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The Role of Significantly Deregulated MicroRNAs in Recurrent Cervical Cancer Based on Bioinformatic Analysis of the Cancer Genome Atlas Data

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ABSTRACT

To screen for differentially expressed microRNAs (miRNAs) between recurrent and primary cervical cancer patient samples, and investigate the prognostic value of the identified miRNAs, based on The Cancer Genome Atlas (TCGA) database. Differentially expressed miRNAs between recurrent and primary cervical cancer, identified from TCGA database, were selected by edgeR package in the R software. Overlapping target genes predicted by TargetScan, miRTarBase, and miRDB online analysis tools were chosen for Gene Ontology (GO) classification and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. Furthermore, the prognostic value of each miRNA was assessed using Kaplan–Meier curves. Nineteen differentially expressed miRNAs were identified, including 14 upregulated and 5 downregulated miRNAs, in recurrent cervical cancer. One hundred and sixteen target genes were predicted by the three prediction tools. GO analysis showed 19 significant categories, including "metal ion binding," "vasculogenesis," and "cytosol component." KEGG analysis identified 54 significant biological pathways, such as "proteoglycans in cancer signaling pathway" and "HTLV-I infection signaling pathway." Three miRNAs were significantly associated with the prognosis of cervical cancer, namely, miR-150 ($p = 0.012$), miR-204 ($p = 0.032$), and miR-194-1 ($p = 0.042$), and high expression of each showed prolonged overall survival. miRNAs differentially expressed between primary and recurrent cervical cancer, such as miR-150, miR-204, and miR-194-1, were identified. Our findings might help clarify molecular mechanisms underlying recurrence, and offer potential specific targets for recurrent cervical cancer treatment.

Keywords: cervical cancer, differentially expressed miRNAs, overall survival, recurrence.

1. INTRODUCTION

STATISTICALLY, CERVICAL CANCER is the fourth most common malignancy worldwide, with an estimated 527,600 new cases diagnosed and 265,700 deaths in 2012 (Torre et al., 2015). Although the wide use of cervical cytology screening has facilitated timely diagnosis and treatment of cervical cancer, there are still a number of patients diagnosed at advanced or metastatic stages, especially in less developed countries.

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Recurrence rate of cervical cancer increases with the disease stage (Perez et al., 1995). Even with accepted radical chemoradiotherapy, patients with advanced or metastatic disease face a high risk of recurrence. It is reported that the total recurrence rate of cervical cancer is about 20%–30% (Legge et al., 2015; Yoshida et al., 2018), and the prognosis of recurrent cervical cancer is poor; effective treatment options are not widely available. The main therapeutic methods for recurrent cervical cancer include surgery, radiotherapy, and/or chemotherapy, based on the primary treatment and the site of recurrence; there are no effective drugs against cervical cancer yet.

The prediction of recurrence is critical in improving clinical outcomes; however, recurrence of malignant tumors is a complex and dynamic biological event, and the molecular mechanism is not well studied. It is unclear whether the specific signaling pathways involved in initial tumorigenesis are dysregulated or whether new genes and pathways are involved in recurrence. In addition, there is a lack of valuable molecular biomarkers that predict cancer recurrence. In this study, we aimed to identify possible microRNA (miRNA) biomarkers that specifically predict recurrence.

miRNAs are small noncoding RNAs, which act at the post-transcriptional level as epigenetic regulators. They can bind to the 3′-untranslated region (3′-UTR) of target messenger RNAs (mRNAs), inhibiting the translation process, or initiating the process of mRNA degradation (Guo et al., 2010). miRNAs have been found to be significantly deregulated in several tumors (Peng et al., 2016). Recently, the clinical significance and biological functions of some miRNAs have been elucidated in cervical cancer (Liu et al., 2012; Yang et al., 2015; Zhou et al., 2015; Gao et al., 2018), but few reports focused on recurrent cervical cancer.

In this study, using the miRNA expression profiles of primary and recurrent cervical cancer samples from The Cancer Genome Atlas (TCGA) database, we identified differentially expressed miRNAs and the potential molecular mechanisms underlying recurrent cervical cancer. Our findings shed further light on the molecular basis of recurrent cervical cancer and may provide new therapeutic targets for prevention and treatment of recurrent cervical cancer.

2. METHODS

2.1. miRNA expression profiles and identification of differentially expressed miRNAs

The miRNA-seq data at level 3 and the corresponding survival information of cervical cancer patients were downloaded from TCGA. Data for a total of 309 samples were obtained, including 286 primary and 23 recurrent cervical cancer samples. Differentially expressed miRNAs between primary and recurrent cervical cancer were selected based on their fold change (FC) and adjusted *p*-values, which were generated by the edgeR package in the R software (www.bioconductor.org/packages/release/bioc/html/edgeR.html). We defined false discovery rate <0.05 and $|\log_2 FC| > 1$ as the thresholds for this analysis.

2.2. Predicting target genes of differentially expressed miRNAs

The target genes of differentially expressed miRNAs were predicted using the TargetScan (www.targetscan.org), miRTarBase (http://mirtarbase.mbc.nctu.edu.tw), and miRDB (http://mirdb.org/miRDB) online analysis tools. Overlapping target genes among the three tools were selected to make the bioinformatic analysis more reliable.

2.3. Gene Ontology classification and Kyoto Encyclopedia of Genes and Genomes pathway analysis

The online Database for Annotation Visualization and Integrated Discovery (DAVID; http://david.abcc.ncifcrf.gov) was used to obtain functional Gene Ontology (GO) term and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation of target genes. *p*-Values <0.05 were selected.

2.4. Survival analysis

Complete clinical information, available for 307 patients of the cervical cancer cohort within TCGA, was individually reviewed for overall survival (OS) time. Differentially expressed miRNAs were normalized by $\log_2$ transformation, and high or low expression was defined by their median values. The prognostic value of each miRNA was assessed using the log-rank test, based on Kaplan–Meier curves.

3. RESULTS

3.1. Differentially expressed miRNAs

Volcano plots and heat maps were generated to select differentially expressed miRNAs, as shown in Figure 1A and B. According to the cutoff criteria, 19 miRNAs were screened to be differentially expressed in recurrent cervical cancer in comparison with primary cervical cancer (14 upregulated and 5 downregulated) The upregulated miRNAs included miR-592, miR-891a, and miR-582, and the downregulated miRNAs included miR-133a-1 and miR-150, among others. The complete list of differentially expressed miRNAs is shown in Table 1.

3.2. Target gene prediction

The target genes of the differentially expressed miRNAs were predicted by TargetScan, miRTarBase, and miRDB. For some miRNAs, target genes have not yet been predicted. In all, 116 genes overlapping between the three prediction tools were selected for further analysis. They were mainly the target genes of miR-150, miR-194, miR-204, and miR-375.

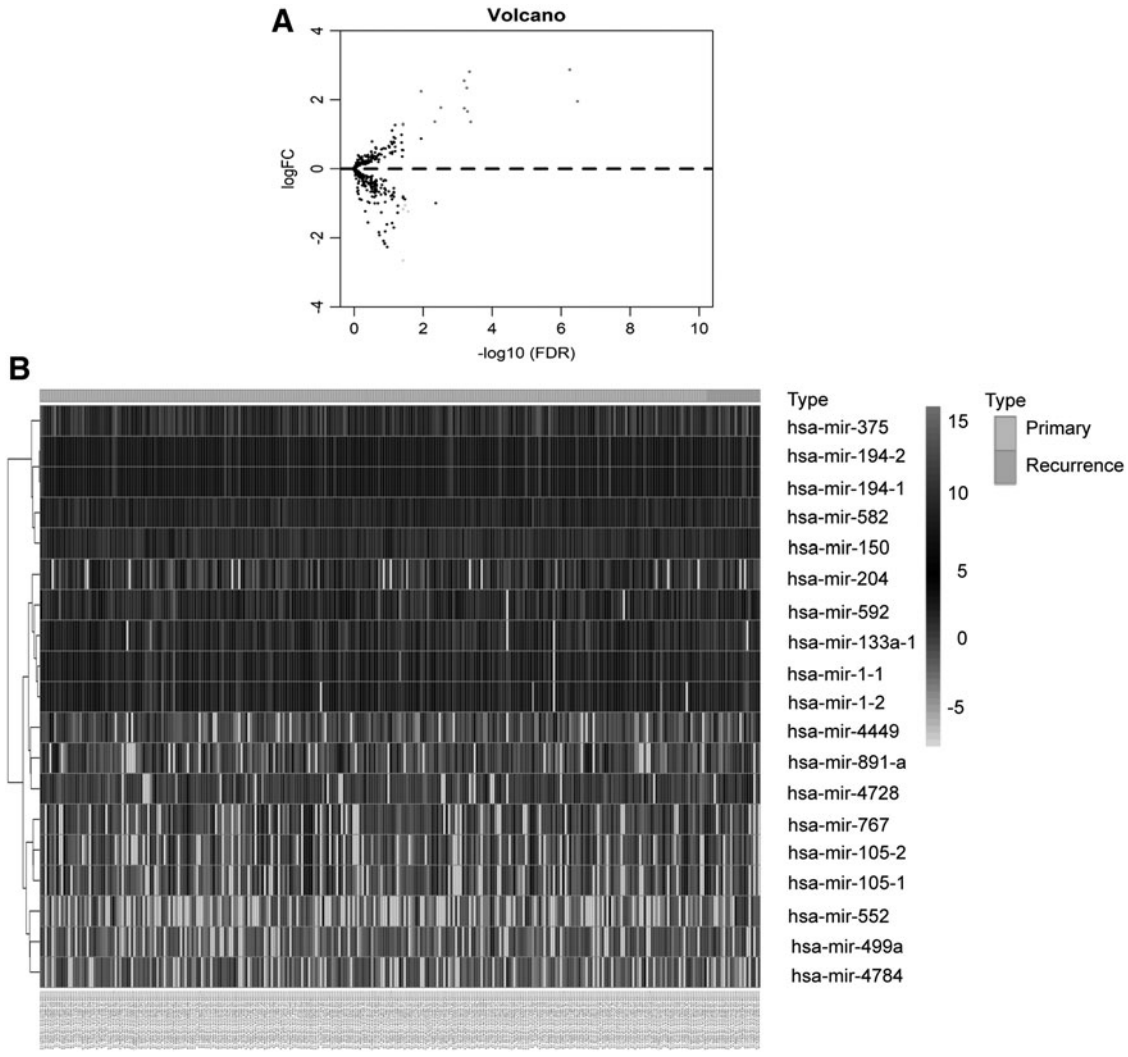

FIG. 1. **(A)** Volcano plots for expression of differentially expressed miRNAs. *X* axis: $-\log_{10}$ (FDR), *Y* axis: logFC. Dark dots represent upregulated miRNAs, whereas lighter dots represent downregulated miRNAs. **(B)** Heat map showing hierarchical gene clustering analysis of the differentially expressed miRNAs. (Values are normalized by $\log_{10}$ transformation.) Dark represents upregulated miRNAs, whereas lighter represents downregulated miRNAs. FC, fold change; FDR, false discovery rate; miRNA, microRNA.

Table 1. Differentially Expressed MicroRNAs in Recurrent Cervical Cancer

miRNA	p	*FDR*	*Regulation*
miR-592	8.24E-10	3.36E-07	Up
miR-891a	2.75E-09	5.62E-07	Up
miR-582	3.09E-06	0.000421	Up
miR-552	4.41E-06	0.00045	Up
miR-4728	6.34E-06	0.000518	Up
miR-499a	7.93E-06	0.000539	Up
miR-204	1.11E-05	0.000644	Up
miR-767	1.27E-05	0.000649	Up
miR-375	6.78E-05	0.003073	Up
miR-4449	0.000124	0.004583	Up
miR-105-2	0.000355	0.011457	Up
miR-105-1	0.000382	0.011457	Up
miR-133a-1	0.000997	0.027126	Down
miR-150	0.001296	0.033042	Down
miR-194-2	0.001764	0.038442	Up
miR-1-1	0.001862	0.038442	Down
miR-1-2	0.001911	0.038442	Down
miR-4784	0.002167	0.038442	Down
miR-194-1	0.002356	0.038456	Up

FDR, false discovery rate; miRNA, microRNA.

3.3. GO classification analysis

GO includes molecular function, biological process, and cellular component analyses. Through GO analysis of the target genes, we found that the genes clustered in 19 significant GO categories, including ''positive regulation of histone H3-K9 methylation,'' ''metal ion binding,'' and ''vasculogenesis,'' as shown in Figure 2A and Table 2.

3.4. KEGG pathway analysis

KEGG pathway enrichment analysis identified 54 significant biological pathways related with the target genes (Fig. 2B). Table 3 shows the top 10 enriched signaling pathways, the most significant of which are ''proteoglycans in cancer signaling pathway'' and ''HTLV-I infection signaling pathway.''

3.5. Survival analysis

To further explore the role of the identified miRNAs, we statistically evaluated the association between miRNA expression and patient OS, based on data from the 307 patients with complete follow-up information. Three miRNAs were statistically associated with the prognosis of cervical cancer, namely, miR-150 ($p=0.012$), miR-204 ($p=0.032$), and miR-194-1 ($p=0.042$); high expression of each was significantly associated with prolonged OS (Fig. 3). In addition, a survival advantage was associated with high expression of miR-194-2, miR-133a-1, and miR-4728; however, this was not statistically significant.

4. DISCUSSION

The high incidence and unfavorable prognosis of recurrent cervical cancer make it a challenging disease to effectively combat. Clinically, there are generally accepted predictive risk factors for recurrence, such as ''Sedlis Criteria'' and ''Four-factor model'' (Estape et al., 1998; Diaz et al., 2014; Ryu et al., 2014). These mainly take into consideration pathological and clinical factors, such as stromal invasion, tumor size, tumor histology, and lymph vascular space invasion. However, the mechanism of recurrence is yet unclear. To address this, we aimed to uncover a common molecular characteristic in recurrent cervical cancer samples, and to identify biomarkers for recurrent cervical cancer prediction and diagnosis.

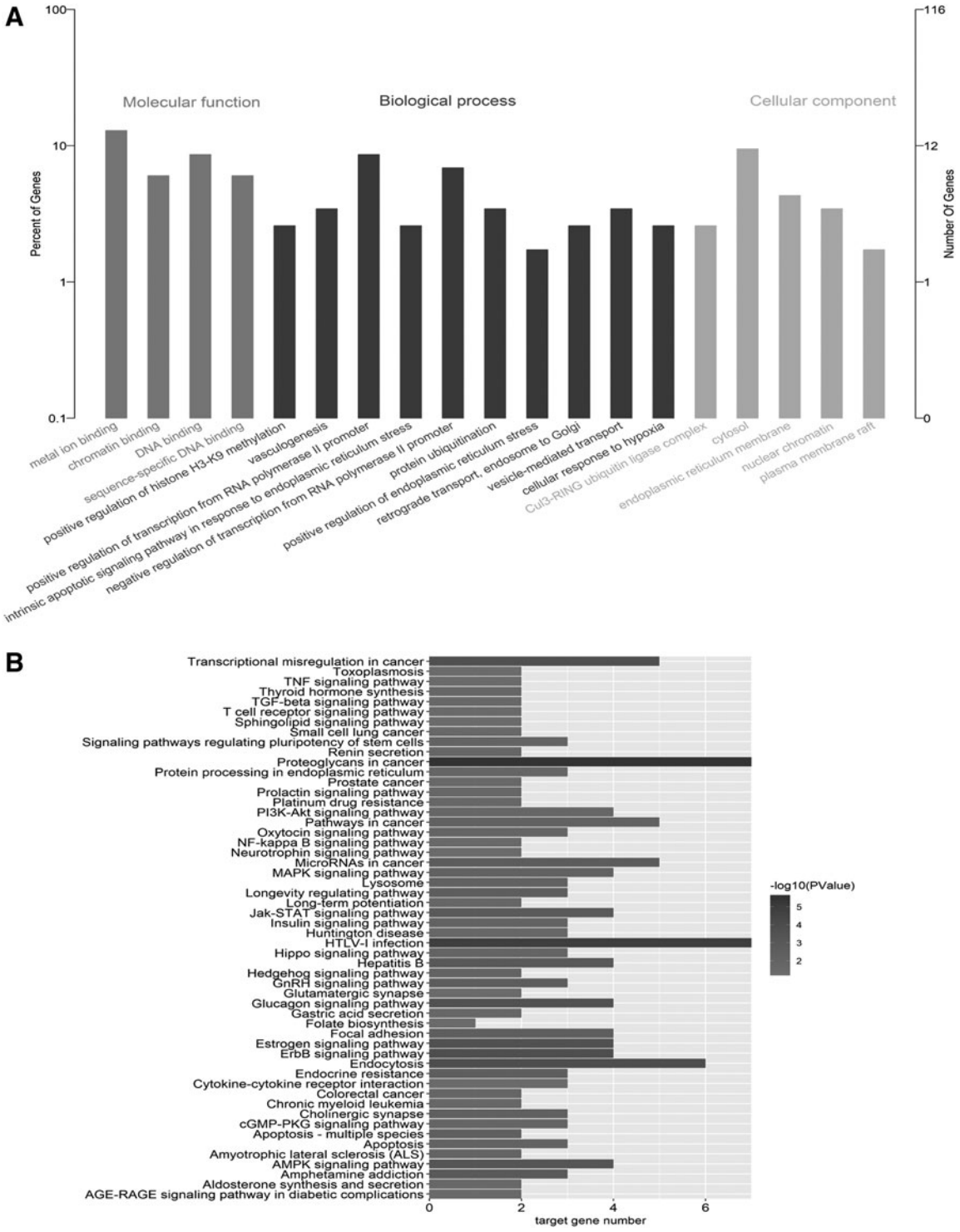

FIG. 2. **(A)** GO enrichment analysis of target genes. *X* axis: statistically enriched GO biological process terms, *Y* axis: the number/percentage of target genes in each GO term. **(B)** KEGG pathway analysis of target genes. *X* axis: the number of target genes in each pathway, *Y* axis: statistically enriched KEGG pathway. Grayscale represents *p*-value, as shown in the legend. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table 2. The Top 10 Significant Gene Ontology Terms for the Target Genes

Term	*Count*	p
GO:0051574—positive regulation of histone H3-K9 methylation	3	3.67E-04
GO:0001570—vasculogenesis	4	0.004698
GO:0046872—metal ion binding	15	0.006818
GO:0003682—chromatin binding	7	0.010058
GO:0031463—Cul3-RING ubiquitin ligase complex	3	0.010416
GO:0045944—positive regulation of transcription from RNA polymerase II promoter	10	0.012743
GO:0070059—intrinsic apoptotic signaling pathway in response to endoplasmic reticulum stress	3	0.014053
GO:0005829—cytosol	11	0.016523
GO:0000122—negative regulation of transcription from RNA polymerase II promoter	8	0.017442
GO:0016567—protein ubiquitination	4	0.024575

GO, Gene Ontology.

miRNAs have garnered attention recently due to their roles in tumors. It has been reported that cancer cells with abnormal miRNA expression might evolve characteristics of cell proliferation, cell death resistance, invasion and metastasis, and angiogenesis induction (Peng and Croce, 2016). To date, few studies have identified miRNAs with a role in recurrence of malignant tumors, and recurrent cervical cancer is no exception. Although there are increasing reports with bioinformatic analyses of cancer data from public databases (Gao et al., 2018; Ge et al., 2018; Wu and Zhang, 2018), there are few reports on recurrent tumors, especially on the involvement of miRNAs.

By preprocessing data from 286 primary and 23 recurrent cervical cancer samples, we identified 19 differentially expressed miRNAs. Among these identified miRNAs, most have been shown to function as oncogenic or antioncogenic regulators. However, only a few were reported to regulate biological activities in cervical cancer. For example, miR-133a was found to be significantly downregulated in cervical cancer tissues compared with matched adjacent normal tissues, and it could suppress cervical cancer growth in vitro and in vivo through targeting EGFR (Song et al., 2015b). miR-375 was shown to be associated with high-risk HPV-positive cervical cancer, modulating proliferation, invasion, radiosensitivity, and drug resistance through different signaling pathways (Wang et al., 2011; Shen et al., 2013; Song et al., 2015a). In terms of recurrence predictors, the only report available is regarding the combination of miR-375 and miR-142-5p in tissue samples of gastric cancer patients (Zhang et al., 2011).

Pathway analysis of the target genes of the identified miRNAs showed that they were significantly enriched in ''proteoglycans in cancer'' and ''HTLV-I infection signaling pathway.'' Proteoglycans, major components of the extracellular matrix, are considered to contribute to cancer pathogenesis and metastasis in specific tumor types (Theocharis and Karamanos, 2017). Moreover, the extracellular matrix plays a key role in regulating cancer cell stemness (Liu et al., 2015); in fact, cervical cancer stem cells are recognized

Table 3. The Top 10 Significantly Enriched Kyoto Encyclopedia of Genes and Genomes Pathways for the Target Genes

Pathway ID	*Description*	p	*No. of genes*	*Involved genes*
hsa05205	Proteoglycans in cancer	2.93E-06	7	*ELK1*, *IP3R*, *PDCD4*, *C-CB1*, *Frizzled*, *Ezrin*, *HB-EGF*
hsa05166	HTLV-I infection	1.29E-05	7	*TLN*, *FRZ*, *CN*, *TGF-βR*, *TCF*, *EGR-2*, *C-MYB*
hsa04144	Endocytosis	0.000128	6	*TGF-βR*, *ArfGAP*, *CAPZA*, *Rab22*, *Rab10*, *CBL*
hsa04012	ErbB signaling pathway	0.000151	4	*HB-EGF*, *EPR*, *CBL*, *ELK*
hsa05202	Transcriptional misregulation in cancer	0.000207	5	*TEFb*, *RUNX2*, *ZEB1*, *SP-1*, *TGFBR2*
hsa04915	Estrogen signaling pathway	0.000233	4	*HB-EGF*, *IP3R*, *TF*, *CREB*
hsa04922	Glucagon signaling pathway	0.00026	4	*IP3R*, *CREB*, *CALN*, *SIRT1*
hsa04152	AMPK signaling pathway	0.000548	4	*CREB*, *AdipoR*, *RAB*, *SIRT1*
hsa05161	Hepatitis B	0.000962	4	*BCL2*, *CREB*, *ELK-1*, *EGR2/3*
hsa05031	Amphetamine addiction	0.001111	3	*PP2B*, *CREB*, *SIRT1*

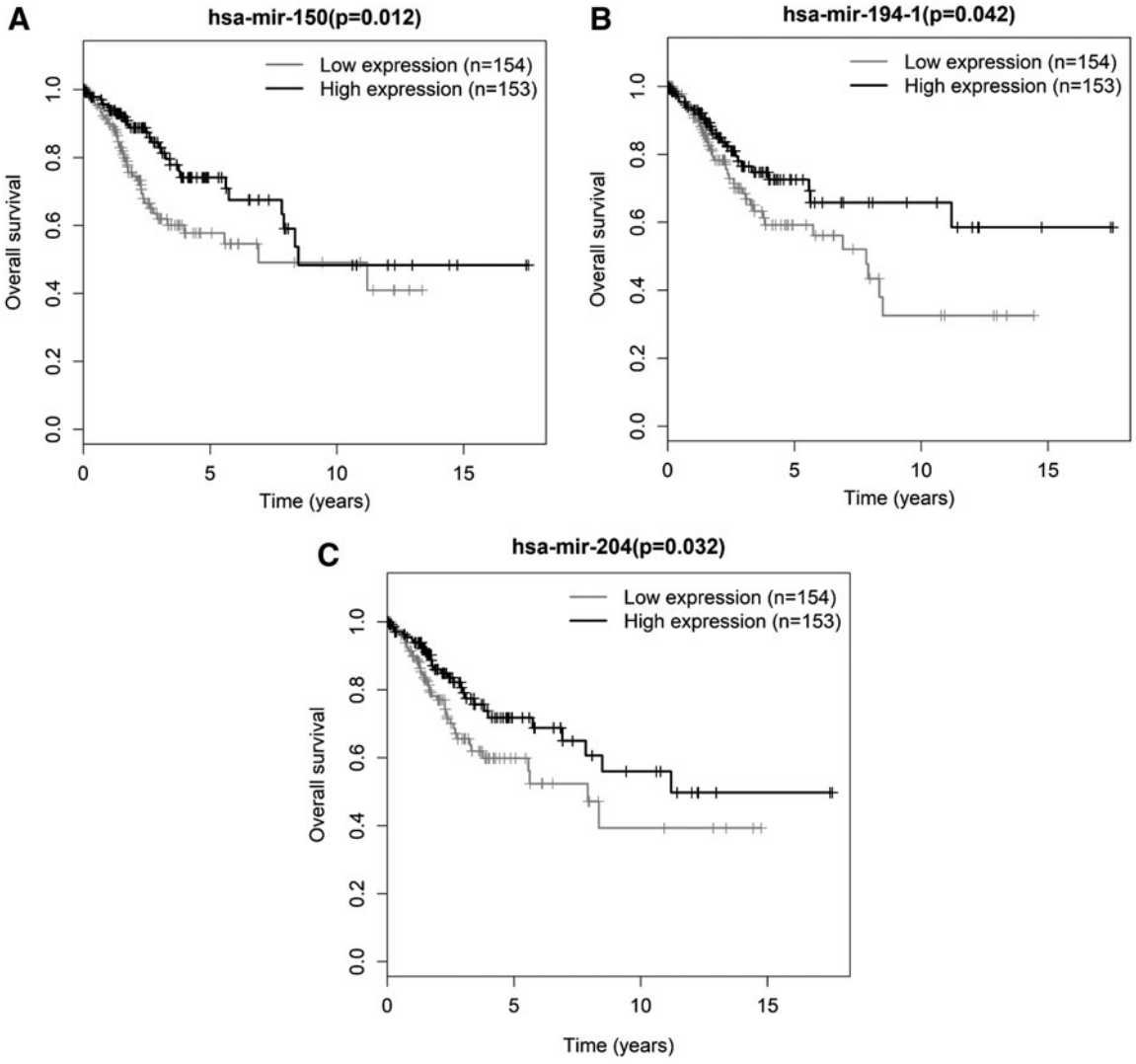

FIG. 3. Association of overall survival with the statistically deregulated miRNAs. **(A)** miR-150, **(B)** miR-194-1, **(C)** miR-204. Dark lines represent high expression, and lighter lines represent low expression. *X* axis: overall survival time (years), *Y* axis: overall survival probability.

as the origin of recurrence (Kidd and Grigsby, 2008; Cooke et al., 2011). Using proteoglycans as biomarkers or therapeutic targets is a recently developed innovative diagnostic and treatment strategy (Nikitovic et al., 2018). Genes of other classical cancer-related pathways, such as ErbB and AMPK signaling pathways, which were found to be enriched in our study, might also be involved in the recurrence of cervical cancer. In addition, the most enriched GO terms such as ''vasculogenesis'' and ''metal ion binding'' are closely related to cancer (Folkman, 1971; Koedrith and Seo, 2011).

Investigation of the clinical value of the miRNAs revealed that among the 19 miRNAs, 3 miRNAs showed prognostic significance. miRNA-150 was shown to exert a tumor-suppressive role in melanoma and colorectal cancer (Li et al., 2018; Sun et al., 2018), but an oncogenic role in cervical cancer (Li et al., 2015; Zhang et al., 2018). Our data indicated a lower expression in recurrent patients and a shorter OS in all patients, implying a potential role of miRNA-150 in suppressing tumors. A previous study showed that miR-204, another tumor suppressor, might inhibit cell proliferation and invasion by directly targeting EphB2 in cervical cancer cells (Duan et al., 2018). miR-204 was observed to be significantly decreased in primary cervical cancer tissues, and lower miR-204 expression was associated with poor survival (Shu et al., 2018). Our survival analysis of miR-204 was consistent with these results, but we surprisingly found out that it was upregulated in recurrent cervical cancer. Similarly, high expression of miR-194-1 was

associated with both recurrence and good survival prognosis. We do not have any concrete data to explain this inconsistency between recurrence and prognosis, but one possibility may be that miRNAs have multiple functions in cancer biology, and could change their roles at different stages, either promoting or suppressing tumor progression.

In conclusion, we identified significant miRNAs and possible signaling pathways involved in recurrent cervical cancer by bioinformatic analyses. Owing to the difficulty in obtaining fresh recurrent cervical cancer tissue samples, we were unable to verify the expression of these identified miRNAs. Nevertheless, our study highlights the importance of studying miRNAs in both recurrent and primary cervical cancer samples. Since the roles of most identified miRNAs remain unexplored in cervical cancer or in cancer recurrence in general, the results revealed in our study provide new perspectives for further research. In addition, the miRNAs might be valuable as diagnostic biomarkers and effective targets for cervical cancer management.

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AUTHOR DISCLOSURE STATEMENT

The authors declare there are no competing financial interests.

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