Original Article

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The role of APOBEC3A in cervical cancer development and progression: A retrospective study

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SUMMARY The majority of cervical cancer cases are contributed to chronic infection with high-risk human papillomavirus (HPV), while only a fraction of infected women finally develop cancer. It is suggested that apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A (APOBEC3A), a type of mRNA editing enzyme, may be involved in the development and progression of HPV-related tumors. This study aimed to explore the role and potential mechanisms of APOBEC3A in cervical cancer. First, the expression levels, prognostic values and genetic alterations of *APOBEC3A* in cervical cancer were explored using various bioinformatics tools and databases. Then, functional enrichment analyses were performed. Finally, genetic polymorphisms (rs12157810 and rs12628403) of *APOBEC3A* were genotyped in our clinical sample of 91 cervical patients. The associations between *APOBEC3A* polymorphisms and clinical characteristics as well as patient overall survival were further evaluated. Compared with normal tissues, the expression level of APOBEC3A was significantly elevated in cervical cancer. High expression of APOBEC3A had better survival compared with the low expression group. The immunohistochemistry results showed that the expression of APOBEC3A protein was localized in the nucleus. APOBEC3A expression level in cervical and endocervical cancer (CESC) was negatively correlated with the infiltration level of cancer-associated fibroblasts, and positively correlated with the infiltration level of gamma delta T cells. No association was observed between *APOBEC3A* polymorphisms and patient survival. The expression of APOBEC3A was significantly higher in cervical cancer tissues, while high expression was associated with better prognosis in cervical cancer patients. APOBEC3A has the potential of being used in prognostic evaluation in cervical cancer patients.

Keywords APOBEC3A, expression, cervical cancer, bioinformatics, SNP, survival

1. Introduction

Worldwide, cervical cancer is the fourth most commonly diagnosed and the fourth leading cause of cancer death among women (*1*). There were an estimated 569,847 new cases of and 311,365 deaths caused by cervical cancer in 2018. The burden of cervical cancer is even higher in countries and regions with lower human development index (HDI) (*1*). Almost all cases of cervical cancer are attributed to persistent infection with high-risk human papillomavirus (HPV) genotypes (*2*). However, only a small fraction (about 10%) of infected women will develop viral persistence, and only some of those chronically infected with carcinogenic HPV types will eventually progress to neoplastic lesions (*3*). In addition, invasive cervical cancer is preventable through HPV vaccination (*4*). Furthermore, screening and removing precancerous cervical lesions can prevent its development into cervical cancer (*5*). Despite implementation of above public health intervention measures, health system barriers such as accessibility and affordability exist, especially in lower HDI countries and regions. Cervical cancer is and will continue to be a public health burden in China in the foreseeable future (*6*). It is important to have a better understanding of the molecular mechanisms so as to provide more opportunities for early diagnosis and prognosis assessment.

Apolipoprotein B mRNA editing enzyme, catalytic

polypeptide-like 3A (APOBEC3A) is a member of the APOBECs family, which plays an important role in the defense process of anti-viral infection (*7*). It is reported that APOBEC3A can enhance the ability of human immune system to recognize HPV infection (*8*). Research has shown that APOBEC3A has the function of genetic editing HPV DNA in the nucleus, thus playing an important role in combating and clearing HPV. Therefore, it is speculated that APOBEC3A may be involved in the inhibition of the occurrence and development of HPV-related tumors (*9*). However, some studies have shown that APOBEC3A may damage the DNA of its own cells, and the signature mutation of *APOBEC3A* increases in HPV-associated tumors, suggesting that APOBEC3A may also be closely related to tumorigenesis (*10-12*). Cancer is a complex disease resulting from interactions of various factors, and the same factor may also act differently at different stages of tumor development and progression. Furthermore, genetic variations may also affect an individual's susceptibility to cervical cancer and its prognosis. Therefore, it is important to conduct bioinformatics analysis of interested genes to assess its correlation with clinical prognosis and fully explore potential molecular mechanisms using publicly available database.

In this study, we first utilized various bioinformatics databases and tools to comprehensively analyze the relationship between APOBEC3A and the occurrence, development, and prognosis of cervical cancer. We further evaluated the effects of *APOBEC3A* genetic polymorphisms on the overall survival (OS) of cervical cancer in our own clinical samples.

2. Materials and Methods

2.1. Tumor Immune Estimation Resource (TIMER)

TIMER (version 2.0) (*http://timer.cistrome.org/*) is a resource for systematic analyses of immune cell infiltration across various cancer types based on The Cancer Genome Atlas (TCGA) database (*13*). In this study, "Exploration" module was used to display the differential gene expression of APOBEC3A in various tumor tissues (and corresponding normal tissues). The "Immune" module of the TIMER web server was used to explore the association between APOBEC3A expression and immune infiltrates of TCGA cervical and endocervical cancer (CESC). Purity-adjusted Spearman's rank correlation test was used to obtain *p*-values and partial correlation (rho) values. Algorithms of TIMER, EPIC, MCPCOUNTER, CIBERSORT, CIBERSORT-ABS, QUANTISEQ, XCELL, naïve_XCELL, and TIDE were used for immune infiltration estimations.

2.2. Oncomine database

Oncomine database (*http://www.oncomine.org*) is a web-based chip data-mining platform, including 715 tumor microarrays, and 86,733 cancer and normal tissue samples (*14*). Oncomine was used to analyze the mRNA expression of APOBEC3A in cervical cancer tissues and normal tissues, using the following parameters: Gene: *APOBEC3A*; Analysis Type: Cancer *vs.* Normal Analysis; Data Type: mRNA; threshold: *p* value < 0.05, Fold change > 2 and gene rank = top 10%.

2.3. Gene Expression Profiling Interactive Analysis (GEPIA) dataset analysis

GEPIA (version 2) (*http://gepia.cancer-pku.cn/*) is a database containing RNA sequencing expression data from TCGA and Genotype-tissue Expression dataset (GTEx) projects. It is a visual analysis website including information from 33 tumor types, 9736 tumor samples, and 8587 normal samples (*15*). In this study, GEPIA was applied to evaluate the differential expression of APOBEC3A in cervical squamous cell carcinoma and endocervical adenocarcinoma *vs.* normal cervical tissues. The criteria were: |Log2FC| Cutoff: 2; *p*-value Cutoff: 0.05. GEPIA was also used to evaluate the prognostic value of APOBEC3A expression in cervical cancer patients, with group cutoff set as Median.

2.4. TCGA data mining

The expression data of cervical squamous cell carcinoma tissues were downloaded from TCGA (https://cancergenome.nih.gov/) in TCGA-CESC dataset and utilized to analyze the expression of APOBEC3A. The TCGA-CESC dataset contains data of 308 cervical cancer cases; however, only 304 cases have expression data needed and hence were selected for relative expression analysis. Among them, 304 cervical cancer cases have detailed follow-up information of OS and 174 with recurrence-free survival (RFS) information, and were used for Kaplan-Meier analysis. These patients were divided into high and low APOBEC3A expression groups based on the RNA-Seq by Expectation-Maximization (RSEM) with an auto selected best cutoff value of 2.105.

2.5. Human Protein Atlas (HPA)

HPA (*https://www.proteinatlas.org/*) (Version: 20.0, updated date: 2020-11-19) is a free public platform that can be used for genome-wide exploration of individual proteins on clinical outcome in major human cancers (*16*). The database can provide the location, expression and prognosis of proteins in normal tissues, tumor tissues, cell lines and blood cells with immunology method. In this study, HPA database was used to analyze the immunohistochemical staining of APOBEC3A in cervical cancer tissues.

2.6. Tumor-Immune System Interactions (TISIDB) immune analysis

TISIDB database (*http://cis.hku.hk/TISIDB*) (*17*) integrates data related to immune-associated anti-tumor genes, high-throughput screening techniques, molecular profiles, and paracancerous multi-omics. In this study, TISIDB is used to explore the correlations of APOBEC3A expression with lymphocyte, immunomodulators, and major histocompatibility molecules (MHCs) in ovarian cancer.

2.7. Clinical samples and follow-up

The study patients were recruited at the Obstetrics and Gynecology Hospital of Fudan University in Shanghai. The study protocol was approved by the Institutional Review Board of the hospital, and all patients provided written informed consent. Cases were randomly selected newly diagnosed sporadic cervical cancer patients undergoing surgery at our hospital from November 2013 to September 2017. Pathological diagnosis was confirmed independently by two pathologists. Patients received any pre-operative therapies were not included. All patients were ethnic Han Chinese. Follow-up started after 6 months of the surgery. A dedicated unit in our hospital performed the follow-up every 3 months on an outpatient bases and/or by telephone calls according to standard protocol (*18*).

2.8. APOBEC3A SNP and genotyping

QIAquick PCR purification kits (QIAGEN, Hilden, Germany) were used to extract genomic DNA from blood samples. *APOBEC3A* single nucleotide polymorphism (SNP) rs12157810 (-535 A>C) was selected because it represented the haplotype block in the promoter region of APOBEC3A determined by Haploview 4.2. Intronic SNP rs12628403 (+4340 A>C) was selected for genotyping based on previous literatures and as the proxy tag of *APOBEC3B* deletion (*19,20*). Genotyping was conducted using fluorescent probe real-time quantitative PCR in a LightCyclerTM480 (Roche, Basel, Switzerland). Primers and probes (Minor Groove Binder [MGB]) were designed by GeneCore Bio Technologies Co. Ltd. (Shanghai, China). The primer and probe sequences were presented at Table S1 (*http://www.ddtjournal.com/action/getSupplementalData.php?ID=139*). Blind duplicates (5% of the samples) were included to assess laboratory reliability, and 100% concordance rate was achieved.

2.9. Statistical analysis

Categorical variables were summarized as number (percentage), and continuous variables were presented as median (range). Fisher's exact test was used to determine the differences of discrete variables between high- and low-expression subgroups. Kaplan-Meier survival analysis and log-rank test were used to assess the influence of *APOBEC3A* SNPs on cervical cancer prognosis. All significance tests were two sided; p value of < 0.05 was considered as statistically significant. Data analyses were performed by STATA version 15 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Expression level of APOBEC3A mRNA in patients with various cancer types

The expression of APOBEC3A was evaluated in different tumor types and adjacent normal tissues using TIMER database. As shown in Figure 1A, the expression level of APOBEC3A was significantly higher than that in adjacent normal tissues in the following cancers: breast invasive carcinoma (BRCA), CESC, cholangiocarcinoma (CHOL), esophageal carcinoma (ESCA), head and neck cancer (HNSC), kidney renal clear cell carcinoma (KIRC), stomach adenocarcinoma (STAD), and uterine corpus endometrial carcinoma (UCEC).

We further detected the level of APOBEC3A mRNA in different cervical cancer types *vs.* normal tissues using Oncomine (Figure 1B and Table 1). In Pyeon Multi-cancer statistics, the level of APOBEC3A mRNA expression was significantly upregulated in cervical cancer compared with normal tissues (fold change = 2.010, $p = 0.026$). Although not meeting our screening criteria, in Biewenga Cervix statistics, the level of APOBEC3A mRNA expression was also elevated in cervical squamous cell carcinoma compared with normal tissues (fold change = 1.791, $p = 0.046$).

3.2. Differential expression level of APOBEC3A mRNA and protein in patients with cervical cancer

Cervical squamous cell carcinoma consists about 80% of cervical cancer cases and cervical adenocarcinomas accounts for 10%-20% of the cases (*7*). We then investigated APOBEC3A expression in cervical squamous cell carcinoma and endocervical adenocarcinoma *vs.* normal cervical tissues. GEPIA results showed that the expression level of APOBEC3A was significantly higher in cervical cancer tissues than that in normal tissues ($p < 0.05$) (Figure 1C), while there was no association between APOBEC3A mRNA level and Federation of Gynecologists and Obstetricians (FIGO) stage (Figure 1D).

We further explored the expression of APOBEC3A protein in cervical cancer tissues and normal tissues using immunohistochemistry with the HPA database. The immunohistochemistry staining results showed

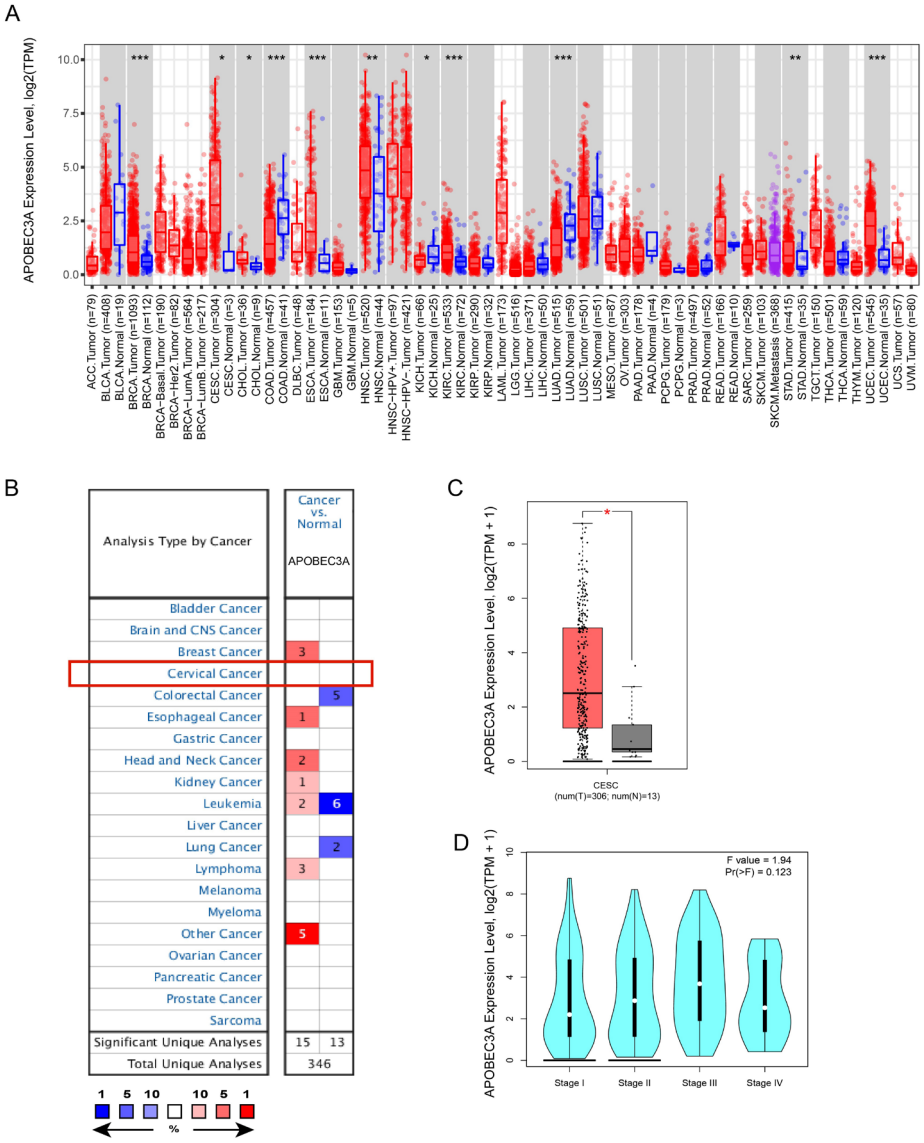

Figure 1. **Expression of APOBEC3A mRNA in different cancer types and correlation between APOBEC3A expression and tumor stages in cervical cancer (TIMER, Oncomine and GEPIA).** (**A**) Expression status of the *APOBEC3A* gene in different cancers or specific cancer subtypes was analyzed using TIMER. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. (**B**) Expression of APOBEC3A in cervical cancer explored using Oncomine. The value represents the number of unique analyses. (**C**) APOBEC3A in cervical and normal tissues from GEPIA dataset. *$p < 0.05$ (**D**) APOBEC3A in different tumor stages in cervical cancer patients from GEPIA dataset. TPM: Transcripts Per Kilobase Million. T: tumor; N: normal.

that in both normal tissues and cervical squamous cell carcinoma tissues, the expression of APOBEC3A protein was localized in the nucleus. In normal cervix and uterine tissues, the intensity was moderate, and the staining was medium. While in cervical cancer tissues, the intensity was between moderate to strong, and the staining was between medium to high (Figure S1, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=139*).

3.3. Prognostic value of APOBEC3A expression in cervical cancer patients

The prognostic value of APOBEC3A expression in cervical cancer was first explored by GEPIA, a total of 292 cases were selected. No association was found for APOBEC3A expression and OS [hazard ratio (HR) = 0.83, log-rank $p = 0.44$] (Figure 2A). At 200 months follow-up, the high APOBEC3A expression group had a significantly better disease-free survival (DFS) compared with the low APOBEC3A expression group (HR = 0.53, log-rank $p = 0.033$) (Figure 2B).

TCGA dataset analysis showed that the median survival time was 45.73 months and 21.4 months in the high expression group and low expression group, respectively. Kaplan-Meier analysis revealed that the high APOBEC3A expression group was associated with both better 10-year OS (HR = 0.62, 95% CI: 0.39-1, log-rank $p = 0.047$, Figure 2C) and RFS (HR = 0.3, 95% CI: 0.14-0.66, log-rank $p = 0.0015$, Figure 2D)

Table 1. APOBEC3A mRNA expression in different types of cervical cancer and normal cervical tissues (Oncomine).

Dataset	Tumor (cases)	Normal (cases)	Fold change	*t*-test	*p*-value
Zhai Cervix	Cervical Squamous Cell Carcinoma (21)	Cervix Squamous Epithelium (10)	1.631	1.035	0.160
	High Grade Cervical Squamous Intraepithelial Neoplasia (7)	Cervix Squamous Epithelium (10)	-2.019	-1.456	0.916
TCGA Cervix	Cervical Non-Keratinizing Squamous Cell Carcinoma (13)	Blood (93) + Cervix Uteri (3)	1.034	0.752	0.233
	Cervical Squamous Cell Carcinoma (82)	Blood (93) + Cervix Uteri (3)	-1.002	-0.107	0.543
	Cervical Keratinizing Squamous Cell Carcinoma (5)	Blood (93) + Cervix Uteri (3)	-1.033	-0.470	0.669
Scotto Cervix 2	Cervical Squamous Cell Carcinoma (32)	Cervix Squamous Epithelium (21) + Cervix Uteri (3)	-1.103	-0.291	0.614
Pyeon Multi-cancer	Cervical Cancer (20)	Cervix Uteri (8) + Oral Cavity (9) + Palate (1) + Tonsil (4)	2.010	2.002	0.026
Biewenga Cervix	Cervical Squamous Cell Carcinoma (40)	Cervix Uteri (5)	1.791	2.032	0.046
Scotto Cervix	Cervical Squamous Cell Carcinoma (79)	Cervix Squamous Epithelium (7)	1.035	1.663	0.067
	Cervical Adenocarcinoma (5)	Cervix Squamous Epithelium (7)	-1.004	-0.120	0.546

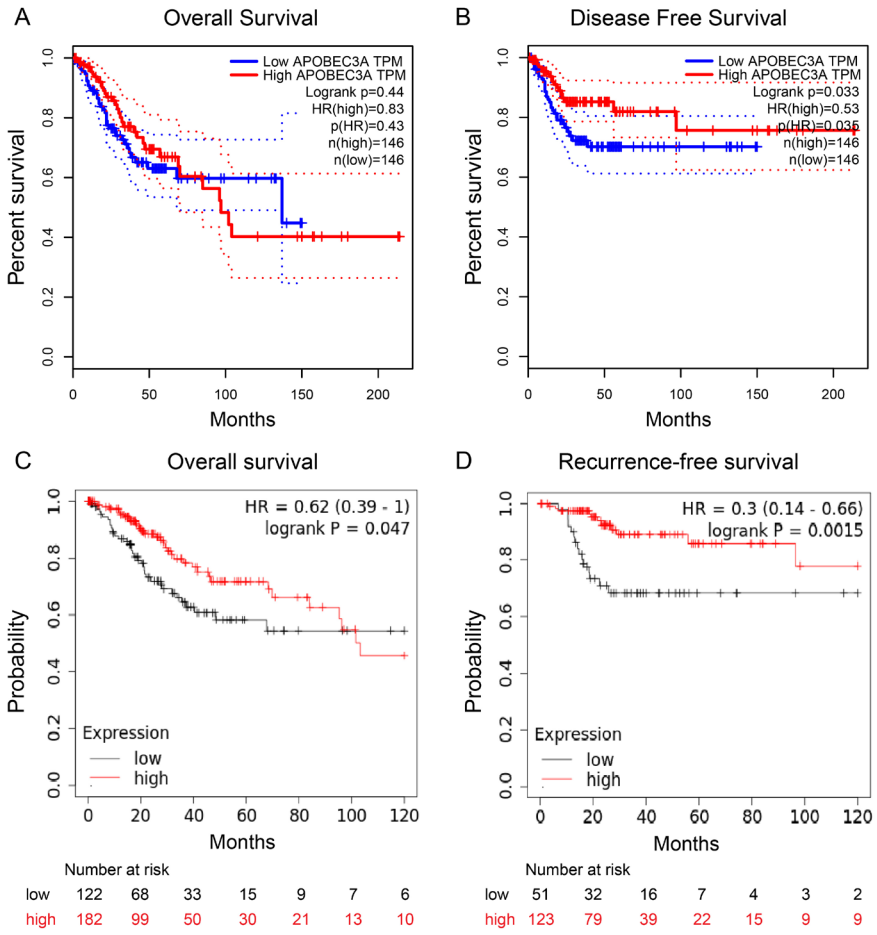

Figure 2. Prognostic value of APOBEC3A in cervical cancer (GEPIA and TCGA). (**A**) Relationship between the expression of APOBEC3A and overall survival in cervical cancer patients from GEPIA. (**B**) Relationship between the expression of APOBEC3A and disease-free survival in cervical cancer patients from GEPIA. (**C**) Relationship between the expression of APOBEC3A and overall survival in cervical cancer patients from TCGA. (**D**) Relationship between the expression of APOBEC3A and recurrence-free survival in cervical cancer patients from TCGA.

compared with the low APOBEC3A expression group.

3.4. Correlation between APOBEC3A expression and immune factors in cervical cancer

We evaluated the correlation of APOBEC3A expression and the estimated infiltration value of cancer-associated fibroblasts for the TCGA tumors of CESC (n = 306) using TIMER. The scatterplot data shows the correlation analysis of APOBEC3A expression with immune infiltration of cancer-associated fibroblasts. The APOBEC3A expression level in CESC was negatively

correlated with the infiltration level of cancer-associated fibroblasts based on EPIC, MCPCOUNTER, XCELL, and TIDE algorithms (Figure 3). The APOBEC3A expression level in CESC was positively correlated with the infiltration level of gamma delta T cells based on XCELL algorithm (rho = 0.395, p = 8.60e-12).

TISIDB database was utilized to analyze the correlations of APOBEC3A expression with tumor-infiltrating lymphocytes (TILs) and immunomodulators by Spearman correlation. Table S2 (*http://www.ddtjournal.com/action/getSupplementalData.php?ID=139*) presents detailed information of TILs, immunoinhibitors, immunostimulators, and MHCs that were significantly correlated with APOBEC3A expression in CESC.

3.5. Relationship of *APOBEC3A* SNPs with clinicopathological parameters and survival of cervical cancer patients

All patients were high-risk HPV associated cervical cancer. Table S3 (*http://www.ddtjournal.com/action/getSupplementalData.php?ID=139*) presents the clinicopathological characteristics of the 91 study patients. Briefly, most of the patients (71/91, 78%) were more than 39 years old, and about half (50/91, 54.9%) were before menopause. The majority of the patients were diagnosed as squamous cell carcinoma (82/91, 90.1%) and well differentiated (79/91, 86.8%). About 60% (n = 56) of the patients were diagnosed at the early FIGO stage (IA1-IB1), and a significant proportion of them received chemotherapy (61/91, 67%) and/or radiotherapy (56/91, 61.5%) after surgery.

In terms of associations between clinicopathological characteristics and *APOBEC3A* SNPs, only SNP rs12157810 was statistically significantly associated with FIGO stage (p = 0.02) (Table 2). Wide type of rs12157810 (AA genotype) was more prevalent in early stage (FIGO stage IA1-IB1) cervical cancer patients.

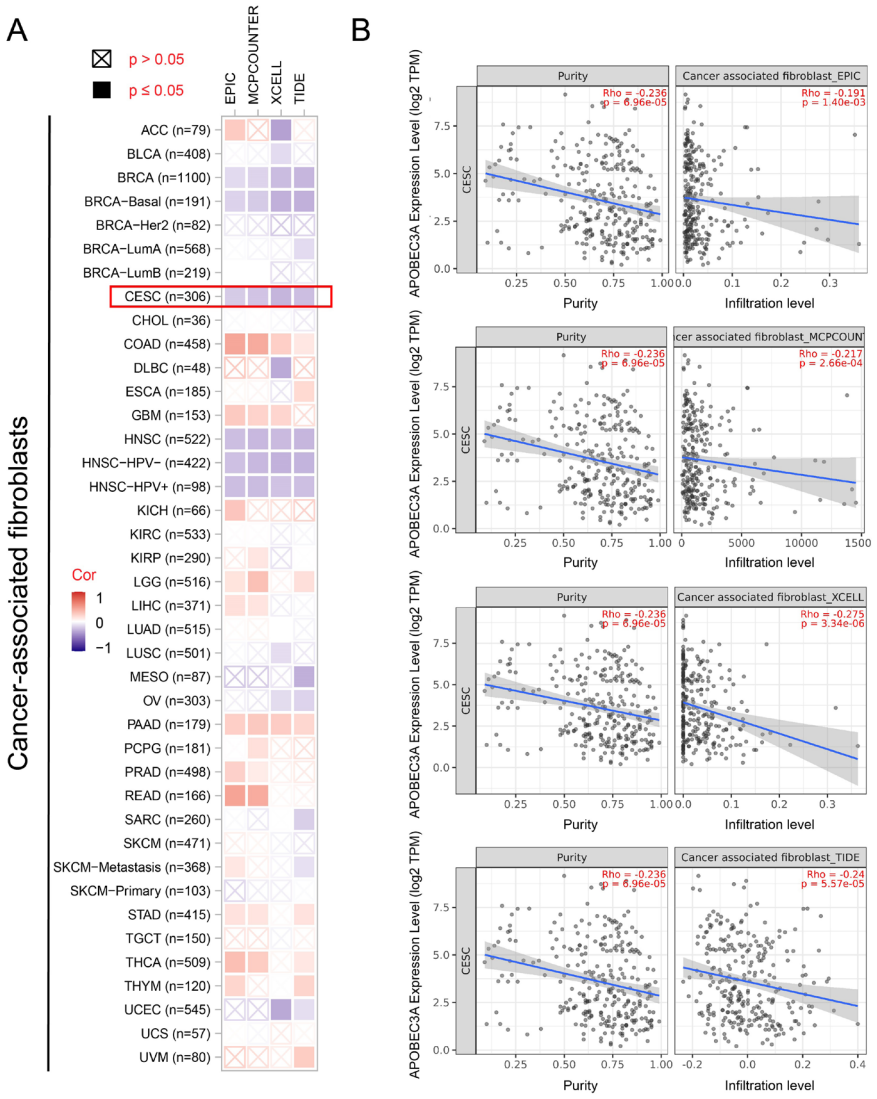

Figure 3. Correlation analysis between APOBEC3A expression and immune infiltration of cancer-associated fibroblasts (TISIDB). (A), Correlation between APOBEC3A expression and the infiltration level of cancer-associated fibroblasts based on EPIC, MCPCOUNTER, XCELL, and TIDE algorithms. **(B),** Negative correlation between APOBEC3A expression and cancer-associated fibroblasts.

After a median observation of 60 months (range 24.17-74.17 months), 3 patients had died. In general, no association was observed between *APOBEC3A* SNPs and OS in our cohort of cervical cancer patients (Figure 4).

4. Discussion

In this study, we used a series of public bioinformatics databases and tools to conduct analyses of APOBEC3A and cervical cancer. We explored a number of aspects, including gene expression, survival status, immune factors and immune infiltration, to investigate the probable mechanism of APOBEC3A in the occurrence and/or prognosis of cervical cancer. Furthermore, we tested the association of genetic polymorphisms of *APOBEC3A* with clinicophathological characteristics and survival of cervical cancer patients.

Our bioinformatics analyses showed that the expression of APOBEC3A was significantly higher in the cervical tumor tissues compared with normal tissues. *APOBEC3A*, located on chromosome 22q13.1, is a member of the cytidine deaminase gene family. It has two transcript variants encoding different isoforms. It is suggested that APOBEC3A may link immunity and viral infection during HPV-driven carcinogenesis. The protein encoded by *APOBEC3A* plays a role in immunity, by restricting viral infection (*21*). APOBEC3A protein can recognize HPV infection and restrict foreign DNA *via* catalyzing the deamination of cytosine bases in nucleic acids, causing the conversion of target cytosine (C) to uracil (U), which leads to DNA degradation. APOBEC3A may play a role in cancer development and progression through mediating the interactions between HPV and the host genome (*7*). Of the cancer types with high APOBEC3A expression

Table 2. Correlation of clinicopathological characteristics with APOBEC3A SNPs in cervical cancer patients. (*n* = 87)

Characteristics	rs12157810		*p* value*	rs12628403		*p* value*
	AA (*n* = 49)	AC+CC (*n* = 40)		AA (*n* = 13)	AC+CC (*n* = 75)	
Age			0.44			0.14
≤39	13	7		5	15	
>39	36	33		8	60	
Histology			0.55			1.00
Squamous cell carcinoma	45	35		12	67	
Adenocarcinoma	2	4		1	5	
Adenosquamous carcinoma	2	1		0	3	
Tumor size (cm)※ (*n* = 63)			0.22			0.62
≤5	30	21		6	46	
>5	5	8		2	9	
Differentiation			0.53			0.41
Well	43	35		11	65	
Moderate	1	3		0	4	
Poor	1	1		1	1	
Unknown	4	1		1	5	
FIGO stage			0.02			0.79
IA1-IB1	36	20		9	45	
IB2-IIA2	12	20		4	29	
IIB	1	0		0	1	

FIGO, Federation of Gynecologists and Obstetricians. *Fisher's exact test. ※ *n* = 64 for rs12157810 and *n* = 63 for rs12628403.

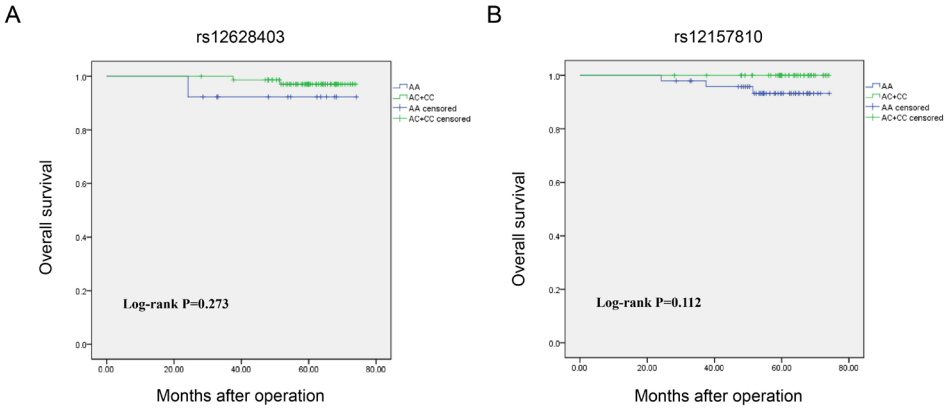

Figure 4. Association between *APOBEC3A* SNPs and overall survival in clinical samples. (**A**) Association between *APOBEC3A* rs12628403 and overall survival. (**B**) Association between *APOBEC3A* rs12157810 and overall survival.

discovered by TIMER database analyses, CESC, ESCA, and HNSC are HPV-related cancers. It is speculated that APOBEC3A may play a role in cancer occurrence *via* generating DNA mutations. Previous studies have found signature mutations of *APOBEC3A* in cervical cancer and other HPV-related tumor cancers (*22-24*). In addition, APOBEC3A was up-regulated in HPV-positive keratinocytes and cancer cells (*25,26*).

APOBEC family members are closely related to the occurrence and development of a variety of tumors. A recent meta-analysis of 20 eligible studies including 26,225 cases and 37,201 controls has reported that *APOBEC3* deletion was significantly associated with increased cancer risk in homozygous codominant inheritance model (*27*). After stratified by cancer type, the positive association was observed in breast cancer (10 studies including 14,757 cases and 17,930 controls) in heterozygous codominant, dominant, overdominant and allele inheritance models (*27*). *APOBEC3* may promote hepatocellular carcinoma (HCC) development through promoting the generation of high-risk hepatitis B virus mutations. A study by Liu *et al*. reported that *APOBEC3B* genetic polymorphisms (rs2267401-G allele) significantly increased HCC risk; and *APOBEC3B* rs2267401-GG genotype, higher APOBEC3B expression, and higher APOBEC3B/ uracil DNA glycosylase (UNG) expression ratio predicted poor prognosis of HCC patients (*19*). Our previous research has found that higher APOBEC3B expression independently predicted worse survival of ovarian cancer patients. Our cell line experiments suggested that APOBEC3B may play a role in ovarian cancer prognosis possibly *via* affecting viability of ovarian cancer (*28*).

Interestingly, our bioinformatics analyses showed that higher expression of APOBEC3A was associated with better OS and DFS/RFS. Cancer is a complex disease that results from gene-gene and gene-environment interactions. It is also very likely that the same factor may function differently at various stages of cancer development and progression. Furthermore, the favorable role of APOBEC3A expression in cervical cancer was supported by its negative association with the infiltration level of cancer-associated fibroblasts, and positive association with gamma delta T cell. As important elements constituting the tumor microenvironment, tumor-infiltrating immune cells are closely associated with cancer initiation, progression and/or metastasis (*29*). The functions of tumor-infiltrating immune cells are thought to be modulated by cancer-associated fibroblasts, which regulate cell-cell contact, release regulatory factors, and synthesize and remodel the extracellular matrix (*30*). Human gamma delta T cell is an important component of natural tumor surveillance and has the capacity for tumor cell killing. It has been a focus for the development of new cancer immunotherapy, especially for tumors lacking effective treatment (*31*). Moreover, a group of Chinese investigators studied the effect of APOBEC3A on the biological behaviors of cervical cancer using Hela cells. They found that transfection of APOBEC3A can suppress the migration ability and promote apoptosis of Hela cells, through inhibiting cell proliferation and growth (*32*). Therefore, high expression of APOBEC3A may facilitate better survival of cervical cancer patients, and may become a new therapeutic target for the treatment of cervical cancer.

Even though we detected a significant association between APOBEC3A expression and cervical cancer survival *via* bioinformatics analyses, we did not observe significant association between *APOBEC3A* polymorphisms and cervical cancer patient survival in our own clinical samples. One possible explanation is that the survival of early-stage cervical cancer is optimal, with a 4,5-year OS of about 90% for early-stage patients (*33*). We did not have enough follow-up time and enough events (only 3 deaths in our clinical samples) to detect a significant association between SNP and survival. Future prospective studies with a large sample size are needed to evaluate the associations. Functional studies are also required to further elucidate the underlying mechanisms.

5. Conclusion

To summarize, our bioinformatics analyses found that APOBEC3A expression was significantly higher in cervical cancer tissues compared with normal tissues, while high expression of APOBEC3A predicted better prognosis for cervical cancer patients. The APOBEC3A expression level in CESC was negatively correlated with the infiltration level of cancer-associated fibroblasts, and positively correlated with the infiltration level of gamma delta T cells. APOBEC3A has the potential of being used in prognostic evaluation in cervical cancer. Further studies are needed to investigate the mechanism and multilevel function of APOBEC3A in cervical cancer development and progression.

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