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Original Research

Searching for biomarkers in the progression from polycystic ovary syndrome to endometrial carcinoma

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Background: Polycystic ovary syndrome is a female reproductive system disease closely related to endocrine and highly correlated with the development of endometrial carcinoma in women, it is important to identify the key genes involved in the development of polycystic ovary syndrome. *Methods*: To identify the hub genes, microarray datasets GSE48301, GSE115810 and GSE3013 were downloaded from Gene Expression Omnibus database. We performed in-depth cross-tabulation bioinformatic analysis to identify differentially expressed genes (DEGs) among four types of endometrial cells in GSE48301 and two endometrial carcinoma datasets GSE115810 and GSE3013, followed by gene ontology, KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment, protein-protein interaction network analysis. *Results*: Thirteen seed DEGs and 4 significantly expressed DEGs were identified, and potential drugs and mRNAs were found. *Conclusion*: *EDNRA*, *FBN1*, *PMP22*, *SPARC* and *IGF-1* may be potential and their miRNAs, especially hsa-miR-29a-3p and hsa-miR-29b-3p may be potential biomarkers in the progression from PCOS to endometrial carcinoma.

Keywords

Differentially expressed genes; Endometrial carcinoma; Insulin-like growth factor 1; Polycystic ovary syndrome

1. Introduction

Polycystic ovary syndrome (PCOS) is a very complex endocrine and metabolic disorders in women of reproductive age [1]. Rotterdam diagnostic criteria is generally adopted as diagnosis of PCOS, it affects 8%–20% of women of reproductive age worldwide [2, 3]. Developmental, genetic and environmental are involved in the etiology of PCOS [4, 5], typical characters are hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology and associated with other abnormalities, such as insulin resistance, metabolic syndrome, and dyslipidemia that cause more than 75% cases of anovulatory infertility [6] which is caused by follicular arrest and ovulatory dysfunction. Despite intensive research, the mechanisms underlying aberrant follicular development and anovulation in PCOS remain largely obscure.

The dysfunction of endometrium causes endometrial hyperplasia and endometrial carcinoma (EC) in PCOS [7]. The endometrium is an ovarian steroid hormone-responsive tissue composed of mesenchymal stem cells, epithelial cells, endothelial cells and stromal fibroblasts [8]. It has been shown that 17β-estradiol (E2) drives endometrial cells proliferation whereas progesterone inhibits endometrial cells proliferation [9], prolonged E2 excess or lack of progesterone (P4) widely accepted results in hyperplasia of endometrial or atypical endometrial, and the majority of EC are estrogen-dependent [10, 11]. Due to chronic anovulation, PCOS patients experience persistent estrogen stimulation [12], so endometrial hyperplasia in patients with PCOS have a four-fold greater risk that results in increased of endogenous developing EC than non-PCOS controls [13, 14]. Moreover, PCOS is a hyperandrogenic state unopposed estrogens due to the increased peripheral conversion of endogenous androgens such as androstenedione and testosterone into estrogen [15]. However, obesity, type-2 diabetes, insulin resistance, exposure to estrogen therapy can also contribute to the development of EC. Insulin resistance is also a central characteristic of PCOS driving hyperandrogenism, prevalence of insulin resistance has been reported in up to 95% of women with PCOS [16, 17]. EC cell lines exposed to exosomes derived from PCOS patients serum exhibited an enhanced migration and invasion phenotype [18], and PCOS is established as an independent risk factor for EC [19]. So in our study, we try to explore the mechanism between PCOS and EC.

2. Materials and methods

Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/gds/) is a public repository containing kinds of gene expression data submitted by research institutions. Protein-protein interaction (PPI) network for the differentially expressed genes (DEGs) was constructed to further explore the relationships among these genes and identify hub DEGs. Gene Ontology (GO) and KEGG enrichment analyses were performed to investigate the biological role of DEGs. Dataset GSE48301 of PCOS and two EC datasets GSE115810 and GSE3013 were downloaded from GEO. The 3 datasets were analysed with GSE 2R from network of GEO. The GSE48301 contained 4 types of endometrium samples, mesenchymal stem cells, epithelial cells, endothe-

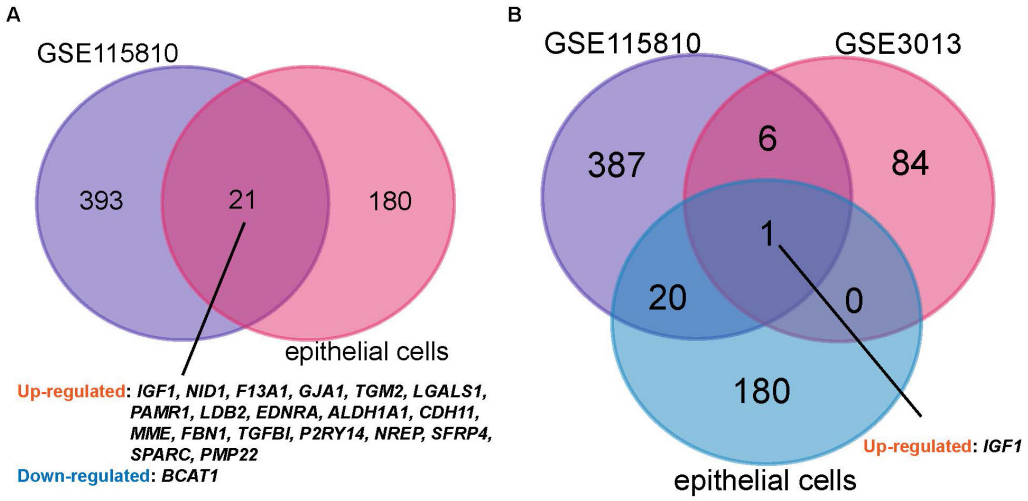

Fig. 1. Venn diagram. (A) DEGs of epithelial cells and GSE115810. (B) The DEGs of GSE115810, GSE3013 and epithelial cells.

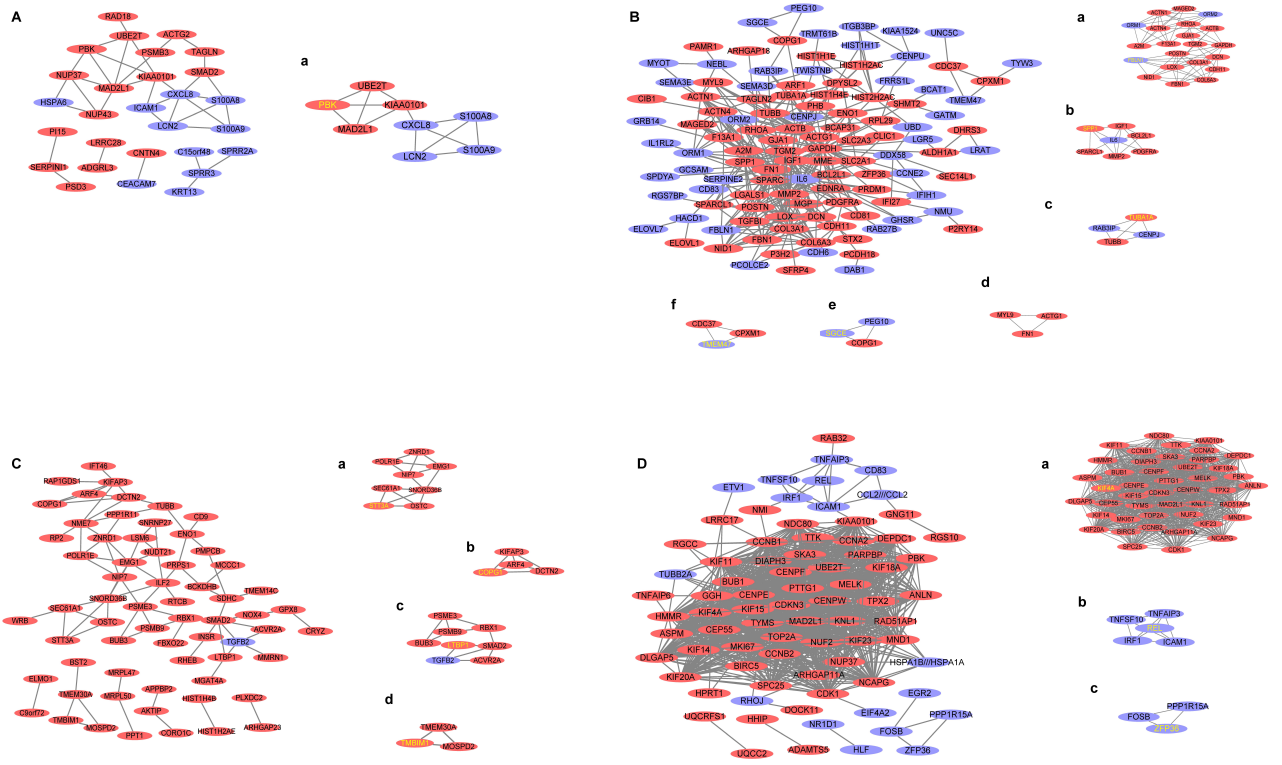

Fig. 2. PPI network and the most significant module in mesenchymal stem cells (A, a), epithelial cells (B, a–f), endothelial cells (C, a–d), and stromal fibroblasts (D, a–c). Up-regulated genes are marked in light red, down-regulated genes are marked in light blue, and seed DEGs are marked in yellow.

lial cells and stromal fibroblasts, we analysed the 4 types of endometrial cells to find DEGs between PCOS and control groups. GSE115810 contained 24 EC samples and 3 normal endometrium samples. GSE3013 contained 2 samples with E2 therapy and 2 EC samples without E2 therapy.

2.1 Identification of DEGs

The 3 gene expression microarray datasets obtained from GEO database were screened by an interactive online tool, GEO2R (www.ncbi.nlm.nih.gov/geo/geo2r). The raw data of microarray datasets were pre-processed via background correction and normalization, then $|\log2\text{-fold change (FC)}| \geq 1$ and p value < 0.05 were considered as the cutoff criteria for statistically significant.

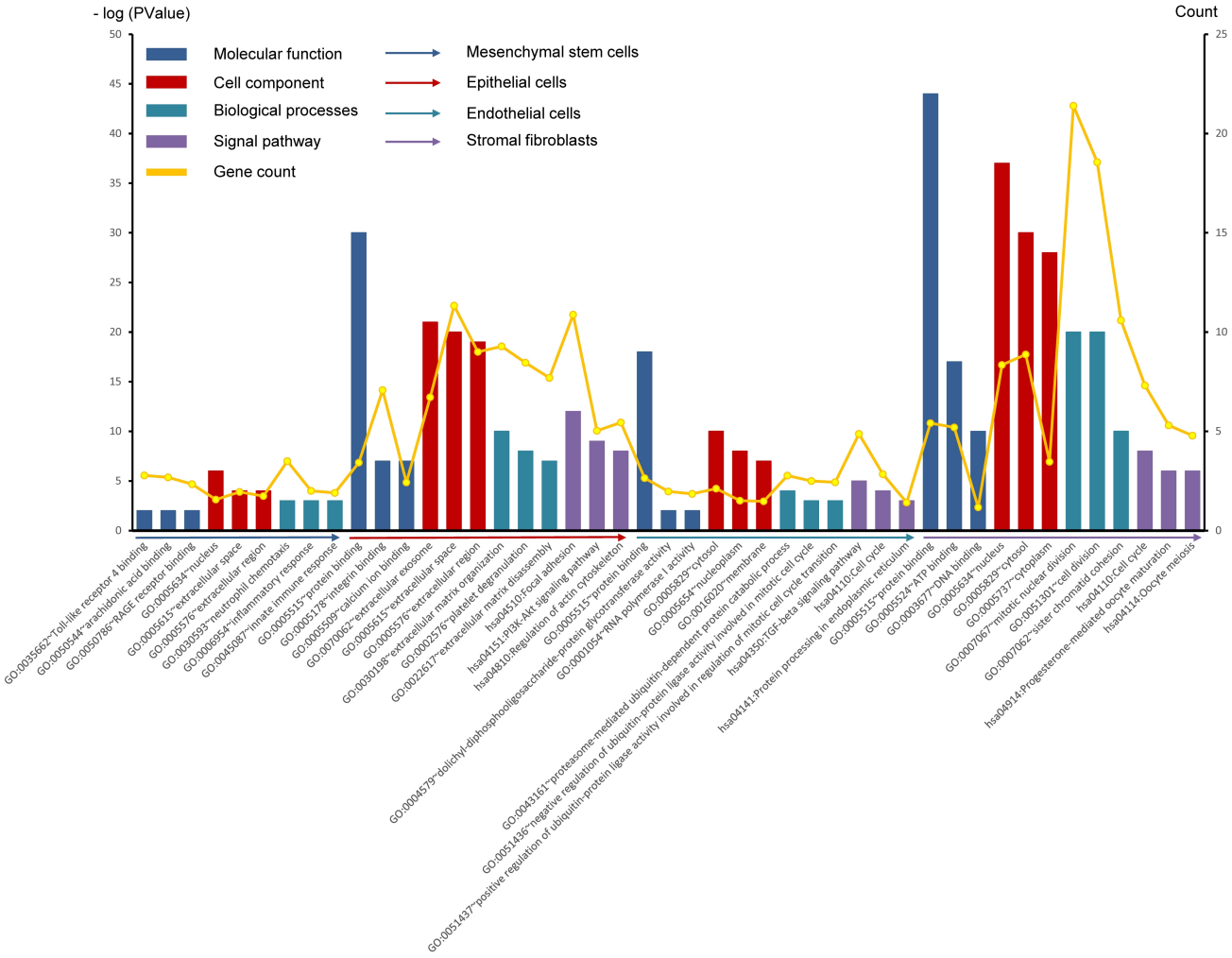

Fig. 3. GO function and signal pathway in four types of PCOS.

2.2 PPI networks were constructed and most significant modules were obtained in PCOS

The PPI network is predicted using STRING (http://string-db.org/) (version 11.0) online tool. In the our study, PPI network of 4 type cells were constructed, and combined score >0.4 meet the criterion. Then PPI network was integrated by Cytoscape software (version 3.8.1). The plug-in Molecular Complex Detection (MCODE) (version 2.0.0) of Cytoscape is an APP to find densely connected regions. The criteria for selection were as follows: MCODE degree cut-off = 2, node score cut-off = 0.2, Max depth = 100 and k-score = 2.

2.3 GO function in most significant modules of PCOS

GO functions including molecular function (MF), cell component (CC), biological processes (BP), and KEGG pathway by using DAVID (http://www.david.abcc.ncifcrf.gov/, version 6.8), $p < 0.05$ as the cutoff criterion.

2.4 Validation of DEGs in TCGA/GTEx

We performed gene expression level and survival analysis with Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn/). Gene expression validation involved in Uterine Corpus Endometrial Carcinoma (UCEC, Tumor: 174 Normal: 91) and Uterine Carcinosarcoma (UCS, Tumor: 57 Normal: 78) datasets built in TCGA/GTEx database, the thresholds with $|\log2\ FC| \geq 1$ & p value < 0.01 were considered statistically significant, with setting jitter size = 0.4. For overall survival (OS) analysis, time data were sorted into low-expression and high-expression groups by the median transcripts per kilobase million (TPM), and significance was decided by the log-rank test with $p < 0.05$.

2.5 Possible drugs for target genes

Drug-Gene Interaction Database (DGIdb, http://www.dgidb.org) is a web resource that consolidates disparate data sources describing drug-gene interactions. We input 13 seed DEGs to find approved drugs and 4 significantly validated DEGs in DGIdb to find potential drugs.

2.6 Possible miRNA biomarkers for target genes

To find possible miRNA, we putted 4 significantly validated DEGs in miRDB (http://www.mirdb.org/), TargetScan (http://www.targetscan.org/) and miRTarBase (http://www.targetscan.org/) databases, then to find the common miRNAs of the 4 DEGs.

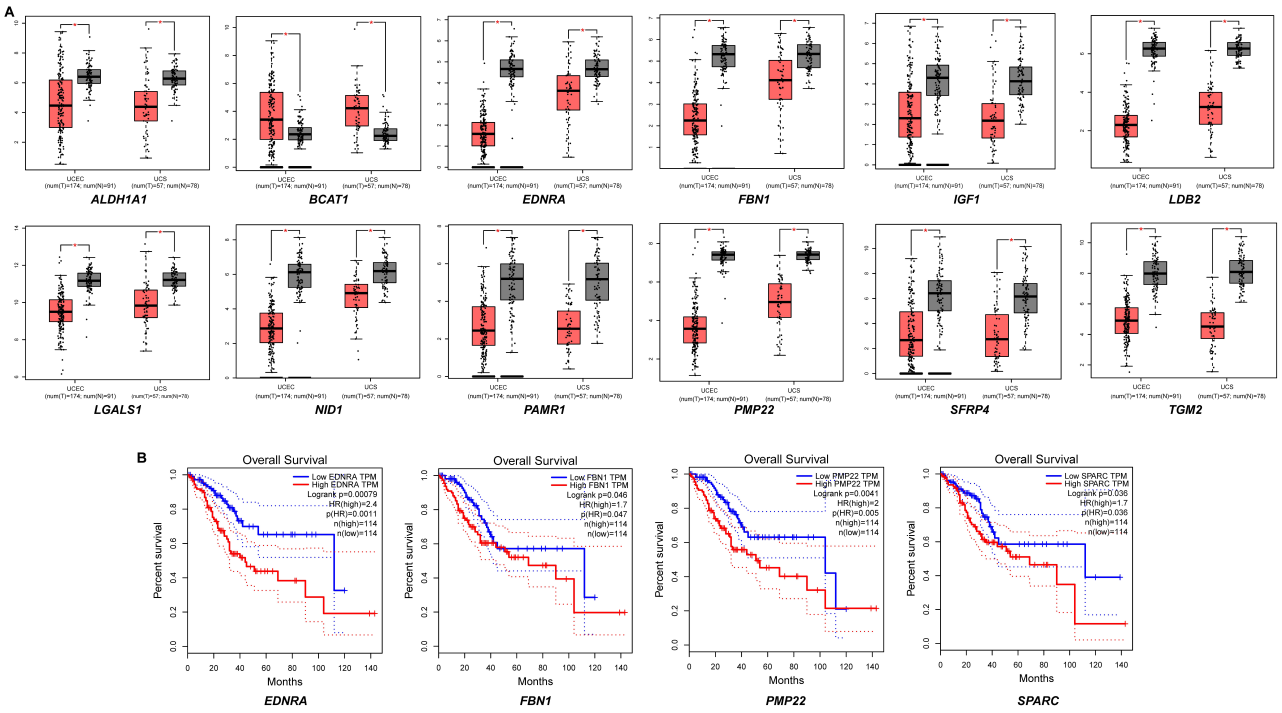

Fig. 4. Box plots and survival analysis plots of DEGs. (A) Significant expression of 12 DEGs in UCEC (Tumor: 174 Normal: 91) and UCS (Tumor: 57 Normal: 78) built in TCGA/GTEx database. (B) Significant analysis of OS in four DEGs between high expression and low expression on GEPIA.

3. Results

3.1 Identification of DEGs

After standardization, there were 73, 214, 150 and 148 DEGs respectively in mesenchymal stem cells, epithelial cells, endothelial cells and stromal fibroblasts. Then 483 DEGs were identified in GSE115810, 92 DEGs were identified between estrogen therapy and control EC groups in GSE3013. 21 DEGs were found between epithelial cells and GSE115810, containing 19 consistent up-regulated and 1 consistent down-regulated genes as shown in Fig. 1A, *IGF-1* was the only up-regulated DEGs among GSE48301, GSE115810 and GSE3013 in epithelial cells (Fig. 1B), DEGs behaved differently in the datasets due to the heterogeneity of the human.

3.2 PPI networks were constructed and most significant modules were obtained in PCOS

The PPI network of DEGs were constructed in mesenchymal stem cells, epithelial cells, endothelial cells and stromal fibroblasts (Fig. 2A–D) by hiding disconnected nodes and the most significant modules were obtained by using MCODE in mesenchymal stem cells (Fig. 2A, a), epithelial cells (Fig. 2B, a–f), endothelial cells (Fig. 2C, a–d) and stromal fibroblasts (Fig. 2D, a–c), the seed genes marked with yellow in Fig. 2.

3.3 GO function in most significant modules of PCOS

In mesenchymal stem cells, MF enriched in Toll-like receptor 4 binding, arachidonic acid binding and RAGE receptor binding, CC mainly enriched in nucleus, extracellular space, and extracellular region, BP mostly enriched in neutrophil chemotaxis, inflammatory response and innate immune response. In epithelial cells, MF enriched in protein binding and integrin binding, CC mostly enriched in extracellular exosome, extracellular space and extracellular region, BP enriched in extracellular matrix organization, platelet degranulation and extracellular matrix disassembly, KEGG enriched in focal adhesion and PI3K-Akt signaling pathway. In endothelial cells, MF enriched in protein binding, CC enriched in cytosol, nucleoplasm, and membrane, BP mostly enriched in proteasome-mediated ubiquitin-dependent protein catabolic process, negative regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle, and positive regulation of ubiquitin-protein ligase activity involved in regulation of mitotic cell cycle transition, pathway enriched in TGF-beta signaling pathway, cell cycle and protein processing in endoplasmic reticulum. In stromal fibroblasts, MF enriched in protein binding, ATP binding and DNA binding, CC enriched in nucleus, cytosol, and cytoplasm, BP mostly enriched in mitotic nuclear division, cell division and sister chromatid cohesion, signal pathway most enriched in cell cycle, progesterone-mediated oocyte maturation and oocyte meiosis (Fig. 3).

3.4 GO analysis of overlap DEGs between PCOS and endometrial carcinoma

Twenty consistent DEGs showed that MF mostly enriched in calcium ion binding, collagen binding and integrin binding, CC mostly enriched in plasma membrane, extracellular exosome, extracellular region, extracellular space

Table 1. Go functions of 20 consistent DEGs between GSE115810 and epithelial cells of PCOS (MF: Molecular function, CC: cell component, BP: biological processes).

Category	Term	Count	Genes
MF	calcium ion binding	5	*SPARC, CDH11, NID1, PAMR1, FBN1*
	collagen binding	3	*SPARC, TGFBI, NID1*
	integrin binding	3	*TGFBI, IGF1, FBN1*
	protein-glutamine gamma-glutamyltransferase activity	2	*F13A1, TGM2*
	laminin binding	2	*LGALS1, NID1*
	extracellular matrix binding	2	*SPARC, TGFBI*
CC	plasma membrane	10	*EDNRA, GJA1, SPARC, MME, P2RY14, CDH11, PMP22, TGFBI, IGF1, TGM2*
	extracellular exosome	9	*GJA1, LGALS1, MME, CDH11, ALDH1A1, TGFBI, NID1, FBN1, TGM2*
	extracellular region	8	*SFRP4, SPARC, F13A1, TGFBI, IGF1, NID1, PAMR1, FBN1*
	extracellular space	6	*SFRP4, LGALS1, SPARC, TGFBI, IGF1, FBN1*
	extracellular matrix	5	*LGALS1, TGFBI, NID1, FBN1, TGM2*
	basement membrane	4	*SPARC, TGFBI, NID1, FBN1*
	proteinaceous extracellular matrix	4	*LGALS1, SPARC, TGFBI, FBN1*
	platelet alpha granule lumen	3	*SPARC, F13A1, IGF1*
	focal adhesion	3	*GJA1, MME, TGM2*
BP	signal transduction	5	*EDNRA, GJA1, LGALS1, SPARC, IGF1*
	heart development	4	*EDNRA, GJA1, SPARC, FBN1*
	extracellular matrix organization	4	*SPARC, TGFBI, NID1, FBN1*
	cell proliferation	4	*EDNRA, TGFBI, IGF1, BCAT1*
	G-protein coupled receptor signaling pathway	4	*SFRP4, EDNRA, P2RY14, TGM2*
	platelet degranulation	3	*SPARC, F13A1, IGF1*
	skeletal system development	3	*CDH11, IGF1, FBN1*
	positive regulation of I-kappaB kinase/NF-kappaB signaling	3	*GJA1, LGALS1, TGM2*
	myoblast differentiation	2	*LGALS1, IGF1*
	negative regulation of endothelial cell proliferation	2	*GJA1, SPARC*
	negative regulation of neuron projection development	2	*LGALS1, PMP22*
	response to peptide hormone	2	*GJA1, SPARC*
	peptide cross-linking	2	*F13A1, TGM2*
	positive regulation of smooth muscle cell proliferation	2	*IGF1, TGM2*
	positive regulation of osteoblast differentiation	2	*GJA1, IGF1*
	extracellular matrix disassembly	2	*NID1, FBN1*
	ossification	2	*SPARC, CDH11*

and extracellular matrix, BP enriched in signal transduction, extracellular matrix organization and cell proliferation (Table 1).

3.5 Validation of DEGs in TCGA/GTEx

12 DEGs had significant expression in TCGA/GTEx dataset (Fig. 4A), *EDNRA*, *FBN1*, *PMP22* and *SPARC* had significantly difference between high expression and low expression in OS (Fig. 4B).

3.6 Possible drugs for target genes

Twelve seed DEGs and 4 significantly expressed DEGs were putted in DGIdb database to find drug-gene interactions. *PBK, SPP1 and TUBA1A* had 25 kinds of approved drugs in seed DEGs (Table 2, Fig. 5A, a), *EDNRA, SPARC* and *PMP22* had 23 kinds of drugs in all, and 6 kinds of drugs have been approved by FDA (Table 3, Fig. 5A, b).

3.7 Possible miRNA biomarkers for target genes

EDNRA had 2 miRNAs: hsa-miR-200c-3p and hsa-miR-27b-3p, *FBN1* had 5 miRNAs: hsa-miR-29b-3p, hsa-miR-29a-3p, hsa-miR-29c-3p, hsa-miR-486-5p and hsa-miR-767-5p, *PMP22* had 6 miRNAs: hsa-miR-1233-5p, hsa-miR-4769-5p, hsa-miR-299-3p, hsa-miR-4648, hsa-miR-6778-5p and hsa-miR-4654, and *SPARC* had 5 miRNAs: hsa-miR-3149, hsa-miR-29b-3p, hsa-miR-29a-3p, hsa-miR-591 and hsa-miR-29c-3p (Fig. 5B). hsa-miR-29a-3p and hsa-miR-29b-3p were common miRNAs between *FBN1* and *SPARC*.

4. Discussion

In summary, protein binding may be common MF in PCOS. GO analysis of most significant modules in mesenchymal stem cells and epithelial cells were associated with formation of extracellular substances, such as extracellular exosome, extracellular space and extracellular region. Endothelial cells and stromal fibroblasts majored in function of intranuclear substances and cell dividing, such as cytosol, nucleoplasm and cell division. KEGG pathway showed that epithelial cells may highly related to the progression of carcinoma, and stromal cells may be associated with development and maturation of the oocyte, this may help us understand the mechanism of ovarian polycystic changes and ovulation failure.

Table 2. The approved drugs of three seed DEGs.

Gene	Drug	Interaction types	Sources
PBK	GEFITINIB	N/A	CIViC
SPP1	ALTEPLASE	N/A	NCI
	GENTAMICIN	N/A	NCI
	TACROLIMUS	N/A	NCI
	CALCITONIN	N/A	NCI
TUBA1A	IXABEPILONE	inhibitor	ChemblInteractions
	TRASTUZUMAB EMTANSINE	inhibitor	ChemblInteractions
	VINCRISTINE	N/A	DTC
	ARTENIMOL	ligand	DrugBank
	VINCRISTINE SULFATE	inhibitor	ChemblInteractions
	MEBENDAZOLE	inhibitor	DrugBank|TdgClinicalTrial
	ALBENDAZOLE	inhibitor	DrugBank
	VINBLASTINE SULFATE	inhibitor	ChemblInteractions
	ERIBULIN MESYLATE	inhibitor	ChemblInteractions
	VINFLUNINE	inhibitor	ChemblInteractions
	COLCHICINE	inhibitor	DTC|ChemblInteractions
	CABAZITAXEL	inhibitor	ChemblInteractions
	PACLITAXEL	inhibitor	DTC|ChemblInteractions
	VINORELBINE	N/A	DTC
	BRENTUXIMAB VEDOTIN	inhibitor	ChemblInteractions
	VINBLASTINE	adduct	DTC|DrugBank
	PODOFILOX	N/A	DTC
	VINORELBINE TARTRATE	inhibitor	ChemblInteractions
	DOCETAXEL	inhibitor	ChemblInteractions
	VORINOSTAT	N/A	DTC

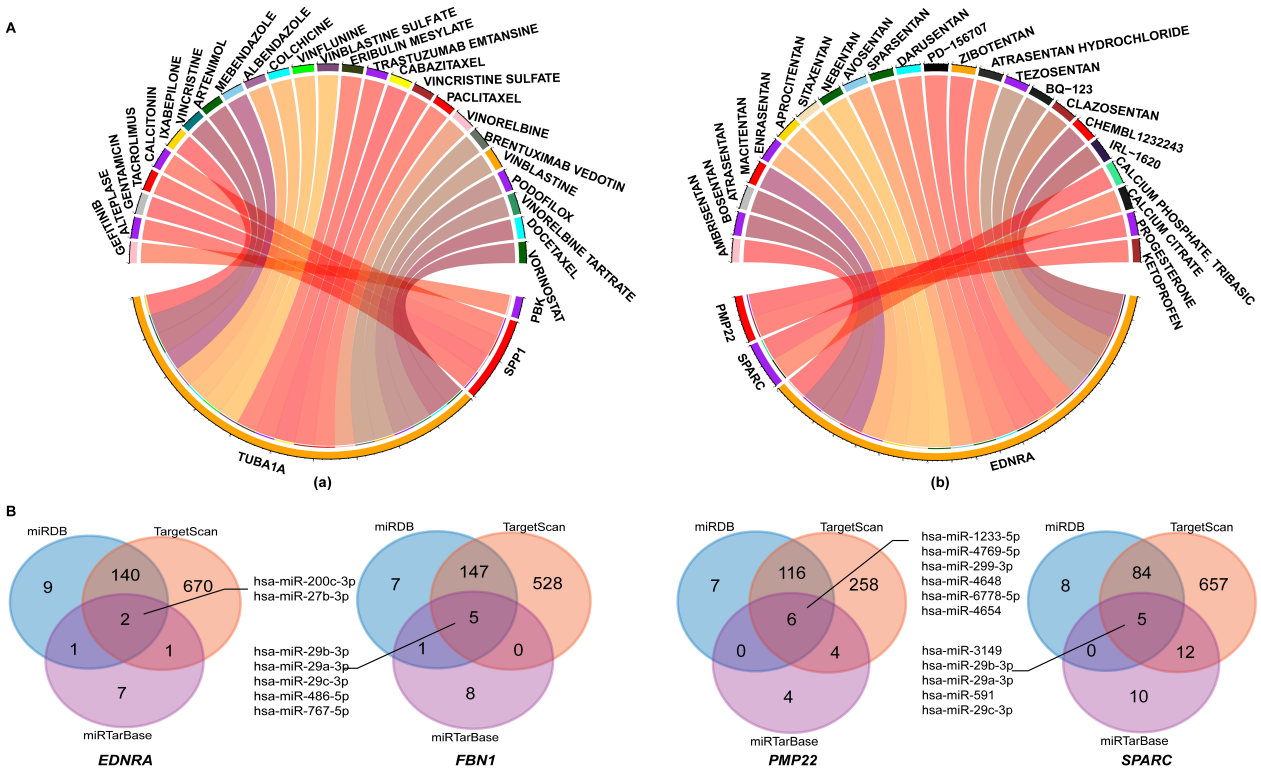

Fig. 5. Chord diagram of Drug-Gene and Venn diagrams of miRNAs. (A) Drug-gene interactions of 3 seed DEGs (a) and 3 significant expressed DEGs in OS (b). (B) The overlap miRNAs of 4 DEGs in miRDB, TargetScan and miRTarBase database.

Table 3. The drugs of three significant DEGs.

Gene	Drug	Types	Approved	Sources
EDNRA	AMBRISENTAN	antagonist	yes	DrugBank|TdgClinicalTrial|ChemblInteractions|TEND|GuideToPharmacology|TTD
	BOSENTAN	antagonist	yes	DrugBank|TdgClinicalTrial|ChemblInteractions|TEND|TTD
	ATRASENTAN	antagonist	no	DrugBank|TdgClinicalTrial|GuideToPharmacology|TTD
	MACITENTAN	antagonist	yes	DrugBank|TdgClinicalTrial|ChemblInteractions|GuideToPharmacology|TTD
	ENRASENTAN	antagonist	no	DrugBank|ChemblInteractions
	APROCITENTAN	antagonist	no	GuideToPharmacology
	SITAXENTAN	antagonist	no	DrugBank|TdgClinicalTrial|GuideToPharmacology
	NEBENTAN	antagonist	no	TdgClinicalTrial|ChemblInteractions|TTD
	AVOSENTAN	antagonist	no	TdgClinicalTrial|ChemblInteractions|GuideToPharmacology
	SPARSENTAN	antagonist	no	DrugBank|ChemblInteractions|GuideToPharmacology|TTD
	DARUSENTAN	antagonist	no	DrugBank|TdgClinicalTrial|ChemblInteractions|GuideToPharmacology|TTD
	PD-156707	antagonist	no	GuideToPharmacology
	ZIBOTENTAN	antagonist	no	TALC|TdgClinicalTrial|ChemblInteractions|GuideToPharmacology
	ATRASENTAN HYDROCHLORIDE	antagonist	no	ChemblInteractions
	TEZOSENTAN	antagonist	no	DrugBank|ChemblInteractions
	BQ-123	antagonist	no	GuideToPharmacology|TTD
	CLAZOSENTAN	antagonist	no	DrugBank|TdgClinicalTrial|ChemblInteractions|TTD
	CHEMBL1232243	N/A	no	DrugBank
	IRL-1620	N/A	no	TdgClinicalTrial
SPARC	CALCIUM PHOSPHATE TRIBASIC	ligand	no	DrugBank
	CALCIUM CITRATE	ligand	yes	DrugBank
PMP22	PROGESTERONE	N/A	yes	NCI
	KETOPROFEN	N/A	yes	DTC

PCOS patients often have abnormally endometrium, our study suggested that stromal fibroblasts were highly associated with mitotic nuclear division and cell division, it may be the major proliferation of cells in endometrium. KEGG pathway indicated that stromal cells involved in procession of P4-mediated oocyte maturation and oocyte meiosis, this may implied that the development of oocytes were correlated to stromal fibroblasts. A study showed that stromal fibroblasts transformation process secrete pro-gestational proteins including IGFBP-1 and PRL, IGFBP-1 was first observed during Days 1–3, and high levels of IGFBP-1 were detected from Day 4 through at least Day12, PRL was first detected on Days 4–6, and the peak occurred on Days 26–28 [20]. And we conjectured that the IGFBP-1 and PRL may be involved into the procession of maturation and meiosis of oocyte. Until now there were no studies showing the secretion of endometrial stromal fibroblasts on the development of oocytes. The exact mechanism of action is not yet known, but it could be a new direction for study of ovarian maturation disorders, anovulation and polycystic ovarian changes. In our study, *PBK, SPP1* and *TUBA1A* had 25 kinds of approved drugs, it may be potential drugs for PCOS.

Moreover, our study showed that epithelial cells may related to the progression of EC. Endometrial hyperplasia and EC are due to steroid hormone-driven endometrial gene transcription and cellular function resulted in tissue dyshomeostasis [21, 22]. Several studies indicate that androstenediol with estrogenic activity [23], that can be highly generated from the precursor dehydroepiandrosterone in the endometrium [24]. Higher concentration of androstenediol was detected in women with PCOS and EC, suggesting a potential role of the pathophysiology of carcinoma [25]. The androgens on EC risk has come from studies in women with PCOS where the risk of EC is higher in women with symptoms of androgen excess [14]. Our study found that PI3K-Akt signaling pathway may be the most important pathway in epithelial cells from PCOS to EC. Synthesis or the activation of certain molecules with stimulus of androstenediol or estradiol, which in turn activate PI3K-AKT pathway [26]. *EDNRA, FBN1, PMP22* and *SPARC* were validated both significant in both expression and survival analysis, and *EDNRA, SPARC* and *PMP22* had 23 kinds of drugs in all, and 6 kinds of drugs have been approved by FDA, which may be potential drugs for stopping the progression of PCOS to endometrial cancer or EC. mRNAs were identified for the 4 DEGs, which may be potential mRNA biomarkers for PCOS.

In our research, IGF-1 was the only up-regulated DEGs among the epithelial cells in PCOS and two EC datasets, but IGF-1 is not a cancer gene. Several studies showed a significant correlation between components of the IGF system and EC risk [27, 28]. IGF-1 is produced by the liver under the stimulation of growth hormone, it have autocrine, endocrine, and paracrine actions, and takes significantly roles in growth, development, and metabolism [29]. Growth hormone-IGF-1 endocrine axis to carcinoma development [30]. In patients with PCOS, elevated IGF-1 levels in insulin

resistance, obesity and hyperinsulinemia is a higher risk of EC [31]. Impaired glucose management, hyperglycemia and expression of insulin receptor trigger carcinoma cells proliferation and inhibit carcinoma cells apoptosis [32]. The heightening circulating levels of IGF-1 caused by hyperinsulinemia, IGF-1 binding to IGF-1 receptor (IGF-1R) leading to proliferative and anti-apoptotic events [33, 34]. IGF-1 and its receptor IGF-1R may be the new therapeutic targets for both PCOS and EC.

In our research, stromal fibroblasts may be involved in the procession of maturation and meiosis of oocyte, *EDNRA*, *FBN1*, *PMP22*, *SPARC* and *IGF-1* may be potential DNA biomarkers, and their miRNAs, especially hsa-miR-29a-3p and hsa-miR-29b-3p may be potential miRNA biomarkers in the progression from PCOS to endometrial carcinoma.

Author contributions

We certify that YG has participated sufficiently in the intellectual content, and ZZL involved in work of conception and design of this research or the analysis and interpretation of the data, as well as the writing of the manuscript. All author contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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