in 25% of tonsillar and 70% of BOT SCC (Jiang et al., 2015). Six EBV-positive tumor samples were shown to contain an integrated HPV, suggesting a clonal expansion of tumor cells carrying an integrated HPV genome. Thus, detection of EBV in tumors with integrated HPV further suggested that co-infection must have occurred within the same cell (Jiang et al., 2015).

HPV-positive OSCC is an emerging clinical entity with features that distinguish it from HPV-negative OSCC, which is strongly correlated to smoking and alcohol consumption. HPV-positive OSCC exhibit a more rapid onset developing in younger adults (Gillison et al., 2000; Mellin et al., 2000). Patients with HPV-positive OSCC frequently present with disseminated metastatic disease, yet HPV-positive OSCC does exhibit a better prognosis compared to HPV-negative OSCC (Benson et al., 2014). In addition, HPV-positive OSCC display features of poorly or undifferentiated epithelial cells (Dahlstrom et al., 2003; Gillison et al., 2000). These features are reminiscent of what is seen in EBV-associated NPC, and phenotypes associated with EBV infection of epithelial cells. EBV LMP2A has been shown to induce a delay in epithelial differentiation (Scholle et al., 2000); a phenotype also observed in EBV-infected keratinocytes (Birdwell et al., 2014). In addition, EBV

infection can enhance the invasive phenotype observed in epithelial cells expressing HPV16 E6 and E7, suggesting that EBV may contribute to the rapid progression of HPV-positive OSCC (Jiang et al., 2015).

Further support for interactions between EBV and HPV has also been noted in NPC, a squamous cell carcinoma that is endemic in certain populations. NPC is a rare cancer in Caucasians, but is common in South China and Southeast Asia accounting for up to 20% of all cancers in endemic regions. A high incidence of NPC is also observed in Mediterranean Africa and among the Inuit population (Nielsen et al., 1977). The World Health Organization has categorized NPC into 3 types that describe the tumor's differentiation and keratin states. Type 1 NPC is a rare keratinizing, differentiated squamous cell carcinoma, accounting for 20–25% of all NPC. Type 2 NPC is a non-keratinizing, differentiated squamous cell carcinoma, whereas Type 3 NPC is non-keratinizing, undifferentiated squamous cell carcinoma. EBV is an established etiological factor in the development of NPC, being associated with nearly all type 2 and 3 NPC from endemic regions. Elevated IgA antibody titers to EBV capsid and early antigens is predictive of NPC development within a window of about 3 years (Henle et al., 1970; Ji et al., 2007). Despite the nearly complete association of EBV in type 2/3 endemic NPC, HPV has been detected at frequencies ranging from 10 – 47% in endemic NPC cohorts from Japan, Iran, Morocco, and China (Deng et al., 2014; Laantri et al., 2011; Mirzamani et al., 2006; Tung et al., 1999). Although both low-risk and high-risk HPVs (6, 11, 16, and 18) were detected, HPV16 and 18 were more prevalent, accounting for 66.7% of HPV-positive NPC tumors in a Chinese cohort (Tung et al., 1999). In contrast, co-infections were rarely detected in NPC from non-endemic areas (Stenmark et al., 2014), and several studies have suggested that HPV and EBV appear to be mutually exclusive in NPC with oncogenic HPV types 16, 18, 39, 45, and 59 only detected in EBV-negative NPC (Dogan et al., 2014; Lin et al., 2014; Lo et al., 2010; Maxwell et al., 2010; Robinson et al., 2013). The presence of EBV or HPV in NPC correlated with an overall improved survival compared to virally-negative NPC, a similarity noted for HPV-positive OSCC (Dogan et al., 2014; Stenmark et al., 2014). Future studies are clearly warranted to determine if EBV and HPV co-infection in NPC contributes to the development and/or progression of cancers or if co-infections simply reflect coincidental infections with no oncogenic contributions.

Although limited in scope, in vitro studies have provided some evidence that EBV and HPV co-infections may have consequences to each other's lifecycles. Differentiated epithelial cells support EBV replication, while EBV is latent in its associated carcinomas. In NPC, EBV infection has been shown to follow early genetic alterations in the nasopharyngeal epithelium that facilitate a stably maintained and latent EBV infection (Lo et al., 2004). EBV latent infection is consistently seen in high grade NPC dysplastic lesions, but not in low grade lesions with frequent loss of p16, p14, and RASSF1 tumor suppressor genes (Lo et al., 2004). In culture, nasopharyngeal epithelial cells (NPE) undergo growth arrest and subsequent senescence in the presence of EBV. However, upon overexpression of Cyclin D1, NPE were able to support a stable, latent EBV infection (Tsang et al., 2012). HPV infection and expression of the E6 and E7 oncogenes may induce cellular changes that favor the establishment of EBV latency over replication. For example, HPV E7 degradation of the retinoblastoma protein stimulates cell cycle progression independent of p16 inhibition of

cyclin D/cyclin-dependent kinase complexes, recapitulating the events shown to establish EBV latency in NPE cells. Furthermore, we have observed that EBV infection of HPV- or E7-immortalized human keratinocytes in organotypic raft culture showed a dramatic reduction in EBV DNA replication compared to efficient EBV DNA replication in organotypic rafts from primary keratinocytes, suggesting that HPV may promote EBV latency (Guidry and Scott unpublished observations). In contrast, Makielski et al. (2016) reported that EBV latently infected human telomerase (hTERT) immortalized oral keratinocytes (NOK) transfected with HPV genomes aided in the maintenance of EBV episomes and increased EBV lytic replication in organotypic raft culture (Makielski et al., 2016). In addition, a block in HPV18 amplification and late gene expression was observed in the presence of EBV. Regardless of the outcome, these observations provide evidence for co-infection increasing EBV persistence through either latency or enhanced viral replication and by extending HPV oncogene expression.

4. HPV and Polyomaviruses

Polyomaviruses share structural and functional similarities with papillomaviruses. Polyomaviruses harbor a small circular double-stranded DNA genome enclosed within a non-enveloped icosahedral capsid. Human polyomaviruses, such as BKV and JCV, infect epithelial cells lining various organs, but have also been detected in other cell types as well. Polyomavirus infections persist for the lifetime of the host as latent or subclinical infections with periodic shedding in urine and saliva. The main oncogenic feature of polyomaviruses is large T antigen, which much like HPV oncoproteins E6 and E7 is able to block the functionality of p53 and pRb family members, respectively. It is therefore conceivable that polyomaviruses could possibly augment the transformative properties of HPV during viral co-infection.

Several studies have examined a potential role for polyomaviruses in HPV-associated malignancies. The majority of the global population are thought to harbor BKV (Padgett and Walker, 1976) with primary infection likely occurring early during childhood. The tumorigenic potential of BKV is controversial but supported by in vitro studies and in animal models (Grossi et al., 1982; Kenan et al., 2015; Pagnani et al., 1988; Portolani et al., 1975; Tognon et al., 2003). A role for HPV/BKV co-infection in the initiation and progression of cervical cancer has been suggested. BKV has been detected in cervical swabs in both HPV-positive (4%) and HPV-negative (12%) samples (Fraase et al., 2012). BKV has also been detected in 35% of high-grade precancerous lesions of the cervix, with no BKV detected in low grade CIN or in normal tissues (Comar et al., 2011). The presence of BKV correlated with infection of high-risk HPV types in the high grade CIN. Furthermore, BKV DNA copy number was greater in high-grade CIN, suggesting that HPV might enhance BKV replication (Comar et al., 2011). BKV may also play a role in HPV-associated oral cancer. Some postulate that the oropharynx may be the primary site for BKV infection, and BKV has been detected in tonsil tissues (Goudsmit et al., 1982). BKV genetic material has also been found in saliva, suggesting a potential site of residence in salivary glands (Jeffers et al., 2009). However, a cofactorial role for BKV in HPV-positive oral carcinoma has yet to be firmly established, with one recent study showing only 4.8% of oropharyngeal cancers exhibiting HPV/BKV co-infection (Polz-Gruszka et al., 2015).

Another polyomavirus implicated in HPV-linked disease is JC polyomavirus (JCV), which has been detected in 9% of low grade CIN and in 7% of high grade CIN, and not in normal cervical samples (Comar et al., 2011). However, JCV infection did not correlate with HPV infection (Alosaimi et al., 2014; Comar et al., 2011); In contrast, JCV detection was three-fold higher in cervical carcinomas versus normal cervical smears among HIV-positive women, suggesting a role for JCV in cervical cancer in the context of HIV co-infection and immunosuppression (Alosaimi et al., 2014).

5. HPV and Parvoviruses

Adeno-associated viruses (AAV) have also been shown to interact with HPV. AAV are small, non-enveloped, single-stranded DNA viruses that are non-pathogenic and require co-infection with a helper virus to replicate. HSV, adenoviruses, and HPV are able to serve as helper viruses for AAV. Eleven AAV serotypes have been identified, with each having a wide cellular tropism, and with some AAV serotypes detected at similar anatomical sites as HPV (Blacklow et al., 1967). In contrast to the other viruses discussed thus far, epidemiological studies have suggested AAV as a protective cofactor in HPV-associated cancers. Serologically, women with invasive cervical carcinoma have significantly lower AAV2 or AAV3 antibody titers compared to healthy controls (Smith et al., 2001; Sprecher-Goldberger et al., 1971). Although lower AAV2 antibody titers did not correlate with high grade CIN, cervical AAV infection as well as AAV/HPV co-infection was associated with a reduced risk for high-grade cervical lesions with no association noted in low-grade lesions (Coker et al., 2001; Freitas et al., 2012). In vitro studies have suggested mechanisms for the protective role for AAV in HPV-associated cancers. Expression of HPV16 E1, E2, and E6 were shown to play a significant role in enhancing AAV type 2 (AAV2) replication. In addition, AAV replication has been suggested to interfere with the replication and oncogenic potential of the helper virus. AAV2 Rep78 protein was shown to inhibit the HPV16 P97 early promoter, required for expression of the HPV E6 and E7 oncogenes (Hermonat et al., 1997). AAV has become an attractive gene therapy vector, facilitating intracellular gene delivery in both dividing and non-dividing cells with robust, long term transgene expression (Kozlowska et al., 2013). Clinical trials with recombinant AAVs (rAAV) have been initiated to correct a number of genetic disorders such as cystic fibrosis, muscular dystrophy, and hemophilia. In regards to the effects of HPV on rAAV, the HPV gene products E1, E2, and E6 did not induce rAAV replication. However, each HPV gene alone in conjunction with adenovirus 5 infection significantly increased rAAV replication and virion production (Cao et al., 2012). Thus, these studies support the possibility for development of an AAV oncolytic vector for use against HPV-associated cancers.

6. Summary

Co-infection of HPV with both closely- and distantly-related viruses has been studied in the context of HPV-linked cancers arising in the anogenital tract as well as in the head and neck. HIV as well as members of the Herpesviridae (HSV, HCMV, and EBV) and Polyomaviridae (BKV and JCV) families have been detected in HPV-positive tumors, and some studies have revealed correlations between co-infection and disease progression and/or alterations to viral life cycles. Experimental models of co-infection have identified a variety of mechanisms by

which viral cofactors might contribute to tumorigenesis. However, incomplete association has precluded assigning cofactorial roles to any of these viral agents in HPV-associated cancers. These viruses, except for HIV, are also ubiquitous in the human population, further confounding their assignment as viral cofactors in HPV-associated disease. With the wide assortment of viruses that have been partially associated with HPV-associated cancers, co-infection with any one or multiple viruses may establish an environment that enhances tumor initiation and progression. These viral cofactors share the ability to establish life-long infections, which can increase the risk of adverse oncogenic events decades after the initial infection. Alternatively, life-long infection may increase the probability of detecting these infectious agents. Clearly, viruses have evolved mechanisms to evade immune surveillance, which can affect HPV clearance and persistence. Direct infection of HPV-infected cells may not be required as nearby virally infected cells can secrete cytokines such as viral IL-10 homologs and other viral products packaged in exosomes, which can impact neighboring cells. HPV-infected or immortalized cells may enhance infection of other viruses localizing such viral cofactors near other HPV-infected cells. Co-infection, through expression of additional viral oncogenes or epigenetic reprogramming, can replace deleterious mutations required for tumor progression. As epigenetic modifications result in heritable changes to gene expression, epigenetic alterations would have long-term effects on tumor progression in the absence of viral gene expression or infection. HCMV infection has been shown to epigenetically reprogram NK cells, while EBV infection has been observed to epigenetically reprogram epithelial cells with an undifferentiated, invasive phenotype (Birdwell et al., 2014; Queen et al., 2013; Schlums et al., 2015). Such epigenetic changes would provide a mechanistic framework for viral “hit-and-run” oncogenesis. Further study into how co-infection of HPV with other pathogenic viruses in the context of the microbiome will reveal their contributions in the etiology of HPV-linked tumors and guide future efforts in the development of effective therapeutic treatments and vaccines.

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Highlights

- Epidemiological evidence has identified several viral cofactors in HPV-associated cervical and oral carcinomas.
- A common feature of viral cofactors in HPV-associated carcinoma is their ability to establish lifelong persistent infections.
- Viral cofactors in HPV-associated cancer may act through direct infection of tumor cells or indirectly through various mechanisms.