Journal of Biosciences and Medicines, 2025, 13(8), 395-409
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Construction of a Cervical Cancer-Specific CeRNA Prognostic Regulatory Network

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How to cite this paper: Liu, D., Yan, S.Q. and Yang, Y.H. (2025) Construction of a Cervical Cancer-Specific CeRNA Prognostic Regulatory Network. *Journal of Biosciences and Medicines*, **13**, 395-409.
https://doi.org/10.4236/jbm.2025.138031

Received: July 10, 2025
Accepted: August 19, 2025
Published: August 22, 2025

Abstract

Objective: Cervical Cancer is the most common malignant tumor of the female genital tract. Previous studies have shown that ceRNA regulation plays an important role in cervical cancer. This study explored biomarkers related to the prognosis of cervical cancer by constructing a ceRNA network. **Methods:** Using bioinformatics, and the lncRNA was used for survival analysis, thus constructing a ceRNA network associated with cervical cancer. **Results:** MSRB3 expression was positively associated with B cell, $CD4^+$ T cell, macrophage, and dendritic cell infiltration, and negatively associated with $CD8^+$ T cell and neutrophil infiltration. MSRB3 expression also correlated with significantly higher expression of programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein4 (CTLA4). MSRB3 was found to be expressed in higher levels in cervical cancer tissues than in normal tissues and patients with high MSRB3 expression had a worse prognosis than those with low MSRB3 expression. **Conclusion:** The increase in the expression of MSRB3 related to CESC is significantly associated with the level of immune cell infiltration. The MSRB3 gene is a promising candidate for the treatment of endocervical adenocarcinoma and could serve as a potential biomarker for the treatment and diagnosis of endocervical carcinoma.

Keywords

Biomarkers, Cervical Cancer, Competitive Endogenous RNA, Differentially Expressed RNA

1. Introduction

Cervical cancer is the fourth most common cancer among women worldwide. Despite being the only human cancer with a known cause, cervical cancer incidence

and mortality have not decreased significantly [1]. Cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) are the second leading causes of female cancer-related death after breast cancer, accounting for 10% - 15% of cancer-related mortality in women; however, their diagnostic and treatment targets remain limited [2] [3]. Almost all cervical cancer can be attributed to human papillomavirus (HPV) infection [4]. While the HPV vaccine has become popularized, cervical cancer incidence still ranks first among gynecological tumors, especially in low- and middle-income countries [5] [6]. Surgery and radiotherapy are effective methods for early-stage patients, but prognosis remains poor among those diagnosed with late-stage disease [6]. A better understanding of the biological mechanism of this disease and the CESC molecular subtypes will aid the identification of new biomarkers for reliable prognosis and targeted treatment.

In 2011, Sardina *et al.* hypothesized the concept of competitive endogenous RNA (ceRNA), suggesting that mRNA, lncRNA, and other transcripts can be used as ceRNAs to compete and combine with microRNAs (miRNAs) through the same miRNA response element (MRE). CeRNA activity has formed a large-scale regulatory network across the transcriptome, greatly expanding the functional genetic information in the human genome and playing an important role in cancer and other diseases [7]. These RNAs are involved in a variety of biological processes, including cell proliferation, differentiation, angiogenesis, and apoptosis [8]. The ceRNA network links the functions of protein-coding mRNA and non-coding RNA (microRNA, pseudogenes and circRNAs). Any transcripts that contain miRNA response elements can theoretically act as ceRNAs, allowing for a wide range of physiological and pathological forms of post transcriptional gene regulation.

Some ceRNAs are dysregulated or reprogrammed in cancer and may contribute to the initiation and progression of cancer, suggesting that they have the potential to serve as diagnostic markers or therapeutic targets [9]. CeRNA networks play an important role in post-transcriptional regulation. LncRNAs can function as ceRNAs by binding miRNA to messenger RNA (mRNA) [10] and lncRNAs, miRNAs, and mRNA networks are related to the pathogenesis and progression of malignant tumors such as gastric and gallbladder cancer [11]. However, few studies have evaluated the role of ceRNA in CESC. A comprehensive analysis of CESC-related lncRNA-miRNA-mRNA-ceRNA network function is required using a large sample size study and appropriate research methods.

2. Methods

2.1. Data Extraction

Using UCSC Xena (https://xena.ucsc.edu/), genomic data commons (GDC) downloads of the expression, mutation, and survival data of CESC patients, as well as Pan-cancer clinical data were obtained from TCGA. MiRNA data from CESC patients (three normal samples and 309 tumor samples) was also downloaded. Data on lncRNAs that can bind with miRNA was obtained from the ENCORI database. These data were sorted and standardized for subsequent analysis.

2.2. Screening for Differential Genes

Using the limma package in R (edge) software, the p-value was adjusted to the false discovery rate (FDR), and the differentially expressed genes (DEGs) were screened using |log2 fold change (FC)| > 1 and fdr < 0.05 as the cut-off criteria. Survival analysis was conducted on the screened DEGs using the R survival package, and the conditions were set as km < 0.05, HR > 1, and cox P-value < 0.05 using the GEPIA database (http://gepia.cancer-pku.cn/). The filter conditions were set as logfc > 1.0 and P-value < 0.01 to determine whether target gene expression differed in CESC.

2.3. Single Gene Survival Analysis

Survival analysis was performed using the R survival package to evaluate the prognostic value of DEGs in CESC patients. Survival curves were drawn using the Kaplan-Meier method. The Log-rank test was used to evaluate statistical significance. Significance was defined as $P < 0.05$.

2.4. DEG MiRNA Co-Expression

MiRNA that bound the target gene was screened using ENCORI. The R limma, ggpubr, and ggextra packages were used to assess the correlation between miRNA and the target genes, conduct differential expression analysis on the samples, and carry out visual processing to screen DEmiRNAs. The filtering conditions were corfilter <−0.2 and P-value < 0.01. To evaluate the prognostic value of DEmiRNAs in CESC patients, survival analysis was performed using the R survival package.

2.5. MiRNA and lncRNA Co-Expression

LncRNA that specifically binds to miRNA was screened using ENCORI (https://starbase.sysu.edu.cn/). Co-expression analysis of lncRNA and miRNA, correlation analysis of lncRNA and the target gene, and differential expression analysis of lncRNA in the samples were conducted using the limma, ggpubr, and ggExtra packages in R (edge). Visual processing was carried out using R to screen the differentially expressed lncRNAs (DElncRNAs). The filtering conditions were corfilter < −0.2, P-value < 0.01, and diff P-value < 0.05.

2.6. CeRNA Network

Using the obtained miRNA-mRNA and miRNA-lncRNA relationship pairs to predict miRNA targeting and co-expression, the screened DEmRNA was shown to interact with DEmiRNAs, and the DEmiRNAs were shown to interact with DElncRNAs. A ceRNA network of the DElncRNAs-DEmiRNAs-DEmRNA was constructed and visualized using Cytoscape v3.8.2 software, an open-source software platform for visualizing molecular interaction networks and biological pathways and integrating annotations, gene expression profiles, and other state data into these networks. Cytoscape plug-in (BINGO) 18 provides researchers with a comprehensive set of functional annotation tools to understand the biological sig-

nificance behind gene ontology (GO) and the gene list of the Kyoto Encyclopedia. To further understand the functions of the DEGs, BiNGO was used for functional enrichment analysis of the DEG molecular functions (MF), biological processes (BP), and cellular components (CC). For the graphene oxide condition, $p < 0.05$ was used as the cut-off [12].

2.7. Correlation between Target Genes and Immune Cells, Immune Infiltration and Immune Checkpoints

TIMER is a network resource used to systematically evaluate the clinical impact of different immune cells in diverse cancer types (https://cistrome.shinyapps.io/timer/). Using the TIMER "SCNA" module, the relationship between the target gene copy number and the composition of the immune infiltrate was analyzed. The distribution of immune cells in different somatic copy number alteration (SCNA) states of the target gene was analyzed using a violin diagram. SCNAs are a marker of tumorigenesis and progression that can impact the immune treatment response. The correlation between target gene expression and the infiltration of B cells, $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells, was assessed using the TIMER "GENE" module, and the relationship between the target gene and the number of each cell type was determined using a scatter diagram. R software was used to analyze the correlation between the target gene and the immune cell marker gene. A corfilter >0 and P-value <0.05 were used as the screening conditions. Visual analysis was determined using a scatter diagram. Three immune checkpoint genes (ICGs) were identified and the correlation between ICGs and the target genes was analyzed using the Gene-Corr module. A scatter diagram was used for visual analysis.

3. Results

3.1. Target Gene Screening

Table 1. Differential genes of Cervical squamous cell carcinoma and endocervical adenocarcinoma.

Gene	miRNA	cor	pvalue	logFC	diffPval
MSRB3	hsa-miR-33b-5p	−0.25650864	5.49E-06	2.209226194	0.003882911
MSRB3	hsa-miR-363-3p	−0.213992589	0.000167559	3.567804638	0.004850797
MSRB3	hsa-miR-32-5p	−0.204225837	0.000332181	2.673587379	0.002905589

CESC patient data was downloaded from UCSC Xena and sorted into standardized original data (**Table 1**) for subsequent analysis. A total of 2277 DEGs, including 1163 up-regulated and 1114 down-regulated genes were screened. Survival analysis was conducted to screen a total of 38 DEGs. The GEPIA database (http://gepia.cancer-pku.cn/) was used to define differences in the expression of CESC target genes (**Figure 1**). Of these, 16 DEGs were up-regulated, 17 were down-regulated, and five were unchanged in CESC. A total of 19 DEGs correlated significantly with both overall and disease-free survival. One of the target genes,

MSRB3, was selected for subsequent analysis (**Figure 2**).

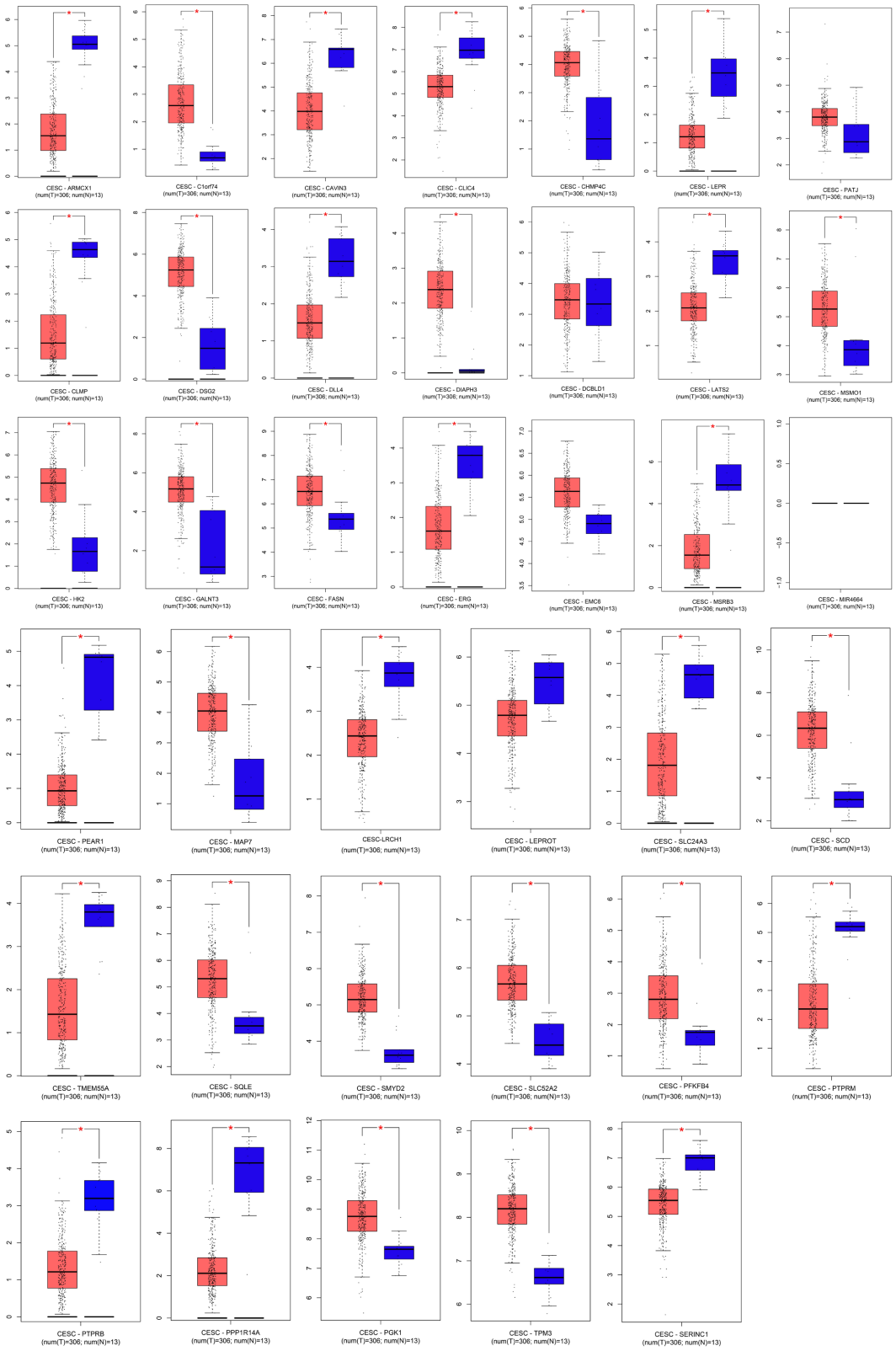
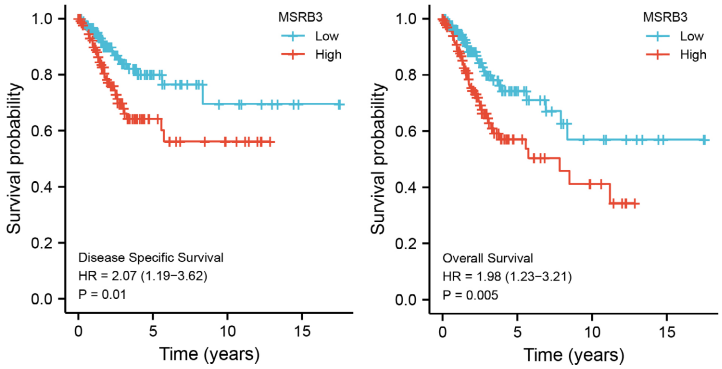


Figure 1. Box diagram of the expression difference of 38 target genes in CESC.



(a) (b)

Figure 2. (a) Overall survival curve of MSRB3; (b) Disease free survival curve of MSRB3.

3.2. Differentially Expressed MiRNA and the MiRNA-mRNA Regulatory Network Screening

MiRNA from CESC patients (three normal and 309 tumor samples) was downloaded from TCGA, and standardized to develop a miRNA expression matrix. DEmiRNAs were paired with DEmRNA and 93 miRNAs were predicted to interact with DEmRNA (**Table 2**). Hsa-miR-33b-5p, hsa-miR-32-5p, and hsa-miR-363-3p co-expressed with MSRB33 were screened using the miRNA expression matrix downloaded from TCGA (**Table 3**). A miRNA and MSRB3 correlation scatter diagram (**Figure 3**) and a miRNA differential expression diagram in normal and tumor samples (**Figure 4**) were obtained. Survival analysis was performed and visualized to evaluate the prognostic characteristics of DEmiRNAs (**Figure 5**). Cytoscape 3.8.2 was used to integrate the interaction pairs and construct the miRNA-mRNA regulatory network, including nodes and edges (**Figure 6**).

Table 2. MiRNAs that target genes can bind.

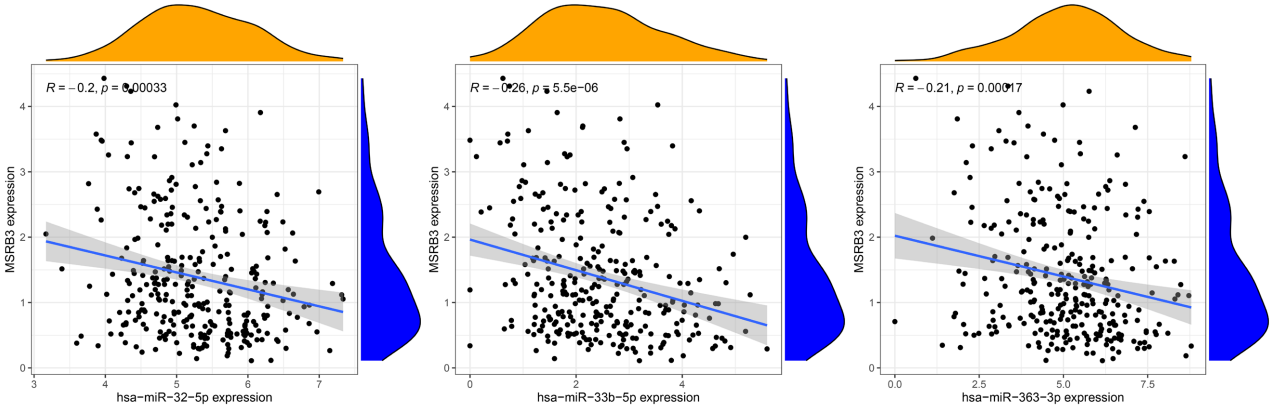
geneName	miRNAname	PITA	RNA22	miRmap	microT	miRanda	PicTar	TargwtScan
MSRB3	has-miR-32-5p	1	0	1	1	1	0	1
MSRB3	hsa-miR-363-3p	1	0	1	1	1	0	1
MSRB3	hsa-miR-33b-5p	1	0	0	1	0	0	0
MSRB3	hsa-miR-33a-5p	1	0	1	1	0	0	0
MSRB3	hsa-miR-92a-3p	1	0	1	1	1	0	1
MSRB3	hsa-miR-129-5p	1	0	0	1	0	0	0
MSRB3	hsa-miR-139-5p	1	0	1	0	0	0	0
MSRB3	hsa-miR-217	1	0	1	0	0	0	0

Table 3. Co-expression analysis of mRNA and miRNA.

gene	conMean	treatMean	logFC	pValue	fdr
MIR4269	1.733863749	0.052750214	−1.681113536	1.89E-06	0.00127781
RYR3-DT	1.603770675	0.088909528	−1.514861148	0.000133275	0.03814225
PAGE4	1.824901369	0.052575243	−1.772326125	0.000438033	0.046670882
PGM5P4	2.411105049	0.075557976	−2.335547073	0.001334966	0.046670882

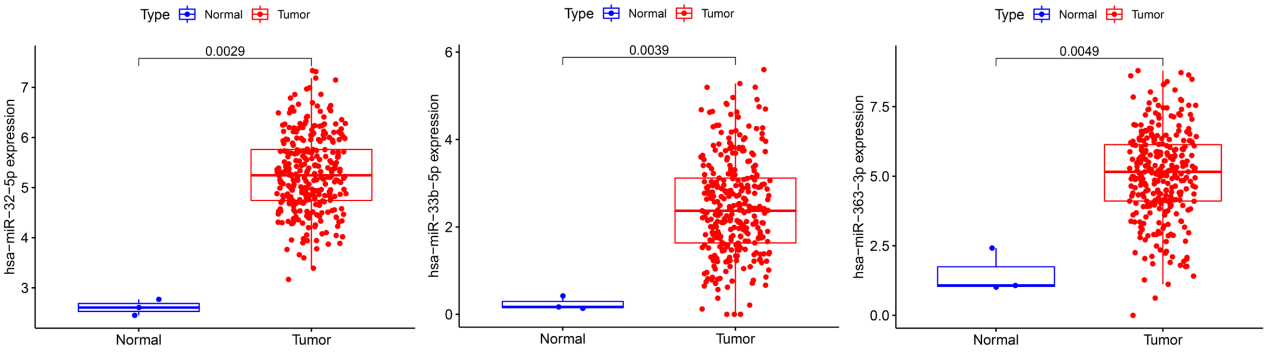
Continued

TCEAL6	2.597483828	0.029360795	−2.568123033	0.001402316	0.046670882
RNU5B-4P	1.7746578	0.180633462	−1.594024338	0.001411833	0.046670882
LINC02310	1.764257278	0.099888464	−1.664368814	0.001686668	0.046670882
SLITRK3	1.684815484	0.040314455	−1.644501029	0.001687954	0.046670882



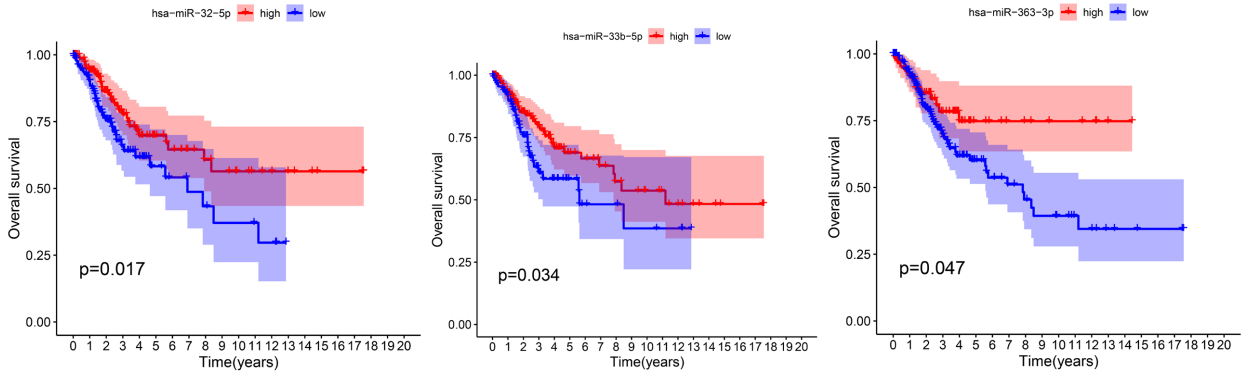
(a) (b) (c)

Figure 3. Correlation scatter diagram of miRNA and MRSB3.



(a) (b) (c)

Figure 4. Box diagram of differential expression of miRNA in normal and tumor samples.



(a) (b) (c)

Figure 5. Survival analysis of hsa-miR-33b-5p.

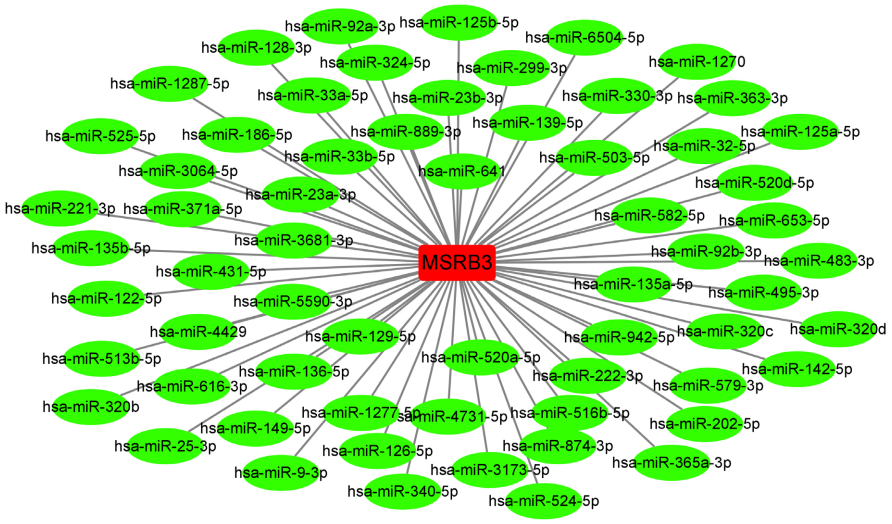


Figure 6. Regulatory network of miRNA-mRNA.

3.3. Differentially Expressed lncRNA Screening

Among the identified DEmiRNAs, hsa-miR-33b-5p was selected for follow-up analysis, and the DEmiRNAs and DElncRNA were paired. A total of 59 lncRNAs were predicted to interact with DEmiRNA (**Table 4**). The DElncRNAs (MSC-AS1) were screened using the DEmiRNA expression matrix, DEmiRNA, and miRNA data. The hsa-miR-33b-5p and MSC-AS1 co-expression and the MSC-AS1 and MSRB3 correlation analysis files were obtained (**Table 5**) and a correlation scatter diagram of MSC-AS1 and hsa-mia-33b-5p (**Figure 7(a)**), a correlation scatter diagram of MSC-AS1 and MSRB3 (**Figure 7(b)**), and a box diagram of differential MSC-AS1 expression in normal and tumor samples (**Figure 7(c)**) were developed. Survival analysis was performed on the screened lncRNA to evaluate the prognostic characteristics of differentially expressed lncRNA (MSC-AS1) (**Figure 8**).

Table 4. Expression relationship between miRNA and lncRNA.

miRNAname	geneID	geneName	geneType
hsa-miR-33b-5p	ENSG00000272145	NFYC-AS1	antisense
hsa-miR-33b-5p	ENSG00000235947	EGOT	lincRNA
hsa-miR-33b-5p	ENSG00000231177	LINC00852	antisense
hsa-miR-33b-5p	ENSG00000273014	AC018645.2	lincRNA
hsa-miR-33b-5p	ENSG00000281103	TRG-AS1	antisense
hsa-miR-33b-5p	ENSG00000235531	MSC-AS1	antisense
hsa-miR-33b-5p	ENSG00000245532	NEAT1	lincRNA
hsa-miR-33b-5p	ENSG00000279865	AC006511.3	TEC
hsa-miR-33b-5p	ENSG00000246695	RASSF8-AS1	antisense
hsa-miR-33b-5p	ENSG00000280426	AC084876.2	TEC

Table 5. Co-expression relationship between miRNA and LncRNA.

lncRNA	miRNA	cor	pvalue	logFC	diffPval
MSC-AS1	hsa-miR-33b-5p	−0.287226176	3.19E-07	−0.968460041	0.005078575
NFYC-AS1	hsa-miR-33b-5p	−0.201677436	0.000385199	0.20026353	0.322036977
RASSF8-AS1	hsa-miR-33b-5p	−0.15894411	0.005324051	−0.976309778	0.005841439
C9orf106	hsa-miR-33b-5p	−0.155648918	0.006367178	−0.150435134	0.031751191
KCNQ1OT1	hsa-miR-33b-5p	−0.125430149	0.028248162	0.023609668	0.777580473
MORF4L2-AS1	hsa-miR-33b-5p	−0.110115356	0.05432903	−0.090663145	0.407704745
FGD5-AS1	hsa-miR-33b-5p	−0.104500309	0.067921304	−0.2342053	0.50982847
ZNF503-AS2	hsa-miR-33b-5p	−0.101309361	0.076811756	0.001326199	0.914673856

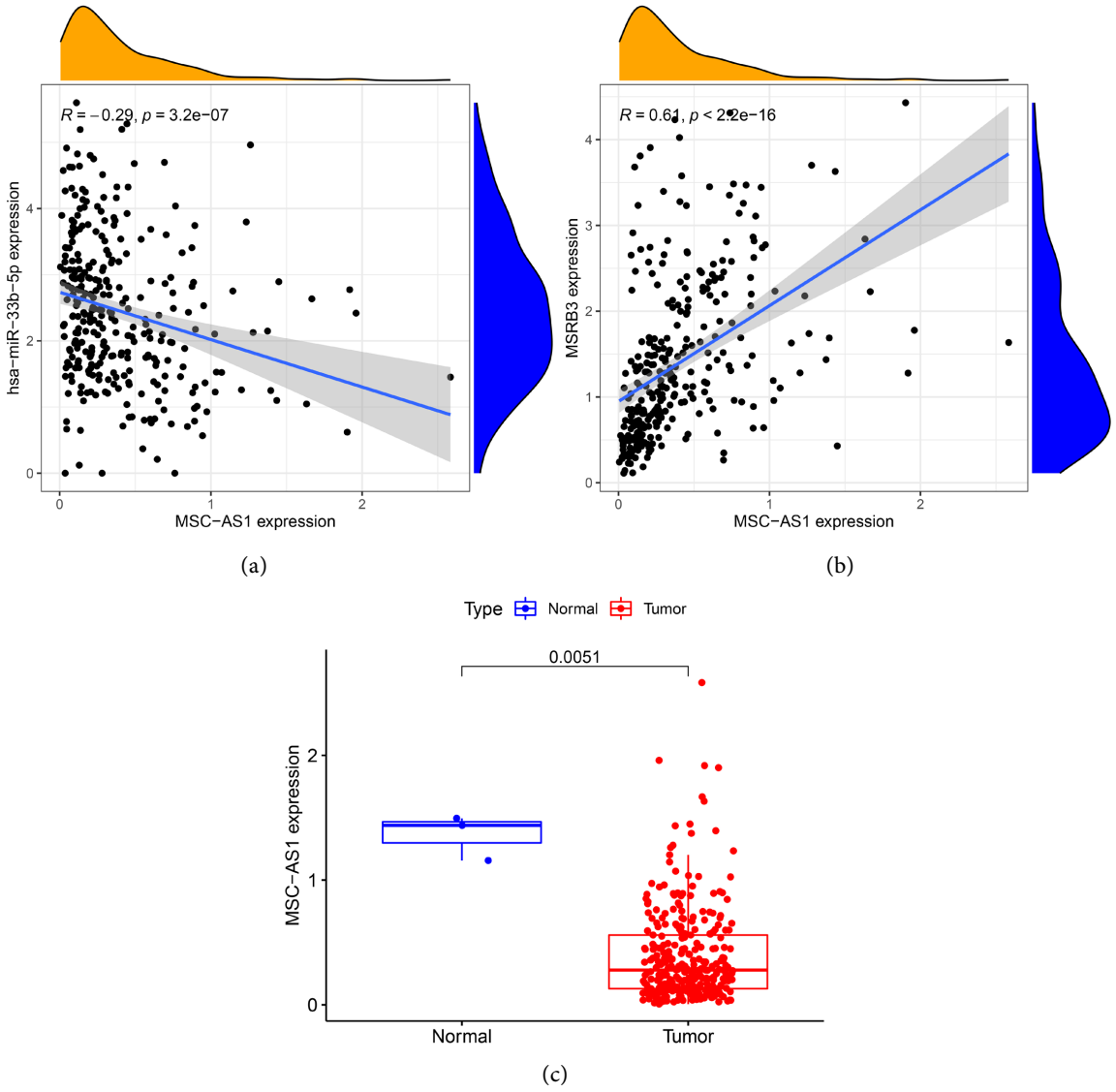


Figure 7. (a) Scatter diagram of co-expression of MSC-AS1 and hsa-miR-33b-5p; (b) Scatter diagram of correlation between MSC-AS1 and target gene MSRB3; (c) Box diagram of MSC-AS1 expression differences in normal and final samples.

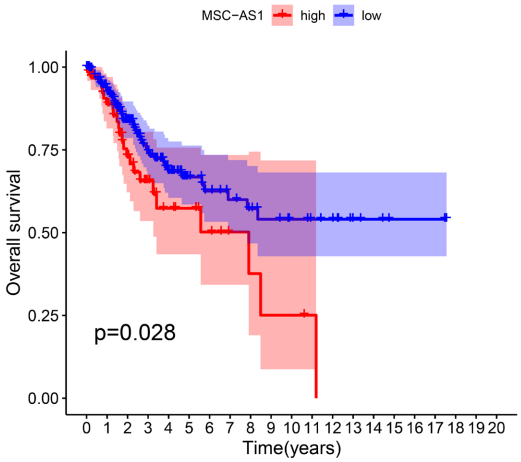


Figure 8. Survival analysis of MSC-AS1.

3.4. CeRNA Network

The screened DEmRNA, DEmiRNAs, and DElncRNA were integrated to construct a lncRNA-miRNA-mRNA ceRNA network (**Figure 9**), including three nodes and two edges. A DEmiRNA (hsa-miR-33b-5p) and a DElncRNA (MSC-AS1) were obtained. The results indicated that these RNA are particularly important in CESC occurrence, development, and prognosis.

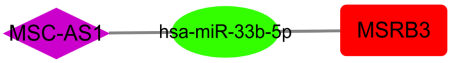


Figure 9. CeRNA network of single gene hsa-miR-33b-5p.

3.5. Relationship between MSRB3 and Immune Copy Number, Immune Infiltration and Immune Checkpoint

The estimated degree of CD8 T cell infiltration was compared between tumors with different MSRB3 gene SCNA statuses in CESC. The loss of MSRB3 expression was significantly correlated with the level of immune cell infiltration in CESC (**Figure 10**). MSRB3 expression was positively correlated with B cell, $CD4^+$ T cell, macrophage, and dendritic cell infiltration and negatively correlated with $CD8^+$ T cell and neutrophil infiltration (**Figure 11**). MSRB3 expression was also positively correlated with the expression of the marker gene, PTGS2, on the surface of macrophage M1 cells, the marker gene, CD163, on the surface of macrophage M1 cells, and the expression of VSIG4, MS4A4A, and marker gene, NRP1, on the surface of dendritic cells (**Figure 12**). MSRB3 expression was also found to correlate with significantly high expression of several immune checkpoints, including programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein 4 (CTLA4). These findings indicate that anti-PD-1/L1 or anti-CTLA4 immunotherapy may be an effective treatment option for CESC patients (**Figure 13**). In addition, MSRB3 expression was higher in cervical cancer tissues than in normal tissues (**Figure 14**), and disease prognosis was worse for patients with a high MSRB3 expression than those with

low expression (Figure 15).

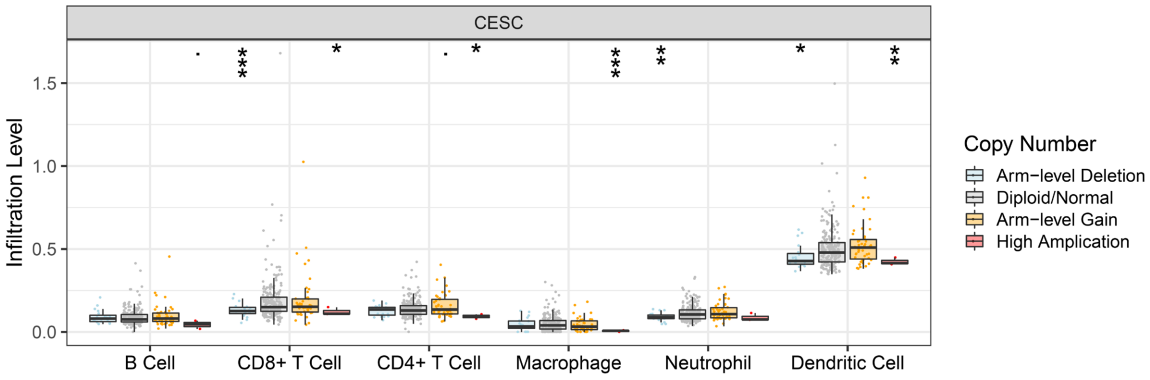


Figure 10. Relationship between MSC-AS1 copy number and immune cells.

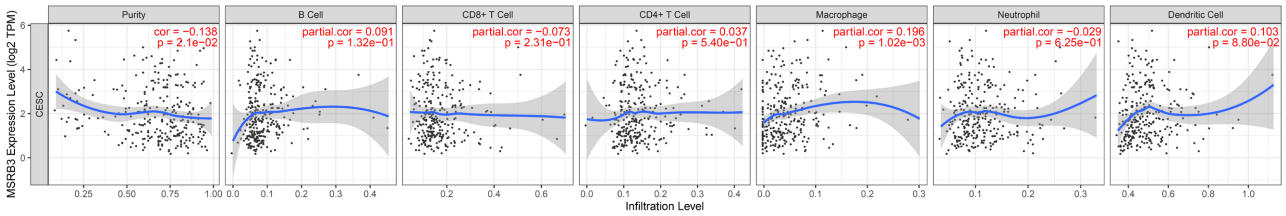


Figure 11. Correlation between the expression of MSC-AS1 in CESE and immune cells.

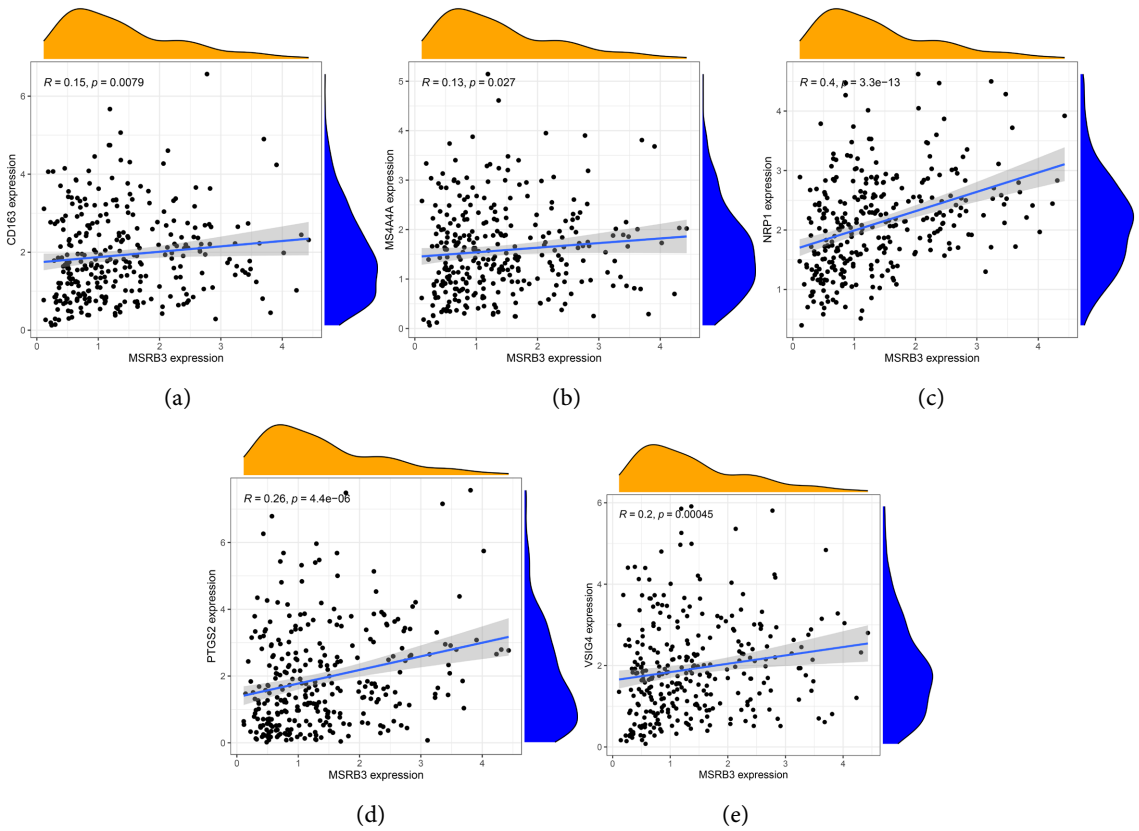


Figure 12. Correlation between MSRB3 expression and macrophage marker gene.

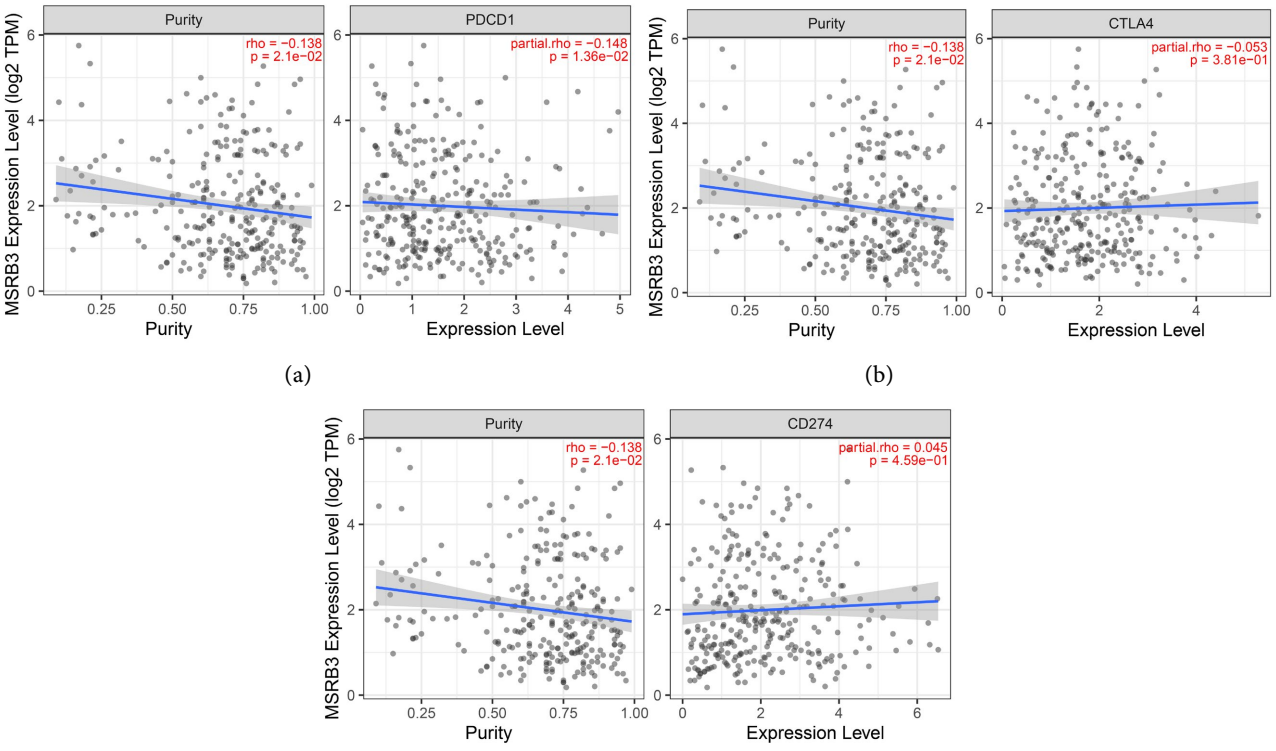
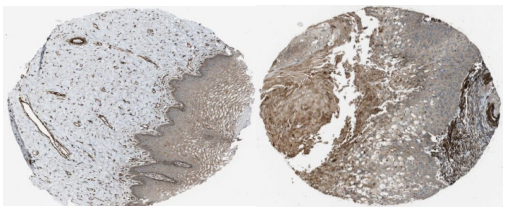


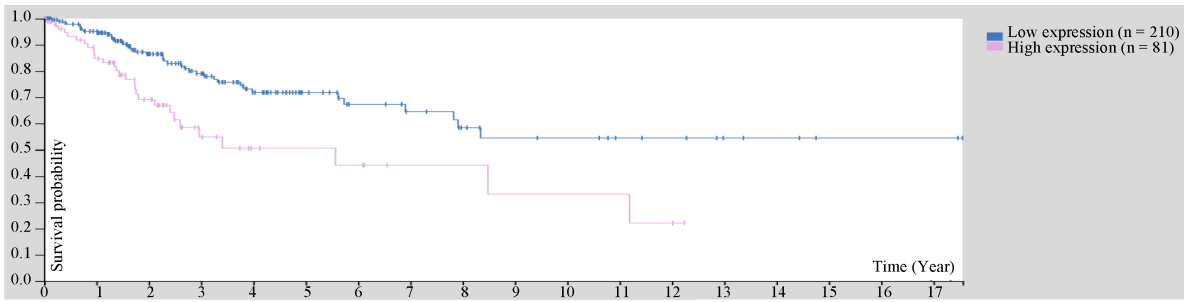
Figure 13. Scatter plot of the correlation between the expression of MSRB3 and immune checkpoints ((a) PDCD1; (b) CTLA4; (c) CD274).



(a) (b)

From: https://www.proteinatlas.org/search/MSRB3.

Figure 14. Expression of MSRB3 in different tissues. ((a) in normal tissues; (b) in Cervical Cancer).



From: https://www.proteinatlas.org/search/MSRB3.

Figure 15. The survival curve about expression level of MSRB3 and cervical cancer prognosis.

4. Conclusions

Several recent studies have explored the molecular mechanism of CESC; however, an understanding of the precise biomarkers and potential treatment targets is limited, and the prognosis for late-stage patients remains poor. The current study sought to identify new biomarkers for better targeted therapy and prognosis prediction. The ceRNA hypothesis proposes a mechanism of RNA interaction in which ceRNA regulates gene expression by competitively binding to microRNA [11]. In the current study, relevant miRNA data from CESC patients were downloaded from TCGA database and 19 genes were found to correlate significantly with both the overall survival and disease-free survival of CESC patients. Among them, MSRB3 is one of the target genes.

Methionine sulfoxide reductase B3 (MSRB3), one of three MSRB enzymes in mammalian cells, is a protein repair enzyme. IT is present in the mitochondria of human cells [12] [13], and have reported that MSRB3 is associated with a variety of cancers, including Gastric Cancer [14], Renal Cancer [15], Breast Cancer [16]. Although the role of MSRB3 in the occurrence and prognosis of various cancers has been partially confirmed, the bioinformatics analysis of cervical cancer needs to be further developed. It is important to analyze the expression of MSRB3 in Cervical Cancer and its prognostic value. One study indicates that MSRB3 may mainly exert its biological functions by participating in the MAPK/TGF-b signaling pathway, thereby influencing the occurrence and development of cervical cancer [17]. In our study, the increase in the expression of MSRB3 related to CESC is significantly associated with the level of immune cell infiltration. As a result, MSRB3 is a great prospect for use in treating and diagnosing cervical CESC. However, this research has limitations, lacks experimental verification, and needs to be studied in vitro or *in vivo*. Although this study was limited by the small number of patients with intracervical adenocarcinoma in TCGA database and the lack of clinical validation, we hope that these findings can provide new ideas for clinical diagnosis, prognostic evaluation and targeted treatment of cervical cancer.

Data Availability Statement

The original data in the study are publicly available in the NCBI (https://www.ncbi.nlm.nih.gov/.) and UCSC (https://xena.ucsc.edu/).

Ethics Statement

This study does not involve human participants.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Abbreviations

BP: Biological Processes
CC: Cellular Components
CD: Clusters of Differentiation
CeRNA: Competitive Endogenous RNA
CESC: Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma
CircRNA: Circular RNA
CTLA4: Cytotoxic T Lymphocyte-Associated Protein4
DE: Differentially Expressed
ENCORI: The Encyclopedia of RNA Interactomes
FDR: False Discovery Rate
G: Gene
GDC: Genomic Data Commons
GEPIA: Gene Expression Profiling Interactive Analysis
HPV: Human Papilloma Virus
ICGs: Immune Checkpoint Genes
LncRNA: Long Non-Coding RNA
MF: Molecular Functions
MiRNA: Micro RNA
MRE: miRNA Response Element
mRNA: Messenger RNA
MSC-AS1: Musculin Antisense RNA 1
MSRB3: Methionine Sulfoxide Reductase B3
MS4A4A: Membrane Spanning 4-Domains A4A
NRP1: Neuropilin 1
PD-1: Programmed Death 1
PD-L1: Programmed Death Ligand 1
RNA: Ribonucleic Acid
TCGA: The Cancer Genome Atlas
UCSC: University of California Santa Cruz
VSIG4: V-Set and Immunoglobulin Domain-Containing 4