Identification of key genes and pathways of diagnosis and prognosis in cervical cancer by bioinformatics analysis

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Abstract

Background: Cervical cancer as one of the most common malignant tumors lead to bad prognosis among women. Some researches already focus on the carcinogenesis and pathogenesis of cervical cancer, but it is still necessary to identify more key genes and pathways.

Methods: Differentially expressed genes were identified by GEO2R from the gene expression omnibus (GEO) website, then gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyzed by DAVID. Meanwhile, protein–protein interaction network was constructed by STRING, and both key genes and modules were found in visualizing network through Cytoscape. Besides, GEPIA did the differential expression of key genes and survival analysis. Finally, the expression of genes related to prognosis was further explored by UNLCAN, oncomine, and the human protein atlas.

Results: Totally 57 differentially expressed genes were founded, not only enriched in G1/S transition of mitotic cell cycle, mitotic nuclear division, and cell division but also participated in cytokine–cytokine receptor interaction, toll-like receptor signaling pathway, and amoebiasis. Additionally, 12 hub genes and 3 key modules were screened in the Cytoscape visualization network. Further survival analysis showed that $\text{TYMS}$ (OMIM accession number 188350), $\text{MCM2}$ (OMIM accession number 116945), $\text{HELLS}$ (OMIM accession number 603946), $\text{TOP2A}$ (OMIM accession number 126430), and $\text{CXCL8}$ (OMIM accession number 146930) were associated with the prognosis of cervical cancer.

Conclusion: This study aim to better understand the characteristics of some genes and signaling pathways about cervical cancer by bioinformatics, and could provide further research ideas to find new mechanism, more prognostic factors, and potential therapeutic targets for cervical cancer.

KEYWORDS
bioinformatics analysis, cervical cancer, diagnosis and prognosis, differentially expressed genes
1 | INTRODUCTION

The morbidity of cervical cancer is the fourth malignant disease of women, and the mortality of cervical cancer is also the fourth in the women's malignancies. Moreover, the incidence of young female of cervical cancer increased in recent decades. Statistics showed that the number of deaths worldwide in 2018 was 311,000 (Bray et al., 2018). The total payments on cervix uteri and corpus uteri cancer treatments in China were estimated to be 11.5 billion RMB in 2015 (Li et al., 2017). With the popularization of cervical cancer screening and the application of HPV vaccine, most patients are diagnosed and treated at early stage. However, the effect of treatment about advanced or recurrent cervical cancer is not significant, and targeted treatment for specific gene mutations may be a new trend. With the application and development of high-throughput sequencing, gene chip in research of tumor genomics, it is significant to find the mechanism, prognostic factors, and potential therapeutic targets of cervical cancer. Some studies have reported that mutations of FOXP3 (Cezar-Dos-Santos et al., 2019), PIK3CA (Razia et al., 2019), XRCC4 (Gupta, Kushwah, Singh, & Banerjee, 2019), FBXW7 (Liu et al., 2019), and some copy number variations of KLF10 and PSG (Marrero-Rodriguez et al., 2018) are related to the carcinogenesis and pathogenesis of cervical cancer, but they were not complete so that to be further studied. This study aim to better understand the characteristics of some genes and signaling pathways that associate with cervical cancer through bioinformatics.

2 | MATERIALS AND METHODS

2.1 | Microarray data

We downloaded three gene expression profiles (GSE63514 (den Boon et al., 2015), GSE6791 (Pyeon et al., 2007), and GSE9750 (Scotto et al., 2008)) from the gene expression omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo) (Edgar, Domrachev, & Lash, 2002), which is one of the most comprehensive public gene expression data resources available today. GSE63514 consists of 28 tumor samples and 24 normal cervical samples, and GSE6791 includes 20 tumor samples and 8 normal cervical samples. The gene chip platform of these two datasets is GPL570 Affymetrix Human Genome U133 Plus 2.0 Array. Moreover, GSE9750 analyzed 33 tumor samples and 24 normal cervical samples. The gene chip platform of GSE9750 is the GPL96 Affymetrix Human Genome U133A Array.

2.2 | Identification of DEGs

We identified the DEGs, differentially expressed genes (DEGs) between cervical cancer and normal tissues by GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r/). GEO2R is a method which could obtain the DEGs between two gene expression profiles in the GEO database by using Bioconductor’s GEOquery and limma R software packages (Barrett et al., 2013). It was set to screen the DEGs by adjusted p value <.01 and logFC (fold change) >2, and we used the Venn diagram to find the overlapped DEGs.

2.3 | GO and KEGG enrichment analysis

The Database for Annotation, Visualization and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov/) (version 6.8) (Huang da, Sherman, & Lempicki, 2009) is a public online bioinformatic database which helps to identify the most significant enriched functional genes and biological pathways. To further analyze the DEGs, gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed by using the DAVID online tool. GO analysis was used to annotate biological process (BP), cytological component (CC), and molecular function (MF) of genes (Ashburner et al., 2000; The Gene Ontology Consortium, 2019), and KEGG enrichment analysis was used to understand the relevant signaling pathways (Kanehisa & Sato, 2019). p value <.05 was considered to be statistically significant.

2.4 | PPI network and key module analysis

We constructed the protein–protein interaction network (PPI) of DEGs by using Search Tool for the Retrieval of Interacting Genes (STRING; http://string-db.org/) (version 11.0) (Szklarczyk et al., 2019) database based on the confidence scores. What’s more, we further visualized the PPI by

FIGURE 1 Venn diagram. Identification of the differentially expressed genes in the GSE63514, GSE6791, and GSE9750 gene expression profile datasets. The three datasets showed an overlap of 57 genes. DEGs, Differentially expressed genes.
Cytoscape (version 3.7.0) (Shannon et al., 2003). And the Molecular Complex Detection (MCODE) plugin in Cytoscape was used to filter the key modules in the network with degree cutoff = 2, node score cutoff = 0.2, k-core = 2, and max. depth = 100.

2.5 Key genes screening and analysis

The genes with degree ≥10 in the network were identified as key genes, and the co-expressed genes were analyzed by cBioPortal (http://www.cbioportal.org) (Cerami et al., 2012; Gao et al., 2013) online platform. Gene Expression Profiling Interactive Analysis (GEPIA; http://gepia.cancer-pku.cn) (Tang et al., 2017) is an interactive web application for gene expression analysis. We visualized the expression of key genes in cervical cancer tissues and normal tissues by box plots in GEPIA, and the overall survival analysis of key genes was also performed. Expression profiles of CXCL8 in human cancers were analyzed by UALCAN (http://ualcan.path.uab.edu/index.html) (Chandrashekar et al., 2017). Oncomine
(https://www.oncomine.org) was used to analyze CXCL8 overexpression in multiple datasets comparing cervical cancer with normal tissues. The protein expression of CXCL8 in cervical cancer and normal tissues was analyzed by the human protein atlas (HAP; https://www.proteinatlas.org) (version 19) (Uhlen et al., 2017).

3 | RESULTS

3.1 | Identification of DEGs

The DEGs of GSE63514, GSE6791, and GSE9750 were obtained by using the GEO2R online analysis tool and we identified the intersection of the three profiles by Venn diagram (Figure 1). Total 57 differential genes were detected, of which 26 were upregulated and 31 were downregulated (Table 1).

3.2 | GO enrichment and KEGG pathway enrichment

In the GO analysis, the screened DEGs mainly participate in the biological process (BP) of G1/S transition of mitotic cell cycle, mitotic nuclear division, cell division, cell–cell signaling, and epithelial cell differentiation. As for the molecular function (MF), DEGs mainly involved in the protein binding, structural molecule activity, and growth factor activity. The cell composition (CC) of DEGs includes cytoplasm, extracellular exosome, nucleoplasm, extracellular space, and extracellular region. In the KEGG pathway analysis found that DEGs significantly enriched in the cytokine receptor interaction, toll-like receptor signaling pathway, and amoebiasis (Table 2, Figure 2).

3.3 | PPI network construction and analysis

PPI network of 57 DEGs was constructed in STRING (Figure 3), the network visualized by Cytoscape including 42 nodes and 137 edges. The red nodes represent 23 upregulated genes, whereas the blue nodes represent 19 downregulated genes (Figure 4a). MOCD plug-in screened out three key modules, two of which were composed by upregulated genes and one by downregulated genes (Figure 4b-d). The degree ≥10 was used as the screening criteria for the identification of hub genes, and 12 key genes were found to compose the key modules; their names and functions are shown in Table 3. We used the cBioportal tool to explore the networks of these hub genes and their coexpressed genes (Figure 4e).

3.4 | Key gene analysis

GEPIA expression analysis showed that these key genes were high expressing in cervical cancer, whereas low expressing in normal cancer tissues, which was consistent with GEO analysis (Figure 5). Moreover, overall survival analysis of GEPIA indicated that high expression of TYMS, MCM2, HELLS, and TOP2A in cervical cancer was correlated with better prognosis. On the other hand, high expression of CXCL8 in cervical cancer tumor tissues is associated with poor prognosis of patients (Figure 6). CXCL8 expression in various tissues from UCLLCAN database showed that CXCL8 upregulated in multiple tumor types including Colorectal cancer, cervical cancer, Esophageal cancer, Head and neck cancer, and so on (Figure 7a). The DEGs between cervical cancer and normal tissues from four datasets analyzed by Oncomine showed that CXCL8 had high expression level (Figure 7b). Clinical immunohistochemistry samples of patients with cervical cancer were inquired through HPA database. Compared with normal tissues, CXCL8 protein was highly expressed in patients with cervical cancer (Figure 7c).

4 | DISCUSSION

As we all know, the morbidity and mortality of cervical cancer are high in female. Although the chemoradiotherapy and surgery might cure early-stage patients, many patients suffered from the recurrence and metastasis. And it is still unsatisfied of the effect of treatment to recurrence. Previous studies reported that some molecules and pathways involved in the HPV-related and the non–HPV-related cervical cancer. However, the molecule pathway is still needed to be explored.

Among 12 key genes we screened, CXCL8, with degree of 11 involved in all KEGG pathways and correlated with the prognosis of cervical cancer, was thought to be
CXCL8, also known as interleukin 8 (IL-8), is a pleiotropic chemokine. CXCL8 binds to its chemokine receptor CXCR1/2, and induces inflammatory responses, neovascularization, and regulates immune responses. Multiple studies have shown that CXCL8/cxcr1/2 axis was highly expressed in lung cancer, malignant melanoma, breast cancer, colorectal cancer, osteosarcoma, pancreatic cancer, and other cancers. It plays an important role in regulating tumor growth, invasion, angiogenesis, and resistance through antiapoptosis, cell signal transduction, and immune evasion. CXCL8 could regulate VEGFR, matrix metalloprotein (MMP), and other mediators through autocrine and paracrine pathways to induce tumor angiogenesis (Kumar, Cherukumilli, Mahmoudpour, Brand, & Bandapalli, 2018). And, CXCL8 involves in the mechanisms of resistance to the apoptosis, thus induces tumorogenesis (Xiao et al., 2015). In addition, Epithelial mesenchymal transformation (EMT) modifies the tumor microenvironments resulting in tumor cells endowed with stem cell characteristics, immune escape, proliferation, and migration, and CXCL8 is conducive to the formation of EMT (Geng et al., 2019; Visciano et al., 2015). Multiple studies suggested that CXCL8 promotes pulmonary metastasis of osteosarcoma (Gross et al., 2018), is the prognosis marker of pancreatic cancer (Litman-Zawadzka, Łukaszewicz-Zająca, Gryko, Kulczynska-Przybik, & Mroczko, 2018), and
FIGURE 4  PPI network, most significant module of DEGs and Interaction network of the hub genes. (a) PPI network of DEGs was constructed in Cytoscape, red nodes represents upregulated genes, and blue nodes represents downregulated genes. (b–d) There modules were obtained from PPI network using MCODE plug-in in Cytoscape. (e) Hub genes and their coexpression genes were analyzed by cBioPortal. Nodes with bold black outline mean hub genes. Nodes with thin black outline the coexpression genes. DEGs, differentially expressed genes; MCODE, molecular complex detection; PPI, protein–protein interaction

TABLE 3  Functional roles of 12 key genes with degree ≥10

| Gene symbol | Full name                                      | Function                                                                 |
|-------------|------------------------------------------------|--------------------------------------------------------------------------|
| ECT2        | Epithelial Cell Transforming 2                  | ECT2 encodes guanine nucleotide exchange factor, and drives the proliferation and invasion of breast cancer, lung cancer, and gastric cancer. |
| WDHD1       | WD Repeat And HMG-Box DNA Binding Protein 1     | WDHD1 is the replication initiation factor and involved in the mechanisms of the cancer promotion of E7 genes by evading mitotic checkpoints and inducing polyploid formation |
| TYMS        | Thymidylate Synthetase                          | TYMS encodes thymidine synthase (TS), an important rate-limiting enzyme that catalyzes the synthesis of pyrimidines, and also a target of fluorouracil medicines. |
| FANCI       | FA Complementation Group I                      | FANCI and FANCD form heterodimers, and participate in DNA repairing and maintain the stability of chromosomes |
| CXCL8       | C-X-C Motif Chemokine Ligand 8                 | CXCL8 is a chemotactic factor and induces inflammatory responses, neovascularization, and regulates immune responses |
| MCM2        | Minichromosome Maintenance Complex Component 2  | Participate in the initiation and elongation of DNA replication, form a cocktail of antibodies with TOP2A for cervical lesions |
| HELLS       | Helicase, Lymphoid Specific                     | This gene encodes a lymphoid-specific helicase. Participates in DNA replication, transcription and repair, and plays a role in cell proliferation |
| DTL         | Dentineless E3 Ubiquitin Protein Ligase Homolog  | DTL is E3 ubiquitin ligase. When DNA is damaged, DTL ubiquitin degrades relevant enzymes to prevent DNA duplication and maintain the stability of genome |
| CEP55       | Centrosomal Protein 55                          | CEP55 is a member of the coiled-coil protein family. Its main function is anchoring the microtubule polymerization-related proteins, involving in spindle formation, then regulating cell proliferation. |
| CDK1        | Cyclin-Dependent Kinase 1                       | Mitotic serine/threonine kinase that contributes to the regulation of cell cycle progression |
| AURKA       | Aurora kinase A                                 | AURKA promotes tumor cell proliferation and invasion, which is related to the resistance of chemotherapy and radiosensitivity |
| TOP2A       | DNA Topoisomerase II Alpha                      | TOP2A can control and alter the topologic states of DNA and can be used to identify advanced cervical lesions |
FIGURE 5 Expression boxplots of key genes using GEPIA website. ECT2, WDHD1, TYMS, FANCI, CXCL8, MCM2, HELLS, DTL, CEP55, CDK1, AURKA, and TOP2A were significantly upregulated in cervical cancer compared with normal tissues (p < .01). GEPIA, Gene Expression Profiling Interactive Analysis; ECT2: NC_000003.12; WDHD1: NC_000014.9; TYMS: NC_000018.10; FANCI: NC_000015.10; CXCL8: NC_000004.12; MCM2: NC_000003.12; HELLS: NC_000010.11; DTL:NC_000001.11; CEP55: NC_000010.11; CDK1: NC_000010.11; AURKA:NC_000020.11
malignant melanoma (Ugurel, Rappl, Tilgen, & Reinhold, 2001) is the recurrence marker of breast cancer (Khazali, Clark, & Wells, 2018). Moreover, CXCL8 is highly expressed in colorectal cancer, and negatively correlated with overall and disease-free survival (Xiao et al., 2015). CXCL8 has also been reported to play an important role in chemotherapy resistance, antivascular-targeted therapy, and immunotherapy of tumors. CXCL8 can induce the accumulation of myeloid-derived suppressor cells (MDSCs), which downregulate the immune activity to tumor cells by inhibiting T cells (Mabuchi, Yokoi, Komura, & Kimura, 2018; Shi et al., 2018). Sanmamed MF et al (Sanmamed et al., 2017) showed that the decrease in baseline level of CXCL8 could predict the better efficacy of anti–pd-l treatment in lung cancer and melanoma, and better overall survival, and the pseudo progress of immunotherapy. On the other hand, CXCL8 works in combination with its cognate receptors cxcr1/2. SINGH S et al (Fields & Justilien, 2010; Varney et al., 2011) found that CXCR1 and CXCR2 inhibitors could inhibit the liver metastasis of colon cancer, and the growth of melanoma in mice tumor model. The combination of CXCR1 inhibitors Reparixin and paclitaxel inhibits breast cancer stem cells (CSC) to suppress the brain metastases from breast cancer model (Brandolini et al., 2015), and the first relevant clinical trial is currently underway (NCT02370238) in breast cancer. Lin et al. (2019) indicate that Reparixin can suppress PD-L1 expression, and improve tumor immune microenvironment. Although the above studies prove the importance of CXCL8 in a variety of tumors, the research and evidence of CXCL8 in cervical cancer still needed to be explored. Our bioinformatics study showed that CXCL8 is a key gene for the carcinogenesis of cervical cancer, and its expression increased in cervical cancer, and might be a marker of poor prognosis. This conclusion shown in Figure 7 has been verified in different databases such as oncomine and UCLCAN. TCGA is the largest cancer gene information database with reliable data sources so that GEPIA using data from TCGA may make the results more reliable. In addition, more basic and clinical studies needed to confirm this conclusion, we could further explore the application of CXCL8/ CXCR1/2 axis inhibitors in the treatment of cervical cancer.

**FIGURE 6** Survival analysis. Expression level of CXCL8, HELLS, MCM2, TYMS, and TOP2A was significantly related to the overall survival of patients with cervical squamous cancer ($p < .05$).
a target of fluorouracil medicines. Multiple studies have shown that the expression level of TYMS may be related to the sensitivity of radiotherapy and chemotherapy for cervical cancer (Saga et al., 2002, 2003). Suzuki, Tsukagoshi, Saga, Ohwada, and Sato (1999) compared the immunohistochemical level of TS and the survival of 66 patients with stage IIIb cervical cancer, showing that the 5-year survival rate with high and low level of TS was 36.8% and 87.2%, respectively. Therefore, high TS may be associated with poor prognosis of cervical cancer. As for the other two factors, both TOP2A and MCM2 regulate cells in S phase. Studies have indicated that TOP2A and MCM2 involved in the occurrence and development of cervical cancer, and the increased expression of them could be viewed as diagnostic markers of cervical cancer (Peres et al., 2016; Zheng, 2015). ProExC, a cocktail of antibodies developed by becton-dickinson for TOP2A and MCM2, can be used to identify advanced cervical lesions (Dixon et al., 2017; Tosuner et al., 2017). Our analysis results showed that the expression levels of TYMS, MCM2, HELS, and TOP2A in cervical cancer increased and positively correlated with the prognosis of cervical cancer. Previous studies have shown that MCM2 and TOP2A may be markers for screening of precancerous lesions and cervical cancer, whereas others believe that the expression level of MCM2 cannot predict tumor stage and posttreatment response (Amaro Filho et al., 2014; Kuku et al., 2015). And few studies have followed patients, and analyzed their survival and prognosis. Thus, our findings may help answer this question. At present, the relevant mechanisms and pathways have not been clearly defined. We consider that in addition

**FIGURE 7** Expression profiles in human cancers, analysis comparison, and protein expression of CXCL8. (a) Expression profiles in human cancers of CXCL8 were analyzed by UALCAN. (b) The expression of the CXCL8 was compared during the four datasets. Normal tissues as control group. Values above the average were deemed to be overexpressed hub genes (red). (c) Immunohistochemistry results from human protein atlas database showed CXCL8 protein was upregulated.
to the influence on other genes, they may also play a role in posttranslational modification or activation of other pathways, and ultimately lead to prolonged survival of patients, which needs further research and exploration.

The E6/E7 gene is thought to be involved in tumorigenesis in cells infected with high-risk HPV. Studies suggest that CDK1 and WDHD1 involved in the mechanisms of the cancer promotion of E6 and E7 genes by evading mitotic checkpoints and inducing polyploid formation, thus resulted in gene instability and cervical cancer (Zhang et al., 2015; Zhou et al., 2016). AUUKA is associated with centrosomal expansion, spindle and chromosomal instability, and its high expression promotes tumor cell proliferation and invasion (Zhang, Wang, Liu, Hua, & Xin, 2009). The researchers (Sun et al., 2015) (Ma et al., 2017) found that AUUKA is related to the resistance of taxol and radiosensitivity. Currently, AUUK inhibitor is being explored as molecular-targeted medicines for the treatment of cervical cancer (Gabrielli et al., 2015; Umene et al., 2013). All the above molecules have been proved to play an important role in the occurrence and development of cervical cancer.

Although the other genes, we got by the bioinformatic analysis, have not been found to work in the occurrence and development of cervical cancer, they are still proved to be involved in the carcinogenesis and progression in tumor. ECT2 encodes guanine nucleotide exchange factor, and drives the proliferation and invasion of breast cancer, lung cancer, and gastric cancer. FANCI and FANCD form heterodimers, and participate in DNA repair (van Twest et al., 2017). However, HPV virus might damage this repair mechanism, leading to the occurrence of tumors and resistance to chemotherapy (Khanal & Galloway, 2019). DTI is involved in cell cycle regulation, and when DNA is damaged, it can stop replication and maintain gene stability (Abbas & Dutta, 2011). HELLS encodes a lymphoid-specific helicase that involved in DNA replication, transcription, and repair during cell proliferation (Geiman, Durum, & Muegge, 1998). Increased expression of HELLS is detected in various malignant tumors, such as head and neck squamous cell carcinoma, melanoma, and kidney cancer (Chen et al., 2017; Kim, Symanowski, Samlowski, Gonzales, & Ryu, 2010; Waseem, Ali, Odell, Fortune, & Teh, 2010). Through our screening methods, we obtained these genes, and the mechanisms of them in cervical cancer deserve further exploration.

To sum up, we utilized the public online database, and bioinformatics analysis tools to successfully identified 57 DEGs in cervical cancer. Among these, 12 genes may be biomarker of cervical cancer, of which five genes (TYMS, TOP2A, MCM2, HELLS, and CXCL8) are related to occurrence and prognosis. These results indicated that our methods are meaningful to screen the key genes by using the public database and tools. On the other hand, some genes related to cervical cancer have been estimated by our analysis, and more experiments are needed to explore these genes.

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CONFLICT OF INTERESTS

There are no conflicts of interest of the authors.

ETHICAL COMPLIANCE

This article does not contain any studies with human participants or animals performed by any of the authors. The authors are accountable for all aspects of the work.

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