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Original Article

APOBEC3B expression has prognostic significance in cervical cancer

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Abstract: Objective: Cervical cancer is one of the leading fatal diseases in women, and the role of Apolipoprotein B mRNA editing enzyme catalytic subunit 3B (APOBEC3B) in cervical cancer is uncertain. Methods: Four Gene Expression Omnibus (GEO) mRNA microarray datasets were analyzed to identify differentially expressed genes (DEGs) between cervical cancer and normal cervical tissues. The results were validated using a The Cancer Genome Atlas (TCGA)-cervical cancer (CESC) dataset. Expression profiles and patients' clinical data were used to investigate the relationship between APOBEC3B expression and cervical cancer survival. APOBEC3B co-expressed genes were subjected to enrichment analyses, and correlations between APOBEC3B expression and immunologic infiltrates were investigated using Tumor Immune Estimation Resource (TIMER). We generated receiver operating characteristic curve (ROC) curves to evaluate the performance of APOBEC3B expression in predicting cervical cancer prognosis. Results: Fourteen overlapping DEGs were obtained, and APOBEC3B was chosen as a candidate gene. TCGA data further confirmed that APOBEC3B was significantly increased in cervical cancer, relative to normal adjacent tissues, and this expression was associated with poor clinical outcome. Results from quantitative real time polymerase chain reaction (RT-qPCR) and immunohistochemical staining of cervical carcinoma tissues supported these findings. Enrichment analysis showed that APOBEC3B co-expressed genes were mainly enriched in cell cycle, DNA replication and chromosomal region. Moreover, APOBEC3B expression was significantly associated with T stage, M stage, primary therapy outcome and poor clinical prognosis in cervical cancer. Similarly, APOBEC3B was closely correlated with gene markers of diverse immune cells. APOBEC3B expression was an independent indicator of cervical cancer prognosis, according to univariate Cox and ROC analyses. Conclusion: High APOBEC3B expression is strongly related to a poor prognosis in cervical cancer patients.

Keywords: APOBEC3B, cervical cancer, GEO, TCGA, bioinformatics analysis

Introduction

Cervical cancer is the fourth most diagnosed and the fourth leading cause of cancer-related deaths worldwide. In 2020 alone, roughly 604,127 new instances of cervical cancer were detected, resulting in 341,831 deaths worldwide [1]. In China, more than 110,000 new cases of cervical cancer were diagnosed in 2015 alone, among which 34,000 died from the disease. The two histologic subtypes of cervical cancer are named squamous cell carcinoma (70%) and adenocarcinoma (25%) [2]. A cervical biopsy is the most critical diagnostic procedure for cervical cancer. It is possible to use surgery, radiation, chemotherapy, targeted therapy, and immunotherapy. When cervical cancer is detected early, the relative five-year survival rate is 92%. When cervical cancer has spread to neighboring tissues, organs, or regional lymph nodes, the relative five-year survival rate is 58%. When cervical cancer has spread to distant organs, the relative five-year survival rate is 18%. The relative five-year survival rate for all cervical cancer patients is 66% [3]. Despite the development and application of multimodal treatment therapies, such as radiotherapy, chemotherapy, and surgery, clinical outcomes have remained unfavorable due to post-surgical recurrence and treatment resistance [4, 5]. Developing novel and effective

therapeutic targets and approaches is crucial in treating cervical cancer effectively.

A member of Apolipoprotein B mRNA editing enzyme catalytic (APOBEC): APOBEC3B catalyzes cytosine conversion to uracil, ultimately inducing mutations in the substrate DNA sequence. Some studies have demonstrated that APOBEC3B relates to cancer evolution and therapeutic resistance, and is associated with the burden of signature C to T mutations [6-9]. The diagnostic and prognostic implications of APOBEC3B expression in cervical cancer remain unknown.

In this study, we analyzed four mRNA datasets from GEO, namely GSE7410, GSE9570, GSE46857, and GSE63514. We identified DEGs associated with the progression of cervical cancer and patient prognosis. Next, we analyzed a TCGA dataset to identify the clinical characteristics, molecular mechanisms, and biological function of APOBEC3B expression in cervical cancer. Lastly, we utilized the TIMER and Cbioportal databases to study the association between APOBEC3B expression and immune infiltration levels, by determining the involvement of APOBEC3B in the tumor microenvironment.

Methods

Patients and specimens

Seventy cervical tissues were obtained from the Gynecology Department of Soochow University's Third Affiliated Hospital from July 2014 to September 2015. Patients diagnosed with cervical cancer were confirmed by histology, without secondary primary tumor. Inclusion criteria were: (1) patients whose cervical lesions were determined based on biopsy; (2) patients who had not undergone immunotherapy, chemotherapy, or radiotherapy. The exclusion criteria were as follows: (1) patients with a history of other malignant tumors; (2) patients with heart, kidney, and other organ failures; (3) patients with immune diseases; (4) pregnant or lactating women. Fresh samples were frozen immediately in liquid nitrogen, after excision, and stored at -80°C until use. Ethical approval following the Helsinki declaration for this study was approved by the ethics committee of Soochow University's Third Affiliated Hospital (NO: 201769). All patients voluntarily signed a written informed consent before study enrollment.

Expression datasets and bioinformatic analyses

Four GEO datasets (GSE7410, GSE9570, GSE46857, and GSE63514) were obtained and analyzed for gene expression. GSE7410 dataset comprises 40 cervical cancer tissue samples and five normal cervical tissue samples, and GSE9570 dataset has 33 cervical cancer and 12 normal cervical tissue samples. GSE46857 dataset contained 25 cervical cancer and 4 normal tissues, whereas GSE63514 dataset contained 28 cancerous and 24 normal cervical tissues, respectively. Differential expression analysis on the samples was performed using the Limma package 9.0 implemented in R software, with $P<0.01$ and $|\log(FC)| > 2$ set as the thresholds. Genes that met the criteria were considered DEGs. Next, we investigated the intersection among DEGs across the four datasets using the web tool Venny 2.1 (https://bioinfogp.cnb.csic.es/-tools/venny/).

Survival analysis and diagnostic valve of APOBEC3B expression in cervical cancer

Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/), which provides publicly accessible information on gene expression and cancer patient survival was utilized to examine APOBEC3B expression in Genotype-Tissue Expression (GTEx) and cervical cancer patients. Then, we correlated APOBEC3B expression levels with patient survival in TCGA and created Kaplan-Meier survival curves. The diagnostic value of APOBEC3B expression in cervical cancer was evaluated using ROC curves. In contrast, the area under the curve (AUC) of the ROC was calculated using ROCR R package.

Correlation between APOBEC3B expression and immune cells

To investigate the relationship between gene expression and tumor-infiltrating immune cell number, we combined RNA sequencing data

Table 1. Primer sequences

Name	Sequence (5'-3')
APOBEC3B forward primer	AGAGCGGGACAGGGACAAG
APOBEC3B reverse primer	TGTAGCTCCGACCATAGAGGAT
GAPDH forward primer	TGACTTCAAC AGCGACACCCA
GAPDH reverse primer	CACCCTGTTGCTGTAGCCAAA

from the TCGA with TIMER database (https://cistrome.shinyapps.io/timer/). Next, we selected 24 immune infiltrating cell types and correlated them with APOBEC3B expression using the Spearman correlation test.

APOBEC3B-related gene enrichment analysis

cBioPortal (http://www.cbioportal.org/) was utilized to investigate the signal pathways involving the APOBEC3B genes, The top 50 genes with a similar expression pattern to APOBEC3B (|Pearson's r| >0.3, $P<0.05$) were selected as co-expression genes. These were then subjected to Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses to determine their function.

APOBEC3B expression analysis in cervical cancer tissues

Next, we analyzed APOBEC3B protein and RNA expression levels in cervical cancer and normal cervical tissues using immunohistochemical (IHC) staining, respectively, as described earlier [10]. Briefly, formalin-fixed paraffin-embedded sections were deparaffinized, dehydrated and rehydrated, and then incubated at 4°C overnight with antibodies against APOBEC3B (cat. no. ab191695; Abcam). The following day, the sections were incubated with streptavidin peroxidase-conjugated secondary antibody (cat. no ab7171; Abcam), the slides were counterstained with hematoxylin, and then observed under a microscope. IHC scoring was based on the percentage of positive tumor cells and the staining intensity, which was graded as: 0 = negative; 1+ = weak; 2+ = medium; and 3+ = strong. The stained cell percentage was divided into three categories: 1, 0-10%, 2, 11%-50%, and 3, more than 50% stained cells. Total RNA extraction was performed as described in our previous study [11]. The RNA was then subjected to RT-qPCR using SYBR PrimerScript plus RT-PCR (Takara) performed on a Lightcycle. The housekeeping gene GAPDH was utilized as a reference gene. Relative gene expression was examined by the $2^{-\Delta\Delta Ct}$ method. Primer sequences are listed in **Table 1**.

Statistical analyses

All statistical analyses were performed using GraphPad Prism 8 or packages implemented in R (version 3.5.3). Differences in levels of APOBEC3B expression between cancerous and normal cervical tissues were analyzed using Chi-square or Fisher's exact tests. Data represent the mean ± SEM. Values with $P<0.05$ were considered statistically significant.

Results

DEGs between cancerous and normal cervical tissues

Differentially expressed genes between cervical cancer and normal tissues are presented using volcano plots (**Figure 1A-D**). We also generated Venn diagrams to depict overlapping genes and reduce bias from individual investigations. Subsequently, 14 overlapping genes, namely PRC1, CENPF, MCM2, WDHD1, CKS2, MAD2L1, SMC4, APOBEC3B, RSAD2, SPP1, ID4, MAL, CRYAB and CXCL14, were obtained across the four datasets (**Figure 1E**).

APOBEC3B mRNA expression in cervical cancer patients based on TCGA dataset

We analyzed APOBEC3B mRNA expression patterns using GTEx dataset, and found that APOBEC3B mRNA was significantly upregulated in cancer relative to normal tissues (**Figure 2**).

APOBEC3B expression was correlated with adverse clinicopathological data

To understand the significance of APOBEC3B expression, we analyzed its association with clinicopathologic data. We found that APOBEC3B mRNA expression was significantly associated with T stage ($P = 0.008$), M stage ($P = 0.042$) and primary therapy outcome ($P< 0.001$), but not with other clinicopathological data (**Table 2**).

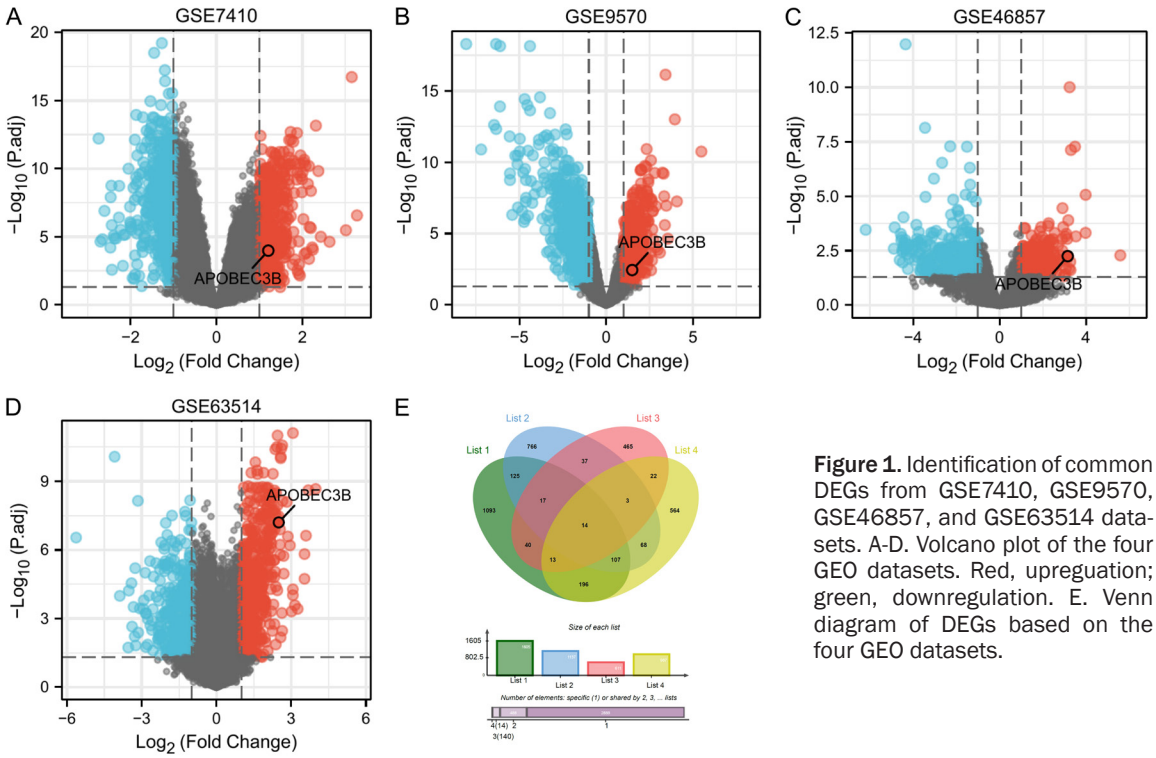

Figure 1. Identification of common DEGs from GSE7410, GSE9570, GSE46857, and GSE63514 datasets. A-D. Volcano plot of the four GEO datasets. Red, upregulation; green, downregulation. E. Venn diagram of DEGs based on the four GEO datasets.

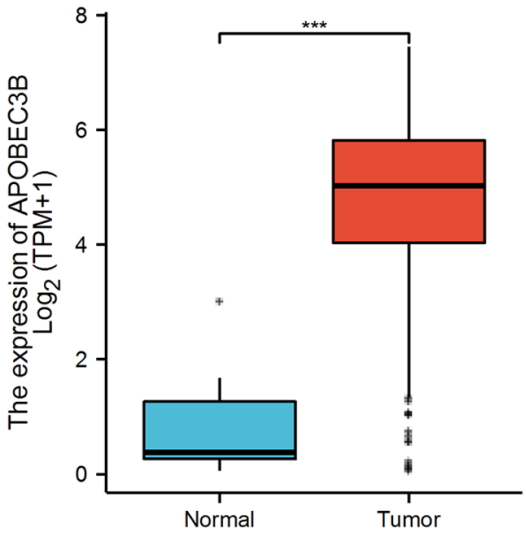

Figure 2. APOBEC3B expression in cervical cancer patients in TCGA.

APOBEC3B is upregulated in cervix cancer tissues

To validate the above results, we analyzed APOBEC3B expression levels in cervical cancer patients using IHC. Notably, APOBEC3B stained spots were mainly located in the nucleus of cells (**Figure 3A**), and the results indicated that APOBEC3B protein level was significantly upregulated in cervical cancer relative to normal cervical tissues (**Figure 3B**). These findings were supported by RT-qPCR analysis, which revealing considerably higher levels of APOBEC3B mRNA in cervical cancer than in normal cervical tissues (**Figure 3C**).

APOBEC3B has prognostic value in cervix cancer

Next, we calculated overall survival (OS), disease-specific survival (DSS) and progress free internal (PFI) to analyze APOBEC3B role in cervix cancer patients. Kaplan-Meier survival curves, based on TCGA cohort, revealed that high APOBEC3B levels were significantly associated with decreased OS (P<0.001) (**Figure 4A**), DSS (P<0.001) (**Figure 4B**) and PFI (P< 0.001) (**Figure 4C**). In addition to TNM stage, univariate Cox analysis indicated that APOBEC3B expression was an independent predictor of survival in cervical cancer patients (**Figure 4D**). The AUC of ROC was 0.97, (95% confidence interval (CI), 0.946-0.994) (**Figure 4E**).

Table 2. APOBEC3B expression in cervical cancer patients with clinical characteristics

Characteristic	Low expression of APOBEC3B	High expression of APOBEC3B	*P*
n	153	153	
T stage, n (%)			0.008*
T1	56 (23%)	84 (34.6%)	
T2	40 (16.5%)	32 (13.2%)	
T3	15 (6.2%)	6 (2.5%)	
T4	7 (2.9%)	3 (1.2%)	
N stage, n (%)			0.838
N0	60 (30.8%)	74 (37.9%)	
N1	29 (14.9%)	32 (16.4%)	
M0	52 (40.9%)	64 (50.4%)	
M1	9 (7.1%)	2 (1.6%)	
Clinical stage, n (%)			0.349
Stage I	74 (24.7%)	88 (29.4%)	
Stage II	37 (12.4%)	32 (10.7%)	
Stage III	24 (8%)	22 (7.4%)	
Stage IV	14 (4.7%)	8 (2.7%)	
Primary therapy outcome, n (%)			<0.001*
PD	20 (9.1%)	3 (1.4%)	
SD	2 (0.9%)	4 (1.8%)	
PR	6 (2.7%)	2 (0.9%)	
CR	78 (35.6%)	104 (47.5%)	

*$P<0.05$.

Functional enrichment analysis

GO functional enrichment revealed that APOBEC3B was mainly enriched in cell cycle, DNA replication and chromosomal region (**Figure 5**).

Immune cell infiltration analysis

Tumor-infiltrating immune cells are an important part of complex microenvironment, where they regulate tumor development and progression. Using TIMER database, we investigated the correlation between APOBEC3B and immune cells infiltrating the tumor microenvironment. The results revealed that APOBEC3B expression was positively associated with tumor purity (R = 0.142, *P* = 1.76e-02), $CD8^+$ T cell infiltration (R = 0.13, *P* = 3.07e-02), B cells (R = 0.106, *P* = 7.85e-02), and neutrophils (R = 0.143, *P* = 1.75e-02). Moreover, the abundance of infiltrating NK cells was negatively related to APOBEC3B expression. However, APOBEC3B expression was not significantly correlated with infiltration levels of $CD4^+$ T cells, B cells, myeloid dendritic cells, or macrophages/monocytes in cervical cancer (**Figure 6**).

Discussion

Multiple mutations are crucial to cancer development. APOBEC3B has not only been implicated in DNA mutation induction, but is also a critical endogenous source of these mutations by converting DNA cytosine to uracil. Moreover, studies have revealed that APOBEC3B initiates cancer development by uracil DNA glycosylase [12]. In this study, we analyzed mRNA expression profiles from public datasets. We found that APOBEC3B was not only highly expressed in cervical cancer tumors relative to normal adjacent tissues, but its expression was also associated with clinical characteristics. Next, we validated these results by analyzing APOBEC3B mRNA and protein expression levels in cervical cancer tissues by RT-qPCR and IHC staining. The integrated bioinformatic analysis revealed that high APOBEC3B expression levels were closely associated with some clinical characteristics, such as T stage, M stage, and primary therapy outcomes. Previous studies have revealed that APOBEC3B exerts a similar effect in other cancers, including lung cancer [13], liver cancer [14] and oral epithelial dysplasia and head and neck cancers [15]. Xia *et al.* reported that APOBEC3B was significantly enriched in tumor-node-metastasis (TNM) stage III tumors, compared to stage II or stage I tumors in gastric cancer [16]. These findings suggest that APOBEC3B is involved in cervical cancer development.

Furthermore, we explored APOBEC3B's prognostic value in cervical cancer, and found that subjects overexpressing APOBEC3B had significantly lower OS, DSS, and PFI than those with low APOBEC3B expression. Some previous studies have demonstrated that APOBEC3B

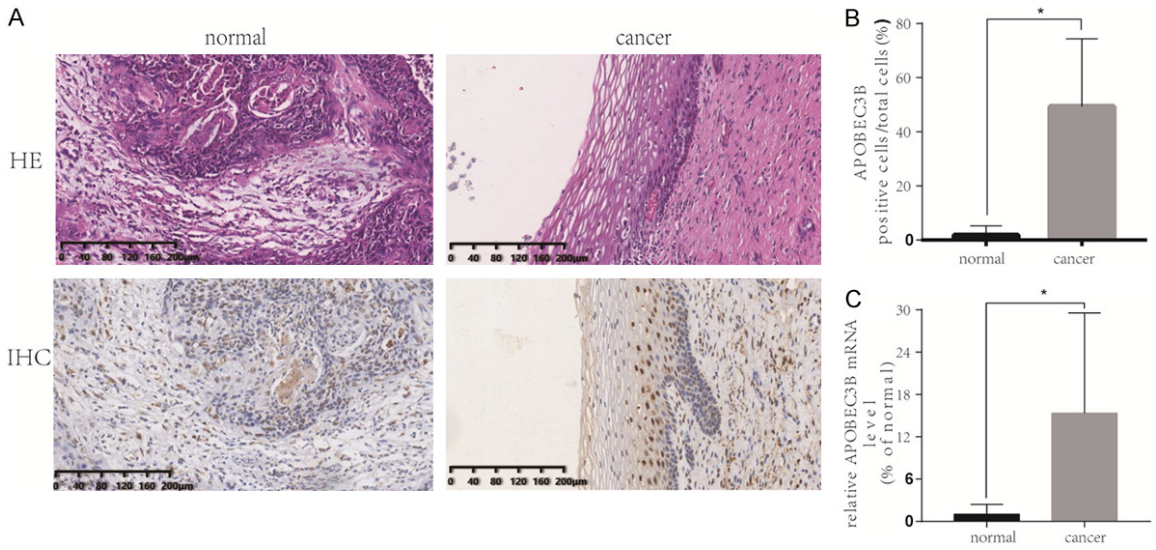

Figure 3. APOBEC3B protein and mRNA expression in cervical cancer tissues: A. H&E and immunohistochemical staining of APOBEC3B in cervical cancer tissues; B. Proportion of APOBEC3B protein positive cells; C. APOBEC3B mRNA expression in cervical cancer tissues. Data represent the mean ± SEM. Mann-Whitney test was used for the statistical analysis. *P<0.05 vs. cancer.

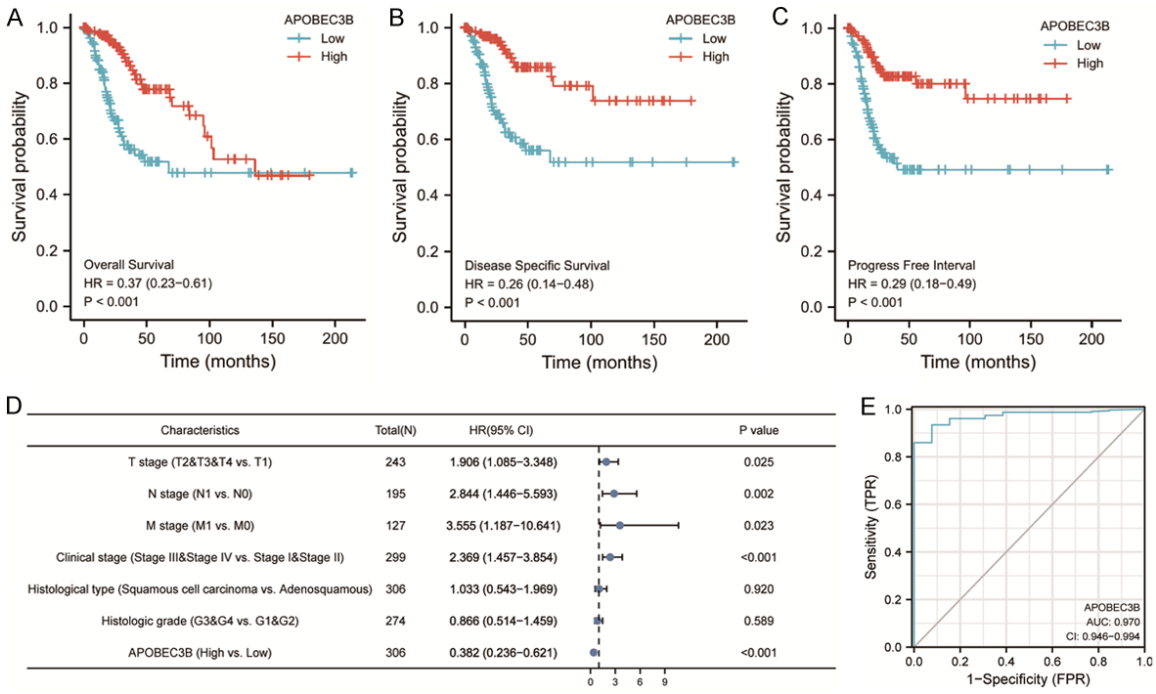

Figure 4. Impact of APOBEC3B expression on cervical cancer prognosis: (A) Overall survival; (B) Disease specific survival; (C) Progress free interval; (D) Forrest plot of univariate Cox regression analyses; (E) ROC curve was constructed to evaluate the diagnostic values of APOBEC3B for the cervical cancer patients.

expression was significantly associated with poor prognosis in some cancers, including gastric cancer, clear cell ovarian cancer [7], and breast cancer [17]. APOBEC3B could hypomethylate Cyclin D1, and promote cervical cancer cell proliferation [18]. Moreover, APOBEC3B drives DNA replication stress and chromosomal instability through incomplete repli-

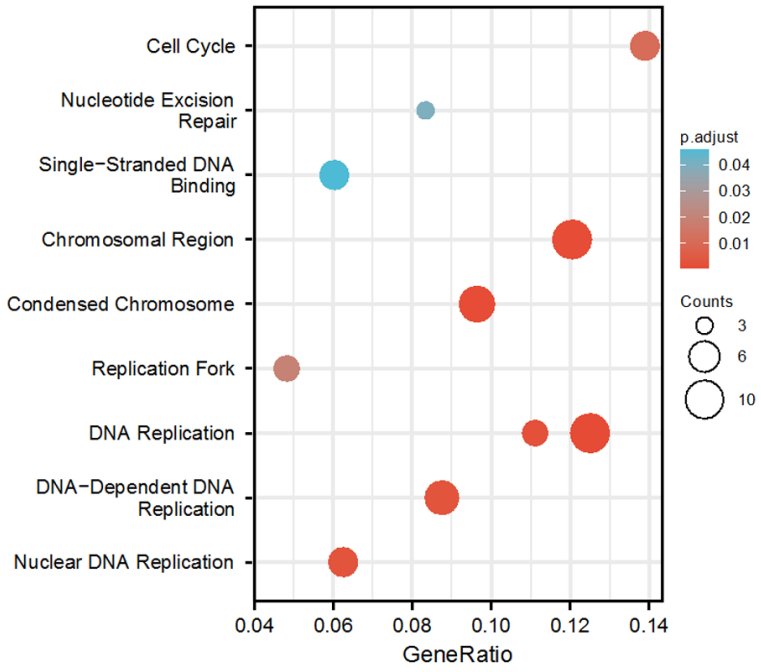

Figure 5. GO annotation enrichment analysis of APOBEC3B.

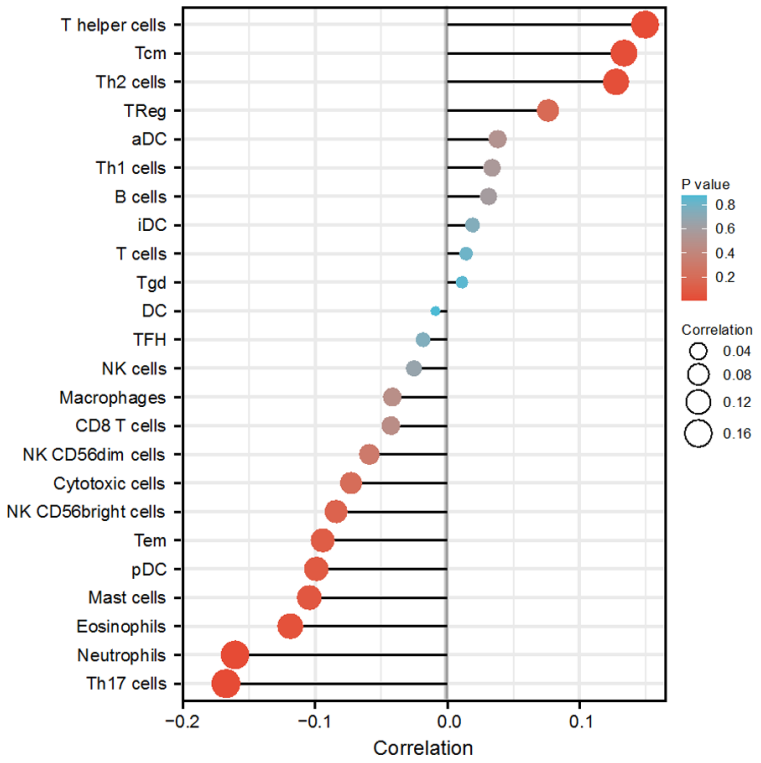

Figure 6. Relationship between APOBEC3B and tumor immune cell infiltration of cervical cancer.

cation of genomic DNA [19]. These findings implicate APOBEC3B in promoting the development of tumors, resulting in poor clinical outcome. ROC curves revealed that APOBEC3B had a high diagnostic value, suggesting that APOBEC3B could be a clinical biomarker in cervical cancer and thus has potential as a prognostic biomarker. To further explore the function of APOBEC3B, we identified its related genes, and performed functional enrichment analyses. Results revealed that DEGs were mainly enriched in the cell cycle, DNA replication, and chromosomal region, suggesting that APOBEC3B plays a role in cell proliferation. Previous studies have indicated that APOBEC3B can induce somatic mutations, which contribute to cancer pathogenesis [20-24]. A recent study revealed that APOBEC3B was predominantly expressed at the G2/M phase in myeloma and normal blood cells [25].

Tumor-infiltrating immune cells are strongly associated with tumor development, and thus could be promising prognostic biomarkers. Previous studies have shown that APOBEC3B plays a crucial role in innate immunity and is also associated with tumor-infiltrating immune cells [26, 27]. APOBEC3B upregulation through non-classical nuclear factor-κB (NF-κB) signaling promotes hepatocellular cancer growth in immunocompetent mice, associated with increased myeloid-derived suppressor cells and tumor-associated macrophages and programmed cell death 1 expressing $CD8^+$ T cells [28]. Results from the present study demonstrated that APOBEC3B expression was significantly associated with several immune infiltrating cell types in cervical cancer, consistent with a previ-

ous study which found that APOBEC3B was strongly associated with an active immune infiltration in high-grade serous ovarian cancer [29]. These findings suggest that APOBEC3B could be involved in tumor immune cell modulation, as a therapeutic target for cervical cancer.

However, there were some shortcomings. In the absence of any in vivo and in vitro experiments, it is difficult to determine the underlying mechanisms, so more research is required.

Conclusions

Integrated bioinformatic analysis and *in vitro* experiments demonstrated that APOBEC3B may be a molecular marker for poor prognosis in cervical cancer. However, further research explorations are required to validate these findings.

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Disclosure of conflict of interest

None.

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