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Review Article

KSHV co-infection, a new co-factor for HPV-related cervical carcinogenesis?

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Abstract: High-risk human papillomavirus (HPV) infection is the etiological agent of cervical cancer and some other cancers. Kaposi sarcoma-associated herpesvirus (KSHV) represents a principal causative agent of several human cancers arising in those immunocompromised patients. In fact, KSHV DNA has been detected in the female genital tract, and this virus may share some transmission routes with HPV, although the detection rate of KSHV in cervical samples is very low and the KSHV/HPV co-infection is seldom reported. Currently, it remains unclear about the role of KSHV co-infection in the development of HPV-related neoplasias. In this article, we have summarized the recent finding from clinic and bench indicating KSHV co-infection may represent a co-factor for the development of HPV-related carcinogenesis.

Keywords: KSHV, HPV, cervical cancer, oncogenic virus

Introduction

Certain subtypes of human papillomavirus (HPV) may cause warts on or around the female and male genital organs, which are called low-risk subtypes because they are seldom linked to cancer. In contrast, high-risk subtypes of HPV are strongly linked to several human cancers, including cervical, penile, anal and oral cancers [1, 2]. Among these, cervical cancer represents one of the most common malignancies in females worldwide. Although infection by HPV is the most important risk factor for cervical cancer, HPV infection is not the only cause of cervical cancer or not enough to initiate cervical cancer development, because most women with HPV infection do not get cervical cancer. In fact, certain other risk factors, like smoking and HIV infection, influence which women exposed to HPV are more likely to develop cervical cancer. In addition, certain other factors including co-infected pathogens, such as human immunodeficiency virus (HIV) and chlamydia, have been reported to increase the risk of women exposed to HPV for developing cervical cancer [3, 4].

Kaposi sarcoma-associated herpesvirus (KSHV, also known as human type 8 herpesvirus, HHV-8) represents a principal causative agent of several human cancers arising especially in those immunocompromised patients, including Kaposi's Sarcoma (KS), Primary effusion lymphoma (PEL) and Multicentric Castleman's disease (MCD) [5-7]. In fact, the immunosuppression (e.g., HIV infection, the use of immunosuppressive drugs) puts women at higher risk for HPV infection and cervical cancer development from precancerous conditions of the cervix. Published literatures have reported that KSHV DNA can be detected in the prostate, semen, oral cavity and the female genital tract [8-12]. KSHV can be transmitted via sexual contact including oral and anal sex, and via non-sexual routes, such as transfusion of contaminated blood and tissues transplants [13].

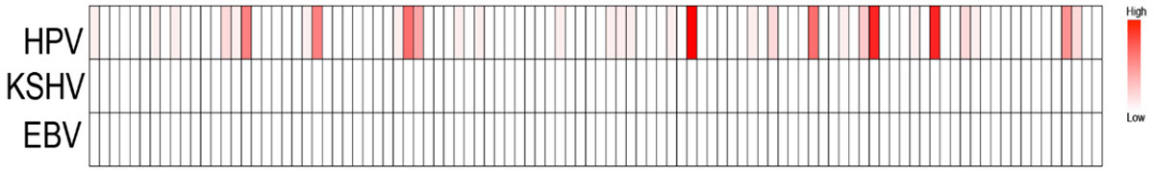

Figure 1. Detection of oncogenic viruses transcripts in the RNA-Seq datasets of cervical cancer samples. One hundred RNA-Seq cervical cancer datasets were obtained from the TCGA cohort and raw sequencing reads were analyzed as previously described [57]. Each vertical bar represents an individual patient and the color intensity reflects the levels of viral transcripts.

Moreover, the salivary transmission is thought to be as the main route of KSHV transmission, especially in children residing in endemic areas. Besides skin-to-skin contact, HPV can also be spread from one person to another through different sexual activities. Based on these common transmission routes, it is reasonable to speculate KSHV and HPV may have co-infection in some particular subpopulations, such as HIV+ individuals, organ transplant recipients. However, currently there are few studies reporting the co-infection of these two oncogenic viruses or their interaction in cervical samples and/or cervical cancer cells. It also remains unclear about the role of KSHV co-infection in the development of HPV-related cervical cancers. Here we have summarized the recent finding from our group and others in this interesting field and given some perspectives, too.

Epidemiology of KSHV and HPV co-infection in cervical samples

Like other herpesviruses, KSHV can also establish life-long latent infection in host cells with the expression of a limited number of viral genes. In contrast to the high prevalence of KSHV shedding in oral cavity, the detection rate of KSHV DNA or virus infection in cervical samples are relatively low or even totally negative in some studies. Whitby *et al* reported that KSHV DNA was detected in 3 of 11 cervical brush scrapes (CBS) obtained from KSHV-seropositive women attending the genitourinary medicine department [12]. In comparison, KSHV DNA was not detected in any of the 78 CBS from KSHV-seronegative women or in 96 CBS from women of unknown KSHV serostatus attending the colposcopy clinic. Another epidemiology study of KSHV infection in sex workers and women from the general population in Spain indicated that KSHV DNA was detected in 2% of the cervical samples of the prostitutes and in 1% of the cervical samples of women in the general population [14]. Moreover, they found that KSHV was more prevalent among HPV DNA-positive women (odds ratio = 2.5). Similarly, one study in 174 KSHV-seropositive female prostitutes in Mombasa, Kenya, showed that the prevalence of detection of KSHV was 4% in cervical swabs and 2.3% in vaginal swabs, although the status of HPV infection in these individuals remains unknown [15]. In contrast, one recent study found that HPV DNA was detected in 18/31 (58%) female genital brushings while none of these female genital brushings were KSHV DNA positive [16]. Another study reported that no cervical secretion from 112 Swedish women contained detectable KSHV DNA, although the antibodies to KSHV latent and lytic antigens were found in 2.7% and 24% of serum samples from the same group, respectively [17].

To detect the potential oncogenic pathogens in cervical cancer patient samples, a total of 100 RNA-Seq cervical cancer datasets were obtained from NIH The Cancer Genome Atlas (TCGA) cohort. Raw sequence data were aligned to a reference human genome (hg38; Genome Reference Consortium GRCH38) plus a library of virus sequences (including the sequences from all known human viruses documented by NCBI). We found that HPV transcripts were present in 31% of these samples but other oncogenic viruses including KSHV and EBV transcripts were not detectable (**Figure 1**). Furthermore, RNA-Seq datasets from a total of 27 cervical and/or endometrial cancer cell lines were downloaded from the NCBI Sequence Read Archive (SRA) and were then subjected to virome screening using the same informatics approach above. Our results show no evidence of KSHV and HPV co-infection in these tested cell lines. However, all these 100 RNA-Seq datasets were collected

from cervical cancer patients in the general non-HIV population, since no HIV reads were detected in these datasets. Actually, we cannot find any similar datasets from immunocompromised patients such as HIV+ individuals from TCGA cohort. As we know, the immunosuppression will greatly increase the chances of these oncogenic viruses co-infection.

Regulation of HPV oncogenic gene expression by KSHV co-infection in cervical cancer cells

High-risk HPV such as subtype 16 and 18 encoded E6 and E7 proteins are major viral oncoproteins which are closely associated with human cervical carcinogenesis [18]. E6 and E7 proteins can bind to the p53 and retinoblastoma (Rb) family proteins, respectively, resulting in the regulation of cell cycle and transformation [19]. Recent research has demonstrated E6 and E7 proteins can interact with or regulate many more cellular factors, including those proteins which regulate epigenetic marks and splicing changes in the cell, also contributing to oncogenesis [20]. Currently, it remains almost unclear how KSHV infection or KSHV-encoded proteins regulate HPV oncogenic gene expression in cervical cancer cells. Our recent studies have demonstrated that KSHV can successfully establish latent infection in a variety of HPV+ cervical cancer cell lines such as HeLa, SiHa and CaSki [21-23]. We also found that these viruses in latently infected cervical cancer cells possess normal replicative potential, since they can be induced into lytic phases by exogenous stimulus and finally produce new infectious particles [22].

Interestingly, our data indicated that KSHV infection significantly reduced both E6 and E7 expression from HPV16+ SiHa cells *in vitro* [22]. By using a cervical cancer xenograft model, we also confirm these results *in vivo* [23]. Furthermore, we found that LANA (Latency associated nuclear antigen) and vFLIP (viral FLICE inhibitory protein), two major KSHV-encoded latent proteins, responsible for the downregulation of E6 and E7 expression from SiHa cells [22]. Zhang *et al* have reported that interferon-β treatment induces one of cellular microRNAs, miRNA129-5p expression, while its levels gradually decrease with the development of cervical intraepithelial lesions and correlate with HPV E6 and E7 expression [24]. Following this discovery, we demonstrate that miRNA-129-5p is required for KSHV and/or viral latent proteins reducing E6 and E7 expression from SiHa cells [22]. Very interestingly, another group found that one of KSHV-encoded lytic protein, RTA (Replication and transcription activator), can bind to various HPV16 genomic regions and induce a significant upregulation of E7 transcription [25]. In fact, we also found that inducing lytic reactivation effectively impaired the reduction of E6 and E7 expression from KSHV-infected SiHa cells [22]. Therefore, these results indicate KSHV latent and lytic proteins may have distinct regulation of HPV oncogenic proteins expression in cervical cancer cells. Since KSHV is a big dsDNA virus with ~165 kb genome which containing 81 viral ORFs, as well as some microRNAs, non-coding RNAs, and a few small ORFs [26], it still requires a lot of work to understand how these viral components differentially regulate HPV oncogenic proteins expression in cervical cancer cells.

Regulation of cellular gene expression and functions by KSHV co-infection in cervical cancer cells

By using a cytokine/chemokine array, our recent study indicate that KSHV co-infection has increased several inflammatory factors production from SiHa cells, including Chemokine (C-X-C motif) ligand 1 (CXCL1), Interleukin 6 (IL-6), Plasminogen activator inhibitor-1 (PAI-1), Chemokine (C-C motif) ligand 5 (CCL5), Interleukin 8 (IL-8) and Macrophage migration inhibitory factor (MIF) [22]. Among these factors, CXCL1, its serum levels were significantly higher in patients with cervical squamous cell carcinoma (CSCC) when compared with patients with cervical intraepithelial neoplasia (CIN) and the healthy controls [27]. IL-6 has been found to promote cervical tumor growth via vascular endothelial growth factor (VEGF)-dependent angiogenesis or by modulating the apoptosis threshold [28, 29]. Interestingly, a recent meta-analysis study indicates that the single-nucleotide polymorphisms (SNP) of IL-6 (rs1800795) is associated with cervical cancer risk [30]. Another upregulated factor, PAI-1, an inhibitor of urokinase-type plasminogen activator, has been found with increased expression in cervical tumor tissue, specifically in aggressive tumors [31]. Moreover, targeting PAI-1 expression or function results in the reduction

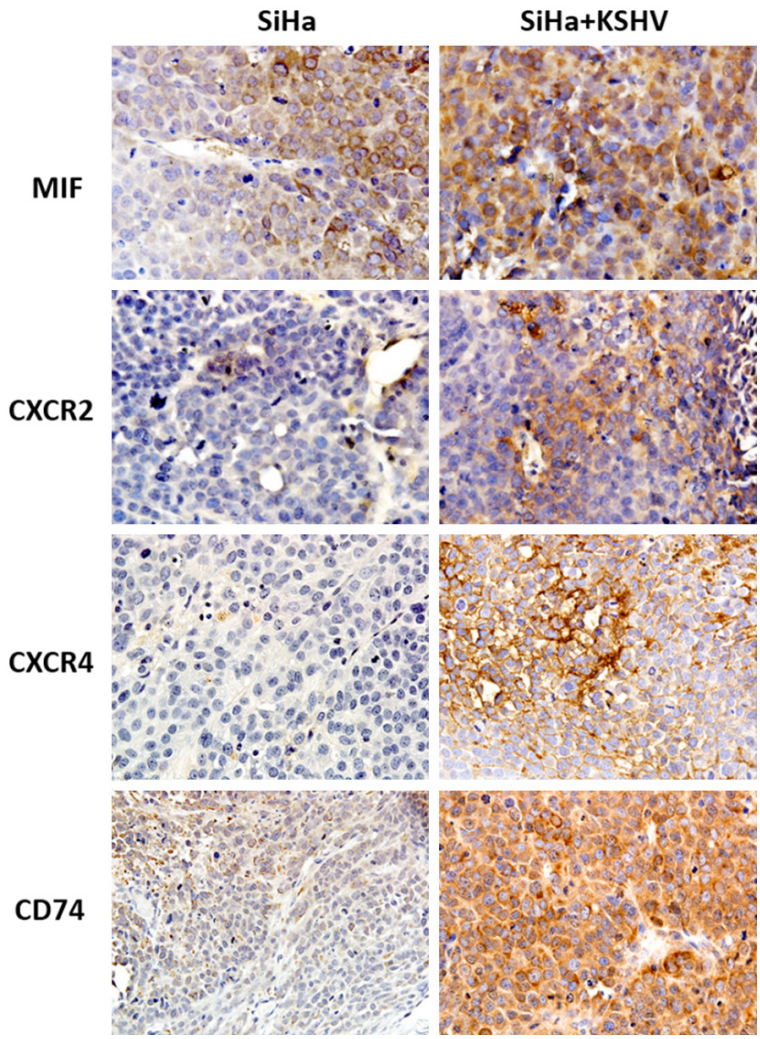

Figure 2. The upregulation of MIF and its receptors by KSHV co-infection in HPV+ cervical cancer tissues. The mock or KSHV co-infected SiHa cells (approximately 5 × 10^5 cells were mixed at a ratio of 1:1 with growth factor-depleted Matrigel) were injected subcutaneously into the right flanks of nude mice, respectively. The mice were observed and measured every 2~3 d for the presence of palpable tumors for ~40 d. Protein expression within tumor tissues from representative injected mice was measured by using immunohistochemistry staining.

of cellular proliferation, cell adhesion, colony formation, while the induction of apoptosis and anoikis in cervical cancer cells [32].

One of these factors, MIF, is well recognized as a cancer biomarker protein, since its expression in normal cells is several orders of magnitude lower than levels observed in cancer cells [33-36]. By using ELISA, we recently have found that KSHV co-infection significantly increases MIF secretion from HPV+ cancer cell lines such as SiHa and CaSki (5-8 folds increasing) [23]. Soluble MIF produced by cancer cells is imported into the cytoplasm and nucleus of its target cancer cells via an autocrine loop [37, 38]. MIF enters target cells by binding to its cellular receptors such as CXCR2, CXCR4 or CD74 [38, 39]. Our recent *in vivo* study indicates that the significant upregulation of MIF and its receptors CXCR2, CXCR4 and CD74 in tumor tissues from KSHV co-infected SiHa injected mice when compared to those from SiHa injected mice (**Figure 2**). In fact, one previous study reported the overexpression of MIF in invasive cervical cancer samples when compared to cervical dysplasias samples [40]. Another study also found that MIF and CD74 expression was significantly higher in CIN or CSCC than in the normal samples [41]. The overexpression of MIF was correlated with deep stromal infiltration, and both MIF and CD74 protein levels were associated with microvessel density [41]. Our recent findings suppose KSHV co-infection may represent one novel mechanism to upregulate MIF and its receptors from cervical cancer cells. Targeting MIF effectively inhibits cervical cancer cell growth, migration, invasion, colony formation and tumorigenesis *in vitro* and *in vivo* [42-44]. Moreover, one recent study indicates that MIF polymorphisms (-794CATT$_{5\text{-}7}$) can be used as a potential biomarker for early-stage cervical cancer [45].

Conclusion and prospective

Currently, there are limited data about the co-infection of KSHV and HPV in cervical samples and/or cervical cancer cells. However, recent findings from both *in vitro* and *in vivo* studies indicate that KSHV may act as one of co-factors for HPV-related cervical carcinogenesis (especially in those immunocompromised patients),

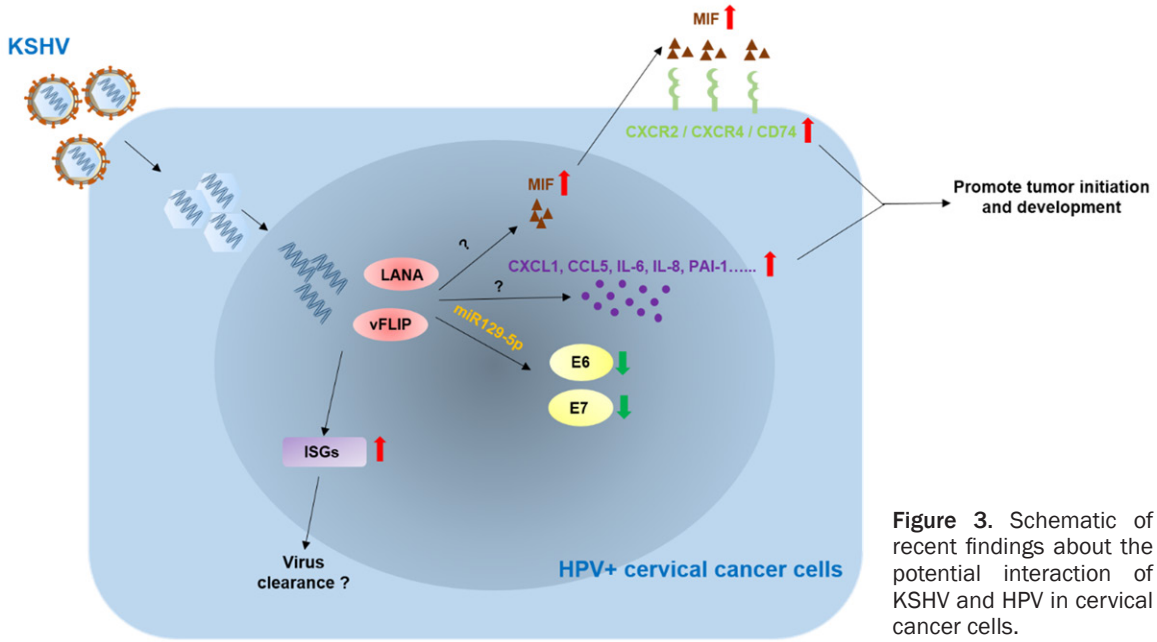

Figure 3. Schematic of recent findings about the potential interaction of KSHV and HPV in cervical cancer cells.

although there are still a lot of remaining questions need to be further investigated:

1) Low detection rate of KSHV shedding as well as of KSHV/HPV co-infection in cervical samples and/or cervical cancer cells. Although cervical cancer cells or other mucosa epithelial cells have been shown fully susceptible to KSHV infection, the detection rate of KSHV (viral DNA) is very low in cervical benign and malignant samples. We think one of reasons is that the upregulated inflammatory cytokines/chemokines as well as Interferon (IFN)-induced genes by KSHV co-infection [22] may promote the recruitment of immune cells, enhance local inflammatory response, and finally facilitate attacking infected cells and/or the clearance of KSHV (especially in the immunocompetent patients). Another possible reason is that there is low number of cervical cells are latently infected by KSHV in most of patients which causing difficultly acquired by cervical biopsy. Finally, the sensitivity and accuracy of current methods for detection of KSHV still need to be improved.

2) Downregulation of E6 and E7 expression by KSHV co-infection of cervical cancer cells. Although these were found from cervical cancer cell lines or xenograft models [22, 23], the underlying mechanisms remain largely unclear. In spite of hijacking these HPV-encoded major oncogenic proteins expression, KSHV co-infection can maintain cervical cancer cells malignant behaviors, such as invasion, colony formation and tumorigenesis in animal models, which are through the manipulation of some certain cellular genes functions such as MIF and its signaling [23]. Therefore, KSHV co-infection may cause some HPV-independent factors contributing to cervical carcinogenesis (summarized in **Figure 3**).

3) Regulation of KSHV infection or viral protein functions by HPVs. On the other hand, we almost do not know whether HPVs including those different subtypes are able to affect KSHV infection of cervical epithelial cells, viral latency/lytic reactivation, virus replication, etc. These may represent an interesting direction for future investigation.

4) KSHV and HPV interaction in other cancers. Besides cervical cancers, these two oncogenic viruses co-infection or interaction may exist in other types of cancer. For example, high-risk HPV infection is also the etiological agent of some oral and oropharyngeal cancers [46-48]. As we know, oral cavity represents the major reservoir of KSHV and exchange of oropharyngeal secretions is an important route for this virus transmission. Interestingly, one recent study indicates that KSHV is similarly detectable across all levels of CD4 counts in HIV+

patients [49]. In addition, oral cavity involvement represents the initial manifestation of KS in 20-60% of HIV-associated cases, with the involvement of the oral cavity ultimately seen in the majority of patients [50-52]. High-risk HPVs are also closely related to anal cancer particularly in HIV+ men having sex with men (MSM) [53, 54], this subpopulation usually having high prevalence of KSHV infection [55, 56]. Therefore, it will be interesting to explore and determine whether KSHV/HPV interaction plays some roles in the development of other cancers in future studies.

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Disclosure of conflict of interest

None.

Abbreviations

HPV, human papillomavirus; HIV, human immunodeficiency virus; KSHV, Kaposi sarcoma-associated herpesvirus; KS, Kaposi's Sarcoma; PEL, Primary effusion lymphoma; MCD, Multicentric Castleman's disease; CBS, cervical brush scrapes; LANA, Latency associated nuclear antigen; vFLIP, viral FLICE inhibitory protein; ORF, Open reading frame; CXCL1, Chemokine (C-X-C motif) ligand 1; IL-6, Interleukin 6; PAI-1, Plasminogen activator inhibitor-1; CCL5, Chemokine (C-C motif) ligand 5; IL-8, Interleukin 8; MIF, Macrophage migration inhibitory factor; CSCC, cervical squamous cell carcinoma; CIN, cervical intraepithelial neoplasia; VEGF, vascular endothelial growth factor; SNP, single-nucleotide polymorphisms; IFN, Interferon; MSM, men having sex with men; TCGA, The Cancer Genome Atlas; SRA, Sequence Read Archive; NCBI, National Center for Biotechnology Information; ISGs, Interferon stimulated genes.

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