Herpes Simplex Virus Type 2: Bystander or Active Player in Cervical Carcinogenesis?

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Abstract

More emphasis have been placed on producing vaccines that prevent host cell entry by Human Papillomavirus (HPV) while less attention has been given to Herpes Simplex virus type 2 (HSV-2) which potentially promotes acquisition and co-habitation of human immunodeficiency virus (HIV), HPV and Epstein-Barr virus (EBV). The tendency for HSV-2 to induce ulcerations and chronic inflammation following reactivation, and its potential to up-modulate both HPV regulatory and oncogenic gene and downregulate host tumour suppressor suggest that it is not a bystander in cervical carcinogenesis. Thus, efforts geared towards finding HSV-2 effective microbicide and vaccine should be intensified so as to reduce cervical cancer related mortality.

Keywords: Herpes Simplex virus type 2; Human papillomavirus; Epstein-Barr virus; Cervical cancer

Abbreviations: HPV: Human Papillomavirus; HIV: Human Immune virus; SSC: Squamous Cell Carcinoma; LMP1: Latent Membrane Protein 1; EBV: Epstein-Barr virus; CIN: Cervical Intraepithelial Neoplasia

Introduction

Cervical cancer is the second most common type of cancer (9.8%) affecting women worldwide [1-3]. It commonly starts as cervical intraepithelial neoplasia progresses over as many as 10 or more years to invasive cervical carcinoma. Since about 93% of all cervical cancers contain human papillomavirus (HPV) DNA, it is believed to be the main cause of the disease [4,5]. However, contrasting reports have been made on the involvement of other viruses. One of the fingered controversial viruses is the HSV-2.

Implication of HSV-2 Infection

An epidemiological study revealed that most people are infected with the HSV-2 by the time they are 10 years old [6]. Globally, serological prevalence of HSV-2 infection ranges from 7 to 30% of the population [7]. The virus increases the risk of HIV acquisition by 5 times [8]. This increased risk of HIV acquisition by HSV-2 is thought to be caused by breaks in the protective epithelial layer, inflammation and recruitment of activated CD4+ T cells to the ulcerated site, which are target cells for HIV. HIV in turn increases cancer risk [8] by facilitating the entry, persistence, replication and reactivation of latent oncoviruses due to the expression of its transactivator protein and gp120 [9]. As a result, people infected with HIV are at least 5 times more likely to be diagnosed with cervical cancer [10]. HSV-2 infection does not only favour HIV entry but it also promotes the invasion of other oncogenic viruses. The persistence of HSV-2 and its tendency to reactivate following latency increases the number of chronic inflammation in a woman's lifetime and may also facilitate EBV infection, a potential oncogenic virus [11]. Hence, it is not surprising that cervical cancer specimens are 5.1 times more positive for HSV-2 compared with cervical specimens from healthy controls [12]. After evaluating 210 cases of cervicitis and 24 cases of squamous cell carcinoma (SCC), Zhao et al. [13] reported that HSV-2 infection is 4.9 and 4.7 times more likely to be associated with cervicitis and SCC, respectively. The connection between chronic cervicitis and cervical malignancy is not farfetched. Circulating reactive oxygen species and inflammatory cytokines from activated inflammatory lymphocytes are capable of promoting DNA damage and genomic instability in proximal epithelial cells. These epithelial cells become susceptible to latent membrane protein 1 (LMP1) positive EBV with concomitant clonal proliferation and survival of EBV-infected premalignant cells following the activation of NF-κB and STAT3 signaling pathways [14].

Epstein-Barr Virus Infection

Epstein-Barr virus (EBV) belongs to the group of gamma-herpes viruses and is responsible for epithelial malignancies including B-cell lymphomas, lymphoproliferative disorders, nasopharyngeal, gastric and salivary gland carcinomas, breast, prostate and oral cancers. It is commonly transmitted through oral secretions. Previous studies demonstrated EBV DNA in cervicitis, precancerous (cervical intraepithelial neoplasia, CIN) and...
invasive cervical carcinoma cells [15]. The level of premalignant or malignant transformation cervical epithelial cells is dependent on EBV load and lesion grade [16]. Some reports revealed higher EBV DNA positivity in CIN3 lesions (15-70%) when compared with cervical carcinoma (5.8%) [17-19]. Despite the low presence of EBV DNA in SCC, SCC is 2 times more likely to be EBV positive than normal cervical samples [12,15]. Additionally, a recent meta-analysis by de Lima et al. shows that EBV infection posed a twofold increased risk of precancerous cervical lesions and fourfold increased risk of cervical cancer in HPV positive women [16]. This risk is explained by the findings of some studies which revealed that EBV infection in the cervix accelerates integration of HPV genome into cervical cell’s genome, enhancing genomic instability of the infected cervical cells [16,20] and in some cases results in lymphoepithelioma-like (non-keratinizing) carcinoma of the cervix [15]. These reports convincingly suggest that EBV plays a direct role in cervical carcinogenesis.

**EBV and HSV-2 Co-Infection**

The higher prevalence of EBV+HSV-2 co-infection when compared with HPV+HSV-2 co-infection observed in recent studies suggest a higher odds for the former than the latter among women with abnormal Pap smears [21,22]. Elsheikh and colleagues reported a 10% and 2.4% prevalence of HPV+HSV-2 and EBV+HSV co-infections in cervical cancer cases, respectively [12]. The low prevalence of EBV+HPV co-infection (in HSV-2 negative women) in their study when compared with previous studies [11,19] suggests that the higher association between EBV and HPV observed by previous studies may have been favored by HSV-2 infection. Unfortunately, these previous early studies failed to investigate HSV-2 infection among their recruits. The fact that a recent study showed that EBV+HSV+HPV-2 tri-infection is associated with higher frequency of cervical abnormalities among sex workers suggests that HSV-2 actively contributes to cervical carcinogenesis.

Interestingly, some oncogenic HSV-2 miRNAs have been identified, among which miR-H25 has been found to exert its effects by down-modulating host miR-143, a tumour suppressor [23]. In turn ensures immuno-escape of EBV bearing miR-BART7 with resultant tumour immunization and resistance to cisplatin [24]. The hypermethylation, p16/CDKN2A inactivation, mutation of PIK3CA, and frequent upregulation of JAK2, PDL-1 and PD-L2 observed EBV infected cells further exposes the oncogenic potential of the virus [25,26].

**HPV and HSV-2 Co-Infection**

Evidence emanating from numerous studies suggest significant association between HSV-2 and HPV in invasive cervical cancer [27-29]. Interestingly, Zhao et al. reported that HPV+HSV-2 co-infection is 34.2 and 61.1 times more likely to be linked with CIN and SCC, respectively [30]. Paba and colleagues went further to demonstrate HPV+HSV-2 co-infection in 23.5% of cervical cancer specimens using PCR based DNA identification [30]. This underscores the importance of HSV-2 infection in HPV related cervical carcinogenesis. In line with this assertion, in vitro assay carried out by Tran-Than and colleagues revealed that herpes simplex virus type 2Bgl IIN transforms epithelial cells with concomitant overexpression of Survivin in CIN [31]. However, in vivo investigation carried out by the same team did not reveal any association between the virus and cervical cancer [31].

Real-time-PCR assay revealed that HSV-2 infection increases the level of transcription of HPV E1, E2 and E6 genes, especially that of HPV 18, up to 3-fold in Caski cells and Hela cells [32-34]. This suggests that HSV-2 infection could increase the risk of cervical cancer by stimulating the overexpression of both HPV regulatory and oncogenic genes. This induces the malignant transformation of HPV -immortalised cervical keratinocytes [35].

**Conclusion**

Since, evidence emanating from recent studies overwhelmingly suggest that HSV-2 actively contributes to cervical carcinogenesis, efforts geared toward finding effective microbicides and vaccines should be intensified so as to reduce cervical cancer related mortality.

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