Investigation of differentially-expressed microRNAs and genes in cervical cancer using an integrated bioinformatics analysis

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Abstract. Cervical cancer is one of the most common types of cancer among women worldwide. In order to identify the microRNAs (miRNAs/miRs) and mRNAs associated with the carcinogenesis of cervical cancer, and to investigate the molecular mechanisms of cervical cancer, an miRNA microarray, GSE30656, and 3 mRNA microarrays, GSE63514, GSE39001 and GSE9750, for cervical cancer were retrieved from Gene Expression Omnibus. These datasets were analyzed in order to obtain differentially-expressed genes (DEGs) and miRNAs using the GEO2R tool. Gene Ontology (GO) and pathway enrichment analysis for DEGs were performed using the Database for Annotation, Visualization and Integrated Discovery. Protein-protein interaction (PPI) analysis for DEGs was conducted using The Search Tool for the Retrieval of Interacting Genes software and visualized using Cytoscape, followed by hub gene identification, and biological process and pathway enrichment analysis of the module selected from the PPI network using the Molecular Complex Detection plugin. In addition, miRecords was applied to predict the targets of differentially-expressed miRNAs. A total of 44 DEGs and 15 differentially-expressed miRNAs were identified. These DEGs were mainly enriched in GO terms associated with the cell cycle. In the PPI network, cyclin-dependent kinase 1, topoisomerase DNA IIα, aurora kinase A (*AURKA)* and minichromosome maintenance complex component 2 (*MCM2*) had higher degrees of connectivity. A significant module was detected from the PPI network. *AURKA*, *MCM2* and kinesin family member 20A exhibited higher degrees in this module, while the genes in the module were mainly involved in the cell cycle and the DNA replication pathway. In addition, estrogen receptor 1 was predicted as the potential target of 13 miRNAs. A total of 10 DEGs were identified as potential targets of miR-203. In conclusion, the results indicated that microarray dataset analysis may provide a useful method for the identification of key genes and patterns to successfully identify determinants of the carcinogenesis of cervical cancer. The functional studies of candidate genes and miRNAs from these databases may lead to an increased understanding of the development of cervical cancer.

Introduction

Cervical cancer is one of the most common types of gynecological malignancy worldwide, with an annual incidence rate of ~454,000 cases in 2010 (1,2). Epidemiological and clinical studies have established a causal association between persistent infection of high-risk human papilloma virus (HR-HPV) types (including HPV 16 and 18) and cervical carcinogenesis (3), with the contribution of additional cofactors including smoking or the use of oral contraceptives (4). It is known that the integration of HR-HPV DNA into the host cell genome results in elevated expression of HPV E6 and E7 oncoproteins (5), which subsequently allows the virus to replicate through inhibitory effects on the tumor suppressor proteins p53 and retinoblastoma protein, respectively (6,7). The inhibition of these tumor suppressors results in uncontrolled cellular proliferation and the accumulation of specific epigenetic changes in the host cell genome, driving progression to a malignant phenotype (3). However, the mechanism of the progression from preneoplastic lesions and cervical intraepithelial neoplasia to carcinoma remains unknown.

HPV infection is necessary, but the E6-p53 and E7-Rb model is not sufficient to inevitably produce cervical carcinoma (8). Only a small number of women who are infected with HR-HPV will develop cervical cancer, highlighting the multistep nature of cervical carcinogenesis and the variety of cofactors required. A range of genetic and epigenetic events contribute to the initiation of cervical cancer. However, more insight is required into the genetic and epigenetic alterations that occur during cervical carcinogenesis in order for the identification of genes that are involved in the development and progression of cervical cancer (4,9).

MicroRNAs (miRNAs/miRs) are small non-coding single-stranded RNAs that regulate gene expression and perform an important role in the regulation of cellular

differentiation, proliferation and apoptosis (10,11). Furthermore, certain miRNAs are considered to be oncogenes or tumor suppressor genes, and exhibit altered expression profiles in cervical cancer tumors (1).

A large amount of data on the transcriptome and the proteome states of cells has recently been created via the wide use of a number of high-throughput technologies. The large amount of publically available molecular data allows for the bioinformatic investigation of numerous factors, including biochip data extraction, sequence alignment, biological data clustering and pathway analysis. These analyses methods provide ways to study the molecular pathogenesis of various types of cancer.

The present study aimed to identify candidate biomarkers or therapeutic targets of cervical cancer, by investigating microarray data detailing the mRNA HR-HPV oncogenes and miRNA expression profiles in cervical cancer. These expression profiles data were retrieved from the Gene Expression Omnibus (GEO) database (12) and were analyzed to identify differentially-expressed genes (DEGs) and miRNAs. Combined bioinformatics methods, including functional annotation and pathway enrichment analysis, protein-protein interaction (PPI) network construction and mRNA-miRNA interaction analysis, were performed to obtain the key genes or miRNAs involved in cervical cancer.

Materials and methods

Acquisition of microarray datasets. Microarray data detailing cervical cancer-associated the miRNA microarray dataset GSE30656 and mRNA microarray datasets GSE63514, GSE39001 and GSE9750 were retrieved and downloaded from the National Center for Biotechnology Information GEO database (http://www.ncbi.nlm.nih.gov/geo). The dataset GSE30656, based on the platform of GPL 6955 Agilent-016436 Human miRNA Microarray 1.0 (Agilent Technologies, Inc., Santa Clara, CA, USA), included 10 patients with HR-HPV-positive cervical cancer and 10 normal cervical (NC) tissues samples. The dataset GSE63514, using the GPL570 Affymetrix Human Genome U133 Plus 2.0 Array (Affymetrix, Inc., Santa Clara, CA, USA), included 28 patients with cervical cancer and 24 NC samples. GSE39001 included 43 patients with HPV16-positive cervical cancer and 12 NC samples, and GSE9750 included 33 patients with cervical cancer that were mainly marked by HPV16 or HPV18 and 24 NC samples, based on the GPL201 Affymetrix Human HG-Focus Target Array and the GPL96 Affymetrix Human Genome U133A Array (both from Affymetrix, Inc.), respectively.

Data processing. In the present study, GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r/) was applied to screen differentially-expressed miRNAs and DEGs between cervical cancer and NC samples. GEO2R is an R programming language-based dataset analysis tool based on a *t*-test or analysis of variance. GEO2R is an interactive tool that allows users to compare two groups of samples in a GEO series in order to identify DEGs or miRNAs under the same experimental conditions (13). In total, >90% of GEO data can be accessed and analyzed in this way, and results are presented as a table of genes in sequence of significance and may be viewed as profile graphs.

GEO2R handles a large quantity of experimental designs and data types, and applies the adjusted P-value (adj. P) to assist in correcting for the occurrence of false-positives. In the present study, differentially-expressed miRNAs and DEGs between cervical cancer and NC tissues were screened using an adj. P<0.05 and a fold-change of >2 as the threshold values.

Gene ontology and pathway enrichment analysis. Significantly changed DEGs were submitted to the Database for Annotation, Visualization and Integrated Discovery (DAVID; http://david.abcc.ncifcrf.gov/), an online tool for functional annotation analysis (14). The significant enrichment analysis of DEGs was assessed based on the gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG; http://www.genome.jp/kegg/kegg2.html) with P<0.05 as the cutoff. GO terms consisted of 3 aspects: Biological process, cellular component and molecular function.

PPI network construction. High-quality protein interaction networks can provide key insights into the functional and biological properties of cellular systems. The Search Tool for the Retrieval of Interacting Genes (STRING; http://string.embl.de/) database (15) is an online tool of known and predicted protein interactions, including physical and indirect functional associations. The PPI network of DEGs was constructed using STRING with a combined score of >0.4 and visualized using Cytoscape (16), an open source software platform for visualizing molecular interaction networks and integrating data.

Modules selection from PPI network. As a plugin to Cytoscape, Molecular Complex Detection (MCODE) (17) was used to detect densely connected regions from the PPI network with the following cutoff values: Degree cutoff, 2; node score cutoff, 0.2; k-core, 2; and maximum depth, 100. Subsequently, based on modules selected from the PPI network, functional enrichment analysis was performed with the criterion of P<0.05.

mRNA-miRNA interaction analysis. Targets of differentially-expressed miRNAs were predicted using miRecords (http://c1.accurascience.com/miRecords/) (18), an integrated resource for miRNA-target interactions, which stores miRNA targets predicted by 11 established target prediction tools. The overlap predicted by at least 3 of these target prediction programs were selected as targets of miRNAs.

Results

Identification of DEGs. In the present study, the mRNA expression profiling datasets GSE63514, GSE39001 and GSE9750 were screened using the GEO2R tool to identify genes that were differentially expressed between normal and cancerous tissues. A total of 939, 113 and 2,117 genes were identified as the DEGs from these datasets, respectively (Fig. 1). There were 44 DEGs that exhibited the same expression trends in all 3 datasets; 20 of these were downregulated and 24 were upregulated in cervical cancer (Table I).

Significant functions and pathway enrichment analysis. To reveal the biological significance of the common DEGs in the

Table I. All 44 differentially-expressed genes that exhibited the same expression trends in all three datasets.

		Log FC	
Gene name	GSE39001	GSE9750	GSE63514
CFD	3.99	2.83	2.91
APOD	3.76	2.55	3.53
CRNN	3.36	8.07	9.51
CXCL14	3.22	2.27	3.77
MAL	3.18	6.35	6.35
CRISP3	3.18	7.21	8.91
ESR1	3.10	3.15	4.12
CRCT1	3.02	5.54	5.34
DEFB1	2.79	1.70	2.68
SPINK5	2.78	4.98	5.85
NDN	2.69	1.53	2.38
ID4	2.63	2.31	2.07
KRT13	2.61	4.50	4.67
ALOX12	2.50	5.56	5.27
SPRR3	2.50	4.64	5.56
PPP1R3C	2.47	4.54	5.12
EDN3	2.36	5.13	5.40
MPPED2	2.31	1.51	3.19
FCGBP	2.22	1.60	4.72
CYP2B6	2.08	1.73	2.63
NEK2	-2.05	-3.40	-2.64
PLOD2	-2.08	-1.92	-3.23
KIF20A	-2.10	-1.78	-2.09
CXCL9	-2.12	-1.50	-3.71
CENPA	-2.13	-1.77	-2.70
AURKA	-2.18	-2.41	-2.52
CXCL10	-2.20	-1.34	-2.97
APOBEC3B	-2.29	-1.50	-2.58
MCM2	-2.39	-2.33	-2.61
SMC4	-2.45	-1.50	-3.02
MMP1	-2.46	-5.49	-2.82
CDK1	-2.49	-2.41	-2.88
SYCP2	-2.51	-3.34	-5.15
CDKN3	-2.58	-1.06	-2.53
TOP2A	-2.60	-2.24	-2.53
CDKN2A	-2.61	-3.78	-6.41
RFC4	-2.75	-1.76	-3.15
KRT17	-2.80	-1.95	-2.63
UBD	-2.81	-3.46	-2.00
PRC1	-2.86	-1.65	-2.25
TYMS	-3.22	-2.03	-2.09
MMP12	-3.23	-2.68	-5.05
NUSAP1	-3.35	-1.73	-2.36
RRM2	-3.48	-1.94	-2.16

A positive log FC value indicates that the gene expression level was down-regulated in the cervical cancer samples, whereas a negative log FC value indicates that the gene expression level was upregulated in the cervical cancer samples. Thresholds used in the GEO2R analysis were adjusted P<0.05, fold >2. Gene names were listed in line with the gene database at the national center for biological information. FC, fold-change.
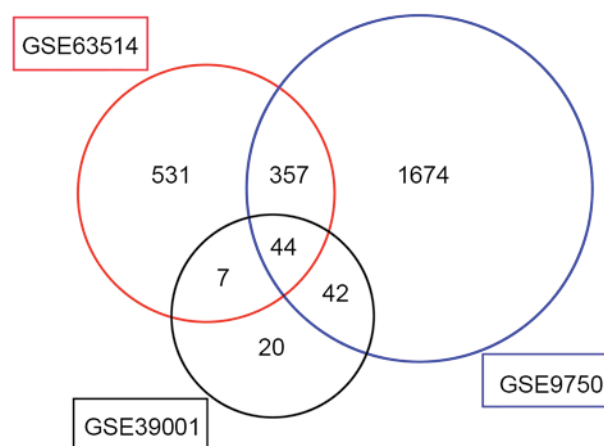

Figure 1. Identification of differentially-expressed genes in mRNA expression profiling datasets GSE63514, GSE39001 and GSE9750 using the GEO2R tool. Thresholds used in the GEO2R analysis were adjusted P<0.05, fold-change >2.

carcinogenesis of cervical cancer, GO functional and pathway enrichment analysis were performed on the 44 aforementioned DEGs using DAVID. As demonstrated in Table II, DEGs are involved in a number of biological processes, including the cell cycle, cellular division, DNA replication and chemotaxis. In terms of cellular components, the DEGs were mainly enriched in the microtubular cytoskeleton, spindle and cytoskeleton. The molecular function terms in the DEGs were chemokine activity and chemokine receptor binding. Based on the KEGG pathway enrichment analysis, the DEGs were identified to be significantly enriched in the p53 signaling pathway.

PPI network of DEGs. The PPI network was constructed to dissect the interactions between DEGs. There were 24 nodes and 75 edges in the network (Fig. 2). A number of upregulated genes had higher node degrees: Cyclin-dependent kinase 1 (*CDK1*; degree, 15), topoisomerase DNA II alpha (*TOP2A*; degree, 14), aurora kinase A (*AURKA*; degree, 13) and kinesin family member 20A (*KIF20A*; degree, 9). Notably, *CDK1* exhibited interactions with *TOP2A*, *AURKA* and *KIF20A*, as well as minichromosome maintenance complex component 2 (*MCM2*) and estrogen receptor 1 (*ESR1*), respectively. *AURKA* was also observed to be associated with *KIF20A*.

Module analysis. A significant module that included 11 nodes and 26 edges was identified from the PPI network with an MCODE score ≥4 (Fig. 3). *AURKA* (degree, 9), *MCM2* (degree, 6) and *KIF20A* (degree, 6) possessed higher degrees of connectivity. *MCM2* had interactions with *AURKA* and *KIF20A*, respectively. Based on DAVID software, overrepresented biological functions were identified for these genes of the module. A total of 37 GO functions were enriched. As demonstrated in Table III, these genes were mainly enriched in the cell cycle, which is similar to the aforementioned result. The KEGG pathway enrichment analysis revealed that these genes were associated with the DNA replication pathway.

Identification of differentially-expressed miRNAs and potential target genes. In the present study, the miRNA

Table II. Gene ontology and pathway enrichment analysis for DEGs.

Category	GO term	Description	Count	P-value
BP	0000278	Mitotic cell cycle	10	7.97×10^{-7}
BP	0022403	Cell cycle phase	10	2.02×10^{-6}
BP	0022402	Cell cycle process	11	3.17×10^{-6}
BP	0007049	Cell cycle	12	7.86×10^{-6}
BP	0048015	Phosphoinositide-mediated signaling	5	1.16×10^{-4}
CC	0015630	Microtubular cytoskeleton	8	7.31×10^{44}
CC	0005819	Spindle	5	7.43×10^{-5}
CC	0044430	Cytoskeletal part	10	1.02×10^{-3}
CC	0005694	Chromosome	7	1.64×10^{-3}
CC	0043228	Non-membrane-bound organelle	16	2.83×10^{-3}
MF	0008009	Chemokine activity	3	7.17×10^{-3}
MF	0042379	Chemokine receptor binding	3	8.10×10^{-3}
KEGG	hsa04115	p53 signaling pathway	3	1.87×10^{-2}

If there were >5 terms enriched by DEGs in this category, the top 5 terms were selected according to the P-value. Count refers to the number of genes significantly enriched in this term. DEGs, differentially-expressed genes; GO, gene ontology; BP, biological process; CC, cellular component; MF, molecular function; KEGG, Kyoto Encyclopedia of Genes and Genomes.
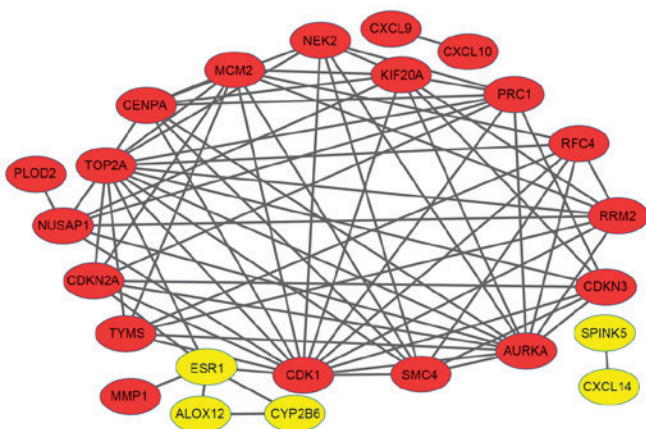

Figure 2. Protein-protein interaction network of differentially-expressed genes. Red nodes represent upregulated genes, whilst yellow nodes represent downregulated genes. The lines (edges) represent interactions between genes.

Figure 3. Significant module in protein-protein interaction network with a molecular complex detection score ≥4. The nodes represent the genes. All genes were upregulated in cervical cancer. The lines (edges) represent interactions between genes.

Table III. Biological process terms of DEGs from the module.

GO term	Description	Count	P-value
0000278	Mitotic cell cycle	7	7.70×10^{-8}
0007049	Cell cycle	8	2.05×10^{-7}
0022402	Cell cycle process	7	9.41×10^{-7}
0022403	Cell cycle phase	6	5.82×10^{-6}
0007017	Microtubule-based process	5	2.30×10^{-5}

If there were >5 terms enriched by DEGs in this category, the top 5 terms were selected according to the P-value. Count refers to the number of genes significantly enriched in this term. DEGs, differentially-expressed genes; GO, gene ontology.
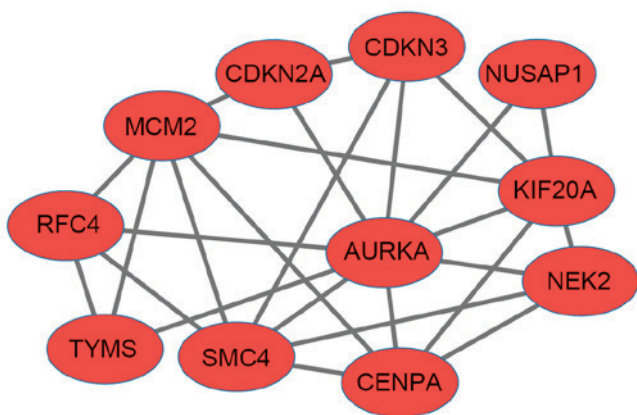
profiling dataset GSE30656 was analyzed to screen the differentially-expressed miRNAs in cervical cancer using the GEO2R tool. As presented in Table IV, a total of 15 differentially-expressed miRNAs were identified from this microarray dataset. A total of 11 miRNAs were significantly downregulated in cervical cancer, whereas the expression levels of the remaining 4 miRNAs were upregulated. The miRNAs with the most significant difference in downregulated and upregulated miRNAs were miR-203 and miR-21, respectively.

The intersections of 44 DEGs in 3 microarray datasets and potential target genes identified by miRecords were determined. As demonstrated in Table IV, by comparing predicted targets of differentially-expressed miRNAs with DEGs, *ESR1* was predicted as the potential target of 13 miRNAs and *CXCL14* was the potential target of 5 miRNAs, including miR-203, miR-494, miR-193b, miR-106b and miR-21. *CXCL9* was identified as a potential target of miR-638 and miR-575, for which their expression levels were negatively associated in cervical cancer tissues. In addition, 10 genes (including *TOP2A*, *SMC4* and *RRM2*) of 44 DEGs were potentially targeted by miR-203.

Table IV. Differentially-expressed miRNAs in cervical cancer and their targets.

miRNAs	P-value	Log FC	Target genes
miR-203	4.76×10^{-5}	2.73	TOP2A, PRC1, CXCL14, CRISP3, ID4, RRM2, TYMS, NDN, ESR1, SMC4
miR-370	7.32×10^{-4}	2.62	AURKA, ESR1, CRCT1
miR-638	8.63×10^{-5}	2.16	CXCL9, ESR1
miR-494	6.72×10^{-4}	1.80	ESR1, PLOD2, CXCL14, MAL
miR-575	5.54×10^{-4}	1.69	ESR1, SMC4, EDN3, CXCL9, CYP2B6, CDKN2A
miR-125b	1.42×10^{-5}	1.67	ESR1, RRM2, SPRR3, CDKN2A
miR-99a	8.47×10^{-4}	1.41	ESR1
miR-572	1.6×10^{-3}	1.31	CRCT1
miR-375	7.39×10^{-6}	1.19	TYMS
miR-193b	1.09×10^{-3}	1.06	CXCL14, ESR1
miR-188	5.91×10^{-3}	1.01	ESR1, MMP1, ID4
miR-106b	6.91×10^{-8}	-1.07	ESR1, CXCL14, CENPA, RRM2, CDKN2A, NDN, CRCT1
miR-15b	2.87×10^{-4}	-1.16	ESR1, CXCL10, MAL, EDN3, CENPA
miR-16	1.39×10^{-4}	-1.22	ESR1, CXCL10, EDN3, CENPA, ID4, PPP1R3C
miR-21	6.34×10^{-6}	-2.51	CXCL14, EDN3, ESR1, NUSAP1

A positive log FC value represents the downregulation of that miRNA in cervical cancer, whilst a negative log FC value represents the upregulation of that miRNA in cervical cancer. Target gene names were listed according to the gene database at national center for biological information. miRNA/miR, microRNA; FC, fold-change.

Discussion

The present study identified 44 DEGs and 15 differentially-expressed miRNAs in cervical cancer compared with control samples. These genes were mainly enriched in the cell cycle, DNA replication and other relevant pathways that were closely associated with cancer, indicating that the present method was effective in identifying key genes.

Through PPI network construction, it was revealed that CDK1, TOP2A, AURKA, MCM2 and KIF20A had higher degrees of connectivity. As a protein kinase of the CDK family, CDK1 performed an important role in cell cycle progression (19). The cell cycle is a strictly regulated process. The main executor protein of the G2/M phase transition is CDK1, the functional activity of which is dependent on the expression of cyclin B proteins. A knockout experiment in mice revealed that CDK1 was required to drive mammalian cellular proliferation (20). Cellular growth of cells was also observed to be successfully inhibited via the functional loss of CDK1 in cervical cancer (21). The TOP2A gene is located on locus q21 of chromosome 17 and encodes a nuclear enzyme involved in DNA replication, transcription and chromosome condensation by altering the topological structure of DNA. Increased expression of TOP2A was identified in cervical cancer using different high-throughput expression profiling technologies (22). The TOP2A and MCM2 genes have been identified as molecular markers for the diagnosis of cervical cancer (23,24). Similar studies have also demonstrated that TOP2A was upregulated in cervical cells and tissues with elevated expression of the HPV E6/E7 proteins (25,26). Notably, the present study revealed that CDK1 interacted with TOP2A and MCM2, suggesting the joint function in cervical cancer.

Additionally, AURKA and KIF20A also had higher degrees in modules of the PPI network. AURKA belongs to serine/threonine protein kinase family. The protein encoded by AURKA is a cell cycle-regulated kinase that is involved in microtubule formation and/or stabilization at the spindle pole during chromosome segregation. Previous studies demonstrated that the overexpression of AURKA promoted tumorigenesis in multiple types of cancer, including neuroblastoma, and ovarian and cervical cancer (27,28). Inhibition of AURKA could improve the sensitivity of cervical cancer cells to taxol by inducing cell cycle arrest and apoptosis (29). In the module of the PPI network, AURKA was observed to interact with KIF20A, a member of the kinesin superfamily of motor proteins. KIF20A attracted attention for its important role in the cell cycle and in cell motility (30,31). KIF20A silencing with small interfering RNA (siRNA) could reduce the proliferation, migration and invasion of pancreatic cancer cells (32). Therefore, these studies support the present finding that AURKA and KIF20A are overexpressed, and are therefore closely associated with cervical cancer.

In the present study, ESR1 was predicted as a potential target of 13 differentially-expressed miRNAs and was downregulated in cervical cancer. ESR1 encodes a ligand-active transcription factor composed of several domains important for hormone binding, DNA binding and the activation of transcription. ESR1 is necessary for sexual development and reproductive function, and performs an important role in cellular development and differentiation. A previous study indicated that the loss of ESR1 enhanced cervical cancer progression and invasion (33). The epigenetic alteration by DNA methylation of ESR1 promoters is associated with the response of patients with advanced invasive cervical carcinoma who are treated

with chemoradiation (34). Furthermore, the present study identified that 3 members of the chemokine family (*CXCL9*, *CXCL10* and *CXCL14*) were potentially targeted by various differentially-expressed miRNAs. Multiplex Luminex immunoassays for cervical cancer cells of patients at different stages demonstrated that *CXCL9* levels progressively increased with the advancement of cervical cancer (35).

Emerging evidence suggests that miRNAs, which regulate gene expression by targeting the 3'-untranslated region of mRNAs to cause translational repression and/or degradation, may be involved in the pathogenesis of several types of human cancer, including cervical carcinoma. Increasing evidence indicates that the dysregulation of miRNAs has been frequently observed in the carcinogenesis of cervical cancer, including metastasis and the drug resistance of tumor cells. Several miRNAs, including miR-9, miR-127, miR-145, miR-146a, miR-199a, miR-200a and miR-424, have been observed to be dysregulated in cervical carcinoma (36). In the present study, 11 downregulated miRNAs and 4 upregulated miRNAs in cervical cancer were identified, as demonstrated in Table IV. miR-203 was observed to be significantly downregulated in cervical cancer, which is consistent with a previous study by Zhao *et al* (37), which demonstrated the lower expression of miR-203 in cervical cancer tissues by quantitative-polymerase chain reaction. miR-203 has been identified as a skin-specific miRNA and it exhibits differential expression between cervical cancer and matched-nontumor cervical tissues (37). miR-203 inhibited cellular proliferation by directly targeting E2F1 in esophageal cancer cells (38). miR-203 has also been reported as being a tumor suppressor by inhibiting tumor growth and angiogenesis in cervical cancer (39).

Among the miRNAs identified in the present study, other miRNAs also have a close association with cervical cancer; for example, miR-375 was revealed to be downregulated >2 fold in cervical cancer samples. Consistent with this finding, Wang *et al* (40) observed that in 170 cervical cancer tissues, miR-375 expression was significantly decreased compared with that in 68 normal tissues. This finding suggested that the miR-375 downregulation should be involved in cervical cancer progression. Additionally, the present study predicted that the *TOP2A* and *ESR1* genes were potential targets of miR-203, as determined by miRecords software, suggesting that miR-203 may affect the progression of cervical cancer by regulating its potential targets of *TOP2A*, *ESR1* or others genes. Therefore, the present results suggested that the downregulation of miRNAs may perform an important role in the progression of cervical cancer, and that novel candidate markers may be presented by the evaluation of specific miRNAs for cancer screening and prognostic purposes in patients with cervical cancer. Furthermore, certain miRNAs may possess the potential to be used as predictors and promising therapeutic targets in the treatment of cervical cancer.

In summary, high-throughput technologies such as microarray analysis aid the identification of the molecular determinants of tumorigenesis. The present study identified 44 DEGs and 15 differentially-expressed miRNAs that may be useful for future studies focused on the assessment of the molecular mechanisms of cervical cancer via comprehensive bioinformatics analysis. In particular, *CDK1*, *TOP2A*, *MCM2*, *AURKA*, *KIF20A*, *ESR1* and several miRNAs may be involved in the carcinogenesis of cervical cancer. The results of the present study also demonstrate the value of data mining in multi-dimensional omics data. The present findings provide novel insights into the development and progression of cervical cancer. However, the network of interactions of miRNAs and mRNAs is extremely complex and expression profiling analysis is a relatively new tool. Therefore, additional experimental studies are essential to confirm the present findings.

Acknowledgements

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