Analysis of the Co-Pro-Cancer Mechanism of BAZ1A and BAZ2A in Cervical Cancer

Guo Jimin[1], Xue Jiarui[1], Dong Fenglin[1], Zhao Lina[1], Wang Shuqing[2*], Liu Yan[1,3*]

Background: *Through transcriptome sequencing, the common mechanism of BAZ1A and BAZ2A in promoting cancer in cervical cancer was discussed*

Methods: *The "DESeq2" package was used to screen Different Expression Genes (DEGs) in BAZ1A group and DEGs in BAZ2A group in the transcriptome sequencing results of cervical cancer. The intersection of DEGs of BAZ1A group and DEGs of BAZ2A group was used to obtain the common DEGs. Enrichment and analysis of GO (Gene Ontology), KEGG (Kyoto Encyclopedia of Genes and Genomes), and PPI networks were performed on three groups, and the core genes in each group of DEGs were screened*

Results: *There were 5662 DEGs in BAZ1A group and 6825 DEGs in BAZ2A in cervical cancer, with a total of 4147 DEGs. DEGs in BAZ1A and BAZ2A were significantly enriched in GO items including cell growth, cell migration, and apoptosis. The KEGG enrichment pathways of the three involve the cancer pathway, AMPK signaling pathway, mTOR signaling pathway, etc. PPI network analysis showed that TNF was the core gene of BAZ1A group, CD44 was the core gene of BAZ2A group and DEGs group.*

Conclusion: *In cervical cancer, both BAZ1A and BAZ2A can affect the development of cervical cancer through cell proliferation, cell differentiation, cell migration, immune response and energy metabolism.*

BACKGROUND

Cancer is a global and growing problem.[1] As the global population ages, cancer has become the leading cause of premature death and shortened life expectancy in many countries.[2] Cervical cancer is the most common gynecological malignant tumor and the fourth most common cancer among women in the world.[3] In 2020, the prevalence rate of cancer is as high as 3.1%, and about 600,000 people are diagnosed with cervical cancer, among which 110,000 people in China are seriously harmful to women's health. .Therefore, the research on the pathological mechanism and treatment scheme of cervical cancer is helpful to discover new tumor markers and treatment targets, and at the same time brings effective intervention means for the prevention and treatment of cervical cancer.[4]

Bromodomain adjacent to zinc finger domain 1A (BAZ1A) and bromodomain adjacent to zinc finger domain 2A (BAZ2A) are both members of the BAZ family.[5] BAZ1A gene encodes an accessory subunit of ATP-dependent chromatin assembly factor (ACF) and plays a regulatory role in cancer cell and normal cell senescence.[6] BAZ2A is a key component of NRC, recruiting NRC to ribosomal RNA genes, resulting in its transcriptional repression.[7] BAZ1A and BAZ2A have been found to to be associated with migration

[1]College of Life Science, North China University of Science and Technology, Tangshan 063210, China
[2]School of Public Health, North China University of Science and Technology, Tangshan 063210, China
[3]Hebei Key Laboratory of Molecular Oncology, Tangshan 063001, China
Address for correspondence to: Liu Yan, North China University of Science and Technology, Caofeidian District, Tangshan City, Hebei Province, Postal Code: 063210
(liuysm@ncst.edu.cn).

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and poor prognosis of cervical cancer cells in previous studies. Therefore, BAZ1A and BAZ2A both play a carcinogenic role in cervical cancer. In this study, transcriptome sequencing and bioinformatics were used to analyze the transcriptome sequencing results of BAZ1A and BAZ2A knockdown in cervical cancer cells. DEGs of BAZ1A group and DEGs of BAZ2A group were obtained respectively, and DEGs shared by both groups were further obtained. Gene ontology (GO), Kyoto Gene and Genome Encyclopedia Kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis and Protein-Protein interaction networks (PPI) to explore the mechanism of BAZ1A and BAZ2A co-promoting cancer in the cervix.

MATERIALS AND METHODS

Materials

Human cervical cancer Hela cells were purchased from Tianjin Cellar Co., Ltd.(cells have been STR validated) and cultured in DMEM medium (C11995500BT, Gibco) containing 10% fetal bovine serum (KY-01002, Kangyuan Bio) and 1% penicillin-streptomycin (15140122, Gibco) at 37°C in a 5% CO2 incubator 0.25% Trypsin (15140122, Gibco);35mm (353001, Corning, USA), 90mm cell culture dish (351006, Corning, USA);1×PBS (P1020, Solebo); siRNAs were purchased from Suzhou Gemma Gene Co., Ltd. (si-BAZ1A: 5'-UGUGCCUAGACCUUCAUCTT-3', si-BAZ2A: 5'-GAGAGUCAGACUAUTT-3', si-NC: 5'-UUCCGAACGUCAUTT-3').

Cell culture

Preheat the water bath to 37°C. Remove the cell cryopreservation tubes from the-80 ° C refrigerator, quickly transfer them to a water bath to thaw, shake them from time to time, accelerate the thawing until there is still a small piece of ice (3-4 mm in diameter), stop resuscitation, spray alcohol and transfer them to the biosafety cabinet. Centrifuge at 800r/min for 5 minutes, discard the cell supernatant, add freshly prepared whole medium (DMEM basal medium +10% FBS +1%, double antibody) to resuspend the cells, transfer the cell suspension to a 35mm cell culture dish, and place it in a 37°C, 5% CO2 incubator for culture. Take the cells cultured for 24h after recovery, observe the cell density and growth state under microscope, if the cell density reaches about 90%, it can be passaged; discard the cell culture medium into the waste tank, add a small amount of PBS along the side wall of the culture dish, gently shake the culture dish to make PBS fully contact with the cells, suck out and discard PBS with a pipette after washing, and repeat twice. Add trypsin for digestion, observe the state with microscope, observe that the cells are dispersed into single circles, gaps appear between cells, move like sand, and suspend in culture medium. Digestion was stopped by adding 1ml of complete medium. The cell suspension was centrifuged at 800r/min for 5 min and the supernatant discarded. Add 1ml complete culture medium to mix the cells evenly, transfer the cell suspension to a new cell culture dish at a ratio of 1:2 for expansion culture, and carry out subsequent functional experiments after the cells are propagated for more than three generations.

Transcriptome sequencing and data organization

Transcriptome sequencing and bioinformatics analysis of BAZ1A and BAZ2A control and knockdown groups were performed based on RNA-Seq technology. Hela cells transfected with si-BAZ1A and si-BAZ2A were used as experimental group, and Hela cells transfected with NC-siRNA were used as control group. Total RNA was extracted from the cell samples using Trizol reagent, and sent to Shanghai Zhongke New Life Company for transcriptome sequencing. Firstly, the extracted RNA was checked for quality. After the samples were qualified, mRNA was purified from 1μg total RNA with magnetic beads with Oligo (dT). Then fragmentation buffer was added to randomly break the mRNA. Using mRNA fragments as templates, the first cDNA chain was synthesized with random primers and reverse transcriptase, and then the second cDNA chain was synthesized with buffer, dNTPs and DNA polymerase I, and then double-stranded

cDNA was purified with AMPure XP beads. The purified double-stranded cDNA was subjected to terminal repair, A tail addition and connection to the sequencing connector, and then fragment size selection was performed with AMPure XP beads, and finally PCR enrichment was performed to obtain the final cDNA library. The inserted fragment length and effective concentration of the library were detected, and finally the sequencing was performed on the computer according to the different target sequencing data of different library. Six samples were designed for BAZ1A transcriptome analysis, including 3 samples each from control group (NCBAZ1A) and knockdown group (siBAZ1A). Using Illumina HiSeqTM2500 second-generation high-throughput sequencing platform and PE150 sequencing strategy, a total of 473600736 raw reads were measured. After quality control, 467455114 clean reads were obtained. On the whole, 49.14 ~ 106.9 million valid data were finally obtained for each sample, the average effective base number of samples was about 11.47 G, the base sequencing error rate was below 0.05%, and Q20 was 97.31%~97.65%, Q30 92.94%~93.81%, GC 52.03%~55.38%. (Table 1).

Table 1: Classification of Sequence Reads

Sample	Raw reads	Clean Reads	Clean bases (G)	Error rate (%)	Q20 (%)	Q30 (%)	Q30 (%)
NCBAZ1A1	49827004	49146384	7.23G	0.04	97.44	93.23	52.58
NCBAZ1A2	103340644	101943318	15.07G	0.04	97.31	92.94	52.03
NCBAZ1A3	106902288	105493566	15.6G	0.04	97.55	93.62	52.64
SiBAZ1A1	83283792	82224842	12.05G	0.04	97.65	93.81	55.38
SiBAZ1A2	68208858	67412154	9.85G	0.04	97.46	93.22	55.12
SiBAZ1A3	62038150	61234850	9.04G	0.04	97.34	92.99	53.56

Note: Q20, Q30: The percentage of bases with base mass fractions greater than 20 and 30 to the total bases0; GC Content: Percentage of total bases with sum of bases G and C.

Table 2: Classification of Sequence Read

Sample	Raw reads	Clean Reads	Clean bases(G)	Error rate (%)	Q20 (%)	Q30 (%)	Q30 (%)
NCBAZ2A1	49904752	49131668	7.28G	0.04	97.71	94.16	51.6
NCBAZ2A2	54010422	53322218	7.9G	0.04	97.38	93.06	51.07
NCBAZ2A3	56099736	55327916	8.15G	0.04	97.76	94.14	51.19
SiBAZ2A1	57300680	56524350	8.35G	0.04	97.85	94.42	52.05
SiBAZ2A2	51110064	50463148	7.44G	0.04	97.8	94.2	51.85
SiBAZ2A3	49904752	49131668	7.28G	0.04	97.71	94.16	51.6

BAZ2A transcriptome analysis A total of 6 samples were designed, including 3 samples from control group (NCBAZ2A) and 3 samples from knockdown group (siBAZ2A). A total of 316640082 raw reads were obtained. After quality control, 312376208 clean reads were obtained. On the whole, 4760~5652 million valid data were finally obtained for each sample, the average effective base number of samples was about 7.69G, the base sequencing error rate was below 0.05%, and Q20 was 97.38%~97.85%, Q30 93.06%~94.42%, GC 51.07%~53.02%. (Table 2). Therefore, the above results fully demonstrate that the sequencing data of the samples are good and can be used for subsequent bioinformatics analysis.

Indicator observation

Acquisition of BAZ1A group DEGs, BAZ2A group DEGs, shared DEGs; GO enrichment analysis results of BAZ1A group DEGs, BAZ2A group DEGs, shared DEGs; KEGG enrichment analysis results of BAZ1A group DEGs, BAZ2A group DEGs, shared DEGs; PPI analysis results of BAZ1A group DEGs, BAZ2A group DEGs, shared DEGs.

Data analysis

Obtain DEGs

After the samples were sequenced by RNA, R4.2.1 software was applied for analysis. The "DESeq2" package was used to analyze the difference between the sequencing results of the BAZ1A experimental group and the BAZ1A control group in cervical cancer, and the BAZ1A group DEGs was screened out. The difference between the sequencing results of BAZ2A experimental group and BAZ2A control group in cervical cancer was analyzed, and the DEGs of BAZ2A group was obtained. The "ggplot2[3.3.6], VennDiagram [1.7.3]" package was applied to screen the common DEGs of BAZ1A and BAZ2A in cervical cancer and draw the Venndiagram.

GO and KEGG enrichment analysis

GO and KEGG enrichment analysis was performed for BAZ1A group DEGs, BAZ2A group DEGs and common group DEGs using R (4.2.1) clusterProfiler [4.4.4] package. The "ggplot2 [3.3.6]" package was used to draw bar charts and bubble charts according to the analysis results.

Protein interaction network analysis

Through the STRING database (https://cn.string-db.org/), the minimum interaction score is set to a high confidence value, that is, 0.700, the nodes that are disconnected from the network are hidden, and the first 2000 DEGs in group BAZ1A and the first 2000 in group BAZ2A are constructed respectively (screening criteria: P value< 0.05, log2fold change absolute value greater than 2) DEGs, a total of 1337 groups of DEGs interaction protein network diagram. Cytoscape (3.9.1) software was used to sort according to Degree to find the core genes in each group of DEGs.

RESULTS

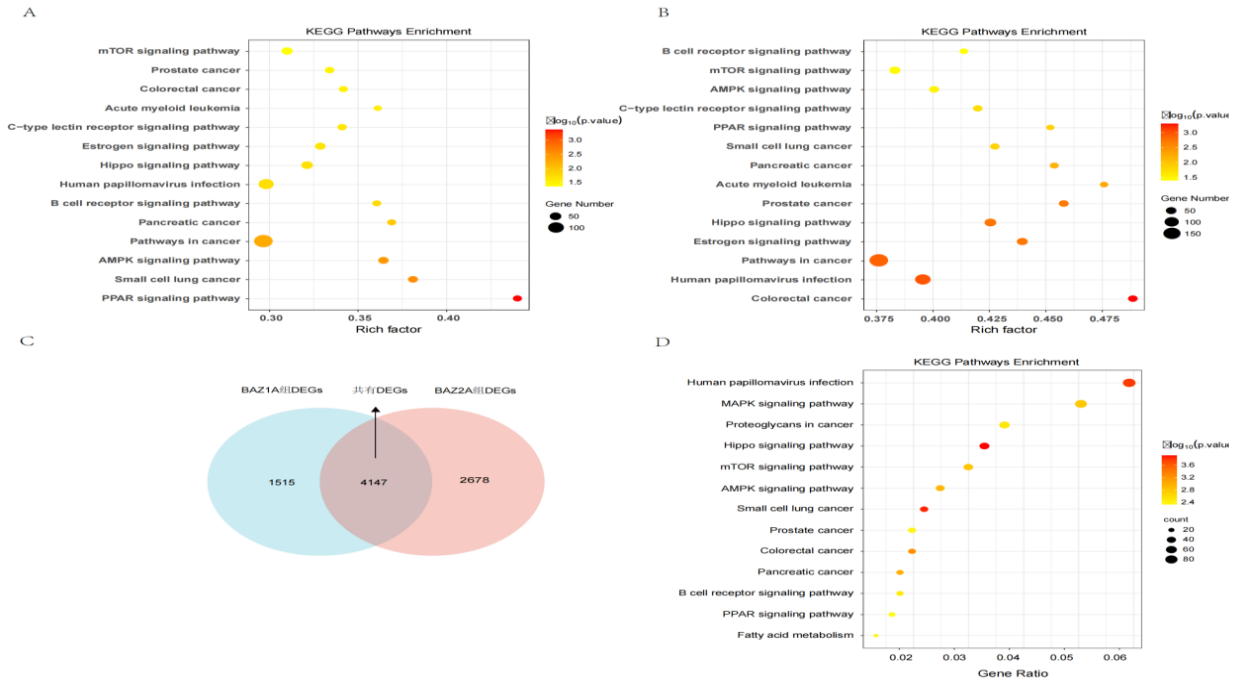
KEGG enrichment analysis results

Figure 1A and 1B show the KEGG common items enriched by DEGs in BAZ1A group and BAZ2A group respectively (P value < 0.05) in cervical cancer. The results show that in cervical cancer, both BAZ1A and BAZ2A are enriched in Colorectal cancer, Prostate cancer, Pancreatic cancer, and small cell lung cancer, Human papillomavirus infection, Pathways in cancer, Hippo signaling pathway, AMPK signaling pathway, PPAR signaling pathway, mTOR signaling pathway, B cell receptor signaling pathway, etc. (Figures 1A and 1B).

In cervical cancer, 5662 DEGs were obtained in BAZ1A group and 6825 DEGs were obtained in BAZ 2A group. Venn analysis was performed on BAZ1A DEGs and BAZ2A DEGs, and a total of 4147 DEGs were screened (Figure 1C). KEGG enrichment analysis was performed on the shared DEGs, and the enriched KEGG items (P value< 0.05) involved 13 pathways in total: Hippo signaling pathway, small cell lung cancer, human tumor virus infection, colorectal cancer, pancreatic cancer, AMPK signaling pathway, mTOR signaling pathway, MAPK signaling pathway, proteoglycans in cancer, B cell receptor signaling,

pathway, prostate cancer, fatty acid metabolism, PPAR signaling pathway (Fig. 1D).

Figure 1: Bubble diagram of KEGG enrichment analysis and Wayne diagram of DEGs



(A) KEGG enrichment analysis results of DEGs in BAZ1A group (B) KEGG enrichment analysis results of DEGs in BAZ2A group (C) KEGG enrichment analysis results of DEGs in common (D) Wayne diagram results of DEGs.

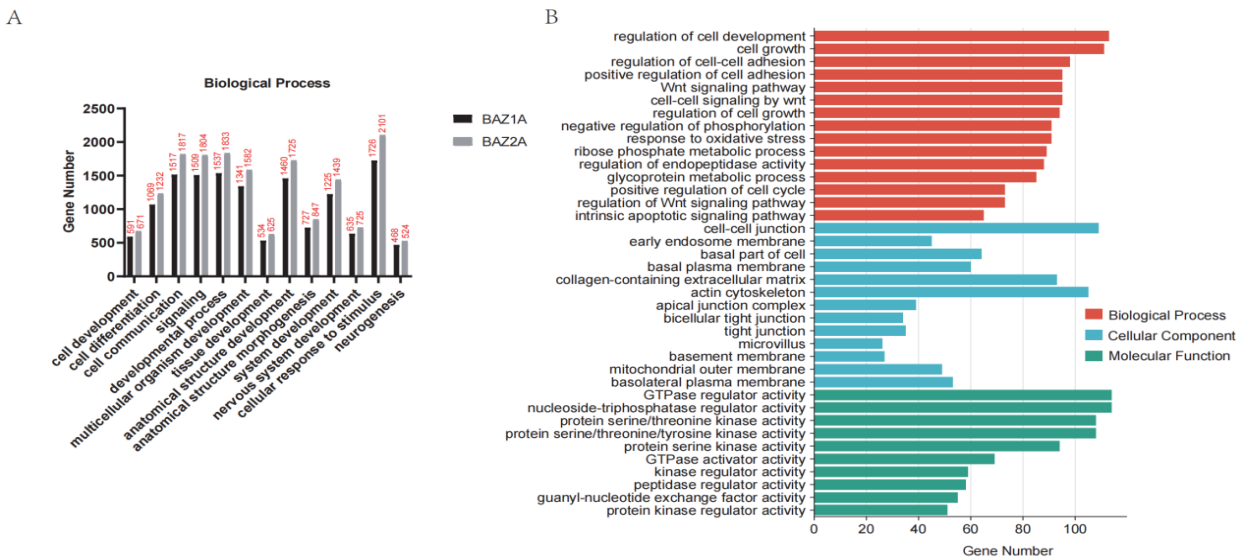
GO enrichment analysis results

The GO entries enriched by BAZ1A DEGs and BAZ2A DEGs in cervical cancer were intersected, and the common GO entries were arranged in descending order of the number of differential genes annotated under each pathway. The top 50 entries were selected. The main enrichment results under Biological Process (BP) type were as shown in Figure 3 (P value＜0.05). There were 591 BAZ1A DEGs and 671 BAZ2A DEGs enriched in Cell Development; 1069 BAZ1A DEGs and 1232 BAZ2A DEGs enriched in Cell Differentiation; and 1571 BAZ1A DEGs and 1817 BAZ2A DEGs enriched in Cell Communication. These functions are mainly involved in cell growth, differentiation and communication. Figure 2B shows the GO enrichment items with common DEGs (P value < 0.05). The classification of BP involves Wnt signaling pathway and intrinsic apoptotic signaling pathway. The enrichment results of CC, (Cellular component) items mainly involved cell-cell junction, basal part of cell, etc. The change of Molecular function MF (Molecular function) is mainly manifested in GTPase regulator activity and protein serine/threonine/tyrosine kinase activity, etc.

Differential Gene Protein Interaction Network Analysis

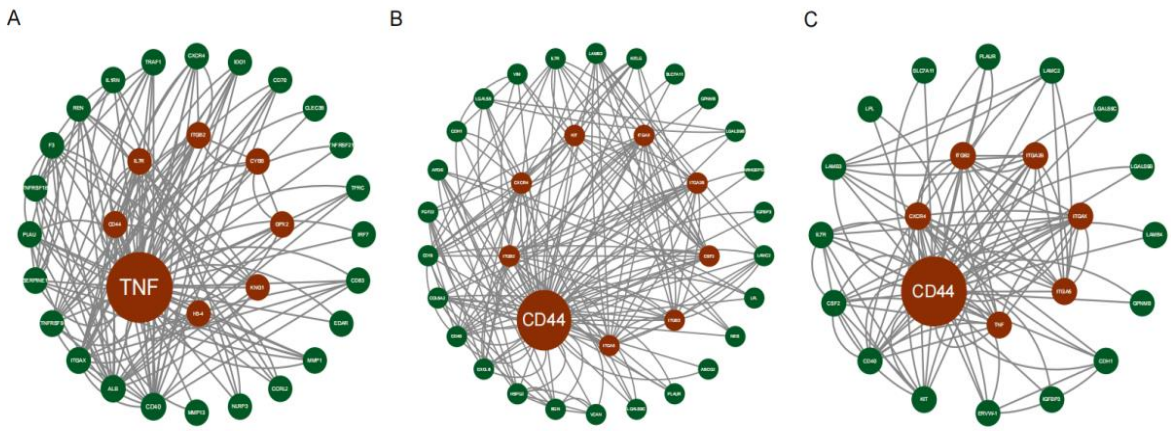
In cervical cancer, the screened top 2000 BAZ1A group DEGs, BAZ2A group DEGs and consensus DEGs were introduced into STRING database, and one core gene, tumor necrosis factor (TNF), was screened from PPI network map generated by BAZ1A group; one core gene, cluster of differentiation (CD44), was screened from PPI network map generated by BAZ2A group; and one core gene, cluster of differentiation 44, was screened from PPI network map generated by consensus group.

Figure2: GO enrichment analysis plot



(A) GO enrichment of DEGs in BAZ1A and BAZ2A DGEs, common BP entries. (B) GO enrichment entries for shared DEGs.

Figure3: PPI network analysis results



(A) PPI network diagram of TNF machine-related genes in BAZ1A group (B) PPI network diagram of CD44 and its related genes in BAZ2A group (C) PPI network diagram of CD44 and its related genes in group BAZ2A.

CD44 receptors are overexpressed in a variety of solid tumors[8]and are involved in collagen, laminin and fibronectin interactions for cell adhesion[9], which are critical for tumor cell migration and motility. It has also been found that HA-CD44 pathway plays an important role in cervical cancer CC[10]. The screened DEGs interacting with core genes were reintroduced into Cytoscape software to generate a new PPI network map of genes interacting with core genes, as shown in Figure 3.

CONCLUSIONS

BAZ1A has been reported to regulate the ATPase activity of ACF complex and promote DNA damage repair,[11] nerve development[12] and cell senescence. Disorder of BAZ1A can lead to many diseases, especially cancer. It has high expression levels in breast cancer, lung cancer and other cancer types,[13,14] and is associated with lower overall survival (OS). Therefore, BAZ1A is often considered a potential target for related diseases.[15] BAZ2A is predominantly localized in nucleoli in differentiated cells, binds to ribosomal RNA (rRNA) genes and establishes its epigenetic silence.[16,17] It has been proved that BAZ2A is highly expressed in many kinds of cancers, which is related to promoting tumor cell proliferation, migration and prognosis.[18,19] For example, in prostate cancer, overexpression of BAZ2A is associated with disease recurrence;[20]

In this study, a comprehensive analysis of DEGs in the BAZ1A group, DEGs in the BAZ2A group and common DEGs in cervical cancer was conducted, and it was found that BAZ1A and BAZ2A were involved in the pathogenesis of multiple cancers. In addition, the KEGG concentration of the three is correlated with AMPK signal pathway, mTOR signal pathway, Hippo signal pathway and PPAR signal pathway. Among them, activated mTOR signaling pathway not only regulates gene transcription and protein synthesis, regulates cell proliferation and immune cell differentiation, but also plays an important role in tumor metabolism;[21] abnormal transduction of Hippo signaling pathway is related to cell proliferation, cancer stem cell characteristics, chemotherapy resistance and metastasis ability;[22] AMPK/PPAR signaling pathway is also related to cell metastasis and cell invasion.[23] Therefore, the above signaling pathways can regulate cell proliferation, differentiation, apoptosis and migration phenotype. Comprehensive analysis of GO enrichment results of BAZ1A DEGs, BAZ2A DEGs and common DEGs in cervical cancer showed that the common BP entries of BAZ1A and BAZ2A DEGs were mainly involved in cell proliferation, cell migration and cell adhesion. Previous studies have shown that down-regulation of BAZ1A and BAZ2A expression in cervical cancer can inhibit proliferation, migration and up-regulate apoptosis. After PPI analysis of BAZ1A group, BAZ2A group and consensus DEGs, the same core gene CD44 was obtained in the latter two groups. CD44 is a complex transmembrane adhesion glycoprotein,[24] which is involved in various physiological processes, such as organ development, multiple immune functions, cell differentiation, proliferation, adhesion and migration.[25] In addition, CD44, as an important regulator of epithelial-mesenchymal transition program,[26] is involved in the occurrence and development of various tumors, and significantly affects its invasion and metastasis in breast cancer,[27]lung adenocarcinoma,[28] prostate cancer[29]and endometrial cancer.[30]

In conclusion, transcriptome sequencing was used to analyze the changes of BAZ1A and BAZ2A transcription levels after knockdown in cervical cancer, and it was concluded that BAZ1A and BAZ2A share a common cancer-promoting mechanism, including promoting cancer proliferation, migration and movement, and inhibiting cancer cell apoptosis.

DECLARATIONS

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Authors' contributions

LY and WSQ conceived and designed the study. ZLN prepares experimental materials. GJM analyzed the data. GJM wrote the manuscript. GJM, XJR and DFL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest to report regarding the present study.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable

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