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Gene co-expression network analysis revealed novel biomarkers for ovarian cancer

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Ovarian cancer is the second most common gynecologic cancer and remains the leading cause of death of all gynecologic oncologic disease. Therefore, understanding the molecular mechanisms underlying the disease, and the identification of effective and predictive biomarkers are invaluable for the development of diagnostic and treatment strategies. In the present study, a differential co-expression network analysis was performed *via* meta-analysis of three transcriptome datasets of serous ovarian adenocarcinoma to identify novel candidate biomarker signatures, i.e. genes and miRNAs. We identified 439 common differentially expressed genes (DEGs), and reconstructed differential co-expression networks using common DEGs and considering two conditions, i.e. healthy ovarian surface epithelia samples and serous ovarian adenocarcinoma epithelia samples. The modular analyses of the constructed networks indicated a co-expressed gene module consisting of 17 genes. A total of 11 biomarker candidates were determined through receiver operating characteristic (ROC) curves of gene expression of module genes, and miRNAs targeting these genes were identified. As a result, six genes (*CDT1*, *CNIH4*, *CRLS1*, *LIMCH1*, *POC1A*, and *SNX13*), and two miRNAs (mir-147a, and mir-103a-3p) were suggested as novel candidate prognostic biomarkers for ovarian cancer. Further experimental and clinical validation of the proposed biomarkers could help future development of potential diagnostic and therapeutic innovations in ovarian cancer.

KEYWORDS

ovarian cancer, transcriptome profiling, differential gene co-expression network, prognostic gene module, biomarkers

Introduction

Ovarian cancer is the second most common gynecologic cancer and remains the leading cause of death of all gynecologic oncologic disease (Didžiapetriene et al., 2014; Madden et al., 2014). High-grade serous ovarian cancer, which accounts for 70% of the patients, is the most aggressive type with low survival rate (Coscia et al., 2016) due to late stage diagnosis of the disease (Egan et al., 2011). The mortality rate can be reduced with early diagnosis and personalized treatments. Thereby, the elucidation of molecular mechanisms of serous ovarian cancer pathogenesis and the identification of alternative diagnostic methodologies, particularly effective, reliable and predictive

biomarkers still remain a high priority, and would be vital to provide new insights on the disease.

The high-throughput microarray profiling has been extensively used for years to understand the underlying mechanisms of human diseases at molecular level. These studies revealed hundreds of genes that were significantly expressed in complex diseases, including cancers. The identification of transcriptionally dysregulated genes and altered molecular mechanisms in the presence of cancer provides information on tumor's biological state and the patients' survival (Otálora-Otálora et al., 2019). Therefore, the integration of these set of genes with biological information at different levels continues to be an effective method to discover molecular targets that may serve as diagnostic and prognostic tools, and help to develop and therapeutic strategies (Gov and Arga, 2017; Venkataramanan and Mathavan, 2020).

A system-based approach is needed to gain a comprehensive view of cancer, and the power of differential co-expression networks was previously shown in cancer research (Gov and Arga, 2017). The construction and analysis of differential co-expression networks have been widely used to discover gene modules and hub genes in various cancers, including retinoblastoma (Mao et al., 2020), pituitary adenoma (Aydin and Arga, 2019), ovarian (Gov and Arga, 2017; Gov, 2020), lung (Liao et al., 2020) and cervical cancers (Kori et al., 2019).

The aim of the present study was to provide further insight to the genetic and molecular underpinnings of ovarian cancer pathogenesis and to identify associated molecular signatures. For this purpose, three independent gene expression datasets of serous ovarian adenocarcinoma were comparatively analyzed and 439 common DEGs were identified. The differential co-expression networks were reconstructed in the diseased and healthy states by using common DEGs, and functional modular organizations of the reconstructed networks were examined. A novel gene module consisting of 17 genes that was differentially co-expressed in ovarian cancer, but not preserved in healthy state, was identified. ROC curve analysis indicated high diagnostic performances of 11 module genes that might serve as potential biomarkers. Moreover, miRNAs targeting these 11 genes were screened to identify regulatory signatures of the disease. As a result, six genes (*CDT1*, *CNIH4*, *CRLS1*, *LIMCH1*, *POCIA*, and *SNX13*) and two miRNAs (mir-147a, and mir-103a-3p) were determined as novel biomarker candidates and putative therapeutic targets that would be invaluable for future studies.

Materials and methods

Gene expression data collection

The gene expression datasets associated with serous ovarian adenocarcinoma from three independent studies [GSE10971

TABLE 1 Gene expression data sets used in this study.

GEO	Control	Disease	Array	References
GSE10971	12	13	GPL570	Tone et al. (2011)
GSE14407	12	12	GPL570	Bowen et al. (2009)
GSE18520	10	53	GPL570	Mok et al. (2009)

(Tone et al., 2011), GSE14407 (Bowen et al., 2009), and GSE18520 (Mok et al., 2009)] were obtained from Gene Expression Omnibus (GEO) database (Table 1). The studies that used the platform GPL570 (Affymetrix Human Genome U133 Plus 2.0 arrays) were selected to avoid altered gene expressions due to microarray differences. GSE10971 contained gene expression profiles of laser capture micro-dissected non-malignant distal fallopian tube epithelium from 12 BRCA1/2-mutation carriers and 12 control women during the luteal and follicular phase, and 13 high grade tubal and ovarian serous carcinomas. Samples of BRCA1/2-mutation carriers were excluded from this dataset. GSE14407 was consisted of 12 healthy ovarian surface epithelia samples and 12 laser-capture micro-dissected papillary serous ovarian adenocarcinoma epithelia samples. GSE18520 contained 53 micro-dissected late stage, high-grade primary papillary serous ovarian adenocarcinoma and 10 normal ovarian surface epithelia samples.

Identification of differentially expressed genes

DEGs were identified using the GEO2R tool (<http://www.ncbi.nlm.nih.gov/geo/geo2r/>), which uses LIMMA (Smyth, 2004) as the statistical test. Benjamini–Hochberg's method was used to control the false discovery rate (FDR). The statistical significance and expression patterns (up- or down-regulation) of DEGs were determined by an adjusted *p*-value threshold and fold-change (FC), respectively. An adjusted *p*-value threshold of 0.01 and FC cut-off of two were used to identify significant DEGs.

Pathway enrichment and gene-disease association analyses

Pathway enrichment analyses were carried out by Metascape (Zhou et al., 2019) (<https://metascape.org/gp/index.html#/main/step1>) to identify significant KEGG (Kanehisa and Goto, 2000) pathways associated with DEGs. The *p*-values were obtained *via* hypergeometric test and corrected using Benjamini–Hochberg algorithm. An adjusted *p*-value threshold of 0.05 was used to identify the statistical significance of the identified pathways. Significant disease associations of DEGs were determined using

DisGeNet database (Piñero et al., 2020) via R (R Core Team, 2020) with a *p*-value threshold of 0.05.

Construction of differential gene co-expression networks and modular analysis

The differential co-expression networks were constructed for the diseased and healthy states separately considering common DEGs in three datasets. Two expression datasets were obtained by separating the expression values of common DEGs in healthy and diseased states. The mean expression values were used for repetitive DEGs. The healthy and disease datasets were composed of 34 and 78 samples, respectively. Both datasets were normalized via quantile normalization performed by RMA (Bolstad et al., 2003). The correlations between the expression profiles of common DEGs were determined by Pearson correlation coefficients (PCCs) computed between each gene pair in both datasets, and the statistical significance of pairwise correlations were determined via asymptotic *p*-values approximated by using the *t*-distribution. An absolute PCC cut-off of 0.8 and an asymptotic *p*-value threshold of 0.05 were maintained to identify the statistically significant correlations. PCC >0.8 and PCC < -0.8 were defined as positive and negative correlations among gene pairs, respectively. The differential gene co-expression networks, i.e., disease network (OC), and control network (non-OC), were constructed around the significantly co-expressed gene pairs in the diseased, and healthy states, respectively.

Constructed networks were visualized via Cytoscape (v3.7.2) (Shannon et al., 2003) and CytoHubba (Chin et al., 2014) was used to compute node scores. Genes were ranked based on degree and 5% of the genes with the highest degree scores were determined as hub genes.

Highly connected subgroups within the gene co-expression networks were identified via MCODE (Bader and Hogue, 2003) plug-in of Cytoscape. In MCODE, network scores were computed by excluding the loops. Modules were identified setting the degree threshold, node score threshold, K-core threshold, and maximum depth to 2, 0.2, 2 and 100, respectively. The fluff parameter was turned off and the haircut parameter was turned on. The most densely connected regions (the top-scoring modules) of both networks were taken into consideration for further analysis.

Diagnostic performances of module genes

The gene expression profiles of OC module (OCM) genes were extracted from the three datasets, and receiver operating characteristic (ROC) curves were plotted. Area under the curve (AUC) representing sensitivity (the proportion of positive test

results in patients) and specificity (the proportion of negative test results in healthy individuals) was used to evaluate the diagnostic performance of the genes.

Nucleosome organization analysis

The nucleosome positioning patterns of ovarian cancer associated co-expressed genes were screened using NucMap database (Zhao et al., 2019), which contains 798 experimental data from 477 samples across 15 species. The enrichment analyses of nucleosome occupancy were carried out using normalized raw reads across four different cell lines representing chronic myelogenous leukemia (K-562), skin melanoma (COLO829), cervical carcinoma (HeLa), and breast adenocarcinoma (MCF-7). The nucleosome enrichment around transcription start sites (TSSs) were visualized.

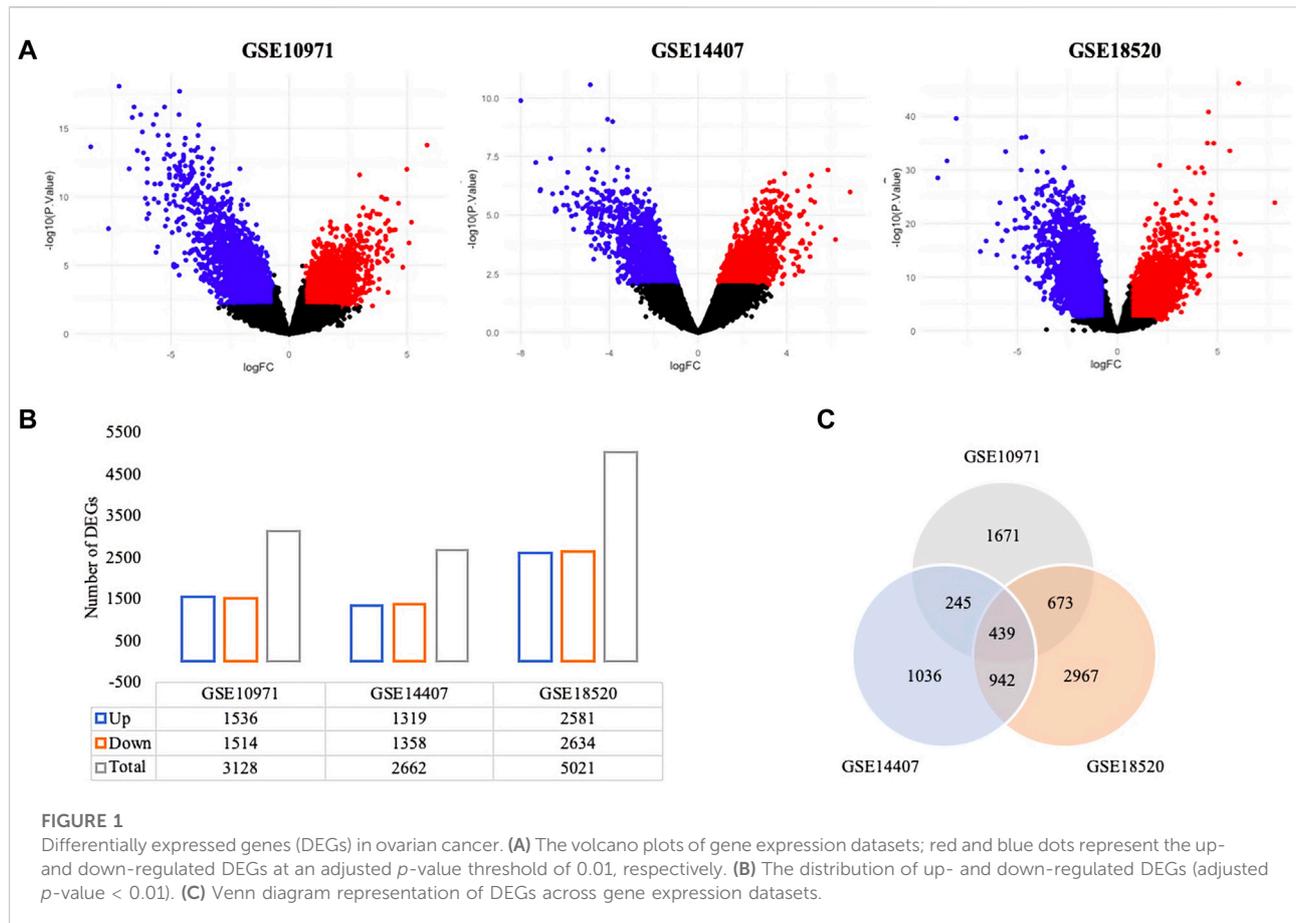
Construction of miRNA-target gene regulatory network

The miRNA-target gene regulatory network was constructed by mapping prognostic module genes to the respective miRNAs. The miRNet 2.0 database (Chang et al., 2020) was used to identify miRNA-gene interactions with a degree cut-off of 3, and to visualize the constructed network.

Results

Differentially expressed genes in ovarian cancer

Genome-wide response of ovarian epithelia cells to the presence of serous ovarian adenocarcinoma at the transcriptional level revealed numerous genes that were significantly and differentially expressed. The individual analysis of gene expression datasets resulted in the identification of 4,263 up-regulated and 4,313 down-regulated DEGs (Figure 1A). A total of 1,536 up- and 1,514 down-regulated genes in GSE10971, 1,319 up- and 1,358 down-regulated genes in GSE14407, and 2,581 up- and 2,634 down-regulated genes in GSE18520 were determined (Figure 1B). Although the numbers of DEGs among datasets varied, comparative analysis revealed 439 common DEGs (Figure 1C). The pathway enrichment analyses of common DEGs revealed cell cycle, oocyte meiosis, Fanconi anemia pathway, and several cancer-associated pathways as significant pathways (Figure 2A). Moreover, the gene-disease association analyses indicated a significant relation between common DEGs and several cancers (Figure 2B).



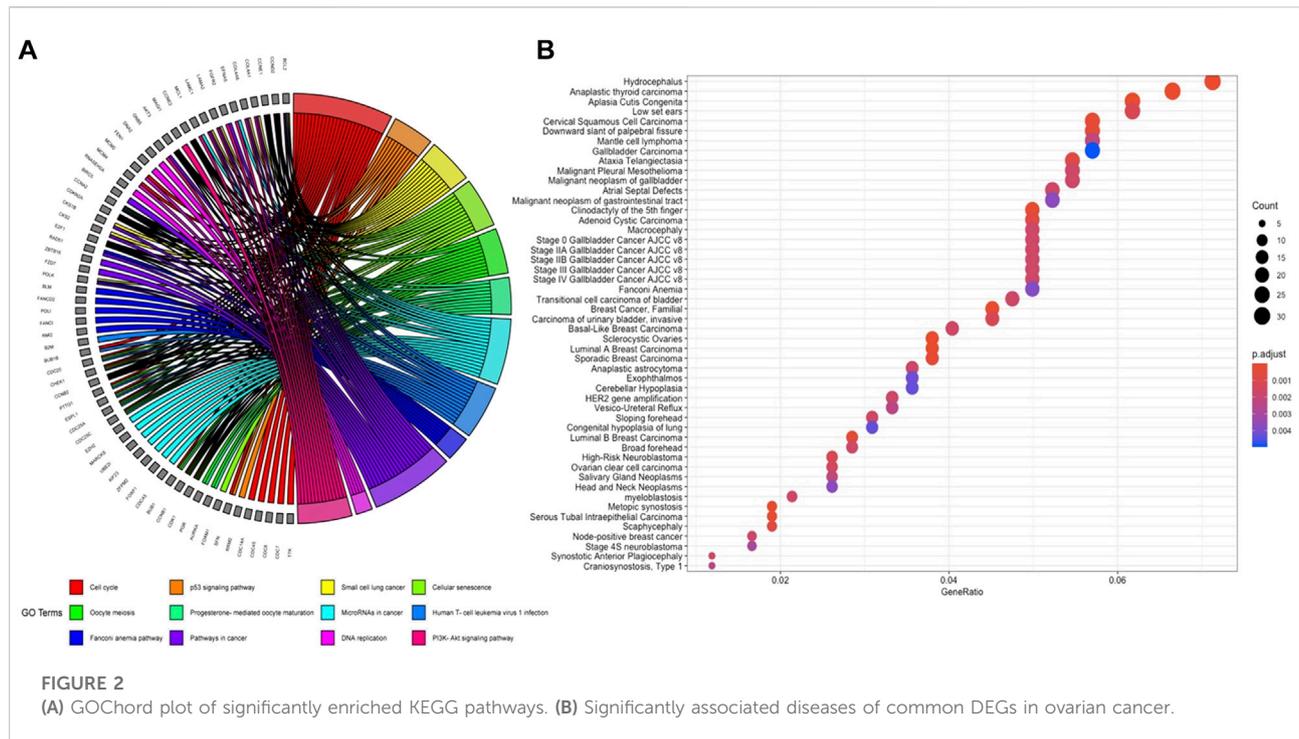
Differential co-expression networks in ovarian cancer

The co-expression patterns of common DEGs were analyzed in the diseased state and healthy state separately to construct diseased and control co-expression networks, respectively. The employment of PCC's resulted in a total of 3,375 significant correlations among 271 genes. OC, constructed around the significantly co-expressed gene pairs in the diseased state, contained 522 associations among 113 DEGs (Figure 3A), and non-OC, constructed around the significantly co-expressed gene pairs in healthy state, consisted of 3,044 associations among 250 DEGs (Figure 3B). The topological analysis indicated that both networks had the same density (%10), although the number of genes showing significant pairwise correlations was 2.2-fold lower in OC when compared to non-OC.

A total of 8 and 16 genes were determined to be hub genes in OC, and non-OC, respectively. *CNIH4*, *PRKD3*, *CRLS1*, *USP53*, and *PYGL* were found to be specific to OC. *ALDH1A2*, *POLI*, *CYBRD1*, *RSPH3*, *SRI*, *EFEMP1*, *GPSM2*, *LSM4*, *PRKCI*, *SEMA5B*, *LRP2*, *NEFH*, *GRAMD2A* were identified as specific hub genes for non-OC. Comparative analysis revealed *FANCD2*, *MYEF2*, and *STK38* as the mutual hub genes (Figures 3C,D).

Co-expressed gene module of ovarian cancer

The most densely connected regions of OC and non-OC were identified by MCODE. OCM contained 125 interactions between 17 genes (Figure 3E), whereas non-OC module (non-OCM) consisted of 1,149 interactions between 51 genes (Figure 3F). Comparative analysis of the modules indicated that only three genes (*FANCD2*, *MYEF2*, and *STK38*), which were also mutual hub genes of OC and non-OC, were found to be common in OCM and non-OCM. To assess the prognostic capability of OCM genes in ovarian cancer, we evaluated whether OCM was preserved in healthy state. The preservation analysis was carried out by comparing the significant correlations among OCM genes with their correlations in healthy samples. PCC values that show the correlations between OCM genes in diseased and healthy samples are presented in Supplementary Table S1. Only 33 associations among 13 OCM genes were found to be significant among healthy samples (Figure 4). The module density, which was 0.919 in the diseased state, was found to be 2.2-fold lower (0.423) in healthy state. Since OCM genes were highly correlated in the diseased state, but not in healthy state, this module was considered as a prognostic module in ovarian cancer. *B2M*, *CDT1*, *CNIH4*, *CRLS1*, *EIF5*,



FANCD2, *H3-3A*, *LIMCH1*, *MYEF2*, *PIF1*, *POC1A*, *PRKD3*, *PYGL*, *SLC38A10*, *SNX13*, *STK38*, and *VWA3A* were the correlated DEGs in OCM. Interestingly seven genes had the highest degree that corresponds to interactions with 16 genes in the module. These genes were *CNIH4*, *CRLS1*, *FANCD2*, *MYEF2*, *PRKD3*, *PYGL*, and *SNX13*, and they were positively correlated with each other, while all of them were negatively correlated with four genes, including *CDT1*, *POC1A*, *SLC38A10*, and *VWA3A*. *CDT1* had the least number of interacting partners (a degree of 10) in the module.

The descriptions and functions of OCM genes are presented in Table 2. Functional enrichment analysis of OCM showed that the prognostic module genes were not significantly associated with any KEGG pathways, but they were significantly enriched with regulation of chromosome organization, negative regulation of cellular component organization, and DNA metabolic process GO biological processes.

ROC curve analysis indicated that 11 module genes (*B2M*, *CDT1*, *CNIH4*, *CRLS1*, *EIF5*, *LIMCH1*, *POC1A*, *PRKD3*, *PYGL*, *SLC38A10*, and *SNX13*) showed high performances ($AUC \geq 0.7$) in discriminating diseased patients from healthy controls (Figure 5).

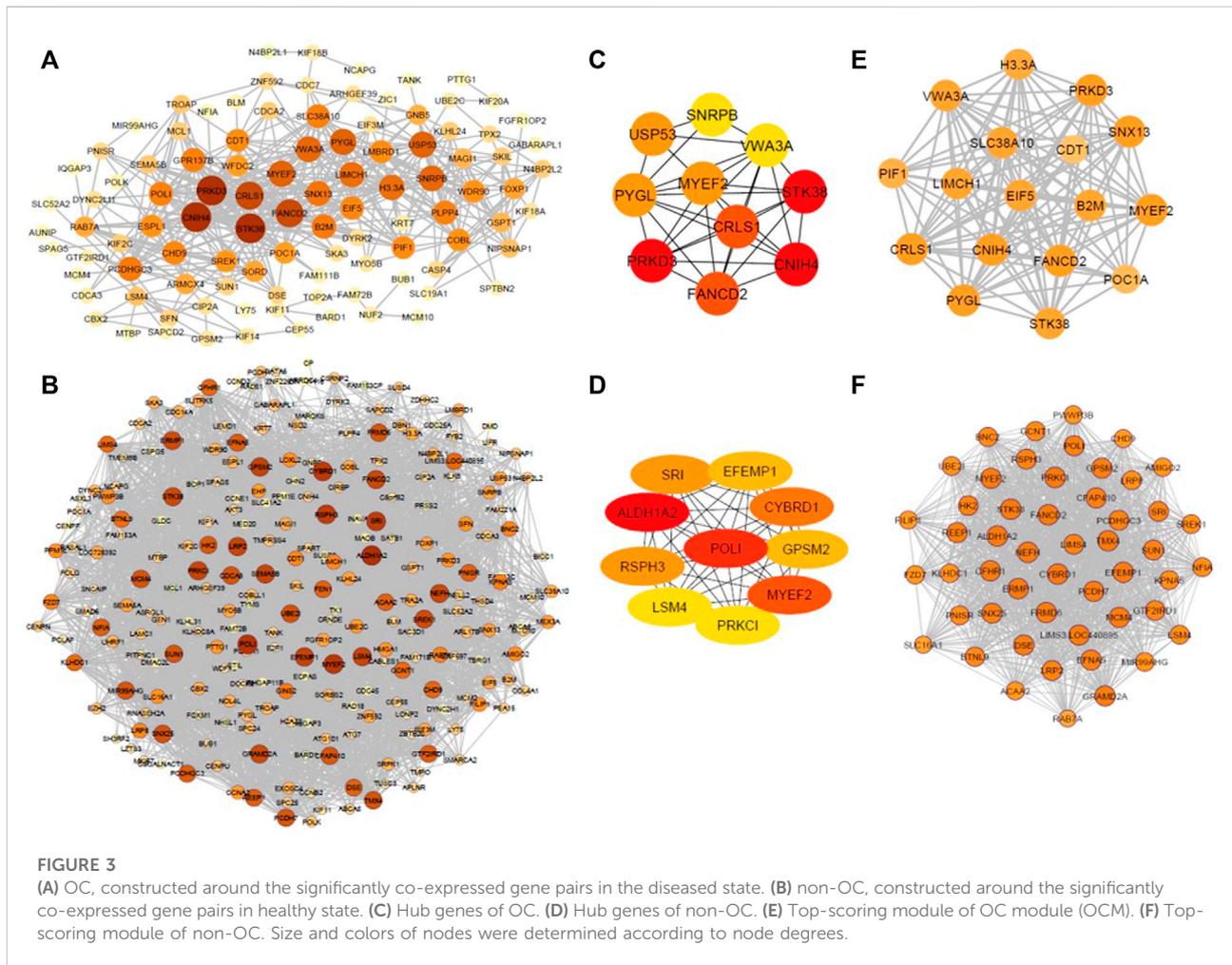
Establishment of miRNA-target gene regulatory network

miRNAs have major roles in the regulation of gene expression. A total of 26 miRNAs targeting 11 prognostic module genes were identified using miRNet 2.0. Only

miRNAs having a degree higher than three were presented (Figure 6A). When miRNA-target gene interactions were analyzed, miR-1-3p, miR-147a, miR-103a-3p, and miR-124-3p came into prominence by regulating at least seven genes (Figure 6B). Two genes, *CDT1* and *POC1A*, were found to be commonly regulated by the top four miRNAs (Figure 6C). The analysis revealed that the majority (91%) of prognostic module genes were regulated by miR-1-3p, and miR-147a.

Nucleosome positioning at transcription start sites of ovarian cancer associated genes

The prognostic module, OCM, contained genes that were already reported to be associated with ovarian cancer together with novel candidates, such as *CDT1*, *CNIH4*, *CRLS1*, *LIMCH1*, *POC1A*, and *SNX13*. The nucleosome enrichment analyses of novel candidate genes were carried out across samples including breast adenocarcinoma, chronic myelogenous leukemia, skin melanoma, and cervical carcinoma cell lines to enlighten the nucleosome distribution around TSSs. Although the nucleosome distribution around TSSs did not show a common pattern across samples, the enrichment scores were found to be higher in skin melanoma, and cervical cancer cells when compared to chronic myelogenous leukemia, and breast adenocarcinoma cells for all genes (Figure 7). Low nucleosome occupancy that corresponds to large nucleosome-free regions were detected at TSSs of *CDT1*,



CRLS1, and *SNX13* in chronic myelogenous leukemia cells, and at TSSs of *POC1A*, and *CRLS1* in breast adenocarcinoma cells. In all samples the nucleosomes were found to be enriched at the downstream of TSS for *CRLS1* (Figure 7).

Discussion

Ovarian cancer is the leading cause of cancer associated deaths among all gynecological cancers (Bowen et al., 2009). Due to its lethality, the identification of predictive and effective biomarkers with high prognosis is still an issue. The interpretation of omics data is needed to enlighten the complex molecular mechanisms behind disease pathogenesis. Microarray technology has been extensively used in clinical applications and integrative analysis of multiple gene expression datasets has been performed for the identification of significant biomarkers (Yang et al., 2019)

Differential co-expression network analysis can serve as a tool for the identification of correlated molecular targets as

potential predictive markers. The elucidation of the alterations in the co-expression patterns of genes in the diseased, and healthy states not only increase our understanding in the pathogenesis of the disease, but also provide valuable information for biomarker discovery. Therefore, in this study, a differential co-expression network analysis was performed to determine ovarian cancer genes and their expression patterns. Comparative analysis of the co-expression networks in the diseased, and healthy states revealed a novel co-expressed gene module that may be regarded as molecular targets offering future development of predictive prognostic biomarkers, and therapeutic strategies in ovarian cancer.

Specifically, we carried out a meta-analysis of three transcriptome datasets, and identified 439 common DEGs. The pairwise correlations amongst common DEGs were determined and the significantly correlated gene pairs were used to construct the differential co-expression networks in the diseased, and healthy states (OC and non-OC, respectively) separately. The modular analyses of the resultant networks exhibited densely connected and functionally related

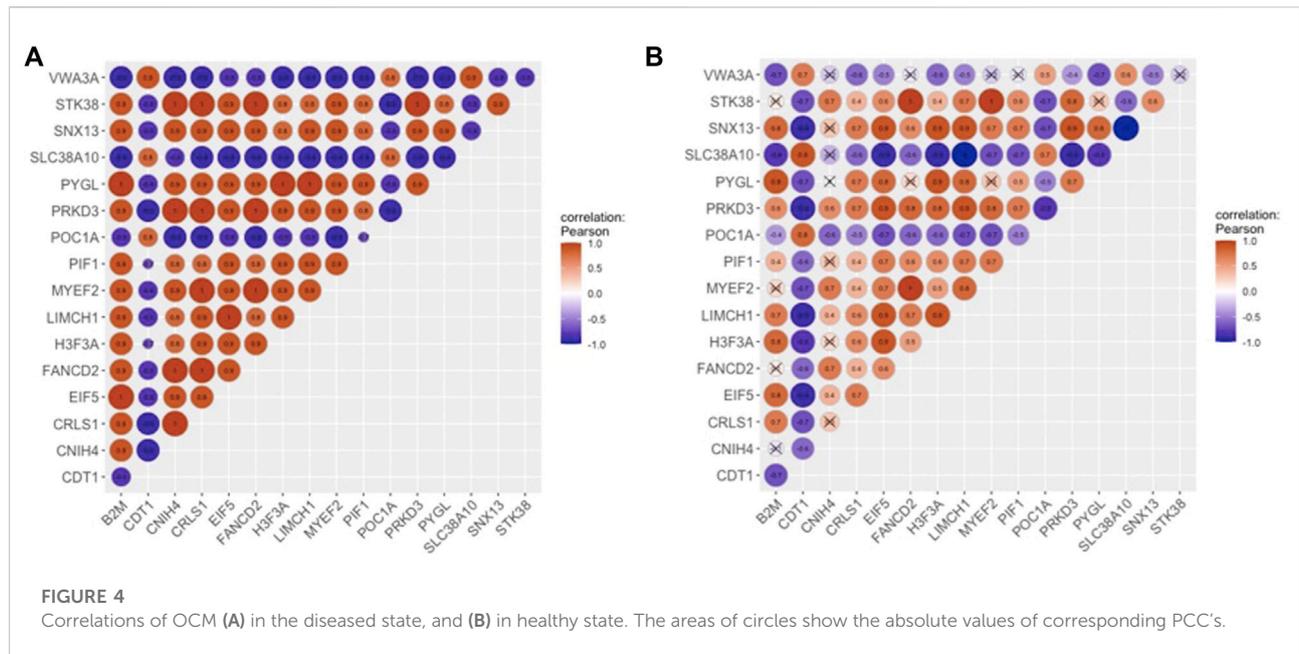
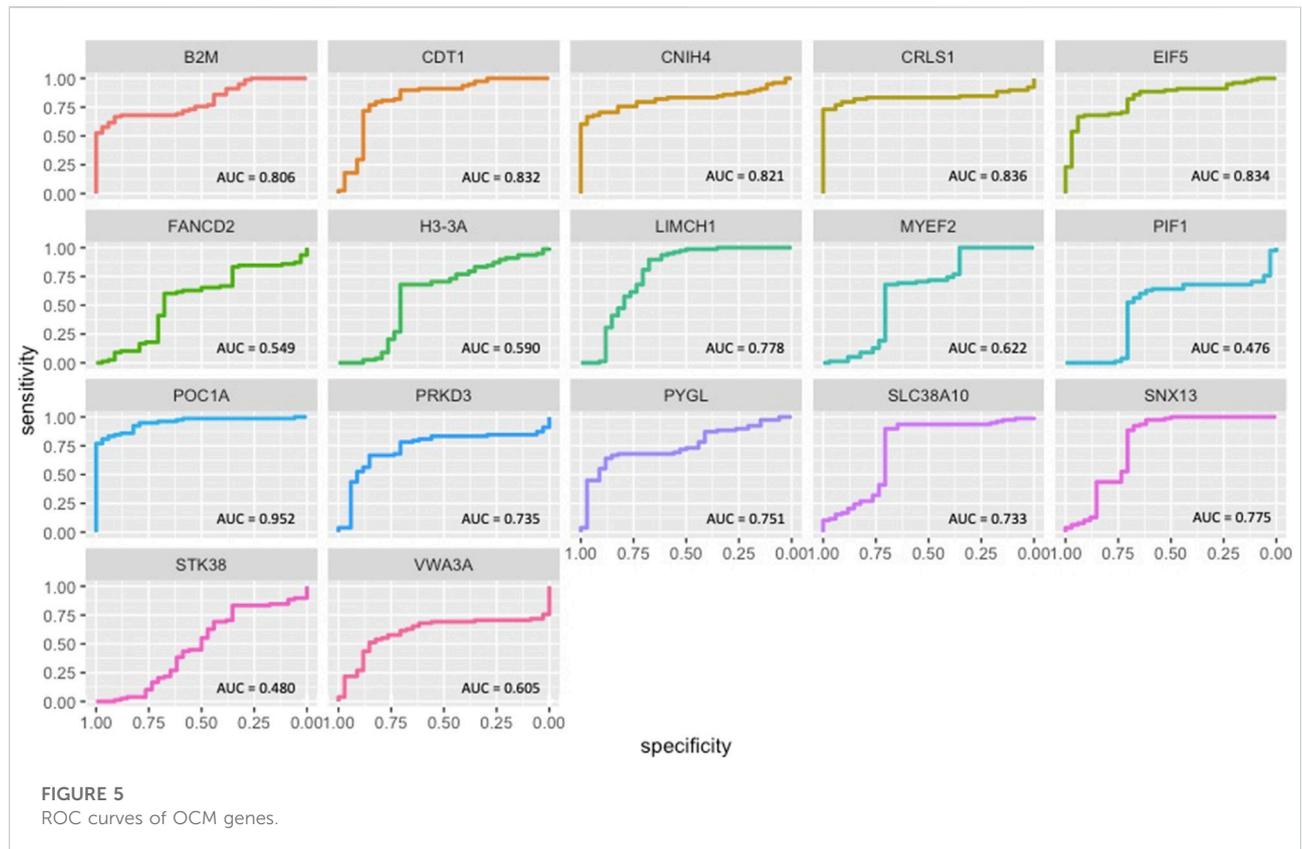


TABLE 2 The descriptions of genes in OCM.

Gene	Description	Function
<i>B2M</i>	beta-2-microglobulin	It encodes a serum protein found in association with the major histocompatibility complex (MHC) class I heavy chain on the surface of nearly all nucleated cells
<i>CDT1</i>	chromatin licensing and DNA replication factor 1	It is required for both DNA replication and mitosis
<i>CNIH4</i>	cornichon family AMPA receptor auxiliary protein 4	It is involved in G protein-coupled receptors (GPCRs) trafficking from the endoplasmic reticulum to the cell surface
<i>CRLS1</i>	cardiolipin synthase 1	It catalyzes the synthesis of cardiolipin which is a key phospholipid in mitochondrial membranes and plays important roles in maintaining the functional integrity and dynamics of mitochondria under both optimal and stress conditions
<i>EIF5</i>	eukaryotic translation initiation factor 5	The related pathways of this gene are activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to 43S and viral mRNA translation
<i>FANCD2</i>	FA complementation group D2	It is required for maintenance of chromosomal stability, promotes accurate and efficient pairing of homologs during meiosis, and involved in the repair of DNA double-strand breaks. It is associated with Fanconi anemia
<i>H3-3A</i>	H3.3 histone A	The related pathways of this gene are transcriptional misregulation in cancer and signaling by GPCR
<i>LIMCH1</i>	LIM and calponin homology domains 1	It positively regulates actin stress fibers assembly and stabilizes focal adhesions, and therefore negatively regulates cell spreading and cell migration
<i>MYEF2</i>	myelin expression factor 2	It is a transcriptional repressor of the gene encoding myelin basic protein
<i>PIF1</i>	PIF1 5'-to-3' DNA helicase	It is required for the maintenance of both mitochondrial and nuclear genome stability. It is associated with diseases including uterine adnexa cancer and Fanconi anemia
<i>POC1A</i>	POC1 centriolar protein A	It plays an important role in basal body and cilia formation
<i>PRKD3</i>	protein kinase D3	It encodes a protein that has several functions including negative regulation of human airway epithelial barrier formation, growth regulation of breast and prostate cancer cells, and vesicle trafficking
<i>PYGL</i>	glycogen phosphorylase L	It encodes a glycogen phosphorylase that is required to release glucose-1-phosphate from liver glycogen stores
<i>SLC38A10</i>	solute carrier family 38 member 10	It is involved in amino acid transmembrane transporter activity
<i>SNX13</i>	sorting nexin 13	It encodes a protein that is the regulator of G protein signaling (RGS) family and may link heterotrimeric G protein signaling and vesicular trafficking
<i>STK38</i>	serine/threonine kinase 38	It has functions in cell cycle and apoptosis
<i>VWA3A</i>	von Willebrand factor A domain containing 3A	It is a protein coding gene

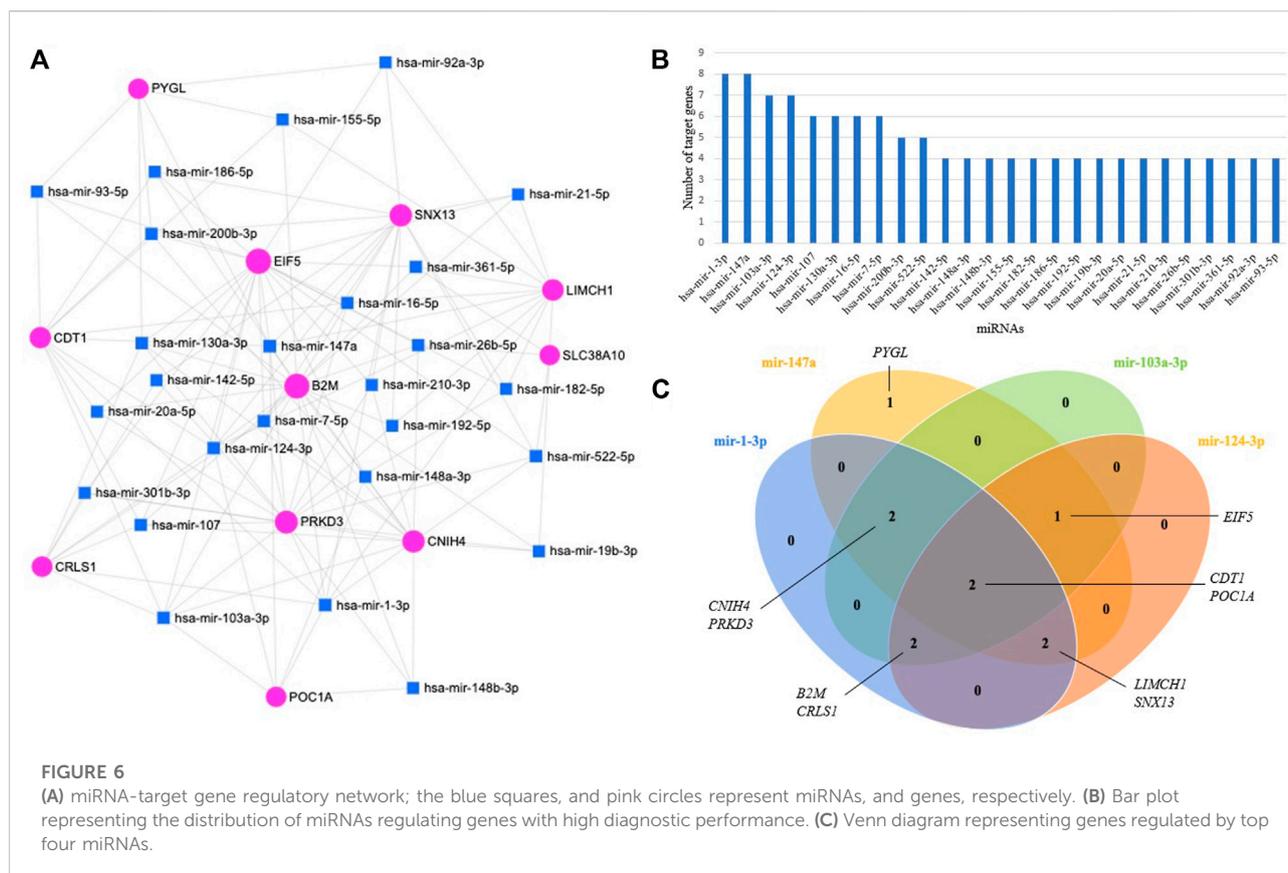


gene groups in both conditions and the comparative analyses of OC and non-OC modules resulted in a prognostic module, namely OCM, composed of 17 genes. The connectedness of the OCM genes was found to be significantly lower in healthy state, which inferred an increased active communication among these genes during the occurrence and/or the development of the disease. Moreover, 11 OCM genes (*B2M*, *CDT1*, *CNIH4*, *CRLS1*, *EIF5*, *LIMCH1*, *POC1A*, *PRKD3*, *PYGL*, *SLC38A10*, and *SNX13*) showed high diagnostic performance. Hence this set of genes were considered as potential prognostic markers.

The candidate prognostic gene set contained genes that were already shown to be associated with ovarian cancer together with novel candidates. *B2M* is the regulator of immune system and its significantly higher expression was observed in the presence of ovarian tumor. *In vitro* analysis using SKOV3 ovarian cancer cell line emphasized that *B2M* knock-down resulted in a decreased cell proliferation, migration and invasion, and an antibody against *B2M* induced apoptosis. Moreover, it was reported that *B2M* was regulated by TGF- β signaling pathway. (Sun et al., 2016). The protein expression of EIF5A1 was induced in epithelial ovarian cancer and high levels of this protein predicted poor survival (Zhang et al., 2018). *PRKD3* belongs to the family of protein kinases, whose members include many oncogenes and growth factor receptors. Some protein kinases

were involved in the pathogenesis and progression of breast cancer, and *PRKD3* was linked to prostate cancer, however, very rare mutations of *PRKD3* was observed in ovarian cancer (Liu et al., 2015). On the other hand, the analysis of phosphoproteomic data indicated that the protein abundance of *PRKD3* was correlated with poor overall survival of patients with high-grade serous ovarian cancer (Tong et al., 2019). The proteomic analysis exhibited the expression of *PYGL*, the liver isoform of glycogen phosphorylase, in SKOV3ip1 and TYK-nu ovarian cancer cell lines (Coscia et al., 2016; Curtis et al., 2019). In another study, it was found that *PYGL* was up-regulated in cisplatin-resistant human ovarian carcinoma cell line SKOV3/DDP when compared to cisplatin-sensitive human ovarian carcinoma cell line SKOV3 (Xu et al., 2018). A study investigating the role of solute carrier family of membrane transporters in ovarian cancer revealed the down-regulation of *SLC38A10* in ovarian cancer tissues when compared to normal ovarian tissues (Sun et al., 2020).

Among candidate gene set, *POC1A* and *SNX13* have limited information on their association with ovarian cancer. *POC1A* that takes part in the formation of centrioles, and plays a role in ciliogenesis, was found to be correlated with lymphatic metastasis in gastric cancer (Lu et al., 2020). *POC1A* was identified as a hub gene in high grade serous ovarian cancer through network

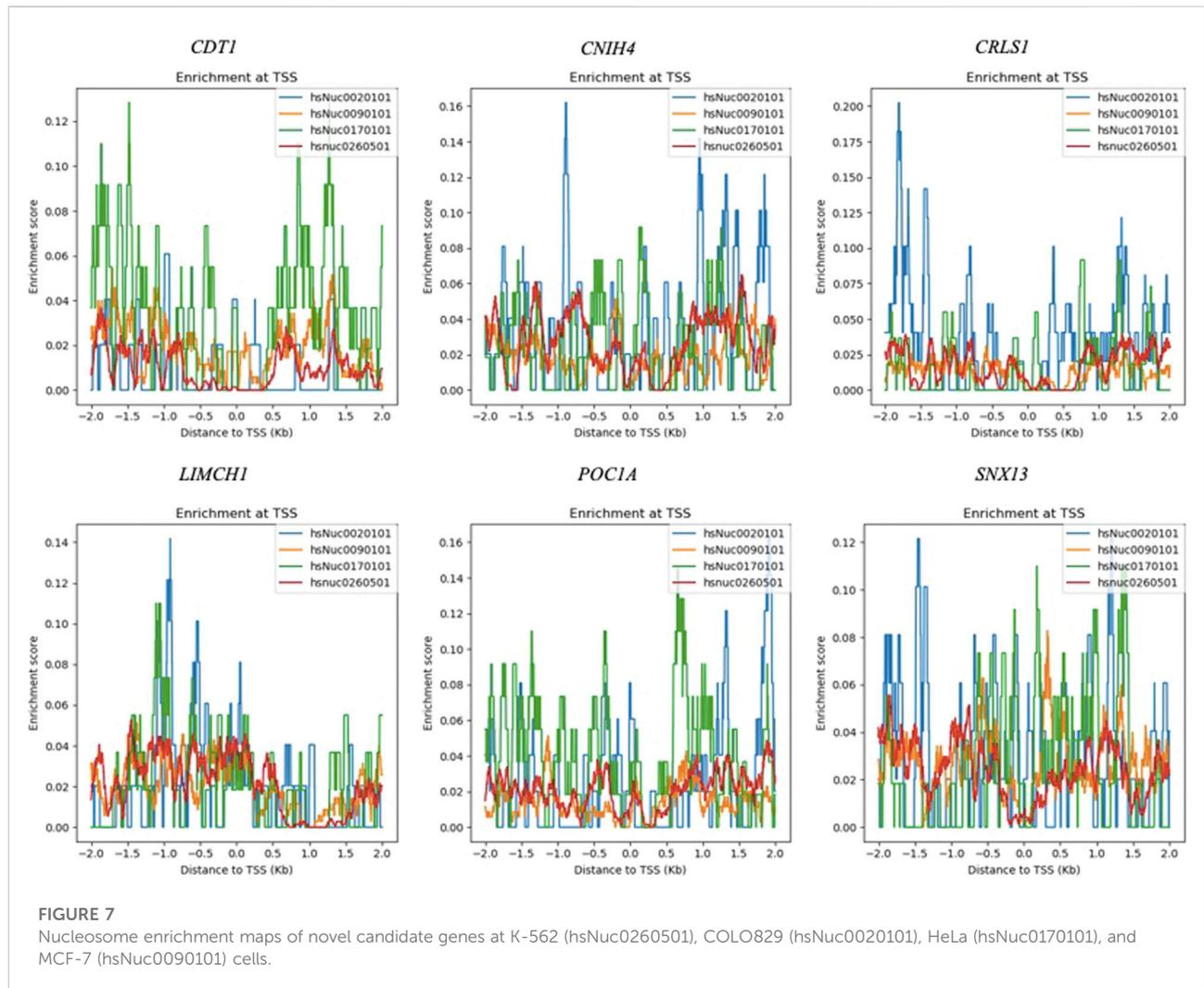


analysis (Wu et al., 2020). In one study, *SNX13* was linked to resistance to chemotherapy in ovarian cancer (Lloyd et al., 2015). In addition, *SNX13* was reported to be related to colorectal cancer migration, invasion, and metastasis (Du et al., 2020). Furthermore, *LIMCH1*, *CRLS1*, *CDT1*, and *CNIH4* were found to be associated with various cancer types, but their roles in ovarian cancer have not been identified yet. *LIMCH1* that regulates non-muscle myosin-II activity and suppresses cell migration, (Lin et al., 2017), was previously proposed in lung (Zhang et al., 2019), breast (Bersini et al., 2020), and endometrial cancers (Bell, 2014). Moreover, *LIMCH1* was identified as a gene signature with high prognostic power in aggressive cervical cancer (Halle et al., 2021). Multiple LIM domain genes, such as *LMX1B* and *PDLIM4* contributed to the tumorigenesis of ovarian cancer. *LMX1B* (LIM homeobox transcription factor 1 beta) was reported as an oncogene in human ovarian cancer based on the correlation between its increased expressions with poor outcome (He et al., 2014). The down-regulation of *PDLIM4* (PDZ and LIM domain 4) was shown to be correlated with short overall survival of ovarian cancer patients (Jia et al., 2019). However, the association of *LIMCH1* with ovarian cancer has not been identified yet.

CRLS1, is responsible for cardiolipin production. Reduced expression of cardiolipin was associated with increased apoptosis

(Egan et al., 2011). A study of cardiolipin metabolism suggested the tumor suppressor activity of *CRLS1* in non-small cell lung cancer, and hepatocellular carcinoma (Ahmadpour et al., 2020). Moreover, increased cardiolipin levels were observed in cells expressing cytoglobin involved in cancer progression (Thorne et al., 2021). However, there is a limited information with regard to its involvement in ovarian cancer.

Cell cycle regulation and DNA damage response contribute to genome stability and integrity. *CDT1* is a central cell cycle regulator, and links the cell cycle regulation and DNA damage response pathways (Kanellou et al., 2020). *CDT1* might be a novel target in ovarian cancer due to its relationship with other cancers, and with the proteins that were reported to be involved in the progression of the disease. *CDT1* was proposed as a potential biomarker in hepatocellular carcinoma through the analysis of gene expression profiles, and its role was validated *in vitro* (Cai et al., 2021). The high expression of *CRL4*, encoding an E3 ligase, in human ovarian cancer tissues was shown and the repression of *CRL4* mimicked the genotoxic effects of an anticancer agent MLN4924. The regulation of cell proliferation by *CLR4*^{CDT12} ubiquitin ligase was due to the degradation of its important substrates, such as *CDT1*, *p21*, and *SET8*. The depletion of *CLR4*^{CDT12} led to the accumulation of *CDT1* and MLN4924 induced apoptotic death was partially rescued by the depletion of *CDT1*, indicating a role to *CDT1* as a



possible target in ovarian cancer development and treatment (Pan et al., 2013; Wu et al., 2021).

CNIH4, which was also a hub gene that played a pivotal role in the flow of information within OC network, has no reported association with ovarian cancer. *CNIH4* was found to be associated with colon cancer (Mishra et al., 2019) and hepatocellular carcinoma (Wang H. et al., 2021). *CNIH4* interacts with GPCRs (Sauvageau et al., 2014). A number of GPCRs have been implicated in cancer progression. They are not only contributed to tumor cell growth, but also have several functions in metastasis. Despite the identification of a number of GPCRs with altered expressions due to tumor development, only a few drugs targeting GPCRs were successful. One of the strategy in drug discovery is to target the specific interactions between GPCRs and their ligands (Arakaki et al., 2018; Usman et al., 2020). Therefore, *CNIH4* might be suggested as a novel therapeutic target due to its topological importance in the network and its role in GPCR trafficking. Although *LIMCH1*,

CRLS1, *CDT1*, *CNIH4* have been associated with various cancers, their relationship with ovarian cancer has been proposed in this study for the first time to the best of our knowledge.

Nucleosome organization plays an important role in regulatory activities that determines the biological function (Beshnova et al., 2014). The distribution of nucleosomes and the presence of nucleosome-free regions at TSS is strongly associated with transcription initiation. Larger nucleosome-free regions at TSS was reported for highly expressed genes (Chen et al., 2021). No common pattern for nucleosome distribution around TSSs could be observed across samples through the analysis of nucleosome enrichment maps of *CDT1*, *CNIH4*, *CRLS1*, *LIMCH1*, *POC1A*, and *SNX13*. However, the nucleosome occupancy of *CRLS1* at the TSS was lower when compared to other genes for all samples. Further experimental analysis should be carried out to uncover nucleosome organization around TSSs of these highly co-expressed genes in ovarian cancer samples.

The alterations in the expressions of miRNAs have been reported to be associated with invasion and metastasis of ovarian cancer (Chen et al., 2019). Here, four miRNAs (miR-1-3p, miR-147a, miR-103a-3p, and miR-124-3p) came to the fore. Of the significant miRNAs, miR-1-3p showed a decreased expression in ovarian cancer tissues and cell lines, and suppressed the growth and metastasis of ovarian cancer cells (Zhu et al., 2020). miR-124-3p regulates tumorigenesis and progression in several cancers, including ovarian, breast, gastric, bladder cancers, leukemia, and hepatocellular carcinoma (Li et al., 2021). Although previous studies showed the association of miR-147a and miR-103a-3p with various cancers, their roles in ovarian cancer have not been identified yet. miR-147 plays important roles in cell proliferation, apoptosis, and migration, and its expression was reported to be significantly altered in various cancers or carcinomas, including gastric cancer, colon cancer, and hepatocellular carcinoma (Lin and Hu, 2021). miR-147a is involved in the regulation of cancer malignancy (Lee et al., 2021), and was previously proposed as a potential prognostic factor for non-small cell lung cancer (Lu and Luan, 2019). miR-103a-3p has been reported to be associated with cisplatin resistance in non-small cell lung cancer (Wang Z. et al., 2021), and docetaxel resistance in prostate cancer (Yi et al., 2022). miR-103a was also reported as a new regulator of Wnt signaling pathway in colorectal carcinoma (Fasihi et al., 2018).

The current lack of robust diagnostic and prognostic biomarkers owing to the complex nature of the disease, together with the high mortality rate, necessitate new approaches for the discovery of novel biomarkers. Within the framework of this study, the transcriptional response of ovarian epithelia samples to the presence of serous ovarian adenocarcinoma was analyzed. We presented a novel prognostic gene module that was differentially co-expressed in ovarian cancer. Together with the genes that were already known to be associated with the disease (i.e., *B2M*, *EIF5*, *PRKD3*, *PYGL*, *SLC38A10*), some novel candidates were identified. Our findings suggested six genes (*CDT1*, *CNIH4*, *CRLS1*, *LIMCH1*, *POC1A*, and *SNX13*), and two miRNAs (mir-147a, and mir-103a-3p) to serve as novel potential biomarkers that permit future development of diagnostic and therapeutic innovations. However, further experimental and clinical studies should be performed to validate the proposed biomarkers and extend our

findings to develop effective clinical strategies for diagnostic and therapeutic purposes.

Data availability statement

Publicly available datasets were analyzed in this study. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Author contributions

CK conceived the study, carried out the analyses, interpreted the results, and wrote the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fgene.2022.971845/full#supplementary-material>

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