Investigation of candidate biomarkers and prognostic values in endometrial cancer based on bioinformatics analysis

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Abstract

Background: Endometrial cancer is a common gynecological cancer whose incidence is increasing annually worldwide. However, the biomarkers that provide the prognosis and progression of endometrial cancer are still lacking.

Methods: The differentially expressed mRNAs and miRNAs were screened out using mRNA and miRNA expression data of endometrial cancer from Gene Expression Omnibus, and then validated in the Cancer Genome Atlas. The Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were conducted using the Database for Annotation, Visualization and Integrated Discovery. A protein–protein interaction network was constructed by STRING and visualized using Cytoscape. OncoLnc was used for studying the prognostic effects of the hub genes. In addition, miRecords were used to predict target genes of differentially expressed miRNAs, and then a miRNA-mRNA regulatory network was constructed.

Results: Two eligible human endometrial cancer datasets (GSE17025 and GSE25405) met the requirement. A total of 520 differentially expressed mRNAs and 30 differentially expressed miRNAs were identified. These differentially expressed mRNAs were mainly enriched in cell cycle, skeletal system development, vasculature development, oocyte maturation, and oocyte meiosis signaling pathways. 160 pairs of differentially expressed miRNAs and mRNAs, including 22 differentially expressed miRNAs and 71 overlapping differentially expressed mRNAs, were validated in endometrial cancer samples using starBase v2.0 project. And the prognosis analysis found that Cyclin E1 (CCNE1, one of the 82 hub genes, which was correlated with hsa-miR-195) was correlated with significantly worse overall survival in endometrial cancer patients.

Conclusions: These hub genes and differentially expressed miRNAs might be used as molecular targets for the treatment of endometrial cancer and prognostic biomarkers for endometrial cancer.

Background

Endometrial cancer (EC), that is, uterine corpus endometrial carcinoma (UCEC), is derived from the endometrium epithelial malignant tumors. With an increase in obesity and an aging population, the incidence and mortality rates of EC are increasing in developed countries [1]. According to the latest
statistics of the American Cancer Society [2], Over 61,000 cases were estimated to be diagnosed with EC in 2017. At present, advanced stage EC still accounts for 20% to 30%, once relapsed, the prognosis of which is very poor.

Currently, the biomarkers of EC are still lacking in efficiency in diagnosis and prognosis. For example, Cancer antigen 125 (CA125), being most frequently used as a biomarker for ovarian cancer, has some diagnostic/prognostic value in EC [3]. However, CA125 level is elevated in a number of physiological and pathological gynecological and non-gynecological conditions, such as age [4,5], pregnancy [6], menstruation [4,6], endometriosis [6], benign ovarian cysts [6], pelvic inflammatory disease [6], peritonitis [6], pancreatitis [6] and pneumonia [6]; human epididymis protein 4 (HE4) also has some diagnosis/prognosis value in EC [7]. Similar to the high expression of CA125, HE4 level is also elevated in many physiological and non-gynaecological diseases, such as age [8], menopausal status [8], Body Mass Index [8], smoking status [8], creatine levels [8], pulmonary adenocarcinoma [9], chronic kidney disease [7], renal failure [10], and kidney fibrosis [11].

Due to these factors reduce the clinical value of the existing biomarkers in the progress and prognosis of EC, it is crucial to discover new biomarkers and investigate the molecular mechanisms in the progression of EC.

Materials And Methods
Microarray expression data
The mRNA and miRNA expression data of the GSE17025 and GSE25405 datasets were respectively downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). The mRNA dataset GSE17025 consisted of data from 103 samples, 91 EC tissue samples and 12 normal endometrium (NE) tissue samples. mRNA expression profiles were measured using the GPL570 [HG.U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array platform [12]. The miRNA dataset GSE25405 contained 41 EC tissue samples and seven NE tissue samples. The miRNA expression profile was detected using the GPL7731 Agilent-019118 Human miRNA Microarray 2.0 G4470B platform.

The RNA-seq data
The mRNA and miRNA-seq data of patients with UCEC were downloaded from TCGA (www.cancergenome.nih.gov) by the tool named shengxin.ren (http://www.shengxin.ren; accessed
June 20, 2019). The mRNA and miRNA-seq data were composed of 544 EC tissue samples, 35 NE tissue samples, 539 EC tissue samples and 33 NE tissue samples, respectively.

Identification of DEGs and DEMs
The Limma package (version 3.36.5) in R/Bioconductor was used to identify DEGs and DEMs between EC and NE tissue samples [13]. The adjusted P-value (adj.P-value) < 0.05 and |log2 fold change (FC)| >1 were set as the threshold value [14]. The original probe-level data in Series Matrix Files were converted into gene symbol based on platform annotation files. The expression values of multiple probes corresponding to the same gene were selected by the minimum adj.P.Value.

Functional and pathway enrichment analysis
The Database for Annotation, Visualization and Integrated Discovery (DAVID, http://david.ncifcrf.gov) facilitates users to perform biological analysis from data collection [15]. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted with DAVID. FDR < 0.05 was set as statistically significant.

Construction of PPI network and module analysis
PPI network of DEGs was constructed using STRING database (version 11.0, https://string-db.org/) and visualized using Cytoscape (version 3.7.1) [16,17]. The parameter was set as medium confidence score ≥ 0.7, module analyses were conducted using Cytoscape software MCODE package with degree cut-off = 2, node score cut-off = 0.2, max depth = 100 and k-score = 2 [18]. The functional enrichment analyses for these DEGs in the modules were conducted with DAVID.

Prediction of the target gene of miRNA
The target gene of miRNA (TG-miRNA) was predicted by employing miRecords (http://c1.accurascience.com/miRecords/), which includes 11 different miRNA target genes predicted databases [19]. A TG-miRNA can only be identified when at least four different prediction databases predict that the gene is a target gene.

Construction of the miRNA-mRNA regulatory network
The intersection of TG-miRNAs and DEGs were considered to be potentially valuable differentially expressed target genes. Pearson correlation analysis was then used in starBase (http://starbase.sysu.edu.cn/) to verify the association between these potentially valuable differentially expressed target genes and DEMs in patients with EC [20,21]. These significant
differentially expression target genes and corresponding miRNAs were used to construct a miRNA-mRNA regulatory network using the Cytoscape software. The Degree of interaction of the node ≥ 5 which was defined as hub miRNA.

Survival analysis of hub genes

The overall survival of patients with EC with regard to hub genes were calculated using Kaplan-Meier analysis in OncoLnc (www.oncolnc.org). The patients were divided into two (high vs. low) groups according to the median values of mRNA expression of the hub gene. The log-rank test was used to examine the significance of difference between two groups.

Results
Identification of DEGs and DEMs

A total of 1,961 DEGs and 149 DEMs were identified from GSE17025 and GSE25405, respectively; 2,339 DEGs and 205 DEMs were identified from the mRNA and miRNA data of uterine corpus endometrial carcinoma in TCGA (named TCGA-UCEC and TCGA-UCEC_miRNA, respectively); 520 common DEGs and 30 common DEMs were screened out with Venny 2.1.0 [22], respectively (Fig. 1a, Fig. 1b). there were 212 upregulated genes and 308 downregulated genes, and 15 upregulated and 15 downregulated miRNAs in EC tissues compared with NE tissues, respectively (Table 1, Table 2).

Functional and pathway enrichment analysis

The functional and pathway enrichment analyses of DEGs were conducted with DAVID. The upregulated genes were mainly enriched in biological processes, which were cell cycle, cell division, and DNA replication signaling pathways, while downregulated genes were mainly enriched in skeletal system development, vasculature development, and cell adhesion signaling pathways (Table 3). Moreover, three KEGG pathways were enriched in upregulated genes, including cell cycle, oocyte maturation, and oocyte meiosis signaling pathways (Table 3). There were no KEGG pathways enriched in downregulated genes.

Construction of PPI network and module analysis

A PPI network consisting of 287 nodes and 1,840 edges was constructed, which included 212 upregulated and 308 downregulated genes (Fig. 2). Then, 82 nodes were screened out as hub genes (Degree of interaction ≥ 10 were selected as the threshold) [23], there were close correlations among
hub genes (Fig. 3, Additional file 1). After analyzing the network with the MCODE app in Cytoscape software, an important module was obtained, including 50 nodes and 1,082 edges (Fig. 4). Functional enrichment analyses of biological processes with regard to this module showed that these genes were enriched in cell cycle, cell division, and DNA replication signaling pathways (Table 4). Three KEGG pathways were enriched in cell cycle, oocyte meiosis, and oocyte maturation signaling pathways (Table 4).

**Analysis of miRNA-mRNA regulatory network**
Thirty commonly identified DEMs were screened out from GSE25405 and TCGA-UCEC_miRNA, including 15 upregulated and 15 downregulated miRNAs (Table 2). Based on miRecords database, 6,865 TG-miRNAs were screened out, of which 199, were validated in 520 common DEGs (Fig. 1a). These 199 commonly identified DEGs and 30 commonly identified DEMs were used to construct a miRNA-mRNA network. In patients with EC, 160 pairs of DEMs-DEGs relationships with reverse association expression were confirmed using starBase v2.0 project, including 22 DEMs and 71 overlapping DEGs (Fig. 5, Additional file 2). In the network, hsa-miR–200b, hsa-miR–200c, hsa-miR–429, hsa-miR–424, hsa-miR–195, hsa-miR–653, and hsa-miR–141 showed a higher degree of interaction (degree of interaction ≥ 5, Table 5).

**Survival analysis**
The prognostic value of 82 hub genes were assessed in OncoLnc. Related results found that high mRNA expression of BUB1, TOP2A, CDCA8, TTK, ASPM, UBE2C, BIRC5, HJURP, CENPA, MCM10, FOXM1, SPAG5, EXO1, ESPL1, OIP5, MCM4, CDC25C, DEPDC1, KIF18B, ERCC6L, CKAP2L, ATAD2, TK1, CCNF, E2F1, and CCNE1 were associated with significantly worse overall survival for EC patients, and low expression of MYC was correlated with significantly worse overall survival in EC patients (data not shown). What makes us interesting was that CCNE1 was also identified as a target gene of hsa-miR–195 (Fig. 6, Fig. 7).

**Discussion**
In recent years, although clinical medical scientists have made significant progress in the treatment of EC with surgery and chemotherapy, the incidence and mortality rate of EC are still increasing [24]. It is necessary to further understand the etiology and mechanism of EC progression to improve the
prognosis of EC.

In this study, by integrating GSE17025 with TCGA-UCEC, 520 common DEGs were screened out in EC tissues compared with NE tissues. These 520 common DEGs were composed of 212 upregulated genes and 308 downregulated genes. These upregulated DEGs were mainly enriched in cell cycle, cell division, and DNA replication signaling pathways, while the downregulated DEGs in skeletal system development, vasculature development, and cell adhesion signaling pathways. Following, 82 hub genes were screened out from PPI network. After analyzing the survival of these 82 hub genes, 26 upregulated genes and one downregulated gene revealed poor prognosis of patients with EC.

Similarly, 30 common DEMs were screened out from GSE25405 and TCGA-UCEC_miRNA. After integrating 6,865 TG-miRNAs with these 520 common DEGs, 71 overlapping DEGs were screened out and showed close correlations with 22 common DEMs in EC (Fig. 5, Additional file 2). Moreover, high mRNA expression of CCNE1 (one of the 82 hub genes, which was correlated with hsa-miR–195) was correlated with significantly worse overall survival in EC patients.

MiRNAs are endogenous small non-coding RNAs, which can inhibit gene expression by mRNA degradation/destabilization or through impaired translation [25,26]. The abnormal expression of miRNAs occurs in a variety of tumors and often appears to be associated with altered malignant potential, such as changes in tumor cell survival, proliferation, and invasion [27].

In this study, 30 common DEMs were screened out from EC tissues compared with NE tissues, such as hsa-miR–200b, hsa-miR–200c, hsa-miR–429, hsa-miR–141, hsa-miR–424, hsa-miR–195, and hsa-miR–653. The microRNA–200 (miR–200) family consists of miR–200a, miR–200b, miR–200c, miR–429 and miR–141, which all have the same seed sequence and homologous targets. The expression of hsa-miR–200b is upregulated in many malignant tumors [28–30], and its role in the inhibition of mesenchymal characteristics and metastasis has been revealed in prostate, gastric carcinoma, and hepatocellular carcinoma by regulating the ZEB1 expression or directly targeting ZEB2 or via Rho/ROCK signaling pathway [31–33]. The current study suggested that hsa-miR–200b was also upregulated, which was consistent with the previous study [34]. Hsa-miR–200c has been widely investigated during the last few years. There have been numerous studies demonstrating the
association between an aberrant expression level of miR–200c and the prognosis of various human malignancies, such as breast cancer [28,35,36], prostate cancer [37], ovarian cancer [38], and endometrial cancer [39]. Some of these studies verified the anti-oncogenic function of miR–200c in certain cancer types, indicating the potential correlation of elevated expression levels of miR–200c and superior prognosis [36,38,39]. However, other studies have provided opposing evidence, suggesting that miR–200c serves as an oncogene [28,35,37]. These conclusions suggest that miR–200c is a notable biomarker for prognosis of cancer. Our present study suggested that hsa-miR–200c was upregulated, which was consistent with the previous study [39]. Recent reports have shown that hsa-miR–429 expression is frequently upregulated and may function as an oncogene in several cancers [40, 41], such as endometrial carcinoma [40], which is consistent with the finding of this study. One study showed that upregulation of hsa-miR–429 can effectively suggest a decrease in overall survival of serous ovarian cancer [42]; in contrast, some studies have shown that hsa-miR–429 was downregulated in some malignant tumors and involved in tumor-suppressor function [43,44]. These results indicate that hsa-miR–429 plays different (even opposite) roles in tumorigenesis and cancer progression in different tumors. Hsa-miR–141 is also an important member in the miR–200 family, several previous studies have shown that has-miR–141 was involved in prognosis of cancer [45–47].

Some previous studies have found that hsa-miR–424 was downregulated and could acts as a tumor suppressor in some cancers [48–50]. Our current study showed that hsa-miR–424 was also downregulated, which was consistent with the previous study [50]. Hsa-miR–195 is one member of the miR–15a, –15b, –16, –195, and –497 families, which participates in the occurrence and developmental progress of many malignant tumors and regulation of malignant biological behaviors [50–53]. In our study, hsa-miR–195 showed a lower level compared EC tissues with NE tissues, which was consistent with the previous study [52]. So far, there have been few reports on the role of hsa-miR–653 in the malignant biological behavior of tumors. According to the above mentioned finding, we speculates that hsa-miR–200b, hsa-miR–200c, hsa-miR–429, hsa-miR–141, hsa-miR–424, hsa-miR–195 and hsa-miR–653 could also play important roles in
biological behavior of EC by multiple pathways.

CCNE1, that is Cyclin E1, belongs to the cyclin family which, through association with cyclin-dependent kinase 2, controls cell cycle progression from G1 to S phase [54]. Previous researches have shown that the upregulation of CCNE1 could contribute to cancer development or tumorigenesis in many cancers [55–60], and CCNE1 can serve as a reliable independent prognostic marker [59,60]. MiRNAs from multiple families have been identified to target CCNE1 in a variety of malignant tumors, such as hepatocellular carcinoma [61], osteosarcoma [62], cervical cancer [63], bladder cancer [64]. In current study, survival analysis of the hub genes related to DEMs showed that high expression of CCNE1 could indicate poor prognosis in EC patients.

Conclusion

Based on bioinformatics analyses of EC-related microarray data in the GEO database and clinical data related to EC in TCGA database, we found that 27 hub genes (BUB1, TOP2A, CDCA8, TTK, ASPM, UBE2C, BIRC5, HJURP, CENPA, MCM10, FOXM1, SPAG5, EXO1, ESPL1, OIP5, MCM4, CDC25C, DEPDC1, KIF18B, ERCC6L, CKAP2L, ATAD2, TK1, CCNF, E2F1, CCNE1, and MYC) were involved in poor prognosis in EC patients, and seven miRNAs (hsa-miR–200b, hsa-miR–200c, hsa-miR–429, hsa-miR–141, hsa-miR–424, hsa-miR–195, and hsa-miR–653) participated in biological behaviors of EC. However, further molecular biological researches are still needed to confirm the actual clinical value of our findings.

Declarations

Authors’ contributions

YL conceived, designed this study and wrote the manuscript; YL and LL performed data analysis; LL reviewed the manuscript.

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Not applicable.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Consent for publication
Not applicable.

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Not applicable.

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Tables

Table 1 Top 10 DEGs in EC tissues compared with NE tissues according to the data from TCGA database.

| DEG   | logFC     | P-value   | adj. P-value |
|-------|-----------|-----------|--------------|
| upregulated genes | | | |
| SFN   | 4.465258403 | 5.76E-42  | 2.15E-40     |
| PRAME | 4.193768196 | 5.79E-69  | 7.66E-67     |
| MYBL2 | 4.109297769 | 2.84E-74  | 4.67E-72     |
| UBE2C | 4.074765041 | 1.71E-69  | 2.33E-67     |
| CDC20 | 3.919322957 | 1.25E-78  | 2.67E-76     |
| AQP5  | 3.427650505 | 2.06E-18  | 2.18E-17     |
| PRSS8 | 3.413404932 | 1.96E-49  | 1.06E-47     |
| TK1   | 3.400033651 | 3.60E-77  | 6.98E-75     |
| PI3   | 3.370250122 | 7.80E-14  | 5.87E-13     |
| TPX2  | 3.308872927 | 1.19E-58  | 9.97E-57     |
| downregulated genes | | | |
| DES   | -6.619094047 | 8.36E-54  | 5.54E-52     |
| MYH11 | -5.635290069 | 6.17E-75  | 1.05E-72     |
| CNN1  | -5.55734654  | 5.08E-64  | 5.45E-62     |
| ACTG2 | -4.902138932 | 4.13E-50  | 2.32E-48     |
| LMOD1 | -4.795641474 | 4.82E-86  | 1.42E-83     |
| OGN   | -4.663558704 | 9.95E-120 | 1.55E-116    |
| DPT   | -4.427179281 | 6.84E-99  | 3.98E-96     |
| SPARCL1| -4.386222474 | 1.33E-70  | 1.90E-68     |
| ZCCHC12 | -4.328794652 | 2.64E-68  | 3.40E-66     |
| SFRP4 | -4.266562157 | 4.62E-26  | 7.95E-25     |

DEGs, differentially expressed genes; EC, endometrial cancer; NE, normal endometrium; FC, fold-change; adj. P-value, adjusted P-value.
Table 2  Top 10 DEMs in EC tissues compared with NE tissues according to the data from GEO database.

| miRNA     | logFC     | P-value   | adj. P-value |
|-----------|-----------|-----------|--------------|
| upregulated miRNA | | | |
| hsa-miR-205 | 5.717071419 | 8.28E-10 | 3.45E-07 |
| hsa-miR-135b | 3.002833732 | 6.43E-05 | 1.87E-03 |
| hsa-miR-182 | 2.827333932 | 2.90E-06 | 2.00E-04 |
| hsa-miR-183 | 2.705891835 | 2.87E-05 | 1.06E-03 |
| hsa-miR-429 | 2.437603498 | 9.52E-07 | 9.11E-05 |
| hsa-miR-200b | 2.244848862 | 1.74E-06 | 1.37E-04 |
| hsa-miR-96 | 2.195969063 | 7.78E-05 | 2.14E-03 |
| hsa-miR-200a | 1.973216466 | 4.25E-05 | 1.43E-03 |
| hsa-miR-202 | 1.943991213 | 4.19E-03 | 4.31E-02 |
| hsa-miR-210 | 1.715073494 | 1.94E-04 | 3.85E-03 |
| downregulated miRNA | | | |
| hsa-miR-424 | -4.875026249 | 1.77E-13 | 3.59E-10 |
| hsa-miR-143 | -4.140227835 | 5.97E-07 | 6.07E-05 |
| hsa-miR-133b | -4.081321667 | 4.19E-06 | 2.54E-04 |
| hsa-miR-376c | -3.636752313 | 9.60E-05 | 2.41E-03 |
| hsa-miR-195 | -3.523216268 | 1.67E-07 | 2.57E-05 |
| hsa-miR-204 | -3.51217031 | 7.22E-04 | 1.10E-02 |
| hsa-miR-145 | -3.493087645 | 1.82E-05 | 7.61E-04 |
| hsa-miR-411 | -3.39771373 | 3.84E-06 | 2.40E-04 |
| hsa-miR-381 | -3.035325968 | 4.20E-05 | 1.41E-03 |
| hsa-miR-379 | -2.971031318 | 2.79E-06 | 1.95E-04 |

DEMs, differentially expressed miRNAs; EC, endometrial cancer; NE, normal endometrium; miRNA or miR, microRNA; FC, fold-change; adj. P-value, adjusted P-value.

Table 3 Top 10 GO terms of biological processes and significant KEGG pathways of upregulated and downregulated DEGs for EC tissues compared with NE tissues.
| Term | Description | Count | P-Value | FDR   |
|------|-------------|-------|---------|-------|
| Upregulated DEGs | | | | |
| GO:0022403 | cell cycle phase | 47 | 1.16E-30 | 1.93E-27 |
| GO:0000279 | M phase | 42 | 2.96E-29 | 4.94E-26 |
| GO:0000278 | mitotic cell cycle | 42 | 3.27E-27 | 5.44E-24 |
| GO:0000280 | nuclear division | 34 | 3.43E-26 | 5.71E-23 |
| GO:0007067 | mitosis | 34 | 3.43E-26 | 5.71E-23 |
| GO:0000087 | M phase of mitotic cell cycle | 34 | 6.25E-26 | 1.04E-22 |
| GO:0022402 | cell cycle process | 48 | 9.63E-26 | 1.60E-22 |
| GO:0048285 | organelle fission | 34 | 1.30E-25 | 2.16E-22 |
| GO:0007049 | cell cycle | 53 | 3.71E-24 | 6.18E-21 |
| GO:0051301 | cell division | 33 | 5.63E-21 | 9.38E-18 |
| KEGG pathway | | | | |
| hsa04110 | Cell cycle | 18 | 1.70E-11 | 1.87E-08 |
| hsa04914 | Progesterone-mediated oocyte maturation | 10 | 1.30E-05 | 1.42E-02 |
| hsa04114 | oocyte meiosis | 11 | 1.48E-05 | 1.62E-02 |
| Downregulated DEGs | | | | |
| GO:0001501 | skeletal system development | 21 | 2.58E-07 | 4.35E-04 |
| GO:0001944 | vasculature development | 16 | 1.53E-05 | 2.57E-02 |
| GO:0007155 | cell adhesion | 28 | 2.67E-05 | 4.50E-02 |
| GO:0022610 | biological adhesion | 28 | 2.74E-05 | 4.61E-02 |

GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes; EC, endometrial cancer; NE, normal endometrium; FDR, false discovery rate.

Table 4 Top 10 GO terms of biological processes and significant KEGG pathways of the DEGs in module.
| Term | Description | Count | P-value | FDR |
|------|-------------|-------|---------|-----|
| Biological processes | | | | |
| GO:0000279 | M phase | 32 | 8.12E-40 | 1.14E-36 |
| GO:0022403 | cell cycle phase | 32 | 1.24E-36 | 1.75E-33 |
| GO:0000278 | mitotic cell cycle | 31 | 2.61E-36 | 3.67E-33 |
| GO:0000280 | nuclear division | 27 | 2.86E-35 | 4.02E-32 |
| GO:0007067 | mitosis | 27 | 2.86E-35 | 4.02E-32 |
| GO:0000087 | M phase of mitotic cell cycle | 27 | 4.67E-35 | 6.57E-32 |
| GO:0048285 | organelle fission | 27 | 8.52E-35 | 1.20E-31 |
| GO:0022402 | cell cycle process | 33 | 4.25E-34 | 5.97E-31 |
| GO:0007049 | cell cycle | 35 | 6.14E-33 | 8.63E-30 |
| GO:0051301 | cell division | 27 | 7.85E-32 | 1.10E-28 |
| KEGG pathway | | | | |
| hsa04110 | Cell cycle | 13 | 4.76E-17 | 2.96E-14 |
| hsa04114 | oocyte meiosis | 9 | 4.14E-10 | 2.58E-07 |
| hsa04914 | Progesterone-mediated oocyte maturation | 7 | 1.37E-07 | 8.55E-05 |

GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes; FDR, false discovery rate.

Table 5 Top 7 miRNAs with the highest degree of interaction in the miRNA-mRNA interactions network (Degree of interaction ≥ 5).

| Node | Degree of interaction |
|------|-----------------------|
| hsa-miR-200b | 10 |
| hsa-miR-200c | 10 |
| hsa-miR-429 | 9 |
| hsa-miR-424 | 6 |
| hsa-miR-195 | 6 |
| hsa-miR-653 | 6 |
| hsa-miR-141 | 5 |
miR, microRNA.

Figures

(a) GSE17025

(b) GSE25405

Figure 1

(a): Venn diagram of the differentially expressed genes among these three datasets. (b):
Venn diagram of the differentially expressed miRNAs between two datasets. TCGA-UCEC: the mRNA data of uterine corpus endometrial carcinoma in the Cancer Genome Atlas, TCGA-UCEC_miRNA: the miRNA data of uterine corpus endometrial carcinoma in the Cancer Genome Atlas, TG-miRNA: the target gene of differentially expressed miRNA.

Figure 2

Protein-protein interaction network of the differentially expressed genes in endometrial cancer tissues compared with normal endometrium tissues. Green and red nodes represent upregulated and downregulated genes, respectively. The edges/lines stand for the regulatory association between nodes.
Figure 3

Protein-protein interaction network of hub genes of the differentially expressed genes in endometrial cancer tissues compared with normal endometrium tissues. Green and red nodes represent upregulated and downregulated genes, respectively. The edges/lines stand for the regulatory association between nodes.
Figure 4

Demonstration of the important module by cytoscape. The edges/lines stand for interaction relationship between nodes.
Figure 5
The miRNA-mRNA regulatory network. Green and red nodes stand for upregulation and downregulation, respectively. The ellipses represent genes and the triangles represent miRNAs.
Figure 6

Overall survival analysis of CCNE1 expression with prognosis of endometrial cancer patients (Logrank p-value = 0.000157). Based on the median expression level of CCNE1, the patients with EC were divided into two (high vs. low) groups.
The correlated expression of CCNE1 and hsa-miR-195-5p (hsa-miR-195) in 538 patients with endometrial cancer. The correlation coefficients -0.355 with p-value = 1.93e-17 indicated that CCNE1 and hsa-miR-195 expression levels were correlated with each other; data source: starBase v3.0 project.

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