Bioinformatics evaluation of the circRNA–miRNA–mRNA axis in cervical squamous cell carcinoma

Murat KAYA*

Division of Medical Genetics, Department of Internal Medicine, Istanbul Faculty of Medicine Istanbul University, 34093 Istanbul, Turkey

*Correspondence: Murat KAYA, Division of Medical Genetics, Department of Internal Medicine, Istanbul Faculty of Medicine Istanbul University, Istanbul, Turkey. kmurat@istanbul.edu.tr

Abstract

Aim: Cervical squamous cell carcinoma (CESC) is a highly prevalent women's gynecologic disease. Because the specific mechanisms associated with the illness are still mostly unclear, more investigation is needed to comprehend the triggers of CESC's initiation and progression. Circular RNAs (circRNAs) are a new type of RNA that control microRNAs' (miRNAs) expressions. Although particular circRNA–miRNA–mRNA regulatory axes for CESC have been defined, little is known about this field of research. Therefore, the current study aimed to identify new circRNA–miRNA–mRNA axes in CESC.

Methods: GSE102686 and GSE169057 GEO datasets were utilized to identify differentially expressed circRNAs (DEcircRNAs). The Cancer Genome Atlas (TCGA) database was used to detect differentially expressed miRNAs (DEmiRs) and mRNAs (DEmRNAs). Various in silico tools were used to identify interactions between circRNAs, miRNAs, and their potential target genes in CESC. Moreover, enrichment analysis, correlation analysis, and survival analysis were performed on potential target genes.

Results: Utilizing publically available data, we found dysregulated circRNAs, miRNAs, and mRNAs in CESC. We showed that the circRNA hsa_circ_0000711 may be involved in the CESC process by inhibiting many target genes via hsa-miR-338-3p and/or hsa-miR-361-3p. Moreover, we found that hsa_circ_0000515 circRNA can contribute to CESC by modulating the expression of some target genes via hsa-miR-296-5p.

Conclusions: The findings of this work contribute to a better understanding of the circRNA–miRNA–mRNA regulation processes in CESC.

Keywords

Introduction

Cervical cancer (CC) is the fourth most common female malignancy. CC death rates rise every year because of a lack of early detection [1, 2]. Despite surgery, radiation, or chemotherapy optioning for 80% of initial

stages CC cases, there is still an enormous percentage of advanced-stage individuals who have poor outcomes [3]. The most prevalent histological subgroup of CC is cervical squamous cell carcinoma (CESC) [4]. The main serious issues with CESC are metastasis and recurrence. Because the particular pathways remain unclear, more study into the underlying tumor initiation and development processes is required for CESC [3, 4]. Non-coding RNAs are well-known actors in cancer biology, serving as a critical part of gene regulation that, when disrupted, contributes to the development of cancer [5]. microRNAs (miRNAs), which are non-coding RNAs with a length of around 20–25 nucleotides, function as critical regulators in the cell by controlling target genes' expressions [6, 7]. Circular RNAs (circRNAs) are covalently closed, endogenous biomolecules in cells with tissue-specific and cell-specific expression patterns that function through specific miRNAs [5, 8, 9]. Unlike ordinary linear RNA, circRNAs have a characteristic closed-loop structure [10]. As a result, circRNAs are resistant to destruction and are expressed in a wide range of organisms. Following miRNA binding by miRNA response elements (MREs), circRNAs may be essential in tumor development as tumor suppressors or proto-oncogenes [11, 12]. Determining the circRNA–miRNA–mRNA axes is critical for understanding the molecular mechanism of cancers. For instance, circ_VPRBP has been found to reduce cell proliferation, migration, and invasion and also induce CC cell apoptosis via modulating the miR-93-5p/*FRMD6* [13]. circRNA_101996 has been shown to increase the development of CC by influencing the miR-1236-3p/*TRIM37* axis [14]. In another investigation, circRNA_400029 has been shown to increase the aggressiveness of CC by controlling the miR-1285-3p/*TLN1* axis. Recent studies have uncovered several circRNA–miRNA–mRNA pathways in CC. However, we are still in the early stages of unraveling the complicated interactions between thousands of circRNAs, miRNAs, and mRNAs found in the cells. Therefore, in the current study circRNA–miRNA–mRNA axes were investigated using various bioinformatics data.

Materials and methods

Selection criteria for circRNA–miRNA–mRNA interactions

The recognized functioning principles of the circRNA–miRNA–mRNA axis guided the selection. Before selecting circRNAs, miRNAs, and mRNAs from the relevant Gene Expression Omnibus (GEO) datasets, Log2 Fold Change (log2FC) and *p*-values were considered. The overexpressed circRNAs were the intended focus of this research. Downregulated miRNAs were considered for sponge miRNAs. The selection of mRNAs was also limited to elevated ones.

GEO is a publicly available functional genomic data resource. Microarrays or sequence-based studies are accepted. Users can use the supplied tools to query and download experiments and determine gene expression profiles. Identifying molecules (circRNA, miRNA, mRNA, etc.) whose expressions alter in common among various datasets may be useful to obtain more accurate information about the association between these molecules and diseases before in vitro or in vivo studies.

Identification of circRNAs

Gene Expression Omnibus 2R (GEO2R) is an interactive web application that enables users to compare two or more sets of samples from a GEO series to find differentially expressed genes, miRNAs, circRNAs, etc. GSE102686 dataset (including 5 CC patient's tissue samples and 5 adjacent normal tissue samples) and GSE169057 (including 3 CC patient tissue samples and 3 adjacent normal tissue samples) datasets were downloaded from the National Center for Biotechnology Information (NCBI) Geodatabase and the differential expression of circRNAs between tumor and normal samples was analyzed via GEO2R. When selecting upregulated circRNAs from the datasets, first we paid attention to the log2FC and *p*-value of circRNAs (log2FC > 1, *p* < 0.001). circRNAs that met these criteria and overlapped in both datasets were selected.

Detection of miRNAs

The Cancer Genome Atlas (TCGA) (https://cancergenome.nih.gov/) is a fundamental cancer genomics program, that molecularly analyzed approximately 20,000 primary cancers and matched normal samples

from 33 different types of cancer. In the TCGA database, miRNAs with log2FC > 2 and $p < 0.05$ were identified in 307 CESC tissue samples and matched 3 normal tissue samples. UALCAN [15] and CancerMIRNome [16] are user-friendly platforms for investigating miRNA dysregulation in various cancer samples from the TCGA. For miRNA expression analysis these web tools were used.

mRNA selection

The Gene Expression Profiling Interactive Analysis (GEPIA2) [17] is beneficial and well accepted online tool for gene expression, survival analysis, etc., using tumor and normal specimens from the TCGA and Genotype-Tissue Expression (GTEx) databases. Overexpressed genes with log2FC > 2 and $p < 0.01$ criterion were chosen in TCGA constructed from 307 CESC patients and 3 adjacent normal tissue samples using GEPIA2 tool (ANOVA method was selected using GEPIA2 tool).

Determination of circRNA–miRNA–mRNA interaction

circRNA interactome (CircInteractome) identifies miRNAs that might possibly target the circRNAs using the Targetscan prediction tool [18]. The CircInteractome web tool was used to identify potential sponge miRNAs of selected circRNAs from the GSE102686 and GSE169057 datasets. miRNet 2.0 is a user-friendly, web-based tool that integrates user data with existing information using network-based visual analytics to assist in unraveling miRNA functions [19]. The putative target genes of the selected miRNAs were defined via miRNet 2.0. Then, those matched genes with the log2FC > 2, $p < 0.01$ criterion in the TCGA database were chosen.

Enrichment analysis

The biological processes, cellular components, and molecular activities in which the selected genes were involved were determined by creating the EnrichR tool (https://maayanlab.cloud/Enrichr/, pathways with $p < 0.05$ were considered).

Correlation analysis

Selected genes' correlation analysis was constructed via Correlation AnalyzeR [20] and GEPIA2 (http://gepia2.cancer-pku.cn/) tools.

Survival analysis

Kaplan-Meier plotter (KM plotter) is an online platform for determining genes/miRNAs' expression and survival rates in many cancer types. It also enables publicly accessible transcriptome data, such as TCGA. The prognostic values of chosen miRNAs in CESC were determined utilizing the KM plotter database. In brief, the miRNAs were entered into the database. Then KM survival plots were constructed, with the hazard ratio (HR), 95% confidence intervals (CI), and log-rank p-value provided on the website. $p < 0.05$ were considered statistically significant.

Statistical analysis

Publicly available platforms were used to conduct functional enrichment assessments. When choosing upregulated circRNAs from the datasets, we evaluated the log2FC and p-value (for GSE102686 analysis: log2FC > 1, $p < 0.001$; for GSE169057 dataset: log2FC > 1; $p < 0.001$). For DEmiRs log2FC > 2 and $p < 0.05$; overexpressed genes with log2FC > 2 and $p < 0.001$ were used. The KM method was utilized for determining overall survival (OS), and the log-rank test was used to determine differences (via KM plotter tool). The statistical cut-off for OS analysis and enrichment analysis in tools was set at a $p < 0.05$. GraphPad Prism 10 was employed to perform statistical calculations and visualize figures.

Results

circRNA identification

In GSE102686, 137 upregulated circRNAs met the log2FC > 1, $p < 0.001$ criteria among the circRNAs whose expression changed in cancer tissue samples compared to normal tissue samples; in GSE169057, 145

upregulated circRNAs met the log2FC > 1, $p < 0.001$ condition. In both datasets, three overlapping circRNAs (hsa_circ_0000711, hsa_circ_0000515, and hsa_circ_0001855) have been chosen by the required parameters (Table 1).

Table 1. Overlapping circRNAs between GSE169057 and GSE102686 datasets

circBase ID	GSE169057		GSE102686	
	p-value	log2FC	log2FC	*p*-value
hsa_circ_0000711	4.28e–02	1.57	1.37	7.30e–02
hsa_circ_0000515	3.66e–03	3.75	1.28	4.39e–06
hsa_circ_0001855	2.99e–02	1.79	1.02	4.52e–02

miRNA selection results

Following study on the circinteractome tool that suggested potential targets of the three selected circRNAs, 26 miRNAs were identified as common targets as seen in Figure 1. Three hundred fifty-nine upregulated miRNAs met the log2FC > 2 and $p < 0.05$ requirements in the TCGA database in CESC tissue samples compared to normal tissues. The 26 miRNAs were screened among these 359 miRNAs to detect overlapping miRNAs. Six possibly sponge miRNAs were overlapped. Among these 6 miRNAs, 3 miRNAs (hsa-miR-296-5p, hsa-miR-338-3p, and hsa-miR-361-3p) with decreased expression were selected (because selected circRNAs were upregulated) (Table 2).
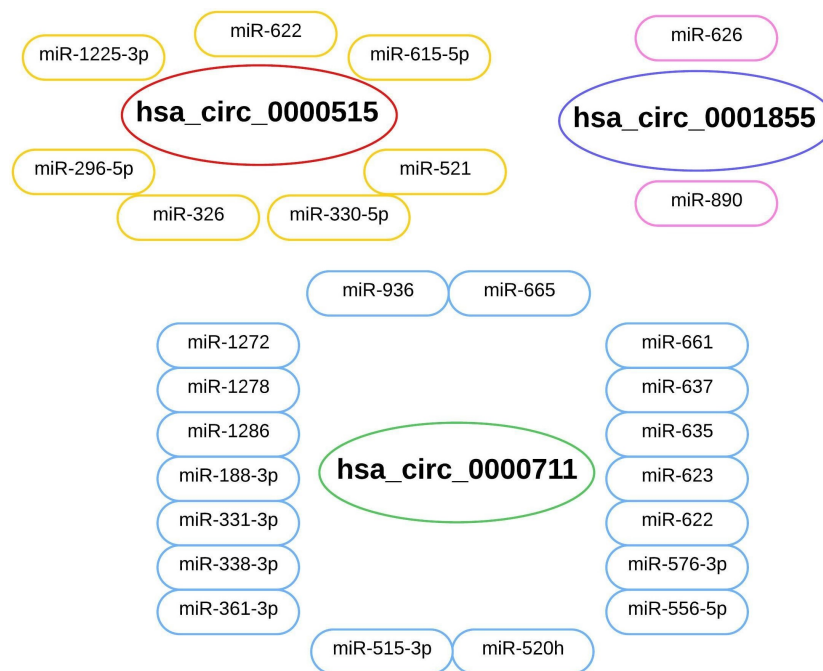

Figure 1. Potential sponge miRNAs of three hsa_circRNAs. According to the circinteractome and circMine tools, it is estimated that hsa_circ_0000711 has 18 potential sponge miRNAs, hsa_circ_0000515 has 7 potential sponge miRNAs, and hsa_circ_0001855 has 2 potential sponge miRNAs

Table 2. Overlapping miRNAs between TCGA database and selected upregulated circRNAs' potential sponge miRNAs in circinteractome and circMine tools

miRNAs	Log2FC	Adj. *p*-value
hsa-miR-296-5p	–2.18	1.43e–12
hsa-miR-326	2.12	1.39e–33
hsa-miR-330-5p	5.41	1.27e–21
hsa-miR-331-3p	4.47	2.40e–12
hsa-miR-338-3p	–8.9	3.75e–15
hsa-miR-361-3p	–7.72	1.45e–28

mRNAs analysis results

Among the overexpressed genes in CESC tumors compared to normal tissues in the TCGA database, it was defined that 778 genes met the conditions of log2FC > 2 and $p < 0.05$.

circRNA–miRNA–mRNA interaction results

Using miRNet 2.0 and miRTarBase v8, the target genes of the 3 selected miRNAs were examined and 355 genes matching these miRNAs were identified (Figure 2). Seven hundred seventy-eight genes which were identified from the TCGA database were compared to 355 genes shown as probable targets of 3 chosen miRNAs, in the end, 10 overlapping genes were selected (Table 3). The heatmap of these 10 genes that are upregulated in CESC is shown in Figure 3. In summary, three circRNAs were chosen because they had the potential to regulate the expression of ten genes via three miRNAs.
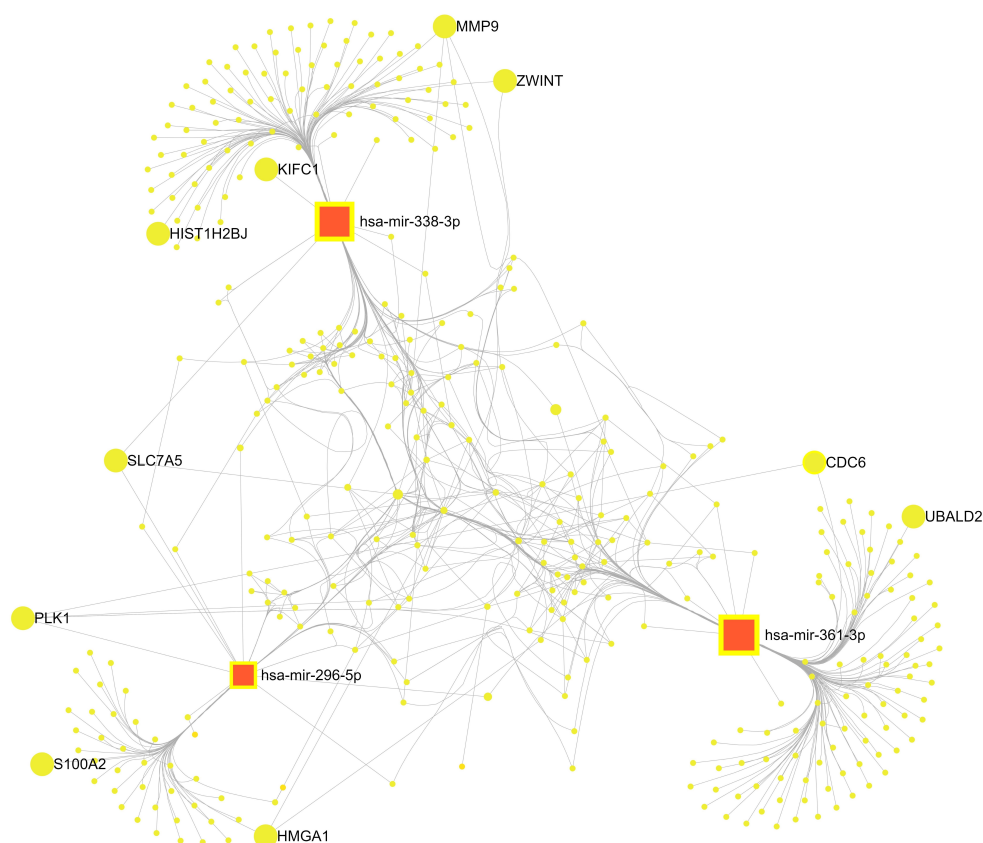

Figure 2. Three selected miRNAs and their possible target genes: a complicated network. Red squares represent selected miRNAs, yellow circles represent possible target genes whereas big yellow circles represent overlapping genes. The figure was created utilizing the miRTarbase v8. and miRNet tools. A $p < 0.05$ value was used to determine significances

Table 3. Selected 10 upregulated genes that could be potential targets for selected downregulated 3 miRNAs

| Gene	Approved name	Log2FC	Adj. p-value
S100A2	S100 calcium binding protein A2	9.183	2.74e–11
ZWINT	ZW10 interacting kinetochore protein	5.099	1.16e–43
KIFC1	Kinesin family member C1	4.492	6.97e–47
MMP9	Matrix metallopeptidase 9	3.920	1.01e–9
PLK1	Polo like kinase 1	3.732	9.80e–32
CDC6	Cell division cycle 6	3.678	2.47e–29
HMGA1	High mobility group AT-hook 1	3.585	4.56e–26
SLC7A5	Solute carrier family 7 member 5	2.941	4.60e–7
HIST1H2BJ	H2B clustered histone 11	2.333	2.42e–4
UBALD2	UBA like domain containing 2	2.190	1.81e–17
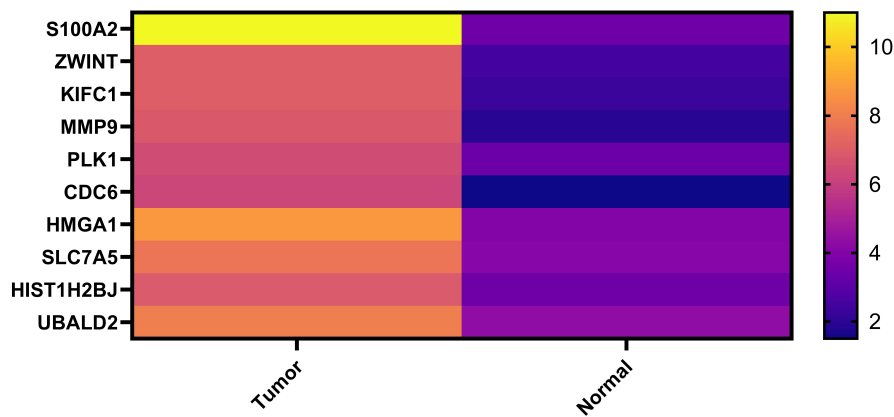
Figure 3. Heatmap image of selected genes. All selected genes were overexpressed in CESC samples. (Tumor and normal samples were compared in heatmap analysis: TCGA Tumor samples vs. TCGA normal and GTEx normal tissue samples)

Enrichment analysis results

Pathway analysis showed that selected potential 10 target genes have been associated with many critical molecular cellular processes like cell cycle, and DNA replication Figure 4A. Enrichment analysis results showed that these genes could have crucial roles in the cancer process as seen in Figure 4B. They are also connected with many essential hub proteins, including the *MYC* oncogene and the *TP53* tumor suppressor gene, as demonstrated in Figure 4C. A correlation study of selected genes revealed that four of them are connected with *CDK1* and *CDK2* genes, which are known key cancer-related genes in CESC, as can be seen in Figure 5.
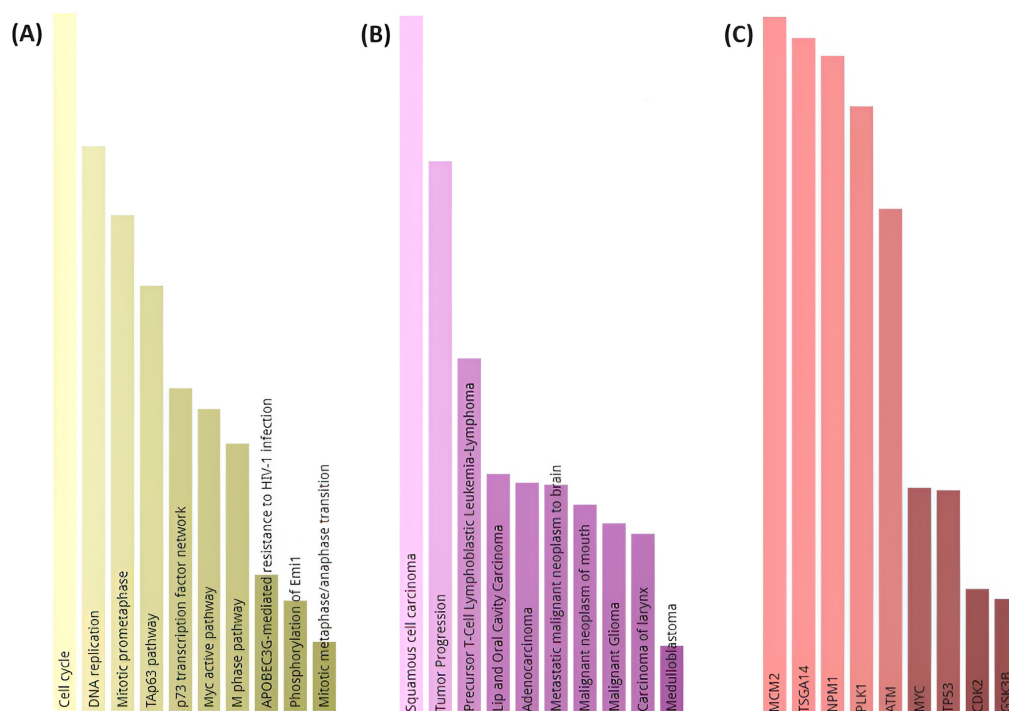

Figure 4. Enrichment analysis. (A) Selected potential 10 target genes have been linked to various fundamental molecular cellular processes. (B) Selected genes have been found to be related to many cancers according to the Disgenet database. (C) Hub proteins of selected 10 genes (Figure has been created using Enrichr. $p < 0.05$ for each of the figure's bars)

Expression change in selected miRNAs may affect overall survival

The all 3 selected miRNAs were found to have reduced expression in CESC samples compared to the control group (Figure 6). OS analysis in TCGA for CESC patients was performed for 3 selected miRNAs and 10 genes. It was found that the miR-361-3p and miR-296-5p miRNAs have prognostic importance for the OS rate of CESC patients (Figure 7). However, any one of the genes did not have a statistically significant effect on the OS of the CESC patients.
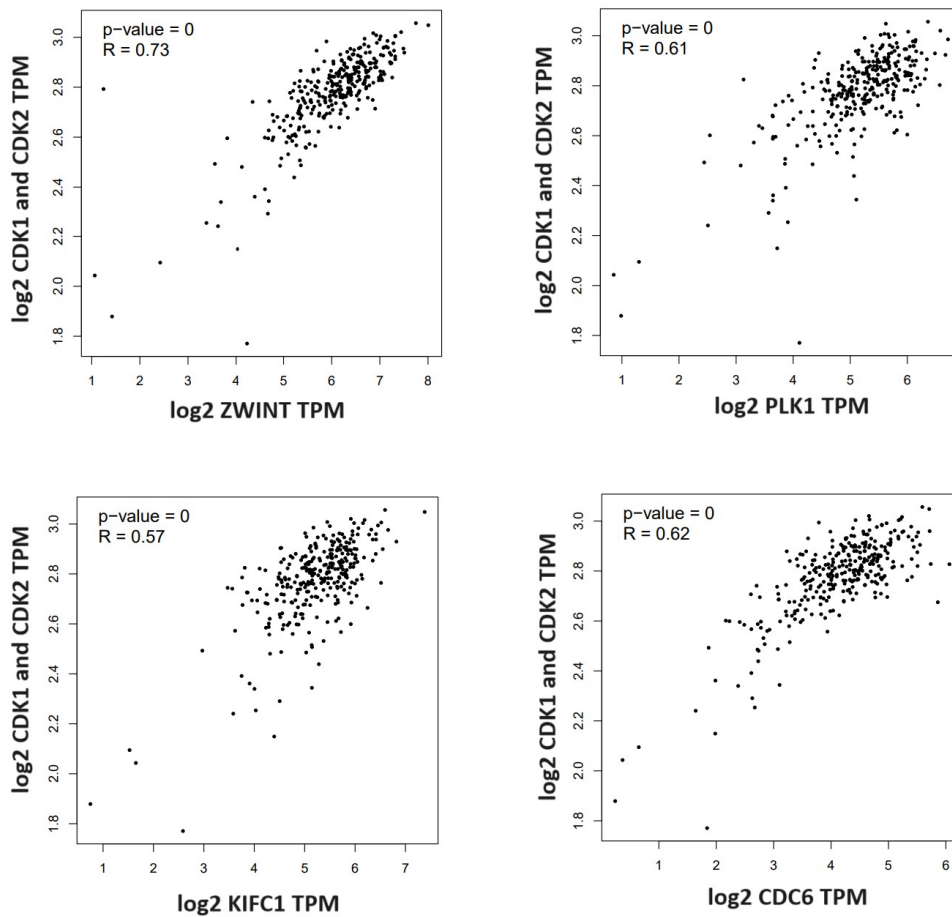
Figure 5. Selected target genes' correlation analysis with *CDK1* and *CDK2* genes. *ZWINT1*, *PLK1*, *KIFC1* and *CDC6* genes found to be correlated with *CDK1* and *CDK2* genes
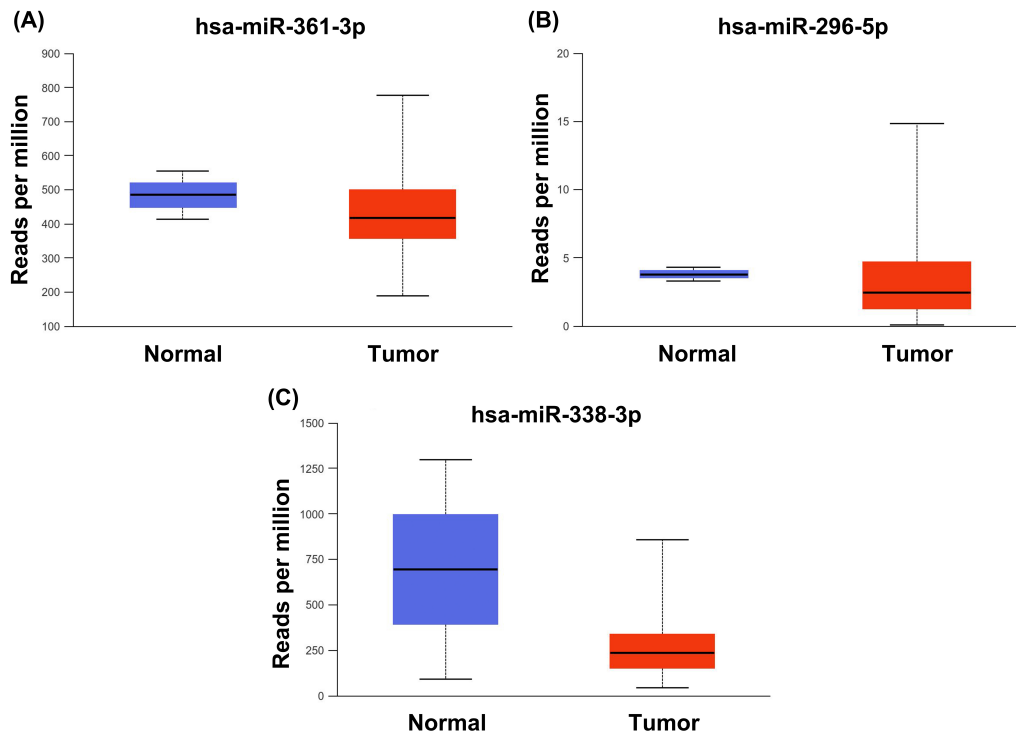

Figure 6. Selected 3 miRNAs' expression rates in 307 tumor vs. 3 Normal CESC samples in TCGA database and these miRNAs effect on survival rates of CESC patients. Selected (A) hsa-miR-361-3p, (B) hsa-miR-296-5p, (C) hsa-miR-338-3p miRNAs have been found to be significantly downregulated in tumor samples ($p < 0.001$)
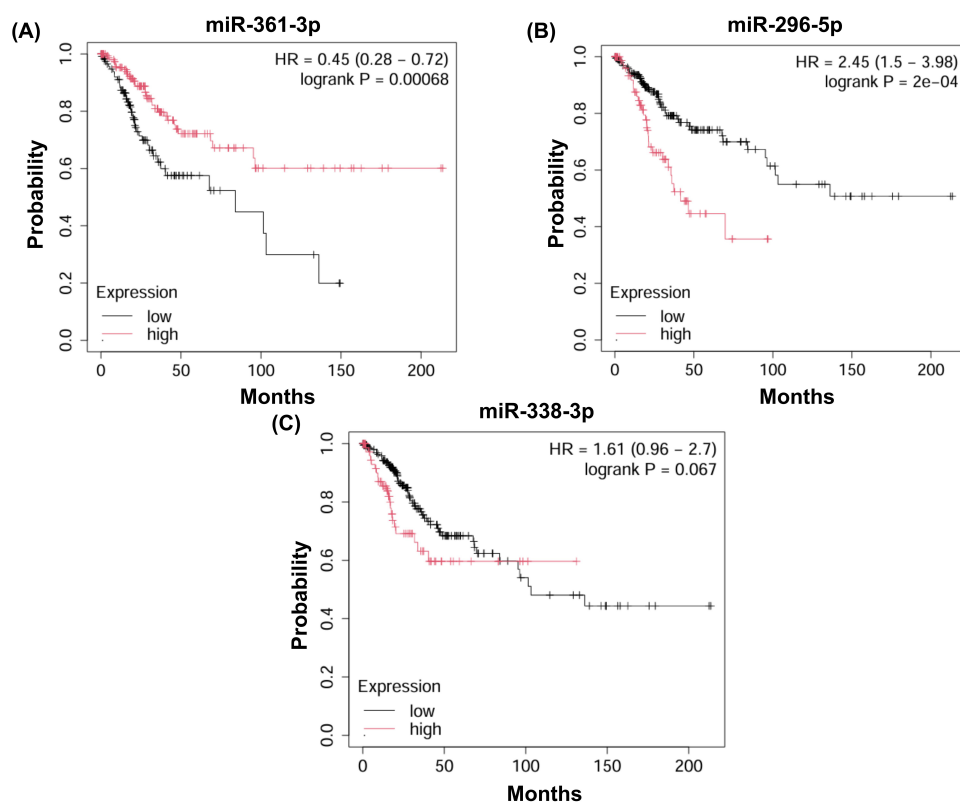
Figure 7. The effect of selected 3 miRNAs' on overall survival rates of 307 CESC patients in the TCGA database. (A) Downregulated miR-361-3p was related to a lower overall survival rate. (B) A high miR-296-5p level was associated with a decreased overall survival rate. (C) Altered hsa-miR-338-3p expression level was not altered with CESC survival rates

Discussion

In human cells, the number of unique circRNAs formed (~100,000) is significantly greater than that of protein-coding genes (~20,000). Despite their widespread prevalence, the biological significance of most circRNAs remains unclear, and they have not been functionally characterized [21]. Studies have shown that miRNAs can serve as potent regulators of various cellular activities, including cell growth, differentiation, development, and apoptosis in many cancers [22–24]. The circRNA–miRNA–mRNA regulation axis plays a crucial role in the progression of several diseases, including malignancies, diabetes, Alzheimer's disease, and cardiovascular disease [25–28]. These networks participate in the signaling mechanisms of several human illnesses by controlling the expression profile of genes linked to pathogenicity. To comprehend the complicated biological processes of cancer, the interaction between circRNAs/miRNAs and mRNAs needs to be clarified [29].

Large-scale bioinformatics databases have been increasingly used in medical research since genetic screening techniques were developed. Among these, GEO datasets stored in the NCBI and TCGA may be useful in the quantitative investigation and analysis of alterations in gene expressions of many diseases, including CESC [30]. For instance, based on GEO and the TCGA databases, Gao et al. [31] identified 4 miRNAs (miR-223, miR-99a, miR-188, and miR-125b) influencing the survival rate of individuals with CESC. In another study, Qi et al. [32] revealed 3 novel miRNAs (miR-7641, miR-585-5p, and miR-216b-5p) expression patterns might be used as a biomarker to indicate the poor prognosis of CESC. Recent studies have shown that circRNAs play key roles in CESC processes by altering the regulation of numerous oncogenes or tumor suppressor genes via miRNAs. For example, it has been found that circ0001955 enhances CESC carcinogenesis and metastasis via the miR-188-3p/*NCAPG2* axis [33]. The circ_POLA2/miR-326/*GNB1* axis has been found to be important in the development and progression of CESC [34].

Using various in silico approaches, circRNAs–miRNAs–mRNAs axes that may be significant in the CESC cancer process have been identified in current study. 3 circRNAs (hsa_circ_0000711, hsa_circ_0000515, and hsa_circ_0001855) that may be more associated with CESC were identified. To our knowledge, two studies

in the literature regarding the relationship between hsa_circ_0000711 circRNA and cancers exist. However, there is no information about the relationship between hsa_circ_0000711 and CESC. In the study of Li et al. [35], it has been suggested that hsa_circ_0000711 may have a significant role in colorectal cancer and may be a possible biomarker for colorectal cancer diagnosis and prognosis. The increased expression of hsa_circ_0000711 has been shown to promote hepatoma cell proliferation and prevent apoptosis by binding has-miR-103a-3p [36]. Among the selected miRNAs in the current study, hsa-miR-338-3p and hsa-miR-361-3p, which are among the candidate potential sponges of hsa_circ_0000711, were shown to be downregulated in many cancers, including CESC. For instance, according to Luan et al.'s study [37], miR-338-3p was considerably downregulated in CC cells and tissues, while lncRNA XLOC_006390 was found to act as a ceRNA and accelerate CC progression and metastasis by reverse regulating miR-338-3p expression. In the study of Meng et al. [38] circUBAP2 has been shown to be a prognostic marker and it may contribute to tumor growth and metastasis in CESC by influencing the miR-361-3p/*SOX4* axis. In Pubmed, there are two research that indicate a link between 'hsa_circ_0000515' and cancers. Cai et al. [39] showed that hsa_circ_0000515 is involved in developing breast cancer via the miR-296-5p/*CXCL10* axis. Another study emphasized that hsa_circ_0000515 may play a role in the development of CESC through miR-326/*ELK1* axis [40]. miR-296-5p found a candidate sponge miRNA of hsa_circ_0000515 in the current study is an important miRNA in many cancers including CESC. For example, KCNQ1OT1 has been demonstrated to accelerate the malignant behavior of CESC and promote tumor formation by altering the miR-296-5p/*HYOU1* axis. The third circRNA that may be associated with CESC, 'hsa_circ_0001855', has not yet been associated with any cancer in the literature, and only one study has stated that it may be associated with preeclampsia [41].

The genes in our study's proposed axes are involved in critical biological functions such as cell division and DNA replication and are linked to various malignancies (Figure 4). All of the selected 10 genes for our investigation have previously been proven to be elevated in many cancers including CESC. For instance, a recent study identified *S100A2* as a hypoxia-induced immunosuppressive factor that regulates the expression of *PD-L1*. *S100A2* has also been identified as an oncogene that enhances the proliferation and migration of CC cells, suggesting that it might be a potential therapeutic target for CESC [42]. There is sufficient evidence supporting *PLK1* overexpression in CESC, and it has been documented that *PLK1* overexpression contributes to the clinical progression of CESC patients [43]. *ZBRK1* has been implicated as inhibiting CC metastasis, perhaps by modulating *MMP9* expression [44].

Increasing evidence indicates that circRNAs have the potential to serve as indicators for early cancer detection, clinical diagnosis, prediction, and even in the evaluation of therapy response [21]. To reveal the effects of the hsa_circ_0000711/hsa-miR-338-3p/*HMGA1*, *HIST1H2BJ*, *ZWINT*, *MMP9*, *KIFC1* and hsa_circ_0000515/hsa-miR-296-5p/*S100A2*, *PLK1*, *SLC7A5*, *HMGA1* axes in CESC, it is necessary to conduct both in vitro and in vivo research. If the appropriate confirmation is achieved, these axes may be used as a biomarker for early diagnosis and in creating targeted therapy.

Conclusions

According to the findings, this reserch suggest that hsa_circ_0000711 may be involved in the CESC process hsa-miR-338-3p/*HMGA1*, *HIST1H2BJ*, *ZWINT*, *MMP9*, *KIFC1* axis and also via hsa-miR-361-3p/*KIFC1*, *UBALD2*, *CDC6* axis. Moreover, the results suggest that hsa_circ_0000515 may affect CESC processes by changing the expressions of *S100A2*, *PLK1*, *SLC7A5*, and *HMGA1* genes through hsa-miR-296-5p. These circRNAs–miRNAs–mRNAs axes, which are considered to be associated with CESC, should be confirmed in vitro and in vivo with new investigations.

Limitations of the study

Although this study was conducted using TCGA data containing a large number of patient samples in mRNA and miRNA selection, GSE102686 and GSE169057 GEO datasets containing a small number of patient samples were used in determining circRNAs. The small number of patient samples can be considered as a limitation of the study. Despite this, circRNA is a new topic, we considered that our study can be considered a clue for in vitro and in vivo studies.

Abbreviations

CC: cervical cancer

CESC: cervical squamous cell carcinoma

CircInteractome: circRNA interactome

circRNAs: circular RNAs

GEO: Gene Expression Omnibus

GEPIA2: The Gene Expression Profiling Interactive Analysis

KM plotter: Kaplan-Meier plotter

Log2FC: log2 Fold Change

miRNA: microRNA

OS: overall survival

TCGA: The Cancer Genome Atlas

Declarations

References

1. Sharma S, Deep A, Sharma AK. Current Treatment for Cervical Cancer: An Update. Anticancer Agents Med Chem. 2020;20:1768–79. [DOI] [PubMed]
2. Vaghasia H, Sakaria S, Prajapati J, Saraf M, Rawal RM. Interactive bioinformatics analysis for the screening of hub genes and molecular docking of phytochemicals present in kitchen spices to inhibit CDK1 in cervical cancer. Comput Biol Med. 2022;149:105994. [DOI] [PubMed]

3.   Yi Y, Liu Y, Wu W, Wu K, Zhang W. Reconstruction and analysis of circRNAmiRNAmRNA network in the pathology of cervical cancer. Oncol Rep. 2019;41:2209–25. [DOI] [PubMed] [PMC]

4.   Liu J, Nie S, Li S, Meng H, Sun R, Yang J, et al. Methylation-driven genes and their prognostic value in cervical squamous cell carcinoma. Ann Transl Med. 2020;8:868. [DOI] [PubMed] [PMC]

5.   Nemeth K, Bayraktar R, Ferracin M, Calin GA. Non-coding RNAs in disease: from mechanisms to therapeutics. Nat Rev Genet. 2024;25:211–32. [DOI] [PubMed]

6.   Capik O, Sanli F, Kurt A, Ceylan O, Suer I, Kaya M, et al. CASC11 promotes aggressiveness of prostate cancer cells through miR-145/IGF1R axis. Prostate Cancer Prostatic Dis. 2021;24:891–902. [DOI] [PubMed]

7.   Kaya M, Karataş ÖF. The relationship between larynx cancer and microRNAs. Van med J. 2020;27: 535–41. [DOI]

8.   Kristensen LS, Jakobsen T, Hager H, Kjems J. The emerging roles of circRNAs in cancer and oncology. Nat Rev Clin Oncol. 2022;19:188–206. [DOI] [PubMed]

9.   Erdoğan C, Suer İ, Kaya M, Kurt Z, Öztürk Ş, Aydın N, Kurt Z. Bioinformatics analysis of the potentially functional circRNA-miRNA-mRNA network in breast cancer. PLoS One. 2024;19:e0301995. [DOI] [PubMed] [PMC]

10. Huang W, Wu Y, Qiao M, Xie Z, Cen X, Huang X, et al. CircRNA-miRNA networks in regulating bone disease. J Cell Physiol. 2022;237:1225–44. [DOI] [PubMed]

11. Zhang M, Bai X, Zeng X, Liu J, Liu F, Zhang Z. circRNA-miRNA-mRNA in breast cancer. Clin Chim Acta. 2021;523:120–30. [DOI] [PubMed]

12. Erdoğan C, Kaya M, Suer İ. A Bioinformatics Analysis of circRNA/miRNA/mRNA Interactions in Acute Myeloid Leukemia. Experimed. 2023;13:45–53. [DOI]

13. Shen L, Dang J, Liu S, Xian B, Deng Y, Qu D. CircRNA VPRBP inhibits tumorigenicity of cervical cancer via miR-93-5p/FRMD6 axis. Reprod Sci. 2022;29:2251–64. [DOI] [PubMed]

14. Song T, Xu A, Chen X, Gao J, Gao F, Kong X. Circular RNA circRNA_101996 promoted cervical cancer development by regulating miR-1236-3p/TRIM37 axis. Kaohsiung J Med Sci. 2021;37:547–61. [DOI] [PubMed]

15. Chandrashekar DS, Karthikeyan SK, Korla PK, Patel H, Shovon AR, Athar M, et al. UALCAN: An update to the integrated cancer data analysis platform. Neoplasia. 2022;25:18–27. [DOI] [PubMed] [PMC]

16. Li R, Qu H, Wang S, Chater JM, Wang X, Cui Y, et al. CancerMIRNome: an interactive analysis and visualization database for miRNome profiles of human cancer. Nucleic Acids Res. 2022;50:D1139–46. [DOI] [PubMed] [PMC]

17. Tang Z, Kang B, Li C, Chen T, Zhang Z. GEPIA2: an enhanced web server for large-scale expression profiling and interactive analysis. Nucleic Acids Res. 2019;47:W556–60. [DOI] [PubMed] [PMC]

18. Dudekula DB, Panda AC, Grammatikakis I, De S, Abdelmohsen K, Gorospe M. CircInteractome: A web tool for exploring circular RNAs and their interacting proteins and microRNAs. RNA Biol. 2016;13: 34–42. [DOI] [PubMed] [PMC]

19. Chang L, Zhou G, Soufan O, Xia J. miRNet 2.0: network-based visual analytics for miRNA functional analysis and systems biology. Nucleic Acids Res. 2020;48:W244–51. [DOI] [PubMed] [PMC]

20. Miller HE, Bishop AJR. Correlation AnalyzeR: functional predictions from gene co-expression correlations. BMC Bioinformatics. 2021;22:206. [DOI] [PubMed] [PMC]

21. Pisignano G, Michael DC, Visal TH, Pirlog R, Ladomery M, Calin GA. Going circular: history, present, and future of circRNAs in cancer. Oncogene. 2023;42:2783–800. [DOI] [PubMed] [PMC]

22. Kaya M, Suer I, Ozgur E, Capik O, Karatas OF, Ozturk S, et al. miR-145-5p suppresses cell proliferation by targeting IGF1R and NRAS genes in multiple myeloma cells. Turk J Biochem. 2023;48:563–9. [DOI]

23. Kaya M, Suer İ. The Effect of miR-34a-5p on Overexpressed AML Associated Genes. J Istanb Fac Med. 2023;86:59–68. [DOI]

24. Suer İ, Kaya M. Is the AURKB Gene Involved in Aml Cell Proliferation Since It is Targeted by miR-34a-5p and let-7b-5p? Konuralp Med J. 2023;15:16–23. [DOI]

25. Ayaz H, Aslam N, Awan FM, Basri R, Rauff B, Alzahrani B, et al. Mapping CircRNA-miRNA-mRNA regulatory axis identifies hsa_circ_0080942 and hsa_circ_0080135 as a potential theranostic agents for SARS-CoV-2 infection. PLoS One. 2023;18:e0283589. [DOI] [PubMed] [PMC]

26. Su Q, Lv X. Revealing new landscape of cardiovascular disease through circular RNA-miRNA-mRNA axis. Genomics. 2020;112:1680–5. [DOI] [PubMed]

27. Rong D, Sun H, Li Z, Liu S, Dong C, Fu K, et al. An emerging function of circRNA-miRNAs-mRNA axis in human diseases. Oncotarget. 2017;8:73271–81. [DOI] [PubMed] [PMC]

28. Su Y, Yi Y, Li L, Chen C. circRNA-miRNA-mRNA network in age-related macular degeneration: From construction to identification. Exp Eye Res. 2021;203:108427. [DOI] [PubMed]

29. Tang X, Ren H, Guo M, Qian J, Yang Y, Gu C. Review on circular RNAs and new insights into their roles in cancer. Comput Struct Biotechnol J. 2021;19:910–28. [DOI] [PubMed] [PMC]

30. Zhi S, Jiang B, Yu W, Li Y, Wang H, Zhou T, et al. Identification of candidate miRNA biomarkers correlated with the prognosis of cell carcinoma and endocervical adenocarcinoma via integrated bioinformatics analysis. Am J Transl Res. 2022;14:8146–55. [PubMed] [PMC]

31. Gao C, Zhou C, Zhuang J, Liu L, Liu C, Li H, et al. MicroRNA expression in cervical cancer: Novel diagnostic and prognostic biomarkers. J Cell Biochem. 2018;119:7080–90. [DOI] [PubMed]

32. Qi Y, Lai Y, Shen P, Chen F, Lin L, Wu H, et al. Identification and validation of a miRNA-based prognostic signature for cervical cancer through an integrated bioinformatics approach. Sci Rep. 2020;10:22270. [DOI] [PubMed] [PMC]

33. Wang W, Luo H, Chang J, Yang X, Zhang X, Zhang Q, et al. Circular RNA circ0001955 promotes cervical cancer tumorigenesis and metastasis via the miR-188-3p/NCAPG2 axis. J Transl Med. 2023;21:356. [DOI] [PubMed] [PMC]

34. Cao Y, Li J, Jia Y, Zhang R, Shi H. CircRNA circ_POLA2 Promotes Cervical Squamous Cell Carcinoma Progression via Regulating miR-326/*GNB1*. Front Oncol. 2020;10:959. [DOI] [PubMed] [PMC]

35. Li J, Ni S, Zhou C, Ye M. The expression profile and clinical application potential of hsa_circ_0000711 in colorectal cancer. Cancer Manag Res. 2018;10:2777–84. [DOI] [PubMed] [PMC]

36. Chen K, Pan J, Chen Z, Pan D, Gao T, Huang M, et al. Effects of hsa_circ_0000711 expression level on proliferation and apoptosis of hepatoma cells. Eur Rev Med Pharmacol Sci. 2020;24:4161–71. [DOI] [PubMed]

37. Luan X, Wang Y. LncRNA XLOC_006390 facilitates cervical cancer tumorigenesis and metastasis as a ceRNA against miR-331-3p and miR-338-3p. J Gynecol Oncol. 2018;29:e95. [DOI] [PubMed] [PMC]

38. Meng L, Jia X, Yu W, Wang C, Chen J, Liu F. Circular RNA UBAP2 contributes to tumor growth and metastasis of cervical cancer via modulating miR-361-3p/SOX4 axis. Cancer Cell Int. 2020;20:357. [DOI] [PubMed] [PMC]

39. Cai F, Fu W, Tang L, Tang J, Sun J, Fu G, et al. Hsa_circ_0000515 is a novel circular RNA implicated in the development of breast cancer through its regulation of the microRNA-296-5p/CXCL10 axis. FEBS J. 2021;288:861–83. [DOI] [PubMed]

40. Tang Q, Chen Z, Zhao L, Xu H. Circular RNA hsa_circ_0000515 acts as a miR-326 sponge to promote cervical cancer progression through up-regulation of ELK1. Aging (Albany NY). 2019;11:9982–99. [DOI] [PubMed] [PMC]

41. Jiang M, Lash GE, Zhao X, Long Y, Guo C, Yang H. CircRNA-0004904, CircRNA-0001855, and PAPP-A: Potential Novel Biomarkers for the Prediction of Preeclampsia. Cell Physiol Biochem. 2018;46:2576–86. [DOI] [PubMed]

42. Yang J, Wan S, Zhao M, Cai H, Gao Y, Wang H. Multi-omics Analysis Identifies Hypoxia Subtypes and S100A2 as an Immunosuppressive Factor in Cervical Cancer. Reprod Sci. 2024;31:107–21. [DOI] [PubMed]

43. Gao L, Pang Y, Guo X, Zeng J, Tang Z, Xiong D, et al. Polo like kinase 1 expression in cervical cancer tissues generated from multiple detection methods. PeerJ. 2020;8:e10458. [DOI] [PubMed] [PMC]

44. Lin L, Chuang C, Li C, Liao C, Cheng C, Cheng T, et al. ZBRK1 acts as a metastatic suppressor by directly regulating MMP9 in cervical cancer. Cancer Res. 2010;70:192–201. [DOI] [PubMed] [PMC]