

Identification of hub genes and key pathways associated with the progression of gynecological cancer

XI ZHANG¹ and YUDONG WANG²

¹Department of Gynecology, Changning Maternity and Infant Health Hospital, Shanghai 200051; ²Department of Gynecology, International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University, Shanghai 200030, P.R. China

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Abstract. Gynecological cancer is the leading cause of cancer mortality in women. However, the mechanisms underlying gynecological cancer progression have remained largely unclear. In the present study, 799 dysregulated genes were identified in ovarian serous cystadenocarcinoma (OV), 488 dysregulated genes in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), and 621 dysregulated genes in uterine corpus endometrial carcinoma (UCEC). Bioinformatics analysis revealed that mRNA splicing and cell proliferation-associated biological processes served important roles in OV progression. Metabolism-associated biological processes played important roles in CESC progression, and protein phosphorylation and small GTPase-mediated signal transduction served important roles in UCEC progression. The present study also constructed OV, CESC and UCEC progression-associated protein-protein interaction networks to reveal the associations among these genes. Furthermore, Kaplan-Meier curve analysis showed that progression-related genes were associated with the duration of overall survival. Finally, *NARS2* and *TPT1* in OV, *SMYD2*, *EGLN1*, *TNFRSF10D*, *FUT11*, *SYTL3*, *MMP8* and *EREG* in CESC, and *SLC5A1*, *TXN*, *KDM4B*, *TXNDC11*, *HSDL2*, *COX16*, *MGAT4A*, *DAGLA*, *ELOVL7*, *THRB* and *PCOLCE2* in UCEC were identified as hub genes in cancer progression. Therefore, this study may assist in the identification of novel mechanisms underlying cancer progression and new biomarkers for gynecological cancer prognosis and therapy.

Introduction

In the past decades, gynecological cancer has been the leading cause of cancer mortality in women globally (1). The major types of gynecological cancer include ovarian serous cystadenocarcinoma (OV), uterine corpus endometrial carcinoma (UCEC), and cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) (2). Despite the various therapeutic methods that have been developed, including surgical, hormone therapeutic and chemotherapeutic treatments, the 5-year survival rate of patients with gynecological cancer has remained poor (3,4). For example, the 5-year overall survival (OS) of patients with late-stage OV is <20% (3). The advanced-stage CESC 5-year OS rate has remained as low as 30% (4). Of note, the mechanisms underlying gynecological cancer require further investigation. Exploration the potential regulators involved in gynecological cancer progression is urgently needed to identify novel biomarkers of cancer prognosis and targets for treatment.

Next-generation sequencing (NGS) is an important tool in the generation of new cancer therapies and diagnostic methods (5,6). The Cancer Genome Atlas (TCGA) database, including >30 types of human cancer, is the most widely used NGS database and has played a crucial role in the discovery of cancer-associated genes and mutations (7,8). For example, Sanchez-Vega *et al* (9) analyzed oncogenic signaling pathways across 33 human cancer types using TCGA datasets. In gynecological cancer, a series of key regulators were also identified by using similar strategies. For instance, Berger *et al* (10) identified a series of mutated genes and somatic copy-number alterations in gynecological cancer by comprehensively analyzing TCGA datasets. Song *et al* (11) constructed an aberrant long noncoding RNA-microRNA-mRNA network in CESC using TCGA datasets. Comprehensive analysis of TCGA datasets provides novel insights into the mechanisms involved in tumor progression to allow for the identification of new biomarkers for human cancer, including gynecological cancer.

In order to obtain a comprehensive assessment of the molecular mechanisms underlying gynecological cancer progression, a bioinformatics analysis of OV, CESC and UCEC datasets from TCGA was conducted to identify hub genes and key pathways in the present study. In addition, the prognostic value of these key genes in gynecological cancer was also evaluated.

Correspondence to: Dr Yudong Wang, Department of Gynecology, International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University, 773 WuYi Road, Shanghai 200030, P.R. China
E-mail: wangyudong201x@sina.com

Key words: ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, protein-protein interaction analysis, biomarker

Materials and methods

TCGA dataset analysis. In the present study, TCGA CESC, OV and UCEC datasets were downloaded from the cBioPortal system (12). Level 3 RNA sequencing version 2 data were downloaded from TCGA (<https://www.cbioportal.org/>). A total of 233 stage I + II CESC and 68 stage III + IV CESC samples were included in TCGA CESC dataset. A total of 23 stage I + II OV and 282 stage III + IV OV samples were included in TCGA OV dataset. A total of 122 stage I + II UCEC and 54 stage III + IV UCEC samples were included in TCGA UCEC dataset. All specimens were independently assessed by two experienced pathologists according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system (13). Gene expression with $P < 0.01$ between early-stage (stage I + II) and advanced-stage (stage III + IV) samples was identified to indicate significantly differential expression. Hierarchical cluster analysis was performed, and a hierarchical clustering heat map was generated for the abnormally expressed genes using CLUSTER version 3.0 (14) and the Tree View system (15).

Protein-protein interaction (PPI) networks and module analysis. PPI networks were constructed to reveal the relationships among gynecological cancer progression-associated genes following two steps. Firstly, the combined score between each protein-protein pair was calculated using STRING version 11.0 (<http://www.string-db.org/>); reliable protein-protein interactions (combined score, > 0.4) were selected for PPI network construction. Secondly, an analysis of the degrees of each node was performed, and the key nodes (node degree ≥ 5) in the PPI network were retained using Cytoscape software (version 3.6.0; <http://www.cytoscape.org/>).

Gene ontology (GO) and pathway analysis. The Database for Annotation, Visualization and Integrated Discovery (DAVID) version 6.8 system (<https://david.ncifcrf.gov/tools.jsp>) provides a comprehensive set of functional annotation tools to identify disease-associated biological processes (16). Therefore, DAVID was used to conduct GO analysis (17,18). The top 15 associated 'biological processes' (BPs) are shown. The analysis results of molecular functions and Cellular Component were not shown in this study. BPs with $P < 0.05$ were considered to be significant.

Survival analysis of differentially expressed genes (DEGs). In order to examine whether these DEGs could be the potential biomarkers for the prognosis of gynecological cancer, Kaplan-Meier analysis and log-rank tests were conducted using an online public database, GEPIA (<http://gepia.cancer-pku.cn/index.html>). Patients with gynecological cancer were categorized into 2 groups depending on the expression levels in cancer samples; the median expression of candidate genes in all tumor samples was selected as the cut-off point to divide gynecological cancer samples into high- or low-expression groups. $P < 0.05$ was considered to indicate a statistically significant difference.

Statistical analysis. Differences in gene expression between the individual groups were analyzed using unpaired Student's

t-test or Mann-Whitney U-test. PASW Statistics 23.0 software from SPSS Inc. was used. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Identification of DEGs in the progression of gynecological cancer. Datasets from TCGA were downloaded to identify DEGs in OV, CESC and UCEC progression. Gene expression with $P < 0.01$ between low-stage (stage I + II) and advanced-stage (stage III + IV) samples was identified to indicate differential expression. A total of 153, 335 and 406 upregulated genes and 646, 153 and 215 downregulated genes were identified in OV, CESC and UCEC progression, respectively. Hierarchical clustering showed DEGs in higher-stage compared with lower-stage OV (Fig. 1A), CESC (Fig. 1B) and UCEC (Fig. 1C) samples.

In order to understand whether common or cancer-specific genes drive the progression of gynecological cancer, the dysregulated genes were compared. As shown in Fig. 1, no common dysregulated genes were observed in OV, CESC and UCEC (Fig. 1C and D). Meanwhile, only 11 upregulated and 21 downregulated genes were found in two types of gynecological cancer (Fig. 1C and D). These results suggested that different genes regulate cancer progression in different types of gynecological cancer.

Bioinformatics analysis of DEGs in gynecological cancer. Next, bioinformatics analysis was performed on the DEGs in gynecological cancer. GO analysis revealed that the DEGs associated with OV progression were mainly involved in regulating 'mRNA splicing', 'transcription', 'G2/M transition of mitotic cell cycle', 'cellular response to DNA damage stimulus', 'mitophagy', 'protein phosphorylation', 'cell-cell adhesion', 'cell division' and 'DNA repair' (Fig. 2A). DEGs in CESC progression were mainly involved in regulating 'gluconeogenesis', 'response to muramyl dipeptide', 'protein import into nucleus', 'canonical glycolysis', 'circadian regulation of translation', 'apoptotic cell clearance', 'positive Notch signaling pathway', 'glycolytic process', 'protein kinase activity' and 'oxygen homeostasis' (Fig. 2B). The study also indicated that DEGs in UCEC were associated with 'protein phosphorylation', 'small GTPase mediated signal transduction', 'transcription', 'intracellular signal transduction', 'hippo signaling', 'cytoskeleton organization', 'negative regulation of execution phase of apoptosis', 'bicellular tight junction assembly', 'positive regulation of apoptotic process' and 'protein destabilization' (Fig. 2C).

Construction of progression-associated gene-mediated PPI networks in gynecological cancer. As presented in Fig. 3, the OV progression-associated PPI networks included 258 proteins and 1,872 edges (Fig. 3A). The top 10 hub genes with highest degrees involved in OV progression were identified, including *EHMT1*, *EHMT2*, *BRCA1*, *PRDM10*, *CKAP5*, *SNRNP70*, *ATR*, *MTOR*, *SETD2* and *MIB2*. The UCEC progression-associated PPI networks included 99 proteins and 375 edges (Fig. 3B). The top 10 hub genes with the highest degrees involved in UCEC progression were identified, including *RHOA*, *ISG15*, *LATS2*, *ACTL8*, *CDK2*, *SPTB*, *TTK*, *EDN1*, *FBXO41* and

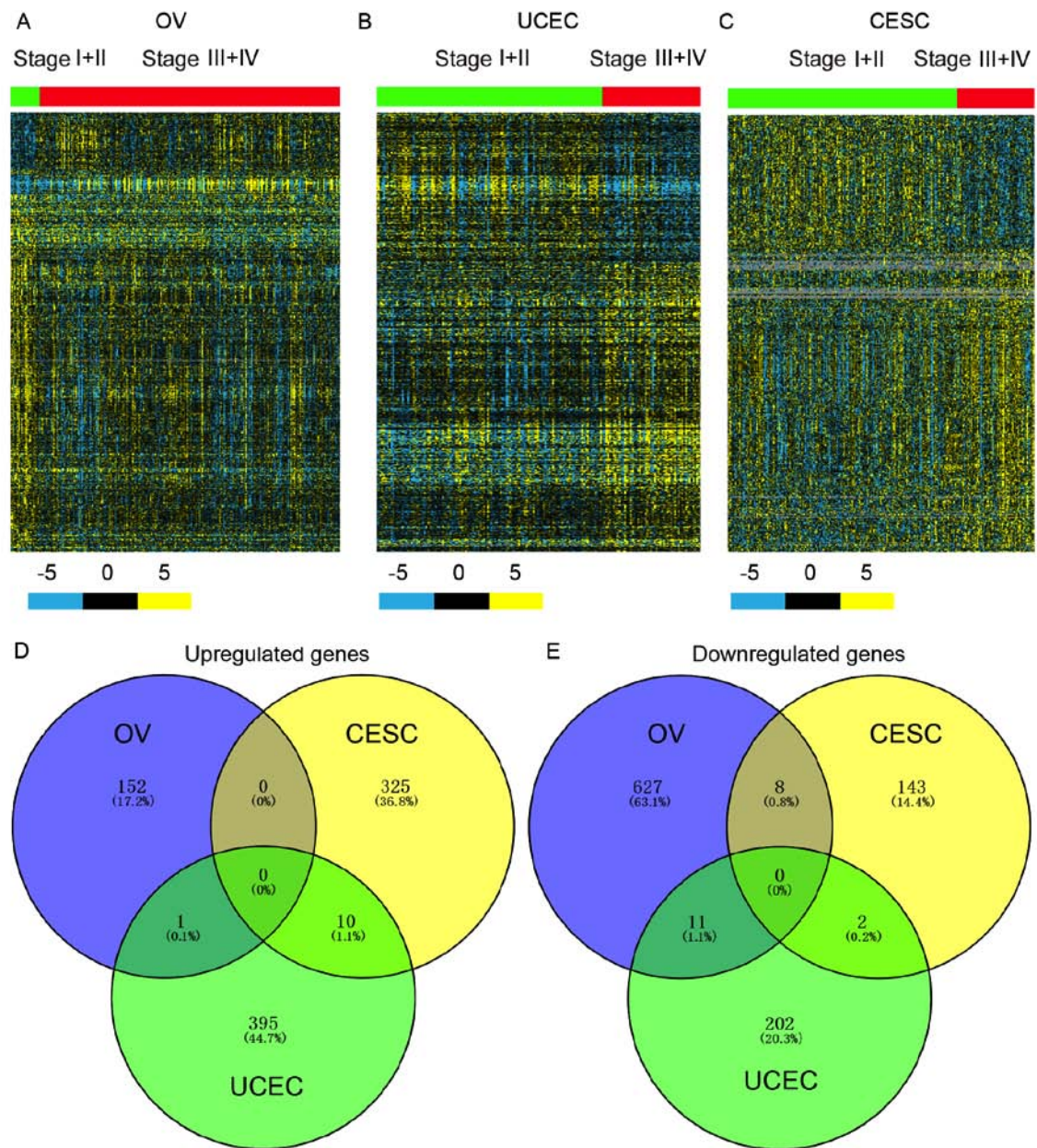


Figure 1. Identification of DEGs in gynecological cancer progression. Hierarchical clustering analysis showing the DEGs ($P < 0.01$) between (A) Stage I + II and Stage III + IV OV samples, (B) Stage I + II and Stage III + IV UCEC samples, and (C) Stage I + II and Stage III + IV CESC samples. The blue, black and yellow colors refer to 5-, 0- and 5-folds changes in expression, respectively. Venn diagrams for DEGs whose expression was significantly (D) upregulated and (E) downregulated in OV, UCEC and CESC samples. OV, ovarian serous cystadenocarcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; UCEC, uterine corpus endometrial carcinoma; DEGs, differentially expressed genes.

RBBP7. The CESC progression-associated PPI networks included 69 proteins and 228 edges (Fig. 3C). The top 10 hub genes with the highest degrees involved in CESC progression were identified, including *EDN1*, *GNG10*, *AGT*, *EPRS*, *HSPA4*, *RIT1*, *CUL2*, *GNAIL*, *GPI* and *GPR68*.

Prognostic significance of progression-associated genes in gynecological cancer. Furthermore, Kaplan-Meier curve analysis was conducted to determine the association between progression-associated gene expression and OS in gynecological cancer, using TCGA datasets. The median expression of progression-associated genes was selected as the cut-off to divide the gynecological cancer cases into high- and low-expression groups.

Higher expression of *NARS2* and lower expression of *TPT1* were indicated to be associated with a longer OS time in patients with OV (Fig. 4A and B). Meanwhile, the OS times in *SMYD2*-high, *EGLN1*-high, *TNFRSF10D*-high, *FUT11*-high, *SYTL3*-low, *MMP8*-high and *EREG*-high expression groups in patients with CESC were significantly shorter compared with their opposing expression groups (Fig. 4C-I). In patients with UCEC, this study indicated that higher expression of *SLC5A1*, *TXN*, *KDM4B*, *TXNDC11*, *HSDL2* and *COX16*, and lower expression of *MGAT4A*, *DAGLA*, *ELOVL7*, *THRB* and *PCOLCE2* were associated with longer OS times (Fig. 5A-K). These analyses indicated that progression-associated genes could serve as biomarkers for gynecological cancer.

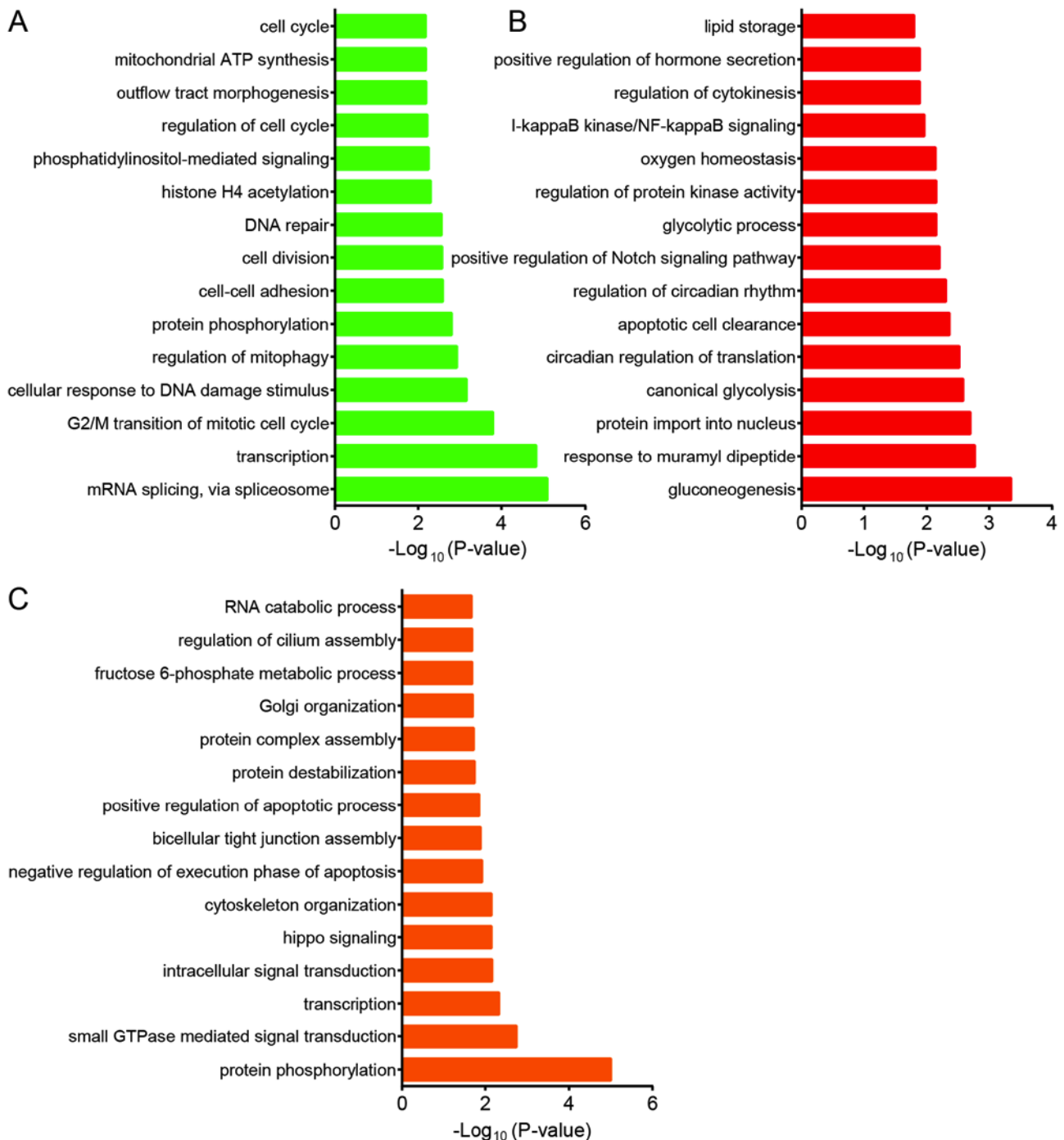


Figure 2. Bioinformatics analysis of DEGs in gynecological cancer progression. Gene Ontology analysis showing DEG-associated biological processes in (A) OV, (B) CESC and (C) UCEC. OV, ovarian serous cystadenocarcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; UCEC, uterine corpus endometrial carcinoma; DEGs, differentially expressed genes.

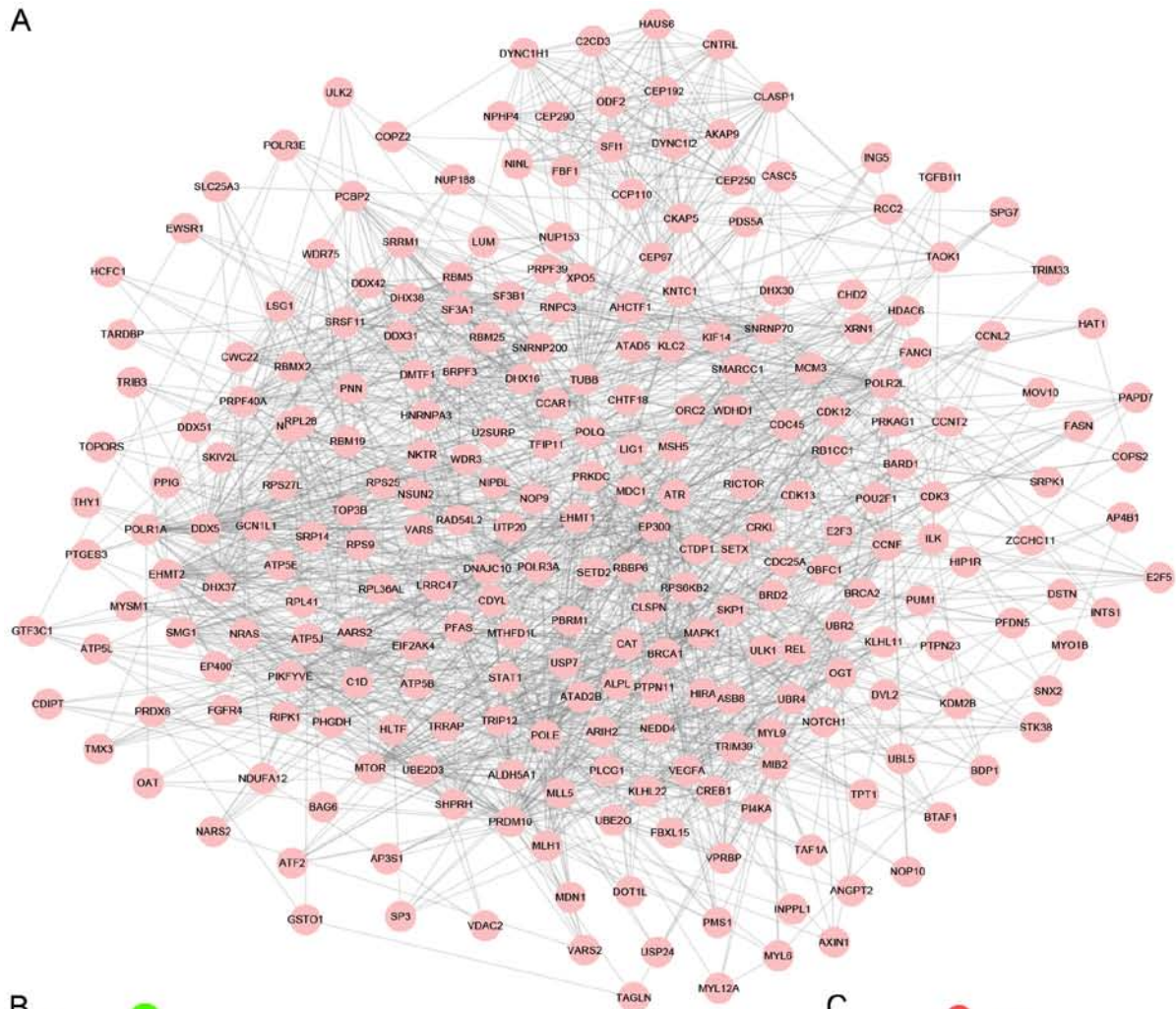
Discussion

Gynecological cancer, including OV, CESC and UCEC, are a leading cause of cancer mortality in women (19). In the present study, TCGA datasets were analyzed to identify gynecological cancer progression-associated genes. A total of 153, 335 and 406 upregulated, and 646, 153 and 215 downregulated genes were associated with OV, CESC and UCEC progression, respectively. In addition, OV, CESC and UCEC progression-associated PPI networks were constructed to reveal the associations among these genes. Furthermore, Kaplan-Meier

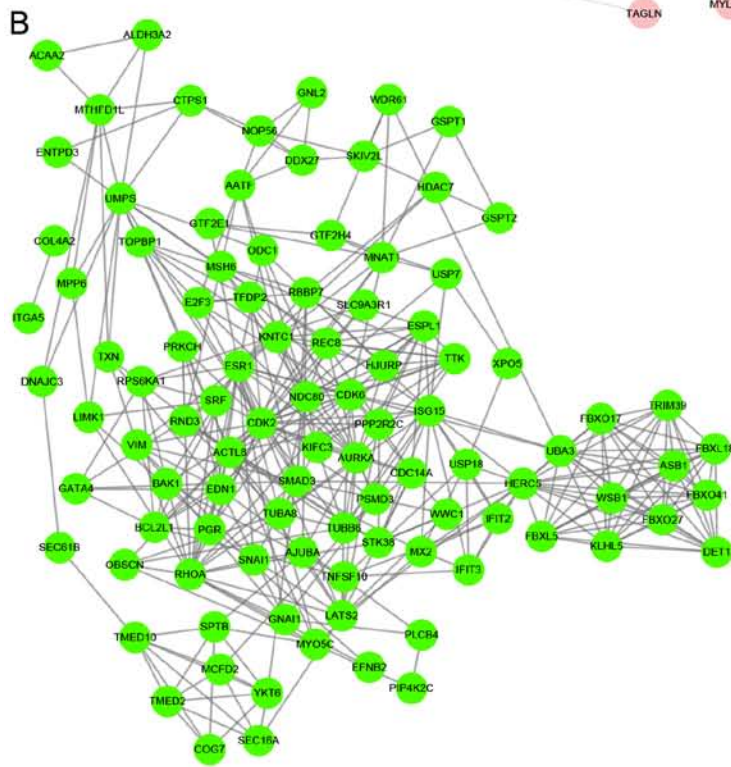
curve analysis showed that progression-related genes, such as *SMYD2*, *EGLN1*, *TNFRSF10D*, *SLC5A1* and *TXN*, could serve as prognostic biomarkers for gynecological cancer.

Previous studies have reported certain drivers that are involved in gynecological cancer (20-22). By using TCGA datasets, Berger *et al* (10) identified various mutated genes in gynecological cancer. *CT45* was identified as a chemosensitivity mediator and immunotherapy target in ovarian cancer (20). *BRCA1* and *BRCA2* are considered to be key regulators of ovarian development and function (21,22). However, the underlying mechanisms regulating cancer progression

A



B



C

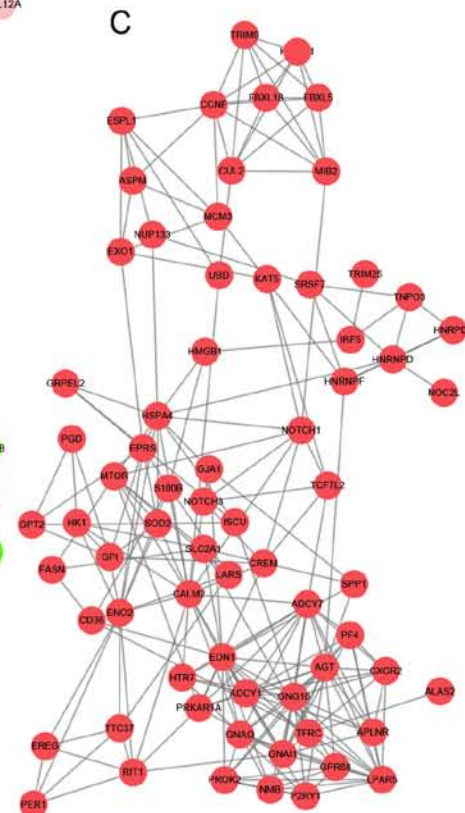


Figure 3. Construction of progression-associated PPI networks in gynecological cancer. Progression-associated PPI networks in (A) OV, (B) UCEC and (C) CESC were constructed. OV, ovarian serous cystadenocarcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; UCEC, uterine corpus endometrial carcinoma; PPI, protein-protein interaction.

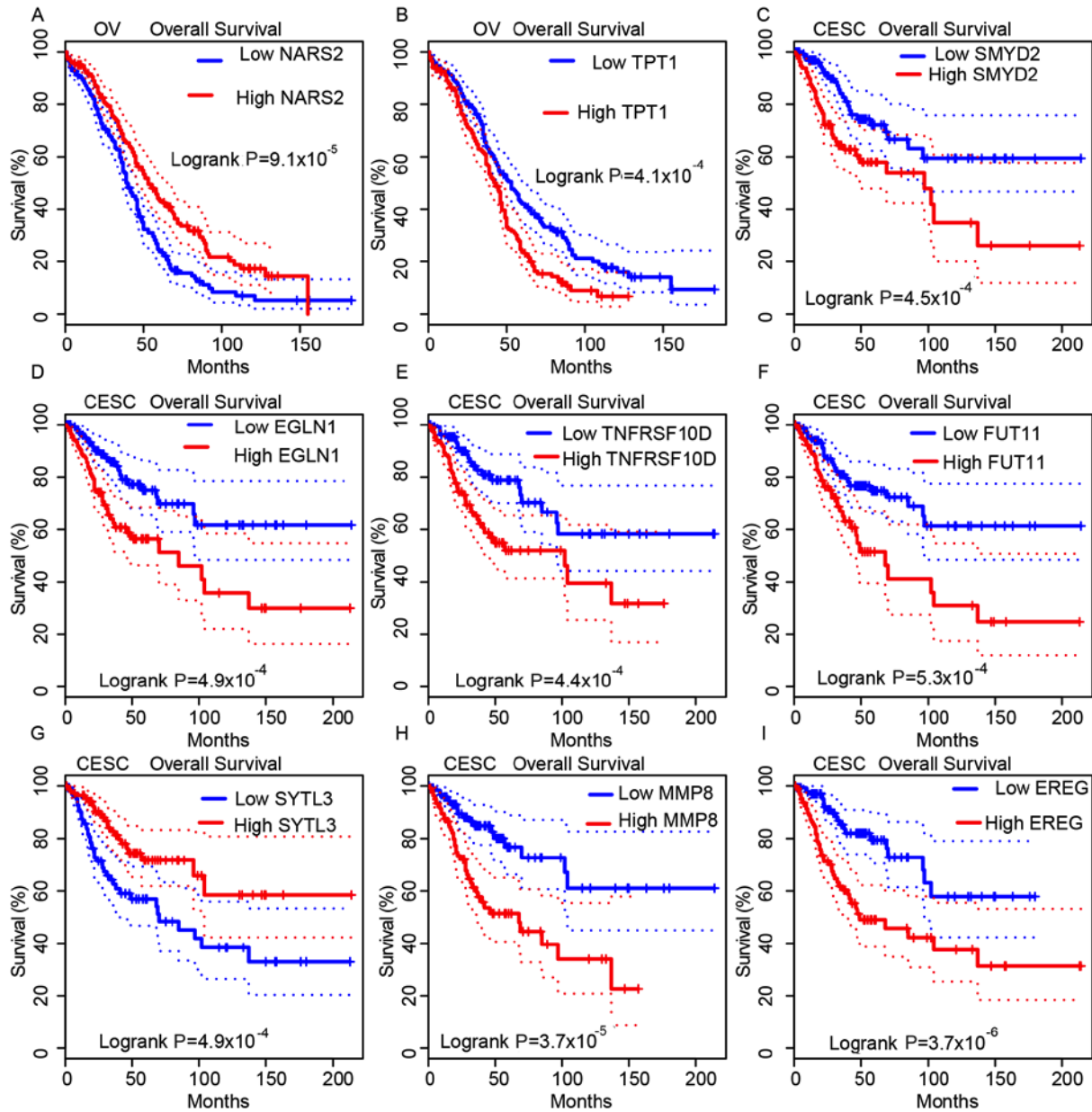


Figure 4. Progression-associated genes are associated with overall survival time in OV and CESC. It was indicated that upregulated expression of (A) NARS2 and lower expression of (B) TPT1 was associated with a longer OS time in patients with OV. The OS times in (C) SMYD2-high, (D) EGLN1-high, (E) TNFRSF10D-high, (F) FUT11-high, (G) SYTL3-low, (H) MMP8-high and (I) EREG-high patients with CESC were significantly shorter. OV, ovarian serous cystadenocarcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma.

require further investigation. The present study identified 799 dysregulated genes in OV, 488 dysregulated genes in CESC, and 621 dysregulated genes in UCEC. Only a small number of genes were observed to be dysregulated in more than one gynecological cancer, suggesting that different mechanisms underlie cancer progression in different types of gynecological cancer.

Bioinformatics analyses were also performed, and showed that OV progression-associated genes were involved in regulating mRNA splicing and cell proliferation-associated BPs. mRNA splicing had been demonstrated to regulate the progression of OV. For example, Snail driving alternative splicing of CD44 by ESRP1 enhances metastasis of OV (23). CESC progression-associated genes were involved in regulating a series of metabolism-related BPs, such as glycolysis and oxygen

homeostasis. Glycolysis played a crucial role for the supplication of energy and precursors for human cancer (24). It was also indicated that DEGs in UCEC were associated with protein phosphorylation and small GTPase-mediated signal transduction. In addition, PPI networks were constructed in this study. A few genes were identified to be key regulators in gynecological cancer progression, such as *EHMT1* and *EHMT2* in OV, *EDN1* and *GNG10* in CESC, and *RHOA* and *ISG15* in UCEC.

Over the past decades, efforts have been made to identify accurate biomarkers for gynecological cancer. For instance, upregulation of TRIM44 predicts poor prognosis in epithelial ovarian cancer (25), and LYL1 amplification predicts a shorter survival time of patients with UCEC (26). However, the prognosis of patients with gynecological cancer remains poor. In this study, Kaplan-Meier curve analysis was conducted

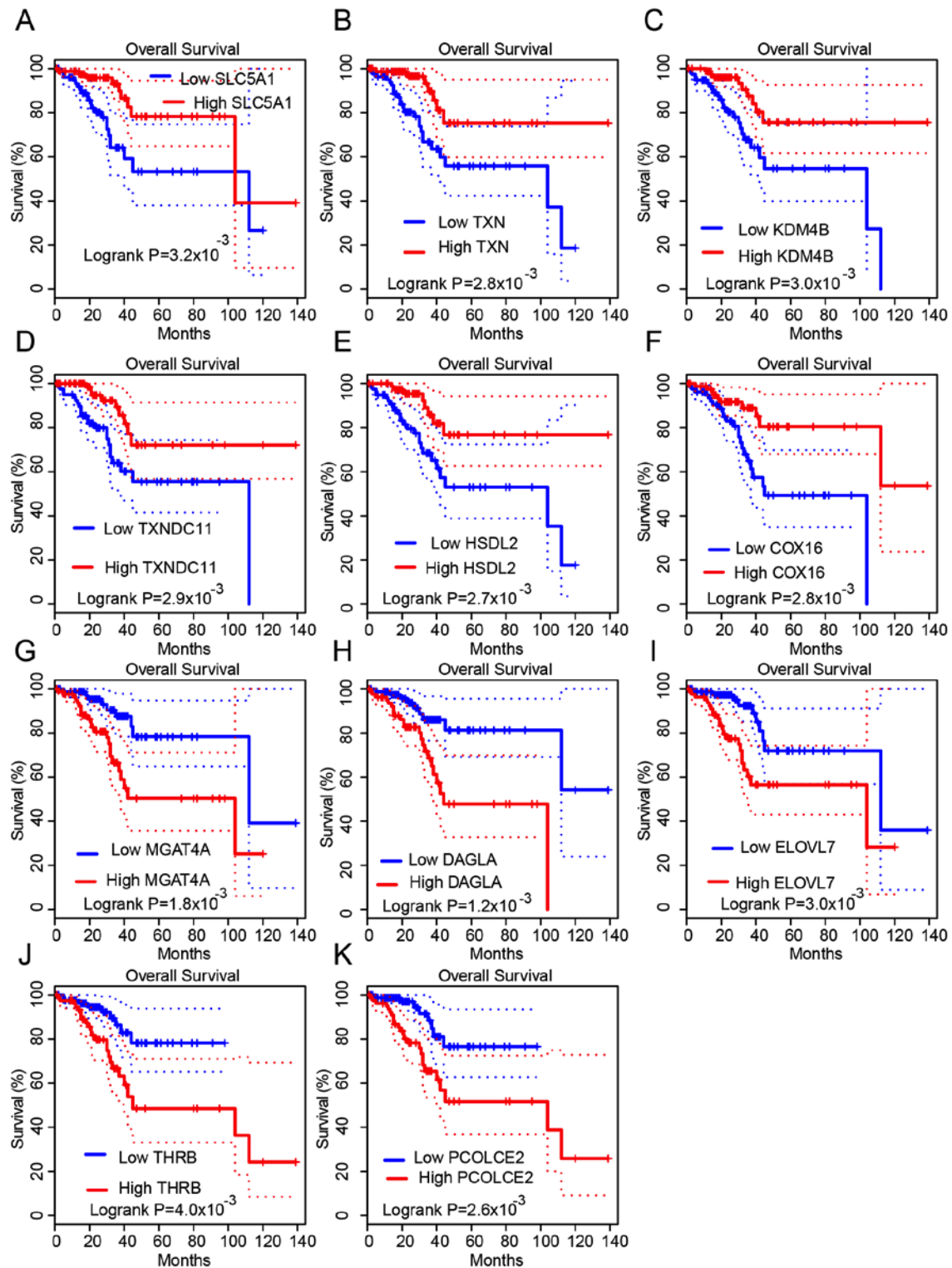


Figure 5. Progression-related genes are associated with overall survival time in UCEC. It was revealed that higher expression levels of (A) SLC5A1, (B) TXN, (C) KDM4B, (D) TXNDC11, (E) HSDL2 and (F) COX16, and lower expression levels of (G) MGAT4A, (H) DAGLA, (I) ELOVL7, (J) THRB and (K) PCOLCE2, were associated with longer OS times in patients with UCEC. UCEC, uterine corpus endometrial carcinoma.

to determine the prognostic value of progression-associated gene expression in gynecological cancer. It was revealed that the dysregulation of *NARS2* and *TPT1* in OV, the dysregulation of *SMYD2*, *EGLN1*, *TNFRSF10D*, *FUT11*, *SYTL3*, *MMP8* and *EREG* in CESC, and the dysregulation of *DC11*, *HSDL2*, *COX16*, *MGAT4A*, *DAGLA*, *ELOVL7*, *THRB* and *PCOLCE2*

in UCSC were associated with OS time. In previous studies, *SMYD2* (which encodes SET and MYND domain containing 2 protein) was found to be an oncogene in various types of cancer, including triple negative breast cancer (27), hepatocellular carcinoma (28) and pancreatic cancer (29). *FUT11* (fucosyl-transferase 11) was identified as a novel prognostic marker for

clear cell renal cell carcinoma (30). Genetic polymorphisms in *MMP8* (encoding matrix metalloproteinase-8) have been reported to be associated with breast cancer (31), bladder cancer (32) and malignant melanoma risk (33,34). *HSDL2* (hydroxysteroid dehydrogenase-like 2) serves as an oncogene in ovarian cancer by promoting cell proliferation and cell motility (35). However, the majority of these genes were for the first time reported to be involved in human cancer progression, and these analyses suggested that these progression-associated genes could serve as biomarkers for gynecological cancer.

In the present study, 799 dysregulated genes were identified in OV, 488 dysregulated genes in CESC and 621 dysregulated genes in UCEC. Bioinformatics analysis revealed that mRNA splicing and cell proliferation-associated BPs played important roles in OV progression. In addition, metabolism-related BPs played important roles in CESC progression, and protein phosphorylation and small GTPase-mediated signal transduction played important roles in UCEC progression. OV, CESC and UCEC progression-associated PPI networks were also constructed to reveal the association among these genes. Furthermore, Kaplan-Meier curve analysis showed that progression-related genes were associated with OS time. Finally, *NARS2* and *TPT1* in OV, *SMYD2*, *EGLN1*, *TNFRSF10D*, *FUT11*, *SYTL3*, *MMP8* and *EREG* in CESC, and *DC11*, *HSDL2*, *COX16*, *MGAT4A*, *DAGLA*, *ELOVL7*, *THRB* and *PCOLCE2* in UCEC were identified as hub genes in cancer progression. Therefore, it is suggested that the present study may assist in the identification of novel mechanisms underlying cancer progression and new biomarkers for gynecological cancer prognosis and therapy.

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Availability of data and material

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

Authors' contributions

XZ and YW were involved in the conception and design of the research and drafting the manuscript. XZ participated in the acquisition of data, analysis and interpretation of data and statistical analysis. YW participated in the design of the study and performed the statistical analysis. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent to publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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