Int J Clin Exp Pathol 2020;13(9):2326-2332
www.ijcep.com /ISSN:1936-2625/IJCEP0116195

Original Article

Expression of PI3K and ERK in Uygur and Han patients with cervical squamous cancer

Jia Li[1*], Xiaoling Rong[2*], Yuwu Liu[3], Jing Du[1]

[1]Department of Laboratory, Xinrui Hospital, Xinwu District, Wuxi City (Wuxi Branch of Ruijin Hospital, Shanghai Jiaotong University School of Medicine), China; [2]Clinical Laboratory, Second Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, China; [3]Department of Pathology, Section Basic Medical College of Xinjiang Medical University, Urumqi, Xinjiang, China. [*]Equal contributors.

Received June 12, 2020; Accepted July 20, 2020; Epub September 1, 2020; Published September 15, 2020

Abstract: Cervical squamous cancer is a common malignancy of the female reproductive system, and the age of onset is getting younger. PI3K and ERK, are key components in maintaining the development of malignant tumor, but have not been studied in cervical squamous cancer. Objective: To explore the differences in disease susceptibility to human papilloma virus-16 (HPV-16), phosphoinositide 3 kinase (PI3K) and extracellular signal regulating kinase (ERK) protein expression in cervical squamous cancer tissues between Uyghur and Han women. The expression of PI3K and ERK and presence of HPV-16 infection were detected by polymerase chain reaction (PCR) and S-P immunohistochemical assay in cervical squamous carcinoma tissue. To detect PI3K and ERK expression in cervical squamous carcinoma tissue and HPV-16 infection condition, polymerase chain reaction (PCR) and S-P immunohistochemical assay were used. HPV-16 infection rate in cervical squamous cancer tissue of Uighur women (40.43%) was significantly higher than Han women (8.33%) ($P < 0.05$). The positive expression of PI3K in cervical squamous carcinoma tissues was 92.41% (Uyghur nationality: 93.09%; Han nationality: 88.89%), and no statistical difference was observed between Uyghur and Han women ($P > 0.05$). The positive expression rate of ERK was 68.3%, while the expression in Uyghur (65.43%) was lower than that in Han (83.33%) ($P < 0.01$). Combining multiple factors, including age, nationality, and HPV-16, the risk ratio of ERK protein high positive expression rate in Han women was 2.466 times that of Uighur women ($P < 0.05$). A correlation between PI3K and ERK in cervical squamous cancer tissue in Uighur women was found. ($r = 0.340$, $P < 0.001$). As compared to Han women, Uyghur women exhibited higher susceptibility to HPV-16. Also, PI3K and ERK protein expression are closely related to cervical cancer occurrence. The expression of ERK in cervical squamous carcinoma tissues differed between the two groups.

Keywords: Cervical cancer, HPV-16, PI3K, ERK

Introduction

Cervical cancer is one of the common malignant tumors of the female reproductive system. The incidence of cervical cancer has seen a tremendous increase in recent years, increasing exponentially every year [1]. A significant increase in the prevalence of cervical cancer has been observed among young adults. China is a multi-ethnic country. It has a different incidence and mortality rate of cervical cancer among ethnic groups in various regions. The incidence of cervical cancer in Xinjiang is also higher than the national average. Uyghur and Han women may show differences in the incidence of cervical cancer because of their ethnic origin, genetic background, social culture and lifestyle differences in Xinjiang. In Xinjiang region, Uygur women exhibit the highest morbidity of cervical cancer, ranking first among Chinese minorities, with 3-4 times higher fatality rate [2, 3]. Molecular biology and epidemiological studies have confirmed that human papilloma virus (HPV) infection is a major cause of cervical cancer, especially HPV-16 type [4]. HPV-16 virus infection plays an important role in the occurrence of cervical cancer and invading intracellular biological signal transduction. Phosphoinositide 3 kinase/serine/threonine protein kinase B and mitogen activated protein kinase/extracellular signal regulated kinase signaling pathway is involved in the occurrence

of tumor by regulating the balance between apoptosis and antiapoptotic mechanisms. PI3K gene mutations and AKT high phosphorylation level are some of the primary characteristics of tumor development. ERK can not only phosphorylate plasmosin, but can also phosphorylate nuclear factor-kappa B, so as to regulate cell proliferation and differentiation. However, whether there is a difference in the expression of PI3K and ERK protein in cervical squamous cancer tissue between women of different groups requires further investigations.

Materials and methods

Collection of specimens

Colposcope cervical biopsy tissue was obtained from patients with evident cervix lesion in Hetian People's Hospital for pathology examination. According to the cervical tumor histologic classification of WHO (2003), the patients were diagnosed with cervical squamous cancer. 250 cases of histopathologic grade G2 (moderate differentiation) specimens in paraffin embedding (36 cases of Han, 188 cases of Uighur, 12 cases of Kazak, 8 cases of Mongolian, and 6 cases of Tatar) were collected. Two hundred and twenty-four cases of Uighur and Hans were selected for the study. The age of Uighur (46.29±10.82) and Han patients (45.5±10.82) had no statistically significance difference ($t = 0.4$, $P > 0.05$).

Reagents

Regent proteinase K, PCR kit, DEPC treated water, agarose, 100 bp DNA ladder Marker used in PCR were purchased from Dalian Takara Bio; 5×TBE, 1×TE, phenol:chloroform: isoamyl alcohol (pH 8.0) (25:24:1) UNIQ-10 Spin Columns were purchased from Shanghai Sangon Biotech. Rabbit anti-human polyclonal antibody PI3Kp85 was bought from Beijing Zhongshan Golden Bridge company (1:150); ERK1 (1:50) was purchased from American SANTA company; HPV-16 (1:50) was purchased from American Ptglab company. Second antibody, diaminobenzidine (DAB) HRP-OPD, was purchased from Beijing Zhongshan Golden Bridge.

Detection of HPV-16 in cervical cancer tissue

DNA was extracted from the tissue fixed in formaldehyde and embedded by paraffin. HPV-16 upstream primer sequence used was: 5'-GGTCGGTGGACCGGTCGATG-3', and downstream primer sequence: 5'-GCAATGTAGGTGTATCTCCA-3'. HPV-16 type genome PCR amplification fragment size was 96 bp and PCR amplification conditions were: 95°C degeneration for 3 min, one round of cycling, 95°C degeneration for 15 s, annealing for 20 s at 60°C, extending for 25 s at 72°C, and cycling for 40 rounds, cycling 7 min at 72°C, storage at 4°C. Total PCR reaction volume was 50 1 μL (TaKaRa Ex Taq (5 U/μL) 0.3 μL, 10×Ex Taq Buffer (Mg^{2+}Plus) 5 μL, dNTP Mixture (2.5 mmol/L/each) 4 μL, template DNA 5 μL, primer 1, 2 (20 pmol/mL) 2 μL, DEPC settlement water was added to 50 μL).

Detection of PI3K and ERK expression

The rabbit anti-phosphatidylinositol 3-kinase (PI3K, ZSGB, ZA -0528, China) and extracellular regulated protein kinases (ERK, SANTA CRUZ., sc-271291, Europe) antibodies used in the study were purchased. Routine paraffin sections were dewaxed and hydrated. Then the slide was pre-treated by microwave retrieval method in 0.01 mmol/L citric acid antigen repair solution. It was placed in 0.3% H_2O_2 for incubation for 10 min to determine blocking endogenous peroxidase activity. Reagent A (containing 10% goat serum) was dropped on biopsy (to cover the inspection site on the section). After incubating for 10 min at room temperature, first antibody was added and incubated at 4°C overnight. Following washing by phosphate buffer solution (PBS) 5 min for 3 times, reagent B was added and whole section was incubated for 10 min at room temperature and washed by PBS for 5 min for 3 times. Reagent C was added for incubation at room temperature for 10 min and the whole section was washed by PBS for 5 min for 3 times. Fresh DAB developing liquid was added at room temperature (the developing time under microscopic should be controlled to 3~10 min) and the section was dyed with hematoxylin, dehydrated, and xylene sealed.

DNA electrophoresis of HPV-16 by PCR amplification

PCR amplification products were electrophoresed in 2% agarose gel (100 V, 10 min; 60 V, 1 h) and an image was generated using Gel DocEQ BIO-RAD.

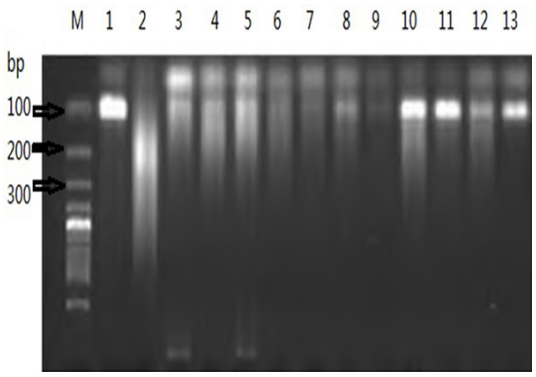

Figure 1. PCR amplification of HPV 16 from the DNA samples extracted from the cervical cancer lesions. Lanes from left to right: M: molecular marker, 1: positive control sample (96 bp), 2: negative control sample (96 bp), 3-13: examined tissue samples (96 bp), and of them 8, and 10-13 were positive for HPV 16.

Table 1. Comparison of HPV-16 infection rate in cervical squamous carcinoma tissues in Han and Uighur groups

Specimens of cervical cancer	n	HPV-16	
		-	+
Han group	36	33 (91.67%)	3 (8.33%)
Uighur group	188	112 (59.57%)	76 (40.43%)*
Total	224	145 (64.73%)	79 (35.27%)

*Comparison of HPV-16 infection rates in the specimens of cervical cancer between Han and Uighur groups = 13.631, $P < 0.05$.

S-P immunohistochemical staining

Cervical epithelial cells' cytoplasm or nucleus is stained brown-yellow, which demonstrates positive standard. The brown-yellow particles following the staining were considered positive cells. At high magnification all-in-view observation, the stained section was divided into 5 grades according to the occupied area of positive cells in the tissue: < 5% is negative (-), 5%~25% is weak positive (+), 26%~50% is positive (++), 51%~75% is moderate degree of positive (+++), and > 75% is strong positive (++++). In negative control, PBS was used instead of the first antibody on cervical tissue.

Statistical analysis

SPSS 16.0 statistical software was used for statistical processing. Hierarchical data using two-sample group design relative rank and inspection, count data with χ^2 inspection rate comparison and correlation analysis, and correlation with rank correlation Spearman rank correlation coefficient and logistic regression analysis were used. $P < 0.05$ was considered significant.

Results

HPV-16 infection positive rate in cervical squamous cancer tissue of Uighur and Han women

HPV-16 infection rate in cervical squamous cancer tissue of Uighur women was higher (40.43%) than in Han women (8.33%). The difference between the two groups was significant ($P < 0.05$) (**Figure 1**; **Table 1**).

PI3K and ERK expression in cervical squamous cancer in Uighur and Han groups

PI3K and ERK positive cells were mostly present as yellow brown or dark brown color in the cytoplasm, with occasional staining in the nucleus (**Figure 2**). The positive expression rate of PI3K in cervical squamous cancer was 92.41% (Han: 88.89%; Uighur: 93.09%); positive expression rate of ERK in cervical squamous cancer was 68.30% (Han: 83.33%; Uighur: 65.43%); ERK in cervical squamous cancer tissue of Uighurs (65.43%) was lower than that in Hans (83.33%), and the difference was statistically significant ($P < 0.01$) (**Tables 2**, **3**). PI3K and ERK expression in cervical squamous cancer tissue of Uighur women showed a correlation ($r = 0.340$, $P < 0.001$), while PI3K and ERK expression in cervical squamous cancer tissue in Han women did not correlate ($r = 0.084$, $P > 0.05$) (**Tables 4**, **5**).

Relevance of PI3K and ERK protein expression and HPV-16, age, and nationality in Uighur and Han groups

Combining multiple factors, including age, nationality, and HPV-16 infection, the risk ratio of ERK protein high positive expression rate in Han women was 2.466 times higher than in Uighur women ($P < 0.05$) (**Tables 6**, **7**).

Discussion

HPV infection is a major pathogenic factor in cervical cancer, especially HPV-16 (accounting for 40.60% of HPV infection), belonging to the high-risk type HPV. Haimiti et al [5, 6] reported

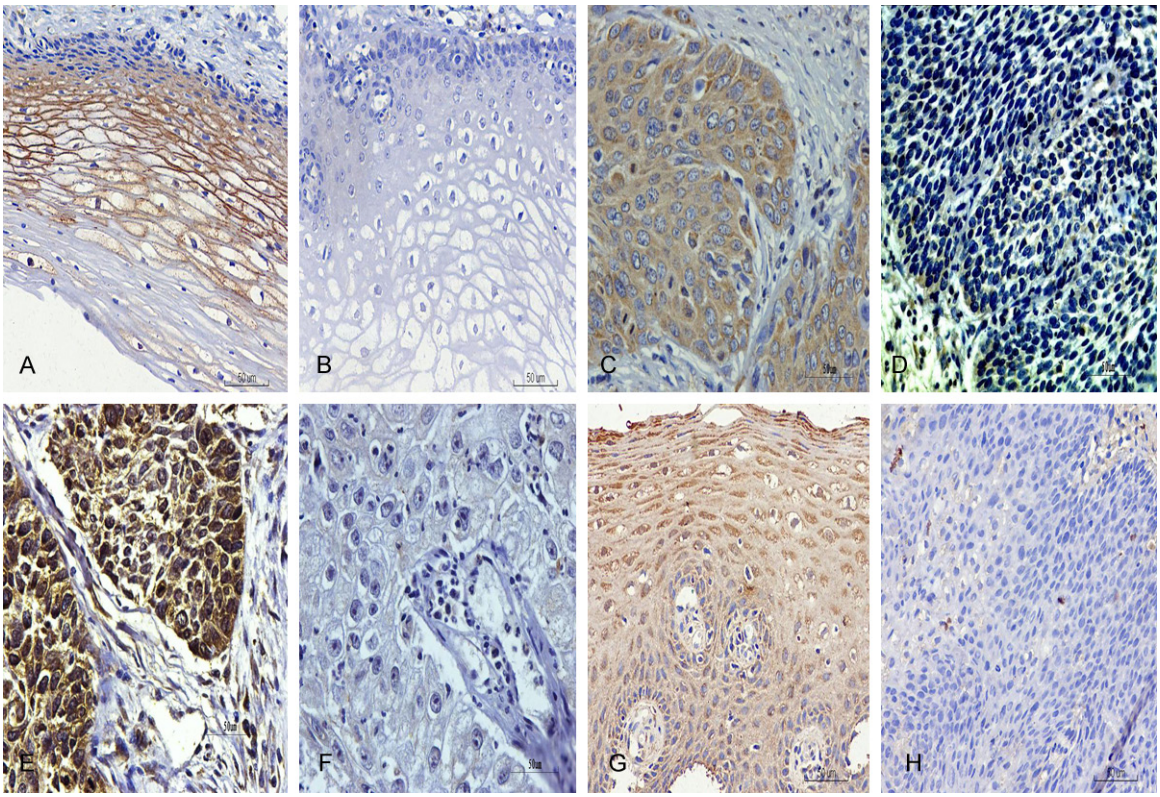

Figure 2. Representative photomicrographs of tissue sections immunostained for Uighur and Han groups. A, B. Positive and negative results of ERK expression in cervical cancer tissues of Uighur group, respectively (×400). C, D. Positive and negative results of ERK expression in cervical cancer tissues of Han group, respectively (×400). E, F. Positive and negative results of PI3K expression in cervical cancer tissues of Uighur group, respectively (×400). G, H. Positive and negative results of PI3K expression in cervical cancer tissues of Han group, respectively (×400). The cytoplasm was brown in epithelial tissue, with no staining in the mesenchyme.

Table 2. Comparison of PI3K expression in cervical squamous carcinoma tissues in Han and Uighur groups

Cervical squamous carcinoma tissues	n	PI3K				
		-	+	++	+++	++++
Han group	36	4 (11.11%)	5 (13.89%)	5 (13.89%)	6 (16.67%)	16 (44.44%)
Uighur group	188	13 (6.91%)	19 (10.11%)	45 (23.94%)	44 (23.40%)	67 (35.64%)
Total	224	17 (7.59%)	24 (10.71%)	50 (22.32%)	50 (22.32%)	83 (37.05%)

Uighur group versus Han group; $Zc = 0.269$, $P > 0.05$.

that the HPV-16 gene is associated with high incidence of cervical cancer in Xinjiang, China. Rong et al [7] reported that HPV-16 is highly expressed in cervical squamous carcinoma tissue. Hao et al [8] reported that Xinjiang's Uygur women exhibit high expression of HPV-16 gene in cervical cancer as compared to Han women. Our results demonstrated that the rate of HPV-16 infection in Xinjiang Uygur women with cervical cancer (40.43%) was higher compared to that in Han women (8.33%) ($P < 0.05$), suggesting that Uighur women are more susceptible to HPV-16 virus. There are many subtypes of HPV. The detection rate of HPV-16 in Uighur women was 40.43% in this study. This may have been because some women were infected with other HPV subtypes, but we detected only HPV-16. HPV-16 was detected in 8.33% of Han women in the study. It is reported that HPV-16 was found in at least 50% of all cervical cancers in the world. It is not clear what were the Han women's pre-sick living conditions. Because

Table 3. Comparison of ERK expression in cervical squamous carcinoma tissues in Han and Uighur groups

Cervical squamous carcinoma tissue	n	ERK				
		-	+	++	+++	++++
Han group	36	6 (16.67%)	7 (19.44%)	12 (33.33%)	7 (19.44%)	4 (11.11%)
Uighur group	188	65 (34.57%)	52 (27.66%)	38 (20.21%)	24 (12.77%)	9 (4.79%)
Total	224	71 (31.70%)	59 (26.34%)	50 (22.32%)	31 (13.84%)	13 (5.80%)

Uighur group versus Han group; $Zc = 2.851$, $P < 0.01$.

Table 4. Correlation analysis of PI3K and ERK expression in cervical squamous carcinoma tissues in the Uighur group

		PI3K	
		+	-
ERK	+	117	6
	-	58	7

PI3K and ERK correlation; $r = 0.340$, $P < 0.001$.

Table 5. Correlation between PI3K and ERK expression in cervical squamous carcinoma tissues in the Han group

		PI3K	
		+	-
ERK	+	27	3
	-	5	1

PI3K and ERK correlation; $r = 0.084$, $P = 0.625$.

patients came to visit with symptoms in this study, different from unselected screening, the results may not reflect the general population infection status.

The whole process of virus infection, from cancer induction to eventual invasion, requires coordination and interaction of multiple factors [9, 10]. Intracellular biological signaling pathways play an important role in the infection development; there is a dynamic balance between cell apoptosis and anti-apoptosis. Any alteration in this balance leads to the occurrence and development of tumor. PI3K/AKT and MAPK/ERK signaling pathways regulate the balance between apoptosis and antiapoptotic mechanisms, thus are involved in the development of tumor.

PI3K, an intracellular phosphatidylinositol kinase, is a heterodimer which is composed of a catalytic subunit and a regulatory subunit. PI3K gene mutations and AKT high phosphorylation level result in tumor development. PI3K/AKT is a cell survival pathway, which promotes tumor cell growth and proliferation, inhibits cell apoptosis, and promotes cell invasion and metastasis through active substrates of phosphorylation [11]. It has been demonstrated that PI3K protein expression in cervical cancer cells is significantly increased [12, 13]. Our study results demonstrated that the positive expression of PI3K in cervical squamous carcinoma tissues was 92.41% (Uyghur women: 93.09%; Han women: 88.89%); however, no statistically significant difference was observed between Uyghur and Han populations ($P > 0.05$). Liao et al [14-16] reported that PI3K/AKT signal pathway abnormal activation is associated with cervical cancer occurrence. PI3K protein expression was correlated with HPV-16 infection ($r = 4.812$, $P < 0.05$); however, after the comprehensive analysis of multiple factors, including age, nationality, and HPV-16 infection, the expression of PI3K protein in cervical squamous cell carcinomas was unrelated to age, nationality, and HPV-16 infection ($P > 0.05$).

The MAPK family is involved in apoptosis and cell cycle regulation and plays an important role in cell proliferation, differentiation, transformation, and apoptosis. ERK, which regulates cell survival, is also involved in cell differentiation and controls cell proliferation, survival, and apoptosis in the MAPK signaling pathway [17, 18]. ERK can not only phosphorylate plasmosin, but can also phosphorylate nuclear factor-kappa B, so as to regulate cell proliferation and differentiation; mutated ERK or its antisense cDNA can inhibit cell proliferation. In addition, ERK can also phosphorylate proteins upstream of the ERK pathway and regulate self-negative feedback. It has been reported that the expression level of ERK protein in tumor from various epithelial tissue sources, except brain tissue, is higher than in normal tissue, for example, it has excessive expression in ovarian epithelial carcinoma tissue [19, 20]. The specific mecha-

Table 6. Correlation analyses of PI3K protein expression, HPV-16 infection, age, and group

Covariate	Partial regression coefficient	Standard error of partial regression coefficient	Wald	*P* value	OR	OR 95% Confidence interval	
						Lower limit	Upper limit
Constant term	2.034	1.519	1.793	0.181	7.643	-	-
Age	0.046	0.027	2.836	0.092	1.047	0.993	1.104
Ethnicity	-0.910	0.668	1.857	0.173	0.402	0.109	1.490
HPV-16	-1.054	0.560	3.546	0.060	0.348	0.116	1.044

Table 7. Correlation analyses of ERK protein expression, HPV-16 infection, age, and group

Covariate	Partial regression coefficient	Standard error of partial regression coefficient	Wald	*P* value	OR	OR 95% Confidence interval	
						Lower limit	Upper limit
Constant term	-0.057	0.861	0.004	0.948	0.945	-	-
Age	-0.003	0.013	0.039	0.843	0.997	0.971	1.024
Ethnicity	0.903	0.483	3.489	0.049	2.466	0.956	6.360
HPV-16	-0.207	0.305	0.461	0.497	0.813	0.447	1.478

nism of the interaction between ERK, upstream activators, and downstream substrates requires further investigation.

The immunohistochemical results of this study demonstrated that ERK exhibited dark brown positive expression in the cytoplasm. The positive expression rate of ERK in cervical squamous cancer was 68.30% (Han: 83.33%; Uighur: 65.43%); there was significant difference between the two groups ($Zc = 2.851$, $P < 0.01$). Combining multiple factors including age, nationality, and HPV-16 infection, the risk rate of ERK protein high positive expression rate in Han women was 2.466 times higher than in Uighur women ($P < 0.05$). ERK-related intracellular signal transduction pathway is regarded as a classic MAPK signal transduction pathway. Considering the differences between ERK expression in Uygur and Han women, it was speculated that a difference in nationality-corresponds to special physiologic function, which results in inactivation or development of mutations in the ERK gene. However, further investigation is required to confirm whether the mechanism is a direct effect influencing tumor cell proliferation and differentiation, or another physiologic function regulating the cells.

ERK and PI3K are important factors of the level 3 kinase cascade reaction of the MAPK signal transduction pathway. In this study, the expression of ERK and PI3K in Uighur cervical squamous carcinoma tissue was significantly related ($r = 0.340$, $P < 0.001$), suggesting that both ERK and PI3K were involved in the occurrence of Uighur cervical squamous carcinoma. Preventing and treating Xinjiang Uygur cervical cancer by inhibiting key protein or kinase activity in the ERK pathway and cutting off signal transduction is the objective of our future research.

The occurrence of cervical cancer is the result of the interaction of multiple factors. Cervical cancer in Xinjiang's Uygur women is characterized by a high incidence and high mortality, with a very complex pathogenesis. However, understanding the mechanism of activation of PI3K/AKT and MAPK/ERK signaling pathways and various kinases may be helpful in preventing and treating cervical cancer in these women. Detection of both should be a tumor marker for early diagnosis and prognosis of cervical cancer. It can also be used for targeted gene treatment of cervical cancer and as a starting point for research on the mechanism of cervical cancer in Uygur women.

Acknowledgements

The study was supported by University's Scientific Research Project of Autonomous Region (XJEDU2012I24).

Disclosure of conflict of interest

None.

Address correspondence to: Jing Du, Department of Physiology Teaching and Research, Section Basic Medical College of Xinjiang Medical University, Urumqi, Xinjiang, China. Tel: +86-13899828379; E-mail: 598733481@qq.com

References

[1] Qi J, He P, Yao H, Song R, Ma C, Cao M, Cui B and Ning G. Cancer risk among patients with type 2 diabetes: a real-world study in Shanghai, China. J Diabetes 2019; 11: 878-883.

[2] Ding Y, Chen ZF and Ding JB, et al. The characteristics of HPV infection of cervical lesions in Uighurs in some areas of Xinjiang and research on the pathogenesis and immune mechanism. The First Affiliated Hospital of Xinjiang Medical University 2015.

[3] Lu L. Research on the relationship between HPV infection, high-grade cervical lesions and cervical cancer with behavioral factors, trace elements and vitamins in Uyghur women in Bachu County, Xinjiang. Xinjiang: Xinjiang Medical University; 2016.

[4] Croswell J and Costello A. Screening for cervical cancer. Am Fam Physician 2012; 86: 563-4.

[5] Feng B, Wang Y and Liu NN. The effect of HPV-16E6/E7 on the survival, tumor growth and metastasis of cervical cancer model mice by regulating epithelial-mesenchymal transition. J Med Mol Biol 2019; 16: 46-51.

[6] Zhang DD, Wang Q and Wang Y, et al. Expression and significance of HPV16-E6, P53, BTG1 in cervical diseases. Commun Med 2019; 33: 217-221.

[7] Rong XL. Expression and significance of MHC-I molecular antigen presentation-related proteins GRP78, CRT, ERP57 in cervical cancer. Xinjiang Medical University 2011.

[8] Hao Z, Suzuke L, Abudulimu H and Jing D. The expression and possible diagnostic significance of MHC class I antigen presentation associated proteins (CNX, HSP90, and GRP94) in human cervical cancer. Chinese Journal of Clinical Oncology 2008; 35: 1109-16.

[9] zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer 2002; 2: 342-50.

[10] Alsbeih G, Al-Harbi N, El-Sebaie M and Al-Badawi I. HPV prevalence and genetic predisposition to cervical cancer in Saudi Arabia. Infect Agent Cancer 2013; 8: 15.

[11] Mabuchi S, Kuroda H, Takahashi R and Sasano T. The PI3K/AKT/mTOR pathway as a therapeutic target in ovarian cancer. Gynecol Oncol 2015; 137: 173-9.

[12] Pan H. Significance of expression of genes related to eEF1A2 and PI3K-Akt signaling pathway in cervical cancer. Xinjiang: Shihezi University; 2016.

[13] Ning C, Rong XL and Du J. Expression and significance of PI3K, ERK, IGF-1R and ER protein in cervical cancer cell lines. Journal of Xinjiang Medical University 2016; 39: 1044-1047.

[14] Du J, Rong XL and Ning C. The relationship between cervical squamous cell carcinoma lesions and the expression of PI3K, ERK, IGF-1R, ER protein in Xinjiang Uygur and Han people. Chongqing Medical 2016: 2484-2487.

[15] Xiao SX, Le AW and Shan LL, et al. Research on the expression of thin endometrium PI3K, AKT, p-AKT. Hebei Medicine 2016; 3: 348-350, 351.

[16] Hu XW. PI3K-AKT signaling pathway expression in cervical lesions and its relationship with HPV infection. Anhui: Bengbu Medical College; 2017.

[17] Ma ZG and An Y. The expression of ERK2 and its relationship with the biological behavior of cervical cancer. Journal of Hebei Medical University 2013; 24: 1460-1.

[18] Zhou JW, Gan NY and Zhang WJ. The expression of MKP-1 and p-ERK(1/2) in primary ovarian epithelial tumor tissues. Fen Zi Xi Bao Sheng Wu Xue Bao 2009; 42: 224-30.

[19] Cheng Y, Yuan J and Nie ML, et al. VEGF-C activates ERK1/2 and up-regulates the expression of Slug protein to promote cervical cancer cell invasion. Journal of Tropical Medicine 2018; 18: 846-849, 868.

[20] Zhou JW, Qian NY and Zhang WJ. Study on the expression of MKP-1 and p-ERK1/2 protein in epithelial ovarian tumor tissue. Fen Zi Xi Bao Sheng Wu Xue Bao 2009; 42: 224-230.