Histopathological performance of an HPV18/KSHV co-infection with Kisspeptin expression in cervical precancer and cancer tissues

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Abstract

Background: Cervical cancer (CC) is one of the most 12th recurrent neoplasia among Iraqi women turning it into significant health issue, it had been currently supposed that the co-infection of High-risk human papillomavirus (HPV) and Kaposi sarcoma-associated herpesvirus (KSHV) which both share some transmission routes from one side, and the disruption of Kisspeptin expression in cervical tissues from the other side, which are collectively act as a causative agents and co-factors of cervical cancer progression.

Aim: to compare the infection and or co-infection of HPV18 and KSHV and the dysregulation of Kisspeptin expression between cervical dysplasia (pre-cancerous tissues) and cervical cancer (cancerous tissues) progression.

Results: Overall, results showed a significant association between infection and or co-infection of HPV18 and KSHV with both types of test tissues (pre-cancerous and cancerous), although the detection rate of KSHV DNA was very low in comparing with HPV18 DNA in both cervical tissue samples. Furthermore, a significant interaction of Kisspeptin low expression in cancerous samples compared to pre-cancerous tissues with viruses existence seem to involve significantly in Kisspeptin expression of CC.

Conclusions: Data suggest KSHV co-infection may act as co-factor in the development of HPV related cervical carcinogenesis. Besides, the defect of low Kisspeptin expression serves as a great candidate for cervical carcinoma progression or maybe as a therapeutic target for CC.

Keywords: cervical cancer, cervical dysplasia, HPV18, KSHV, Kisspeptin.

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Introduction

Cervical cancer is considered to be one of the world's most commonly known diseases in women. It pathogenesis occurs after continuous high risk human papillomavirus (HPV) specifically infections of sub-type 16 and 18[1].
Protein E6 and E7 consider high risk, cervical carcinogenic oncoproteins encoded with HPV [2]. E6 and E7 proteins may instinctively bind separately to p53 and the retinoblastoma (Rb) and result in the dysregulation of the cell cycle [3]. Many individuals who have been infected with HPV alone may be unable to develop cervical cancer [2,3]. However, these are less significant, so that there are other risk factors, such as smoking, alcohol, oral contraception pills, starting sex at a young age and having several sexual partners[1][3]. Cervical malignancy is steadily growing as result of precancerous changes over 10 to 20 years and about 90% of cervical disease cases are squamous cell carcinomas, 10% are adenocarcinoma [4].

Moreover, cervical intraepithelial neoplasia (CIN), otherwise called cervical dysplasia, is the abnormal development of cells on the outside of the cervix that could possibly prompt cervical cancer.[5] More explicitly, CIN refers to the conceivable precancerous change of cervix cells. Human papilloma infection is an important factor for the CIN development, however not all produce cervical malignancy.[3] However, those with an HPV infection that keeps for a long two years have a great opportunity for CIN development [5,6].

Clearly, KSHV is related with some of human illnesses, including Kaposi’s sarcoma (KS) and primary effect lymphoma (PEL) in those immune-compromised patients[7]. In addition, the prostate, semen, oral cavity, or female genital tract were identified with KSHV DNA, and beside the elevated level of KSHV shedding in the oral cavity, KSHV DNA in cervical sample is moderately small [8].

Kisspeptin (known as metastin) is a protein coded by the KISS1 which was originally characterized as a human metastasis[9]. In a model system, a study was conducted to test the chromosome six genes of the malignant tumor cells. Then KISS1 became apparent as the only non-metastatic gene that was absent from metastatic. It suggests that Kisspeptin is a crucial factor for regulating whether or not a cell has metastatic effects and has shown a low expression of KISS1 and Kisspeptin in main, metastatic tumors and tumor growth in clinical studies [10].

In conclusion, Kisspeptin plays a significant role in tumour suppression. by it is activation in tumour cells, make the last not spread or extendedly grow.

So, our current study presented to explore the role of KSHV as a co-factor with HPV18 in the cervical carcinogenesis and its impact on pre-cancerous changes, beside dysregulation of Kisspeptin expression in pre-cancer and cancer tissues.

Materials and Methods

Tissue sample collection and preparation

A retrospective (86) cases of archival paraffin-embedded tissue blocks (those with better slide fixation & better blocks processing) during the period of 2010 to 2018, which were selected from the Medical City / Teaching Laboratories/department of Histopathology, in addition to, one of the private laboratories in Baghdad, other demographic data were recorded from the case sheets. All eighty-six tissue blocks re-examined as a second confirmative diagnosis by specialized histopathologist using standard histological criteria, and classified into:-

First Group (Cancerous tissues): Cervical cancer 61 (70.9%); which were sub-divided into 48 (55.8%) of squamous cell cervical carcinoma (SCC) and 13 (15.1%) of adenocarcinoma (AD).

Second Group (Pre-cancerous tissues): Cervical intraepithelial neoplasia (CIN) or called (cervical dysplasia) as 25 (29.1%).

Hematoxylin and eosin stain procedure was applied on 4 μm thick sections on ordinary slides from each tissue block and subjected to confirm the tumour diagnosis. Another 4 μm thick sections were made on positively charged slides for each In Situ Hybridization technique (ISH) to detect the (HBV18 \ KSHV) DNA signals and
Immunohistochemistry technique (IHC) to evaluate the Kisspeptin protein expression. The current study was approved by the Center Ethical Committee.

**Laboratory procedures**

**In situ hybridization assay**

The detection of HPV18 and KSHV DNA signals were made by ISH detection kit (ZytoVision GmbH, Fischkai, Bremerhaven, Germany; ZytoFast Cat. Numbers: T-1070-40), using two ZytoFast probes (PF30, PF33) in hybridization buffer. The probes contain Biotinylated -labelled oligo-nucleotides which target the DNA of Human papillomavirus (HPV18: product number; T-1114-400: 0.4 ml) and Kaposi sarcoma-associated herpesvirus (KSHV: product number; T-1154-465: 0.4 ml).

Tissue slides were put to de-paraffinized in 60°C — hot air oven for the night, then in xylene for 15 minutes, then treatment with graded alcohols, washing slides in distilled water for 5 minutes to remove remaining alcohol. Slides were then permitted to dry and incubate for 5 minutes at room temperature.

Pepsin solution (ES1) for hybridization, was added to the tissue digestion, slides were washed to remove the solution of pepsin after incubation in the humidity chamber. In addition, to each slide, 10 μl of HPV18 and KSHV DNA probes have been added and coated by covers.

After hybridization, at a room temperature wash the slides in the washing buffer until the cover covers were dropped down for about 3 minutes. Then a conjugating agent was added to tissue section of streptavidin-alkaline phosphatase. Then hold for 20 minutes in a humid chamber. Slides were then rinsed for 5 minutes and then dried in the detergent wash-buffer. Adding 5-bromo3-chloro3-indole / phosphate/ nitroblue tetrazolium to the substratum-chromogenic solution (BCIP / MBT) was then added to the tissue section.

Slides have been rinsed for 5 minutes in distilled water, then immersed 30 seconds (counterstain) with Nuclear Fast Red and washed the slides in distilled water for 1 minute. The slides were made using graduated ethyl alcohol after dehydration. Finally, Xylene cleared the slides, and the permanent mounting medium (DPX) was installed. Wait 30 minutes or until under the light microscope the dark blue color has developed.

**Immunohistochemistry assay**

Evaluation of KISS1 protein signals (Kisspeptin) was made by IHC detection kit (Cat. Number: Ab80436, Abcam, England) using polyclonal Rabbit Anti-Kisspeptin antibody which can recognize the targets of Kisspeptin-10 region of Kisspeptin or KISS1 antigen (Cat. Number: ab172022, Abcam, England).

At 60°C overnight slides have been deparaffinized in an oven. After that the rehydration procedure was performed with serial concentrations of xylene and ethanol, the tissue sections were washed and allowed to dry. After 20 minutes washed by distilled water 1x PBS after every incubation period with different times, the slides had been rinsed with Sodium Citrate buffer at 95°C until normal Serum / PBS drops off the tissue sections for 30 minutes at room temperature.

The slide was incubated in a humid chamber for 60 minutes, then added to the complement at room temperature and incubated for 2 hours, with PBS-diluted primary antibodies. Applied and incubated 1.5-hour HRP conjugation, then combined to 1-10-minutes incubation with 30μl DAB chromogen and 1.5ml DAB tissue-related substrate. Lastly, the lines are stained (use Harris, Hematoxylin, and Eosin to stain the cytosol).

The method of dehydration was performed with 3 minutes of soaking for each solution for the graded alcohol set, then the slides were twice, for 10 minutes, incubated into xylene. Sections of tissue with mounting medium (DPX) were installed. In the tissue zone under a light-microscope, the positive signals should be like brown colored precipitate at the antigen site.
Controls of the study

**Positive control probe:** was included for each run of In Situ Hybridization Assay. Which is prepared and processed in an identical manner to the test section but was hybridized with housekeeping gene probe and denatured at 75°C for 5 minutes.

**Positive control tissue:** for HPV18 was prepared from a cervical carcinoma and for KSHV was prepared from Kaposi's sarcoma – an angioproliferative skin tumour. While positive Kisspeptin expression was prepared from the positive mRNA KISS1 gene expression in breast cancers.

**Negative control:** was included for each run of in situ hybridization, all reagents were added except the diluted probe. While for IHC was prepared by adding PBS instead of the diluted antibody.

Evaluation of ISH and IHC Signals

Proper use of the hybridization/detection system and secondary polyclonal Rabbit Anti-Kisspeptin IgG to detect primary antibody-antigen complexes, will produce an intensely blue signal at the specific location of the hybridizing probe and brown precipitate positive cells on tissue sections respectively. Signal quantification with 100 X, 400 X and oil immersion 1000 X was assessed under the light microscopy. Positive cell counting was conducted at 1000 X.

Intensity and percentage scores were provided to the signals. The comparative intensity scale of 0-3 has been used for 0 without the detecting ISH or IHC signals and the response intensity of 1, 2, 3, equal respectively to low, moderate and high response intensity. For each sample, ten distinct areas have been counted with 100 cells, and the 10 fields have determined the average favorable cells to assign case for one of the following three classifications of the sample (Zlobec et al, 2006).

- Score (1) = 1-25%.
- Score (2) = 26-50%.
- Score (3) > 50%.

In addition, the ISH viral signals were divided into punctate, diffuse, or mixed. A dot-liking model represents scattered nucleus signals or that are regarded to indicate an integrated viral genome. A diffuse pattern, however, which was an episomal virus, consistently dark, thick blue stained in the nucleus or cytoplasm. The integrated and episomal viral genomes in the same sample have been finally evaluated by mixed models (Jung et al. 2010).

Statistical analysis

Significance for differences between cervical dysplasia and cervical cancer was determined using The SPSS 25.0 software, chi-square test, was employed to analyze the expression rate in all groups. Significance was defined as P<0.05.

Results
In total of eighty-six formalin-fixed, paraffin embedded cervical tissue blocks in table (1): which were with three age categories (ranged: 28 to 65 years), which were included 25 (29.1%) as pre-cancerous cervical tissues of cervical intraepithelial neoplasia (CIN) or called (cervical dysplasia) and other sixty-one cancerous blocks (70.9%) of malignant cervical tissues as 48 (55.8%) of squamous cell cervical carcinoma (SCC) and 13 (15.1%) of adenocarcinoma (AD); most of the patients 32 (37.2%) were in the (41-53) age interval. The HPV-18 DNA signals were detected in 33 (52%), while KSHV DNA signals were detected in 24 (27.9%). Furthermore, 19 (22.1%) of them showed positive signals for KISS1 protein expression.
Table (2): Scoring results of studied biomarkers

<table>
<thead>
<tr>
<th>Biomarkers Signals</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV18-ISH (DNA)</td>
<td>33</td>
<td>38.4%</td>
</tr>
<tr>
<td>Scoring Number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score-1</td>
<td>7</td>
<td>8.1%</td>
</tr>
<tr>
<td>Score-2</td>
<td>15</td>
<td>17.4%</td>
</tr>
<tr>
<td>Score-3</td>
<td>11</td>
<td>12.8%</td>
</tr>
<tr>
<td>Intensity of replication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>16</td>
<td>18.6%</td>
</tr>
<tr>
<td>Moderate</td>
<td>12</td>
<td>14.0%</td>
</tr>
<tr>
<td>Low</td>
<td>5</td>
<td>5.8%</td>
</tr>
<tr>
<td>Patterns of replication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffused</td>
<td>16</td>
<td>18.6%</td>
</tr>
<tr>
<td>Mixed</td>
<td>9</td>
<td>10.5%</td>
</tr>
<tr>
<td>Punctate</td>
<td>8</td>
<td>9.3%</td>
</tr>
<tr>
<td>KSHV-ISH (DNA)</td>
<td>24</td>
<td>27.9%</td>
</tr>
<tr>
<td>Scoring Number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score-1</td>
<td>9</td>
<td>10.5%</td>
</tr>
<tr>
<td>Score-2</td>
<td>12</td>
<td>14.0%</td>
</tr>
<tr>
<td>Score-3</td>
<td>3</td>
<td>3.5%</td>
</tr>
<tr>
<td>Intensity of replication</td>
<td></td>
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<tr>
<td>HIGH</td>
<td>3</td>
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<tr>
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<td>13</td>
<td>15.1%</td>
</tr>
<tr>
<td>Patterns of replication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffused</td>
<td>20</td>
<td>23.3%</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>3.5%</td>
</tr>
<tr>
<td>Punctate</td>
<td>1</td>
<td>1.2%</td>
</tr>
<tr>
<td>KISS1-IHC</td>
<td>19</td>
<td>22.1%</td>
</tr>
<tr>
<td>Scoring Number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score-1</td>
<td>8</td>
<td>9.3%</td>
</tr>
<tr>
<td>Score-2</td>
<td>5</td>
<td>5.8%</td>
</tr>
<tr>
<td>Score-3</td>
<td>6</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

Table (2) showed fifteen (17.4%) cases from HPV-18 DNA signals revealed score 2, while 16 (18.6%) cases revealed for both high intensity and diffused patterns of virus replication. KSHV-DNA signals were prominent in score 2 as 12 (14.0%), with a low intensity of replication 13 (15.1%), and most of the DNA singles were in a diffused patterns of replication 20 (23.3%). On the application of KISS1-IHC protein expression signals, the intensity was predominantly low whereby it was shown in 9 (10.5%) cases. Eight (9.3%) cases revealed score 1.

Table (3): Association of viruses scoring signals with study groups

<table>
<thead>
<tr>
<th>Biomarkers Signals</th>
<th>Study Groups N (%)</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-cancerous tissues</td>
<td>Cancerous Tissues</td>
</tr>
<tr>
<td><strong>HPV18-ISH (DNA)</strong></td>
<td>33 (38.4%)</td>
<td></td>
</tr>
<tr>
<td>Scoring Number</td>
<td>Score-1 2 (2.3%)</td>
<td>5 (5.8%)</td>
</tr>
<tr>
<td></td>
<td>Score-2 1 (1.2%)</td>
<td>14 (16.3%)</td>
</tr>
<tr>
<td></td>
<td>Score-3 0 (0.0%)</td>
<td>11 (12.8%)</td>
</tr>
<tr>
<td>Intensity of replication</td>
<td>High 0 (0.0%)</td>
<td>16 (18.6%)</td>
</tr>
<tr>
<td></td>
<td>Moderate 1 (1.2%)</td>
<td>11 (12.8%)</td>
</tr>
<tr>
<td></td>
<td>Low 2 (2.3%)</td>
<td>3 (3.5%)</td>
</tr>
<tr>
<td>Patterns of replication</td>
<td>Diffused 3 (3.5%)</td>
<td>13 (15.1%)</td>
</tr>
<tr>
<td></td>
<td>Mixed 0 (0.0%)</td>
<td>9 (10.5%)</td>
</tr>
<tr>
<td></td>
<td>Punctate 0 (0.0%)</td>
<td>8 (9.3%)</td>
</tr>
</tbody>
</table>
HPV-18 DNA signal intensity was predominantly high in the cancerous tissue group whereby it was shown in 16 (18.6%) cases with score 2 as 14 (16.3%) and diffused patterns of replication as 13 (15.1%). Two cases (2.3%) revealed low intensity in pre-cancerous tissue group with score 1 as 2 (2.3%) and all three cases (3.5%) in the same group showed diffused patterns of replication with significant differences (p<0.05).

Regarding KSHV-DNA signals in cervical cancer, biopsies revealed low intensity in 10 (11.6%) cases with prominent score 2 as 12 (14.0%) and diffused pattern of replication as 17 (19.8%). While all the three of cervical dysplasia biopsies as (2.3%) were revealed score 1 with low intensity and diffused pattern of replication with significant differences with a scoring number only (p<0.05) as figured out in the table (3).

The total HPV18 and KSHV DNA signals in table (4) were significantly detected with high percentage which made 30 (34.9%) and 21 (24.4%) in cervical cancer and in cervical dysplasia biopsies respectively (p<0.05), while a low KISS1 protein expression signals were detected in 4 (4.7%) and there was no KISS1 protein expression in 57 (66.3%) in cervical cancer biopsies. On the other hand, pre-cancerous tissue biopsies showed KISS1 protein expression which made 15 (17.4%) with high significant differences between groups (p<0.001).

The presence of both HPV-18 and KSHV DNA signals as co-infections in cervical carcinoma cases were detected significantly in 14 (16.3%) biopsies, while there was only one co-infection case in cervical dysplasia patients (1.2%). Furthermore, there was no significant association of co-infection in 7 (8.1%) at (41 – 53) of
patients age interval, a significant association was found in HPV18-KSHV co-infections with the KISS1 expression signals (P<0.05%) as presented in table (5).

Figure (1): ISH, HPV18, SCC, score 3, high intensity, diffused

Figure (2): ISH, KSHV, SCC, score 2, high intensity, diffused

Figure (3): ISH, HPV18, CIN, score 1, low intensity, diffused

Figure (4): IHC, KISS1, CIN, score 2, low intensity,
Discussion

The distinguishability of the resent research was the first Iraqi study in the evaluation of HPV18 \ KSHV co-infection of both cervical precancer and cancer status withdetermination of the Kisspeptininteraction roles. However, this study has boundaries and is crucial to understand the biological effects of these co-factors with more biomarkers in a bigger sample size with various genetic markers and laboratory techniques.

There is currently limited data in cervical and cervical cancer cell co-infection KSHV and HPV. Nevertheless, in-vitro and in-vivo trials show that KSHV can behave as one of the co-factors of cervical carcinogenesis (particularly in immunocompromised patients), while a great deal of further research remains to be done.

KSHV also establish latent life-long infection in host cells with a limited number of viral genes, as can other herpes viruses. The detection frequency of KSHV DNA or virus infection in cervical specimens in some research is comparatively small or even negative in comparison with the elevated incidence of KSHV shedding of the oral cavity[11]. A study recorded the detection of KSHV DNA in 3 of the 11 scraps of the cervical brush (CBS) from females in the genitourinary department of the KSHV-Seropositive [12]. Controversy, KSHV DNA, was not identified by KSHV-seronegative females in any of the 78 CBS or by 96 CBS by females of an unidentified KSHV-serostatus in colposcopy. Another KSHV epidemiology studies have shown that KSHV DNA has been identified in 2% of cervical prostate specimens and 1% of women's cervical specimens in the general population[12] for both sex employees and women of the general population. In addition, KSHV was found to be more common among women with HPV-positive DNA (Odds ratio= 2.5). Similarly, one study in Mombasa, Kenya, in 174 seropositive female prostitutes, shows a prevalence of 4% (KSHV) in cervical swab detection and of 2, 3% (KSHV) in the vaginal swab, although the HPV infection status of these individuals remains unknown [13].

In comparison, the latest research showed that 18/31 (58 percent) of female genital brush studies have identified HPV DNA, whereas none of those female brushstrokes is positively KSHV DNA[14]. Another study found that there was no detectable KSHV DNA in the cervical secretion of 112 females, although 2.7% and 24% respectively of serum samples from the same group were found to contain latent and lytic KSHV antibodies [15].It's now almost unclear whether HPV oncogenic gene expression in cervical cancer cells is regulated by KSHV infection or by KSHV-encoded proteins. [12-16].The major viral oncoproteins closely related to cervical human carcinogenesis are high-risk HPV, as encoded E6 and E7 proteins, for example, under the subtypes 16 and 18[1,2]. Proteins E6 and E7 can bind to the family proteins P53 and Rb resulting in the control and conversion of the cell cycle[3], respectively.E6 and E7 proteins have been recently shown to be interacting, regulating or contributing to the oncogenesis, and many more cellular elements, including proteins that control cell epigenetic traces and splicing modifications [1,3].

Consequently, these findings show that latent KSHV and lytic proteins can be regulated separately to the expression of HPV oncogenic proteins in cervical cell cancer. Since KSHV is a big dsDNA virus with ~165 kb genome which containing 81 viral ORFs, as well as somemicro-RNAs, non-coding RNAs, and a few small ORFs[17], it still requires a lot of work to understand how these viral components differentially regulate HPV oncogenic proteins expression in cervical cancer cells.

Furthermore, KSHV Co-infection of cervical cancer cells Downregulation of E6 and E7 expression. Although they were identified from cervical cancer cell lines or models of xenograft[12,16], they still stay mainly ambiguous. In spite of hijacking these HPV-encoded major oncogenic proteins expression, KSHV co-infection can maintain cervical cancer cells malignant behaviours, 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 [16]. Therefore, KSHV co-infection may lead to HPV-independent carcinogenesis variables.

Data mining was conducted in the current paper to recognize Kisspeptinin cervical expressions. In cervical tissues, KISS1 has been shown to be absent in ordinary cervix. The selected KISS1 gene, which is located on chromosome
region 1q32.1, has been studied in several types of cancer and has been suggested to play several roles in cancer[18]. For example, the absence of ofKISS1 gene expression has been associated with increased metastasis and cancer progression in bladder [19], ovarian [20] and pancreatic cancer [21]. In contrast, increased KISS1 expression is related to metastatic capacity in breast [22] and hepatocellular carcinomas [23]. This suggests that KISS1 gene could be a dual-faced gene in cancer and its tissue-specific function. Also, the KISS1 gene is highly expressed in the placenta, nervous system, testis, ovary, pancreas and intestine. Again, of 1q32 was observed in 20% of CC sample as its reported [23], therefore, no relation between 1q32.1 and KISS1, and this could be controlled by the epigenetic mechanism. It could be suggested. There are some reports of KISS1 regulation through a methylation mechanism[24,25], although further experimentation is required to corroborate this mechanism in Cervical cancer cell lines were used as a model for our first approach, observing KISS1 expression in the cell lines with or without HPV sequences and suggesting that KISS1 expression could be an event independent from HPV infection or genotype.

KISS1 expression of the KISS1 gene was observed in the CC sample 10 times higher than that of normal tissue in the neck. Especially in one of the discarded samples from the uterine myomatosis patient, low expression KISS1 suggested hormonal distortion by the estrogen-receptor (ER) as described[26]. In order to support this preliminary result, we also consider the increase in normal samples.

Finally, this study revealed an innovative approach in KISS1 expression to the search for cancer markers (embryonic antigens). The expression of KISS1 in CC suggests that this gene may be a great candidate for molecular marker and/or therapeutic target for CC. In addition, extra trials are necessary to elucidate the CC function of KISS. And Low detection in cervical specimens of KSHV shedding and KSHV / HPV co-infection also need further exploration.

Despite, many reports explored the association of herpesviruses infection with heart diseases, blood pressure, allergic diseases, autoimmune diseases or even cancers had been carried out[27-31]. Finally, it is necessary to further improve the sensitivity and precision of the present techniques to detect KSHV. Therefore, it is important to examine and determine if KSHV / HPV interactions play a part in future studies in the development of other cancers.

Conclusions

Our recent data highlights the involvement of very low detection rate of KSHV shedding along with of KSHV/HPV co-infection and down-regulation of Kisspeptin protein in cervical dysplasia and/or cervical cancer carcinogenesis, but, it remains unclear in the development of HPV-related neoplasia’s, Further work is required to extend these findings.

Financial support and sponsorship

Nil.

Conflicts of interest

There is no conflict of interest.

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