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Correlation of APOBEC3G Polymorphism with Human Papillomavirus (HPV) Persistent Infection and Progression of Cervical Lesions

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Background: We studied the effect of APOBEC3G on persistent human papillomavirus (HPV) infection and the correlation between APOBEC3G polymorphism and HPV persistent infection and cervical disease progression in Uygur women in China.

Material/Methods: From January 2015 to December 2017, we enrolled 529 Uygur ethnic group patients with HPV infection. SIHA cells were transfected with APOBEC3G. Real-time quantitative polymerase chain reaction (RT-qPCR) and Western blot analysis were used to detect mRNA and protein expression levels of APOBEC3G and HPV E6 and p53. Exon 3 of APOBEC3G was sequenced by first-generation sequencing.

Results: The mRNA and protein expression levels of APOBEC3G in the cervical cancer group were significantly higher than in the cervical intraepithelial neoplasia (CIN) group ($p<0.05$). The mRNA and protein expression levels of APOBEC3G in the CIN group were significantly higher than in the non-cervical lesions group ($p<0.05$). The mRNA and protein expression levels of HPV E6 in SIHA cells transfected with APOBEC3G were significantly lower than in the control group and the no-load group ($p<0.05$), and the mRNA and protein expression levels of p53 were significantly higher than in the control group and the no-load group ($p<0.05$). There was a polymorphic locus rs5757465 on exon 3 of APOBEC3G in Uygur women, and this rare CC type was a risk factor for cervical lesions and cervical cancer (OR=3.714, 95%CI: 1.916–7.202, $p<0.05$).

Conclusions: APOBEC3G is involved in continuous HPV infection, cervical prelesions, and the development of cervical cancer, and the rare genotype (CC) of APOBEC3G may be one of the factors causing cervical lesions in Uygur women who have HPV infection.

MeSH Keywords: Human papillomavirus 16 • Polymorphism, Genetic • Uterine Cervical Neoplasms

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Background

Cervical cancer is the second most common cancer among women worldwide and is a leading cause of death in developing countries [1]. Persistent infection with the high-risk human papillomavirus (HPV) is considered to be an important factor closely related to the incidence of cervical cancer [2]. HPV is small double-stranded DNA virus with strict tissue specificity [3]. According to oncogenic potential, HPVs can be classified as the high-risk (e.g., HPV16 and HPV18) or low-risk (e.g., HPV6 and HPV11) genotypes [4]. Most HPV infection is harmless and clears spontaneously, but persistent infection with high-risk HPV (especially type 16) can cause cancer of the cervix, vulva, vagina, anus, penis, and oropharynx [5]. The major high-risk oncoproteins are encoded by the E6 and E7 genes, and E6 is a potent target for therapeutic intervention in the treatment of cervical cancer [6]. The p53 protein contributes to tumor suppression by stimulating the transcription of specific cellular genes [7]. The thin-cytologic test (TCT) is an important method for screening of cervical lesions by using the liquid-based TLC detection system, which has been widely used in large populations due its simplicity and efficiency [8,9].

Apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3 (APOBEC3, A3) proteins are cellular cytidine deaminases. The A3 proteins are cell-intrinsic immune factors that combat viruses, including lentiviruses and retrotransposons [10]. A3 consists of 7 members: APOBEC3A, APOBEC3B, APOBEC3C, APOBEC3DE, APOBEC3F, APOBEC3G, and APOBEC3H. In the past few years, A3 has been linked to other viruses associated with human disease, including HCV, HBV, Human T-lymphotropic virus (HTLV), Herpes simplex virus (HSV-1), and Epstein-Barr virus (EBV) [11]. Vartanian et al. confirmed that the A3 family protein was involved in the encoding of HPV in pre-cervical cancer lesions, and found that APOBEC3G had a highly mutated editing effect on HPV DNA [12]. Some studies also showed that APOBEC3G was involved in the occurrence and development of HPV and cervical cancer [13, 14]. A3 polymorphism is also associated with many other diseases, such as AIDS, breast cancer, oral cancer, and epithelial ovarian cancer [6,15,16].

Epidemiological research shows that cervical lesions in Uygur women in Xinjiang, China and the HPV infection rate in Uygur women is low, but the incidence of cervical cancer is high [17]. It is suggested that HPV infection in Uygur patients differed from that in other ethnic groups. Recently, a common germline deletion polymorphism in the A3 gene cluster was reported to be involved in increasing cancer susceptibility [18]. We hypothesized that the APOBEC3G gene polymorphism is associated with persistent HPV infection and cervical lesions in Uygur women. To explore the role of APOBEC3G in persistent HPV infection in Uygur women and to assess the effect on various outcomes of persistent HPV infection, we assessed the expression levels of APOBEC3G mRNA and protein and APOBEC3G gene polymorphisms in the cervical tissues of Uygur patients with cervical lesions and cervical cancer. SIHA cells were transfected with APOBEC3G adenovirus and the expression of HPV E6 and P53 in SIHA cells was detected to provide reliable data to elucidate the antiviral effect of APOBEC3G on cervical cancer and its role in tumor cell regulation, as well as to provide a theoretical basis for future studies on HPV persistent infection, cervical cancer pathogenesis, and immunotherapy.

Material and Methods

Patients

We enrolled 529 Uygur women (125 with HPV-negative non-cervical lesions, 162 with HPV transient infection, 114 with cervical intraepithelial neoplasia (CIN), and 128 with cervical cancer) who were patients at People's Hospital of Xinjiang Uygur Autonomous Region from January 2015 to December 2017. All patients underwent TCT, HC-II high-risk HPV test, and histopathology analysis. The study protocol was approved by the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region (No. 2014914). All patients provided written informed consent. Cervical tissue was collected from all patients.

DNA extraction

DNA was extracted from cervical tissue using a DNA extract kit (Tiangene Biotech Co., Beijing, China) according to the manufacturer's instructions [19].

RNA extraction

Total RNA was extracted from tissue using the traditional TRIzol (Life, Shanghai, China) [20]. The value of A260/A280 was detected using a K5500 model Nucleic acid protein quantitation meter (Kaiao Technology Development Co., Beijing, China). Extraction quality was detected by 1% formaldehyde denaturing gel electrophoresis. Extracted RNA samples were stored at –80°C.

Protein extraction

An appropriate amount of cervical tissue was frozen in liquid nitrogen and crushed. Protein lysate (Biosharp, Anhui, China) was added at a ratio of 1: 10. The supernatant was assayed for protein concentration using the BCA Protein Quantitation Kit (Biosharp, Anhui, China) and the remaining samples were stored at –80°C.

APOBEC3G exon 3 polymorphism locus detection

The APOBEC3G exon 3 was amplified, and the positive amplification product was selected and sent to Xinjiang Kuntailui

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Biotechnology Co. (Xinjiang, China) for sequencing. Briefly, the reaction mixture included PCR buffer (50 mM KCl, 10 mM Tris-HCl, 2.5 mM $MgCl_2$, pH 8.3), Taq DNA polymerase (2.5U), Forward primers (0.2μM), Reverse primers (0.2μM), dNTP (200μM), RNase-Free water (7.2μl/20 μl), and DNA (2μl/20 μl). Amplification conditions were: 1 cycle of 3 min at 94°C, 35 cycles of 30 s at 94°C, 30 s at 64°C, 45 s at 72°C, and 1 cycle of 2 min at 72°C. The following primers were used:
Forward primer: AGCAGACAAACACTCAAACC,
Reverse primer: GTGTCTGTGATGGGTCCTTC;

Reverse transcription and Real-time Quantitative polymerase chain reaction (RT-qPCR)

The reaction mixture consisted of RNA (500 ng/10 μl), Random 6 mers (2.5 mM), OligodT primer (2.5 mM), PrimeScript RT Enzyme Mix I (1 μl/10 μl), 5×PrimeScript Buffer (2 μl/10 μl). We added diethyl pyrocarbonate water to 10 μl and used the mixture for cDNA synthesis with amplification conditions of 60 min incubation at 37°C and 5 min incubation at 90°C. RT-qPCR was performed on a Bio-Rad PCR meter. Briefly, the reaction mixture included 2×QuantiNova SYBR Green PCR Master Mix (10 μl/20 μl), primers (0.4 μM), RNase-Free water (7.2 μl/20 μl), and cDNA (2 μl/20 μl). Amplification conditions were: 1 cycle of 2 min at 95°C, 40 cycles of 5 s at 95°C, and 30 s at 60°C. The following primers were used:
GADPH: F: TCTCCTCTGACTTCAACAGCGAC,
R: CCCTGTTGCTGTAGCCAAATTC;
APOBEC3G: F: TCTGGCTGTGCTACGAAGT,
R: GTGGAAGAATCTCATCTCTGG;
HPVE6: F: GTGGACCGGTCGATGTATGTCT,
R: TCCGGTTVTGCTTGTCCAGC;
P53: F: CCTCAGCATCTTATCCGAGTGG,
R: TGGATGGTGGTACAGTCAGAGC.

Western blotting

The protein samples (40 μg) were boiled for 5 min and then immediately placed in an ice bathed for 5 min, then centrifuged at 12 000 rpm for 5 min at 4°C. The supernatant (25 μg) were electrophoresed in sodium dodecyl sulfate polyacrylamide gel (SDS-PAGE). After electrophoresis, the targeted proteins on the gel were transferred onto a polyvinylidene difluoride (PVDF) membrane and blocked with 5% BSA for 1 h at room temperature. After washing with TBST for 5 min, the PVDF membrane was incubated with 5 ml primary antibodies overnight at 4°C. After 3 washes with TBST, the membrane was incubated with 10 mL secondary antibodies diluent for 1 h at room temperature. After 3 washes with TBST, the ECL Chemiluminescence reagent A and B (100 μl) were mixed 1: 1 and uniformly applied near the target strip. The primary antibodies used in this study were as follows: APOBEC3G (Bioss, MA, USA), HPV E6 (Abcam, Cambridge, MA), p53 (Abcam, Cambridge, MA), with GADPH (Abcam, Cambridge, MA) and was considered as the internal reference. The secondary antibodies used in this study were: ZB-2301 (Zhongshan Jinqiao Biotechnology Co., Beijing, China) and ZB-5305 (Zhongshan Jinqiao Biotechnology Co., Beijing, China). The experiments were repeated 3 times.

Transfection

SIHA cells were digested by 0.25% trypsin (Gibco, NY, USA). After the density of cells was adjusted in DMEM medium containing 10% serum, the cells were inoculated into 6-well plates at a density of 5×10^4/ml (2.5 ml/well) and incubated at 37°C in humidified air containing 5% CO_2. When the cell density grew to 70%, the fresh medium was changed for transfection. PLVX-mCMV-ZsGreen-PGK-Puro-homo-APOBEC3G virus (Jikai, Shanghai, China) was added to cell culture plates with MOI=20, then incubated for 16 h at 37°C in humidified air containing 5% CO_2. The transfection solution was discarded, and then 2.5 ml fresh medium was added for further culture. After 72 h of culture, fluorescence protein was observed using an Axio Observer A1 model fluorescence microscope (Zeiss, Germany). When green fluorescence was observed in about 70% of the cells, cells were digested by 0.25% trypsin and transferred into a 15-ml centrifuge tube. The supernatant was centrifuged at 1800 rpm for 6 min to retain the bottom precipitated cells. Then, cells were mixed with PBS and centrifuged at 1800 rpm for 6 min and cells were stored at –80°C.

Statistical analysis

All data were expressed as means ± standard deviation (SD). All statistical analyses were performed using SPSS 18.0 (SPSS, Inc., Chicago, IL, USA). The significance of differences between 2 groups was determined by independent *t* test. $p<0.05$ was considered to indicate statistical significance.

Results

The APOBEC3G mRNA expression level

The mRNA expression level of APOBEC3G in the CIN was 1.79 times higher than that in the non-cervical lesions group, and the difference was statistically significant ($p<0.05$). The mRNA expression level of APOBEC3G in the cervical cancer group was 2.67 times higher than that in the non-cervical lesions group, and the difference was statistically significant ($p<0.05$). The mRNA expression level of APOBEC3G in the cervical cancer group was 1.49 times higher than that in CIN, and the difference was statistically significant ($p<0.05$) (Figure 1).

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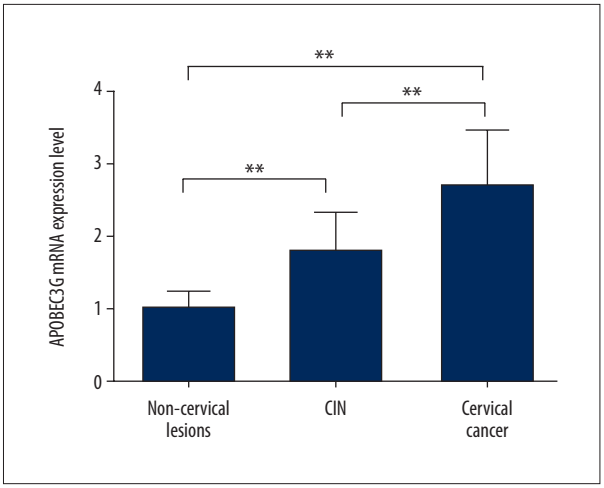

Figure 1. Expression level of APOBEC3G mRNA in cervical cancer, CIN, and non-cervical lesions. CIN – cervical intraepithelial neoplasia; ** p<0.05.

The APOBEC3G protein expression level

The protein expression level of APOBEC3G in the CIN was 2.96 times higher than that in the non-cervical lesions group, and the difference was statistically significant (p<0.05). The protein expression level of cervical cancer group was 6.52 times higher than that of the non-cervical lesions group, and the difference was statistically significant (p<0.05). The protein expression level of APOBEC3G in the cervical cancer group was 2.21 times higher than that in the CIN, and the difference was statistically significant (p<0.05) (Figure 2).

APOBEC3G 3 exon polymorphism locus detection

After sequencing comparison, there was a polymorphism locus on exon 3 of APOBEC3G in cervical tissues of Uygur patients with cervical precancerous lesions and cervical cancer. NCBI login number of polymorphism locus is rs5757465. The ratio of the rare type (CC type) in the population is about 0.087, which is far lower than that of the Han population (0.221) and slightly higher than that of the European and American populations

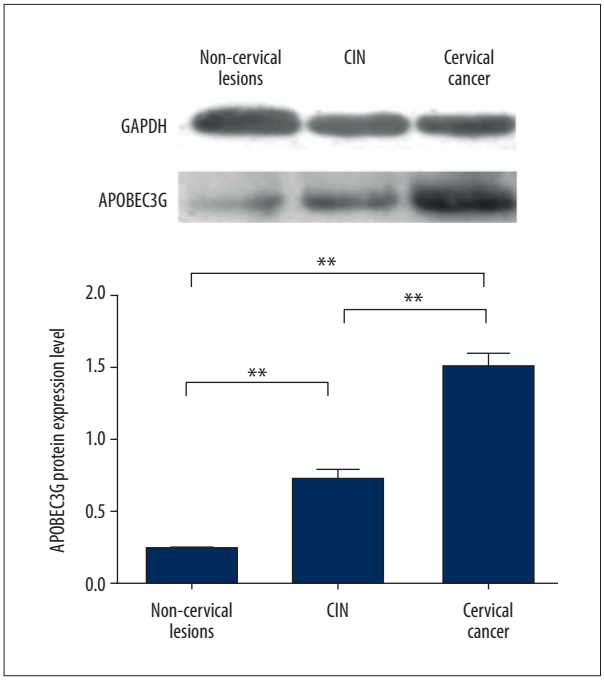

Figure 2. Expression level of APOBEC3G protein in cervical cancer, CIN, and non-cervical lesions. CIN – cervical intraepithelial neoplasia; ** p<0.05.

(0.070) (data above from 1000 GENOMES-phase_3_ensembl_v87_hg19) (Figures 3, 4).

Relationship between allele and genotype distribution at rs5757465 and HPV susceptibility

Hardy-Weinberg test was performed on the genotype analysis results of rs5757465 locus, and the results showed that all groups were in line with the genetic balance and had population representativeness (p>0.05). There were statistically significant differences regarding the distribution of the 3 genotypes of CC, CT, and TT among the HPV-negative group, HPV-infected non-cervical lesions, CIN group, and cervical cancer group (χ^2=25.154, p<0.05) (Table 1). The proportion of CC type in the CIN group (21.05%) was higher than in the cervical cancer group (12.5%)

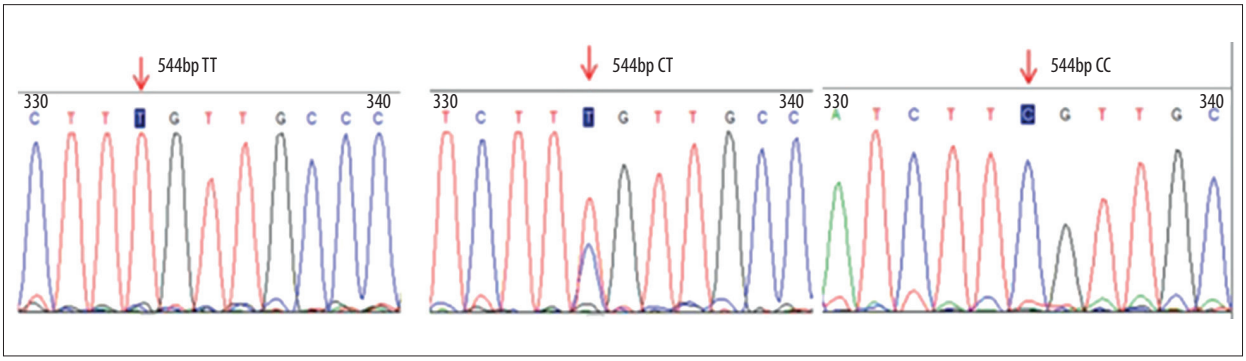

Figure 3. rs5757465 sequencing results.

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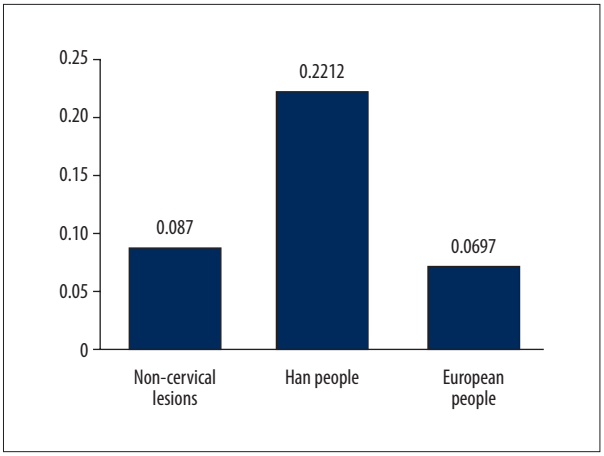

Figure 4. APOBEC3G Exon3 genotype in Uyghur people, Han population, and European and American people.

(p>0.05). The proportion of CC type in the CIN group was significantly higher than that in the HPV-infected non-cervical lesions group (4.00%) and HPV-negative group (5.56%) (p<0.05).

Association of APOBEC3G Rs5757465 genotype with the persistent infection to HPV

There were significant differences (χ^2=19.838, p=0.01) in the 3 phenotypes of the gene among the HPV-negative group, the HPV-infected non-cancerous group, and the HPV-infected carcinogenic group (CIN combined with cervical cancer group) (Table 2). There was no significant difference in the distribution frequency of CC genotype between the HPV-negative group and the HPV-positive non-cervical lesions group (p=0.814).

Table 1. Distribution pattern of APOBEC3G gene rs5757465 locus genotype in Uygur cervical lesions.

Genotype	HPV-negative	Non-cervical lesions	CIN	Cervical cancer
CC	5 (4.00%)	9 (5.56%)	24 (21.05%)	16 (12.50%)
CT	62 (49.60%)	81 (50.00%)	48 (42.11%)	54 (42.19%)
TT	58 (46.40%)	72 (44.44%)	42 (36.84%)	58 (45.31%)
Total	125	162	114	128
χ^2	5.48	5.14	2.12	0.38
P	0.064	0.076	0.346	0.83

HPV – human papillomavirus; CIN – cervical intraepithelial neoplasia.

Table 2. Relationship between rs5757465 locus genotype and persistent infection of HPV.

Genotype	HPV negative (n=125)	HPV positive (n=162)	CIN + cervical cancer (n=242)	χ^2	P
CC	5	9	40	19.838	0.001
CT	62	81	102		
TT	58	72	100		

HPV – human papillomavirus; CIN – cervical intraepithelial neoplasia.

Table 3. Relationship between rs5757465 locus genotype and Uygur cervical lesions.

Genotype	Non-cervical lesions	CIN+ cervical cancer	OR	95% CI	*P*
TT	130	100	1		
CT	143	102	0.684	0.644~1.334	0.684 >0.05
CC	14	40	3.714	1.916~7.202	0.001 <0.05

CIN – cervical intraepithelial neoplasia.

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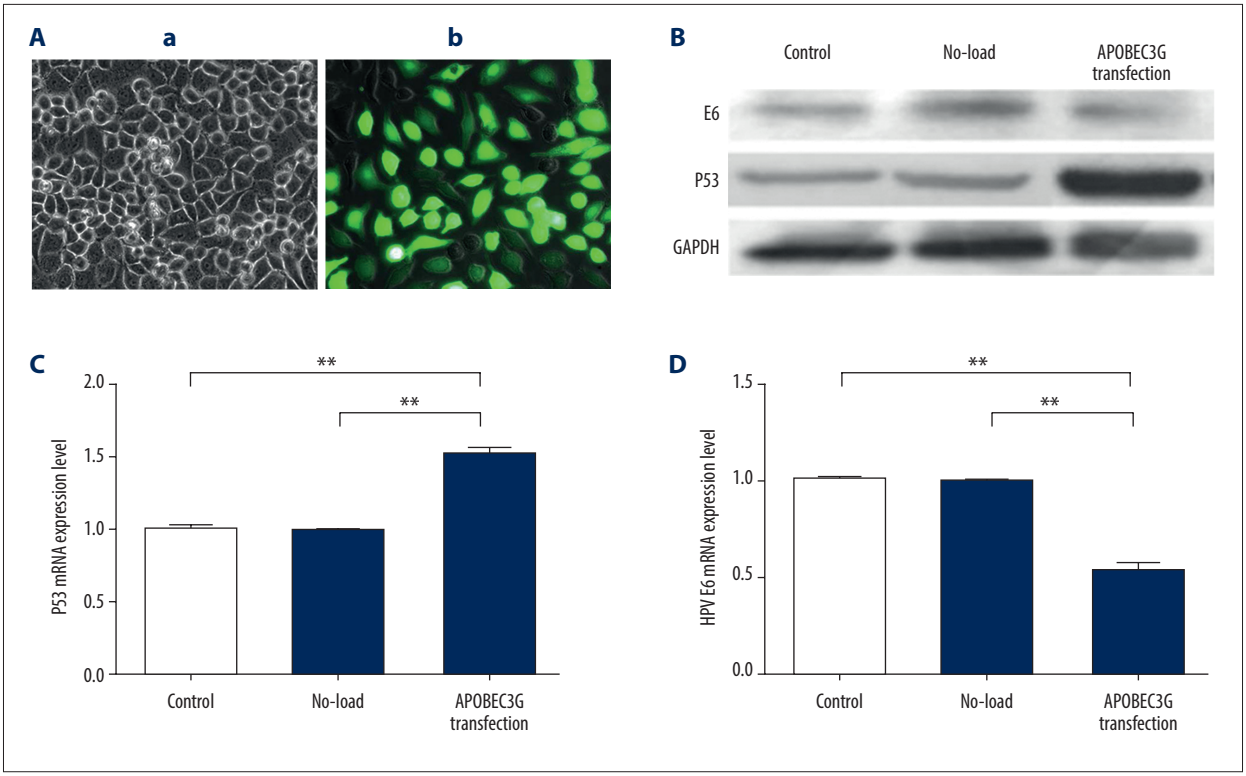

Figure 5. Expression levels of HPV E6 and p53 mRNA and protein in SIHA cells transfected with APOBEC3G gene. (**A**) Fluorescent protein in SIHA cells before and after transfection. (**a**) Fluorescent protein in SIHA cells before transfected with APOBEC3G gene; (**b**) Fluorescent protein in SIHA cells after transfected with APOBEC3G gene. (**B**) Expression levels of HPV E6 and p53 protein in SIHA cells transfected with APOBEC3G gene. (**C**) Expression levels of p53 mRNA in SIHA cells transfected with APOBEC3G gene. (**D**) Expression levels of HPV E6 mRNA in SIHA cells transfected with APOBEC3G gene. ** p<0.05.

Relationship between APOBEC3G Exon3 genotype and cervical lesions

In order to study the relationship between APOBEC3G Exon3 genotype and cervical lesions, we combined the HPV infection-negative group and -positive non-cervical lesions group without cervical lesions into a single group. We combined the CIN group and cervical cancer group with cervical lesions into another group. The relative risk between genotype and allele and cervical lesions was analyzed. The OR value of CC genotype was 3.714 (95%CI: 1.916–7.202, p=0.01), suggesting that the CC genotype at rs5757465 is a risk factor for cervical cancer (Table 3).

The mRNA and protein expression levels of HPV E6 and P53 in APOBEC3G transfection SIHA cells

The mRNA and protein expression levels of HPV E6 in APOBEC3G transfection SIHA cells was significantly lower than in the control group and the no-load group (p<0.05). The mRNA and protein expression level of P53 in APOBEC3G transfection SIHA cells was significantly higher than in the control group and the no-load group (p<0.05) (Figure 5).

Discussion

APOBEC3G originated from the CEM-SS cell line, also known as CEM15, is located on the long arm of human chromosome 22q12-q13.2 and contains 8 exons and 7 introns and encodes 384 amino acids [21,22]. APOBEC3G has a broad spectrum of antiviral activity, and the virus is lost to normal function by deamination of the retrovirus; APOBEC3G participates in the development of certain diseases, especially tumors [23]. APOBEC3G can edit the HPV genome, increasing the frequency of viral genome mutations [24]. There are few reports regarding the expression of APOBEC3G in cervical tissues during the progression of cervical cancer. In this study, the mRNA and protein expression levels of APOBEC3G in the process of cervical cancer and precancerous lesions in Uygur women were detected. The expression level of APOBEC3G in cervical tissue in Uygur women is increasingly expressed in HPV intraepithelial neoplasia and with disease progression. It was demonstrated that APOBEC3G was involved in the occurrence and development of cervical cancer in Uygur women. Takashi et al. [13] found that APOBEC3G expression level was increased along with the progression stages of the lesion in Japanese, which is consistent with our findings.

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Compared with the Han population in other areas with high incidence of cervical cancer in China, Uygur women in Xinjiang have lower HPV infection rate and higher incidence of cervical cancer [17]. Most lentiviral genomes contain an antagonist of A3 to overcome the restriction imposed by A3. This has led to an evolutionary "arms race" between hosts and viruses that has left a signature of positive selection, or rapid evolution, in host and viral genes [25]. A3s are highly polymorphic in nature, which greatly influences their viral restriction potential and cancer predisposition [26–28]. There was a significant variation in rs8177832 genotype AA in healthy control and HIV-1-infected subjects in Pakistan (42.25% *vs.* 66%; p-value <0.001). APOBEC3G contributes to genetic predisposition to HIV-1 infection [29]. Tegwinde et al. found that APOBEC3G is a susceptibility gene for HIV-1/HBV co-infection in Burkina Faso [30]. A previous study demonstrated that functional APOBEC3H polymorphisms were associated with susceptibility to HIV-1 infection and progression to AIDS in Japan [15]. Qi et al. found that the loss genotypes of APOBEC3 deletion predisposed their carriers to epithelial ovarian cancer in China [16]. Persistent infection with high-risk HPV is considered to be an important factor closely related to the incidence of cervical cancer [2]. In this study, a polymorphism site (rs5757465) on exon 3 of APOBEC3G was found in Uygur women. The 3 phenotypes – CC, CT, and TT – in the HPV-negative non-cervical lesions group, the HPV-infected non-cancerous group, and the HPV-infected carcinogenic group were significantly different (χ^2=25.154, p<0.05). The rate of rare type (CC type) in rs5757465 is about 0.087, which is a risk factor for cervical lesions and cervical cancer (OR=3.714, 95%CI: 1.916–7.202, p=0.01), suggesting that the polymorphism of APOBEC3G rs5757465 may be the reason why the incidence of cervical cancer in Uygur is different from other populations.

APOBEC3G is involved in the occurrence and development of cervical cancer in Uygur women. However, the role of APOBEC3G in cervical cancer in Uygur women is not clear. Cervical cancer is initiated by infection with a high-risk HPV (HPV16 or HPV18), and gene transfer studies have identified the E6 and E7 genes as the major viral oncogenes [31,32]. Chen et al. found that APOBEC3A possesses anticancer and antiviral effects by differential inhibition of HPV E6 and E7 expression in cervical cancer [14]. Hela cells transfected with APOBEC3G showed that APOBEC3G could inhibit the proliferation and invasion of cervical cancer cells [33]. P53 is a tumor suppressor gene [34]. In this study, we successfully established an APOBEC3G gene-transfected SIHA cell model to study the role of APOBEC3G in persistent HPV infection and cervical disease progression. HPV E6 expression level was decreased in the APOBEC3G gene-transfected SIHA cell model, while p53 expression level was increased. This suggests that APOBEC3G expression could inhibit HPV by decreasing HPV E6 and upregulating p53.

Conclusions

APOBEC3G is involved in the continuous infection of HPV, cervical prelesions, and the development of cervical cancer. It inhibits the transcription and expression of oncogene HPV E6 and upregulates the transcription and expression of oncogene p53. Moreover, the rare genotype of APOBEC3G (CC) may be one of the factors affecting cervical lesions caused by HPV in Uygur women. This study provides reliable data elucidating the antiviral role of APOBEC3G in regulation of cervical cancer in tumor cells, and provides a theoretical basis for the future study of HPV persistent infection, cervical cancer pathogenesis, and immunotherapy.

Conflict of interest

None.

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